Title Page

A Randomized, Double-blind, Placebo-controlled, Parallel Group Clinical Study to Assess the Safety and Efficacy of Three Doses of Clobetasol Propionate when Administered Intra-orally Twice Daily in Patients with Oral Lichen Planus (OLP) using Rivelin®-CLO Patches

Date: 29-Jun-2020

Study number: **EUDRACT No:** **IND No.:**	**DT-001-R-004** **2017-002193-40** **129603**	**Name of the sponsor:**	**Afyx Therapeutics A/S; Lergravsvej 57, 2. tv; 2300 København S, Denmark** Formerly: Dermtreat ApS, Abildgaardsvej 174, 2830 Virum; Denmark (both names and addresses were valid throughout the study)
Investigational product:	**Rivelin®-CLO Patches**	**Clinical Study Phase:**	**II**
Indication:	**Oral lichen planus**	**Early Termination:**	**Not applicable**
Study initiation date:	**28-Jun-2018**	**Study completion date:**	**20-Dec-2019**

International Coordinating Investigator and Chief Investigator USA	**Prof. Michael Brennan, DDS** **Atrium Health, Dept. of Oral Medicine** **1000 Blythe Blvd.** **Charlotte, NC 28203, USA** **Phone: +1 704 355 4197; e-mail: mike.brennan@carolinas.org**
Coordinating Investigator EU and national Chief Investigator GER	**Prof. Dr. Thomas Ruzicka** **Klinik und Poliklinik für Dermatologie und Allergologie, Klinikum der Universität München** **Frauenlobstraße 9-11, 80337 Munich, Germany** **Phone: +49 89 4400 56001; e-mail: Thomas.Ruzicka@med.uni-muenchen.de**
Person responsible for the study report at the sponsor:	**Lars Siim Madsen, PhD** **Afyx Therapeutics A/S** **Lergravsvej 57, 2. Tv** **2300 København S, Denmark** **Phone: +45 51912315; e-mail: lsm@afyxtx.com**
Earlier reports from the same study:	**Not applicable**
Study design:	**Randomized, multicenter, double-blind, placebo-controlled, parallel group phase II study.**

This study was conducted in accordance with Good Clinical Practice (GCP), including the archiving of essential documents.

Final Version 1.0

1 APPROVAL STATEMENT

The following persons have approved this clinical trial report by signing an approval form located in Appendix 16.1.5.

Lars Siim Madsen, PhD

Sponsor's representative

Michael Brennan, DDS

International Coordinating Investigator and Chief Investigator USA

Prof. Thomas Ruzicka, MD

Coordinating Investigator EU and national Chief Investigator GER

Thomas Bengtsson

Biostatistician (statistical analysis)

2 SYNOPSIS

Name of sponsor: Afyx Therapeutics (formerly: Dermtreat ApS)		
Name of finished product:	Rivelin®-CLO patches	
Name of active ingredient:	Clobetasol propionate	
Reference to the according CSR: DT-001-R-004 CSR, final version 1.0, dated 29-Jun-2020		**Date of synopsis:** 29-Jun-2020

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Investigators:

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A total of 28 principal investigators participated in this study – a list of all principal investigators and study sites is given in Appendix 16.1.4.

Study sites:

2 study sites in Germany, 7 in Great Britain, 2 in Denmark, 14 in the USA, 1 in Ireland and 2 in Canada

Studied period:	Date of first patient first visit: 28-Jun-2018 Date of last patient completed: 20-Dec-2019	**Clinical study phase:** Phase II

Objectives:

Primary objective:

1. To demonstrate the efficacy of three different doses of Rivelin®-CLO patches in treating OLP lesions over 4 weeks of treatment assessed by change in ulcer area.

Secondary objectives:

1. To demonstrate the efficacy of three different doses of Rivelin®-CLO patches in treating OLP lesions over 4 weeks of treatment assessed by change in lesion area.
2. To demonstrate the efficacy of three different doses of Rivelin®-CLO patches in treating OLP lesions over 4 weeks of treatment assessed by change in 5-point erythema score.
3. To demonstrate the efficacy of three different doses of Rivelin®-CLO patches in treating OLP lesions over 4 weeks of treatment assessed by change in Clinical global impression of site score.

4. To demonstrate the effect on patient reported daily symptoms (OLP Symptom Severity Measure [OLPSSM] total score, items #1 to #7) when OLP lesions are treated by three different doses of Rivelin®-CLO patches over 4 weeks of treatment.
5. To investigate the comfort and sensation of wearing the Rivelin®-CLO and Rivelin® plain patches after first administration and after 2 weeks of treatment.
6. To investigate the adhesion time of Rivelin®-CLO and Rivelin® plain patches applied to one OLP lesion over 4 weeks of treatment.
7. To evaluate the safety of Rivelin®-CLO patches in treating OLP lesions over 4 weeks of treatment.

Exploratory objectives:

1. To demonstrate the effect on patient reported daily symptoms (OLP Symptom Severity Measure [OLPSSM], items #8 to #12) when OLP lesions are treated by three different doses of Rivelin®-CLO patches over 4 weeks of treatment.
2. To demonstrate the efficacy of three different doses of Rivelin®-CLO patches in treating OLP lesions over 4 weeks of treatment assessed by change in 3-point erythema score.
3. To demonstrate the efficacy of three different doses of Rivelin®-CLO patches in treating OLP lesions over 4 weeks of treatment measured by change in Guy's disease severity score, Guy's total site score, Guy's disease activity score and Guy's pain score.
4. To investigate the onset of effect when OLP lesions are treated by three different doses of Rivelin®-CLO patches as assessed by clinical and patient reported outcomes.
5. To investigate the feasibility for patients to self-apply Rivelin®-CLO and Rivelin® plain patches to OLP lesions.
6. To demonstrate the effects of three different doses of Rivelin®-CLO patches with respect to cleared lesions over 4 weeks of treatment.
7. To demonstrate the effects of three different doses of Rivelin®-CLO patches with respect to the use of rescue analgesics (pain killers) over 4 weeks of treatment including follow up.
8. To demonstrate the effects of three different doses of Rivelin®-CLO patches on Quality of Life (QoL) in OLP over 4 weeks of treatment, as measured by Chronic Oral Mucosal Disease Questionnaire (COMDQ).
9. To investigate exposure level of clobetasol and morning cortisol level after 7 days dosing at clinical visit (visit 3).
10. To document the measurement properties of the OLPSSM and OLP Clinician Reported Outcome Measure (OLPClinROM) including test-retest reliability, construct validity, and ability to detect change.
11. To explore the interpretability of clinically meaningful change in the OLPSSM and the OLPClinROM.
12. To perform supportive photo documentation of OLP lesions selected and measured (at all study sites where photo documentation is or can be established as a standard procedure).

Exploratory objectives #10 and #11 were evaluated in a separate psychometric analysis. No analysis was performed regarding objective #12.

Methodology (design of study):

This study was performed as a multi-center, randomized, four-armed, parallel group and double-blinded phase II study testing three dose strengths (20µg, 5µg and 1µg) of Rivelin®-CLO patches compared to application of a non-medicated Rivelin® patch (placebo) in the treatment of active and symptomatic OLP lesions.

Patients who met the entry criteria were randomly assigned in a 1:1:1:1 ratio to the 4 treatment groups respecting a stratification depending on the number of patches needed (1-3 or 4-6) at Baseline. Patients applied up to 6 patches to their symptomatic OLP lesions twice daily for 4 weeks. The maximum study duration per patient was approximately 8 weeks. During study course, patients returned to study sites for assessments of efficacy, compliance with treatment regimen and safety at week 1, 2, 3, 4 and 6 (Follow-up). The end of study was defined as the last visit of the last patient.

Number of patients (planned and analyzed):

Approximately 180 patients (*number decreased via Amendment 04: former 240 patients*) were planned to be randomized into this study. As a result of the interim analysis, it was decided to stop enrollment at 138 patients randomized. All 138 patients randomized were available for analysis (FAS: 138; Safety Set: 138; PPS: 116).

Diagnosis and main criteria for inclusion:

The study included male or female patients aged at least 18 years, clinically diagnosed with active OLP and with histologically confirmed diagnosis of (O)LP (*a biopsy confirmation of (O)LP was added as an inclusion criterion via Amendment 03*) and presenting at Baseline with at least one visual and measurable symptomatic ulcerative lesion.

The clinical diagnosis had to supported by a sum score (of individual items #1 to #7) of the OLPSSM of 5 or more on at least 4 days (consecutive or not consecutive) during the last week prior to Baseline. At maximum 6 patches per application were allowed during this study.

Test products: Rivelin®-CLO Patches / Rivelin® plain patches (placebo)

Dose: 20µg, 5µg, 1µg Clobetasol propionate / no active ingredient for placebo

Route of administration: topical, oral patches

Batch numbers: Unblinded batch number[1]/Blinded batch number[2]/Expiry date:

20µg	1µg
BIL18010311/815491/Dec-2019	BIL18020921/815491/Dec-2019
BIL18010811/813790/Jan-2020	BIL18020702/813790/Jan-2020
BIL18061412/820890/Jan-2020	BIL18012305/820890/Jan-2020
BIL18022212/819590/Feb-2020	BIL18060708/819590/Feb-2020
5µg	**Placebo**
BIL18012412/815491/Dec-2019	BIL18021511/815491/Dec-2019
BIL18021912/813790/Jan-2020	BIL18013013/813790/Jan-2020
BIL18042410/820890/Jan-2020	BIL18030210/820890/Jan-2020
BIL18042510/819590/Feb-2020	BIL18022222/819590/Feb-2020

[1]: batch numbers used during the study on IMP kits, not reflecting the strength of clobetasol coating

[2]: production batch numbers of the manufacturer, not used on IMP kits

Duration of treatment: 4 weeks, twice daily intra-oral application

Endpoints:

Primary efficacy endpoint:

1. Change in ulcer area from Baseline (visit 2) to average of visit 5 and visit 6.

Secondary efficacy endpoints:

1. a) Change in lesion area from Baseline to average of visit 5 (week 3) and visit 6 (week 4).
   b) Change in 5-point erythema score from Baseline to average of visit 5 and visit 6.
   c) Change in Clinical global impression of site score from Baseline to average of visit 5 and visit 6.
2. a) Change in OLPSSM total score (item #1 to #7) from Baseline (run-in mean) to mean over weeks 3 and 4.
   b) Change in individual diary symptom scores (item #1 to #7 of the OLPSSM) from Baseline (run-in mean) to mean over weeks 3 and 4.
3. Change in worst symptoms at anatomical sites from Baseline to average of visit 5 and visit 6.
4. The proportion of positive outcomes (score 0 or 1) on each of the 11 questions in the Patch Sensation Questionnaire assessed at day 1 and after 2 weeks of treatment.

5. The proportion of patients with successful (>=80% of days on treatment) patch applications defined as an adhesion time >=30 minutes during the 4 weeks treatment.
6. a) Frequency and intensity of adverse events (AEs) reported during the study.
   b) Laboratory values and vital signs.
   c) Pseudomembranous candidiasis assessed by visual inspection.

Exploratory endpoints:

1. a) Change in individual diary symptom scores (item #8 to #10 of the OLPSSM) from Baseline (run-in mean) to mean over weeks 3 and 4.
   b) Change in individual weekly diary symptom score (item #11 of the OLPSSM) from Baseline to visit 6.
   c) Individual symptom score (item #12 of the OLPSSM) at visit 6.
2. The change in 3-point erythema score from Baseline to average of visit 5 and visit 6.
3. Change in Guy's 106 total site score, Guy's disease severity score, Guy's disease activity score and Guy's pain score from Baseline to average of visit 5 and visit 6.
4. All endpoints based on OLP Clinician Reported Outcome Measure (OLPClinROM), including assessment of worst symptoms at anatomical sites and Guy's Scores assessed at visits 3, 4, 5 and 6 and all applicable endpoints based on OLPSSM assessed over weeks 1, 2, 3 and 4 to investigate the onset of treatment effect.
5. The proportion of patients with successful patch applications assessed by the Instructions for Use Questionnaire at clinical visits (visit 2, Baseline and visit 3).
6. a) The proportion of patients with cleared lesions (defined by no lesion area) at each clinic visit over 4 weeks of treatment.
   b) The proportion of patients with cleared ulcers (defined by no ulcer area) at each clinic visit over 4 weeks of treatment.
7. Change from Baseline (the run-in mean) to each of the means over weeks 1, 2, 3 and 4, and the follow-up period in use of rescue analgesics, i.e. pain killers.
8. Change from Baseline to 2 and 4 weeks of treatment in total COMDQ score and each of the 4 COMDQ subdomain scores.
9. Systemic exposure level of clobetasol and morning serum cortisol level (between 7 and 9 AM) after 7 days dosing at clinical visit (visit 3).
10. Supportive photo documentation at each clinic visit (at all study sites where photo documentation is or can be established as a standard procedure).

Statistical methods:

Continuous variables were summarized using descriptive statistics (number of patients [N], arithmetic mean, standard deviation [SD], median, minimum and maximum values) and for categorical (nominal) variables, the number and percentage of patients will be used. For continuous variables with an expected skew distribution (plasma clobetasol concentrations, serum cortisol levels), geometric mean and coefficient of variation (CV) will be given instead of arithmetic mean and SD.

All hypothesis testing was done using two-sided alternative hypotheses. P-values less than 4.9% were considered statistically significant, this to account for the interim analysis performed including the first 90 patients and at which testing was made at the 0.1% level. To account for multiplicity when testing for efficacy, a closed testing procedure was applied for each endpoint:

First the highest dose of clobetasol was tested versus placebo and if statistically significant, then the mid dose of clobetasol was tested versus placebo and, if statistically significant then finally the lowest dose of clobetasol was tested versus placebo. No other adjustment for multiple testing were done. If appropriate, active doses of clobetasol were compared pairwise to investigate the dose-response.

For continuous endpoints, treatments were compared using an analysis of covariance (ANCOVA model with fixed factors treatment, country and strata and with the baseline value as a covariate. For each test the estimated treatment difference was given together with 95% confidence limits and corresponding 2-sided p-value. Primary evaluation was based on an average of values from weeks 3 and 4. In addition, values from each week were analyzed separately to investigate the onset of effect. Primarily all endpoints were compared on the linear scale. For ulcer area and lesion area, a similar analysis but with changes expressed as percentage change from baseline instead, was performed as a secondary analysis.

For categorical outcome, treatments were compared using a logistic regression model with fixed factors treatment and strata. Country was planned to be included as factor but dropped from these models due to convergence problems for the algorithm. Treatment differences from the logistic regression models were expressed as odds ratios with 95% confidence intervals and associated two-sided p-values. Endpoints tested using logistic regression included, cleared ulcers/lesions, positive responses on the patch sensitivity questionnaire and successful applications (patch adhesion data).

The full analysis set (FAS) consisted of all randomized and treated patients with data collected post first dose administration. The FAS population was used for evaluation of all efficacy and feasibility data and for exploratory analyses. Patients were analyzed according the randomized treatment assigned.

The per-protocol set (PPS) consisted of all patients in FAS without major/important protocol deviations having impact on the efficacy analysis and was used for sensitivity analyses of ulcer area, lesion area and 5-point erythema scores. The safety dataset consisted of all randomized and treated patients with safety data collected post first dose administration and was used for all safety evaluation. Patients were analyzed according to treatment dispensed at Baseline.

Summary of Efficacy:

- Overall, Rivelin®-CLO patches 20 µg were shown to be effective in reducing OLP severity and symptoms and improving QoL as assessed by clinicians and patients. Thus, this dose strength is recommended for further clinical projects investigating Rivelin®-CLO patches from the efficacy perspective.
- Reducing OLP severity was shown in significantly reducing the total ulcer area (primary endpoint) and the Guy´s 106 ODSS. Borderline significance was observed in reducing the total lesion area on the FAS, with significant differences seen on the per protocol population.
- Reducing OLP symptoms was shown in significantly reducing the total OLPSSM Q1-7 score, single items OLPSSM Q8-11 scores, the Guy´s pain score. Borderline significance could be observed in reducing the worst symptoms at anatomical site score.
- Quality of life was shown to significantly improve measured by COMDQ and OLPSSM Q12.
- Rivelin®-CLO patches 5µg were shown to be effective in reducing total ulcer area (primary endpoint). Trends could be observed for improvement of some items of the OLPSSM questionnaire.
- For Rivelin-CLO patches 1µg only trends could be observed for improvement of some items of the OLPSSM questionnaire.
- None of the doses was able to significantly improve the erythema scores (5-point/3-point) or the Clinical Global Impression at anatomical site score. An exploratory analysis of maximum 5-point erythema score at clinical visits (see statistical report in Appendix) showed significant improvements for the 20µg group.
- No difference could be shown between any dose of Rivelin®-CLO and Rivelin® plain patches in reducing the use of rescue analgesics or completely clearing OLP lesions (total lesion area=0) or ulcers (total ulcer size=0).
- All doses of Rivelin®-patches were shown to be easy to handle, well tolerable and adhered very well to the oral mucosa for about 90 minutes.
- No indication for an impact of Rivelin®-CLO patches on the cortisol levels of patients and no indication for patch induced systemic availability of clobetasol propionate (as measured by means of morning-serum sampling after 1-week IMP treatment) could be observed.
- The new OLPSSM measure showed to be sensitive in revealing change in OLP symptoms and is recommended for the detailed assessment of patient reported OLP symptoms in future clinical projects investigating OLP and/or Rivelin®-CLO patches.

Summary of Safety:

- In total, 121 treatment emerged AEs occurred in 63 patients (45.7%). The incidence and type of events were similar between the 4 treatment groups without any increases in the two higher dose groups. On PT level, the most common AEs were ‘periodontal disease’ and ‘nasopharyngitis’. The intensities of most AEs were mild (in 31.9% of patients) or moderate (in 21% of patients) and only 5 events (in 3.6% of patients) were severe, all assessed unrelated. Adverse Drug Reactions (ADRs) and Adverse Device Effects (ADEs) were reported for a total of each 16 patients (12%), Most of them occurred in the oral cavity, and only a minority of 6 events in 5 patients occurred outside the oral

cavity or systemically.

- No safety concerns emerged from the ADR-profile: Frequencies of ADRs ranged from each only 6% in the higher 5µg- and 20µg groups, to 16% in the placebo- and 18% in the 1µg group, respectively. (Incidence of overall ADRs would decrease to 10% (11 patient), if 5 patients from the placebo group would be excluded). The most common ADRs comprised different PTs of oral candidiasis infections within the SOC 'infections and infestations' (in 8 patients [6%]) with highest occurrences in the 1µg- and placebo-groups (in each 3-4- patients), only 1 occurrence in the 5µg group and surprisingly no occurrence in the highest dose group. This indicates that clobetasol was not mainly responsible for increased susceptibility to fungal infection, but rather the physical patch properties themselves. No clustering of events could be observed within events of the next common SOC 'gastrointestinal disorders' (in 5 patients [4%]). Different sorts of 'general disorders and administration site conditions' (4 patients [3%] within this SOC) were only observed in the three clobetasol groups. Contrary to expectations of clustering of ADRs in the highest 20µg treatment arm, ADR-incidence was lowest here, suggesting that most reactions need to be interpreted rather in the context of device effects and not as 'real' clobetasol reactions. A minority of 5 patients experienced systemic ADRs (i.e. occurring outside the oral cavity) with 'nausea' being the only event that occurred twice. Systemic reactions occurred in all groups except for the medium 5µg dose and most of them were also rated ADE.
- The ADE-profile was uncritical, too: ADE-frequencies were also quite heterogenous, and ranged from 6% in the 20µg group, over 10% in the placebo group, 13% in the 1µg group, to 18% in the 5µg group. Only 2 events of candidiasis infection were assessed as ADEs. The major represented SOC here was 'gastrointestinal disorders' (9 patients of all treatment groups [7%]), with the main PTs 'salivary hypersecretion', 'altered saliva', 'nausea', and 'gingival bleeding'. The next common SOC 'General disorders and administration site conditions' (7 patients [5%]) included PTs of different application site reactions (namely 'AS-pain', 'AS-hypersensitivity', 'AS-hemorrhage', and 'AS-injury'), which were only observed in the clobetasol groups.
- Related AEs in oral cavity: 13 patients (9%) had different types of ADRs in the oral cavity, mainly *infections with candidiasis*. Slightly more patients were reported to have oral ADEs (15 patients ([11%]), mainly different types of *application site conditions (-pain, -hypersensitivity, -hemorrhage, and -injury)*. Except for the events of infection, most of local reactions were limited to a trigger like patch procedure or daily activity procedure and did not represent a constant side effect during IMP treatment. This was clarified by the evaluation of the respective verbatims of local reactions. Most events of candidiasis infections in the oral cavity were of mild intensity. Infections were treated medically and recovered completely in all cases. IMP treatment had not to be interrupted nor discontinued in any of these patients.
- AEs that led to permanent IMP-discontinuation, and SAEs: There were no death cases and only 2 SAEs in 2 patients ("myocardial infarction", "multiple fractures") - none of them was considered related to treatment. 4 AEs in 2 patients (1.4%) led to permanent discontinuation of the IMP: 2 events in one patient of the 1µg group were 'Gastrointestinal disorders' (PTs 'stomatitis' and 'oral pain'), both judged as oral reactions and both recovered after discontinuation of treatment. A third event in the same patient ('increased insomnia') was judged as unrelated. The fourth event ('Varicella zoster virus infection') occurred in the placebo group and was judged unrelated, too.
- Laboratory data on serum biochemistry, serum hematology, and urine, as well as data on pregnancy testing did not reveal any evidence for clinically relevant changes during the trial that called for attention. The same applies to the data of vital signs (blood pressure, pulse, body temperature) and body weight parameters.
- No accidental ingestion of the patches occurred during the trial and no AEs indicative for any significant influence of clobetasol on the cortisol levels of patients could be observed in any of the clobetasol groups.

Overall conclusions:

Significant efficacy in the treatment of OLP could be clearly shown for Rivelin®-CLO patches 20µg:

- for the primary endpoint: total ulcer area [cm^2]
- for the overall disease severity, as well as all sub-scores (total site, disease activity and pain) as measured with the Guy`s 106 ODSS
- for patient reported symptom severity as measured with the OLPSSM
- for overall quality of life, as well as for the sub-domains 'pain and functional limitations' and 'medication and treatment' as measured with the COMDQ questionnaire

For all these endpoint improvements with statistically significant differences compared to placebo could be observed at least for the change from Baseline to the average of weeks 3 and 4, in some cases even with earlier onsets.

Thus, Rivelin-CLO patches 20µg can be regarded as effective in the 4 weeks treatment of all important OLP symptom manifestations.

Rivelin® patches were shown to be easy to handle (even for an elderly patient population), adhered very well (even to ulcerative parts of) the oral mucosa and long enough for the clobetasol propionate to be absorbed. Even though the patches were assessed to be a quite disturbing foreign object by the patients, they were rated as rather well tolerable and non-irritable as well. Combined with the result that half of the patients assessed their OLP symptoms as much better after 4 weeks of treatment, the disturbances are most probable to be overweight by the positive treatment effects, at least for the 20µg patches.

Profiles and incidences of side effects were uncritical and revealed no safety concerns, not even in the highest clobetasol group. From the vital signs and laboratory data no safety concerns could be observed, too. The two most frequent groups of side effects ('oral candidiasis infections' and different types of 'application site reactions') were expected, reversible, mostly of mild intensity, and did not require IMP-discontinuation. Also, no significant systemic availability of clobetasol propionate or any significant influence on the cortisol levels of patients could be observed in any of the treatment groups, suggesting that even the 20µg dose was safe and well tolerated by the patients. Therefore, the application of Rivelin®-CLO patches can be regarded as safe and well tolerated in all tested dosages in patients with OLP. Further clinical development is clearly encouraged.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AP	Alkaline Phosphatase
ASA	Acetylsalicylic Acid
AST	Aspartate Aminotransferase
ATC	Anatomical-Therapeutical-Chemical (interactions/co medication)
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
BL	Baseline
°C	Degree Celsius
CA	Competent Authority
CAN	Canada
CD	Compact Disc
CDMS	Clinical Data Management System
CDISC	Clinical Data Interchange Standards Consortium
CGIM	clinical global impression of anatomical site score
CLO	Clobetasol(-17-proprionate)
cm	Centimeter
cm^2	Square Centimeter
Cmax	Maximal concentration
COMDQ	Chronic Oral Mucosal Disease Questionnaire
CS	Clinically Significant
CV	Coefficient of Variation
dL	Deciliter
DNK	Denmark
DMC	Data Monitoring Committee
DMP	Data Management Plan

DSMB	Data Safety and Monitoring Board
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EoS	End of Study Visit
EoT	End of Treatment
ET	Early Termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
°F	Degree Fahrenheit
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FUP	Follow-up Period
g	Gram
GCP	Good Clinical Practice
GER	Germany
Guy's106 ODSS	Guy's 106 Oral Disease Severity Score
hCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
HRQoL	Health-related Quality of Life
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identifier
IEC	Independent Ethics Committee
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IFU	Instructions for Use
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug

IRB	Institutional Review Board
IRE	Ireland
IAP	Interim Analysis Plan
IWRS	Interactive WEB Response System
JPMA	Japan Pharmaceutical Manufacturers Association
L	Left / Liter
LMU	Ludwig-Maximilians-University
LOCF	Last Observation Carried Forward
LOQ	Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare products Regulatory Agency
mg	Milligram
µg	Microgram
mm	Millimeter
mm^2	Square Millimeter
mmHG	Millimeter Mercury
NCS	Not Clinically Significant
NHS	United Kingdom National Health Service
NIR	Number of patients at the time of interim results
nIR	NIR/4/group rounded down to nearest integer
ODSS	Oral Disease Severity Score
OLP	Oral Lichen Planus
OLPClinROM	Oral Lichen Planus Clinician Reported Outcome Measure
OLPSSM	Oral Lichen Planus Symptom Severity Measure
P-gp	Permeability glycoprotein
PhRMA	Pharmaceutical Research and Manufacturers of America
PI	Principal Investigator
PK	Pharmacokinetic
PPS	Per Protocol Set
PRO	Patient reported outcome
PT	Preferred Term
QoL	Quality of Life
R	Right

RA	Rheumatoid arthritis
RBC	Red blood cell count
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCC	Squamous Cell Carcinoma
SCR	Screening
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SDV	Source Data Verification
SOC	System Organ Class
SUSA[D]R	Suspected Unexpected Serious Adverse [Drug] Reaction
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures and Listings
U	Unit(s)
UK	United Kingdom
USA	United States of America
V	Visit
WBC	White blood cell count
WHO	World Health Organization
WOCP	Woman of childbearing potential

5 ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Study recruitment started with protocol version 4.0 (dated 15-Mar-2018) This protocol version, all following protocol amendments (resulting in protocol versions final 6.0, dated 07-Jul-2018 and final 8.0, dated 29-Mar-2019), as well as any information provided to patients and any recruitment advertisements were reviewed and approved by each study site's IEC/IRB before the start of the study and before implementation of the amendments respectively.

A list of IECs/IRBs consulted can be found in Appendix 16.1.3.1.

A list of all protocol versions, valid during the study can be found in Appendix 16.1.1.

5.2 Ethical Conduct of the Study

This study was carried out in compliance with the protocol and the applicable laws and regulatory requirements of the appropriate regulatory agencies. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki (October 2008)[1] and the ICH-GCP Guidelines of Jan. 17th, 1997 including ICH-GCP Addendum (ICH E6(R2), November 2016)[2].

5.2.1 Public Registration of the Clinical Study

The study was registered on Clinicaltrials.gov on 19-Jul-2018, registration identifier NCT03592342.

5.3 Patient Information and Consent

At Screening, each patient was required to provide written informed consent to participate in the study. No study-specific procedures were performed before a patient's informed consent had been obtained.

Patient information included full and adequate verbal and written information (informed consent form, ICF) regarding the objective and procedures of the study and the possible risks involved.

The ICF and other written information provided to the patients (e.g. Instructions for Use, Map of Lesions, eDiary device/paper Diary [*original protocols stated the use of an electronic diary; a paper diary was introduced via Amendment 04*]) were revised several times during study conduct, as protocol amendments came into force which affected these documents. The investigator informed the patient of those changes in a timely manner and asked the patient to confirm to continue his / her participation in the study by signing the revised ICF versions. The original ICF, as well as any revised ICF versions and any other written information provided to the patient were reviewed and approved by the respective IRB or IEC before their use.

Sample master ICFs and samples of other written information given to the patients are located in Appendix 16.1.3. The patient`s diary can be found in Appendix 16.1.2.

5.4 Insurance / Compensation for Health Damage of Patients

All patients participating in the study had clinical study insurance coverage by Dermtreat ApS /Afyx Therapeutics A/S [*The name of the sponsor company changed during the study; both names were valid during study course*], which was in accordance with the laws and regulations of the countries in which the study was performed.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Detailed information about the trial administrative structure including a list of trial sites, investigators and other persons whose participation materially affected the conduct of the trial can be found in Appendix 16.1.4.

7 INTRODUCTION

7.1 Study Disease

Sensitive mucosal lesions in the oral cavity can be located on the buccal, palate, gingiva, lips, floor of the mouth and tongue (including ventral tongue) and lesions to treat would range from sensitive areas of erythema, atrophy, blisters and ulcers. Such lesions can arise from 1) trauma or 2) oral inflammatory diseases and infections.

Traumatic lesions can arise from routine daily practices, i.e. brushing teeth, bite during ingestion of food etc. Whether lesions arise from a disease or a trauma, discomfort and pain from such lesions can be severe and impact activities of daily living such as talking, ingestion of food, drinking, swallowing and dental hygiene practices.[3; 4]

An example of an oral inflammatory/infectious disease, and the condition in focus for the present study, is Oral Lichen Planus (OLP), one manifestation of Lichen Planus that can also involve skin, nails and other mucosal surfaces. OLP is a common, chronic mucosal disease associated with a cell-mediated immunological dysfunction and characterized by exacerbations of inflammation and presented as symptomatic lesions. In general, patients with inflammatory OLP have a demanding medical need because of severe symptoms and consequently lower quality of life and propensity for depressions.[3;4] The prevalence of OLP in the general population is approximately 1% and the typical age of presentation is 30-60 years.[5] A proportion of OLP patients are asymptomatic and only diagnosed during routine dental examinations. The clinical manifestation varies but is characterized by keratotic (plaque, reticular etc.), ulcerative and erythematous lesions – including erosions, atrophies and erythema that require long-term treatment, because of inflammation and severe symptoms.[6] The precise cause of OLP is unknown, but on the oral mucosa lichenoid lesions may sometimes be precipitated by contact allergy to metals in dental restorations such as mercury and gold.[7] Long lasting follow-up is recommended because of the documented risk for cancer transformation of the lesions.[5; 8] It is a clinical opinion that optimal treatment combined with high standard of dental hygiene is the best preventive measures.[9-11]

7.2 Treatment Options (available at the time of protocol design)

The treatment options of OLP, that were available at the time of protocol design, were application of potent topical corticosteroid treatments which cannot be applied isolated to the lesion alone and therefore are absorbed via the healthy oral mucosa or by swallowing; both causing a degree of systemic exposure. Further treatment options are topical tretinoin, lidocaine or *Aloe vera* preparations, intralesional steroid injections, systemic steroids as well as topical or systemic immunosuppressive drugs (e.g. calcineurin inhibitors). Both local and systemic adverse events are main concerns with treatment alternatives and the likelihood of lesion recurrence after treatment removal is substantial. Reducing sharp teeth or broken restorations causing physical destruction in the oral cavity could also be done as a supportive action.[12]

7.3 Rivelin® Patches

With the intention to meet the medical need from OLP patients, the Sponsor developed a mucosal adhesive patch technology to be applied for relief of complications related to

symptomatic lesions in the oral cavity. The Rivelin® patch features constitute a barrier to protect the lesions from irritating consumables (associated with intake of food and beverages such as spices, acidic foods or sodium lauryl sulfate (SLS) containing toothpastes) and mechanical stimuli (from saliva, contact with teeth, mouth/tongue movements and inhaled air). Additionally, it displays high flexibility and subsequent ability to conform to mucosal contours and dynamics. Previous clinical data showed that the patch is generally well tolerated in healthy volunteers, without any unfavorable effect on the mucosa or occurrence of hypersensitivity reactions. It has been shown also that adhesion is acceptable on healthy tissue (Clinical investigation DT-R0-002).[13] At the time of protocol design, no SAE and only one AE (Light burning and stinging one hour after application of first patch) assessed as possibly related to Rivelin® plain patch had been reported from another clinical investigation (DT-001-R-003)[14] assessing the tolerability and usability of Rivelin® plain patches in OLP patients.

7.4 Study Rationale

It has been difficult to achieve effective and targeted application of topical treatments for inflammatory conditions in the oral mucosa without risking unnecessary systemic uptake. Thus, there had been no regulatory authority approved licensed product for this medical need.

Rivelin® patches can carry effective drugs and deliver topical drugs targeted, focused and enhanced to the human oral mucosa.

The highly potent corticosteroid ‘clobetasol propionate’ is effective for topical treatment of various skin disorders, thus making it an ideal combination agent with the Rivelin® patch for the treatment of OLP.

This study was performed to assess the efficacy and safety of 3 doses of clobetasol propionate coated patches (Rivelin®-CLO patches: 1 µg, 5 µg and 20 µg /patch) compared to placebo (Rivelin® plain patch) in the treatment of active and symptomatic OLP.

The main objectives of this study were to show that Rivelin®-CLO patches are effective in the treatment of OLP and that they are safe and practical in their daily use.

The FDA in the USA and the EMA in Europe were consulted prior to initiation of the study. However, shortly after study initiation, the FDA recommended only to include patients with biopsy confirmed OLP. As a consequence, biopsy confirmation of OLP was added as an inclusion criterion with Amendment 03.

This report presents the study results of all patients enrolled, based on release of the clinical database following database lock on 03-Mar-20.

8 STUDY OBJECTIVES AND ENDPOINTS

8.1 Study Objectives

8.1.1 Primary Objective

The primary objective of this study was:

1. To demonstrate the efficacy of three different doses of Rivelin®-CLO patches in treating OLP lesions over 4 weeks of treatment assessed by change in ulcer area.

8.1.2 Secondary Objectives

Secondary Objectives of this study were:

1. To demonstrate the efficacy of three different doses of Rivelin®-CLO patches in treating OLP lesions over 4 weeks of treatment assessed by change in lesion area.
2. To demonstrate the efficacy of three different doses of Rivelin®-CLO patches in treating OLP lesions over 4 weeks of treatment assessed by change in 5-poing erythema score.
3. To demonstrate the efficacy of three different doses of Rivelin®-CLO patches in treating OLP lesions over 4 weeks of treatment assessed by change in Clinical global impression of site score.
4. To demonstrate the effect on patient reported daily symptoms (OLP Symptom Severity Measure [OLPSSM] total score, items #1 to #7) when OLP lesions are treated by three different doses of Rivelin®-CLO patches over 4 weeks of treatment.
5. To investigate the comfort and sensation of wearing the Rivelin®-CLO and Rivelin® plain patches after first administration and after 2 weeks of treatment.
6. To investigate the adhesion time of Rivelin®-CLO and Rivelin® plain patches applied to one OLP lesion over 4 weeks of treatment.
7. To evaluate the safety of Rivelin®-CLO patches in treating OLP lesions over 4 weeks of treatment.

8.1.3 Exploratory Objectives

1. To demonstrate the effect on patient reported daily symptoms (OLP Symptom Severity Measure [OLPSSM], items #8 to #12) when OLP lesions are treated by three different doses of Rivelin®-CLO patches over 4 weeks of treatment.
2. To demonstrate the efficacy of three different doses of Rivelin®-CLO patches in treating OLP lesions over 4 weeks of treatment assessed by change in 3-poing erythema score.
3. To demonstrate the efficacy of three different doses of Rivelin®-CLO patches in treating OLP lesions over 4 weeks of treatment measured by change in Guy's disease severity score, Guy's total site score, Guy's disease activity score and Guy's pain score.
4. To investigate the onset of effect when OLP lesions are treated by three different doses of Rivelin®-CLO patches as assessed by clinical and patient reported outcomes.

5. To investigate the feasibility for patients to self-apply Rivelin®-CLO and Rivelin® plain patches to OLP lesions.
6. To demonstrate the effects of three different doses of Rivelin®-CLO patches with respect to cleared lesions over 4 weeks of treatment.
7. To demonstrate the effects of three different doses of Rivelin®-CLO patches with respect to the use of rescue analgesics (pain killers) over 4 weeks of treatment including follow up.
8. To demonstrate the effects of three different doses of Rivelin®-CLO patches on Quality of Life (QoL) in OLP over 4 weeks of treatment, as measured by Chronic Oral Mucosal Disease Questionnaire (COMDQ).
9. To investigate exposure level of clobetasol and morning cortisol level after 7 days dosing at clinical visit (visit 3).
10. To document the measurement properties of the OLPSSM and OLP Clinician Reported Outcome Measure (OLPClinROM) including test-retest reliability, construct validity, and ability to detect change.
11. To explore the interpretability of clinically meaningful change in the OLPSSM and the OLPClinROM.
12. To perform supportive photo documentation of OLP lesions selected and measured (at all study sites where photo documentation is or can be established as a standard procedure).

Exploratory objectives #10 and #11 were evaluated in a separate psychometric analysis. The Report for the psychometric analysis is available on request.

No analysis was performed regarding objective #12.

8.2 Study Endpoints

8.2.1 Primary Endpoint

The primary endpoint in this study was:

1. Change in ulcer area from Baseline (visit 2) to average of visit 5 and visit 6.

8.2.2 Secondary Endpoints

Secondary endpoints in this study were:

1. a) Change in lesion area from Baseline to average of visit 5 and visit 6.

   b) Change in 5-point erythema score from Baseline to average of visit 5 and visit 6.

   c) Change in Clinical global impression of site score from Baseline to average of visit 5 and visit 6.

2. a) Change in OLPSSM total score (item #1 to #7) from Baseline (run-in mean) to mean over weeks 3 and 4.

   b) Change in individual diary symptom scores (item #1 to #7 of the OLPSSM) from Baseline (run-in mean) to mean over weeks 3 and 4.

3. Change in worst symptoms at anatomical sites from Baseline to average of visit 5 and visit 6.
4. The proportion of positive outcomes (score 0 or 1) on each of the 11 questions in the Patch Sensation Questionnaire assessed at day 1 and after 2 weeks of treatment.
5. The proportion of patients with successful (>=80% of days on treatment) patch applications defined as an adhesion time >=30 minutes during the 4 weeks treatment.
6. a) Frequency and intensity of adverse events (AEs) reported during the study.

   b) Laboratory values and vital signs.

   c) Pseudomembranous candidiasis assessed by visual inspection.

8.2.3 Exploratory Endpoints

Exploratory endpoints in this study were:

1. a) Change in individual diary symptom scores (item #8 to #10 of the OLPSSM) from Baseline (run-in mean) to mean over weeks 3 and 4.

   b) Change in individual weekly diary symptom score (item #11 of the OLPSSM) from Baseline to visit 6.

   c) Individual symptom score (item #12 of the OLPSSM) at visit 6.
2. The change in 3-point erythema score from Baseline to average of visit 5 and visit 6.
3. Change in Guy's 106 total site score, Guy's disease severity score, Guy's disease activity score and Guy's pain score from Baseline to average of visit 5 and visit 6.
4. All endpoints based on OLP Clinician Reported Outcome Measure (OLPClinROM), including assessment of worst symptoms at anatomical sites and Guy's Scores assessed at visits 3, 4, 5 and 6 and all applicable endpoints based on OLPSSM assessed over weeks 1, 2, 3 and 4 to investigate the onset of treatment effect.
5. The proportion of patients with successful patch applications assessed by the Instructions for Use Questionnaire at clinical visits (visit 2, Baseline and visit 3).
6. a) The proportion of patients with cleared lesions (defined by no lesion area) at each clinic visit over 4 weeks of treatment.

   b) The proportion of patients with cleared ulcers (defined by no ulcer area) at each clinic visit over 4 weeks of treatment.
7. Change from Baseline (the run-in mean) to each of the means over weeks 1, 2, 3 and 4, and the follow-up period in use of rescue analgesics, i.e. pain killers.
8. Change from Baseline to 2 and 4 weeks of treatment in total COMDQ score and each of the 4 COMDQ subdomain scores.
9. Systemic exposure level of clobetasol and morning serum cortisol level (between 7 and 9 AM) after 7 days dosing at clinical visit (visit 3).
10. Supportive photo documentation at each clinic visit (at all study sites where photo documentation is or can be established as a standard procedure).

9 INVESTIGATIONAL PLAN

The study was conducted according to the following documents:

- Original protocol, CSP version 4.0, dated 15-Mar-2018
  (18 patient randomized according to this CSP version)
- Amendment 03, resulting in CSP version 6.0, dated 07-Jul-2018
  (65 patients randomized)
- Amendment 04, resulting in CSP version 8.0, dated 29-Mar-2019
  (*55 patients randomized*)

The original protocol, all other CSP versions valid during the time of active patient recruitment as well as details on patients recruited according to the different CSP versions can be found in Appendix 16.1.1. An overview of protocol amendments and changes introduced therein are given in section 9.8.

A blank sample of each CRF version used for documentation during the study can be found in Appendix 16.1.2. The documents specifying the statistical analysis of this study are identified in section 9.7.

9.1 Overall Study Design and Plan Description

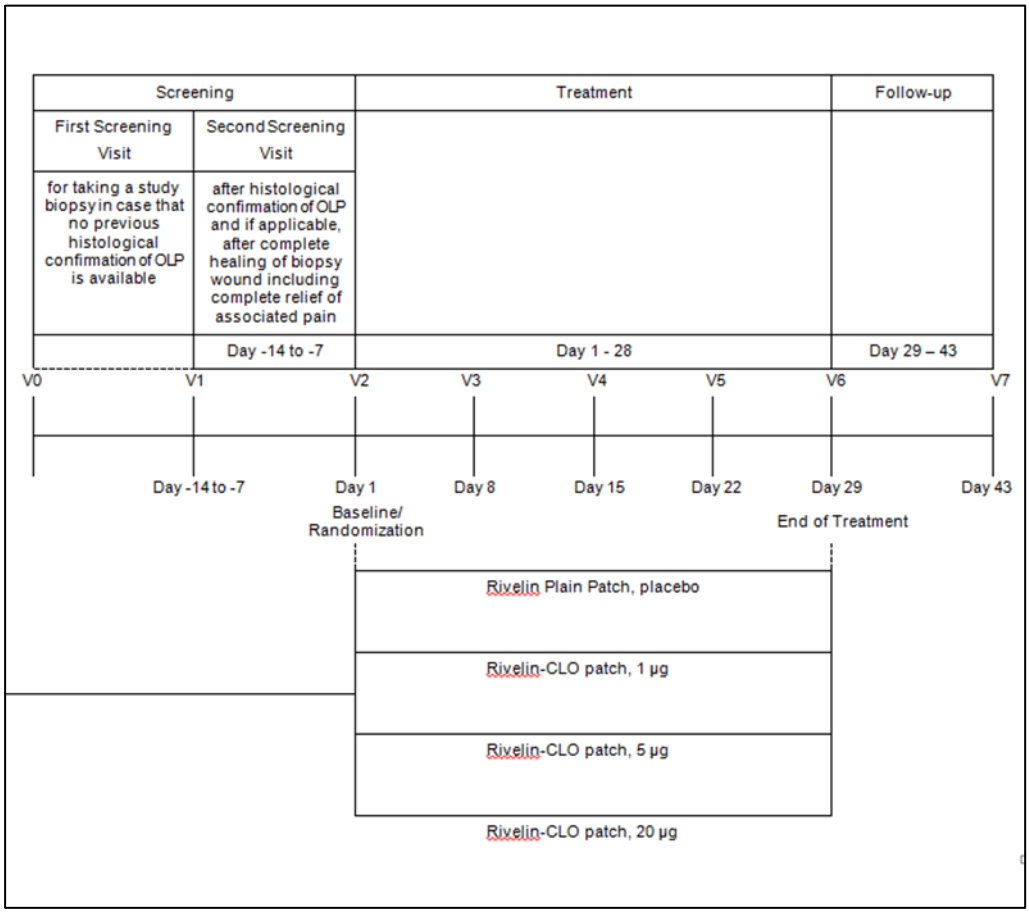
This study was performed as a multi-center, randomized, four-armed, parallel group and double-blinded phase II study testing three dose strengths of Rivelin®-CLO patches compared to application of a non-medicated Rivelin® patch in the treatment of active and symptomatic OLP lesions.

The study included male or female patients aged at least 18 years, clinically diagnosed with active OLP and with histologically confirmed diagnosis of (O)LP *(*a *biopsy confirmation of (O)LP was added as an inclusion criterion via Amendment 03*) and presenting at Baseline with at least one visual and measurable symptomatic ulcerative lesion. Approximately 180 patients (*number decreased via Amendment 04: former 240 patients*) were planned to be randomized at approximately 25 study sites in Europe (Denmark, Germany, Ireland, UK) and North America (Canada and USA). Patients who met the study entry criteria were randomly assigned in a 1:1:1:1 ratio to one of the treatment arms:

- Rivelin®-CLO patch 1 µg,
- Rivelin®-CLO patch 5 µg,
- Rivelin®-CLO patch 20 µg,
- Rivelin® plain patch (placebo).

In addition, patients were stratified according to the number of patches needed (1-3 or 4-6) at Baseline.

The general, study design is summarized in Text Figure 9-1 and a detailed schedule of assessments is given in section 9.5.5.



Text Figure 9-1: Study design

The study included a flexible period between study biopsy (if applicable) and screening, a 1-2-week screening period, a 4-week treatment period, and a 2-week post-treatment follow-up period. The maximum trial duration for each patient was approximately 8 weeks (plus flexible study biopsy period). The end of the study was defined as the last visit of the last patient.

Over a 4 weeks treatment period patients applied up to 6 patches to affected OLP lesions in the oral cavity (twice daily, morning and evening). Patients were thouroughly trained on the technique of application and removal of the patches. To standardize self-treatment at home, patients were provided with a lesion map (schematic picture of their oral cavity), indicating all lesions to be treated and patches to be applied.

After having provided written informed consent, the patients underwent screening procedures. This could include a study biopsy in case OLP had not been histologically confirmed in the past. At the end of the screening period, eligible patients were randomly assigned to one of the treatment groups on Day 0 (Visit 2/Baseline).

Weekly during treatment and once at the end of the follow-up period, subjects returned to the study sites for efficacy assessments, assessments of compliance with the treatment regimen, and safety assessments.

The investigator scored the disease severity of the patients using the newly developed OLP Clinician Reported Outcome Measure (OLPClinROM: disease status per anatomical site

affected) as well as the established Guy's 106 Oral Disease Severity Score[15] (Guy´s ODSS: overall disease status of the oral cavity including patient-reported pain assessment). After one week of treatment, clobetasol and morning cortisol blood levels were determined. The patients were asked to complete several questionnaires: Chronic Oral Mucosal Disease Questionnaire[16] (COMDQ: established quality of life assessment), parts of the OLPSSM questionnaire (newly developed assessment of OLP symptoms), instructions for use questionnaire (feasibility of instructions provided), patch sensation questionnaire (patch tolerability). Safety assessments (examination of oral cavity, AEs, safety laboratory, vital signs and BMI) were performed. All study assessments are described in detail in sections 9.5.

From Screening (V1) to end of study (V7), patients completed a diary with daily assessments of OLP symptoms (parts of OLPSSM questionnaire), IMP application details and use of predefined, patient-specific rescue analgesics. (*Original protocol required an electronic diary; a switch to paper diary was introduced via Amendment 04.)*

Safety data were planned to be monitored by an independent Data and Safety Monitoring Board (DSMB) throughout the study. DSMB should have advised the Sponsor of any potential risk for the safeguard of patients. See section 9.7.4 for further details.

An interim analysis (*introduced via Amendment 04*) was performed by an independent statistician after 90 randomized and evaluable patients. Cut-off for randomization into IA was on 17-Jul-2019. Safety data, primary endpoint and key secondary endpoints were evaluated to assess the safety profile and to re-estimate sample size. Unblinded interim results were reviewed by a sponsor-independent Data Monitoring Committee (DMC). Following their recommendation, randomization was stopped per protocol at the time interim results were available (11-Nov-2019).

9.2 Discussion of Study Design, including the Choice of Control Groups

Trial design

This multi-center, randomized, parallel group and double-blinded study design was chosen to evaluate the efficacy and safety of three dose strengths of Rivelin®-CLO patches compared to application of a non-medicated Rivelin® patch in the treatment of active and symptomatic OLP.

The target population for the present study was the intended population at the time of protocol design for the planned approval; adult patients clinically diagnosed with OLP presenting symptomatic ulcerative and erythematous lesions.

The three active treatment arms (1 µg, 5 µg and 20 µg Clobetasol propionate) were chosen to identify the most relevant dose for clinical efficacy vs. safety.

The placebo control was chosen to rule out any study effect of the patch ifself on the lesions.

Randomization to treatment groups was 1:1:1:1 and patients were stratified according to number of patches needed at Baseline (1-3 and 4-6) to ensure comparable disease severity in the four arms.

The trial was double-blind, to ensure that neither the investigator, the site personnel nor the patients did know which treatment was administered. Several precautions were taken to maintain the blinding (refer to section 9.4.3.2).

A multi-center approach was chosen to ensure reasonable recruitment in an appropriate time frame.

Dosing Regimen and Treatment Duration

Twice daily dosing and doses loaded on Rivelin®-CLO patches were chosen according to current experimental topical corticosteroid dosing schedules for OLP at the time of protocol design. These approaches indicated that a clinical dose of 5 µg clobetasol propionate/patch would be comparable to typical dosing with creams and gels under occlusion. In order to capture a dose response, three active doses with a 4 to 5-fold dose increase were chosen to cover a broad dose-range. Residence time of up to 2 hours was chosen, based on the release profile and the sticking properties of the patch. Within 30 minutes a mucosal C_{max} was expected to be reached, and after 2 hours of adhesion most patches would have self-detached without any need of active removal which would be expected to be necessary with shorter adhesion times. For further details on selection of dosing and timing, please refer to section 9.4.4.

At the time of protocol design, there were different treatment opinions regarding the ideal duration of treatment which is necessary to provide symptom relief and clear OLP lesions. This ranged between 2 and 8 weeks. The variation in treatment length can be explained by differences in standard of care and differences in the severity of referred patients. As reported by personal communication, clinicians applying clobetasol under occlusion (by cotton rolls or gauze) or sticky ointments/gels in general see a faster recovery than clinicians using clobetasol based aerosols or mouth washes.

Rivelin®-CLO patches are an occlusive dressing system, delivering the active component directly to the target area. But as clinical effect is not defined in clinical practice and the patient population varied from mild to severely affected OLP patients, a treatment period of 28 days has been chosen for this phase II study.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Patients had to meet all the following criteria to be eligible for participation in the study:

1. OLP patients with at least one visible and measurable symptomatic ulcerative OLP lesion[1], assessed via OLP Clinician Reported Outcome Measure (OLPClinROM).
2. Clinical diagnosis of symptomatic OLP supported by the Oral Lichen Planus Symptom Severity Measure (OLPSSM): The sum score of individual items #1 to #7 of the OLPSSM has to be 5 or more on at least 4 days (consecutive or not consecutive) during the last week prior to Baseline/Randomization Visit
(*as defined via Amendment 04*; *original definition: "Clinical diagnosis of symptomatic OLP with a total score of ≥ 5 for at least 4 days during the last week prior to*

[1] Ulcerative OLP lesions are areas presenting with full-thickness loss of epithelium exposing the underlying connective tissue, often granulating or with a fibrinopurulent surface. Key point is loss of epithelial integrity. The ulceration is typically accompanied by surrounding erythema.
Erythematous/white OLP lesions (i.e. "without ulceration") are characterized as regions in the mouth that are abnormally red in color. These areas are consistent with an erosive lesion, which is characterized by an incomplete loss of the epithelium.

Baseline/Randomization Visit, when summarizing the individual scores of items #1 – #7 of the Oral Lichen Planus Symptom Severity Measure (OLPSSM)").

3. Diagnosis of LP histologically confirmed by result of either an existing clinically relevant biopsy or a new clinically representative biopsy taken at first screening visit (i.e., a biopsy report either indicative of OLP, LP or indicative of lichenoid inflammation will be sufficient). *This criterion was added via Amendment 03.*
4. The written informed consent form has been signed and dated by the patient following receipt of verbal and written information about the study prior to carry out any study related activity.
5. Patients aged ≥ 18 years.
6. Patients practicing daily oral hygiene (by tooth brushing and/or mouth rinse) and willing to maintain at least their routine oral hygiene procedure during study participation.
7. Willingness to keep already used permitted concomitant medication, food supplements (e.g. probiotics) or herbals, which might have in the discretion of the investigator a potential influence on OLP, on a stable basis **from second screening (visit 1) to the end of study (visit 7)**
(*as defined via Amendment 03*; *original definition: "on a stable basis **during the study**"*).
8. Only if a diagnostic biopsy needs to be taken at first screening visit: Complete healing of biopsy wound, including complete relief of pain associated with the biopsy site (defined as no / no further need to use any pain relief medication) at date of second screening visit (visit 1). *This criterion was added via Amendment 03*

9.3.2 Exclusion Criteria

Patients who fulfilled one or more of the criteria listed below were not allowed to be included in this study:

1. Patients requiring more than 6 patches (corresponding to an area of approximately 3 cm^2 per patch) to cover symptomatic ulcerative and erythematous OLP lesions[2] at Baseline visit.

2. Ongoing active visible fungal, bacterial or viral infection of oral mucosa, including ongoing treatment of **fungal or bacterial infection at second screening visit (visit 1) and/or at** Baseline **visit**
(*As defined via Amendment 03*; *original definition: "treatment of **those at Baseline.** Re-screening is allowed after successful treatment and specific wash-out period."*)

3. Patient with any **not completely healed** (*former: un-healed*) oral surgery (including recent diagnostic biopsies, if applicable) or oral laser therapeutic wound(s) **at second**

[2] Ulcerative/erythematous lesions are treated with up to 6 patches.

screening visit (visit 1) (as defined *via Amendment 03*; *original definition: "at Baseline visit"*).

4. Any of the following systemic treatments prior to Baseline visit and throughout the study:

   - Protease inhibitors used for the treatment of HIV (e.g. atazanavir, idinavir, nelfinavir, etc.): 1 week
   - Antimycotics: 4 weeks
   - Corticosteroids (i.v., intra-lesional, intra-articular): 4 weeks

     Note: intra-articular injections for the treatment of concomitant conditions (e.g. RA, activated arthrosis, acute gout, etc.) will be allowed if needed for non-OLP related disease flares during the study.

   The following systemic treatments are allowed, **if on stable dose** for a defined period of time prior to Baseline (as stated below) and throughout the study.

   If not on stable dose as defined, these treatments are forbidden throughout the study and have to be washed out for the periods of time prior to Baseline (as stated below):

   - Corticosteroids (oral, rectal, inhalative): wash-out/stable with maximum dose of 10 mg daily prednisolone or equivalent for 4 weeks
   - Antibiotics: wash-out/stable for 4 weeks
   - Retinoids: wash-out/stable for 12 weeks
   - Immunosuppressive drugs (e.g. azathioprine, cyclosporine, mycophenolate mofetil, hydroxychloroquine or biologics): wash-out/stable for 12 weeks

   (*as defined via Amendment 04*; *original definition:*
   *"Any of the following **systemic** treatments prior to Baseline visit:*
   - *Protease inhibitors used for the treatment of HIV (e.g. atazanavir, idinavir, nelfinavir, etc.): 1 week*
   - *Corticosteroids (oral, rectal, i.v., i.a., inhalative, intra-lesional): 4 weeks*
   - *Antibiotics: 4 weeks*
   - *Retinoids: 12 weeks*
   - *Immunosuppressive drugs (e.g. azathioprine, cyclosporine, mycophenolate mofetil, or biologics): 12 weeks*
   - *Antimycotics: 12 weeks")*

5. Any of the following topical treatments used in the oral cavity prior to Baseline visit:

   - Corticosteroids: 2 weeks
   - Antibiotics: 2 weeks
   - Cyclosporine: 2 weeks
   - Tacrolimus, pimecrolimus: 2 weeks
   - Antimycotics: 2 weeks
   - Retinoids: 4 weeks

6. Phototherapy in oral cavity prior to Baseline visit: UVB: 2 weeks, PUVA: 4 weeks.

7. Current participation in another clinical study and/or having received treatment with any non-marketed / investigational medicinal product (drug substance or medical device) within 4 weeks prior to **the first** screening **visit (visit 0)** (*as defined via Amendment 03*; *original definition: "prior to screening"*).

8. Known or suspected intolerance/hypersensitivity/resistance to clobetasol propionate or any component of the investigational medicinal product.

9. This criterion was deleted via Amendment 04.

   Original wording: Patients who previously have failed to respond to OLP treatments with systemic glucocorticosteroids, methotrexate, cyclosporine, retinoids and/or azathioprine.

10. Any history of **oral** squamous cell carcinoma (even if resected), as well as other non-squamous cell carcinoma (e.g. sarcoma, salivary gland tumors) that have been managed with radiation or chemotherapy.
    (A*s defined via Amendment 03*; *original definition: "of squamous cell carcinoma"*).

11. History of cancer (except resected cutaneous basal cell carcinoma, **except resected cutaneous squamous cell carcinoma** and except **resected** in situ cervical cancer) unless it can be documented that the patient has been in a disease-free state for at least 5 years, **or at least 2 years in a disease-free state for low-grade cancers**. In case of clinical suspicion of malignancy in the oral cavity, a patient can only be included after an excluding biopsy.
    (*As defined via Amendment 04*; *original definition: "History of cancer (except resected cutaneous basal cell carcinoma and except in situ cervical cancer) unless it can be documented that the patient has been in a disease-free state for at least 5 years."*).

12. Any condition or disease or circumstances that in the Investigator's opinion would put the patient at any undue risk, prevent completion of the trial, or interfere with the analysis of the trial results.

13. Professional dental cleaning within 2 weeks prior to Baseline and unwillingness to refrain from professional dental cleaning during study conduct.

14. Patients known or suspected of not being able to comply with the study protocol (e.g. due to patient's physical or mental inability, alcoholism, drug dependency, drug abuse, psychological disorder or other conditions).

15. Close affiliation with the investigator (e.g. a close relative) or persons working at the study sites **if financially dependent on the investigator** or patient who is an employee of the Sponsor's company.
    (*As defined via Amendment 03; original definition "… persons working at the study sites or patient who is an employee of the Sponsor`s company."*.

16. Pregnant, confirmed by a positive pregnancy test, or nursing (lactating) women, or

women of childbearing potential (WOCP)[3] planning to become pregnant or WOCP not using or willing to continue to use a defined highly effective method of contraception[4] throughout the complete study.

17. Only if a diagnostic biopsy needs to be taken at first screening visit (visit 0): Patients with any contraindication to biopsy procedures.
(*as defined with Amendment 03 and adapted for all countries except Germany via Amendment 04*; original text/text for Germany: *"e.g.., allergy to local anesthetics and/or topical antiseptics (e.g. chlorhexidine), treatment with anticoagulant drugs other than ASA (≤ 100 mg/d) or clopidogrel (≤ 75 mg/d), and a history of bleeding disorders (tendency to bleeding)")*

9.3.3 Removal of Patients from IMP Treatment or Study

9.3.3.1 General Procedures for Withdrawal and Discontinuation

While patients were encouraged to complete the study, they had the right to discontinue from IMP or completely withdraw from the study at any time and for any reason without disclosing why and without having disadvantages. A genuine effort had to be made to determine the reason(s) why patient decided to discontinue IMP treatment or withdraw from the study, whenever possible.

Patients who discontinued treatment or withdrew from the study prior to the regular end of treatment after having received at least one dose of the IMP were encouraged to undergo all procedures normally performed at visit 6 (EoT / ET visit) and the safety assessments (vital signs, clinical laboratory and weight) regularly scheduled for visit 7 (FUP = EoS). Patients who withdrew during the follow-up period were encouraged to conduct the visit 7 procedures at time of early discontinuation. For procedures to be performed at the respective visits, please refer to section 9.5.5.

All patients who withdrew from the study with an ongoing serious adverse event (SAE) were to be followed until the event was resolved or deemed chronic or stable by the investigator. All follow-up information on SAEs had to be reported.

9.3.3.1 Discontinuation from IMP Treatment

A patient could stay in the study, even if IMP treatment was stopped/interuppted for single or all OLP lesions. The patient was encouraged to complete study assessments as scheduled until the EoS/FU Visit.

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[3] WOCP was defined as any woman or adolescent who has begun menstruation. A post-menopausal woman was defined as a woman who was over the age of 45 and has not had a menstrual period for at least 12 months. WOCP (including pubertal girls and peri-menopausal women) had to receive contraceptive counselling and use effective contraception. A WOCP was to begin using her chosen method of contraception 4 weeks prior to randomization to study medication, unless abstinence was the chosen method. She was to continue contraceptive use during therapy and for 4 weeks after discontinuation of study medication.

[4] Highly effective means a method of birth control with a failure rate of less than 1% per year. For definition of contraception methods accepted as highly effective please refer to Attachment 2 of the CSP.

The reason for discontinuation of treatment may have been:

- Clearance of lesions. The investigator had to use his/her discretion to determine wether a cleared lesion could still be treated with the IMP or if treatment was no longer justified for any reason (e.g. due to potential development of AE, any other risk for the patient).

  Nonetheless, patients were advised to continue to treat all symptomatic OLP lesions present at Baseline until the end of the regular treatment period without any change of the originally assigned application pattern, whenever possible.

9.3.3.2 Withdrawal of Patients from the Study

The reasons for withdrawal of patients from the study may have been among others:

- Withdrawal of consent
- Occurrence of a serious or non-serious AE that in the investigator's opinion deemed the patient's participation not safe
- No longer in compliance with in- and exclusion criteria
- Patient not in compliance (not able or willing to use the IMP)
- Investigator's decision based on best interest of patients
- Lack of efficacy
- Lost to follow-up
- Other
- Worsening of lesions. The investigator had to use his/her discretion to determine if OLP symptoms could still be accaptably managed by the use of IMP and predefined rescue analgesics or if the patient was in need to start any other OLP treatment. In that case, patient should have been withdrawn from the study early.
- New lesions: If new symptomatic lesions appeared that could not be treated with IMP (as 6 patches per application were already used) and emerging symptoms could not be acceptably managed by the use of predefined rescue analgesics, the investigator had to use his/her discretion to determine if the patient was in need to start any other OLP treatment. In that case, patient should have been withdrawn from the study early.

9.3.3.3 Replacement of Patients

Patients who prematurely withdrew from the study after having received at least one dose of the IMP were assessed as **dropouts**. All patients not prematurely withdrawn from the study for any reason were assessed as completers, irrespective of missing visits or assessments.

Patients who were included but not randomized / treated were considered as **screening failures**.

Screening failures were replaced until the planned number of randomized patients was reached. Dropouts were not substituted.

Generally, re-screening was allowed for any reason, but only once for each patient.

Exception: Additional re-screening(s) could be planned for administrative/logistical reasons (e.g. due to loss of laboratory samples, patient´s non-ability to attend the randomization visit for personal reasons, etc.). Prior to any additional re-screening; project management had to be consulted and had to approve the process.

(Re-screening options were broadened via Amendments 03 and 04. Original protocol allowed re-screening only once, and only if a patient was not randomized due to on-going active visual fungal, bacterial or viral infection of oral mucosa, including ongoing treatment of those prior to randomization. Via Amendment 03 re-screening was also allowed if patient was not randomized due to un-healed wounds in the oral cavity or due to un-assessable study biopsy.)

In any case, the investigator had to ensure that the repeated screening procedures did not expose the patient to an unjustifiable health risk with regards to repetition of laboratory assessments or study biopsy.

A re-screened patient had to re-consent to study participation and was assigned to a new patient number.

9.3.4 Stopping or Suspending the Study

9.3.4.1 Premature Termination of the Study

The Sponsor retained the right to terminate the study at any time after carefully having weighed the benefits against any possible risks. This decision would have been taken in agreement with the Coordinating Investigator.

In case of premature termination of the study, the Sponsor would have promptly informed the investigators, regulatory authorities and the Institutional Review Boards (IRBs) / Independent ethics committees (IECs) and Competent Authorities (CAs) of the termination, giving the reason for premature termination.

Conditions that might have warranted termination of the study included, but were not limited to the following:

- The discovery of an unexpected and significant or unacceptable risk to the patients enrolled in the study.
- A decision on the part of Sponsor to suspend or terminate the development of the drug.

9.3.4.2 Premature Termination of one Study Site

The Sponsor had also the right to close a specific study site, at any time, although this only occurred after consultation between involved parties. The respective IRBs/IECs and CAs were informed accordingly.

Four sites (#100, Germany; #206, UK; #402, #416, both USA) were closed as the first patient failed to be randomized within a reasonable period after initiation of the study site.

One site (#408, USA) failed to comply with GCP standards and could have therefore been closed by the sponsor. Instead, it was decided to stop recruitment and to not include the

patients already treated into analysis.

Furthermore, failure to comply with the requirements of the protocol would have justified a premature termination of a specific study site.

9.4 Treatments

9.4.1 Treatments Administered

Each patient eligible for the trial was randomised in a 1:1:1:1 ratio to one of the following treatment groups:

- Rivelin®-CLO patch 20µg, topical administration, twice daily
- Rivelin®-CLO patch 5µg, topical administration, twice daily
- Rivelin®-CLO patch 1µg, topical administration, twice daily
- Rivelin® plain patches (placebo), topical administration, twice daily

Randomization schedule included also assignment to one of the following strata:

- 1-3 patches needed at Baseline
- 4-6 patches needed at Baseline

Instructions provided concerning the handling of IMP:

Subsequent to randomization at Baseline, site staff properly instructed the patients concerning the correct handling, application and removal of patches and how to correctly document patch application data in the patient's Diary. Therefore, patients received a detailed 'Instructions for Use' leaflet and thorough diary training. Furthermore, each patient was provided with a schematic picture of the oral cavity (lesion map) where site staff indicated all OLP lesions to be treated as well as the number and location of patches to be applied to those lesions. One patch was defined as the target patch by the investigator. This target patch was marked on the lesion map to be distinguishable from other patches and needed to be followed by the patients regarding its adhesion times in the diary.

The first patch application and removal at Baseline and the morning application a Visit 3 were performed on site under supervision of the site staff. If a patient was unable to follow the instructions given, this patient was re-instructed.

If the patch application pattern needed to be changed after Baseline, an updated lesion map was provided to the patients.

For details on 'instructions for use leaflet' and 'lesion map', refer to Appendix 16.1.3.

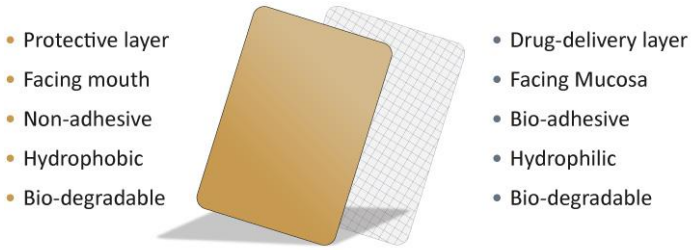
9.4.2 Identity of Investigational Products

9.4.2.1 Rivelin-CLO Patch

The Rivelin®-CLO patch (1.25 cm x 2.5 cm = 3.125 cm^2) is a two-layer patch that comprises of a protective, hydrophobic layer and a muco-adhesive, drug-delivery layer incorporating

clobetasol propionate in different dose-strength (1 µg, 5 µg and 20 µg per patch) as active drug component (see Text Figure 9-2).

Text Figure 9-2: Illustration of the patch layers



The muco-adhesive ability of the patch provides a unique feature of a direct, controlled and potentially longer delivery/exposure of clobetasol propionate to the target area. The protective, hydrophobic layer furthermore ensures long-term adhesion as well as unidirectional drug release towards the mucosa, avoiding washout of the drug due to saliva and subsequent swallowing. The protective layer also makes the patch easy to apply and convenient for the patient to use. The layer can be touched without getting in contact with the active component and due to its color, it is easy to see which side should face the lesion.

The detailed characteristics of the Rivelin®-CLO patches are summarized in Text Table 9-1.

Text Table 9-1: Characteristics of Rivelin®-CLO patch

Formulation	Rivelin®-CLO patch is a two-layer patch comprised of a muco-adhesive, drug-delivery layer and a protective layer
Active ingredient name/concentration	Clobetasol propionate: 1 µg per patch 5 µg per patch 20 µg per patch
Excipients [per patch]	0.044 mg Ferric oxide (Red); for coloring of occlusive layer 5.3 mg Polycaprolactone; non-adhesive layer (occlusive layer) 11.0 mg Povidone K90; hydrophilic layer (bioadhesive substance) 22.1 mg Macrogols, High-Molecular-Mass, 200,000; hydrophilic layer (bioadhesive substance) 13.8 mg Ammonio Methacrylate Copolymer (Type B); hydrophilic layer (control of water influx)
Mode of administration	Topical
Manufacturer	Bioinicia, S.L. C / Algepser, 65 Nave 3 46980 Paterna (Valencia), Spain

Supplier (packaging and release)	HB medical Dr Neergaards Vej 17 2970 Hørsholm, Denmark
Batch numbers/Expiry dates	Blinded batch number[1]/Expiry date: 815491/Dec-2019 813790/Jan-2020 820890/Jan-2020 819590/Feb-2020 Unblinded batch number[1]/Blinded batch number[2]/Expiry date: 20µg BIL18010311/815491/Dec-2019 BIL18010811/813790/Jan-2020 BIL18061412/820890/Jan-2020 BIL18022212/819590/Feb-2020 5µg BIL18012412/815491/Dec-2019 BIL18021912/813790/Jan-2020 BIL18042410/820890/Jan-2020 BIL18042510/819590/Feb-2020 1µg BIL18020921/815491/Dec-2019 BIL18020702/813790/Jan-2020 BIL18012305/820890/Jan-2020 BIL18060708/819590/Feb-2020 ---------- [1]: batch numbers used during the study on IMP kits, not reflecting the strength of clobetasol coating [2]: production batch numbers of the manufacturer, not used on IMP kits

9.4.2.2 Rivelin® plain Patch

The same patch (Rivelin® plain patch), with no active ingredient incorporated in its drug-delivery layer served as placebo. The detailed characteristics of the Rivelin®-plain patches are summarized in Text Table 9-2.

Text Table 9-2: Characteristics of Rivelin® plain patch

Formulation	Rivelin® plain patch is a two-layer patch comprised of a muco-adhesive, drug-delivery layer and a protective layer
Active ingredient name/concentration	No active ingredient
Excipients [per patch]	0.044 mg Ferric oxide (Red); for coloring of occlusive layer 5.3 mg Polycaprolactone; non-adhesive layer (occlusive layer) 11.0 mg Povidone K90; hydrophilic layer (bioadhesive substance) 22.1 mg Macrogols, High-Molecular-Mass, 200,000; hydrophilic layer (bioadhesive substance) 13.8 mg Ammonio Methacrylate Copolymer (Type B); hydrophilic layer (control of water influx)
Mode of administration	Topical
Manufacturer	Bioinicia, S.L. C / Algepser, 65 Nave 3 46980 Paterna (Valencia), Spain
Supplier (packaging and release)	HB medical Dr Neergaards Vej 17 2970 Hørsholm, Denmark
Batch numbers/Expiry dates	Blinded batch number[1]/Expiry date: 815491/Dec-2019 813790/Jan-2020 820890/Jan-2020 819590/Feb-2020 Unblinded batch number[1]/Blinded batch number[2]/Expiry date: BIL18021511/815491/Dec-2019 BIL18013013/813790/Jan-2020 BIL18030210/820890/Jan-2020 BIL18022222/819590/Feb-2020 --- [1]: batch numbers used during the study on IMP kits, not reflecting the strength of clobetasol coating [2]: production batch numbers of the manufacturer, not used on IMP kits

9.4.2.3 Packaging, labeling, storage and destruction

Medication labels for the IMPs complied with the legal requirements of the countries where the study was performed and were provided in English as well as in the local languages.

The Rivelin® patches (Rivelin® plain and Rivelin®-CLO patches) were supplied to the pharmacy/clinical site(s) as 1-week treatment kits. Each kit contained overall 108 patches in 18 non-sterile, ready for use, sealed aluminum pouches (each pouch containing 6 individual patches). This amount was considered sufficient for one week of IMP treatment (7 days between visits and 2 days for window deviations or lost patches). Each 1-week-treatment kit was labeled with a unique kit number, assigning the kit to one of the treatment groups in a blinded way.

The IMPs were supplied by the designated vendor of the sponsor and stored securely (locked facility) at the site under the control of the investigator. The temperature was monitored and documented.

IMP kits were to be protected from light and stored at room temperature (15-25°C, corresponding to 59-77°F) at the site and after being dispensed to the patients. The muco-adhesive layer of the patches might have absorbed moisture that would have changed its adhesive properties. Therefore, pouches should not have been opened before intended use. Any damaged or open pouches should not have been used.

All unused patches – i.e., sealed and broken left-over pouches with remaining patches - were returned for reconciliation and destruction.

9.4.3 Avoidance of Bias

9.4.3.1 Method of Assigning Patients to Treatment Groups

Patient ID

For each enrolled patient a unique 6-digit patient identifier was created via the electronic data capture (EDC) system.

This patient ID was composed of:

Digit 1: Country code for GER (1), UK (2), DNK (3), USA (4), IRE (5) and for CAN (6)

Digits 2 and 3: Site number (00, 01, 02, 03, 04, 05, etc.)

Digits 4, 5 and 6: Individual patient number within the study site (consecutively in the order of enrollment: 001, 002, 003, etc.).

Randomization, Kit Number and IMP Dispensation

Each patient, found to be eligible for the study as a result of the Screening procedures and Baseline assessments, was randomized at Baseline.

Treatment assignment was pre-planned according to a computer-generated randomization schedule in a 1:1:1:1 ratio (Rivelin®-CLO patches 20µg, 5µg, 1µg, Rivelin® pain patch). The randomization schedule also accounted for stratification, respecting two different strata, depending on the number of patches needed at Baseline (1-3 or 4-6 patches).

Randomization was performed centrally within the Interactive Web Response System (IWRS) of the EDC. As a result of the randomization procedure, a unique randomization number was created for every patient assigning the patient to one of the four treatment groups.

Due to erroneous programming of the IWRS, randomization numbers were not assigned consecutively in the order of randomization of patients, but a complete randomization block of 4 randomization numbers (all 4 treatment arms) was reserved for a specific site, as soon as the first randomization number within a block had been assigned by this site. Consequently, an additional stratum – by site – was introduced into the randomization process, even though not intended per protocol.

Furthermore, a unique kit number was created by the IWRS at Visits 2, 3, 4 and 5 assigning a specific IMP kit of the assigned treatment group and stratum to the patient in a blinded way. At each of these visits, the kit with the assigned kit number had to be dispensed to the patient.

The randomization schedule was generated and kept locked by a non-blinded, independent statistician (who was not involved in data evaluation). For unblinding procedures of the interim analysis, a second un-blinded statistician, not involved in final data evaluation or any other study activity, was provided with the randomization schedule. The randomization schedule (including treatment allocation and stratum for each patient) for the study is provided in Appendix 16.1.7.

9.4.3.2 Blinding and Unblinding procedures

Blinding

This study was conducted as a double-blind study. Neither the investigator, the site personnel nor the patient knew the identity of the IMP assigned.

The following measures were taken to ensure the blinding throughout the study:

- All treatments were indistinguishable in appearance
- Appearance and labeling of IMP kits did not provide any information disclosing the IMP treatment group, as they were labeled with a unique kit number, only.
- Blood samples for the determination of plasma clobetasol and serum morning cortisol levels were analyzed centrally, and the results were not communicated to anyone of the study team prior to final closure of the data base.

Un-blinding

Un-blinding of an individual patient´s treatment should have been performed only in case of emergency, which necessitated knowledge of the drug applied for the medical management of the patient. Technically, it could have been done via the IWRS within the EDC for a single patient, while maintaining the overall study blind.

The reason for breaking the code and the date and the name of the investigator requesting un-blinding had to be recorded. Un-blinding required discontinuation of the treatment of an individual patient and the Sponsor should have been informed in a timely manner.

Treatment codes were not broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject had been made and documented.

9.4.4 Selection of Doses and Timing of Dose for Each Patient

9.4.4.1 Selection of Doses in the study

The metered doses chosen for this study are 1 µg, 5 µg, and 20 µg clobetasol propionate per patch or no clobetasol, respectively.

The selection of the doses of clobetasol propionate was built on current dosing – at the time of protocol design - in topical use for treatment of dermal inflammatory disease with gels and creams. Dermal dosing typically is imprecise, based on the "fingertip-unit" that is common for guiding dosage in dermatological practice. One fingertip-unit is equivalent to 0.4–0.5 g and typically will cover a skin area the size of a palm, which is approximately 100-150 cm^2. Clobetasol propionate creams and gels for dermal use usually contained 0.05% clobetasol propionate. Thus, the dose of a fingertip-unit applied to an area of 100 to 150 cm^2 leads to a clobetasol dose of 1.33-2.5 µg/cm^2.

Since the size of a Rivelin® patch is 3.125 cm^2, the clobetasol dose per patch - corresponding to dosing in dermatology practice - will range between 4.1-7.8 µg/patch. This indicated a clinical dose of 5 µg clobetasol propionate/patch to be relevant.

In order to capture a dose response, three active doses with a 4 to 5-fold dose increase were chosen to cover a broad dose-range. For the low-end dose (1 µg/patch) minimal or no dose-effect was expected. The highest dose (20 µg/patch) was intended to capture any dose related adverse events.

Release profile

The delivered dose in a clinical setting was expected to be a proportion of the metered dose in the patch. This assumption was based on the in vitro release profile of clobetasol propionate from Rivelin®-CLO patches, where no difference was observed in Rivelin®-CLO patches loaded with different concentrations of the drug (1, 5 and 20 µg). All the different Rivelin®-CLO patches slowly released clobetasol propionate in a sustained manner over a 6-hour period with approximately 20%, 50% and 80% released after 30, 180 and 360 minutes (source: IMPD section 2.1.P.2.2.3.2)[17]. In comparison, the release profile of clobetasol propionate from creams and ointments was estimated to be 4 to 8 times lower[18]. In addition, preclinical qualitative studies had revealed that clobetasol propionate loaded patches applied to porcine buccal mucosa delivered clobetasol propionate to the mucosa with a C_{max} after 30 mins (source: IB section 4.3.1.1 Clobetasol proprionate patches: PK study in Minipigs CiToxLab study no. 77455)[19]. However, no relation between the in-vitro release and the proportion of the clobetasol propionate release to an intact mucosa or to OLP injured mucosa was established or found in literature at the time of protocol design.

9.4.4.2 Timing of Dose for each patient

Patients were instructed to self-apply the patches at home twice daily during the whole treatment period (Visit 2 to Visit 6).

The following had to be respected regarding the time of patch application:

- First daily application after breakfast and mouth hygiene in the morning (around 8 AM)

- Second daily application after dinner at least two hours before mouth hygiene and bedtime (around 7 PM)
- Preferably at least 9 hours between both applications
- Patches could stay applied for up to 2 hours. Thereafter, patients were instructed to take measures to gently but actively remove the patches.
- Patients needed to abstain from drinking or eating, while patches were applied.
- The patches should have only been applied while the patient was awake.

Deviating from this schedule, the first patch application at Baseline and the morning application at Visit 3 were performed at the study site, to ensure thorough instruction and training of the self-application technique.

Residence time

The maximal residence time of up to two hours was balanced to the expected adhesion time (aiming for self-detachment rather than active removal of patches) and compliance (patients were asked not to eat and drink while patches were applied to secure an optimal adhesion).

A clinical study in OLP patients (DT-001-R-003) where Rivelin® plain patches were applied to symptomatic lesions revealed an approximated maximal mucosal adhesion time of up two hours, implying that most patches would detach by themselves after 2 hours. A time period of 2 hours was judged as a reasonable time period to ask patients to defer from drinking and eating.

In conclusion, the dose selection was regarded as reasonable, based on maximal residence time and release profile. Within 30 minutes a mucosal C_{max} was expected to be reached, and after 2 hours of adhesion most patches would have self-detached without any need of active removal. Given the higher release profile, this approach ensures an efficacious mucosal exposure of clobetasol propionate.

9.4.5 Treatment Compliance

Treatment Compliance was assessed via drug account and patient reported diary entries.

Patients were asked to return all unused Rivelin® patches and their study diary to the study site at each visit. The site staff had to count the remaining patches and to review diary entries while the patients were still on site. Site personnel should have checked patient´s compliance comparing the number of patches used to the number of patches prescribed for the respective treatment interval for both, IMP count and diary entries.

Any relevant discrepancy between patches prescribed and patches applied according to drug account or according to patient´s diary should have been recorded providing the corresponding details and a reason, whenever possible.

A patient who significantly deviated from the dosing regimen had to be re-trained.

9.4.6 Prior and Concomitant Treatment

All medications (prescription, over-the-counter products to account for mouth rinses) taken by the patients up to 28 days prior to Baseline and until the end of study visit (FUP, visit 7) were recorded. To account for wash-out periods of prohibited medication or periods of maintaining

stable doses of predefined medication as defined by corresponding exclusion criteria (refer to section 9.3.2) the documentation period prior to Baseline was extended to at most 12 weeks.

Information regarding the total daily dose, route of administration, start and discontinuation dates, and indication were to be recorded on the eCRF.

9.4.6.1 Restrictions during the study

The following restrictions applied during the study:

- Drinking or eating was prohibited while patches were applied at the lesions.
- Professional dental cleaning was prohibited 2 weeks prior to Baseline and during the study.
- Patients should have at least maintained their routine daily dental hygiene procedures (tooth brushing and/or mouth rinse) throughout the study. A higher frequency or more methods of oral hygiene may have been performed. Patients should have maintained their routine mouths rinses, if these did not contain corticosteroids, antifungals or antibiotics (alcohol or chlorhexidine was allowed) as an active ingredient.
- Medication, which in the opinion of the investigator might have had a potential influence on OLP lesions had to be kept on a stable basis from Visit 1 to end of the study. Exceptions: longer periods on stable dose had to be respected for systemic corticosteroids (oral, rectal, nasal), systemic antibiotics, systemic retinoids and systemic immunosuppressive drugs. For details refer to section 9.4.6.2.

9.4.6.2 Prohibited prior and concomitant treatment

The following medications and treatments were prohibited prior to study start (visit 0 and/or visit 1) or from Baseline onwards until the end of the study:

Text Table 9-3: Prohibited medication including non-drug therapies and procedures prior and during the study

Prohibited medication including non-drug therapies and procedures	Location	Exclusion period prior to start of treatment or prior to screening (visit 0 / visit 1)	Exclusion until the end of the study
Systemic treatment with:			
Protease inhibitors used for the treatment of HIV (e.g. atazanavir, idinavir, nelvinavir, etc.)	systemic	1 week prior to Baseline	x
Antimycotics[1]	systemic	4 weeks prior to Baseline *(original: 12 weeks prior to Baseline)*	X
Corticosteroids (i.v., intra-lesional, intra-articular)[1]	systemic	4 weeks prior to Baseline	X **Note**: intra-articular injections for the treatment of concomitant conditions will be allowed if needed for non-OLP related

Text Table 9-3: Prohibited medication including non-drug therapies and procedures prior and during the study

Prohibited medication including non-drug therapies and procedures	Location	Exclusion period prior to start of treatment or prior to screening (visit 0 / visit 1)	Exclusion until the end of the study
			disease flares during the study. *(original: X)*
Corticosteroids (oral, rectal, inhalative)[1]	systemic	4 weeks prior to Baseline if **not** on stable dose Allowed **if on stable dose** (maximum daily 10mg prednisolone or equivalent) for at least 4 weeks prior to Baseline and througout the study. *(original: 4 weeks prior to Baseline)*	Allowed if **on stable dose** (maximum daily 10mg prednisolone or equivalent) for at least 4 weeks prior to Baseline and througout the study. *(original: X)*
Antibiotics[1]	systemic	4 weeks prior to Baseline if **not** on stable dose Allowed **if on stable dose** for at least 4 weeks prior to Baseline and througout the study. *(original: 4 weeks prior to Baseline)*	Allowed if **on stable dose** for at least 4 weeks prior to Baseline and througout the study. *(original: X)*
Retinoids and Immunosuppressive drugs (e.g. azathioprine, cyclosporine, mycophenolate mofetil, hydroxychloroquine or biologics)[1]	systemic	12 weeks prior to Baseline if **not** on stable dose Allowed if **on stable dose** for at least 12 weeks prior to Baseline and througout the study. *(original: 12 weeks prior to Baseline)*	Allowed if **on stable dose** for at least 12 weeks prior to Baseline and througout the study. *(original: X)*
Pain relief medication that might have an impact on the study outcome, especially NSAIDs (e.g. naproxen, indomethacin, ketorolac, ketoprofen, piroxicam, phenylbutazone) and selective COX-2 inhibitors (e.g. celecoxib, etoricoxib)	systemic	not applicable	Any pain relief medication taken at a stable dose for the treatment of concomitant diseases already pre-existing at date of second screening visit (visit 1) will be allowed. Whenever possible this permanent treatment

Text Table 9-3: Prohibited medication including non-drug therapies and procedures prior and during the study

Prohibited medication including non-drug therapies and procedures	Location	Exclusion period prior to start of treatment or prior to screening (visit 0 / visit 1)	Exclusion until the end of the study
			should not be changed until the end of the study. Rescue analgesics should be determined by the investigator at date of second screening visit (visit 1) on a patient specific basis. Strong analgesics (such as opioids, other morphine-like analgesics, COX-2 inhibitors, etc.) should not be used as rescue analgesics.
Topical treatment with:			
Corticosteroids, antibiotics, cyclosporine, tacrolimus and pimecrolimus Note: Mouth rinses containing alcohol or chlorhexidine will be allowed.	oral cavity	2 weeks prior to Baseline	x
Antimycotics	oral cavity	2 weeks prior to Baseline	Allowed after Baseline for AE treatment only (no preventive treatment).
Retinoids	oral cavity	4 weeks prior to Baseline	x
Phototherapy:			
PUVA[1]	oral cavity *(original: systemic and/or local)*	4 weeks prior to Baseline	x
UVB	oral cavity	2 weeks priot to Baseline	x
Any surgery, laser therapy	oral cavity	No oral surgery or oral laser therapy wound that is not competely healed at date of second Screening visit (Visit 1)	x
Any non-marketed / investigational medicinal product (drug substance or medical device [e.g. Rivelin® plain patch])	systemic and / or local	4 weeks prior to first Screening visit (Visit 0).	x

[1] as defined via Amendment 04. Original wording is given in italics.

9.4.6.3 Permitted [Prior and] Concomitant Treatment

All medication needed for treatment of concomitant diseases could be taken by the patient as long as treatment restrictions (refer to section 9.4.6.1 and 9.4.6.2) were adhered to.

9.4.6.4 Rescue Medication

Patients were advised to not use any treatments of OLP other than the IMP without previous consultation of the investigator. Even if patients were encouraged to abstain from the use of rescue analgesics whenever possible, the use of patient specific rescue analgesics was allowed from Visit 1 to Visit 7 to ensure control of OLP associated symptoms (e.g.: pain, soreness, tenderness, etc.) independent from IMP treatment.

The investigator determined the kind of patient specific rescue analgesics at Visit 1. Thereafter, any use of rescue analgesics needed to be recorded daily in the patient´s diary. Determination of rescue analgesics could be adapted during the study at the discretion of the investigator in case control of OLP symptoms would have not been achieved in a satisfying way. Symptoms requiring use of rescue analgesics were not reported as adverse events.

9.5 Efficacy and Safety Variables: Procedures and Assessments

9.5.1 Efficacy Procedures and Assessments

Whenever possible, clinician reported outcome measures (OLPClinROM, Guy´s ODSS) should have been attempted to be performed by the same investigator throughout the study for consistency reasons.

Patient reported pain or symptom assessments were to be performed prior to any oral examination/procedure possibly causing pain to the patients.

9.5.1.1 OLP Clinician Reported Outcome Measurement (OLPClinROM) – Investigator Assessment

The OLP Clinician Reported Outcome Measurement (OLPClinROM) was used by the investigator to assess single symptomatic anatomical sites in detail. The OLPClinROM was to be performed at each study visit (Visit 1 to Visit 7) for up to 6 symptomatic anatomical sites, containing at least one symptomatic OLP lesion having required treatment at Baseline.

If new symptomatic lesions developed during the study within the original treatment area lesions were also assessed via the OLPClinROM. New symptomatic lesions, which developed at the same anatomical site but outside the treatment area or new symptomatic lesions at different anatomical sites were not assessed via the OLPClinROM.

The OLPClinROM consists of 3 different items:

- Measurement of the total ulcer size
- Measurement of the total lesion size (white part, erythematous parts and ulcerative parts)
- Determination of 5-point erythema score
  [ranging between 0 (= normal/no redness) and 4 (= very severe redness)]

In addition to the items of the OLPClinROM two further measures were assessed at the same time:

- Determination of 3-point erythema score

[ranging between 0 (= no erythema) and 2 (= marked erythema)]
- Determination of clinical global impression of anatomical site score
[to be assessed on a 5-point rating scale ranging between 0 (=no disease) and 4 (= very severe disease)].

9.5.1.2 Worst symptoms at anatomical site – Patient Assessment

At each study visit (Visit 1 to Visit 7), patients provided a symptom rating (ranging between 0 = no symptoms at all and 10 = worst possible symptom severity imaginable) regarding their worst symptoms during the last 24 hours for each of the anatomical sites affected with symptomatic lesions requiring patch treatment. Patients should not only consider pain, but also symptoms like soreness, sensitivity, burning, irritation or tenderness. Anatomical sites were identified to the patient by the investigator touching the site.

For details on worst symptoms at anatomical site assessment, refer to Appendix 16.1.2.

9.5.1.3 Guy's 106 Oral Disease Severity Score (Guy's 106 ODSS) – Investigator Assessment

The Guy's 106 Oral Disease Severity Score (Guy's 106 ODSS) is an established instrument to evaluate the overall disease status of OLP. It was assessed by the investigator at every study visit (Visit 1 to Visit 7).

For this scoring system the oral cavity was divided into 17 anatomical sites. Each of these anatomical sites had to be numerically scored by the investigator considering the lesion extent (site score = 0-2) and the disease activity (activity score: calculated as product of the site score and the severity score (= 0-3) at the anatomical site). For scoring details, please refer to Text Table 9-4.

Text Table 9-4: Investigator's assessment according to the Guy´s Oral Disease Severity Score

Anatomical Site	Site score	Activity score (= Site score x Severity score)
Outer lips	0-1	0-3
Inner lips	0-1	0-3
R Buccal Mucosa	0-2	0-6
L Buccal Mucosa	0-2	0-6
Gingivae		
Lower R (distal)	0-1	0-3
Lower central	0-1	0-3
Lower L (distal)	0-1	0-3
Upper R (distal)	0-1	0-3
Upper central	0-1	0-3
Upper L (distal)	0-1	0-3
Dorsum tongue	0-2	0-6
R ventral tongue	0-1	0-3
L ventral tongue	0-1	0-3
Floor of mouth	0-2	0-6
Hard palate	0-2	0-6
Soft palate	0-2	0-6

Text Table 9-4: Investigator's assessment according to the Guy´s Oral Disease Severity Score

Anatomical Site	**Site score**	**Activity score** (= Site score x Severity score)
Oropharynx	0-2	0-6
	max. score = 24	**max. score = 72**

	Site score		**Severity score**
value	**description**	**value**	**Description**
0	no detectable lesion present	0	keratosis only
1	less than 50% of area affected or evidence of lichen planus seen	1	keratosis with mild erythema (< 3 mm from gingival margins)
2	more than 50% of area affected (buccal mucosa, dorsum of tongue, floor of mouth, hard palate, soft palate or oropharynx)	2	marked erythema (e.g. full thickness of gingivae, extensive with atrophy or oedema on non-keratinized mucosa)
		3	ulceration present

x = multiplication sign
Note: Underside of tongue will be rated as lateral wall of tongue.

Guy's 106 ODSS included as additional component an overall pain score. The patient assessed the pain from overall OLP disease during the last 24 hours on a 11 point-rating scale, ranging from 0 'no pain' up to 10 'worst imaginable pain'.

The overall Guy's 106 ODSS (maximum 106) was calculated as total site score (max. 24) + activity score (max. 72) + pain score (max. 10).

9.5.1.4 OLP Symptom Severity Measure (OLPSSM) - Patient Assessment

The OLP Symptom Severity Measure (OLPSSM) is a patient questionnaire. It consists of overall 12 items on OLP symptoms severity to be assessed at different time points. Item #1 to #10 were completed daily (in the evening) as part of the patient´s diary during the entire study (Visit 1 to Visit 7). Item #11 and #12 were assessed at study visits (for details see below).

- Items #1 to #7,
  assessed the patient's symptom experience over the last 24 h for soreness while brushing teeth, eating, drinking, smiling, breathing through the mouth, speaking, or being touched on a 5-point rating scale (ranging between 0 [most positive response] and 4 [most negative response]).
  These items #1 to #7 were used to calculate a total symptom score.

  The total symptom scores over the last 7 days prior to Baseline served to evaluate patient's eligibility regarding inclusion criterion #2. For being eligible, patients should have had a total symptom sore of ≥ 5 for at least 4 days during the last week prior to Baseline or at least 4 valid entries with a score of ≥ 5 during this time.

- Items #8 to #10
  Items #8 and #9 *("How much of the time did you have oral lichen planus symptoms in the past 24 hours while you were awake"/ "At their worst, how severe were your oral lichen*

planus symptoms in the past 24 hours?") were assessed on a 5-point rating scale (ranging between 0 [most positive response] and 4 [most negative response]).
Item #10 *("Overall, what was the severity of your oral lichen planus symptoms in the past 24 hours?"*) was assessed on an 11-point rating scale (ranging from 0 [most positive response] and 10 [most negative response]). These items were used to assess the measurement properties and interpretability of the OLPSSM.

- Item #11
  evaluated the severity of OLP symptoms over the past week using a 5-point rating scale (ranging between 0 [most positive response] and 4 [most negative response]). It was completed at Baseline and at each subsequent visit until EoS (Visit 7).

- Item #12
  evaluated the overall change in patient's OLP symptoms during the treatment period. It was assessed only once at the end of the treatment (Visit 6). Patients could choose between 7 different answers ranging from 'very much better' to 'very much worse'.

For details on OLPSSM questions, refer to the patient´s diary in Appendix 16.1.2.

9.5.1.5 Chronic Oral Mucosal Disease Questionnaire (COMDQ) – Patient Assessment

The Chronic Oral Mucosal Disease Questionnaire (COMDQ) is an established oral health-related Quality of Life (QoL) instrument containing a total of 26 items, grouped according to clinical judgment into 4 sub-domains:

- pain and functional limitation (with 9 items)
- medication and treatment (with 6 items)
- social and emotional status (with 7 items)
- patient support (with 4 items).

Each individual item was to be assessed by the patient on a 5-point rating scale (ranging between 0 [most positive] and 4 [most negative]), resulting in a total score of maximum 104 points. The COMDQ was completed by the patients at Baseline, Visit 4 (after 2 weeks of treatment) and Visit 6 (end of treatment).

Text Table 9-5: Response Options and Rating Codes for the COMDQ

Response	**Score***
Not at all	0
Slightly	1
Moderately	2
Considerably	3
Extremely	4
Note: Question no. 2 of the medication and treatment domain, and questions no. 1, 2 and 3 of the patient support domain will have reversed response scales ('Not at all' = 4; 'Slightly' = 3; 'Moderately' = 2; 'Considerably' = 1 and 'Extremely' = 0)	

For details on COMDQ questionnaire, refer to Appendix 16.1.2.

9.5.1.6 Instructions for Use Questionnaire (IFU) – Patient/Site Staff Assessment

At Baseline and at Visit 3 (after 1 week of treatment) patients were asked to evaluate the instructions for patch use via a questionnaire. This questionnaire was split into two parts:

- Patient's part:
  2 questions for the patients regarding how clear the instruction for application and removal of the Rivelin® patches was understood on a 5-point scale.
  *"Overall, how clear were the instruction for use leaflet to describe the **application/removal** procedure of the patches in your mouth?"*

Text Table 9-6: Response Options and Rating Codes for patients part of IFU Questionnaire

Response	Score*
Extremely clear	0
Moderately clear	1
Somewhat clear	2
Not quite clear	3
Not at all clear	4

- Site Staff's part:
  2 questions for the site staff regarding number of applied and number of correctly applied patches to the OLP lesions chosen for treatment.
  "How many patches did the patient apply?"
  *"How many patches did the patient apply **correctly**?"*
  A correct application was defined as a patch that adhered to the target lesion, with the right side facing the lesion and staying in place for more than 5 minutes after letting go of the patient's fingers used for application.

For details on Instructions for Use questionnaire, refer to Appendix 16.1.2.

9.5.1.7 Patch Sensation Questionnaire – Patient Assessment

The patients had to assess the sensation of wearing the Rivelin® patches by answering 11 questions according to 5-point rating scales (ranging between 0 [most positive response] and 4 [most negative response]) Due to the content of the questions (e.g. some asking for positive, others for negative characteristics, the order of answering alternatives was not the same for all questions. Some questions needed reversing at the time of analysis.

The Patch Sensation Questionnaire was completed at Baseline after first patch application and at Visit 4 (after 2 weeks of treatment).

For details on Patch Sensation Questionnaire, refer to Appendix 16.1.2.

9.5.1.8 Patch Applications

The following details on patch application were documented by the patient daily (as part of the patient´s diary) during the treatment period (Visit 2 – Visit 6):

- Time of patch application (morning and evening)
- Number of patches applied (morning and evening)

- Number of patches that were still adhering after 5 minutes (morning and evening)
- Adhesion time for one target patch (morning). The target patch was defined by the investigator.
- Number of patches that were still adhering after 2 hours (morning; those that need for active detachment procedures)

9.5.1.9 Rescue Analgesics

The use of pre-defined rescue analgesics (i.e. pain relief medication and/or local anesthetics) was documented daily (last 24 hours by frequency of use) as part of the patient´s diary during the entire study (Visit 1 to Visit 7). Rescue use was not standardized, and patients could have more than one rescue analgesic prescribed. Some patients had no rescue analgesics prescribed, at all.

9.5.1.10 Photo Documentation

Supportive photographs of the oral cavity and all anatomical sites assessed were taken from Visit 1 (prior to treatment) to Visit 7 (end of Study) at study sites which had photo documentation established as a standard procedure.

In the framework of this study, photographs were not used for analysis. They might be used for publication purposes in the future, if patients consented in written to the possible publication of their pictures.

9.5.2 Pharmacokinetic (PK) and Bioanalytical Methods

Plasma levels of clobetasol and morning serum cortisol levels were determined once during the study. Blood samples should have been taken at Visit 3 (after 1 week of treatment) between 7 and 9 AM and before the morning patch application. Samples were analyzed centrally, and results were not communicated to anyone of the study team prior to closure of the data base to protect the blinding.

9.5.3 Safety Procedures and Assessments

9.5.3.1 Adverse Events

The investigator was responsible for obtaining, assessing, and documenting all adverse events (AEs) during the study. AE information was collected from the time of signing the informed consent form until the end of the study (Visit 0 to Visit 7). During the screening phase (time between Visit 0 and Visit 2, including Visit 0 and Visit 1) only procedure related events (e.g. occurrence of an allergic reaction on local anesthetic or other procedure related events), or newly occurring diseases/symptoms previously not known (e.g. a common cold with definite start date after the first screening visit) should have been documented as AEs.

An AE was any untoward medical occurrence in any patient during the study and did not necessarily have to have a causal relationship with the IMP.

Throughout the study, the occurrence of AEs might have been reported spontaneously by the patient or discovered by the site staff during the study examination, or identified while reviewing the patient’s diary, or by general questioning by a member of the site team. Pre-existing conditions that worsened during the trial had also to be recorded as AEs. Worsening

of OLP had not to be reported as AE unless any of the criteria for seriousness would have been fulfilled.

Expected AEs included local reactions to the patch or to clobetasol propionate as well as secondary fungal infection. The occurrence of fungal infections during the study was reviewed by the DSMB on a regular basis.

All AEs had to be documented in the eCRF, including a description of each AE, localization in case of AEs affecting the oral cavity, start and stop dates/times, intensity (severity), frequency, AE relationship to IMP administration, seriousness, action taken and outcome.

The localization (for AEs affecting the oral cavity) should have been documented as 'on application site', 'distant' or 'generalized'.

The intensity (severity) of the complaint or the adverse event was classified as 'mild', 'moderate' or 'severe'.

The frequency of an event was classified as 'isolated (once)', 'intermittent', 'continuous (lasting, after each application)' or 'other'.

The causal relationship of an AE was assessed by the investigator according to the following categories: 'related', 'probably related', 'possibly related', 'unlikely (remote)', 'not related' and 'not assessable'.

For reporting purposes, 'related', 'probably related' and 'possibly related' AEs were treated as related AEs. The causal relationship of an IMP was assessed separately for:

I. the active component (clobetasol propionate) of the IMP in order to account for adverse drug reactions (ADRs),

II. the mechanical/physical properties of the IMP to account for adverse device effects (ADEs)

Additionally, causal relationship could be assessed for 'study procedure' and/or 'rescue medication', if applicable.

Any action on the IMP to resolve the AE was documented using the categories 'IMP not changed', 'IMP withdrawn', 'IMP interrupted', 'not applicable' or 'unknown'.

Other action taken to resolve the AE was documented using the categories 'none', 'drug-treatment', 'other action' or 'withdrawal from study'.

The course and outcome of the AE was commented on using 'recovered/resolved', 'not recovered/not resolved/ongoing', 'recovered/resolved with sequelae', 'fatal' or 'unknown'.

Any AE meeting the serious criteria:

- resulting in death, or
- being life-threatening, or
- requiring inpatient hospitalization or prolongation of existing hospitalization, or
- resulting in persistent or significant disability / incapacity, or
- being a congenital anomaly / birth defect, or
- being an important medical reaction (i.e. a reaction that was not immediately life-threatening or resulting in death or hospitalization but was able to jeopardize the patient or required intervention to prevent one of the other outcomes listed in the definition above).

was defined an SAE.

SAEs had to be reported on the eCRF and on a separate SAEs report form. SAEs had to be reported immediately to the sponsor or designee as soon as it became known to the investigator and not later than within 24 hours of his/her knowledge of the occurrence of an SAE.

All AEs had to be followed until they were resolved or the patient's participation in the study ended. SAEs still ongoing after ended study participation, had to be followed on a regular basis, according to the investigator's clinical judgment, until the event had subsided, stabilized (in the case of persistent impairment), the patient received alternative therapy, the patient was lost to follow-up, or the patient died.

Pregnancies

Female patients had to be instructed to notify the investigator immediately if they became pregnant during the study. A pregnancy test had to be performed then according to normal practice at the investigational site. A confirmed pregnancy during the study period would have led to withdrawal of the patient and would have had to be reported immediately (not later than 24 hours of awareness).

Pregnancies should have been documented as an AE at least. Cases that led to fetal distress, fetal death, or a congenital abnormality or birth defect were to be regarded as SAEs and should have been reported as such. Other complications during the pregnancy that would have been related to a pregnant woman and fulfilled any serious criteria, which would have included pre-eclampsia requiring hospitalization or spontaneous miscarriages, should also been reported as SAEs.

For further details on AE notification, SAE definitions and reporting, and pregnancy reporting, please refer to the CSP in Appendix 16.1.1.

9.5.3.2 Laboratory Procedures and Assessment

The following safety laboratory parameters were assessed during the study:

Hematology	White blood cell count (WBC), Red blood cell count (RBC), Hemoglobin, Platelet count, Differential WBC
Biochemistry	Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (AP), Total Bilirubin, Creatinkinase (CK), Creatinine, Albumin, Sodium, Potassium
Urine (dip stick)	Protein, Blood hemoglobin, Glucose

Blood samples for hematology and serum chemistry and a urine sample were taken at Visit 1 (prior to treatment) and at Visit 7 (end of study) or in case of patient's withdrawal during the treatment period at Visit 6. The blood samples for hematology and serum chemistry were analyzed centrally. The urine status was analyzed locally by using dip-stick tests.

The investigator had to assess the clinical significance of any value outside the normal ranges. Any abnormal and clinically significant laboratory value at Visit 1, had to be documented as medical history finding. An abnormal and clinically significant laboratory value at Visit

6/Visit 7, had to be documented as an AE, if it indicated a newly developed or worsened condition.

The measurements of laboratory values outside of the normal range could have been repeated as judged appropriate to ensure the validity of the abnormal result.

9.5.3.1 Pregnancy Test

For each female patient of childbearing potential, a serum pregnancy test (serum human chorionic gonadotropin (hCG)) was performed at Visit 1 (prior to treatment). Urine pregnancy tests were performed at Visit 0 (prior to biopsy, if a biopsy had to be taken), at Baseline and at Visit 6 (end of treatment). If required by local regulation, additional pregnancy tests would have been performed during the treatment phase.

9.5.3.2 Vital signs and body weight

Vital signs (blood pressure (systolic and diastolic), pulse, body temperature) and body weight were measured at Visit 1 (prior to treatment) and at Visit 7 (end of study) or in case of patient's withdrawal during the treatment period at Visit 6. Height was measured at Visit 1 and the body mass index (BMI) computed based on this height and the weight assessments at Visits 1 and Visit 7.

Blood pressure and pulse recordings were made after the patient had been recumbent and at rest for at least 5 minutes. Measurement of the body temperature were performed according to the standard of care at each participating site.

Abnormal findings in the vital signs and body weight at Visit 1 assessed as clinically significant by the investigator had to be documented as medical history findings. Any clinically significant findings in the vital signs and body weight following Visit 1 had to be documented as an AE, if they indicated a newly developed or worsened condition.

9.5.3.3 Oral examination

The investigator performed a detailed examination of the oral cavity at each study visit (Visit 0 to Visit 7).

At Visit 0 (study biopsy) this examination only focused on the verification of clinical OLP diagnosis (excluding the need to perform complete lesion documentation) and the detection of possible oral infections.

At Visit 1 this examination also included an evaluation of patient's dental status, with regard to any significant findings, that might lead to a progress of OLP at investigator's discretion (e.g. existence of tooth stumps, damaged crowns or dental fillings, poorly fitting dentures or broken restorations, leading to mechanical or chemical irritation).

Abnormal findings at Visit 0 and Visit 1 assessed as clinically significant by the investigator had to be documented in as medical history findings.

Abnormal findings of clinical relevance detected following Visit 2 had to be documented as AEs. This included the possible occurrence of candida infections (pseudomembranous candidiasis) during the treatment period and the follow-up, as secondary fungal infection (*candida albicans*) is a well-known side effect of corticosteroids, topically applied on the oral mucosa as well as of inhaled corticosteroids.

Preventive antifungal treatment was prohibited, but antifungal treatment could have been applied following randomization due to an AE and should then have been listed as concomitant medication.

The occurrence of fungal infections during the study was reviewed by the DSMB on a regular basis.

9.5.4 Other Procedures and Assessments

9.5.4.1 Demographics and Other Baseline Characteristics

Demographic variables, including year of birth (age), sex (plus details on childbearing status for females), race, ethnic origin, smoking status (habitual, occasional, former, never) and alcohol consumption (often, occasional, rare (seldom), never) were collected at Screening (Visit 0 or Visit 1, respectively).

9.5.4.2 Biopsy for histological confirmation of (O)LP

Introduced via Amendment 03.

Histological confirmed OLP via a biopsy was required. If no previous confirmatory biopsy result (from oral lesion or cutaneous/vaginal localization) was available at time of inclusion, a study biopsy had to be taken from a clinically representative site at Visit 0.

The study biopsy could have been taken of affected oral mucosa, i.e. of one characteristic OLP lesion (symptomatic or not) or alternatively of a cutaneous localization of lichen planus. Biopsy sampling and wound treatment was to be performed according to the routine procedures on site. Wound healing had to be followed up appropriately until complete healing and complete relief of associated pain. The biopsy specimen should have been read and interpreted by a local pathologist, experienced in histological examination of OLP (preferable an oral pathologist) or lichen planus (preferable a dermatological pathologist), respectively. For histological confirmation of OLP, biopsy reports indicative for OLP, lichen planus or lichenoid inflammation were regarded as sufficient.[20]

Patients with biopsy reports indicative of dysplasia and/or atypia should not have been included (refer to EC#11, section 9.3.2).

Biopsy details, including kind of biopsy (study biopsy, biopsy in the past), outcome (OLP confirmed, not confirmed), biopsy location (oral [plus anatomical site], cutaneous, vaginal), lesion details (erythematous/white, ulcerative), complete healing and pain relief were collected during the screening phase (Visit 0 to Visit 2).

9.5.4.3 Medical and Surgical History and Concomitant Diseases

Patient's complete medical/surgical history (i.e. former diseases/surgeries as well as concomitant diseases) obtained by questioning and/or as result of the screening procedures (Visit 0 and Visit 1) were documented in the patient's medical record. Findings judged as being clinically relevant by the investigator were documented as medical history / concomitant disease findings (by diagnosis, start/stop dates/ongoing) on the eCRF.

Regarding the OLP a detailed case history, including their duration since first diagnosis, previous treatments of OLP and possible extra-oral manifestations of the lichen planus were obtained at Visit 1.

9.5.4.4 Prior and Concomitant Treatment

All medications (prescription, over-the-counter products to account for mouth rinses) taken by the patients up to 28 days prior to Baseline (Visit 2) until the End of Study Visit (FUP, Visit 7) were documented in the patient's medical records and in the appropriate section of the eCRF. To account for wash-out periods of prohibited medication, the documentation period prior to Baseline was extended to at most 12 weeks.

Medication that was stopped before the first use of IMP (Baseline / Visit 2) was planned to be classified as 'prior medication'. Medications used at least once after the first use of IMP was planned to be classified as 'concomitant medication'.

Medication details, including drug generic name / trade name or active substance, start/stop dates/ongoing, indication, route, dose and frequency, were recorded until Baseline and changes were documented at every following study visit.

9.5.5 Schedule of Procedures

Text Table 9-7 summarizes the assessments that had to be performed at each visit during this study. Details of all methods and assessments that had to be performed are provided in sections 9.5.1 to 9.5.4.

Text Table 9-7: Schedule of Procedures

SCR = Screening visit; BL = Baseline visit; EoT= End of Treatment visit; ET = Early Termination; EoS = End of Study visit; FUP = Follow-up period

	First (initial) SCR	**Second (continued) SCR**	**BL**	**Treatment Period**				**FUP**
	visit 0[5]	**visit 1[6]**	**visit 2**	**visit 3**	**visit 4**	**visit 5**	**visit 6[7] (EoT / ET)**	**visit 7 (EoS)**
Day (in relation to BL)	**---**	**Day -14 to -7**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**visit 6 + 14 days**
Visit window (days)	**---**	**--**	**--**	**±2**	**±2**	**±2**	**±2**	**±3**
Informed consent[8]	X							
In- and exclusion criteria	X[9]	X	X					
Demographics	X							
Medical history / Concomitant diseases	[X][10]	X						

5 For patients with an existing histological confirmation of (O)LP, Visit 0 and Visit 1 can be performed on the same day.

6 For patients with diagnostic biopsy at first screening visit (visit 0), only to be performed after receipt of confirmatory histological report and only after complete healing of the biopsy wound and complete relief of associated pain.

7 Visit 6: Same procedures and additionally safety assessments (vital signs, body weight and clinical laboratory sampling) have to be conducted in case of Early Termination (ET).

8 Patient information should be performed prior to informed consent and prior any other initial assessments during first screening visit to assure sufficient time for patient to think about study participation, as applicable per local standards.

9 Only in- and exclusion criteria relevant for first screening visit need to be checked.

10 As far as relevant for biopsy procedure.

	First (initial) SCR	Second (continued) SCR	BL	Treatment Period				FUP
	visit 0[5]	visit 1[6]	visit 2	visit 3	visit 4	visit 5	visit 6[7] (EoT / ET)	visit 7 (EoS)
Day (in relation to BL)	---	Day -14 to -7	Day 1	Day 8	Day 15	Day 22	Day 29	visit 6 + 14 days
Visit window (days)	---	--	--	±2	±2	±2	±2	±3
Prior and concomitant treatment	[X][7]	X						
Biopsy for confirmation of (O)LP[11]	X							
Histological confirmation of (O)LP		X						
Control of biopsy wound		[X]						
Body height and weight[12]		X					[X]	X
Vital Signs		X					[X]	X
Blood and urine sampling (clinical laboratory)[13]		X					[X]	X
Blood sampling between 7 and 9 AM (clobetasol/morning cortisol)[14]				X				
Pregnancy test[15]	X	X	X				X	

11 Biopsy samples can either be taken from affected oral mucosa (i.e. from a characteristic lesion clinically diagnosed as OLP lesion, including possibly asymptomatic OLP lesions (e.g. reticular or plaque lesions) that do not seek for treatment) as well as from a cutaneous manifestation of lichen planus, if applicable.

12 Body height will be collected at screening visit only. Body weight will be documented at screening visit (visit 1) and at FUP visit (visit 7)

13 Hematology, biochemistry, urine sampling

14 Blood samples for measurement of clobetasol plasma levels and morning serum cortisol must be taken prior to the patch application on site (morning application).

15 Only females of childbearing potential; Visit 1 = serum pregnancy test; visit 0, visit 2 and visit 6 = urine pregnancy tests

	First (initial) SCR	Second (continued) SCR	BL	Treatment Period				FUP
	visit 0[5]	visit 1[6]	visit 2	visit 3	visit 4	visit 5	visit 6[7] (EoT / ET)	visit 7 (EoS)
Day (in relation to BL)	---	Day -14 to -7	Day 1	Day 8	Day 15	Day 22	Day 29	visit 6 + 14 days
Visit window (days)	---	--	--	±2	±2	±2	±2	±3
Clinical assessment of OLP lesions and oral cavity[16]	[X] [17]	X	X	X	X	X	X	X
Patient's rating of worst symptoms at anatomical sites		X	X	X	X	X	X	X
Photo documentation of OLP lesions selected for treatment (supportive documentation) [18]		X	X	X	X	X	X	X
OLPClinROM		X	X	X	X	X	X	X
Guy's 106 Oral Disease Severity Score including patient's rating of OLP associated oral pain		X	X	X	X	X	X	X
COMDQ			X		X		X	
Evaluation of instructions for use[19]			X	X				
Patch sensation questionnaire			X		X			
Patient´s Diary entries		☐---------- ☐						

16 Includes a detailed mapping of OLP lesions and related lesion count as well as an inspection for possible candida infections and other oral diseases.

17 Shortened assessment, only to verify clinical diagnosis of OLP (excluding the need to perform a complete lesion documentation at first screening visit) and to detect possible oral infections (if applicable document infection of oral cavity in medical history/concomitant diseases and treatment(s) for infection as prior/and concomitant medication).

18 To be performed in all sites where photo documentation is or can be established as a standard procedure

19 Patch application feasibility: Evaluation of instructions for use to apply and remove Rivelin® patches (divided into patient's and site staff's part)

		First (initial) SCR	Second (continued) SCR	BL	Treatment Period				FUP
		visit 0[5]	visit 1[6]	visit 2	visit 3	visit 4	visit 5	visit 6[7] (EoT / ET)	visit 7 (EoS)
Day (in relation to BL)		---	Day -14 to -7	Day 1	Day 8	Day 15	Day 22	Day 29	visit 6 + 14 days
Visit window (days)		---	--	--	±2	±2	±2	±2	±3
OLPSSM	Items #1 to #10[20]		----------						
	Item #11			X	X	X	X	X	X
	Item #12							X	
Change in concomitant treatment / concomitant diseases				X	X	X	X	X	X
Record adverse events (AEs)		X	X	X	X	X	X	X	X
Decision on number of patches to be applied (in total and per OLP lesion)[21]				X	(X)	(X)	(X)		
Randomization				X					
Instruction in patch application[22]				X	X				
Dispensing of IMP				X	X	X	X		
Return of IMP					X	X	X	X	
Compliance Check (IMP use)[23]					X	X	X	X	
Determination of rescue analgesics			X						
Dispensing of Patient's Diary			X	X	X	X	X	X	

[20] Items #1 to #10 will be part of Diary and will be obtained on a daily basis in the evening. The total score of items #1 to #7 can be used to perform a preliminary check on symptom severity at second screening visit, visit 1 (based on first entries on site on a paper copy) and will be used to evaluate inclusion criterion #2 at Baseline (based on diary entries during the last week prior to Baseline).

[21] To be decided at Baseline and at subsequent visits, if necessary. Whenever possible the originally assigned patch application pattern should be kept constant during the entire treatment period. If any change is needed, this change needs to be documented accordingly, providing a reason.

[22] Site staff should overview application and provide re-instruction if needed

[23] The site staff will assess the patient's treatment compliance by reviewing the number of remaining Rivelin® patches relative to the number of days since the package was dispensed and depending on the number of Rivelin® patches to be applied by each patient.

	First (initial) SCR	Second (continued) SCR	BL	Treatment Period				FUP
	visit 0[5]	visit 1[6]	visit 2	visit 3	visit 4	visit 5	visit 6[7] (EoT / ET)	visit 7 (EoS)
Day (in relation to BL)	---	Day -14 to -7	Day 1	Day 8	Day 15	Day 22	Day 29	visit 6 + 14 days
Visit window (days)	---	--	--	±2	±2	±2	±2	±3
Return of Patient's Diary			X	X	X	X	X	X
Check of Patient's Diary[24]			X	X	X	X	X	X
Appointment for next study visit		X	X[25]	X	X	X	X	
Completion of Patient's End of Study Form[26]								X

[24] Patients should be advised to bring along their Diary to each of the study visits

[25] Please schedule visit 3 between 7 and 9 AM.

[26] Patient´s End of Study Form must be completed for all patients including screening failures and early withdrawals.

9.5.6 Appropriateness of Measurements

To make sure that only patients with clinically diagnosed and histologically confirmed unifying diagnosis of LP were included in this study, a diagnostic biopsy during a first screening visit (visit 0) and subsequent histological assessment, had been introduced via Amendment 03 for patients without having an existing histological confirmation of LP diagnosis at study entry.

Even though biopsy is an invasive method of assessment, associated with some frequent risks, biopsy of oral mucosal lesions (or alternatively of cutaneous lesions suspicious for lichen planus) is an accepted method used for unifying LP diagnosis, especially if there is clinical doubt or suspicion of invasive malignancy.[21]

Qualitative and quantitative assessment of efficacy by scoring is a widely used non-invasive method to monitor dermatological diseases including the diseases of the mucosa. As no current guidelines on the development of new medicinal products for the treatment of OLP were available at the time of protocol design, the relief of clinical signs and symptoms, assessed by different investigator questionnaires and PRO measurements were used to evaluate the efficacy of the IMP.

The severity of OLP in general was evaluated by using the established and validated Guy's 106 ODSS[15]. To obtain more detailed information focused on single OLP lesions, a new scoring system (OLPClinROM) had been developed shortly prior to protocol design. The likewise newly developed OLPSSM was additionally used as a PRO measurement. Investigators and site staff were provided with detailed trainings on the newly developed measurements for calibration purposes.

Having considered the EMA Reflection Paper[22] on the regulatory guidance for the use of Health-related Quality of Life (HRQoL) measures in the evaluation of investigational medicinal products, the COMDQ[16] was used in this study as an appropriate instrument.

9.6 Data Quality Assurance

9.6.1 Study Management and Monitoring

The following steps were taken to ensure accurate, consistent, and complete data:

- An investigator meeting was conducted by the sponsor where principal investigators and sub-investigators discussed and developed a common understanding of the clinical study protocol, case report form, and study procedures.
- Study initiation meetings were conducted at each study center before subject enrollment to discuss the protocol and review data collection, AE monitoring and reporting procedures, and regulatory requirements. The investigators were provided with instructions regarding specific procedures and terminology required by the clinical study protocol.
- Online trainings on lesion assessment and lesion documentation were performed for every study site prior to inclusion of the first patient. Trainings needed to be refreshed during the study (after approximately 6 months)

- Trainings Manuals (OLP trainings manual, eDiary manual) were provided to each study site.
- Monitoring visits were conducted for the purpose of reviewing the data for (i) completeness and clarity, (ii) adherence to GCP and the protocol and (iii) cross-checking with source documents.
- Remote ongoing medical monitoring of key safety parameters and the lesion documentation were performed for 5-10% of baseline data and 3 random full data sets per month during the study.
- Regular calls with all study sites invited were held to discuss frequent questions and refresh documentation details.
- Newsletters were sent by the sponsor to the study sites to clarify questions concerning the clinical study protocol and provide information to the study center personnel.
- All patients´ data sets were medically reviewed as one step of data cleaning regarding key safety parameter and correct lesion documentation prior to interim or final data base lock, respectively.
- Clinical laboratory tests were performed by certified centralized laboratories
- Data Safety Monitoring Board (DSMB) reviewed AEs regularly and advised on safety thresholds for the patients.

9.6.2 Source Documents

Source documents were all documents used by the investigator or study team that related to the patient's medical history and that verified the existence of the patient, the inclusion and exclusion criteria, and all records covering the patient's participation in the study. They included laboratory notes, histological reports or corresponding referral letters, memoranda, material dispensing records, photographs, lesion maps and patient files. Source documents of a patient participating in this study contained, where applicable: documentation of the informed consent process, patient's identity and date of birth, patient number, assigned kit number and randomization number, inclusion diagnosis, dates of study visits, results of study specific assessments, reports of laboratory analyses, documentation of adverse events and serious adverse events, prior and concomitant medication, date of individual study end and reason of withdrawal (if applicable).

Diary entries were considered as source data.

Direct access to all source documentation (medical records) had to be allowed for the purpose of verifying that the data recorded in the eCRF were consistent with the original source.

As specified in the investigator's agreement, the investigator agreed to allow study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with direct access to all the required source records, and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues.

9.6.3 Case Report Forms and Data Management Procedures

The primary data collection tool for the study was an eCRF specifically designed for the study. Laboratory and eDiary data were not entered into the eCRF but provided in online portals and afterwards transferred directly to the database.

For each patient enrolled, an eCRF was completed by the study coordinator and signed by the investigator. The investigator was responsible for ensuring the accuracy of all data entered in the eCRFs. All eCRFs were to be completed in a timely manner.

For the eCRF, a validated electronic data capture (EDC) system for the clinical study data capture was used. EDC is a user interface module of the Clinical Data Management System (CDMS) so eCRF data entered in EDC were entirely integrated with the CDMS system. Electronic transfers of external data (i.e. laboratory, eDiary data) were transmitted and handled via a secure file transfer. eCRF data were extracted from the CDMS and external data were combined to the data repository and mapped to a CDISC SDTM format.

The EDC system entailed an audit trail carrying a user identification code and a date-time stamp and allowed to audit all changes made to the electronic data, including the identification of the user who made the change and the date and time when the change was made. Appropriate back-up and archiving of electronic data were secured as well.

All data management activities were conducted by the DM CRO following their standard operating procedures and the data management plan (DMP), specifying all relevant aspects of data processing (including data entry, data validation, data clarification process and data base closure). The database was built by the DM CRO, and they handled the data cleaning process, including logical check and query processes. Medical checks were performed by the medical review team of the coordinating CRO. Computerized validation check programs on completeness, correctness, plausibility (such as range checks, cross-checks) verified the data according to the data validation plan. All identified discrepancies were queried by online checks generated within the EDC system during data entry or by manual queries posted by data managers or the medical review team in the eCRFs and addressed by site personnel. This systematic validation ensured that a clean and consistent database was provided prior to the statistical analysis being performed. Details on data handling and database lock had been described in the data management plan.

A Blind Data Review Meeting (BDRM) was arranged prior to data base lock and unblinding of data on 20-Feb-2020. During the BDRM the rating of protocol deviations was decided between all parties and fixed in a final PD listing that was integrated into the data base. The database was locked on 03-Mar-2020.

9.6.4 Audit and Inspection

The investigator had to make his site and the study documents which originated there available to study related audits, IRB/IEC review, and regulatory inspections.

Such audits could have been arranged by the Sponsor (or designee), IRB/IEC representatives or by health authority representatives (domestic or foreign) at any time.

The investigator had to notify the Sponsor or designee of any such audit or inspection immediately.

One sponsor-initiated routine site audit was performed during this study at site 601 in Canada on 29/30-Oct-2019. The purpose of the audit was to observe if the site was performing the study according to study protocol, to ICH-GCP and the applicable local laws and regulations. Two critical and 3 major nonconformities were noted. All nonconformities were addressed in a comprehensive corrective and preventive action (CAPA) plan and thereby resolved. A copy of the audit report, the CAPA plan and the audit certificate can be found in Appendix 16.1.8.

9.7 Statistical Methods and Determination of Sample Size

In the following sections the statistical analyses planned according to the final CSP, version 8.0, dated 29-Mar-2019 (see Appendix 16.1.1) and the final SAP, version 4.0, dated 02-Mar-2020 (see Appendix 16.1.9) are summarized.

The following section covers all pre-planned statistical analysis except for methods for evaluation of the exploratory objectives #10 and #11 (measurement properties and interpretability of newly developed scales OLPClinROM and OLPSSM) which were presented in a separate psychometric analysis plan (available on request) and the exploratory objective #12 (photo documentation) which was not analyzed within this study. Analysis planned for the interim analysis (for details, refer to section 9.7.3), were presented in a separate Interim Analysis Plan which can be found in Appendix 16.1.9.

9.7.1 Statistical and Analytical Plans

The statistical analysis was conducted using SAS version 9.4 or higher. Validation was performed using Gauss 6.25.

The statistical analyses and reporting of results (tables, figures and listings [TFL]) for this study followed the International Conference on Harmonization (ICH) guidelines.

9.7.1.1 Description of Analysis Sets

The full analysis set (FAS) consisted of all randomized and treated patients with data collected post first dose administration. The FAS population was used for evaluation of all efficacy and feasibility data. The FAS population was also used for exploratory analyses. Patients were analyzed according the randomized treatment assigned.

The per-protocol set (PPS) consisted of all patients in FAS without major/important protocol deviations. Reasons from exclusion included but were not limited to violations of inclusion/exclusion criteria, withdrawal criteria and the use of prohibited medication. Final decisions on each patient's inclusion in the PPS was taken at the Blind Data Review Meeting prior to Data Base Lock. The PPS population was used for sensitivity analyses of ulcer area, lesion area and 5-point erythema scores.

The safety dataset consists of all randomized and treated patients with safety data collected post first dose administration. The safety dataset was used for all safety evaluation.

9.7.1.2 Summary Statistics

Continuous variables were summarized using descriptive statistics (number of patients [N], arithmetic mean, standard deviation [SD], median, minimum and maximum values) and for categorical (nominal) variables, the number and percentage of patients was used. For continuous variables with an expected skew distribution (plasma clobetasol concentrations,

serum cortisol levels), geometric mean and coefficient of variation (CV) are given instead of arithmetic mean and SD.

Mean value graphs are based on imputed data using last value carried forward to fill out potential missing values. Only data collected post-first dose and within the treatment period were used for imputation of post-dose data, baseline data were not carried forward. The run-in period data were similarly imputed. For graphs including the follow-up period (Visit 7) only observed means are shown for Visit 7.

All available data from all patients who have received study treatment were listed and summarized. Any unscheduled or unplanned readings are presented within the patient listings, but only the scheduled readings were used in any summaries. If a visit was rescheduled for any reason, the rescheduled visit is listed but only summarized if it replaced the scheduled visit. When summarizing efficacy variables, data collected at end-of study visits are presented as belonging to the next scheduled visit. End-of visit data were not summarized separately.

9.7.1.3 Primary Endpoint analysis methodology

The primary endpoint was the absolute change in ulcer area from Baseline (Visit 2) to the average of assessments at Visits 5 and 6. Ulcer areas from all baseline measured ulcers were summed to a total area within a patient. Treatments were compared using an analysis of covariance (ANCOVA) model with fixed factors treatment, country and strata and with baseline ulcer area as a covariate. A closed test-order was used for testing the effect of clobetasol treatment. The highest dose of clobetasol was compared to placebo, if this test was statistically significant, the next highest dose would have been compared to placebo and finally, if second test was statistically significant, the lowest dose would have been compared to placebo. Secondarily, active doses of clobetasol were compared pairwise to investigate the dose-response.

For each test the estimated treatment difference was given together with 95% confidence limits and corresponding 2-sided p-value. The FAS population was used for primary analysis and the PPS population as a sensitivity analysis. Missing data due to withdrawals were imputed and the impact of imputation checked.

A similar analysis of ulcer area, but with changes expressed as percentage change from Baseline instead, was performed as a secondary analysis.

All data were listed and summarized by treatment and assessment point as well as the change from Baseline. Graphics included individual and mean value curves over time (expressed as change from Baseline on absolute scale).

9.7.1.4 Secondary Endpoint analysis methodology

9.7.1.4.1 Lesion area

Lesions areas from all baseline measured lesions within a patient were summed to a total for analysis. The absolute change in lesion area from Baseline (Visit 2) to the average of assessments at Visits 5 and 6 was compared between treatments with a similar ANCOVA model as for the primary endpoint and the same closed test procedure.

The FAS population was used for primary analysis and the PPS population as a sensitivity analysis. Missing data due to withdrawals were imputed and the impact of imputation

checked. A similar analysis, but with changes expressed as percentage change from baseline instead, was performed as a secondary analysis.

All data were listed and summarized by treatment and assessment point as well as the change from Baseline. Graphics included individual and mean value curves over time (expressed as change from Baseline on absolute scale).

9.7.1.4.2 5-point Erythema score

The 5-point erythema score was assessed for each anatomical site involved and the average value over the sites involved for a patient was calculated for each visit. The change from Baseline to the average of Visits 5 and 6 was used for analysis. The analysis of the 5-point erythema score was similar to the primary endpoint using the same ANCOVA model and closed test procedure.

The FAS population was used for primary analysis and the PPS population as a sensitivity analysis. Missing data due to withdrawals were imputed and the impact of imputation checked.

All data were listed and summarized by treatment and assessment point as well as the change from Baseline. Graphics included mean value curves over time.

9.7.1.4.3 Worst symptoms at anatomical sites

The worst symptoms at anatomical site were assessed for each anatomical site involved and the average value over the sites involved for a patient was calculated for each visit. The change from Baseline to the average of Visits 5 and 6 was used for analysis. The analysis was similar to the primary endpoint using the same ANCOVA model and closed test procedure.

All data were listed and summarized by treatment and assessment point as well as the change from Baseline. Graphics included mean value curves over time.

9.7.1.4.4 Global impression of anatomical site score

The clinical global impression of anatomical site score (CGIM) was assessed for each anatomical site involved and the average value over the sites involved for a patient was calculated for each visit. The change from Baseline to the average of Visits 5 and 6 was used for analysis. The analysis was similar to the primary endpoint using the same ANCOVA model and closed test procedure.

All data were listed and summarized by treatment and assessment point as well as the change from Baseline. Graphics included mean value curves over time.

9.7.1.4.5 OLPSSM

Secondary endpoints from the Diary included the first seven questions (#1 - #7) on symptoms from the OLPSSM. The sum of these seven symptom scores (total score) was the primary outcome, but also the individual questions were evaluated. The change from Baseline (mean over the last 7 days of the run-in period) to the mean over the third and fourth treatment week (between Visits 4 and 6) was used for analysis. Analysis used the same ANCOVA model and closed test procedure as for the primary endpoint.

All data were listed, and weekly means were summarized by treatment and assessment time. Data were presented using individual (total score only) and mean value graphs of symptom levels over time (by day) and by plots of the weekly means.

9.7.1.4.6 Patch sensation questionnaire

The number of patients with positive response (defined as a score of 0 or 1) at Visits 2 (day 1) and 4 for each question on the patch sensation questionnaire were compared between treatments using a logistic regression model adjusting for treatment, strata. Differences between treatments were expressed as the odds ratio with 95% confidence intervals.

All data were listed and summarized by treatment and assessment point. Outcomes were visualized using histograms.

9.7.1.4.7 Patch applications

The number of patients with successful patch applications (defined as an adherence time of ≥ 30 minutes on ≥ 80% of the days on treatment based on morning recordings in the Diary regarding the target patch) was compared between treatments using a logistic regression model adjusting for treatment, strata. Differences between treatments were expressed as the odds ratio with 95% confidence intervals. Further, the individual proportion of successful applications were estimated over the full treatment period and over each of the 4 treatment weeks. An analysis of variance (ANOVA) model with fixed factors treatment, country and strata was used to compare treatments regarding success rate over the full treatment period.

All data were listed, and weekly means were summarized by treatment and assessment time. Data were presented using mean value graphs of adherence times over time (by day) and by scatter plots of the success rates.

9.7.1.5 Exploratory Endpoint analysis methodology

9.7.1.5.1 OLPSSM

Exploratory endpoints from the Diary included the three questions 8 to 10 on symptoms from the OLPSSM and the daily use of rescue analgesics. These endpoints were compared between treatments similar to the handling of symptom questions 1 to 7 of the OLPSSM in the secondary endpoints, using ANCOVA models.

All data were listed, and weekly means were summarized by treatment and assessment time. Data were presented using mean value graphs of symptom levels over time (by day) and by plots of the weekly means.

Questions 11 and 12 in the OLPSSM were collected in the eCRF at clinic visits. The change from Baseline to the average of Visits 5 and 6 for question 11 was compared between treatments using ANCOVA. The value at Visit 6 for question 12 was compared between treatments using an analysis of variance (ANOVA) model adjusting for treatment, country and strata.

All data were listed and summarized by treatment and assessment point. Data were presented using mean value graphs of symptom levels over time (11) and by histograms of the distribution by treatment (12).

9.7.1.5.2 3-point Erythema score

The 3-point erythema score was assessed for each anatomical site involved and the average value over the sites involved for a patient was calculated for each visit. The change from Baseline to the average of assessments at Visits 5 and 6 in 3-point erythema score was analyzed with a similar ANCOVA model as for the primary endpoint.

All data were listed and summarized by treatment and assessment point as well as the change from Baseline. Graphics included mean value curves over time.

9.7.1.5.3 Cleared lesions/ulcers

The number of patients with cleared lesions respective cleared ulcers at each post-dose visit, were summarized by treatment group. A total lesion or ulcer size of 0 was considered definition of a cleared lesion/ulcer. Further the number of patients with cleared lesions/ulcer at last treatment visit and the number of patients with cleared lesions/ulcers at any treatment visit were summarized. For the latter two endpoints, treatments were compared between treatments using a logistic regression model adjusting for treatment, strata. Differences between treatments were expressed as the odds ratio with 95% confidence intervals. Outcomes were visualized using histograms.

9.7.1.5.4 Guy's 106 oral disease severity score

Endpoints were the total disease severity score as well as the three subdomains: total site score, disease activity score and the 0-10 pain score. The change in Guy's scores from Baseline to the average of assessment at Visits 5 and 6 was compared between treatments using the same ANCOVA model and closed test procedure as for the primary endpoint.

All data were listed and summarized by treatment and assessment point as well as the change from Baseline. Graphics included individual and mean value curves over time.

9.7.1.5.5 Onset of action

Onset of action was investigated by analyzing data from variables measured by OLPClinROM including assessment of worst symptom at anatomical site, OLPSSM and Guy's 106 oral disease severity score at each post-dose visit or each treatment week (defined as period between two consecutive visits) for diary variables. Data were imputed before analysis to get the same number of patients included at each time point. Separate ANCOVA models were applied to each assessment point. Testing started at visit 6 (week 4) and went backwards as long as a continuous sequence of statistical significances was seen.

9.7.1.5.6 COMDQ

Endpoints for COMDQ included the total questionnaire, the pain and functional limitation domain, the medication and treatment domain, the social and emotional status domain and the patient support domain. The change from Baseline to Visit 4 and the change from Baseline to Visit 6 in the COMDQ were compared between treatments using the same ANCOVA model and closed test procedure as for the primary endpoint.

All data were listed and summarized by treatment and assessment point as well as the change from Baseline. Graphics included individual and mean value curves over time.

9.7.1.5.7 Instruction for use questionnaire

The proportion of patients with successful patch applications at Visit 2 (day 1) and Visit 3 as assessed by the IFU questionnaire (site staff part) were listed and summarized by treatment group. The patient's part of the IFU regarding instructions for application and removal was similar summarized. Outcomes were visualized using histograms.

9.7.1.5.8 Rescue analgesics use

The number of patients with prescribed rescue analgesics during the study and which types were summarized by treatment and ATC class levels 2 and 4. The actual use of rescue analgesics was summarized as weekly means. Primarily days were coded as 1=use, 0=no use in summaries/analysis, but exploratory analyses quantifying the extent of use were also performed. Since not all patients might have had a rescue analgesic prescribed, analysis was performed in the subset of patients with records of either use or non-use of their rescue analgesics recorded in the database.

Endpoints were compared between treatments similar to the handling of OLPSSM endpoints, using ANCOVA models.

All data were listed, and weekly means were summarized by treatment and assessment time. Data were presented using mean value graphs of rescue use over time (by day) and by plots of the weekly means.

9.7.1.5.9 Plasma clobetasol

Plasma concentrations of clobetasol from samples collected at Visit 3 were summarized by treatment group using descriptive statistics (geometric means and CV). Concentrations below the lower LOQ were handled as LOQ/2 in the summaries and concentrations above the upper LOQ were handled as LOQ*2. Outcome were visualized using scatter plots with mean levels indicated.

9.7.1.5.10 Serum cortisol

Morning serum cortisol levels were summarized by treatment group using descriptive statistics (geometric means and CV). Graphics included scatter plots of assessed serum concentrations with mean levels indicated.

9.7.1.6 Safety assessments analysis methodology

9.7.1.6.1 Adverse Events

Adverse events (AEs) were collected throughout the study from date of signing the informed consent to follow-up and AEs were coded according to the current version of the MedDRA dictionary (version 21.1). A treatment-emergent adverse event (TEAE) was defined as an AE that started or worsened after first intake of study treatment. If the start date was unknown then the AE was assumed to be treatment emergent unless the partial start date, or other data (i.e. stop date) indicated differently. In summaries, causally related AEs consist of AEs classified as Possibly Related, Probably Related or Related to active component or mechanical/physical properties of the IMP.

Adverse events are presented by system organ class (SOC) and preferred term and summarized by treatment group. A summary table by treatment group with total number of AEs and number of patients with AEs, SAEs, AEs leading to discontinuation of randomized treatment, related AEs (both types), each frequency and each severity type of AE was produced. Further SAEs, related AEs and AEs of different intensity were summarized by SOC and preferred term.

AEs are presented in decreasing frequency of the total number of patients with TEAEs. All AEs, including those which are not treatment emergent, were listed. SAEs and AEs having led to discontinuation of study treatment were also listed separately.

9.7.1.6.2 Pseudomembranous candidiasis

Occurrence of pseudomembranous candidiasis assessed by visual inspection was reported as adverse events and included in the adverse event summaries/listings.

9.7.1.6.3 Laboratory tests

Continuous laboratory parameters were summarized using descriptive statistics for each visit (Baseline visit 1 and follow-up Visit 7) and for the change over the study. Categorical laboratory parameters were summarized using numbers and percentages for each class. Data were further illustrated by tables of abnormalities (showing number and percentages of values considered normal, abnormal not clinically significant and abnormal clinically significant) and shift plots for changes over the study.

The baseline value was defined as the last scheduled, unscheduled or repeat value collected prior to first dosing. Values from End-of study visits (Visit 6) were used as representative for Visit 7 follow-up. For patients with both assessments at Visit 6 and Visit 7, the Visit 7 value was used in the summaries. If repeat values were taken at follow-up, the values from the first occasion were used in the summaries. The tabulation will only include scheduled visits; all unscheduled assessments are displayed in the listing as appropriate.

All laboratory values were listed showing reference ranges and flagging all abnormal findings and their clinical significance (CS or NCS). Out of reference range values were flagged as high (H) or low (L). A similar listing including all post-dose laboratory values found abnormal, including the baseline result and clinical significance, was also produced.

9.7.1.6.4 Vital Signs and body weight

Vital signs and body weight data were summarized by treatment group and Visit (Baseline, Visit 1 and follow-up Visit 7). The change from Baseline to follow-up was also calculated and summarized. Data were further be illustrated by shift plots for the changes during the treatment period.

The baseline value was defined as the last scheduled, unscheduled or repeat value collected prior to first dosing. Values from End-of study visits (Visit 6) were used as representative for Visit 7 follow-up. For patients with both assessments at Visit 6 and Visit 7, the Visit 7 value was used in the summaries. The tabulation only included scheduled visits; all unscheduled assessments were displayed in the listing as appropriate.

9.7.1.6.5 Examination of oral cavity

Examinations included dental status (Visit 1 only), mouth infections and oral cavity examination. Outcomes were classified as normal, abnormal not clinically significant and abnormal clinically significant and summarized by visit. All data were listed.

9.7.1.6.6 Prior and Concomitant Medications

Prior medications are defined as those medications used prior to randomization independent of if the use was stopped or not. Concomitant medications are defined as those medications with either a start date or a stop date that is after the date of first dose of study treatment. If the start date was unknown then it was assumed to be concomitant unless the partial start date, or other data (i.e. stop date) indicated differently.

All prior and concomitant medications were listed by reported name, medication class, standardized medication name, indication, dose, dose unit, route of administration, dosing

frequency, start and end dates. Concomitant medications were summarized by ATC class levels 2 and 4 for each treatment group.

9.7.1.6.7 Pregnancy tests

Pregnancy test results or reasons for not performing the test(s), from females of child-bearing potential, were listed and summarized by outcome for each visit.

9.7.1.7 Other assessments analysis methodology

9.7.1.7.1 Disposition

A summary of the patient flow (number and percentage) was made of all patients enrolled in the study, randomized in the study, belonging to each of the analysis sets, completing the study or being withdrawn from the study (discontinuing the investigational product). The primary reason for withdrawal from the study was further summarized by category. Patient disposition data including individual reasons for withdrawal were listed.

9.7.1.7.2 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics including age, sex, race, ethnic origin, height, weight, BMI, smoking status, alcohol habits and childbearing status for females were listed and summarized by treatment group.

Prior medications for treatment of OLP were listed and summarized by ATC class level 2 and 4 for each treatment group. Medical history was coded using the current version of the MedDRA Dictionary in addition to the verbatim, listed and summarized by SOC and preferred term.

Lesion sites and characteristics at Baseline were listed and summarized by treatment group. Characteristics of biopsies used to confirm the OLP diagnosis were summarized by treatment group.

9.7.1.7.3 Extent of Exposure and Treatment Compliance

The Rivelin-CLO compliance was calculated in two ways:

- based on the number of dispensed and collected (returned) patches in relation to the expected number of patches to be used in the period

$$\frac{\text{(Actual number of days between two adjacent visits x Planned number of patches to be applied) x 2 times daily}}{\text{Number of patches dispensed – Number of patches returned}}$$

For each week of treatment patients were dispensed 108 patches. If the planned number of patches used in a period exceeded the maximum 108, the planned number of patches to be used was set to 108. Similar, the actual number of days between adjacent visits were used when computing diary compliance (see below).

- and based on the entries of number of patch applications in the Diary in relation to the period length.

For treatment compliance the total number of days between first application of IMP and last application excluding days with approved IMP discontinuation was respected.

Compliance data were listed and summarized by treatment group. A compliance rate of ≥70% over the full treatment period (defined at time between Visit 2 and last visit in the treatment period) was deemed acceptable and patients with lower compliance were considered protocol deviators.

The total exposure to clobetasol is given as the total dose administered during study, calculated as the number of patches applied times the nominal dose of the patch. Exposure data were listed and summarized by treatment group.

9.7.1.7.4 Protocol Deviations

Prior to database lock all protocol deviations were reviewed and classified as being of major or minor importance and consequences for inclusion of patients in various analysis population sets determined and documented. All details of protocol deviations collected in the study were listed. Further protocol deviations were summarized by category of deviation and by minor/major assessment.

9.7.1.8 Methods for Statistical Issues Encountered During the Analysis

9.7.1.8.1 Handling of multiplicity

All hypothesis testing was done using two-sided alternative hypotheses. P-values less than 5% were considered statistically significant.

To account for multiplicity when testing for efficacy of the active patches, a closed testing procedure was applied for each endpoint: first the highest dose of clobetasol was tested versus placebo and if statistically significant, then the mid dose of clobetasol would have been tested versus placebo and, if statistically significant then finally the lowest dose of clobetasol would have been tested versus placebo.

No other adjustment for multiple testing were done.

9.7.1.8.2 Imputation of missing data

Intent was to collect as complete data as possible from each patient, also after a potential stop of study treatment, in order to minimize the number of missing data. Imputation of missing data for analysis was planned to be done using two different approaches:

(1) if a sufficient number of data was collected after withdrawal from treatment, the data collected after withdrawal would be used for imputations of week 4 data.

(2) a standard last observation carried forward (LOCF) approach.

In the end the majority of withdrawn patients performed an end-of-study visit so a modified option 1 was used. The end-of-study values were used for imputation of week 4 and by backward imputation also as representative for missing visits between last scheduled standard visit and Visit 6. For patients with no end-of-study visit performed or with missing data prohibiting imputation this way, a LOCF imputation was performed instead. Patients with no post-randomization data were not imputed using this approach. For diary-based endpoints on a daily basis, LOCF was used for imputation.

For diary card data (OLPSSM, rescue medication), weekly means were calculated if including at least 4 valid entries during the evaluated period, otherwise the mean was set to missing. The 7 days preceding the randomization visit was used as the baseline period, the days between adjacent visits (starting on the day of first visit and ending the day before next visit)

was used to define treatment and follow-up periods. If an intermediate visit was missing in the treatment period and the adjacent visits differed with more than 8 days, this period was split in two subperiods representing the two scheduled weeks between visits; otherwise the data were considered belonging to the first of these scheduled weeks and the second week mean was set to missing. Missing weekly means (completely missing or due to less than 4 entries) were handled by imputation using the methods described above for visit based endpoints.

9.7.1.8.3 Additional analyses

Sensitivity analyses of primary and selected secondary endpoints were done to explore the impact of outliers, withdrawals and the use of prohibited medication/rescue medication during the study. Outcomes are not included in the Clinical Study Report.

Subgroup analysis was exploratory on a data-driven basis. These analyses included groupings by patient demographics and Baseline characteristics. Also, the correlations between various endpoints were investigated in an exploratory manner. Outcomes are not included in the Clinical Study Report.

9.7.1.8.4 Multiple/duplicate entries

For all statistical analysis, only a single entry was allowed as the representative for each scheduled time-point. On days of study visits, the diary may have been filled in both in the morning/at the study visit and as scheduled in the evening. Of such multiple entries, only the evening recordings were kept in the statistical analysis. All entries were kept in the clinical database though.

9.7.2 Determination of Sample Size

No background data was available at the time of protocol design from a randomized, placebo-controlled study for a formal sample size computation based on the primary endpoint. Preliminary data on ulcer area indicated that a standard deviation of about 25 mm^2 could be expected. 45 patients per group would then have had 90% power to detect a true difference of 17 mm^2 between any two treatments using a two-sided test at 5% significance level. This patient number had been considered sufficient to meet the primary objective in the study.

9.7.3 Interim Analysis

An interim analysis (IA) was performed with a cut-off date for randomization at 17-Jul-2019. At this time point 90 patients had been randomized and considered evaluable for the IA. The IA was performed based on these patients, however recruitment to the study continued at least up to the time of the interim results were available and a decision regarding the further progress of the study had been taken. Thus, the interim analysis was not the final analysis. In all scenarios a second and final analysis would have been performed using the total number of patients randomized. Test at the interim was therefore done at the 0.001 level and significance level for final analysis was changed to 0.049.

The aim of the interim was to perform a sample size re-estimation based on a selected set of endpoints: ulcer area (primary endpoint), worst symptoms at anatomical site score, clinical CGIM site score and the OLPSSM individual question #10. The change from Baseline to the average of values of weeks 3-4 was used for the sample size calculations.

Depending on outcome, the decision could have been to stop recruitment at the time the interim results were available (at about 30 extra patients compared to the interim population) or to continue the recruitment until 45 patients/group (totally 180 patients) had been randomized. Thus, the original target of 240 randomized was no longer an option. At the interim, if study recruitment was to continue, decision could also have been taken to drop doses from the continued study due to safety reasons or lack of efficacy.

Details of the IA were specified in a separate Interim Analysis Plan which can be found in Appendix 16.1.9

An un-blinded and independent statistician, who was not involved in any other study processes, performed the analysis and assigned data to treatment groups.

Unblinded IA results were reviewed by a sponsor-independent Data Monitoring Committee (DMC) and advise on further study progress was provided to the sponsor.

The DMC meeting was performed on 11-Nov-2019 and the recommendation was given to terminate the study as soon as possible. For details refer to the blinded minutes of the DMC meeting in Appendix 16.1.13. The sponsor followed the recommendations of the DMC and randomization was stopped on 13-Nov-2019. No further patients were randomized after this date.

9.7.4 Data Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) was established by the Sponsor to review the safety results of the study. The members of the DSMB were medical doctors with expertise in the therapeutic area and experience with clinical studies.

To monitor safety, the DSMB should have received all reported AEs (irrespective of seriousness), all reported SAEs, irrespective of relationship to test product or study procedure, and other safety relevant data, such as laboratory data.

Based on their findings the DSMB should have advised the Sponsor of any potential risk for the safeguard of patients and submitted corresponding recommendations to the Sponsor. The Sponsor was responsible to respond to the recommendations of the DSMB and to take appropriate action, if necessary.

The composition of the DSMB, responsibilities, organization, workflow, evaluation and decision principles, timelines, communication plan and content of the data package needed was specified in a DSMB charter, which can be found in Appendix 16.1.13.

In fact, no DSMB meeting was held during this study.

9.7.5 Randomization

The randomization list was prepared by an independent statistician (who was not involved in data evaluation) using SAS, Procedure Plan. The randomization list was a document that consisted of randomization numbers, which uniquely assigned each patient to one of the treatments at a 1:1:1:1 ratio and patients were stratified according to number of patches needed at Baseline (1-3 and 4-6), dependent on the Baseline severity of OLP. The assignment was performed centrally within the IWRS of the EDC.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Changes in the Conduct of the Study

Protocol version 2.0, dated 27-Nov-2017 was used for initial submissions to competent authorities and IEC/IRBs. To account for the changes required in the participating countries, Amendment 01 and 02 were issued resulting finally in one global CSP version (version 4.0, dated 15-Mar-2018).

Thus, upon inclusion of the first patient (28-Jun-2018), protocol version 4.0, dated 15-Mar-2018 was valid for all countries.

Amendment 03 (1st global amendment after start of enrollment) resulted in CSP version 6.0, dated 07-Sep-2018 and introduced the following main changes:

Amendment number	Summary of amendment	Reason for Change
03	A biopsy, confirmatory for study disease, was introduced as an IC. The biopsy was to be performed as a study procedure, if not available from the past at Screening.	FDA recommended that the OLP disease should be verified histologically via a biopsy.
	Supportive photo documentation was turned into an optional assessment for the sites.	As the procedure was not standard for all sites and no evaluation of photos was planned, the assessment needed only to be done by sites, for which it was standard.
	Imprecisions were corrected, clarifications were added, and administrative changes adapted.	Improvement of readability, clarity and conciseness.

Amendment 04 (2nd global amendment after start of enrollment) resulted in CSP version 8.0, dated 29-Mar-2019 and introduced the following main changes:

Amendment number	Summary of amendment	Reason for Change
04	An interim analysis, to be performed after about 90 randomized patients, analyzing safety data, primary efficacy and selected secondary efficacy endpoints, was introduced.	The interim analysis was introduced to re-estimate sample size and to decide about termination of active treatment groups due to safety concerns or due to lack of efficacy.
	The electronic diary was replaced by a paper diary.	Technical issues with the electronic device resulted in failures of data capture. To obtain diary data, paper versions were provided to the patients.
	Certain systemic treatments were allowed if on stable dose and thus not influencing the status of OLP disease.	Adapted to allow enrolment of OLP patients that need systemic medications to keep their OLP or other chronic conditions under control, but still suffer from ulcerative lesions and would thus benefit from the addition of topical steroids.
	EC#11 was adapted.	Adapted to allow enrolment of patients with a history of resected skin squamous cell carcinoma (SCC), as treatment of this kind of cancer has only local impact and will not cause negative systemic impact and a history of skin SCC is regarded as being at very low risk to develop oral cancer.

Amendment number	Summary of amendment	Reason for Change
	EC#17 was adapted for all countries, but not for Germany.	Adapted as the examples given are not absolute contraindications for a biopsy. It will be at the investigators discretion what is regarded as biopsy contraindication on a patient specific basis.
	Re-screening criteria were broadened.	Introduced to improve recruitment.
	A statement was introduced to clarify that all OLP assessment should be attempted to be performed by the same investigator throughout the study whenever possible.	Introduced to assure consistency in disease ratings.
	Imprecisions were corrected, clarifications were added, and administrative changes adapted (including new sponsor name and address).	Improvement of readability, clarity and conciseness.

For more details on Amendment 03 and 04 as well as on the amendments made prior to inclusion of the first patient, please refer to Appendix 16.1.1.

9.8.2 Changes in the Planned Analyses

The following items changed compared to the planned analyses, as outlined in section 9.7.

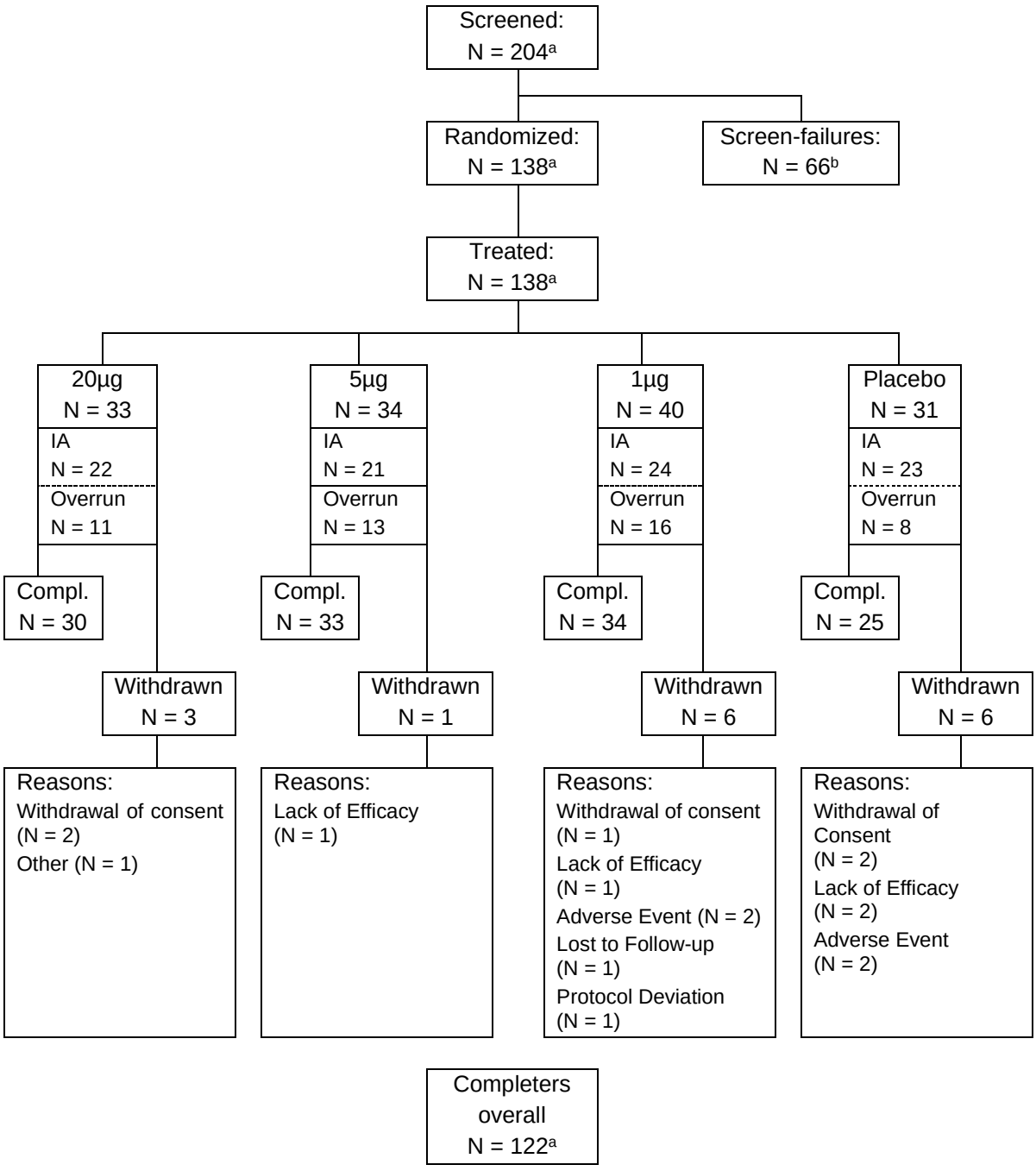
- For compliance computations, the actual number of days between the adjacent visits (scheduled visit or end-of-study visit) was multiplied with the planned number of patches to be applied time 2 (to account for bid dosing). Patients were dispensed 108 patches for each period (study week), if the planned number of patches used in a period exceeded the maximum 108, the planned number of patches to be used was set to 108. Similarly, the actual number of days between adjacent visits were used when computing diary compliance.
- P-values less than 4.9% were considered statistically significant, this to account for the interim analysis performed including the first 90 patients and at which testing was made at the 0.1% level.
- For categorical outcome, treatments were compared using a logistic regression model with fixed factors treatment and strata. Country was planned to be included as factor. but dropped from these models due to convergence problems for the algorithm. Endpoints tested using logistic regression included, cleared ulcers/lesions, positive responses on the patch sensation questionnaire and successful applications (patch adhesion data).
- Prior medication was defined as any medication with start date prior to randomization, irrespective if this stopped prior to the first use of IMP at Baseline or not. Medications that were used at least once after the first use of IMP and medications with start date later than randomization were classified as concomitant medication.
- Regarding imputation of missing data in the patient´s diary, the criterion “If follow-up visit extended more than 14 days after Visit 6, the follow-up mean was based on the first 14 days.” was deleted.

- New safety tables regarding related AEs in oral cavity were produced: 14.3.3.3 Summary of adverse events in oral cavity causally related to clobetasol treatment by SOC and preferred term; 14.3.3.4 Summary of adverse events in oral cavity causally related to patch applications by SOC and preferred term.
- Table 14.3.3.2 was complemented with data on application side infections to account for all PT contributing to oral candidiasis.
- A new table regarding Baseline characteristics was produced: 14.1.3.5 Summary of lesion characteristics at screening/baseline: f) summary of number of patches assigned to be used at Visit 2 and patients with changes over study period.

10 STUDY PATIENTS

10.1 Disposition of Patients

The assignment of patients to the 4 different treatment groups and the ratio of patients' study completion by treatment group are given in Text Figure 10-1.



Text Figure 10-1: Patients disposition

[a] 2 patients (both completers) were excluded from the analyses due to unreliability of data (major GCP issues on site) [b] 14 patients were not randomized, as it was decided to stop randomization as a result of the IA
Source: Table 14.1.1.1; Listing 16.2.1.1 and Listing 16.2.1.2

Subjects disposition is also summarized in Text Table 10-1.

Text Table 10-1: Subject Disposition

Category	20 ug	5 ug	1 ug	Placebo	Total
Enrolled Patients					204
Randomized	33	34	40	31	138
Completers	30	33	34	25	122
Withdrawn	3	1	6	6	16
-- Withdrawal Of Consent	2	0	1	2	5
-- Lack Of Efficacy	0	1	1	2	4
-- Adverse Event	0	0	2	2	4
-- Lost To Follow-Up	0	0	1	0	1
-- Other	1	0	0	0	1
-- Protocol Deviation	0	0	1	0	1
No Emergency Unblinding	5	5	4	3	17
Re-Screened Patients	0	1	1	0	2
Safety Set	33	34	40	31	138
Full Analysis Set	33	34	40	31	138
Per Protocol Set	25	30	35	26	116
Source: Table 14.1.1.1. Listing(s): Derived from Listings 16.2.1.1 and 16.2.1.2					

In total 206 patients were screened, but data from 2 patients of site 408 were excluded from the database for analysis due to major GCP issues on site and hence unreliability of collected data. Correspondingly data of 204 patients were available in the data base used for analysis. Thereof 138 patients were randomized, and 66 patients left the study as screen failures. Two of these were re-screened and finally randomized (each one to the 1µg and the 5µg group) as a result of the re-screening procedures.

The interim analysis was performed on a total of 90 randomized patients and additional 48 patients were randomized (overrun) until decision on terminating the study was taken according to the recommendation provided by the Data Monitoring Committee on 11-Nov-2019.

Until the data cut-off for the interim analysis patients were randomized evenly into treatment groups, whereas randomization after that date showed some skewness, as 16 patients were randomized to the 1 µg group but only 8 patients to the placebo group. As a result, the number of patients randomized to treatment groups of 20µg (33 patients), 5µg (34 patients) and placebo (31 patients) were comparable for the final analysis, but approximately 20% more patients were randomized to the 1µg group (40 patients). This skewness was caused by erroneous programming of the automated randomization system, as randomization numbers were not assigned consecutively in the order of randomization of patients, but a complete randomization block of 4 randomization numbers (all 4 treatment arms) was reserved for a specific site, as soon as the first randomization number within a block had been assigned by this site.

Additional 14 patients which were in screening at time of study termination were not randomized due to the decision to stop recruitment at the IA.

As further detailed in section 10.1.2 in total 16 randomized patients withdrew from the study. Predominately patients withdrew from the placebo group and the 1µg group, whereas withdrawal from the higher dosing groups occurred less frequently.

Assignment of patient to analysis sets is described in section 10.3

Information on emergency unblinding are given in section 10.6.

10.1.1 Assignment of Patients to Treatment Groups

As shown in Text Table 10-4 a total of 60.9% of patients belonged to the 1-3 patch stratum, and 39.1% of patients belonged to the 4-6 patch stratum. Comparing the different treatment groups, the highest percentage of patients allocated to 1-3 patches was found in the 20µg group and the placebo group, whereas the percentage of patients needing 4-6 patches was approximately 8-10% higher in the 5µg group and the 1µg group, respectively. Imbalanced distribution among treatment groups (especially in the 4-6 patch stratum) is again a consequence of the erroneous randomization process, as described in section 10.1.

A majority of patients were randomized in North America (58.7%). Among the European countries, Great Britain randomized most patients (19.6% of all patients) and Germany with distance the lowest number (only 4.3% of all patients).

According to the protocol no stratification by country nor by site was planned, but especially the USA shows a skewed randomization with relatively more patients in the 1µg and in the 5µg group and fewer patients in placebo and 20µg group. As detailed in section 10.1 skewed randomization was caused by erroneous programming of the automated randomization system. Consequently, an additional stratum – by site – was introduced into the randomization process, even though not intended per protocol. This finally led to the observed imbalance in randomization in favor to the 1µg group.

10.1.2 Early Discontinuation from Study

In total 16 randomized patients withdrew from the study (see Text Table 10-1). Main reasons for withdrawal were withdrawal of consent (in overall 5 of 16 patients), lack of efficacy and the occurrence of an intolerable adverse event (each 4 of 16 patients). All remaining reasons occurred only once.

Thirteen of the 16 withdrawn patients performed the early termination safety assessments (as per protocol) at date of their individual end of treatment (=Visit 6). Two further patients did not, due to the circumstances of their withdrawals (lack of efficacy and refusal to have safety assessment and lost to follow-up). One patient was withdrawn early during the follow-up phase (due to an AE, reported as ‘Candidiasis on application site’) and had the end of study (V7) safety assessments as per protocol (see Listing 16.2.1.1).

10.2 Protocol Deviations

10.2.1 Summary of Protocol Deviations

Any deviation from the specifications in the study protocol was assessed and reported as protocol deviation (PD).

Prior to un-blinding the database, all reported PDs were assessed in the blind data review meeting (BDRM) as minor or major PD and it was assessed if the patient had to be excluded from the per-protocol set (PPS) due to the respective PD. Patients with major PDs that had an impact on the efficacy analysis were excluded from the PPS (for details see section 10.3).

Summaries of protocol deviations overall and leading to exclusion form PPS are given in Text Table 10-2 and Text Table 10-3.

Text Table 10-2: Summary of protocol deviations [FAS]

Category	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Any Protocol Deviation	9 (27.3)	6 (17.6)	11 (27.5)	8 (25.8)	34 (24.6)
- Informed Consent	0 (0.0)	3 (8.8)	4 (10.0)	1 (3.2)	8 (5.8)
- Inclusion / Exclusion Criteria And Eligibility Status	6 (18.2)	2 (5.9)	1 (2.5)	4 (12.9)	13 (9.4)
- Randomization Procedures / Emergency Envelopes / Unblinding	3 (9.1)	1 (2.9)	2 (5.0)	1 (3.2)	7 (5.1)
- Administration Of Prohibited Concomitant Medication / Therapy	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (0.7)
- Handling And Application Of Ip	4 (12.1)	0 (0.0)	3 (7.5)	1 (3.2)	8 (5.8)
- Laboratory Assessments	0 (0.0)	0 (0.0)	2 (5.0)	0 (0.0)	2 (1.4)
- Study Related Assessments And Questionnaires / Diaries	2 (6.1)	0 (0.0)	0 (0.0)	1 (3.2)	3 (2.2)
- Visit Schedule/Interval	1 (3.0)	1 (2.9)	1 (2.5)	1 (3.2)	4 (2.9)

N=number of patients in the subgroup considered or in total; (%)=percentages are based on N;
Source: Table 14.1.2.1. Listing(s): Derived from Listings 16.2.2.1

In total 34 patients (24.6% of patients) had at least one major PD. Most common were deviations from inclusion/exclusion criteria (9.4% of patients), followed by deviations from the informed consent procedures and deviations concerning the handling and application of the IMP (in 5.8% of all patients, each).

Text Table 10-3: Summary of protocol deviations: Reason for exclusion from PPS

Category	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Any Protocol Deviation	8 (24.2)	4 (11.8)	5 (12.5)	5 (16.1)	22 (15.9)
- Inclusion / Exclusion Criteria And Eligibility Status	6 (18.2)	2 (5.9)	1 (2.5)	4 (12.9)	13 (9.4)
- Randomization Procedures / Emergency Envelopes / Unblinding	0 (0.0)	1 (2.9)	1 (2.5)	0 (0.0)	2 (1.4)
- Administration Of Prohibited Concomitant Medication / Therapy	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (0.7)
- Handling And Application Of Ip	3 (9.1)	0 (0.0)	3 (7.5)	1 (3.2)	7 (5.1)
- Study Related Assessments And Questionnaires / Diaries	2 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)
- Visit Schedule/Interval	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (0.7)
N=number of patients in the subgroup considered or in total; (%)=percentages are based on N; Source: Table 14.1.2.2. Listing(s): Derived from Listings 16.2.2.1					

Twenty-six of the major PDs in overall 22 patients (15.9%) were considered to have an impact on the efficacy analysis and thus led to exclusion of respective patients from the PPS. More patients in the 20 µg group (8 patients, 24.2%) were excluded from PPS than in the other treatment groups.

Further details on major protocol deviations broken down by categories of PDs are given in section 10.2.2).

10.2.2 Display of Major Protocol Deviations

Details on major PDs on patient level are provided with Listing 16.2.2.1.

10.2.2.1 Informed consent

All PDs (in 8 patients [5.8%]; for individual patients concerned, refer to Listing 16.2.2.1) concerning the informed consent procedures (like signing an incorrect version of the ICF) were judged as being major PDs from GCP perspective, but none of these PDs was regarded as having an impact on the analysis of the efficacy. Correspondingly no patient was excluded from the PPS due to a deviation from the informed consent procedure.

10.2.2.2 Inclusion/Exclusion Criteria

At least one inclusion or exclusion criterion was violated in a total of 13 patients (9.4%). As an impact on the efficacy outcomes cannot be ruled out, all patients with a violation of the inclusion or exclusion criteria were excluded from the PPS.

Most frequently inclusion criterion #2 was violated (in 9 of all patients, 6.5%; for individual patients concerned, refer to Listing 16.2.2.1), i.e. that sum score of individual items #1 to #7 of the OLPSSM did not reach a value of at least 5 on at least 4 days (consecutive or not consecutive) during the last week prior to Baseline/Randomization Visit. This was mainly due to technical difficulties with the eDiary, that was used at the beginning of the study.

Correspondingly patients were not able to document the OLPSSM scores as per protocol and consequently, IC#2 was finally not verifiable via the eDiary entries.

10.2.2.3 Randomization Procedures

Overall, 7 patients (5.1%) had a major PD related to the randomization procedure. Five of these PDs (wrong stratification, randomization prior to baseline) were rated as major from GCP perspective, but judged as having no impact on the efficacy analysis and hence none of these patients were excluded from the PPS due to this type of major PD.

Two patients received IMP kits from different treatment groups during the study (due to an error within the IWR System used for randomization and treatment kit allocation) and were thus excluded from the PPS.

10.2.2.4 Prohibited Medication

One single patient had a major PD related to the administration of prohibited concomitant medication and was excluded from the PPS.

10.2.2.5 Handling and Application of IMP

Overall, there were 8 patients (5.8%) with a major PD related to handling and application of the IMP. Seven of these PDs were judged to have an impact on the efficacy analysis (treatment compliance below 70%, wrong treatment kit dispensed) and led to the exclusion of 7 patients from the PPS.

One more patient received an additional treatment kit at date of Visit 6, i.e. at date of the regular end of treatment. Since this violation formally occurred in the follow-up period it had no impact on pre-planned efficacy analyses. Correspondingly this protocol deviation did not lead to an exclusion from the PPS.

10.2.2.6 Laboratory Assessments

Only 2 PDs in 2 patients related to laboratory assessments were judged as being major PDs from GCP perspective, as sites missed to perform a safety measurement (pregnancy test) at patient's early termination visit (=Visit 6). An impact on the efficacy analysis was not assumed, thus none of both patients was excluded from the PPS due to this major PD.

10.2.2.7 Study related Assessments/Diaries and Questionnaires

Overall major PDs related to study assessments were detected in 3 patients. PDs of two patients were regarded as having an impact on the efficacy analysis (no OLPClinROM available) and thus led to exclusion of respective patients from the PPS.

For one more patient no patient reported data were stored in the eDiary due to technical problems with the eDiary, thus that IC#2 was finally not verifiable (see section 10.2.2.2, also). This patient was not excluded from the PPS.

10.2.2.8 Visit Schedule/Interval

Four PDs detected in a total of 4 patients) were rated as being major PDs, but only one PD was judged to have an impact on the efficacy analysis. In this patient the distance between the screening visit and baseline visit was 40 days and data regarding the OLPSSM necessary for

verification of IC#2 were only collected from day -40 to day -27, such that the status of OLP based on the OLPSSM was finally not verifiable at Baseline (see section 10.2.2.2, also).

10.3 Data Sets Analyzed

The composition of the statistical analysis sets by treatment group is presented in Text Table 10-1. Individual allocation of patients to statistical analysis sets is provided in Listing 16.2.3.1.

Based on the rating of the protocol deviations during the BDRM, each patient was assigned to the corresponding analysis population.

The safety analysis was performed on 138 patients treated with at least one dose of study medication and presenting at least one follow-up value for safety analysis. None of the patients randomized was to be excluded from the safety analysis set.

The FAS population also consists of 138 patients and was used for evaluation of all efficacy and feasibility data. The FAS population was also used for exploratory analyses.

Patients in the FAS were analyzed according to the randomized treatment assigned and patients in the Safety Set according to the treatment dispensed at Visit 2.Thereof 2 patients from the 1µg group and 1 patient from the 5µg group received other treatments than the originally assigned ones (1 µg group: 400002: 20 µg patches from V3 onwards until patients individual end of treatment and 406003: 20 µg patches between V3 and V4; 5µg group: 400001: 1µg patches from V3 onwards until patients individual end of treatment).

The PP analysis was performed on 116 patients. A total of 22 patients (15.9% of all randomized patients) were excluded from the PPS due to the occurrence of at least one major protocol deviation as described in detail in section 10.2. A summary of the reasons leading to exclusion from the PP analysis set is presented in Text Table 10-3.

10.4 Demographics and Other Baseline Characteristics

10.4.1 Demographic Characteristics

Demographics and baseline characteristics are summarized by treatment group and for the total safety population in Text Table 10-4. Individual patient data are provided in Listing 16.2.4.1. Demography and baseline characteristics for each stratum (1-3 patches and 4-6 patches, respectively) and for the per-protocol population are summarized in Table 14.1.3.1 b, Table 14.1.3.1 c and Table 14.1.3.1 d.

Text Table 10-4: Summary of demographics and baseline characteristics – Safety Set

		20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N = 138
Stratum	1-3 Patches	22 (66.7)	19 (55.9)	23 (57.5)	20 (64.5)	84 (60.9)
	4-6 Patches	11 (33.3)	15 (44.1)	17 (42.5)	11 (35.5)	54 (39.1)

Text Table 10-4: Summary of demographics and baseline characteristics – Safety Set

		20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N = 138
Country	Canada	8 (24.2)	7 (20.6)	7 (17.5)	7 (22.6)	29 (21.0)
	Germany	1 (3.0)	1 (2.9)	2 (5.0)	2 (6.5)	6 (4.3)
	Denmark	3 (9.1)	3 (8.8)	5 (12.5)	3 (9.7)	14 (10.1)
	Great Britain	7 (21.2)	7 (20.6)	6 (15.0)	7 (22.6)	27 (19.6)
	Ireland	3 (9.1)	2 (5.9)	3 (7.5)	2 (6.5)	10 (7.2)
	USA	11 (33.3)	14 (41.2)	17 (42.5)	10 (32.3)	52 (37.7)
Age (yrs)	Mean	58.6	59.7	62.2	63.9	61.1
	SD	11.8	10.5	12.1	11.5	11.6
	Median	60.0	61.0	63.0	66.0	61.0
	Range	33-77	37-75	19-89	30-81	19-89
Sex	Male	9 (27.3)	13 (38.2)	12 (30.0)	5 (16.1)	39 (28.3)
	Female	24 (72.7)	21 (61.8)	28 (70.0)	26 (83.9)	99 (71.7)
Race	White	26 (78.8)	32 (94.1)	36 (90.0)	29 (93.5)	123 (89.1)
	Black	1 (3.0)	0	2 (5.0)	1 (3.2)	4 (2.9)
	Asian	4 (12.1)	1 (2.9)	2 (5.0)	1 (3.2)	8 (5.8)
	American Indian or Alaska	0	1 (2.9)	0	0	1 (0.7)
	Other	2 (6.1)	0	0	0	2 (1.4)
Ethnic origin	Hispanic or Latino	3 (9.1)	4 (11.8)	5 (12.5)	4 (12.9)	16 (11.6)
	Not hispanic or Latino	30 (90.9)	30 (88.2)	35 (87.5)	27 (87.1)	122 (88.4)
Weight (kg)	Mean	83.6	85.1	81.6	80.2	82.6
	SD	19.4	21.0	17.9	23.3	20.2
	Median	82.7	81.4	81.6	76.0	79.7
	Range	51-129	60-154	49-136	39-130	39-154
Height (cm)	Mean	163.7	169.3	167.4	162.8	165.9
	SD	9.3	10.4	10.2	14.4	11.4
	Median	162.0	167.8	165.0	162.0	164.8
	Range	145-190	153-187	141-188	105-188	105-190
BMI (kg/m^2)	Mean	31.2	29.6	29.0	30.0	29.9
	SD	6.9	6.0	5.3	7.6	6.4
	Median	30.3	27.7	28.3	28.5	28.7

Text Table 10-4: Summary of demographics and baseline characteristics – Safety Set

		20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N = 138
	Range	18.7-46.9	18.9-48.2	17.8-42.3	21.2-50.9	17.8-50.9
Alcohol habits	Never	7 (21.2)	6 (17.6)	8 (20.0)	9 (29.0)	30 (21.7)
	Rare (seldom)	9 (27.3)	7 (20.6)	16 (40.0)	8 (25.8)	40 (29.0)
	Occasional	16 (48.5)	9 (26.5)	11 (27.5)	11 (35.5)	47 (34.1)
	Often	1 (3.0)	12 (35.3)	5 (12.5)	3 (9.7)	21 (15.2)
Smoking status	Never smoked	17 (51.5)	17 (50.0)	27 (67.5)	19 (61.3)	80 (58.0)
	Habitual	2 (6.1)	1 (2.9)	0	1 (3.2)	4 (2.9)
	Occasional	1 (3.0)	0	1 (2.5)	1 (3.2)	3 (2.2)
	Ex-smoker	13 (39.4)	16 (47.1)	12 (30.0)	10 (32.3)	51 (37.0)
Reproduc. status	No	20 (83.3)	20 (95.2)	26 (92.9)	26 (100.0)	92 (92.9)
	Yes	4 (16.7)	1 (4.8)	2 (7.1)	0 (0.0)	7 (7.1)
Time since first diagnosis	Mean	3.9	4.9	4.7	3.7	4.3
	SD	4.7	9.3	6.5	6.1	6.8
	Median	2.0	1.8	1.5	1.5	1.9
	Range	0.0-16.7	0.0-50.1	0.0-24.7	0.0-25.5	0.0-50.1
Previous OLP treatment last 12 months	No	8 (24.2)	11 (32.4)	12 (30.0)	7 (22.6)	38 (27.5)
	Yes	25 (75.8)	23 (67.6)	27 (67.5)	24 (77.4)	99 (71.7)
	Missing	0	0	1 (2.5)	0	1 (0.7)
Extra-oral manifestations of LP	No	27 (81.8)	29 (85.3)	35 (87.5)	24 (77.4)	115 (83.3)
	Yes	6 (18.2)	5 (14.7)	5 (12.5)	7 (22.6)	23 (16.7)

N=number of patients in the subgroup considered or in total; n=number of patients among N; (%)=percentages are based on N; SD=Standard Deviation; BMI=Body mass index

Source: Table 14.1.3.1 a; Listing(s): Derived from Listing 16.2.4.1

Overall treatment groups were comparable, but some differences can be noted:

Patients in the placebo group were on average older (63.9 years) than patients in the 20µg group (58.6 years). There were relatively more females in the placebo group (83.9%) than in the 5µg group (61.8%). White patients were relatively fewer in the 20µg group (78.8%) compared to the 5µg group (94.1%) and never-smokers were more frequent in the 1µg group (67.5%) than in the 5µg group (50.0%).

10.4.2 OLP-related Baseline Characteristics

By protocol amendment 03, resulting in protocol version final 6.0, dated 07-Sep-2018 biopsies to confirm the (O)LP diagnosis were introduced in the study.

120 out of the 138 randomized patients were enrolled with protocol version 6.0 in force and therefore needed (O)LP biopsy confirmation (were in scope for biopsies). Data on biopsy collection are provided in Text Table 10-5. Individual patient data on biopsies are provided in Listing 16.2.4.2.

Text Table 10-5: Summary of Biopsy Data: Study inclusion – Safety Set

Category	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
In scope for biopsy[a]		27	31	35	27	120
Hist. conf. in the past	Yes	23 (85.2)	22 (71.0)	28 (80.0)	23 (85.2)	96 (80.0)
	No	4 (14.8)	9 (29.0)	7 (20.0)	4 (14.8)	24 (20.0)
Biopsy type	Existing Biopsy	23 (85.2)	22 (71.0)	28 (80.0)	23 (85.2)	96 (80.0)
	Study Biopsy	4 (14.8)	9 (29.0)	7 (20.0)	4 (14.8)	24 (20.0)
Confirmatory of OLP inflammation	Yes	26 (96.3)	31 (100)	35 (100)	27 (100)	119 (99.2)
	No	1 (3.7)	0	0	0	1 (0.8)
Existing biopsy loc.	Oral Lesion	21 (91.3)	22 (100)	28 (100)	22 (95.7)	93 (96.9)
	Cutaneous Lesion	2 (8.7)	0	0	0	2 (2.1)
	Vaginal Lesion	0	0	0	1 (4.3)	1 (1.0)
Study biopsy loc.	Oral Lesion	4 (100)	9 (100)	6 (85.7)	4 (100)	23 (95.8)
	Cutaneous Lesion	0	0	1 (14.3)	0	1 (4.2)
-Complete healing	Yes	4 (100)	9 (100)	7 (100)	4 (100)	24 (100)
-Complete pain relief	Yes	4 (100)	9 (100)	7 (100)	4 (100)	24 (100)
-Study biopsy lesion	Erythematous /White Lesion (Without Ulceration)	1 (25.0)	0	2 (33.3)	0	3 (13.0)
	Ulcerative Lesion	3 (75.0)	9 (100)	3 (50.0)	4 (100)	19 (82.6)
	Missing	0	0	1 (16.7)	0	1 (4.3)

Text Table 10-5: Summary of Biopsy Data: Study inclusion – Safety Set

Category	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
-Oral biopsy location	Lower Labial Mucosa	0	1 (11.1)	0	0	1 (4.3)
	Right Buccal Mucosa	1 (25.0)	4 (44.4)	3 (50.0)	2 (50.0)	10 (43.5)
	Left Buccal Mucosa	1 (25.0)	2 (22.2)	3 (50.0)	1 (25.0)	7 (30.4)
	Gingivae: Lower Right (Distal)	0	0	0	1 (25.0)	1 (4.3)
	Gingivae: Lower Left (Distal)	0	1 (11.1)	0	0	1 (4.3)
	Gingivae: Upper Left (Distal)	2 (50.0)	0	0	0	2 (8.7)
	Right Lateral Ventral Tongue	0	1 (11.1)	0	0	1 (4.3)
	Not Applicable	0	0	1 (16.7)	0	1 (4.3)

N=number of patients in the subgroup considered or in total; n=number of patients in scope for biopsy; (%)=percentages are based on patients in scope for biopsy
a: included as an additional inclusion criterion with Amendment 03 (protocol version 6.0, dated 07-Sep-2018)
Source: Table 14.1.3.4; Listing(s): Derived from Listing 16.2.4.2

Of 120 patients in scope for histological confirmation of (O)LP, 96 patients (80%) already had a biopsy taken in the past and a study biopsy at Visit 0 was only taken in 24 patients (20%). Except in one case (patient 201004 from the 20µg group), biopsies were confirmative for OLP.

A wide majority of biopsies were taken from oral lesions and only very few biopsies (less than 5%) were taken from extraoral lesions. All 24 patients with study biopsies had complete healing and pain relief before entering the run-in period (Visit 1).

The locations of oral anatomical sites containing at least one symptomatic OLP lesion at Screening (Visit 1) and/or Baseline (Visit 2) are summarized in Text Table 10-6. Types of lesions are summarized in Text Table 10-7. Individual patient data are given in Listing 16.2.4.3.

Text Table 10-6: Summary of lesion characteristics at screening/baseline: Locations assessed at Visit 1 and Visit 2 – Safety Set

Location	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Upper Labial Mucosa	1 (3.0)	0	0	1 (3.2)	2 (1.4)
Lower Labial Mucosa	2 (6.1)	2 (5.9)	4 (10.0)	3 (9.7)	11 (8.0)
Right Buccal Mucosa	19 (57.6)	16 (47.1)	23 (57.5)	15 (48.4)	73 (52.9)
Left Buccal Mucosa	16 (48.5)	19 (55.9)	27 (67.5)	20 (64.5)	82 (59.4)
Gingivae: Lower Right (distal)	8 (24.2)	9 (26.5)	6 (15.0)	9 (29.0)	32 (23.2)
Gingivae: Lower Central	1 (3.0)	3 (8.8)	4 (10.0)	4 (12.9)	12 (8.7)
Gingivae: Lower Left (distal)	4 (12.1)	11 (32.4)	3 (7.5)	7 (22.6)	25 (18.1)
Gingivae: Upper Right (distal)	5 (15.2)	4 (11.8)	4 (10.0)	6 (19.4)	19 (13.8)
Gingivae: Upper Central	1 (3.0)	1 (2.9)	7 (17.5)	7 (22.6)	16 (11.6)
Gingivae: Upper Left (distal)	3 (9.1)	4 (11.8)	5 (12.5)	9 (29.0)	21 (15.2)
Mandibular Lingual Gingivae: Lower Right (distal)	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Central	1 (3.0)	0	0	0	1 (0.7)
Mandibular Lingual Gingivae: Lower Left (distal)	0	0	0	1 (3.2)	1 (0.7)
Dorsum Tongue	2 (6.1)	0	3 (7.5)	5 (16.1)	10 (7.2)
Right Lateral Ventral Tongue	3 (9.1)	8 (23.5)	6 (15.0)	0	17 (12.3)
Left Lateral Ventral Tongue	3 (9.1)	3 (8.8)	8 (20.0)	3 (9.7)	17 (12.3)
Floor of Mouth	0	0	0	0	0
Hard Palate	2 (6.1)	3 (8.8)	1 (2.5)	1 (3.2)	7 (5.1)
Soft Palate	0	0	0	0	0

Numbers are n (%); location counted once within patient
Source: Table 14.1.3.5 a; Listing(s): Derived from Listing 16.2.4.3

Text Table 10-7: Summary of lesion characteristics at screening/baseline: Total number and type of lesions by location, lesions assessed at Visit 1 and Visit 2 – Safety Set

Location	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
All sites	78/45/33	89/60/29	109/82/27	96/54/42	372/241/131
Upper Labial Mucosa	1/1/0	0	0	1/0/1	2/1/1
Lower Labial Mucosa	2/2/0	3/1/2	4/2/2	3/1/2	12/6/6
Right Buccal Mucosa	23/14/9	17/14/3	24/15/9	15/11/4	79/54/25
Left Buccal Mucosa	18/11/7	22/20/2	29/25/4	20/16/4	89/72/17
Gingivae: Lower Right (distal)	8/5/3	9/6/3	7/7/0	9/4/5	33/22/11
Gingivae: Lower Central	1/1/0	3/2/1	4/2/2	4/2/2	12/7/5
Gingivae: Lower Left (distal)	4/2/2	11/6/5	3/2/1	7/2/5	25/12/13
Gingivae: Upper Right (distal)	5/3/2	4/1/3	4/3/1	6/2/4	19/9/10
Gingivae: Upper Central	1/0/1	1/0/1	9/6/3	11/3/8	22/9/13
Gingivae: Upper Left (distal)	3/1/2	4/2/2	5/3/2	9/4/5	21/10/11
Mandibular Lingual Gingivae: Lower Right (distal)	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Central	1/0/1	0	0	0	1/0/1
Mandibular Lingual Gingivae: Lower Left (distal)	0	0	0	1/0/1	1/0/1
Dorsum Tongue	3/2/1	0	5/3/2	6/5/1	14/10/4
Right Lateral Ventral Tongue	3/2/1	8/5/3	6/6/0	0	17/13/4
Left Lateral Ventral Tongue	3/1/2	3/1/2	8/7/1	3/3/0	17/12/5
Floor of Mouth	0	0	0	0	0
Hard Palate	2/0/2	4/2/2	1/1/0	1/1/0	8/4/4
Soft Palate	0	0	0	0	0

Numbers are Total lesions/Ulcerative/Erythematous
Source: Table 14.1.3.5 b. Listing(s): Derived from Listing 16.2.4.3

OLP lesions identified at Visit 1 or Visit 2 and which were still symptomatic at Visit 2 (Baseline) were selected for patch treatment and formed the basis for the efficacy assessments during the study.

Most frequent anatomical sites presenting at least one symptomatic OLP lesion were left and right buccal mucosa in overall 59.4% and 52.9% of patients, respectively.

In total 372 symptomatic OLP lesions were identified, of these 241 lesions (64.8%) were ulcerative and 131 lesions (35.2%) were erythematous, only. Regarding the most prominent anatomical sites affected 89 (23.9%) OLP lesions were present at left buccal mucosa and 79 (21.2%) at right buccal mucosa. Thereof a majority of 80.9% and 68.4% were ulcerative.

Details on lesion locations and pattern in the different strata are summaries in Table 14.1.3.5 c to f. For details on lesions having developed during study course (Visit 3 to Visit 7), refer to Table 14.2.1.10 .

A summary of number of patches applied at Screening (Visit 1) and/or Baseline (Visit 2) by treatment group is presented in Text Table 10-8.

Text Table 10-8: Summary of lesion characteristics at screening/baseline: summary of number of patches assigned to be used at Visit 2 and patients with changes over study period – Safety Set

	no. patched applied						patients with	
Treatment	**1**	**2**	**3**	**4**	**5**	**6**	**reduction**	**increase**
20 ug	5 (15.2)	13 (39.4)	4 (12.1)	4 (12.1)	6 (18.2)	1 (3.0)	2 (6.1)	7 (21.2)
5 ug	7 (20.6)	10 (29.4)	2 (5.9)	8 (23.5)	1 (2.9)	6 (17.6)	2 (5.9)	7 (20.6)
1 ug	4 (10.0)	11 (27.5)	8 (20.0)	7 (17.5)	5 (12.5)	5 (12.5)	3 (7.5)	8 (20.0)
Placebo	3 (9.7)	9 (29.0)	8 (25.8)	2 (6.5)	6 (19.4)	3 (9.7)	3 (9.7)	6 (19.4)
Total	19 (13.8)	43 (31.2)	22 (15.9)	21 (15.2)	18 (13.0)	15 (10.9)	10 (7.2)	28 (20.3)
Source: Table 14.1.3.5 g. Listing(s): Derived from Listing 16.2.5.1								

Among all treatment groups, the highest percentage of patients (about 30-40%) used 2 patches at Baseline. Second highest percentage of patients applied 5 patches in the 20µg group, 4 patches in the 5µg group and 3 patches in the 1µg and placebo groups.

Number of patches was kept stable during study course for most patients. Increases in patch numbers were seen for about 20% of patients in all treatment groups, reductions were seen in about 6-10% of patients among treatment groups, with the highest percentage (9.7%) in the placebo group.

10.4.3 Medical History and Concomitant Diseases

Patient's medical history (including prior and concomitant diseases, as well as patient's surgical history) is summarized in Text Table 10-9 by System Organ Class (SOC) coded using the Medical Dictionary for Regulatory Activities (MedDRA) Individual patient data are provided in Listing 16.2.4.3.

Text Table 10-9: Summary of Medical History by MedDRA SOC/PT– Safety Set

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
ANY MEDICAL HISTORY	31 (94)	28 (82)	36 (90)	29 (94)	124 (90)
VASCULAR DISORDERS	16 (48)	12 (35)	17 (43)	15 (48)	60 (43)
- HYPERTENSION	16 (48)	11 (32)	17 (43)	13 (42)	57 (41)
- AORTIC ARTERIOSCLEROSIS	0	0	1 (3)	0	1 (1)
- DEEP VEIN THROMBOSIS	0	0	0	1 (3)	1 (1)
- DIABETIC VASCULAR DISORDER	0	0	1 (3)	0	1 (1)
- ESSENTIAL HYPERTENSION	0	0	0	1 (3)	1 (1)
- HOT FLUSH	0	1 (3)	0	0	1 (1)
- PERIPHERAL VASCULAR DISORDER	0	0	1 (3)	0	1 (1)
- VARICOSE VEIN	0	0	0	1 (3)	1 (1)
METABOLISM AND NUTRITION DISORDERS	14 (42)	14 (41)	14 (35)	10 (32)	52 (38)
- OBESITY	4 (12)	6 (18)	5 (13)	3 (10)	18 (13)
- TYPE 2 DIABETES MELLITUS	6 (18)	3 (9)	5 (13)	2 (6)	16 (12)
- HYPERCHOLESTEROLAEMIA	3 (9)	1 (3)	3 (8)	3 (10)	10 (7)
- HYPERLIPIDAEMIA	0	5 (15)	4 (10)	1 (3)	10 (7)
- DIABETES MELLITUS	1 (3)	1 (3)	3 (8)	3 (10)	8 (6)
- VITAMIN D DEFICIENCY	1 (3)	1 (3)	2 (5)	0	4 (3)
- DYSLIPIDAEMIA	0	0	2 (5)	1 (3)	3 (2)
- TYPE 1 DIABETES MELLITUS	0	2 (6)	0	0	2 (1)
- VITAMIN B12 DEFICIENCY	0	1 (3)	0	1 (3)	2 (1)
- FLUID RETENTION	0	1 (3)	0	0	1 (1)
- GLUCOSE TOLERANCE IMPAIRED	0	0	1 (3)	0	1 (1)
- GOUT	0	0	0	1 (3)	1 (1)
- HYPERGLYCAEMIA	1 (3)	0	0	0	1 (1)
- IRON DEFICIENCY	1 (3)	0	0	0	1 (1)
- OVERWEIGHT	0	1 (3)	0	0	1 (1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	7 (21)	15 (44)	15 (38)	10 (32)	47 (34)
- ARTHRITIS	4 (12)	5 (15)	3 (8)	2 (6)	14 (10)
- OSTEOPOROSIS	0	3 (9)	4 (10)	1 (3)	8 (6)
- OSTEOARTHRITIS	0	2 (6)	4 (10)	1 (3)	7 (5)
- ARTHRALGIA	0	3 (9)	0	1 (3)	4 (3)
- OSTEOPENIA	0	0	3 (8)	1 (3)	4 (3)

Text Table 10-9: Summary of Medical History by MedDRA SOC/PT– Safety Set

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- BACK PAIN	1 (3)	1 (3)	1 (3)	0	3 (2)
- FIBROMYALGIA	0	0	1 (3)	2 (6)	3 (2)
- SJOGREN'S SYNDROME	1 (3)	0	2 (5)	0	3 (2)
- INTERVERTEBRAL DISC DEGENERATION	1 (3)	0	1 (3)	0	2 (1)
- PLANTAR FASCIITIS	1 (3)	0	1 (3)	0	2 (1)
- ROTATOR CUFF SYNDROME	0	1 (3)	0	1 (3)	2 (1)
- DIABETIC ARTHROPATHY	0	1 (3)	0	0	1 (1)
- LUMBAR SPINAL STENOSIS	0	0	1 (3)	0	1 (1)
- MORPHOEA	0	1 (3)	0	0	1 (1)
- MUSCLE SPASMS	0	0	0	1 (3)	1 (1)
- MYALGIA	1 (3)	0	0	0	1 (1)
- NECK PAIN	0	1 (3)	0	0	1 (1)
- PAIN IN EXTREMITY	0	1 (3)	0	0	1 (1)
- POLYARTHRITIS	0	0	1 (3)	0	1 (1)
- POLYMYALGIA RHEUMATICA	0	0	1 (3)	0	1 (1)
- PSORIATIC ARTHROPATHY	1 (3)	0	0	0	1 (1)
- SPINAL COLUMN STENOSIS	0	1 (3)	0	0	1 (1)
- SPINAL DEFORMITY	0	1 (3)	0	0	1 (1)
- SPINAL OSTEOARTHRITIS	0	0	1 (3)	0	1 (1)
- SYNOVIAL CYST	0	0	1 (3)	0	1 (1)
- SYSTEMIC LUPUS ERYTHEMATOSUS	0	0	1 (3)	0	1 (1)
- TENDONITIS	1 (3)	0	0	0	1 (1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	11 (33)	10 (29)	10 (25)	10 (32)	41 (30)
- LICHEN PLANUS	5 (15)	2 (6)	2 (5)	4 (13)	13 (9)
- LICHEN SCLEROSUS	2 (6)	4 (12)	4 (10)	3 (10)	13 (9)
- PSORIASIS	2 (6)	1 (3)	3 (8)	3 (10)	9 (7)
- ECZEMA	2 (6)	0	1 (3)	1 (3)	4 (3)
- DRY SKIN	0	0	1 (3)	1 (3)	2 (1)
- ACNE	1 (3)	0	0	0	1 (1)
- ACTINIC KERATOSIS	0	1 (3)	0	0	1 (1)
- GRANULOMA ANNULARE	0	1 (3)	0	0	1 (1)
- PRURITUS	0	1 (3)	0	0	1 (1)

Text Table 10-9: Summary of Medical History by MedDRA SOC/PT– Safety Set

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- URTICARIA	1 (3)	0	0	0	1 (1)
- VITILIGO	0	1 (3)	0	0	1 (1)
GASTROINTESTINAL DISORDERS	8 (24)	7 (21)	18 (45)	7 (23)	40 (29)
- GASTROOESOPHAGEAL REFLUX DISEASE	6 (18)	2 (6)	12 (30)	3 (10)	23 (17)
- CONSTIPATION	1 (3)	0	0	2 (6)	3 (2)
- GASTRITIS	1 (3)	1 (3)	1 (3)	0	3 (2)
- COELIAC DISEASE	0	1 (3)	0	1 (3)	2 (1)
- DRY MOUTH	0	1 (3)	0	1 (3)	2 (1)
- DYSPEPSIA	0	1 (3)	1 (3)	0	2 (1)
- OESOPHAGITIS	0	1 (3)	1 (3)	0	2 (1)
- APTYALISM	0	0	0	1 (3)	1 (1)
- CHRONIC GASTRITIS	0	0	1 (3)	0	1 (1)
- DIAPHRAGMATIC HERNIA	0	0	1 (3)	0	1 (1)
- DIARRHOEA	0	0	0	1 (3)	1 (1)
- DIVERTICULUM	0	0	0	1 (3)	1 (1)
- HIATUS HERNIA	0	0	1 (3)	0	1 (1)
- IMPAIRED GASTRIC EMPTYING	0	1 (3)	0	0	1 (1)
- IRRITABLE BOWEL SYNDROME	0	0	1 (3)	0	1 (1)
- LARGE INTESTINE POLYP	0	0	1 (3)	0	1 (1)
- PERIODONTAL DISEASE	0	0	1 (3)	0	1 (1)
- RECTAL PROLAPSE	0	1 (3)	0	0	1 (1)
- UPPER GASTROINTESTINAL HAEMORRHAGE	1 (3)	0	0	0	1 (1)
SURGICAL AND MEDICAL PROCEDURES	8 (24)	8 (24)	12 (30)	7 (23)	35 (25)
- HYSTERECTOMY	2 (6)	3 (9)	6 (15)	1 (3)	12 (9)
- CAESAREAN SECTION	1 (3)	0	2 (5)	1 (3)	4 (3)
- CHOLECYSTECTOMY	1 (3)	1 (3)	1 (3)	1 (3)	4 (3)
- INTERVERTEBRAL DISC OPERATION	1 (3)	1 (3)	1 (3)	0	3 (2)
- KNEE OPERATION	1 (3)	1 (3)	1 (3)	0	3 (2)
- APPENDICECTOMY	0	0	1 (3)	1 (3)	2 (1)
- HERNIA REPAIR	1 (3)	0	1 (3)	0	2 (1)
- KNEE ARTHROPLASTY	1 (3)	1 (3)	0	0	2 (1)
- TONSILLECTOMY	0	0	1 (3)	1 (3)	2 (1)

Text Table 10-9: Summary of Medical History by MedDRA SOC/PT– Safety Set

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- WRIST SURGERY	1 (3)	0	1 (3)	0	2 (1)
- ANGIOPLASTY	0	0	0	1 (3)	1 (1)
- BONE LESION EXCISION	0	1 (3)	0	0	1 (1)
- BONE OPERATION	1 (3)	0	0	0	1 (1)
- BUNION OPERATION	1 (3)	0	0	0	1 (1)
- CANCER SURGERY	0	1 (3)	0	0	1 (1)
- CORONARY ARTERIAL STENT INSERTION	0	1 (3)	0	0	1 (1)
- CORONARY ARTERY BYPASS	0	0	1 (3)	0	1 (1)
- FEMALE STERILISATION	1 (3)	0	0	0	1 (1)
- GINGIVAL GRAFT	1 (3)	0	0	0	1 (1)
- HAEMORRHOID OPERATION	0	0	0	1 (3)	1 (1)
- HIP SURGERY	0	0	0	1 (3)	1 (1)
- HYSTEROSALPINGO-OOPHORECTOMY	1 (3)	0	0	0	1 (1)
- LIMB OPERATION	1 (3)	0	0	0	1 (1)
- LIPOMA EXCISION	0	1 (3)	0	0	1 (1)
- LITHOTRIPSY	0	1 (3)	0	0	1 (1)
- MAMMOPLASTY	0	1 (3)	0	0	1 (1)
- MEDICAL DEVICE IMPLANTATION	1 (3)	0	0	0	1 (1)
- NAIL OPERATION	1 (3)	0	0	0	1 (1)
- NASAL SEPTAL OPERATION	0	0	1 (3)	0	1 (1)
- PERINEAL OPERATION	0	0	1 (3)	0	1 (1)
- ROTATOR CUFF REPAIR	0	0	1 (3)	0	1 (1)
- SHOULDER OPERATION	1 (3)	0	0	0	1 (1)
- SPINAL LAMINECTOMY	0	1 (3)	0	0	1 (1)
- STENT PLACEMENT	1 (3)	0	0	0	1 (1)
- THYROIDECTOMY	0	0	0	1 (3)	1 (1)
- TOE OPERATION	1 (3)	0	0	0	1 (1)
- URETHRAL DILATION PROCEDURE	1 (3)	0	0	0	1 (1)
- WISDOM TEETH REMOVAL	1 (3)	0	0	0	1 (1)
ENDOCRINE DISORDERS	6 (18)	10 (29)	8 (20)	10 (32)	34 (25)
- HYPOTHYROIDISM	5 (15)	7 (21)	7 (18)	10 (32)	29 (21)
- HYPERTHYROIDISM	0	1 (3)	1 (3)	0	2 (1)
- THYROID DISORDER	0	2 (6)	0	0	2 (1)

Text Table 10-9: Summary of Medical History by MedDRA SOC/PT– Safety Set

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- AUTOIMMUNE THYROIDITIS	1 (3)	0	0	0	1 (1)
INVESTIGATIONS	8 (24)	7 (21)	11 (28)	5 (16)	31 (22)
- BLOOD CHOLESTEROL INCREASED	6 (18)	3 (9)	6 (15)	4 (13)	19 (14)
- BLOOD POTASSIUM DECREASED	1 (3)	0	2 (5)	0	3 (2)
- BLOOD TRIGLYCERIDES INCREASED	0	2 (6)	0	0	2 (1)
- COLONOSCOPY	0	1 (3)	1 (3)	0	2 (1)
- HEPATIC ENZYME INCREASED	1 (3)	1 (3)	0	0	2 (1)
- ARTHROSCOPY	0	0	1 (3)	0	1 (1)
- BIOPSY BREAST	0	0	1 (3)	0	1 (1)
- BLOOD ALKALINE PHOSPHATASE INCREASED	0	0	1 (3)	0	1 (1)
- BLOOD POTASSIUM INCREASED	1 (3)	0	0	0	1 (1)
- BLOOD URINE PRESENT	0	0	0	1 (3)	1 (1)
- BONE DENSITY ABNORMAL	0	0	1 (3)	0	1 (1)
- GLUCOSE URINE PRESENT	0	1 (3)	0	0	1 (1)
- HAEMOGLOBIN DECREASED	1 (3)	0	0	0	1 (1)
- OESOPHAGOGASTRODUODENOSCOPY	0	1 (3)	0	0	1 (1)
- PLATELET COUNT DECREASED	1 (3)	0	0	0	1 (1)
PSYCHIATRIC DISORDERS	5 (15)	8 (24)	8 (20)	6 (19)	27 (20)
- DEPRESSION	4 (12)	2 (6)	6 (15)	1 (3)	13 (9)
- ANXIETY	0	4 (12)	0	3 (10)	7 (5)
- INSOMNIA	1 (3)	2 (6)	0	1 (3)	4 (3)
- ANXIETY DISORDER	1 (3)	0	1 (3)	0	2 (1)
- ATTENTION DEFICIT/HYPERACTIVITY DISORDER	1 (3)	0	0	0	1 (1)
- MAJOR DEPRESSION	0	0	1 (3)	0	1 (1)
- MERYCISM	0	0	0	1 (3)	1 (1)
- PERSISTENT DEPRESSIVE DISORDER	0	1 (3)	0	0	1 (1)
- SLEEP DISORDER	0	0	1 (3)	0	1 (1)
NERVOUS SYSTEM DISORDERS	6 (18)	4 (12)	8 (20)	7 (23)	25 (18)
- MIGRAINE	1 (3)	0	3 (8)	2 (6)	6 (4)
- EPILEPSY	1 (3)	1 (3)	0	1 (3)	3 (2)
- HEADACHE	1 (3)	0	0	2 (6)	3 (2)
- NEUROPATHY PERIPHERAL	2 (6)	0	0	0	2 (1)

Text Table 10-9: Summary of Medical History by MedDRA SOC/PT– Safety Set

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- POLYNEUROPATHY	0	0	2 (5)	0	2 (1)
- SCIATICA	1 (3)	1 (3)	0	0	2 (1)
- AUTONOMIC NEUROPATHY	0	1 (3)	0	0	1 (1)
- CAROTID ARTERY DISEASE	0	0	1 (3)	0	1 (1)
- CAUDA EQUINA SYNDROME	0	1 (3)	0	0	1 (1)
- CEREBROVASCULAR ACCIDENT	0	0	1 (3)	0	1 (1)
- DIABETIC NEUROPATHY	0	0	1 (3)	0	1 (1)
- ORTHOSTATIC INTOLERANCE	0	1 (3)	0	0	1 (1)
- TENSION HEADACHE	0	0	0	1 (3)	1 (1)
- TRANSIENT ISCHAEMIC ATTACK	0	0	0	1 (3)	1 (1)
- VOCAL CORD PARALYSIS	0	0	1 (3)	0	1 (1)
- VOCAL CORD PARESIS	0	1 (3)	0	0	1 (1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (15)	8 (24)	8 (20)	4 (13)	25 (18)
- ASTHMA	2 (6)	4 (12)	6 (15)	4 (13)	16 (12)
- CHRONIC OBSTRUCTIVE PULMONARY DISEASE	1 (3)	1 (3)	2 (5)	0	4 (3)
- SLEEP APNOEA SYNDROME	2 (6)	1 (3)	0	0	3 (2)
- RHINITIS ALLERGIC	1 (3)	1 (3)	0	0	2 (1)
- COUGH	0	0	1 (3)	0	1 (1)
- NASAL CONGESTION	0	1 (3)	0	0	1 (1)
IMMUNE SYSTEM DISORDERS	7 (21)	3 (9)	8 (20)	6 (19)	24 (17)
- SEASONAL ALLERGY	6 (18)	2 (6)	7 (18)	5 (16)	20 (14)
- DRUG HYPERSENSITIVITY	1 (3)	1 (3)	1 (3)	1 (3)	4 (3)
- FOOD ALLERGY	0	1 (3)	0	0	1 (1)
- IODINE ALLERGY	0	0	1 (3)	0	1 (1)
CARDIAC DISORDERS	4 (12)	2 (6)	6 (15)	4 (13)	16 (12)
- MYOCARDIAL INFARCTION	2 (6)	0	2 (5)	1 (3)	5 (4)
- CORONARY ARTERY DISEASE	0	0	2 (5)	1 (3)	3 (2)
- ANGINA PECTORIS	2 (6)	0	0	0	2 (1)
- ATRIAL FIBRILLATION	1 (3)	0	0	1 (3)	2 (1)
- BUNDLE BRANCH BLOCK	0	1 (3)	0	0	1 (1)
- CARDIAC FAILURE CHRONIC	0	0	1 (3)	0	1 (1)
- CARDIOVASCULAR DISORDER	0	0	1 (3)	0	1 (1)

Text Table 10-9: Summary of Medical History by MedDRA SOC/PT– Safety Set

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- PAROXYSMAL ARRHYTHMIA	0	0	0	1 (3)	1 (1)
- PERICARDITIS	0	0	0	1 (3)	1 (1)
- SINUS TACHYCARDIA	0	1 (3)	0	0	1 (1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (6)	4 (12)	4 (10)	6 (19)	16 (12)
- VULVOVAGINAL DRYNESS	0	2 (6)	1 (3)	1 (3)	4 (3)
- BENIGN PROSTATIC HYPERPLASIA	0	0	1 (3)	2 (6)	3 (2)
- ENDOMETRIOSIS	0	0	1 (3)	1 (3)	2 (1)
- BREAST MASS	0	0	1 (3)	0	1 (1)
- ERECTILE DYSFUNCTION	0	1 (3)	0	0	1 (1)
- GENITAL DISCOMFORT	0	0	0	1 (3)	1 (1)
- HAEMATOSALPINX	1 (3)	0	0	0	1 (1)
- MENOPAUSAL SYMPTOMS	0	0	0	1 (3)	1 (1)
- PROSTATOMEGALY	0	1 (3)	0	0	1 (1)
- VAGINAL EROSION	1 (3)	0	0	0	1 (1)
EYE DISORDERS	4 (12)	1 (3)	3 (8)	4 (13)	12 (9)
- DRY EYE	0	0	2 (5)	2 (6)	4 (3)
- GLAUCOMA	1 (3)	0	1 (3)	0	2 (1)
- BLEPHARITIS	0	1 (3)	0	0	1 (1)
- MACULAR DEGENERATION	1 (3)	0	0	0	1 (1)
- MYOPIA	1 (3)	0	0	0	1 (1)
- NORMAL TENSION GLAUCOMA	0	0	0	1 (3)	1 (1)
- OPTIC NEUROPATHY	1 (3)	0	0	0	1 (1)
- RETINAL DETACHMENT	0	0	0	1 (3)	1 (1)
- RETINAL DISORDER	0	0	1 (3)	0	1 (1)
INFECTIONS AND INFESTATIONS	3 (9)	2 (6)	3 (8)	1 (3)	9 (7)
- ORAL CANDIDIASIS	1 (3)	0	1 (3)	0	2 (1)
- ORAL HERPES	1 (3)	1 (3)	0	0	2 (1)
- GENITAL HERPES	0	1 (3)	0	0	1 (1)
- HEPATITIS A	0	0	1 (3)	0	1 (1)
- HEPATITIS C	0	0	1 (3)	0	1 (1)
- ONYCHOMYCOSIS	0	0	1 (3)	0	1 (1)
- PERIODONTITIS	0	0	0	1 (3)	1 (1)

Text Table 10-9: Summary of Medical History by MedDRA SOC/PT– Safety Set

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- STAPHYLOCOCCAL INFECTION	1 (3)	0	0	0	1 (1)
- URINARY TRACT INFECTION	1 (3)	0	0	0	1 (1)
SOCIAL CIRCUMSTANCES	1 (3)	3 (9)	1 (3)	4 (13)	9 (7)
- POSTMENOPAUSE	1 (3)	3 (9)	0	3 (10)	7 (5)
- MENOPAUSE	0	0	1 (3)	1 (3)	2 (1)
RENAL AND URINARY DISORDERS	2 (6)	2 (6)	3 (8)	1 (3)	8 (6)
- HYPERTONIC BLADDER	0	0	2 (5)	1 (3)	3 (2)
- INCONTINENCE	1 (3)	1 (3)	0	0	2 (1)
- NEPHROLITHIASIS	1 (3)	1 (3)	0	0	2 (1)
- CHRONIC KIDNEY DISEASE	0	0	1 (3)	0	1 (1)
- MICROALBUMINURIA	0	0	1 (3)	0	1 (1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1 (3)	5 (13)	0	6 (4)
- BENIGN NEOPLASM OF THYROID GLAND	0	0	3 (8)	0	3 (2)
- BASAL CELL CARCINOMA	0	0	2 (5)	0	2 (1)
- BENIGN OVARIAN TUMOUR	0	1 (3)	0	0	1 (1)
- MALIGNANT MELANOMA	0	0	1 (3)	0	1 (1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	2 (6)	2 (5)	1 (3)	5 (4)
- ANAEMIA	0	0	1 (3)	1 (3)	2 (1)
- IRON DEFICIENCY ANAEMIA	0	2 (6)	0	0	2 (1)
- PLASMACYTOSIS	0	0	1 (3)	0	1 (1)
EAR AND LABYRINTH DISORDERS	1 (3)	1 (3)	2 (5)	1 (3)	5 (4)
- VERTIGO	0	1 (3)	1 (3)	1 (3)	3 (2)
- DEAFNESS NEUROSENSORY	1 (3)	0	0	0	1 (1)
- DEAFNESS UNILATERAL	0	0	1 (3)	0	1 (1)
HEPATOBILIARY DISORDERS	2 (6)	0	3 (8)	0	5 (4)
- HEPATIC STEATOSIS	1 (3)	0	2 (5)	0	3 (2)
- HEPATIC FIBROSIS	1 (3)	0	0	0	1 (1)
- NON-ALCOHOLIC FATTY LIVER	0	0	1 (3)	0	1 (1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	2 (6)	2 (5)	1 (3)	5 (4)
- CONCUSSION	0	1 (3)	0	0	1 (1)
- DENTAL RESTORATION FAILURE	0	1 (3)	0	0	1 (1)

Text Table 10-9: Summary of Medical History by MedDRA SOC/PT– Safety Set

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- JAW FRACTURE	0	0	0	1 (3)	1 (1)
- JOINT DISLOCATION	0	0	1 (3)	0	1 (1)
- LIGAMENT RUPTURE	0	0	1 (3)	0	1 (1)
- LOWER LIMB FRACTURE	0	0	1 (3)	0	1 (1)
- MENISCUS INJURY	0	0	1 (3)	0	1 (1)
- POST CONCUSSION SYNDROME	0	0	1 (3)	0	1 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (3)	1 (3)	1 (3)	1 (3)	4 (3)
- CHEST PAIN	0	1 (3)	1 (3)	0	2 (1)
- PAIN	1 (3)	0	0	1 (3)	2 (1)
- ACCESSORY CARPAL BONE	0	1 (3)	0	0	1 (1)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	1 (3)	0	0	1 (1)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1 (3)	0	0	0	1 (1)
- ECTOPIC PREGNANCY	1 (3)	0	0	0	1 (1)

N=number of patients in the subgroup considered or in total; n=number of patients among N; (%)=percentages are based on N; SOC=System Organ Class
Counts reflect numbers of patients reporting at least one disease in the respective category.
Source: Table 14.1.3.6; Listing(s): Derived from Listing 16.2.4.4

124 patients (90%) reported at least one prior or concomitant disease (other than OLP). The most common diseases on SOC level were ‘vascular disorders’ in 43% of all patients (with ‘hypertension’ as most frequent diagnosis on PT-level affecting 41% of patients), followed by ‘metabolism and nutrition disorders’ in 38% of patients (with ‘diabetes mellitus’ as most common diagnosis, when summarizing PTs ‘type 2 diabetes mellitus’ ‘type 1 diabetes mellitus’ and ‘diabetes mellitus’, followed by ‘hyperlipidemia’ when summarizing PTs ‘hypercholesterolemia’, ‘hyperlipidemia’ and ‘dyslipidemia’ and ‘obesity) and ‘musculoskeletal and connective tissue disorders’ in approximately one-third of all patients.

Extraoral manifestations of lichen planus within the SOC ‘skin and subcutaneous disorders’ were reported in a total of 13 (9%) patients.

Comparing the medical history as well as the concomitant diseases among treatment groups, no conspicuous differences are detected.

10.4.4 Prior and Concomitant Treatment

10.4.4.1 Prior Treatment of OLP

A summary of prior medication that was used within the last 12 months for treatment of OLP by level 2 and level 4 ATC code is provided in Text Table 10-10. Individual patient data are presented in Listing 16.2.4.2.

Text Table 10-10: Summary of OLP prior medications – Safety Set

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
ANY PREVIOUS OLP MEDICATION	25 (76)	23 (68)	27 (68)	24 (77)	99 (72)
STOMATOLOGICAL PREPARATIONS	24 (73)	22 (65)	26 (65)	24 (77)	96 (70)
- CORTICOSTEROIDS FOR LOCAL ORAL TREATMENT	21 (64)	22 (65)	24 (60)	23 (74)	90 (65)
- ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREATMENT	5 (15)	4 (12)	6 (15)	4 (13)	19 (14)
- OTHER AGENTS FOR LOCAL ORAL TREATMENT	3 (9)	5 (15)	4 (10)	3 (10)	15 (11)
- STOMATOLOGICAL PREPARATIONS	0	0	0	3 (10)	3 (2)
CORTICOSTEROIDS FOR SYSTEMIC USE	3 (9)	7 (21)	3 (8)	5 (16)	18 (13)
- GLUCOCORTICOIDS	3 (9)	7 (21)	3 (8)	5 (16)	18 (13)
OTHER DERMATOLOGICAL PREPARATIONS	2 (6)	3 (9)	6 (15)	2 (6)	13 (9)
- AGENTS FOR DERMATITIS, EXCLUDING CORTICOSTEROIDS	2 (6)	3 (9)	6 (15)	2 (6)	13 (9)
ANTIBACTERIALS FOR SYSTEMIC USE	1 (3)	2 (6)	0	0	3 (2)
- TETRACYCLINES	1 (3)	1 (3)	0	0	2 (1)
- IMIDAZOLE DERIVATIVES	0	1 (3)	0	0	1 (1)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0	1 (3)	1 (3)	0	2 (1)
- OTHER ANTIINFLAMMATORY AND ANTIRHEUMATIC AGENTS, NON-STEROIDS	0	0	1 (3)	0	1 (1)
- PROPIONIC ACID DERIVATIVES	0	1 (3)	0	0	1 (1)
ALL OTHER THERAPEUTIC PRODUCTS	0	0	1 (3)	0	1 (1)
- OTHER THERAPEUTIC PRODUCTS	0	0	1 (3)	0	1 (1)
ANESTHETICS	0	0	1 (3)	0	1 (1)
- AMIDES	0	0	1 (3)	0	1 (1)
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE	0	1 (3)	0	0	1 (1)
- OTHER ANTIBIOTICS FOR TOPICAL USE	0	1 (3)	0	0	1 (1)

Text Table 10-10: Summary of OLP prior medications – Safety Set

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
ANTIMYCOTICS FOR SYSTEMIC USE	0	0	1 (3)	0	1 (1)
- TRIAZOLE DERIVATIVES	0	0	1 (3)	0	1 (1)
ANTISEPTICS AND DISINFECTANTS	0	0	0	1 (3)	1 (1)
- OTHER ANTISEPTICS AND DISINFECTANTS	0	0	0	1 (3)	1 (1)
ANTIVIRALS FOR SYSTEMIC USE	0	1 (3)	0	0	1 (1)
- NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	0	1 (3)	0	0	1 (1)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	0	1 (3)	0	0	1 (1)
- CORTICOSTEROIDS, POTENT (GROUP III)	0	1 (3)	0	0	1 (1)
IMMUNOSUPPRESSANTS	0	1 (3)	0	0	1 (1)
- SELECTIVE IMMUNOSUPPRESSANTS	0	1 (3)	0	0	1 (1)

N=number of patients in the subgroup considered or in total; n=number of patients among N; (%)=percentages are based on N
Source: Table 14.1.3.2. Listing(s): Derived from Listing 16.2.9.3

Overall, 99 patients (72%) had used OLP medications within 12 months prior to the study. On level 4 ATC code ‘corticosteroids for local oral treatment’ were used most frequently in 65% of all patients. Corticosteroids for systemic use were applied by 18% of patients. Beside treatment with corticosteroids (local and systemic) all other treatments were used much less frequently.

10.4.4.2 General Prior and Concomitant Treatment

‘Prior medication’ is all medication used prior to randomization, irrespective if this stopped prior to the first use of IMP at Baseline / Visit 2 or not. Medications that were used at least once after the first use of IMP and medications introduced after start of study treatment at Baseline / Visit 2 were classified as ‘concomitant medication’.

Since a majority of medications are used throughout the study these are counted as both, prior and concomitant. Correspondingly there is a great overlap between ‘prior medications’ and ‘concomitant medications’.

A listing of all prior and concomitant medication on patient level is provided with Listing 16.2.9.3.

Prior medication:

In total 116 patients (84%) had used prior medications not related to OLP but related to patient’s medical history. Most common classes of medications were lipid-modifying agents (32%), agents acting of the renin-angiotensin system (29%) and drugs for acid-related

disorders (25%, predominantly proton pump inhibitors). Data revealed no major differences between the treatment groups.

A detailed tabulation of prior medications sorted by ATC level 2 and level 4 for the Safety Set is provided in Table 14.1.3.3.

Concomitant medications:

Text Table 10-11 presents all concomitant medications coded by ATC level 2 and level 4.

Any use of a not permitted treatment had been documented as protocol deviation and was assessed during the BDRM concerning its relevance on the primary endpoint (see section 10.2 for details).

In total, 118 patients (86%) used any concomitant medication.

The most common therapies were lipid modifying agents taken by 44 of all patients (32%), agents acting on the renin-angiotensin system in 39 patients (28%) and drugs for acid related disorders taken by 34 (25%) patients. Other frequently used medications were 'thyroid therapies' used by 31 patients (22%), 'drugs used in diabetes' in 25 patients (18%) and different kinds of antihypertensive drugs like 'calcium channel blockers' used by 17 patients (12%), 'beta blocking agents' and 'diuretics' in 13 patients (9%), each. This in general reflects the background morbidity of the trial population with 'vascular disorders' (hypertension as the most prevalent concomitant disease) and 'metabolism and nutrition disorders' like 'diabetes', 'obesity' and 'hyperlipidaemia' representing the most frequent concomitant diseases within this SOC (see section 10.4.3).

Compared to the prior medications no relevant shifts in regard to a special kind of medications were observed.

Text Table 10-11: Summary concomitant medications – Safety Set

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
ANY MEDICATION	30 (91)	26 (76)	35 (88)	27 (87)	118 (86)
LIPID MODIFYING AGENTS	10 (30)	8 (24)	16 (40)	10 (32)	44 (32)
- HMG COA REDUCTASE INHIBITORS	10 (30)	7 (21)	15 (38)	10 (32)	42 (30)
- OTHER LIPID MODIFYING AGENTS	0	0	2 (5)	2 (6)	4 (3)
- FIBRATES	0	2 (6)	0	0	2 (1)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	11 (33)	6 (18)	12 (30)	10 (32)	39 (28)
- ANGIOTENSIN II ANTAGONISTS, PLAIN	5 (15)	4 (12)	7 (18)	5 (16)	21 (15)
- ACE INHIBITORS, PLAIN	6 (18)	1 (3)	5 (13)	4 (13)	16 (12)
- ANGIOTENSIN II ANTAGONISTS AND DIURETICS	0	1 (3)	0	1 (3)	2 (1)
DRUGS FOR ACID RELATED DISORDERS	8 (24)	5 (15)	18 (45)	3 (10)	34 (25)
- PROTON PUMP INHIBITORS	6 (18)	4 (12)	16 (40)	3 (10)	29 (21)
- H2-RECEPTOR ANTAGONISTS	1 (3)	1 (3)	2 (5)	1 (3)	5 (4)

Text Table 10-11: Summary concomitant medications – Safety Set

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- OTHER DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	2 (6)	0	0	0	2 (1)
THYROID THERAPY	6 (18)	9 (26)	7 (18)	9 (29)	31 (22)
- THYROID HORMONES	6 (18)	8 (24)	7 (18)	9 (29)	30 (22)
- SULFUR-CONTAINING IMIDAZOLE DERIVATIVES	0	1 (3)	0	0	1 (1)
ANTITHROMBOTIC AGENTS	2 (6)	5 (15)	10 (25)	8 (26)	25 (18)
- PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	2 (6)	5 (15)	10 (25)	5 (16)	22 (16)
- DIRECT FACTOR XA INHIBITORS	0	0	0	3 (10)	3 (2)
- HEPARIN GROUP	0	0	0	1 (3)	1 (1)
- OTHER ANTITHROMBOTIC AGENTS	1 (3)	0	0	0	1 (1)
DRUGS USED IN DIABETES	7 (21)	7 (21)	8 (20)	3 (10)	25 (18)
- BIGUANIDES	6 (18)	5 (15)	7 (18)	3 (10)	21 (15)
- INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING	1 (3)	1 (3)	4 (10)	0	6 (4)
- INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	0	2 (6)	2 (5)	0	4 (3)
- SULFONYLUREAS	1 (3)	0	2 (5)	1 (3)	4 (3)
- DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS	0	1 (3)	2 (5)	0	3 (2)
- GLUCAGON-LIKE PEPTIDE-1 (GLP-1) ANALOGUES	0	0	1 (3)	2 (6)	3 (2)
- SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS	2 (6)	0	1 (3)	0	3 (2)
- COMBINATIONS OF ORAL BLOOD GLUCOSE LOWERING DRUGS	1 (3)	0	0	0	1 (1)
VITAMINS	6 (18)	4 (12)	7 (18)	8 (26)	25 (18)
- VITAMIN D AND ANALOGUES	6 (18)	4 (12)	4 (10)	6 (19)	20 (14)
- COMBINATIONS OF VITAMINS	1 (3)	2 (6)	3 (8)	2 (6)	8 (6)
- OTHER PLAIN VITAMIN PREPARATIONS	1 (3)	0	2 (5)	1 (3)	4 (3)
- ASCORBIC ACID (VITAMIN C), PLAIN	0	1 (3)	0	0	1 (1)
- MULTIVITAMINS WITH MINERALS	1 (3)	0	0	0	1 (1)
- VITAMIN A AND D IN COMBINATION	0	1 (3)	0	0	1 (1)
- VITAMIN A, PLAIN	0	1 (3)	0	0	1 (1)

Text Table 10-11: Summary concomitant medications – Safety Set

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	4 (12)	10 (29)	6 (15)	4 (13)	24 (17)
- PROPIONIC ACID DERIVATIVES	4 (12)	4 (12)	3 (8)	2 (6)	13 (9)
- COXIBS	0	3 (9)	2 (5)	0	5 (4)
- ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	0	0	1 (3)	2 (6)	3 (2)
- OXICAMS	0	3 (9)	0	0	3 (2)
PSYCHOANALEPTICS	5 (15)	3 (9)	9 (23)	6 (19)	23 (17)
- SELECTIVE SEROTONIN REUPTAKE INHIBITORS	3 (9)	1 (3)	4 (10)	3 (10)	11 (8)
- OTHER ANTIDEPRESSANTS	1 (3)	2 (6)	3 (8)	2 (6)	8 (6)
- NON-SELECTIVE MONOAMINE REUPTAKE INHIBITORS	0	0	2 (5)	1 (3)	3 (2)
- CENTRALLY ACTING SYMPATHOMIMETICS	1 (3)	0	0	0	1 (1)
ANALGESICS	7 (21)	1 (3)	7 (18)	6 (19)	21 (15)
- ANILIDES	5 (15)	0	2 (5)	4 (13)	11 (8)
- OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	2 (6)	1 (3)	2 (5)	1 (3)	6 (4)
- OTHER OPIOIDS	2 (6)	0	1 (3)	1 (3)	4 (3)
- NATURAL OPIUM ALKALOIDS	0	0	2 (5)	1 (3)	3 (2)
- OTHER ANTIMIGRAINE PREPARATIONS	0	0	0	2 (6)	2 (1)
- SELECTIVE SEROTONIN (5HT1) AGONISTS	0	0	1 (3)	1 (3)	2 (1)
- ORIPAVINE DERIVATIVES	0	0	0	1 (3)	1 (1)
- SALICYLIC ACID AND DERIVATIVES	0	0	1 (3)	0	1 (1)
MINERAL SUPPLEMENTS	2 (6)	3 (9)	9 (23)	6 (19)	20 (14)
- CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	0	1 (3)	5 (13)	2 (6)	8 (6)
- POTASSIUM	1 (3)	0	3 (8)	0	4 (3)
- CALCIUM	0	1 (3)	1 (3)	1 (3)	3 (2)
- MAGNESIUM	0	1 (3)	0	2 (6)	3 (2)
- FLUORIDE	1 (3)	0	0	1 (3)	2 (1)
- SELENIUM	0	0	0	1 (3)	1 (1)
CALCIUM CHANNEL BLOCKERS	5 (15)	2 (6)	5 (13)	5 (16)	17 (12)
- DIHYDROPYRIDINE DERIVATIVES	5 (15)	0	3 (8)	5 (16)	13 (9)

Text Table 10-11: Summary concomitant medications – Safety Set

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- BENZOTHIAZEPINE DERIVATIVES	0	2 (6)	2 (5)	0	4 (3)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	4 (12)	4 (12)	6 (15)	3 (10)	17 (12)
- SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	3 (9)	3 (9)	1 (3)	3 (10)	10 (7)
- ADRENERGICS IN COMBINATION WITH CORTICOSTEROIDS OR OTHER DRUGS, EXCL. ANTICHOLINE	1 (3)	0	4 (10)	2 (6)	7 (5)
- LEUKOTRIENE RECEPTOR ANTAGONISTS	1 (3)	1 (3)	3 (8)	0	5 (4)
- ANTICHOLINERGICS	1 (3)	1 (3)	1 (3)	1 (3)	4 (3)
- GLUCOCORTICOIDS	1 (3)	0	2 (5)	0	3 (2)
- XANTHINES	0	0	1 (3)	0	1 (1)
ANTIHISTAMINES FOR SYSTEMIC USE	1 (3)	4 (12)	4 (10)	5 (16)	14 (10)
- PIPERAZINE DERIVATIVES	0	3 (9)	2 (5)	3 (10)	8 (6)
- OTHER ANTIHISTAMINES FOR SYSTEMIC USE	1 (3)	0	1 (3)	2 (6)	4 (3)
- AMINOALKYL ETHERS	0	1 (3)	0	0	1 (1)
- SUBSTITUTED ALKYLAMINES	0	0	1 (3)	0	1 (1)
ANTIEPILEPTICS	5 (15)	2 (6)	2 (5)	4 (13)	13 (9)
- OTHER ANTIEPILEPTICS	4 (12)	1 (3)	2 (5)	2 (6)	9 (7)
- BENZODIAZEPINE DERIVATIVES	0	1 (3)	0	1 (3)	2 (1)
- CARBOXAMIDE DERIVATIVES	1 (3)	0	0	1 (3)	2 (1)
- HYDANTOIN DERIVATIVES	1 (3)	0	0	0	1 (1)
BETA BLOCKING AGENTS	3 (9)	1 (3)	6 (15)	3 (10)	13 (9)
- BETA BLOCKING AGENTS, SELECTIVE	3 (9)	1 (3)	5 (13)	3 (10)	12 (9)
- ALPHA AND BETA BLOCKING AGENTS	0	0	2 (5)	0	2 (1)
DIURETICS	2 (6)	3 (9)	5 (13)	3 (10)	13 (9)
- SULFONAMIDES, PLAIN	1 (3)	0	2 (5)	2 (6)	5 (4)
- THIAZIDES, PLAIN	1 (3)	1 (3)	2 (5)	1 (3)	5 (4)
- ALDOSTERONE ANTAGONISTS	0	0	1 (3)	0	1 (1)
- HIGH-CEILING DIURETICS AND POTASSIUM-SPARING AGENTS	0	1 (3)	0	0	1 (1)
- LOW-CEILING DIURETICS AND POTASSIUM-SPARING AGENTS	0	1 (3)	0	0	1 (1)
ANTIANEMIC PREPARATIONS	1 (3)	3 (9)	4 (10)	3 (10)	11 (8)

Text Table 10-11: Summary concomitant medications – Safety Set

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	0	2 (6)	3 (8)	3 (10)	8 (6)
- IRON BIVALENT, ORAL PREPARATIONS	1 (3)	1 (3)	1 (3)	0	3 (2)
- FOLIC ACID AND DERIVATIVES	0	0	1 (3)	0	1 (1)
- IRON PREPARATIONS	0	1 (3)	0	0	1 (1)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	3 (9)	0	3 (8)	4 (13)	10 (7)
- CORTICOSTEROIDS, VERY POTENT (GROUP IV)	1 (3)	0	2 (5)	2 (6)	5 (4)
- CORTICOSTEROIDS, POTENT (GROUP III)	1 (3)	0	1 (3)	2 (6)	4 (3)
- CORTICOSTEROIDS, POTENT, COMBINATIONS WITH ANTIBIOTICS	1 (3)	0	0	1 (3)	2 (1)
- CORTICOSTEROIDS, WEAK (GROUP I)	0	0	1 (3)	0	1 (1)
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	2 (6)	2 (6)	2 (5)	4 (13)	10 (7)
- NATURAL AND SEMISYNTHETIC ESTROGENS, PLAIN	0	2 (6)	1 (3)	3 (10)	6 (4)
- PROGESTOGENS AND ESTROGENS, FIXED COMBINATIONS	2 (6)	0	0	1 (3)	3 (2)
- OTHER ESTROGENS	0	0	1 (3)	0	1 (1)
- PREGNEN (4) DERIVATIVES	0	0	0	1 (3)	1 (1)
GENERAL NUTRIENTS	2 (6)	2 (6)	3 (8)	2 (6)	9 (7)
- OTHER COMBINATIONS OF NUTRIENTS	1 (3)	2 (6)	2 (5)	2 (6)	7 (5)
- OTHER NUTRIENTS	1 (3)	0	1 (3)	0	2 (1)
OPHTHALMOLOGICALS	2 (6)	1 (3)	2 (5)	4 (13)	9 (7)
- OTHER OPHTHALMOLOGICALS	1 (3)	1 (3)	1 (3)	2 (6)	5 (4)
- PROSTAGLANDIN ANALOGUES	1 (3)	0	1 (3)	1 (3)	3 (2)
- ANTIBIOTICS	0	0	0	1 (3)	1 (1)
- BETA BLOCKING AGENTS	1 (3)	0	0	0	1 (1)
- SYMPATHOMIMETICS IN GLAUCOMA THERAPY	1 (3)	0	0	0	1 (1)
PSYCHOLEPTICS	1 (3)	4 (12)	1 (3)	3 (10)	9 (7)
- BENZODIAZEPINE DERIVATIVES	1 (3)	2 (6)	0	2 (6)	5 (4)
- BENZODIAZEPINE RELATED DRUGS	1 (3)	1 (3)	1 (3)	0	3 (2)
- OTHER ANXIOLYTICS	1 (3)	1 (3)	0	1 (3)	3 (2)

Text Table 10-11: Summary concomitant medications – Safety Set

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- OTHER HYPNOTICS AND SEDATIVES	0	0	0	1 (3)	1 (1)
STOMATOLOGICAL PREPARATIONS	1 (3)	0	4 (10)	3 (10)	8 (6)
- ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREATMENT	0	0	3 (8)	1 (3)	4 (3)
- OTHER AGENTS FOR LOCAL ORAL TREATMENT	1 (3)	0	1 (3)	1 (3)	3 (2)
- CARIES PROPHYLACTIC AGENTS	0	0	0	1 (3)	1 (1)
UROLOGICALS	1 (3)	2 (6)	3 (8)	2 (6)	8 (6)
- DRUGS FOR URINARY FREQUENCY AND INCONTINENCE	1 (3)	1 (3)	2 (5)	0	4 (3)
- ALPHA-ADRENORECEPTOR ANTAGONISTS	0	0	0	2 (6)	2 (1)
- TESTOSTERONE-5-ALPHA REDUCTASE INHIBITORS	0	1 (3)	1 (3)	0	2 (1)
DRUGS FOR CONSTIPATION	2 (6)	1 (3)	1 (3)	3 (10)	7 (5)
- OSMOTICALLY ACTING LAXATIVES	1 (3)	1 (3)	0	2 (6)	4 (3)
- BULK-FORMING LAXATIVES	1 (3)	0	0	0	1 (1)
- CONTACT LAXATIVES	0	0	1 (3)	0	1 (1)
- ENEMAS	0	0	0	1 (3)	1 (1)
- OTHER DRUGS FOR CONSTIPATION	0	0	0	1 (3)	1 (1)
- SOFTENERS, EMOLLIENTS	0	0	0	1 (3)	1 (1)
NASAL PREPARATIONS	1 (3)	2 (6)	1 (3)	1 (3)	5 (4)
- ANTIALLERGIC AGENTS, EXCL. CORTICOSTEROIDS	1 (3)	0	1 (3)	0	2 (1)
- CORTICOSTEROIDS	0	1 (3)	1 (3)	0	2 (1)
- SYMPATHOMIMETICS, COMBINATIONS EXCL. CORTICOSTEROIDS	0	0	0	1 (3)	1 (1)
- SYMPATHOMIMETICS, PLAIN	0	1 (3)	0	0	1 (1)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	3 (9)	1 (3)	0	1 (3)	5 (4)
- UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	3 (9)	1 (3)	0	1 (3)	5 (4)
ANTIBACTERIALS FOR SYSTEMIC USE	2 (6)	0	0	2 (6)	4 (3)
- COMBINATIONS OF SULFONAMIDES AND TRIMETHOPRIM, INCL. DERIVATIVES	1 (3)	0	0	0	1 (1)
- FIRST-GENERATION CEPHALOSPORINS	0	0	0	1 (3)	1 (1)

Text Table 10-11: Summary concomitant medications – Safety Set

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- FLUOROQUINOLONES	0	0	0	1 (3)	1 (1)
- NITROFURAN DERIVATIVES	1 (3)	0	0	0	1 (1)
ANTIHYPERTENSIVES	2 (6)	0	0	2 (6)	4 (3)
- ALPHA-ADRENORECEPTOR ANTAGONISTS	1 (3)	0	0	2 (6)	3 (2)
- IMIDAZOLINE RECEPTOR AGONISTS	1 (3)	0	0	0	1 (1)
CARDIAC THERAPY	2 (6)	1 (3)	0	1 (3)	4 (3)
- ORGANIC NITRATES	2 (6)	0	0	1 (3)	3 (2)
- OTHER CARDIAC PREPARATIONS	0	1 (3)	0	0	1 (1)
DRUGS FOR TREATMENT OF BONE DISEASES	0	2 (6)	2 (5)	0	4 (3)
- BISPHOSPHONATES	0	2 (6)	2 (5)	0	4 (3)
MUSCLE RELAXANTS	2 (6)	1 (3)	0	1 (3)	4 (3)
- OTHER CENTRALLY ACTING AGENTS	2 (6)	1 (3)	0	1 (3)	4 (3)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	1 (3)	0	2 (5)	1 (3)	4 (3)
- VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS	1 (3)	0	2 (5)	1 (3)	4 (3)
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE	1 (3)	1 (3)	0	1 (3)	3 (2)
- OTHER ANTIBIOTICS FOR TOPICAL USE	1 (3)	0	0	1 (3)	2 (1)
- ANTIVIRALS	0	1 (3)	0	0	1 (1)
ANTIFUNGALS FOR DERMATOLOGICAL USE	0	2 (6)	1 (3)	0	3 (2)
- IMIDAZOLE AND TRIAZOLE DERIVATIVES	0	2 (6)	0	0	2 (1)
- OTHER ANTIFUNGALS FOR TOPICAL USE	0	0	1 (3)	0	1 (1)
CORTICOSTEROIDS FOR SYSTEMIC USE	0	2 (6)	1 (3)	0	3 (2)
- GLUCOCORTICOIDS	0	2 (6)	1 (3)	0	3 (2)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	0	2 (6)	1 (3)	0	3 (2)
- PROPULSIVES	0	2 (6)	0	0	2 (1)
- BELLADONNA ALKALOIDS, SEMISYNTHETIC, QUATERNARY AMMONIUM COMPOUNDS	0	0	1 (3)	0	1 (1)

Text Table 10-11: Summary concomitant medications – Safety Set

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
OTHER DERMATOLOGICAL PREPARATIONS	0	1 (3)	2 (5)	0	3 (2)
- AGENTS FOR DERMATITIS, EXCLUDING CORTICOSTEROIDS	0	1 (3)	1 (3)	0	2 (1)
- OTHER DERMATOLOGICALS	0	0	1 (3)	0	1 (1)
TONICS	0	2 (6)	1 (3)	0	3 (2)
- TONICS	0	2 (6)	1 (3)	0	3 (2)
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	0	0	1 (3)	1 (3)	2 (1)
- ANTIDIARRHEAL MICROORGANISMS	0	0	0	1 (3)	1 (1)
- BISMUTH PREPARATIONS	0	0	1 (3)	0	1 (1)
ANTIMYCOTICS FOR SYSTEMIC USE	0	1 (3)	1 (3)	0	2 (1)
- TRIAZOLE DERIVATIVES	0	1 (3)	1 (3)	0	2 (1)
ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	0	2 (6)	0	0	2 (1)
- ANESTHETICS FOR TOPICAL USE	0	1 (3)	0	0	1 (1)
- OTHER ANTIPRURITICS	0	1 (3)	0	0	1 (1)
COUGH AND COLD PREPARATIONS	0	0	1 (3)	1 (3)	2 (1)
- EXPECTORANTS	0	0	0	1 (3)	1 (1)
- HERBAL DIAPHORETICS AND OTHER HERBAL COUGH AND COLD REMEDIES	0	0	0	1 (3)	1 (1)
- HERBAL EXPECTORANTS AND EMOLLIENTS	0	0	0	1 (3)	1 (1)
- MUCOLYTICS	0	0	0	1 (3)	1 (1)
- OPIUM ALKALOIDS AND DERIVATIVES	0	0	1 (3)	0	1 (1)
EMOLLIENTS AND PROTECTIVES	0	1 (3)	1 (3)	0	2 (1)
- OTHER EMOLLIENTS AND PROTECTIVES	0	1 (3)	1 (3)	0	2 (1)
- SOFT PARAFFIN AND FAT PRODUCTS	0	1 (3)	0	0	1 (1)
OTHER NERVOUS SYSTEM DRUGS	0	0	1 (3)	1 (3)	2 (1)
- OTHER PARASYMPATHOMIMETICS	0	0	1 (3)	1 (3)	2 (1)
ALL OTHER THERAPEUTIC PRODUCTS	1 (3)	0	0	0	1 (1)
- OTHER THERAPEUTIC PRODUCTS	1 (3)	0	0	0	1 (1)
ANESTHETICS	0	0	0	1 (3)	1 (1)
- AMIDES	0	0	0	1 (3)	1 (1)

Text Table 10-11: Summary concomitant medications – Safety Set

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
ANTI-ACNE PREPARATIONS	1 (3)	0	0	0	1 (1)
- RETINOIDS FOR TOPICAL USE IN ACNE	1 (3)	0	0	0	1 (1)
ANTIEMETICS AND ANTINAUSEANTS	0	0	0	1 (3)	1 (1)
- SEROTONIN (5HT3) ANTAGONISTS	0	0	0	1 (3)	1 (1)
ANTIHEMORRHAGICS	0	0	0	1 (3)	1 (1)
- AMINO ACIDS	0	0	0	1 (3)	1 (1)
ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS	0	0	1 (3)	0	1 (1)
- CENTRALLY ACTING ANTIOBESITY PRODUCTS	0	0	1 (3)	0	1 (1)
ANTIPSORIATICS	0	0	1 (3)	0	1 (1)
- OTHER ANTIPSORIATICS FOR TOPICAL USE	0	0	1 (3)	0	1 (1)
ANTIVIRALS FOR SYSTEMIC USE	0	1 (3)	0	0	1 (1)
- NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	0	1 (3)	0	0	1 (1)
BILE AND LIVER THERAPY	1 (3)	0	0	0	1 (1)
- LIVER THERAPY	1 (3)	0	0	0	1 (1)
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	0	0	0	1 (3)	1 (1)
- ELECTROLYTE SOLUTIONS	0	0	0	1 (3)	1 (1)
- SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	0	0	0	1 (3)	1 (1)
DIGESTIVES, INCL. ENZYMES	1 (3)	0	0	0	1 (1)
- HERBAL DIGESTIVES, OTHER	1 (3)	0	0	0	1 (1)
ENDOCRINE THERAPY	0	0	1 (3)	0	1 (1)
- GONADOTROPIN RELEASING HORMONE ANALOGUES	0	0	1 (3)	0	1 (1)
IMMUNOSUPPRESSANTS	0	0	1 (3)	0	1 (1)
- OTHER IMMUNOSUPPRESSANTS	0	0	1 (3)	0	1 (1)
OTHER GYNECOLOGICALS	1 (3)	0	0	0	1 (1)
- INTRAUTERINE CONTRACEPTIVES	1 (3)	0	0	0	1 (1)
THROAT PREPARATIONS	0	0	0	1 (3)	1 (1)
- ANTISEPTICS	0	0	0	1 (3)	1 (1)
- THROAT PREPARATIONS	0	0	0	1 (3)	1 (1)

Text Table 10-11: Summary concomitant medications – Safety Set

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	0	1 (3)	0	0	1 (1)
- ANTIINFLAMMATORY PREPARATIONS, NON-STEROIDS FOR TOPICAL USE	0	1 (3)	0	0	1 (1)
VACCINES	0	0	1 (3)	0	1 (1)
- INFLUENZA VACCINES	0	0	1 (3)	0	1 (1)

N=number of patients in the subgroup considered or in total; n=number of patients among N; (%)=percentages are based on N
Source: Table 14.3.5.3; Listing(s): Derived from Listing 16.2.9.3

10.5 Measurement of Treatment Compliance and Extent of Exposure

Treatment Compliance was assessed via drug account and patient reported diary entries.

Descriptive statistics on treatment compliance based on patches dispensed and returned is given in Text Table 10-12 for each week in the treatment period and for the full treatment period.

Text Table 10-12: Summary of compliance: Drug compliance (%) based on number of patches dispensed and returned – FAS

Period	Stats	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Week 1	N	33	34	40	31	138
	Used patches, median	32	35	51	42	42
	Range	10, 108	10, 84	8 , 95	12, 108	8 , 108
	Compliance, median	100	100	100	100	100
	Range	9.3, 279	79, 179	46, 226	22, 207	9.3, 279
	Total dose, median	640	175	51	0	
	Range	200, 2160	50, 420	8 , 95	0 , 0	
	Daily dose, median	97	26	6.4	0	
	Range	2 , 223	9.3, 60	1 , 13.6	0 , 0	

Text Table 10-12: Summary of compliance: Drug compliance (%) based on number of patches dispensed and returned – FAS

Period	Stats	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Week 2	N	31	34	35	26	126
	Used patches, median	39	40	43	55	43
	Range	14, 77	11, 96	8 , 108	12, 108	8 , 108
	Compliance, median	100	103	100	106	100
	Range	22, 161	79, 133	71, 117	71, 129	22, 161
	Total dose, median	780	188	43	0	
	Range	280, 1540	55, 480	8 , 1340	0 , 0	
	Daily dose, median	91	22	6.1	0	
	Range	34, 270	9.3, 64.3	1.8, 191	0 , 0	
Week 3	N	30	33	36	27	126
	Used patches, median	44	42	45	44	44
	Range	8 , 78	9 , 84	9 , 84	14, 108	8 , 108
	Compliance, median	100	100	100	100	100
	Range	43, 133	60, 131	64, 110	96, 147	43, 147
	Total dose, median	870	200	45	0	
	Range	160, 1560	45, 420	9 , 84	0 , 0	
	Daily dose, median	109	30	6.4	0	
	Range	23, 260	9 , 60	1.8, 12	0 , 0	
Week 4	N	28	32	35	27	122
	Used patches, median	43	40	43	41	42
	Range	9 , 84	13, 90	11, 84	14, 90	9 , 90
	Compliance, median	100	100	100	100	100
	Range	75, 257	36, 233	26, 107	43, 136	26, 257
	Total dose, median	860	178	43	0	
	Range	180, 1680	65, 450	11, 84	0 , 0	
	Daily dose, median	128	23	6.1	0	
	Range	40, 264	10, 60	0.2, 12	0 , 0	

Text Table 10-12: Summary of compliance: Drug compliance (%) based on number of patches dispensed and returned – FAS

Period	Stats	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Total	N	33	34	40	31	138
	Used patches, median	151	162	172	163	165
	Range	10, 324	46, 342	8 , 341	12, 384	8 , 384
	Compliance, median	100	102	100	100	100
	Range	9.3, 159	71, 134	50, 143	22, 136	9.3, 159
	Total dose, median	3020	735	172	0	
	Range	200, 6480	230, 1710	8 , 1469	0 , 0	
	Daily dose, median	108	26	6.5	0	
	Range	2 , 231	10, 61.1	1 , 70	0 , 0	

N=number of patients in the subgroup considered or in total; n=number of patients among N; (%)=percentages are based on N
Source: Table 14.1.3.7 a; Listing(s): Derived from Listing 16.2.5.1

Clobetasol exposure:

Maximum total clobetasol exposure during this study ranged from 6480µg in the 20µg group over 1710µg in the 5µg group to 1469µg in the 1µg group. Median clobetasol exposure over the whole study period was 3020µg for the 20µg group, 735µg for the 5µg and 172µg in the 1µg group. Daily median clobetasol exposure ranged from 108µg in the 20µg group over 26µg in the 5µg group to 6.5µg in the 1µg group.

Treatment compliance:

The median percentage treatment compliance (as assessed by drug account) was at least 100% in all treatment groups and for all weeks in the study, with individual percentages ranging between 9.3 and 159% compliance. The median number of patches applied over the whole treatment period was 165 patches, with the highest median number in the placebo group (172 patches) and the lowest median number in the 20µg group (151 patches). Several patients had a percentage treatment compliance exceeding 100% (overall 159% in maximum), which could most probably be explained by the fact that not all unused patches have been returned as requested. In addition, some patches were lost as single patients had difficulties with correct application of patches depending on location of lesions that need to be patched.

Descriptive statistics of treatment compliance based on the number of patches used as recorded in the diary are presented in Text Table 10-13.

Text Table 10-13: Summary of drug compliance (%) based on number of patches used and recorded in diary – FAS

		Treatment				
Period	**Stats**	**20 ug, N=33**	**5 ug, N=34**	**1 ug, N=40**	**Placebo, N=31**	**Total**
Total study	n	33	34	40	30	137
Total study	Used patches, median	110	157.5	155	136	140
Total study	range	4, 318	38, 342	8, 341	12, 336	4, 342
Total study	Compliance, median	96.6	100	100	100	100
Total study	range	5.6, 103	35, 106	43, 102	3.7, 103	3.7, 106
Source: Table 14.1.3.7 c. Listing(s): Derived from Listing 16.2.5.1						

The median number of patches used over the entire treatment period (as documented in the diary) was 140 patches, with the highest median number in the 5µg group (157.5 patches) and the lowest median number in the 20µg group (110 patches). Median treatment compliance was 100% in total and among all treatment groups, except for the 20µg group with a slightly lower median compliance of 96.6%. Individual patient had treatment compliances exceeding 100% (with a maximum of 106%). This might have been most probably due to patient initiated treatment of lesions not foreseen for treatment by the investigator.

Descriptive statistics for the diary compliance (that is number of days the diary was filled in in relation to the planned number of days) are given in Text Table 10-14, respecting only diary data from patients (overall 116 patients) having used a paper diary or both, i.e. eDiary and paper diary (2 patients only: 102005 and 400006). This was introduced with Amendment 04 resulting in CSP version 8.0, dated 29-Mar-2019, due to technical issues with the electronic device that resulted in multiple failures to capture data.

Text Table 10-14: Summary of treatment compliance: diary compliance (%) – FAS (Only patients using paper diaries are respected)

		Days recorded			Compliance (%)	
Treatment	**Period**	**N**	**Median**	**Range**	**Median**	**Range**
20 ug	Run-in	25	8	5, 14	100	82.4, 100.0
	Treatment	25	28	2, 34	96.6	2.0, 100.0
5 ug	Run-in	30	7	6, 15	100	35.0, 100.0
	Treatment	30	29	15, 35	96.8	93.1, 100.0
1 ug	Run-in	34	7	6, 18	100	90.0, 100.0
	Treatment	34	29	4, 32	96.6	44.4, 100.0

Text Table 10-14: Summary of treatment compliance: diary compliance (%) – FAS (Only patients using paper diaries are respected)

		Days recorded			Compliance (%)	
Treatment	**Period**	**N**	**Median**	**Range**	**Median**	**Range**
Placebo	Run-in	27	7	0, 26	100	0.0, 100.0
	Treatment	27	28	3, 33	96.6	27.6, 100.0
Total	Run-in	116	7	0, 26	100	0.0, 100.0
	Treatment	116	29	2, 35	96.7	2.0, 100.0

N=number of patients in the subgroup considered or in total
Source: Table 14.1.3.7 b; Listing(s): Derived from Listing 16.2.6.6

For the run-in-period (Screening phase) the median percentage compliance in all treatment groups was 100% (the maximum number achievable). During the treatment period median compliance was on average 96.7%, ranging between 2 and 100%. Withdrawn patients have been counted up to the last visit they performed in the study (normally the End of Study Visit). This may explain some of the lower compliances, as patients may not always have completed their diaries on a regular basis until their last visit.

According to the trial protocol, patients who completed the study should have applied the IMP for a period of 28 ± 2 days (until Visit 6).

Assuming that the number of days the diary was completed during the treatment phase reflects the duration of treatment (from first application to last application of the IMP), the extent of exposure ranges between 2 and 35 days (see Text Table 10-14).

With a median duration of treatment of 28 or 29 days in all treatment groups, the extent of exposure did not differ notably between treatment groups.

10.6 Premature Emergency Unblindings at Study Site

Unblinding of an individual patient´s treatment should have been performed only in case of emergency. Technically, emergency un-blinding for a single patient could have been done via the IWRS within the EDC, while maintaining the overall study blind. In each case of emergency unblinding, a corresponding alert would have gone out from the EDC system informing the sponsor as well as the responsible CRO automatically.

If no premature emergency unblinding became necessary, the associated eCRF module for emergency unblinding via the IWRS did not have to be completed.

Even though not necessary, the eCRF module for emergency unblinding was completed for a total of 17 patients. Nonetheless the corresponding question, asking if emergency unblinding was necessary was always answered ’NO’(refer to Text Table 10-1). Hence no case of emergency unblinding occurred during the entire study.

10.7 Database Errata

Inconsistencies within the database that could have had an impact on the analysis are described in the following:

In general patients that withdrew prematurely from the study should have had an ET Visit performed. In contrast patients who completed the study as per protocol, should have performed their regular End of Study Visit at date of Visit 7 (FU, including a final safety assessment).

Already at time of the FDA interaction prior to study start the intention to use data collected post withdrawal for imputation was declared. This data is identified by presence of the Early Termination (ET) Visit (Visit 6) and the algorithm for data handling (in terms of imputation rules to be applied) was then different for patients with documented ET compared to regular completers.

Among 16 patients who prematurely discontinued from the study, 3 patients had no ET Visit performed: patient 102009 was withdrawn at Visit 4 due to lack of efficacy, patient 403003 was withdrawn after Visit 3 and was lost to follow-up and patient 411003 was withdrawn due to an adverse event (AE) during the follow-up phase but completed all visits (including Visit 6 and 7) as planned (see Listing 16.2.1.1 and Listing 16.2.1.3).

Deviating from the protocol, site 418 had 4 randomized and completed patients (418001, 418003, 418004, 418006) for whom Visit 6 was stated as an ET Visit (see Listing 16.2.1.3). As safety assessments for these patients (required to be performed at the End of Study Visit, Visit 7 for a regular completer) were already done at date of Visit 6, i.e. at the end of the treatment phase by mistake (and repeated at date of Visit 7 after site recognized the mistake). Due to the configuration of the eCRF it became necessary to document Visit 6 as Early Termination Visit, as modules for safety assessments (especially for laboratory assessments) in the eCRF were only editable after assigning Visit 6 as Early Termination Visit.

Incorrect assignment of ET could have had an impact, in terms of faulty imputation due to application of different imputation rules for missing visits for patients with or without documented ET. In case of the patients from site 418, this finally did not have any impact, as patients were regular completers without any missing data.

Nonetheless to avoid this problem ET should never be used for a completed patient.

Another issue derived from erroneous programming of the automated randomization system and led to the introduction of an additional stratum – by site – into the randomization process, that was not intended by the protocol. Consequently some skewed randomization with relatively more patients in the 1µg and in the 5µg group and fewer patients in placebo and 20µg group occurred as already stated in section 10.1.

As no by site-stratification was originally planned, the change in randomization pattern could have had marked impact on the outcome of the study in a worst-case scenario. Theoretically, all sites could have randomized only one patient of a random block (or of one of the strata) and this could have led to major skewness and a marked reduction of power of the statistical tests applied. As the sample size was relatively small in this phase II study, the outcome of the study could have been influenced markedly by major skewness, even to the extent that the conclusion of the study could have been reversed. Additionally, the up-scaling from the population of the interim analysis to the final population was done assuming balanced randomization after the interim. As it in fact was imbalanced, this could have led to a faulty decision on study progress at the time of the interim analysis in terms of a reversion of the study conclusion after the interim analysis.

In fact, the impact of the unbalanced randomization was smaller than it could have been and was regarded as tolerable (also by 2 independent consultant statisticians that were not involved in any other study activities). Although skewness was seen between treatment groups, comparable numbers of patients were randomized into the most important treatment groups (20µg, 5µg and placebo; the 1µg group was not assumed to have any treatment effect) and statistically significant differences between those treatments were shown. Nevertheless, the actual randomization may have had a relevant effect on the conclusion of the study.

11 EFFICACY RESULTS AND OTHER EVALUATIONS

The primary efficacy analyses were performed on the FAS. The PPS was only used for sensitivity analyses of changes in ulcer area, lesion area and 5-point erythema score. Results of the sensitivity analyses are summarized accompanying the main analysis results in the respective section. All results of all efficacy data analyses that were performed according to the SAP are presented in section 14.2. Additional analyses and result presentations can be found in a separate Statistical Report (see Appendix 16.1.9).

11.1 Efficacy Results

11.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the change in total ulcer area from Baseline to average of weeks 3 and 4. Ulcer area was measured as part of the OLPClinROM at every study visit (Visit 1 to Visit 7) and a summed up for all ulcerative lesions present at each of the visits.

The distribution of ulcer areas at Baseline was very skew (for details refer to Figure 6 of Statistical Report in Appendix 16.1.9 or Listing 16.2.6.1), with a large proportion of patients having only small ulcers (with no possibility to show larger changes) and a small set of patients with large ulcers (making it possible to show larger changes). It was planned to present the changes both on a linear scale (change in cm^2) and as relative changes in %, respectively, but with the linear scale as the main outcome. Changing to the relative scale, set the maximum improvement to 100% independent of Baseline ulcer area, but at the same time opened for large worsening if the Baseline ulcer was small, thus distribution of changes on relative scale showed even larger skewness.

Descriptive statistics of the total ulcer area over time, including the change from Baseline to the respective weeks are given in Text Table 11-1 (linear scale) and Text Table 11-2 (relative scale). The baseline average in the 5µg group was 2.5 to 3 times higher than the baseline value in the other groups due to most of the patients with large baseline ulcers were randomized to this treatment group (for details refer to Listing 16.2.6.1).

On the linear scale, reductions of mean ulcer areas between Baseline and Week 3 and Week 4 can be observed in all active treatment groups, whereas in the placebo group the mean ulcer area increases from Baseline to Week 3 and Week 4. The most prominent reduction can be seen in the 5µg group, followed by the 20µg group. Variability was always markedly higher in the 5µg group than in the other treatment groups.

Text Table 11-1: Summary of ulcer area (cm^2) by treatment group and visit, [FAS]

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	31	34	40	31
	Mean(SD)	0.585 (0.84)	1.476 (2.69)	0.556 (0.57)	0.630 (1.29)
	Median	0.250	0.410	0.390	0.180
	Min, Max	0.02-3.21	0.01-12.02	0.01-2.55	0.03-6.17

Text Table 11-1: Summary of ulcer area (cm^2) by treatment group and visit, [FAS]

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Week 1	n	30	34	39	31
	Mean(SD)	0.340 (0.55)	1.063 (2.52)	0.466 (0.69)	0.588 (1.30)
	Median	0.080	0.090	0.240	0.120
	Min, Max	0.00-2.11	0.00-10.35	0.00-2.58	0.00-5.15
Change from baseline Week 1	n	30	34	39	31
	Mean(SD)	-0.260 (0.52)	-0.413 (1.21)	-0.104 (0.43)	-0.042 (0.53)
	Median	-0.130	-0.135	-0.090	-0.040
	Min, Max	-2.08-0.83	-6.27-1.97	-1.13-1.09	-1.94-1.31
Week 2	n	29	34	37	28
	Mean(SD)	0.270 (0.56)	0.993 (2.48)	0.447 (0.99)	0.806 (2.18)
	Median	0.030	0.060	0.070	0.045
	Min, Max	0.00-2.49	0.00-10.50	0.00-5.06	0.00-9.70
Change from baseline Week 2	n	29	34	37	28
	Mean(SD)	-0.345 (0.52)	-0.483 (1.32)	-0.065 (0.96)	0.118 (0.85)
	Median	-0.180	-0.175	-0.180	-0.080
	Min, Max	-2.44-0.35	-6.39-2.12	-1.58-4.87	-0.52-3.53
Week 3	n	27	33	36	27
	Mean(SD)	0.222 (0.39)	0.806 (2.22)	0.438 (0.95)	0.791 (2.16)
	Median	0.020	0.050	0.100	0.010
	Min, Max	0.00-1.44	0.00-10.00	0.00-4.17	0.00-8.92
Change from baseline Week 3	n	27	33	36	27
	Mean(SD)	-0.401 (0.65)	-0.677 (1.29)	-0.084 (0.87)	0.105 (1.03)
	Median	-0.200	-0.300	-0.175	-0.100
	Min, Max	-2.71-0.31	-6.45-0.02	-1.54-3.50	-0.60-5.08
Week 4	n	28	33	35	27
	Mean(SD)	0.150 (0.29)	0.722 (1.98)	0.307 (0.72)	0.760 (1.76)
	Median	0.000	0.020	0.030	0.020
	Min, Max	0.00-1.14	0.00-9.17	0.00-3.76	0.00-7.78
Change from baseline Week 4	n	28	33	35	27
	Mean(SD)	-0.462 (0.67)	-0.761 (1.62)	-0.218 (0.78)	0.075 (0.88)
	Median	-0.230	-0.170	-0.230	-0.080
	Min, Max	-2.76-0.20	-6.45-0.79	-1.66-3.51	-1.28-3.94

N=number of patients in the subgroup considered or in total; n=number of patients among N; SD=Standard Deviation
Source: Table 14.2.1.1 a. Listing(s): Derived from Listing 16.2.6

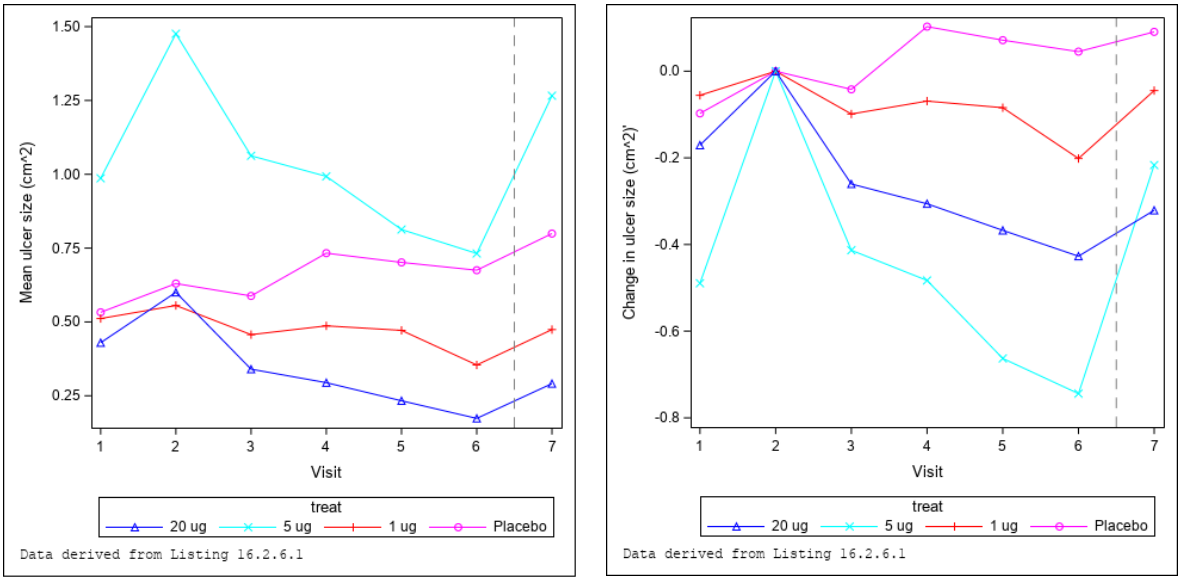
On the relative scale, reductions of ulcer areas between Baseline and Week 3 and Week 4 can be seen in all treatment groups. The most prominent relative reduction can be observed in the 5µg group, followed by the 20µg group. Variability was always higher in the 1µg group than in the other treatment groups, due to worsening of some small Baseline ulcers.

Text Table 11-2: Summary of ulcer area (% changes) by treatment group and visit, [FAS]

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Week 1	n	30	34	39	31
	Mean(SD)	-30.1 (124.94)	-44.4 (64.04)	-9.8 (134.45)	-4.1 (147.05)
	Median	-68.2	-43.5	-42.9	-57.1
	Min, Max	-100.00-488.24	-100.00-233.33	-100.00-573.68	-100.00-600.00
Week 2	n	29	34	37	28
	Mean(SD)	-68.7 (38.91)	-38.9 (136.74)	48.9 (463.22)	-54.7 (57.32)
	Median	-83.3	-72.8	-81.6	-78.8
	Min, Max	-100.00-52.24	-100.00-700.00	-100.00-2563.16	-100.00-77.78
Week 3	n	27	33	36	27
	Mean(SD)	-49.4 (99.29)	-69.3 (40.37)	-1.0 (256.80)	-50.2 (72.69)
	Median	-84.4	-77.8	-68.4	-95.5
	Min, Max	-100.00-300.00	-100.00-66.67	-100.00-1400.00	-100.00-150.00
Week 4	n	28	33	35	27
	Mean(SD)	-54.4 (127.75)	-75.8 (33.89)	-12.5 (257.79)	-12.3 (188.04)
	Median	-100.0	-93.5	-89.6	-93.9
	Min, Max	-100.00-500.00	-100.00-9.43	-100.00-1404.00	-100.00-800.00

N=number of patients in the subgroup considered or in total; n=number of patients among N; SD=Standard Deviation
Source: Table 14.2.1.1 b. Listing(s): Derived from Listing 16.2.6.1

Text Figure 11-1 shows the mean value curves by treatment as absolute values and change from Baseline for the linear scale. The placebo group showed no improvement from Baseline during the treatment period whereas the 20 and 5µg groups showed reductions already after one week, an improvement that increased for each visit up to Week 4.



absolute values change

Text Figure 11-1: Mean ulcer area over time (absolute value and change from Baseline; linear scale)
Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up
Source: Figure 14.2.1.2 a + b

The result of the statistical analysis of ulcer area is summarized in Text Table 11-3 (linear scale) and Table 14.2.1.4 (relative scale). For the primary evaluation of change to average of weeks 3 and 4 on linear scale, statistically significant reductions versus placebo were seen for both the 20µg and 5µg groups. Statistically significant reductions were also seen at week 4 for both these doses but no significance was found at earlier time points for any dose. When analyzed as relative changes, no significant differences versus placebo were found.

Text Table 11-3: Statistical analysis of ulcer area [FAS]: ulcer area (cm^2)

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-0.333	20 ug vs placebo	-0.216	(-0.569, 0.137)	0.2291
	5 ug	-0.357	5 ug vs placebo	-0.240	(-0.587, 0.107)	0.1741
	1 ug	-0.191	1 ug vs placebo	-0.073	(-0.403, 0.257)	0.6614
	Placebo	-0.118				
Week 2	20 ug	-0.403	20 ug vs placebo	-0.420	(-0.906, 0.066)	0.0894
	5 ug	-0.487	5 ug vs placebo	-0.504	(-0.982, -0.026)	0.0388
	1 ug	-0.144	1 ug vs placebo	-0.161	(-0.615, 0.293)	0.4836
	Placebo	0.017				
Week 3	20 ug	-0.367	20 ug vs placebo	-0.416	(-0.880, 0.048)	0.0786
	5 ug	-0.491	5 ug vs placebo	-0.540	(-0.997, -0.084)	0.0207
	1 ug	-0.074	1 ug vs placebo	-0.124	(-0.557, 0.310)	0.5733
	Placebo	0.049				

Text Table 11-3: Statistical analysis of ulcer area [FAS]: ulcer area (cm^2)

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 4	20 ug	-0.509	20 ug vs placebo	-0.485	(-0.936, -0.033)	0.0356
	5 ug	-0.502	5 ug vs placebo	-0.478	(-0.922, -0.034)	0.0350
	1 ug	-0.287	1 ug vs placebo	-0.263	(-0.685, 0.159)	0.2197
	Placebo	-0.024				
Week 3-4	20 ug	-0.438	20 ug vs placebo	-0.450	(-0.894, -0.007)	0.0468
	5 ug	-0.497	5 ug vs placebo	-0.509	(-0.945, -0.073)	0.0226
	1 ug	-0.181	1 ug vs placebo	-0.193	(-0.608, 0.221)	0.3579
	Placebo	0.013				

CI=Confidence Interval
Source: Table 14.2.1.2. Analysis performed by PROC MIXED. Listing(s): Derived from Listing 16.2.6.1

The result of the statistical analysis of the PPS is shown in Text Table 11-4. It underlines the result of the FAS with a statistically significant difference versus placebo for both the 20µg (p=0.0374) and 5µg (p=0.0359) groups for the change from Baseline to average of weeks 3 and 4 endpoint and a statistically significant difference between the 20µg and placebo group at Week 4 (p=0.0308). The difference between 5µg and placebo at Week 4 showed a borderline significance (p=0.0544).

Text Table 11-4: Statistical analysis of ulcer area [PPS]: ulcer area (cm^2)

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-0.289	20 ug vs placebo	-0.248	(-0.548, 0.052)	0.1040
	5 ug	-0.232	5 ug vs placebo	-0.191	(-0.479, 0.096)	0.1906
	1 ug	-0.088	1 ug vs placebo	-0.047	(-0.324, 0.230)	0.7370
	Placebo	-0.041				
Week 2	20 ug	-0.370	20 ug vs placebo	-0.493	(-0.979, -0.006)	0.0471
	5 ug	-0.326	5 ug vs placebo	-0.448	(-0.914, 0.018)	0.0595
	1 ug	-0.045	1 ug vs placebo	-0.167	(-0.616, 0.282)	0.4630
	Placebo	0.122				
Week 3	20 ug	-0.305	20 ug vs placebo	-0.446	(-0.921, 0.028)	0.0649
	5 ug	-0.351	5 ug vs placebo	-0.493	(-0.948, -0.038)	0.0341
	1 ug	0.052	1 ug vs placebo	-0.090	(-0.528, 0.349)	0.6855
	Placebo	0.142				
Week 4	20 ug	-0.483	20 ug vs placebo	-0.529	(-1.008, -0.050)	0.0308
	5 ug	-0.404	5 ug vs placebo	-0.451	(-0.911, 0.009)	0.0544
	1 ug	-0.202	1 ug vs placebo	-0.249	(-0.692, 0.194)	0.2675
	Placebo	0.047				

Text Table 11-4: Statistical analysis of ulcer area [PPS]: ulcer area (cm^2)

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 3-4	20 ug	-0.394	20 ug vs placebo	-0.488	(-0.947, -0.029)	0.0374
	5 ug	-0.378	5 ug vs placebo	-0.472	(-0.912, -0.032)	0.0359
	1 ug	-0.075	1 ug vs placebo	-0.169	(-0.593, 0.255)	0.4301
	Placebo	0.094				

CI=Confidence Interval
Analysis performed by PROC MIXED.
Source: Table 14.2.1.3. Listing(s): Derived from Listing 16.2.6.1

11.1.2 Secondary Efficacy Endpoints

11.1.2.1 Lesion Area

Secondary endpoint #1a was the change in lesion area from Baseline to the average of weeks 3 and 4. Lesion area was assessed at every study visit (Visit 1 to Visit 7) as part of the OLPClinROM. As for the ulcer area, change in lesion area was presented on a linear scale (change in cm^2) and as relative changes in %, respectively.

Descriptive statistics of the lesion area are given in Text Table 11-5 (linear scale) and Text Table 11-6 (relative scale). On the linear scale, the Baseline averages were nearly comparable between treatment groups with the largest average for the placebo group. Reductions were seen in all treatment groups at Week 3 and Week 4, with the most prominent reduction for the 20µg group at Week 4.

Text Table 11-5: Summary of lesion area (cm^2) by treatment group and visit, [FAS]

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	32	34	40	31
	Mean(SD)	6.472 (5.82)	7.764 (6.82)	6.846 (5.36)	8.840 (13.22)
	Median	4.780	5.560	5.010	4.710
	Min, Max	0.48-23.01	0.24-25.92	1.20-25.29	0.15-67.20
Week 1	n	31	34	39	31
	Mean(SD)	4.515 (5.42)	5.938 (6.80)	5.806 (5.30)	6.535 (8.54)
	Median	2.400	3.855	4.240	3.640
	Min, Max	0.00-21.62	0.00-31.01	0.00-22.40	0.20-37.85
Change from baseline Week 1	n	31	34	39	31
	Mean(SD)	-2.014 (2.25)	-1.826 (3.39)	-1.054 (3.38)	-2.306 (7.80)
	Median	-1.370	-1.000	-0.640	-0.290
	Min, Max	-7.30-0.10	-11.43-5.09	-17.50-6.04	-42.45-3.50

Text Table 11-5: Summary of lesion area (cm^2) by treatment group and visit, [FAS]

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Week 2	n	30	34	37	28
	Mean(SD)	4.252 (4.69)	5.967 (5.90)	4.774 (4.62)	7.150 (12.27)
	Median	2.565	3.490	2.300	2.955
	Min, Max	0.00-15.21	0.01-26.79	0.00-16.20	0.00-58.25
Change from baseline Week 2	n	30	34	37	28
	Mean(SD)	-2.464 (2.66)	-1.797 (3.85)	-1.797 (3.58)	-1.976 (2.77)
	Median	-1.530	-1.315	-1.540	-0.980
	Min, Max	-8.61-1.91	-11.89-5.90	-17.50-5.05	-8.95-3.84
Week 3	n	28	33	36	27
	Mean(SD)	4.206 (5.17)	5.905 (7.25)	4.482 (4.46)	7.809 (13.33)
	Median	1.715	3.380	3.100	3.000
	Min, Max	0.00-20.93	0.00-30.36	0.00-16.63	0.00-59.80
Change from baseline Week 3	n	28	33	36	27
	Mean(SD)	-2.789 (3.31)	-1.958 (3.84)	-1.965 (4.31)	-1.481 (4.46)
	Median	-1.830	-1.430	-2.235	-1.080
	Min, Max	-10.13-3.68	-13.20-7.25	-17.50-8.05	-10.27-14.94
Week 4	n	29	33	35	27
	Mean(SD)	3.342 (4.12)	5.366 (6.74)	4.571 (5.05)	7.466 (15.08)
	Median	1.420	2.880	2.660	3.000
	Min, Max	0.00-12.17	0.00-28.18	0.00-16.95	0.00-73.50
Change from baseline Week 4	n	29	33	35	27
	Mean(SD)	-3.487 (3.40)	-2.497 (4.32)	-1.880 (4.14)	-1.824 (3.96)
	Median	-2.100	-2.190	-1.700	-1.600
	Min, Max	-11.79-3.05	-14.10-12.50	-17.50-10.55	-9.31-6.76

N=number of patients in the subgroup considered or in total; n=number of patients among N; SD=Standard Deviation
Source: Table 14.2.1.1 c. Listing(s): Derived from Listing 16.2.6

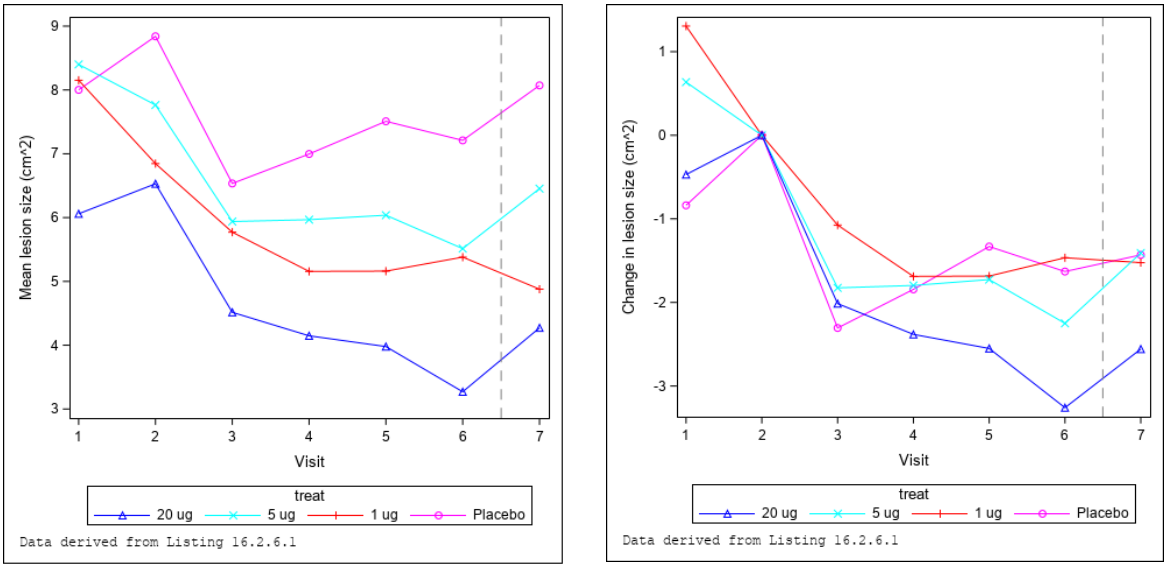
On the relative scale, reductions of lesion areas between Baseline and Week 3 and Week 4 can be seen in all treatment groups. The most prominent reduction was observed for the 20µg group, whereas reductions were nearly comparable for the 1µg, the 5µg and the placebo group.

Text Table 11-6: Summary of lesion area (% changes) by treatment group and visit, [FAS]

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Week 1	n	31	34	39	31
	Mean(SD)	-35.6 (33.39)	-24.9 (36.53)	-12.8 (35.78)	-14.3 (41.05)
	Median	-31.0	-20.7	-11.4	-12.4
	Min, Max	-100.00-8.70	-100.00-56.00	-100.00-56.76	-87.79-81.35
Week 2	n	30	34	37	28
	Mean(SD)	-42.5 (34.48)	-9.7 (68.03)	-29.3 (39.20)	-26.8 (38.55)
	Median	-37.4	-33.8	-32.2	-25.3
	Min, Max	-100.00-26.90	-99.81-200.00	-100.00-81.45	-100.00-78.37
Week 3	n	28	33	36	27
	Mean(SD)	-50.4 (38.85)	-29.9 (52.16)	-23.1 (81.52)	-30.3 (54.17)
	Median	-48.4	-34.7	-48.1	-42.3
	Min, Max	-100.00-36.13	-100.00-166.67	-100.00-348.65	-100.00-127.26
Week 4	n	29	33	35	27
	Mean(SD)	-57.4 (36.27)	-33.6 (68.01)	-25.6 (68.95)	-26.5 (59.42)
	Median	-54.5	-43.7	-47.2	-42.3
	Min, Max	-100.00-42.96	-100.00-224.82	-100.00-185.81	-100.00-100.00

N=number of patients in the subgroup considered or in total; n=number of patients among N; SD=Standard Deviation
Source: Table 14.2.1.1 d. Listing(s): Derived from Listing 16.2.6.1

Text Figure 11-2 shows the mean value curves by treatment as absolute values and as change from Baseline for the linear scale. Reductions in lesion area were similar between placebo and the 20µg and 5µg groups after one week. The placebo group reversed in the following weeks but the 20µg group showed continuous reduction over all four weeks.



Text Figure 11-2: Mean lesion area over time (absolute values and change from Baseline on linear scale)
Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up
Source: Figure 14.2.1.4 a + b

The result of the statistical analysis of lesion area on the FAS is summarized in Text Table 11-7 (linear scale) and Table 14.2.1.7 (relative scale). For the primary evaluation of change from Baseline to average of weeks 3 and 4 on linear scale, there were no statistically significant differences although the difference between 20µg and placebo showed a borderline significance (p=0.0661). There were no statistically significant differences shown when analyzing lesion area by visit. When analyzed as relative changes, results were very similar to the analysis on linear scale and no significant differences versus placebo were found.

Text Table 11-7: Statistical analysis of lesion area [FAS]: lesion area (cm^2)

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-2.589	20 ug vs placebo	-0.552	(-2.348, 1.244)	0.5439
	5 ug	-2.150	5 ug vs placebo	-0.113	(-1.867, 1.641)	0.8986
	1 ug	-1.691	1 ug vs placebo	0.346	(-1.352, 2.044)	0.6876
	Placebo	-2.037				
Week 2	20 ug	-2.532	20 ug vs placebo	-0.956	(-2.383, 0.472)	0.1878
	5 ug	-1.698	5 ug vs placebo	-0.121	(-1.516, 1.273)	0.8634
	1 ug	-1.795	1 ug vs placebo	-0.219	(-1.569, 1.131)	0.7485
	Placebo	-1.576				
Week 3	20 ug	-2.651	20 ug vs placebo	-1.576	(-3.442, 0.290)	0.0971
	5 ug	-1.599	5 ug vs placebo	-0.524	(-2.347, 1.298)	0.5702
	1 ug	-1.699	1 ug vs placebo	-0.624	(-2.388, 1.140)	0.4854
	Placebo	-1.075				

Text Table 11-7: Statistical analysis of lesion area [FAS]: lesion area (cm^2)

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 4	20 ug	-3.208	20 ug vs placebo	-1.794	(-3.768, 0.179)	0.0743
	5 ug	-2.074	5 ug vs placebo	-0.660	(-2.588, 1.267)	0.4991
	1 ug	-1.448	1 ug vs placebo	-0.034	(-1.900, 1.832)	0.9714
	Placebo	-1.414				
Week 3-4	20 ug	-2.931	20 ug vs placebo	-1.687	(-3.487, 0.114)	0.0661
	5 ug	-1.836	5 ug vs placebo	-0.592	(-2.351, 1.166)	0.5064
	1 ug	-1.573	1 ug vs placebo	-0.329	(-2.031, 1.373)	0.7028
	Placebo	-1.244				

CI=Confidence Interval
Analysis performed by PROC MIXED.
Source: Table 14.2.1.5. Listing(s): Derived from Listing 16.2.6.1

The result of the statistical analysis of the PPS is presented in Text Table 11-8. It underlines the result of the FAS analyses, emphasizing the effect of the 20µg group. For the per-protocol population a statistically significant difference versus placebo was seen for the 20µg group (p=0.0214) for the change in lesion area from Baseline to the average of weeks 3 and 4 and a statistically significant difference between the 20µg and placebo groups (p=0.0186) at Week 4. The difference between 20µg and placebo at Week 3 showed a borderline significance (p=0.0561).

Text Table 11-8: Statistical analysis of lesion area [PPS]: lesion area (cm^2)

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-2.374	20 ug vs placebo	-0.044	(-2.023, 1.935)	0.9651
	5 ug	-2.246	5 ug vs placebo	0.084	(-1.798, 1.967)	0.9293
	1 ug	-1.886	1 ug vs placebo	0.444	(-1.383, 2.272)	0.6308
	Placebo	-2.330				
Week 2	20 ug	-2.751	20 ug vs placebo	-1.175	(-2.698, 0.348)	0.1292
	5 ug	-2.028	5 ug vs placebo	-0.452	(-1.901, 0.997)	0.5374
	1 ug	-2.175	1 ug vs placebo	-0.598	(-2.005, 0.808)	0.4008
	Placebo	-1.576				
Week 3	20 ug	-2.578	20 ug vs placebo	-1.936	(-3.923, 0.051)	0.0561
	5 ug	-1.781	5 ug vs placebo	-1.139	(-3.029, 0.751)	0.2349
	1 ug	-1.886	1 ug vs placebo	-1.244	(-3.079, 0.591)	0.1819
	Placebo	-0.642				

Text Table 11-8: Statistical analysis of lesion area [PPS]: lesion area (cm^2)

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 4	20 ug	-3.438	20 ug vs placebo	-2.591	(-4.739, -0.442)	0.0186
	5 ug	-2.266	5 ug vs placebo	-1.419	(-3.462, 0.625)	0.1716
	1 ug	-1.678	1 ug vs placebo	-0.830	(-2.814, 1.154)	0.4087
	Placebo	-0.847				
Week 3-4	20 ug	-3.008	20 ug vs placebo	-2.263	(-4.185, -0.342)	0.0214
	5 ug	-2.023	5 ug vs placebo	-1.279	(-3.106, 0.549)	0.1683
	1 ug	-1.782	1 ug vs placebo	-1.037	(-2.812, 0.738)	0.2493
	Placebo	-0.745				

CI=Confidence Interval

Analysis performed by PROC MIXED.
Source: Table 14.2.1.6. Listing(s): Derived from Listing 16.2.6.1

11.1.2.2 Erythema Scores

Erythema scores were assessed at every visit (Visit 1 to Visit 7) as part of the OLPClinROM. Assessments were done using a 5-point scale (‘no’, ‘mild’, ‘moderate’, ‘severe’ or ‘very severe redness’) and a 3-point scale (‘no’, ‘mild’ or ‘marked erythema’) for every anatomical site affected by symptomatic OLP lesions. The change from Baseline to the average of weeks 3 and 4 of the 5-point erythema scales was secondary endpoint #1b, the change from Baseline to the average of weeks 3 and 4 of the 3-point erythema scales was exploratory endpoint #2.

11.1.2.2.1 5-point erythema score

The average of the 5-point erythema scores over the anatomical sites involved and their change from Baseline to the average of weeks 3 and 4 was used as the endpoint for the analysis presented.

Descriptive statistics of the 5-point average erythema score are given in Text Table 11-9. Baseline values and reductions over time were comparable between treatment groups, with a slightly larger reduction for the 20µg group at Week 4.

Text Table 11-9: Summary of 5-point average erythema score by treatment group and visit [FAS]

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	33	34	40	31
	Mean(SD)	2.434 (0.80)	2.612 (0.82)	2.686 (0.75)	2.603 (0.81)
	Median	2.250	2.450	2.750	2.750
	Min, Max	1.00-4.00	1.00-4.00	1.00-4.00	1.00-4.00
Week 1	n	32	34	39	31
	Mean(SD)	1.820 (1.00)	1.833 (0.83)	2.138 (0.86)	2.012 (0.81)
	Median	1.667	1.708	2.000	2.000
	Min, Max	0.00-4.00	0.00-4.00	0.00-4.00	0.67-4.00

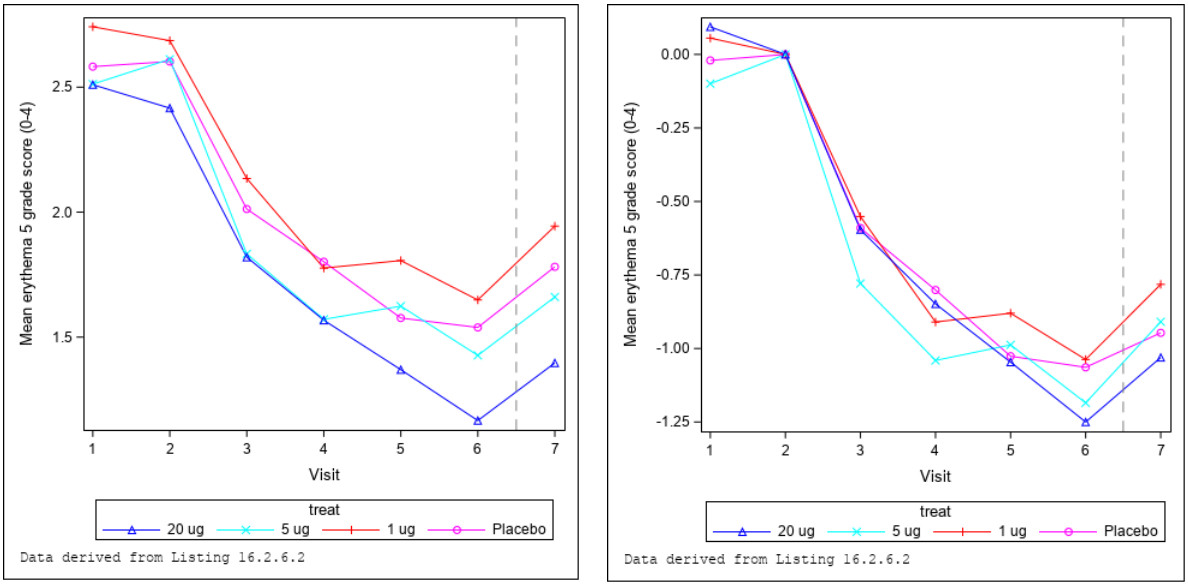
Text Table 11-9: Summary of 5-point average erythema score by treatment group and visit [FAS]

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Change from baseline Week 1	n	32	34	39	31
	Mean(SD)	-0.596 (1.16)	-0.779 (0.89)	-0.579 (0.92)	-0.590 (0.86)
	Median	-0.500	-0.667	-0.333	-0.500
	Min, Max	-4.00-1.50	-4.00-1.00	-4.00-1.00	-2.67-1.00
Week 2	n	31	34	37	28
	Mean(SD)	1.489 (0.97)	1.571 (0.89)	1.713 (0.75)	1.846 (0.99)
	Median	1.250	1.333	2.000	1.750
	Min, Max	0.00-4.00	0.00-4.00	0.00-3.00	0.00-3.00
Change from baseline Week 2	n	31	34	37	28
	Mean(SD)	-0.924 (1.03)	-1.041 (1.02)	-0.979 (1.11)	-0.830 (1.14)
	Median	-0.750	-1.000	-1.000	-0.633
	Min, Max	-4.00-1.00	-4.00-0.50	-4.00-0.67	-4.00-1.00
Week 3	n	29	33	36	27
	Mean(SD)	1.305 (0.97)	1.582 (0.79)	1.725 (0.86)	1.557 (0.85)
	Median	1.000	1.333	1.500	1.667
	Min, Max	0.00-4.00	0.00-4.00	0.00-4.00	0.00-3.25
Change from baseline Week 3	n	29	33	36	27
	Mean(SD)	-1.137 (1.08)	-0.987 (0.71)	-0.978 (1.07)	-1.107 (1.12)
	Median	-1.000	-1.000	-1.000	-1.000
	Min, Max	-4.00-1.00	-2.00-0.00	-4.00-0.50	-4.00-1.00
Week 4	n	30	33	35	27
	Mean(SD)	1.077 (0.85)	1.379 (0.94)	1.537 (0.97)	1.514 (1.03)
	Median	1.000	1.000	1.333	1.333
	Min, Max	0.00-4.00	0.00-4.00	0.00-4.00	0.00-4.00
Change from baseline Week 4	n	30	33	35	27
	Mean(SD)	-1.350 (1.12)	-1.190 (0.95)	-1.169 (1.24)	-1.151 (1.29)
	Median	-1.292	-1.000	-1.000	-1.000
	Min, Max	-4.00-1.00	-3.00-0.00	-4.00-1.00	-4.00-1.00

N=number of patients in the subgroup considered or in total; n=number of patients among N;
SD=Standard Deviation

Source: Table 14.2.2.1 a. Listing(s): Derived from Listing 16.2.6

Text Figure 11-3 shows the 5-point average erythema score mean value curves by treatment as absolute values and as change from Baseline. The erythema score decreased in all treatment groups continuously over the 4 weeks treatment, with the largest reduction seen between Baseline and Week 1 (Visit 3).



absolute values Change

Text Figure 11-3: Mean 5-point average erythema scale over time (absolute values and change from Baseline)
Visit 2=Baseline; Visit 3=Week 1; Visit 4=Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up
Source: Figure 14.2.2.1 a + b

The result of the statistical analysis of the 5-point average erythema score for the FAS is summarized in Text Table 11-10. The largest reduction was seen for the 20µg group, but no statistically significant differences were seen, neither when analyzing the average over weeks 3 and 4 nor individual visits.

Text Table 11-10: Statistical analysis of 5-point average erythema score [FAS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-0.733	20 ug vs placebo	-0.122	(-0.529, 0.286)	0.5549
	5 ug	-0.792	5 ug vs placebo	-0.181	(-0.581, 0.220)	0.3739
	1 ug	-0.549	1 ug vs placebo	0.062	(-0.325, 0.449)	0.7516
	Placebo	-0.611				
Week 2	20 ug	-0.914	20 ug vs placebo	-0.177	(-0.620, 0.266)	0.4315
	5 ug	-0.971	5 ug vs placebo	-0.234	(-0.669, 0.201)	0.2894
	1 ug	-0.828	1 ug vs placebo	-0.091	(-0.511, 0.330)	0.6706
	Placebo	-0.737				
Week 3	20 ug	-1.076	20 ug vs placebo	-0.131	(-0.557, 0.295)	0.5445
	5 ug	-0.902	5 ug vs placebo	0.043	(-0.376, 0.462)	0.8390
	1 ug	-0.778	1 ug vs placebo	0.168	(-0.237, 0.573)	0.4140
	Placebo	-0.945				

Text Table 11-10: Statistical analysis of 5-point average erythema score [FAS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 4	20 ug	-1.288	20 ug vs placebo	-0.319	(-0.809, 0.172)	0.2013
	5 ug	-1.071	5 ug vs placebo	-0.101	(-0.584, 0.381)	0.6781
	1 ug	-0.881	1 ug vs placebo	0.089	(-0.377, 0.555)	0.7071
	Placebo	-0.969				
Week 3-4	20 ug	-1.182	20 ug vs placebo	-0.225	(-0.649, 0.200)	0.2968
	5 ug	-0.987	5 ug vs placebo	-0.029	(-0.446, 0.388)	0.8903
	1 ug	-0.829	1 ug vs placebo	0.128	(-0.275, 0.532)	0.5303
	Placebo	-0.957				

CI=Confidence Interval

Analysis performed by PROC MIXED.
Source: Table 14.2.2.2. Listing(s): Derived from Listing 16.2.6.2

The result of the statistical analysis of the PPS underlines the result of the FAS analyses, with no statistically significant differences between treatment groups (for details, please refer to Table 14.2.2.3).

11.1.2.2.2 3-point erythema score

Descriptive statistics of the 3-point average erythema score are given in Text Table 11-11. Baseline values and reductions over time were comparable between treatment groups, with a slightly larger reduction for the 20µg group at Week 4.

Text Table 11-11: Summary of 3-point average erythema score by treatment group and visit [FAS]

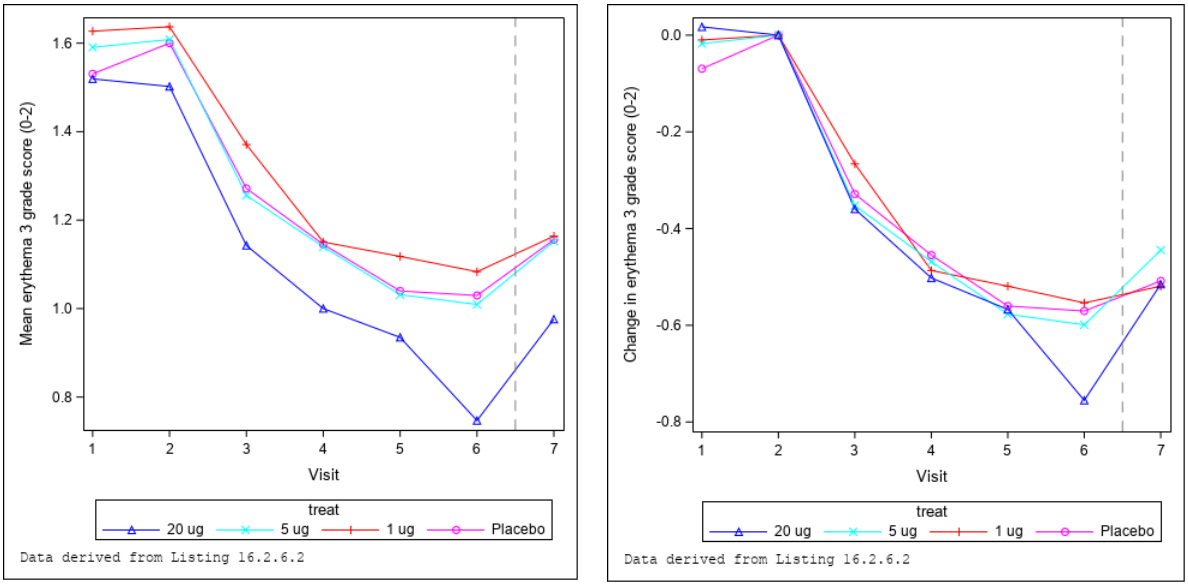
Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	33	34	40	31
	Mean(SD)	1.517 (0.46)	1.608 (0.43)	1.637 (0.38)	1.600 (0.46)
	Median	1.500	1.667	1.708	1.667
	Min, Max	0.50-2.00	1.00-2.00	1.00-2.00	0.33-2.00
Week 1	n	32	34	39	31
	Mean(SD)	1.143 (0.57)	1.256 (0.51)	1.368 (0.50)	1.272 (0.52)
	Median	1.000	1.000	1.400	1.333
	Min, Max	0.00-2.00	0.00-2.00	0.00-2.00	0.00-2.00
Change from baseline Week 1	n	32	34	39	31
	Mean(SD)	-0.359 (0.66)	-0.352 (0.47)	-0.286 (0.54)	-0.328 (0.50)
	Median	-0.250	-0.250	0.000	0.000
	Min, Max	-2.00-1.00	-2.00-0.25	-2.00-1.00	-1.50-0.33

Text Table 11-11: Summary of 3-point average erythema score by treatment group and visit [FAS]

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Week 2	n	31	34	37	28
	Mean(SD)	0.968 (0.47)	1.140 (0.47)	1.118 (0.49)	1.173 (0.60)
	Median	1.000	1.000	1.000	1.000
	Min, Max	0.00-2.00	0.00-2.00	0.00-2.00	0.00-2.00
Change from baseline Week 2	n	31	34	37	28
	Mean(SD)	-0.518 (0.54)	-0.469 (0.60)	-0.540 (0.61)	-0.444 (0.61)
	Median	-0.500	-0.500	-0.500	-0.267
	Min, Max	-2.00-0.50	-2.00-1.00	-2.00-0.50	-2.00-0.33
Week 3	n	29	33	36	27
	Mean(SD)	0.894 (0.63)	1.002 (0.47)	1.071 (0.53)	1.033 (0.52)
	Median	1.000	1.000	1.000	1.000
	Min, Max	0.00-2.00	0.00-2.00	0.00-2.00	0.00-2.00
Change from baseline Week 3	n	29	33	36	27
	Mean(SD)	-0.597 (0.75)	-0.594 (0.47)	-0.591 (0.56)	-0.581 (0.59)
	Median	-0.500	-0.667	-0.500	-0.500
	Min, Max	-2.00-1.00	-1.50-0.00	-2.00-0.25	-2.00-0.33
Week 4	n	30	33	35	27
	Mean(SD)	0.697 (0.51)	0.979 (0.65)	1.033 (0.60)	1.022 (0.54)
	Median	0.750	1.000	1.000	1.000
	Min, Max	0.00-2.00	0.00-2.00	0.00-2.00	0.00-2.00
Change from baseline Week 4	n	30	33	35	27
	Mean(SD)	-0.794 (0.69)	-0.617 (0.71)	-0.630 (0.61)	-0.593 (0.72)
	Median	-1.000	-0.500	-0.500	-0.500
	Min, Max	-2.00-1.00	-2.00-1.00	-2.00-0.00	-2.00-0.67

N=number of patients in the subgroup considered or in total; n=number of patients among N; SD=Standard Deviation
Source: Table 14.2.2.1 d. Listing(s): Derived from Listing 16.2.6

Text Figure 11-4 shows the 3-point average erythema score mean value curves by treatment as absolute values and as change from Baseline. The erythema score decreases in all treatment groups continuously over the 4 weeks treatment, with the largest reduction seen between Baseline and Week 1.



absolute values change

Text Figure 11-4: Mean 3-point erythema scale over time (absolute values and change from Baseline)
Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up
Source: Figure 14.2.2.4 a + b

The result of the statistical analysis of the 3-point average erythema score is summarized in Text Table 11-12. The largest reduction was seen for the 20µg group, but no statistically significant differences were seen, neither when analyzing the average over weeks 3 and 4 nor individual visits.

Text Table 11-12: Statistical analysis of 3-point average erythema score [FAS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-0.456	20 ug vs placebo	-0.096	(-0.342, 0.151)	0.4447
	5 ug	-0.373	5 ug vs placebo	-0.013	(-0.255, 0.230)	0.9178
	1 ug	-0.278	1 ug vs placebo	0.082	(-0.152, 0.317)	0.4878
	Placebo	-0.360				
Week 2	20 ug	-0.500	20 ug vs placebo	-0.114	(-0.355, 0.126)	0.3484
	5 ug	-0.388	5 ug vs placebo	-0.002	(-0.238, 0.234)	0.9868
	1 ug	-0.416	1 ug vs placebo	-0.030	(-0.258, 0.198)	0.7953
	Placebo	-0.386				
Week 3	20 ug	-0.550	20 ug vs placebo	-0.055	(-0.318, 0.209)	0.6828
	5 ug	-0.492	5 ug vs placebo	0.003	(-0.256, 0.262)	0.9819
	1 ug	-0.431	1 ug vs placebo	0.064	(-0.186, 0.315)	0.6121
	Placebo	-0.495				

Text Table 11-12: Statistical analysis of 3-point average erythema score [FAS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 4	20 ug	-0.768	20 ug vs placebo	-0.255	(-0.549, 0.040)	0.0893
	5 ug	-0.525	5 ug vs placebo	-0.012	(-0.301, 0.278)	0.9362
	1 ug	-0.469	1 ug vs placebo	0.045	(-0.235, 0.324)	0.7532
	Placebo	-0.514				
Week 3-4	20 ug	-0.659	20 ug vs placebo	-0.155	(-0.401, 0.092)	0.2173
	5 ug	-0.509	5 ug vs placebo	-0.004	(-0.247, 0.238)	0.9716
	1 ug	-0.450	1 ug vs placebo	0.054	(-0.180, 0.289)	0.6468
	Placebo	-0.504				

CI=Confidence Interval

Analysis performed by PROC MIXED.
Source: Table 14.2.2.6. Listing(s): Derived from Listing 16.2.6.2

11.1.2.3 Worst Symptoms at Anatomical Site

The change from Baseline to the average of weeks 3 and 4 for the worst symptoms of anatomical site scale was secondary endpoint #3. The worst symptoms at anatomical site score was assessed at every study visit (Visit 1 to Visit 7) as part of the OLPClinROM. Assessments were done by the patient on a 0-10 scale (‘no symptoms’ to ‘worst symptoms imaginable’) for every anatomical site affected by symptomatic OLP lesions. The average over the anatomical sites affected was used as the endpoint for the analysis presented.

Descriptive statistics of the average worst symptoms at anatomical site score are given in Text Table 11-13. Baseline scores were comparable at Baseline between treatment groups. Scores reduced in all treatment groups, with the largest reduction seen for the 20µg group.

Text Table 11-13: Summary of average worst symptoms at anatomical site score by treatment group and visit [FAS]

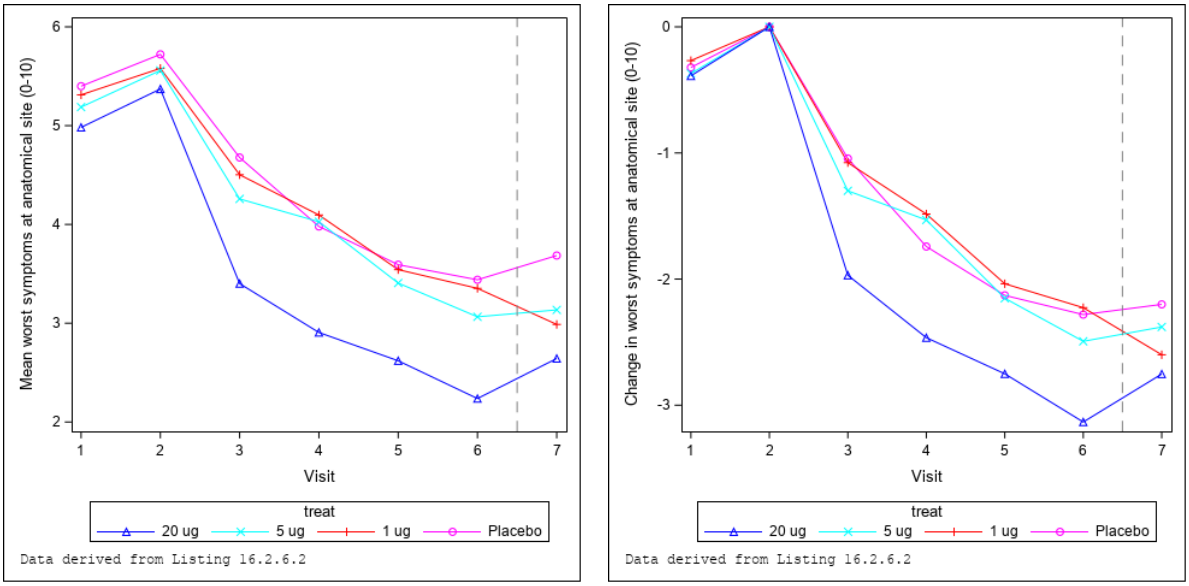
Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	33	34	40	31
	Mean(SD)	5.375 (2.31)	5.558 (2.33)	5.580 (2.37)	5.722 (2.34)
	Median	5.333	6.000	5.875	5.250
	Min, Max	0.00-9.20	1.00-10.00	1.00-9.50	2.00-10.00
Week 1	n	32	34	39	31
	Mean(SD)	3.401 (2.59)	4.258 (2.01)	4.516 (2.48)	4.677 (2.02)
	Median	2.708	4.000	4.667	4.250
	Min, Max	0.00-10.00	1.00-8.00	1.00-9.00	1.25-8.33

Text Table 11-13: Summary of average worst symptoms at anatomical site score by treatment group and visit [FAS]

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Change from baseline Week 1	n	32	34	39	31
	Mean(SD)	-1.970 (1.79)	-1.300 (1.56)	-1.130 (1.68)	-1.044 (1.73)
	Median	-2.000	-1.417	-1.333	-1.000
	Min, Max	-6.00-3.00	-5.00-3.00	-5.50-3.67	-6.00-2.33
Week 2	n	31	34	37	28
	Mean(SD)	2.677 (2.37)	4.027 (2.13)	3.887 (1.97)	4.013 (2.24)
	Median	2.000	4.000	4.000	3.625
	Min, Max	0.00-8.00	0.00-9.00	1.00-8.00	0.20-8.25
Change from baseline Week 2	n	31	34	37	28
	Mean(SD)	-2.641 (1.70)	-1.531 (2.01)	-1.541 (1.93)	-1.833 (2.91)
	Median	-2.667	-1.333	-1.500	-1.500
	Min, Max	-7.00-1.00	-7.00-2.00	-5.60-1.75	-9.00-3.67
Week 3	n	29	33	36	27
	Mean(SD)	2.494 (2.51)	3.237 (1.85)	3.297 (2.15)	3.449 (2.07)
	Median	1.500	3.000	3.167	3.333
	Min, Max	0.00-8.00	0.00-7.00	0.50-7.40	0.00-8.50
Change from baseline Week 3	n	29	33	36	27
	Mean(SD)	-2.829 (2.05)	-2.278 (2.17)	-2.222 (2.19)	-2.392 (2.75)
	Median	-3.000	-2.000	-2.250	-3.000
	Min, Max	-7.00-3.00	-7.00-3.00	-6.67-3.20	-9.00-2.33
Week 4	n	30	33	35	27
	Mean(SD)	2.020 (2.08)	2.885 (2.04)	2.963 (2.22)	3.273 (2.26)
	Median	1.375	3.000	2.800	3.000
	Min, Max	0.00-8.00	0.00-7.00	0.00-8.00	0.00-8.50
Change from baseline Week 4	n	30	33	35	27
	Mean(SD)	-3.376 (2.18)	-2.630 (2.35)	-2.593 (2.51)	-2.567 (2.77)
	Median	-3.875	-2.333	-2.000	-2.750
	Min, Max	-7.50-1.00	-7.67-1.25	-8.00-2.33	-8.50-2.00

N=number of patients in the subgroup considered or in total; n=number of patients among N; SD=Standard Deviation
Source: Table 14.2.2.1 b. Listing(s): Derived from Listing 16.2.6

Text Figure 11-5 shows the average worst symptoms at anatomical site score mean value curves by treatment as absolute values and as change from Baseline. The scores decreased in all treatment groups continuously over the 4 weeks treatment, with the largest reduction seen in the 20µg group.



absolute values Change

Text Figure 11-5: Mean worst symptoms at anatomical site score over time (absolute values and change from Baseline)

Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up
Source: Figure 14.2.2.2 a + b

The result of the statistical analysis of the average worst symptoms at anatomical site score is summarized in Text Table 11-14. No statistically significant differences were seen, but the largest difference was seen between the 20µg and placebo groups reaching borderline significance (p=0.0684) for the primary comparison of the change from Baseline to the average of weeks 3 and 4. Also when analyzing single visits the reduction was larger in the 20µg group with a borderline significance at Week 4 (p=0.0614).

Text Table 11-14: Statistical analysis of worst symptom at anatomical site [FAS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-1.889	20 ug vs placebo	-1.012	(-1.783, -0.242)	0.0105
	5 ug	-1.211	5 ug vs placebo	-0.334	(-1.095, 0.427)	0.3869
	1 ug	-1.049	1 ug vs placebo	-0.172	(-0.906, 0.563)	0.6441
	Placebo	-0.877				
Week 2	20 ug	-2.293	20 ug vs placebo	-0.878	(-1.804, 0.049)	0.0631
	5 ug	-1.266	5 ug vs placebo	0.149	(-0.765, 1.064)	0.7475
	1 ug	-1.300	1 ug vs placebo	0.115	(-0.768, 0.998)	0.7969
	Placebo	-1.415				
Week 3	20 ug	-2.507	20 ug vs placebo	-0.763	(-1.749, 0.224)	0.1285
	5 ug	-1.866	5 ug vs placebo	-0.122	(-1.096, 0.851)	0.8041
	1 ug	-1.835	1 ug vs placebo	-0.091	(-1.032, 0.849)	0.8478
	Placebo	-1.744				

Text Table 11-14: Statistical analysis of worst symptom at anatomical site [FAS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 4	20 ug	-2.748	20 ug vs placebo	-0.995	(-2.038, 0.048)	0.0614
	5 ug	-2.035	5 ug vs placebo	-0.282	(-1.311, 0.748)	0.5890
	1 ug	-1.852	1 ug vs placebo	-0.099	(-1.092, 0.895)	0.8447
	Placebo	-1.753				
Week 3-4	20 ug	-2.634	20 ug vs placebo	-0.887	(-1.841, 0.068)	0.0684
	5 ug	-1.950	5 ug vs placebo	-0.203	(-1.145, 0.739)	0.6710
	1 ug	-1.843	1 ug vs placebo	-0.096	(-1.006, 0.814)	0.8348
	Placebo	-1.747				

CI=Confidence Interval

Analysis performed by PROC MIXED.
Source: Table 14.2.2.4. Listing(s): Derived from Listing 16.2.6.2

11.1.2.4 Clinical Global Impression of Anatomical Site Score

The change form Baseline to the average of weeks 3 and 4 for clinical global impression of anatomical site score (CGIM) was secondary endpoint #1c. The CGIM was assessed at every study visit (Visit 1 to Visit 7) as part of the OLPClinROM. Assessments were done on a 0-4 scale (‘no disease’ to ‘very severe disease’) for every anatomical site affected by symptomatic OLP lesions. The average over the anatomical sites affected was used as the endpoint for the analysis presented.

Descriptive statistics of the average CGIM score are given in Text Table 11-15. Baseline scores were comparable between treatment groups, with slightly lower scores in the 20µg and the 5µg groups. Scores reduced in all treatment groups, with the largest reduction seen for the 20µg group at Week 4.

Text Table 11-15: Summary of average CGIM Score by treatment group and visit [FAS]

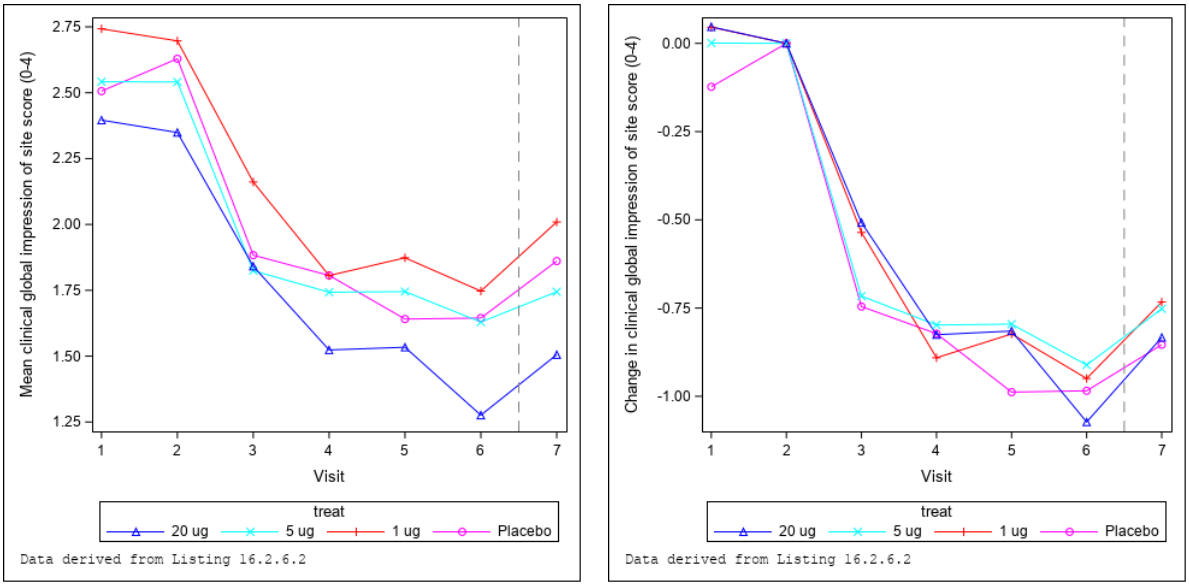
Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	33	34	40	31
	Mean(SD)	2.369 (0.83)	2.541 (0.89)	2.697 (0.76)	2.629 (0.74)
	Median	2.000	2.333	3.000	3.000
	Min, Max	1.00-4.00	1.00-4.00	1.33-4.00	1.33-4.00
Week 1	n	32	34	39	31
	Mean(SD)	1.841 (1.07)	1.825 (0.93)	2.165 (0.83)	1.883 (0.66)
	Median	1.667	1.667	2.000	1.833
	Min, Max	0.00-4.00	0.00-4.00	0.00-4.00	1.00-3.25

Text Table 11-15: Summary of average CGIM Score by treatment group and visit [FAS]

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Change from baseline Week 1	n	32	34	39	31
	Mean(SD)	-0.508 (1.17)	-0.716 (0.89)	-0.562 (0.97)	-0.746 (0.79)
	Median	-0.500	-0.667	-0.200	-0.500
	Min, Max	-4.00-2.00	-4.00-1.00	-4.00-1.00	-2.67-0.50
Week 2	n	31	34	37	28
	Mean(SD)	1.444 (0.93)	1.743 (0.97)	1.727 (0.79)	1.851 (0.92)
	Median	1.000	1.417	2.000	1.875
	Min, Max	0.00-4.00	0.00-4.00	0.00-4.00	0.00-3.33
Change from baseline Week 2	n	31	34	37	28
	Mean(SD)	-0.884 (1.02)	-0.798 (1.08)	-0.963 (1.07)	-0.824 (1.10)
	Median	-1.000	-0.625	-1.000	-0.583
	Min, Max	-4.00-1.00	-4.00-1.00	-4.00-0.67	-4.00-0.67
Week 3	n	29	33	36	27
	Mean(SD)	1.486 (1.02)	1.677 (0.82)	1.790 (0.84)	1.631 (0.93)
	Median	1.250	1.500	1.775	1.600
	Min, Max	0.00-4.00	0.00-4.00	0.00-4.00	0.00-3.50
Change from baseline Week 3	n	29	33	36	27
	Mean(SD)	-0.882 (1.17)	-0.820 (0.76)	-0.933 (1.06)	-1.033 (1.13)
	Median	-1.000	-0.750	-0.875	-1.000
	Min, Max	-4.00-2.00	-2.00-0.20	-4.00-0.50	-4.00-0.50
Week 4	n	30	33	35	27
	Mean(SD)	1.194 (0.97)	1.558 (0.96)	1.645 (1.07)	1.635 (0.99)
	Median	1.000	1.250	1.500	1.500
	Min, Max	0.00-4.00	0.00-4.00	0.00-4.00	0.00-4.00
Change from baseline Week 4	n	30	33	35	27
	Mean(SD)	-1.144 (1.19)	-0.939 (1.02)	-1.076 (1.32)	-1.028 (1.27)
	Median	-1.000	-0.833	-1.000	-0.667
	Min, Max	-4.00-2.00	-3.00-1.00	-4.00-1.00	-4.00-1.00

N=number of patients in the subgroup considered or in total; n=number of patients among N; SD=Standard Deviation
Source: Table 14.2.2.1 c. Listing(s): Derived from Listing 16.2.6

Text Figure 11-6 shows the average CGIM score mean value curves by treatment as absolute values and as change from Baseline. The average CGIM score decreased in all treatment groups continuously over the 4 weeks treatment, with the largest reduction seen between Baseline and Week 1.



absolute values Change

Text Figure 11-6: Mean CGIM score over time (absolute values and change from Baseline)
Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up
Source: Figure 14.2.2.3 a + b

The result of the statistical analysis of the average CGIM score is summarized in Text Table 11-16. No statistically significant differences were seen.

Text Table 11-16: Statistical analysis of average CGIM score [FAS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-0.688	20 ug vs placebo	0.066	(-0.351, 0.483)	0.7550
	5 ug	-0.782	5 ug vs placebo	-0.027	(-0.436, 0.381)	0.8946
	1 ug	-0.529	1 ug vs placebo	0.225	(-0.169, 0.619)	0.2610
	Placebo	-0.754				
Week 2	20 ug	-0.883	20 ug vs placebo	-0.169	(-0.612, 0.274)	0.4522
	5 ug	-0.746	5 ug vs placebo	-0.033	(-0.467, 0.401)	0.8812
	1 ug	-0.779	1 ug vs placebo	-0.065	(-0.484, 0.354)	0.7586
	Placebo	-0.714				
Week 3	20 ug	-0.879	20 ug vs placebo	0.014	(-0.438, 0.465)	0.9524
	5 ug	-0.752	5 ug vs placebo	0.140	(-0.302, 0.582)	0.5314
	1 ug	-0.712	1 ug vs placebo	0.180	(-0.247, 0.607)	0.4049
	Placebo	-0.893				
Week 4	20 ug	-1.093	20 ug vs placebo	-0.289	(-0.802, 0.223)	0.2662
	5 ug	-0.777	5 ug vs placebo	0.027	(-0.475, 0.529)	0.9149
	1 ug	-0.724	1 ug vs placebo	0.080	(-0.404, 0.565)	0.7440
	Placebo	-0.804				

Text Table 11-16: Statistical analysis of average CGIM score [FAS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 3-4	20 ug	-0.986	20 ug vs placebo	-0.138	(-0.596, 0.321)	0.5532
	5 ug	-0.765	5 ug vs placebo	0.084	(-0.365, 0.533)	0.7129
	1 ug	-0.718	1 ug vs placebo	0.130	(-0.303, 0.564)	0.5534
	Placebo	-0.848				

CI=Confidence Interval

Analysis performed by PROC MIXED.
Source: Table 14.2.2.5. Listing(s): Derived from Listing 16.2.6.2

11.1.2.5 OLPSSM Questions 1-7

Questions 1-7 of the OLPSSM score (regarding soreness of OLP when performing daily activities) were completed by the patients daily (Visit 1 to Visit 7) as part of the patient´s diary. Each question was scored on a 0-4 scale (‘not at all sore’ to ‘too sore to do’), giving a total sum score of all 7 questions between 0 and 28. From the daily scores, weekly means were computed and used for analysis. Baseline was the average over the last 7 days of the run-in period (Visit 1 to Visit 2).

The change from Baseline (run-in mean over the 7 days prior to Baseline) to mean over weeks 3 and 4 in OLPSSM sum score was secondary endpoint #2a; the change from Baseline (run-in mean) to mean over weeks 3 and 4 in each of the individual 7 questions was secondary endpoint #2b.

Descriptive statistics of the total sum score are given in Text Table 11-17. Baseline values were nearly comparable between treatment groups with the highest average scores for the 5µg and 1µg groups. The largest reduction was seen for the 20µg group at Week 4.

Text Table 11-17: Summary of OLPSSM Sum Score Q1-7 [FAS]

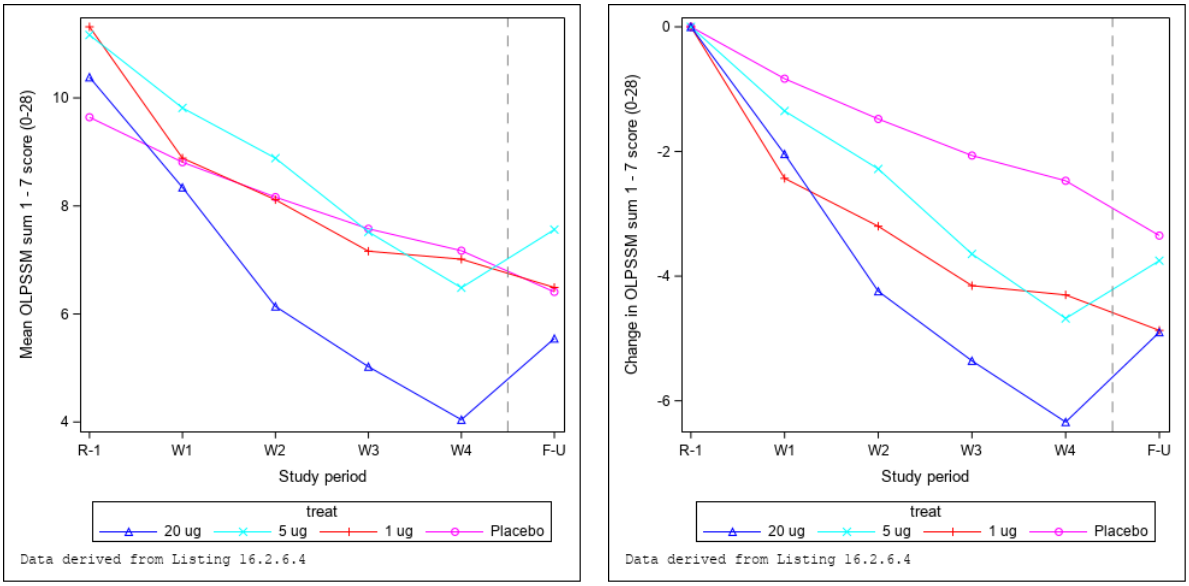
Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	31	32	40	29
	Mean(SD)	10.532 (4.55)	11.165 (4.77)	11.316 (4.53)	9.822 (3.50)
	Median	11.000	10.821	10.488	9.714
	Min, Max	1.86-23.86	4.57-20.14	5.00-21.57	3.86-18.43
Week 1	n	28	33	40	28
	Mean(SD)	8.380 (4.33)	9.820 (4.44)	8.885 (4.10)	8.602 (3.62)
	Median	7.929	10.000	8.200	8.429
	Min, Max	0.17-18.33	2.29-21.00	1.44-19.67	2.88-16.80
Change from baseline Week 1	n	28	32	40	27
	Mean(SD)	-2.142 (3.96)	-1.350 (3.03)	-2.431 (3.69)	-0.832 (2.54)
	Median	-2.593	-1.452	-2.000	-0.500
	Min, Max	-11.43-7.86	-9.60-8.43	-18.86-1.86	-10.14-4.17

Text Table 11-17: Summary of OLPSSM Sum Score Q1-7 [FAS]

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Week 2	n	28	34	34	25
	Mean(SD)	6.299 (4.06)	8.760 (4.60)	8.231 (4.22)	7.682 (3.62)
	Median	6.244	8.071	8.183	7.333
	Min, Max	0.29-15.57	1.25-18.57	0.71-16.29	2.00-14.20
Change from baseline Week 2	n	28	32	34	24
	Mean(SD)	-4.372 (4.49)	-2.280 (4.28)	-3.301 (4.04)	-1.435 (3.19)
	Median	-4.000	-2.586	-2.664	-1.699
	Min, Max	-14.02-4.88	-12.00-7.40	-19.00-3.00	-6.71-6.20
Week 3	n	29	33	35	24
	Mean(SD)	5.045 (4.52)	7.266 (4.28)	6.968 (3.82)	7.062 (3.96)
	Median	4.000	7.000	6.571	6.714
	Min, Max	0.00-20.17	0.00-18.80	0.43-18.14	0.63-15.67
Change from baseline Week 3	n	29	31	35	23
	Mean(SD)	-5.401 (3.89)	-3.870 (4.57)	-4.271 (4.39)	-2.536 (4.02)
	Median	-4.714	-3.524	-3.857	-2.857
	Min, Max	-13.71-0.14	-18.00-6.23	-16.57-2.86	-10.43-5.00
Week 4	n	25	32	35	23
	Mean(SD)	3.952 (3.97)	6.334 (4.60)	6.724 (3.45)	6.800 (3.90)
	Median	2.714	5.429	6.429	7.500
	Min, Max	0.00-16.43	0.00-19.50	0.75-13.00	0.00-14.14
Change from baseline Week 4	n	25	31	35	23
	Mean(SD)	-6.347 (3.66)	-4.938 (5.77)	-4.555 (3.27)	-3.012 (3.95)
	Median	-6.000	-4.243	-4.286	-3.714
	Min, Max	-13.00-0.00	-18.86-6.93	-13.86-0.73	-11.00-3.17

N=number of patients in the subgroup considered or in total; n=number of patients among N; SD=Standard Deviation
Source: Table 14.2.3.1 a. Listing(s): Derived from Listing 16.2.6

Text Figure 11-7 shows the OLPSSM sum score Q1-7 mean value curves by treatment based on the weekly means as absolute values and as change from Baseline. For details on daily mean value curves, refer to Figure 14.2.3.2. The scores decreased in all treatment groups continuously over the 4 weeks treatment, with the largest reduction in the 20µg group compared to the other treatment groups from Week 2.



absolute values change

Text Figure 11-7: Mean OLPSSM sum score Q1-7 over time (absolute values and change from Baseline)
Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up
Source: Figure 14.2.3.3 a + b

The result of the statistical analysis of the OLPSSM sum score Q1-7 is summarized in Text Table 11-18. A highly statistically significant difference was seen between the 20µg group and placebo (p=0.0006) for the primary comparison of change from Baseline to the average over weeks 3 and 4. A reduction in scores was seen also in the 5µg and 1µg groups compared to placebo, but differences did not reach statistical significance. The difference between 20µg and placebo reached statistical significance also for the tests at Week 2, 3 and 4.

Text Table 11-18: Statistical analysis of OLPSSM sum score Q1-7 [FAS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-1.927	20 ug vs placebo	-0.853	(-2.424, 0.718)	0.2845
	5 ug	-1.122	5 ug vs placebo	-0.048	(-1.608, 1.512)	0.9517
	1 ug	-2.180	1 ug vs placebo	-1.106	(-2.598, 0.385)	0.1445
	Placebo	-1.074				
Week 2	20 ug	-4.268	20 ug vs placebo	-2.304	(-4.104, -0.504)	0.0126
	5 ug	-2.064	5 ug vs placebo	-0.100	(-1.887, 1.687)	0.9121
	1 ug	-2.867	1 ug vs placebo	-0.903	(-2.613, 0.806)	0.2973
	Placebo	-1.964				
Week 3	20 ug	-4.788	20 ug vs placebo	-2.712	(-4.545, -0.879)	0.0041
	5 ug	-2.876	5 ug vs placebo	-0.799	(-2.619, 1.020)	0.3862
	1 ug	-3.336	1 ug vs placebo	-1.260	(-3.000, 0.480)	0.1543
	Placebo	-2.077				

Text Table 11-18: Statistical analysis of OLPSSM sum score Q1-7 [FAS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 4	20 ug	-5.561	20 ug vs placebo	-3.224	(-4.974, -1.474)	0.0004
	5 ug	-3.607	5 ug vs placebo	-1.270	(-3.008, 0.467)	0.1504
	1 ug	-3.155	1 ug vs placebo	-0.818	(-2.480, 0.843)	0.3315
	Placebo	-2.337				
Week 3-4	20 ug	-5.170	20 ug vs placebo	-2.967	(-4.643, -1.292)	0.0006
	5 ug	-3.237	5 ug vs placebo	-1.034	(-2.699, 0.630)	0.2208
	1 ug	-3.256	1 ug vs placebo	-1.054	(-2.645, 0.538)	0.1923
	Placebo	-2.203				

CI=Confidence Interval

Analysis performed by PROC MIXED.
Source: Table 14.2.3.2. Listing(s): Derived from Listing 16.2.6.3

Individual questions Q1-7:

Daily mean value curves and weekly mean curves for each of the 7 individual questions contained in the total sum score are shown in Figure 14.2.3.2 and Figure 14.2.3.3.

Each of the seven questions behaved similar to the total sum score with a continuous improvement in scores over the 4 weeks of treatment and with the 20µg group showing the largest improvement compared to the other treatment groups from Week 2.

Descriptive statistics for each week in the treatment period including the change from Baseline and results of the statistical analysis of each of the seven questions are summarized in Table 14.2.3.1 b and Table 14.2.3.2 b.

Statistically significant differences were seen for the 20µg group versus placebo on the primary comparison of a change from Baseline to average of weeks 3 and 4 for questions 1-4 and 6 and 7 *("How sore was your OLP, when brushing teeth, eating, drinking, smiling, talking touching it?")*. Statistical significance was reached for all these questions at Week 3 and Week 4, for questions (1, 2, 3 and 7) also at Week 2.

For question 5 *("How sore was your OLP, when breathing through your mouth?")* no statistically significant difference versus placebo could be observed at any of the time points.

11.1.2.6 Patch Sensation Questionnaire

The patch sensation questionnaire was divided in 11 questions on patch properties, each rated on a 5-grade scale (ranging between 0 [most positive response] and 4 [most negative response]). Due to the content of the questions (e.g. some asking for positive, others for negative characteristics, the order of answering alternatives was not the same for all questions. Some questions needed reversing at the time of analysis. Questionnaire was filled in at Baseline (post first patch application) and at Visit 4 (after 2 weeks of treatment).

Answers have been rearranged so that the most positive outcome is presented first and the most negative outcome last. Positive outcomes were defined as any of the two most positive

answers. The proportion of positive outcomes (score 0 or 1) on each of the 11 questions of the patch sensation questionnaire at both time points were secondary endpoint #4.

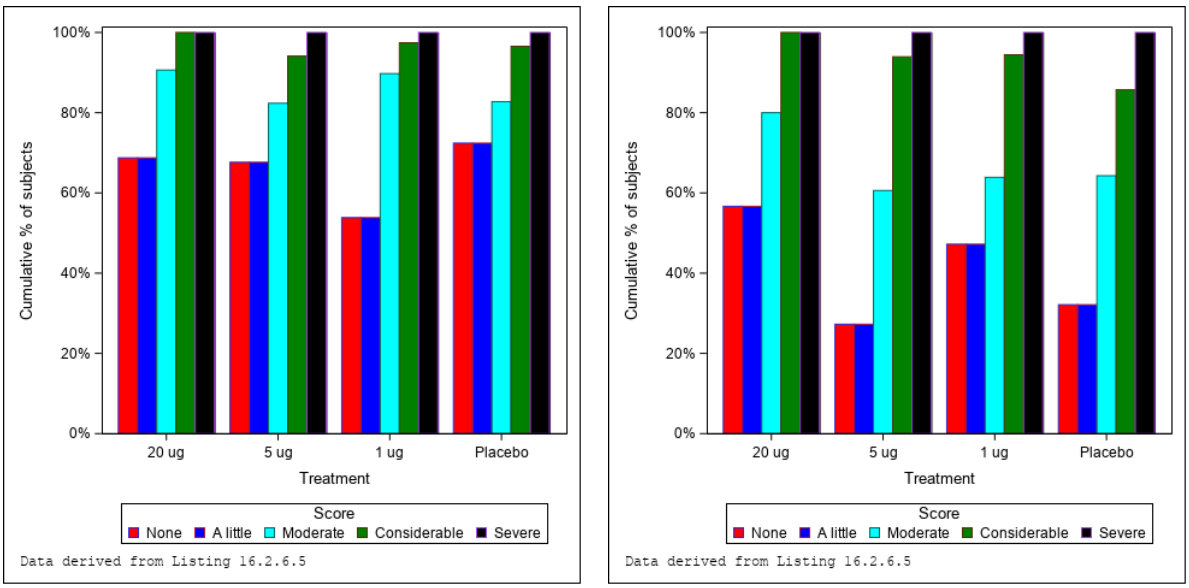
A Summary on answering frequencies for the 11 questions are shown in Text Table 11-19. Histograms showing the distribution of answers cumulatively are presented in Text Figure 11-8 to Text Figure 11-18.

Text Table 11-19: Summary of answers to the Patch Sensation Questionnaire [FAS]

		Frequency of categories[1]			
Variable	**Visit[2]**	**20µg**	**5µg**	**1µg**	**Placebo**
Irritation	2	22/ 0/ 7/ 3/ 0	23/ 0/ 5/ 4/ 2	21/ 0/14/ 3/ 1	21/ 0/ 3/ 4/ 1
	4	17/ 0/ 7/ 6/ 0	9/ 0/11/11/ 2	17/ 0/ 6/11/ 2	9/ 0/ 9/ 6/ 4
Adhesion	2	11/11/ 5/ 1/ 4	10/ 9/ 6/ 1/ 8	11/13/ 6/ 1/ 8	6/ 9/ 7/ 1/ 6
	4	7/ 4/11/ 4/ 4	12/ 7/ 8/ 3/ 3	6/16/ 8/ 1/ 5	5/11/ 4/ 5/ 3
Taste	2	0/13/13/ 3/ 3	0/15/15/ 2/ 2	1/19/13/ 4/ 2	0/17/12/ 0/ 0
	4	1/10/13/ 5/ 1	1/13/13/ 6/ 0	1/16/10/ 8/ 1	0/17/11/ 0/ 0
Application	2	10/13/ 9/ 0/ 0	14/10/10/ 0/ 0	12/14/12/ 1/ 0	9/ 8/11/ 1/ 0
	4	6/13/10/ 1/ 0	11/11/11/ 0/ 0	10/10/16/ 0/ 0	6/13/ 9/ 0/ 0
Speech	2	0/13/15/ 4/ 0	0/13/16/ 4/ 1	0/10/25/ 3/ 1	0/11/16/ 2/ 0
	4	0/ 8/18/ 2/ 2	0/ 7/18/ 6/ 2	0/10/14/ 6/ 6	0/ 6/14/ 4/ 4
Swallowing	2	0/21/10/ 1/ 0	0/24/ 8/ 1/ 1	0/25/12/ 1/ 1	0/20/ 9/ 0/ 0
	4	0/18/12/ 0/ 0	0/16/13/ 3/ 1	0/16/13/ 5/ 2	0/14/ 9/ 3/ 2
Saliva production	2	0/20/ 8/ 3/ 1	0/16/17/ 1/ 0	0/16/16/ 6/ 0	0/13/14/ 1/ 1
	4	0/11/15/ 1/ 3	0/11/16/ 6/ 0	0/11/15/ 7/ 3	0/ 6/13/ 5/ 4
Bothersome	2	0/11/19/ 2/ 0	0/14/16/ 3/ 1	0/ 8/26/ 4/ 0	0/ 7/14/ 8/ 0
	4	0/ 9/17/ 3/ 1	0/ 6/19/ 8/ 0	0/ 6/21/ 7/ 2	0/ 4/17/ 5/ 2
Comfortable	2	4/ 6/20/ 2/ 0	11/ 8/15/ 0/ 0	4/17/16/ 1/ 0	5/ 5/16/ 3/ 0
	4	3/13/14/ 0/ 0	4/12/16/ 1/ 0	1/15/17/ 3/ 0	2/ 9/13/ 4/ 0
Removal	2	16/10/ 6/ 0/ 0	24/ 5/ 1/ 2/ 1	24/ 9/ 4/ 1/ 0	16/ 9/ 3/ 1/ 0
	4	15/11/ 4/ 0/ 0	25/ 6/ 2/ 0/ 0	18/ 9/ 7/ 2/ 0	15/13/ 0/ 0/ 0
Residue	2	0/12/16/ 3/ 1	0/16/12/ 2/ 3	0/17/18/ 2/ 1	0/14/11/ 4/ 0
	4	0/ 2/21/ 5/ 2	0/ 7/21/ 2/ 3	0/ 8/18/ 7/ 3	0/ 5/18/ 2/ 3

[1] ordered with most favorable category first and least favorable category last
[2]Visit 2 = Baseline, Visit 4 = Week 2
Source: Table 14.2.4.1. Listing(s): Derived from Listing 16.2.6.5

Irritation:

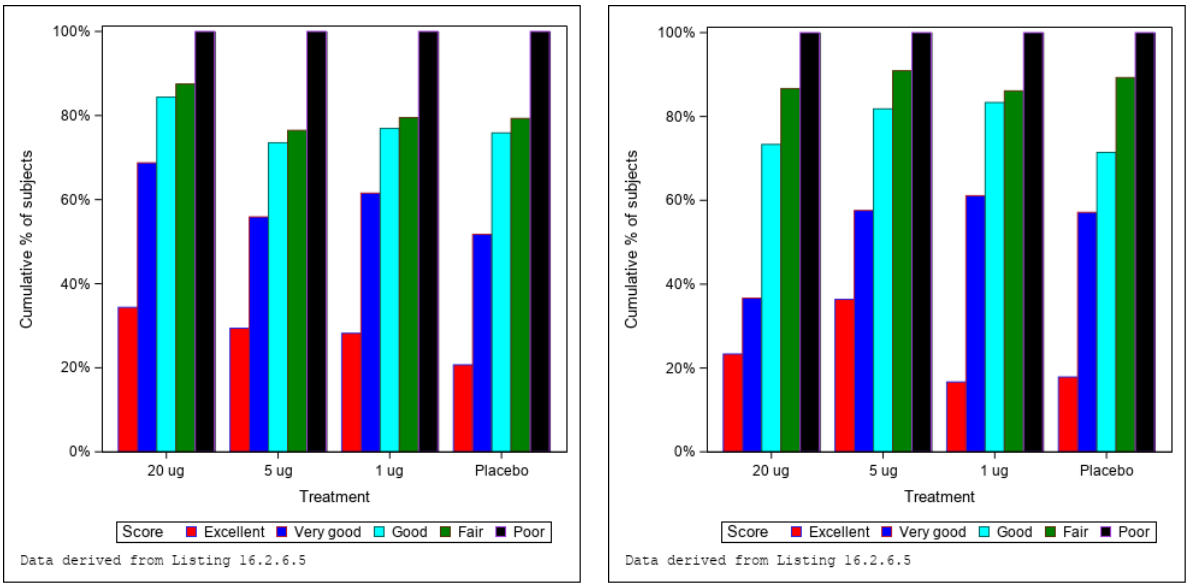


Baseline Visit 4/Week 2

Text Figure 11-8: Histograms on outcome of Patch Sensation Questionnaire – Question 1:
"What do you think about the patches regarding the irritation to the lining of the mouth?"
Source: Figure 14.2.4.1 a +b

Most patients (about 60-70%) felt 'no' irritation from the patches at Baseline (see red and blue column in the figure below). At Visit 4/Week 2 only about 30% of patients in the 5µg and placebo group and about 50% in the 20µg and 1 µg group felt 'no' irritation from the patches.

Adhesion:

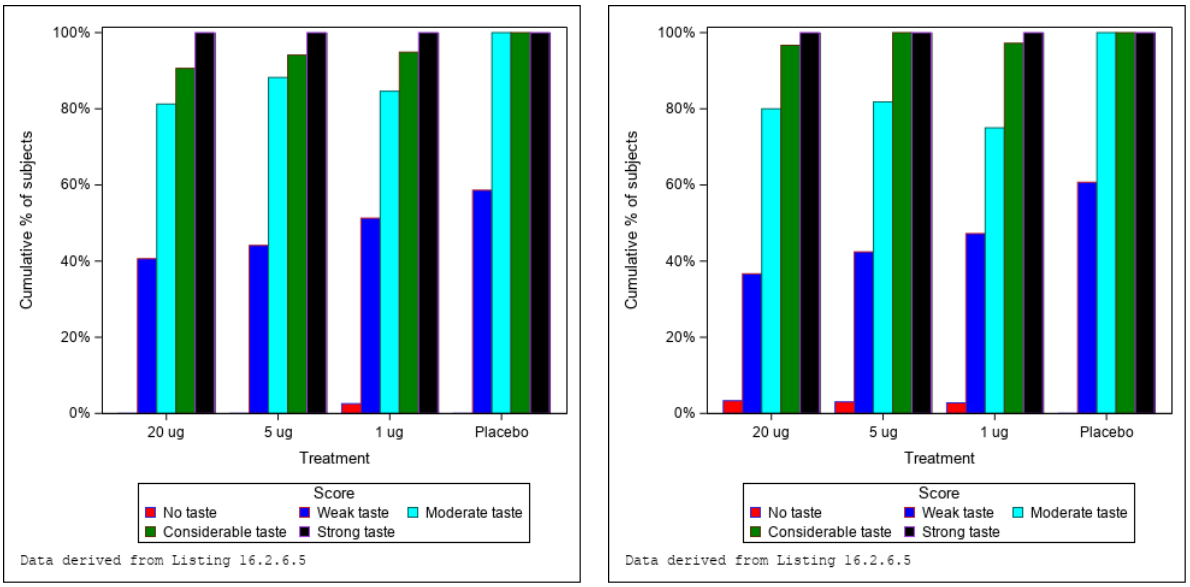


Baseline Visit 4/Week 2

Text Figure 11-9: Histograms on outcome of Patch Sensation Questionnaire – Question 2:
"What do you think about the patches regarding the adhesion to the lining of the mouth?"
Source: Figure 14.2.4.1 c + d

At baseline, patches adhered ‘excellent’ or ‘very good’ for most patients (about 60%) in all treatment groups. This numbers remained at 60% at Visit 4/Week 2, except for the 20µg group, with only 40% ‘excellent’ or ‘very good’ adherence.

Patch Taste:

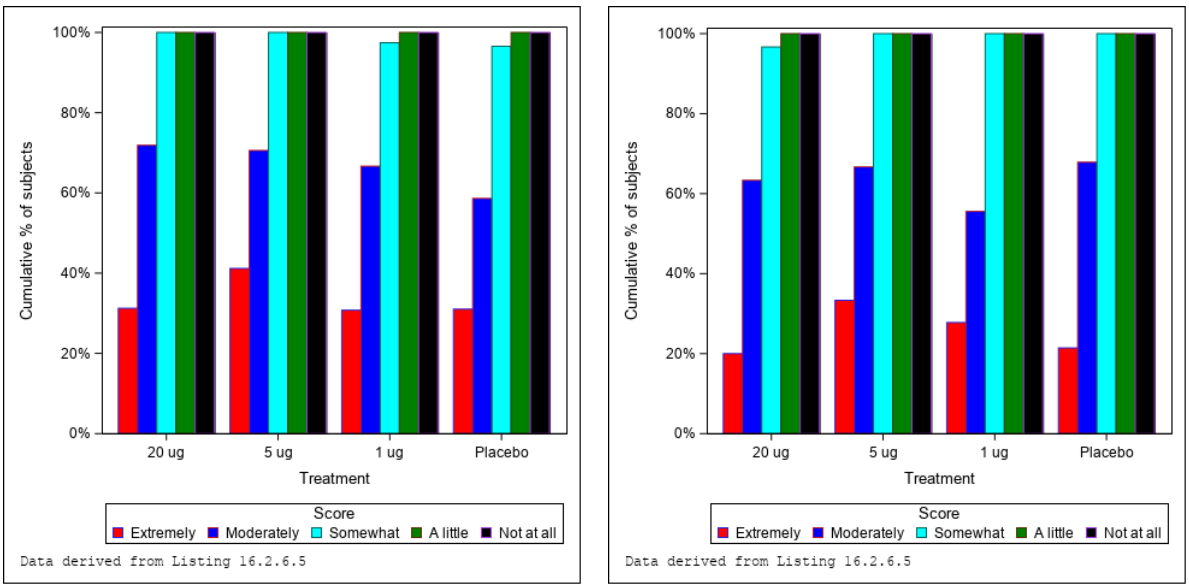


Baseline Visit 4/Week 2

Text Figure 11-10: Histograms on outcome of Patch Sensation Questionnaire – Question 3:
“What taste did the patch have?”
Source: Figure 14.2.4.1 e + f

Patch taste increased with the strength of the clobetasol propionate incorporated. 60% of placebo patients but only 40% of patients in the 20µg group judged the patch with ‘no taste’ or ‘weak taste’. Taste reporting did not differ markedly between Baseline and Visit 4/Week 2.

Acceptability of application procedure:

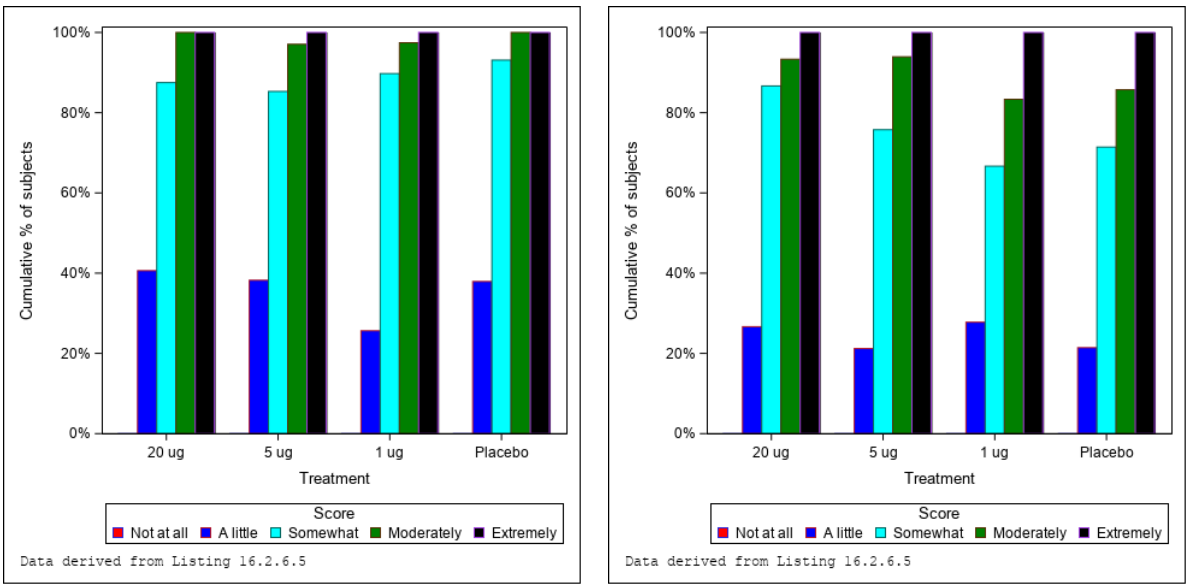


Baseline Visit 4/Week 2

Text Figure 11-11: Histograms on outcome of Patch Sensation Questionnaire – Question 4:
"Overall, how acceptable was the application procedure of the patches to your mouth?"
Source: Figure 14.2.4.1 g + h

In general, for more than 60% of the patients (60-70%) the application procedure was 'extremely' or 'moderately' acceptable at Baseline and at Visit 4/Week 2.

Interference with speech:

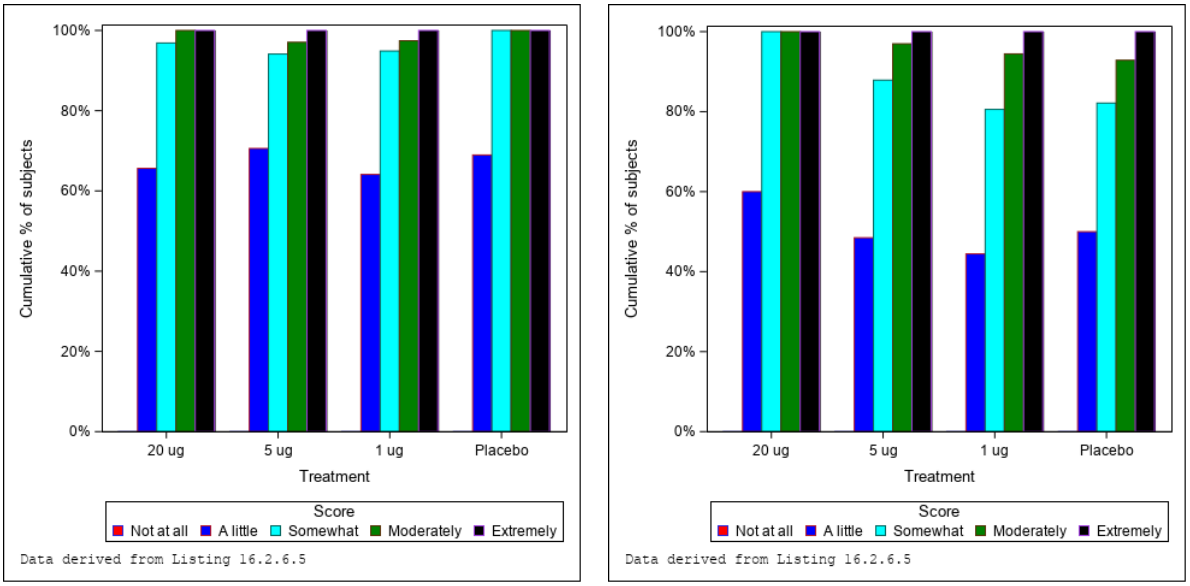


Baseline Visit 4/Week2

Text Figure 11-12: Histograms on outcome of Patch Sensation Questionnaire – Question 5:
"Overall, how much did the patches interfere with your speech?"
Source: Figure 14.2.4.1 i + j

All patients found that the patches interfered with speech. 60-70% of patients rated the patch interfering ‘moderately’, ‘severely’ or ‘extremely’ at Baseline. Percentages even increased (to 70-80%) at Visit 4/Week 2.

Interference with swallowing:

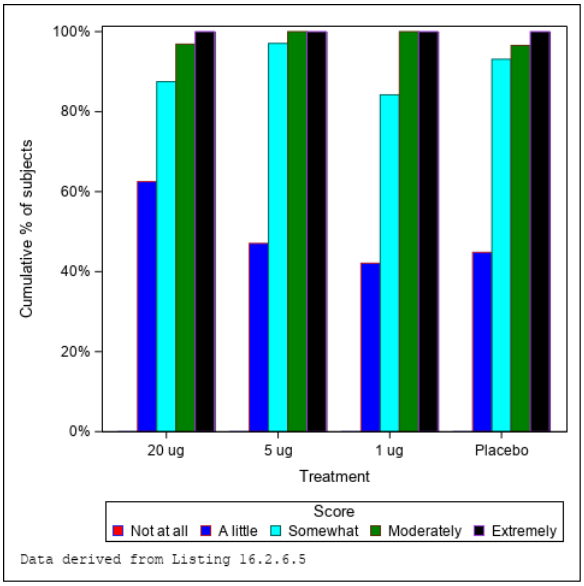


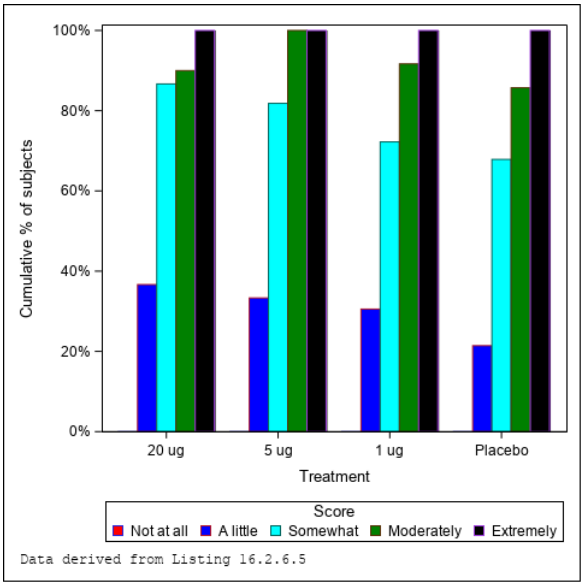
Baseline Visit 4/Week 2

Text Figure 11-13: Histograms on outcome of Patch Sensation Questionnaire – Question 6:
“Overall, how much did the patches interfere with swallowing?”
Source: Figure 14.2.4.1 k + l

All patients found that the patches interfered with swallowing. But more than 60% (Baseline) and 50-60% (Visit 4/Week 2) of patients in all treatment groups judged the patch to interfere with swallowing only ‘a little’.

Alteration of saliva production:



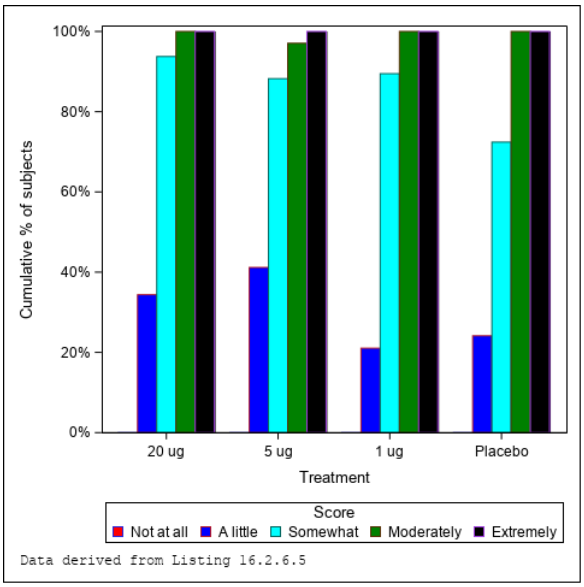


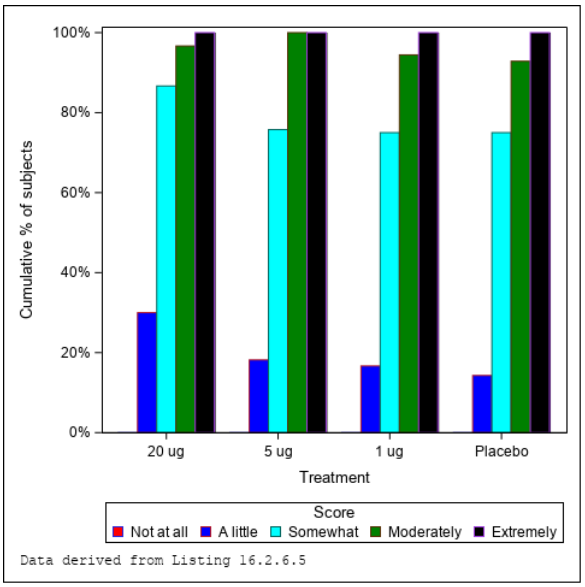
Baseline Visit 4/Week2

Text Figure 11-14: Histograms on outcome of Patch Sensation Questionnaire – Question 7:
"Overall, how much did wearing the patches alter your saliva production?"
Source: Figure 14.2.4.1 m + n

All patients reported that saliva production was altered by wearing the patches. At Baseline, 60-70% of patients rated the change as 'moderately', 'severely' or 'extremely'. These numbers even increased (60-80%) at Visit 4/Week 2.

Inconvenience



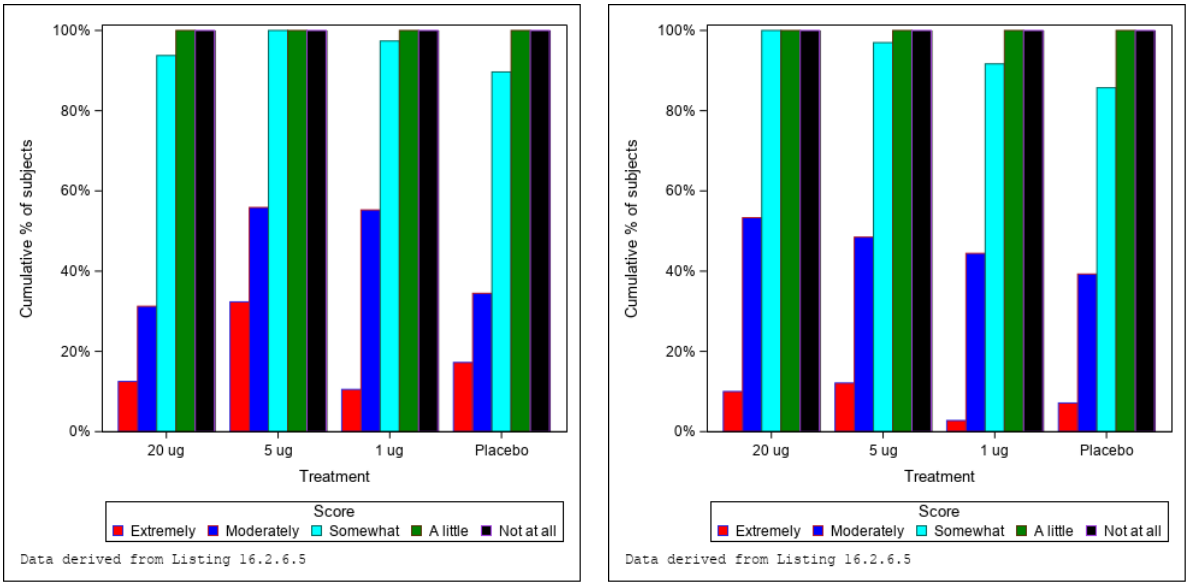


Baseline Visit 4/Week2

Text Figure 11-15: Histograms on outcome of Patch Sensation Questionnaire – Question 8:
"Overall, how bothersome were the patches?"
Source: Figure 14.2.4.1 o + p

All patients reported the patches to be bothersome in any way and most patients at Baseline and Visit 4/Week 2 rated "somewhat bothersome". In general, inconvenience was a bit more pronounced at Visit 4/Week 2.

Comfort

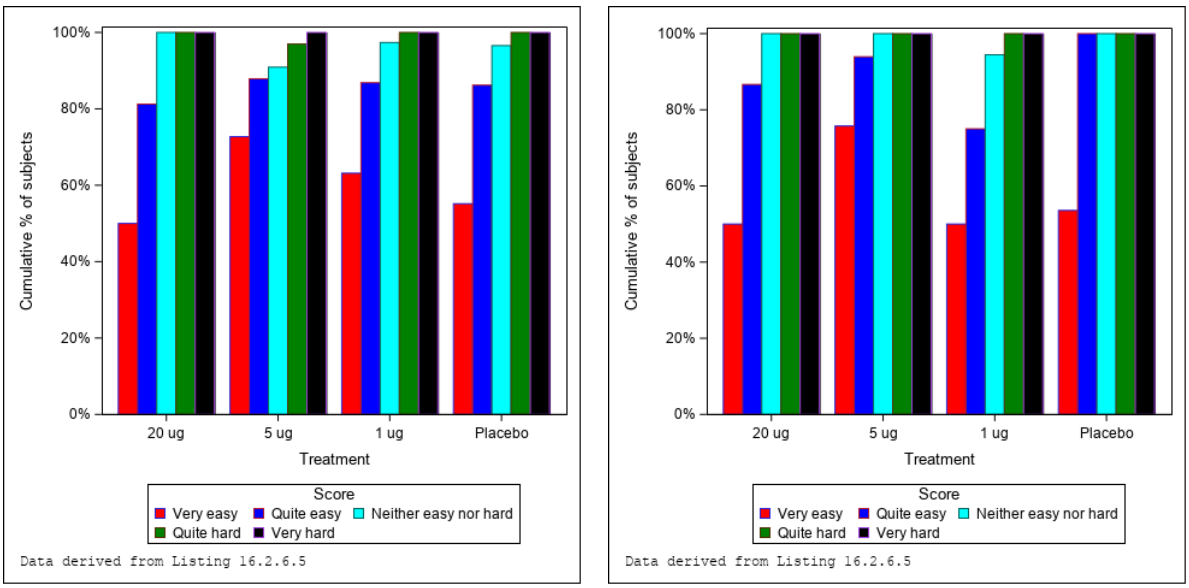


Baseline Visit 4/Week2

Text Figure 11-16: Histograms on outcome of Patch Sensation Questionnaire – Question 9:
"Overall, how comfortable were the patches to wear?
Source: Figure 14.2.4.1 q + r

Patches were reported to be comfortable by about half of the patients at both visits. At Baseline percentages of patients having judged the patches as 'extremely' or 'moderately' comfortable ranged between about 30% (20µg and placebo group) and about 60% (5µg and 1µg group). At visit 4/Week 2 percentages ranged between 40-50% in all treatment groups.

Removal:

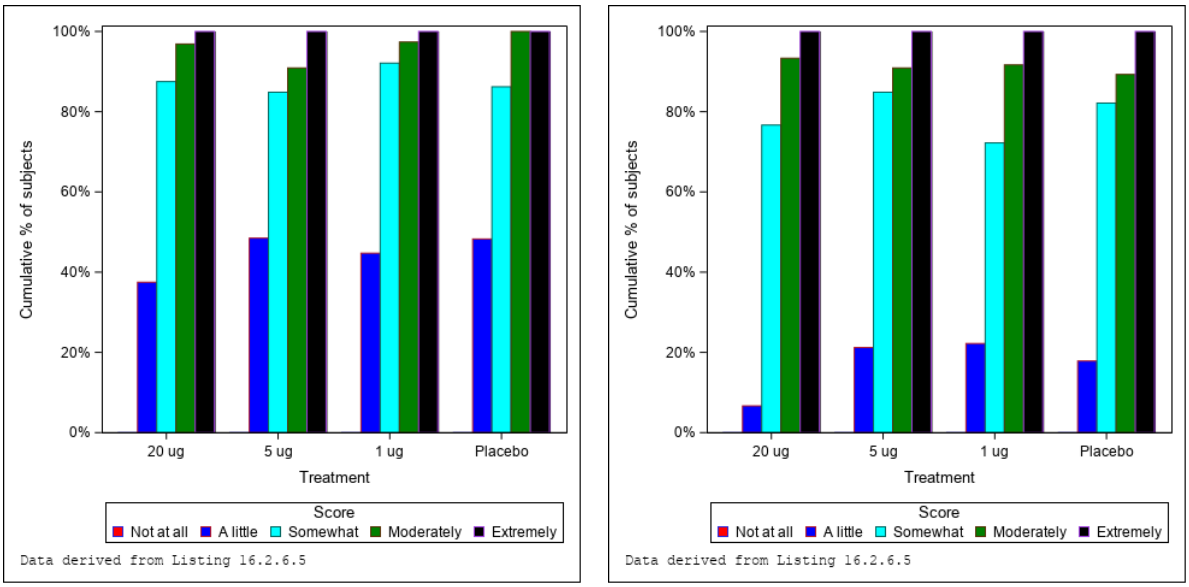


Baseline Visit 4/Week2

Text Figure 11-17: Histograms on outcome of Patch Sensation Questionnaire – Question 10:
"How easy was it for you to remove the patch?"
Source: Figure 14.2.4.1 s + t

Removal of patches was reported as 'very easy' or 'quite easy' by most of the patients (about 80% in all treatment groups at Baseline and a range from about 70% to 100% at Visit 4/Week 2.

Residue



Baseline Visit 4/Week2

Text Figure 11-18: Histograms on outcome of Patch Sensation Questionnaire – Question 11:
"Did you feel a residue after removing the patch?"
Source: Figure 14.2.4.1 u + v

All patients felt a residue after patch removal. Notable residues of patches after removal were reported for nearly half of the patients at Baseline (percentages of patients answering 'not at all' or 'a little' about 40-50%) and by most of the patients at Visit 4/Week 2 (percentages of patients answering "not at all" or "a little" about 10-20%).

Statistical analysis of treatment differences

Positive responses to the individual questions were compared between the treatment groups using logistic regression. The results are summarized in Table 14.2.4.2.

No statistically significant differences were seen for any of the questions at either Baseline or Visit 4/Week 2. At Visit 4/Week 2 there were borderline significances in favor of the 20µg group (versus placebo) on question 1 on irritation of the patches (p=0.0648) and in favor of placebo (versus 20µg) on question 3 on taste of the patches (p=0.0628).

11.1.2.7 Successful Patch Applications

Secondary endpoint #5 was the proportion of patients with successful (>=80% of days on treatment) patch applications defined as an adhesion time of one target patch >=30 minutes during the 4 weeks treatment.

Adhesion times were assessed in the patient´s diary reporting the number of patches applied (morning and evening), the number of patches still adhering 5 minutes after application (morning and evening), the number of patches still adhering after 2 hours and for one pre-defined target patch, the time from application to detachment (adhesion time). Summary statistics on patch adhesion data are given in Text Table 11-20. For details on daily mean value curves of adhesion times, refer to Figure 14.2.5.1.

The mean percentage of patches adhering after 5 minutes varied between 96.5% and 98.4% for morning applications and between 93.4% and 97.3% for evening applications. Median values show 100% of patches in all treatment groups and for both morning and evening adhering after 5 minutes.

The mean percentage of patches adhering after 2 hours ranged between 37.9% and 47.3% with highest numbers for placebo. However, distribution was skew, and the medians were generally lower (21% in the 20µg, 26% in the 5 µg group, 23% in the 1µg groups, and 44% in placebo group).

The median time the target patch was adhering ranged from 90 minutes in the 20µg and 5µg groups to 93 minutes in the 1µg group and 105 minutes in the placebo group.

No or minimal change in adhesion time over time could be noted for all treatment groups. (For details, refer to the Statistical Report in Appendix 16.1.9.)

Text Table 11-20: Summary of patch application data [FAS]

Time	Variable	Stat	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Morning Application	Days recorded	N	33	34	40	30
		median	27	28	28	28
		range	1 - 34	11 - 34	1 - 32	1 - 33
	Patches applied	mean	68	87	79	76
		median	56	79	77	68
		range	2 - 174	22 - 174	4 - 174	6 - 168
	% adhering at 5 min	mean	96.6	98.1	98.4	96.5
		median	100.0	100.0	100.0	100.0
		range	48 - 100	73 - 100	80 - 100	67 - 100
	% adhering at 2 h[1]	N	33	34	40	30
		mean	37.9	40.0	39.2	47.3
		median	21	26	23	44
		range	0.0 - 100	0.0 - 100	0.0 - 100	0.0 - 100
	Target adh. time (min)	mean	85.2	83.0	84.6	90.1
		median	90	90	93	105
		range	22 - 125	0 - 122	20 - 125	20 - 125
Evening Application	Days recorded	N	33	34	40	30
		median	27	28	27	28
		range	1 - 33	8 - 35	3 - 32	1 - 32
	Patches applied	mean	67	86	80	76
		median	56	79	78	69
		range	2 - 145	16 - 168	4 - 168	3 - 168
	% adhering at 5 min	mean	93.4	95.4	96.0	97.3
		median	100.0	100.0	100.0	100.0
		range	23 - 100	64 - 100	0.0 - 100	77 - 100

[1] counting '0' if entries were missing at 2hours

For Target adhesion times the median times was calculated on the subject level.
Source: Table 14.2.5.1. Listing(s): Derived from Listing 16.2.6.5

Successful patch application was reached, if the adhesion time for the target patch was 30 minutes or more on at least 80% of all days. The proportion of patients with successful application were compared between treatment groups using logistic regression and the result is summarized in Table 14.2.5.2. The odds for successful applications was highest in the placebo group but no statistically significant differences between active drug treatment groups (1, 5, and 20µg) and placebo treatment was shown.

The individual success rate (percent of days with an adhesion time of at least 30 minutes) were also compared using ANOVA and result is summarized in Text Table 11-21. Success rates ranged between 90.3% and 94.9% but no statistically significant differences versus placebo were shown.

Text Table 11-21: Statistical analysis of successful patch applications (ANOVA) [FAS]

Variable	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Target (%)	20 µg	92.7	20 ug vs placebo	-2.1	(-12.6, 8.3)	0.6845
	5 µg	90.3	5 ug vs placebo	-4.5	(-14.7, 5.7)	0.3849
	1 µg	94.9	1 ug vs placebo	0.1	(-9.8, 10.0)	0.9850
	Placebo	94.8				
Analysis performed by PROC MIXED. Success rate: % of days in treatment period with >= 30 min adhesion; CI=Confidence Interval Source: Table 14.2.5.3. Listing(s): Derived from Listing 16.2.6.5						

11.1.3 Exploratory Efficacy Endpoints

11.1.3.1 Further OLPClinROM assessments

11.1.3.1.1 Cleared ulcers

The proportion of patients with cleared ulcers at each study visit over 4 weeks of treatment was exploratory endpoint #6b. A cleared ulcer was defined as a total ulcer area (all ulcers treated with IMP of a patient) of 0 cm^2. The number of cleared ulcers was assessed via the OLPClinROM at every study visit (Visit 1 to Visit 7).

Descriptive statistics of cleared ulcers by treatment group are given in Text Table 11-22.

The highest proportion of patients with cleared ulcers was seen in the 20µg group when summarizing patients with cleared ulcers at their last assessment in the treatment period (with 53.3% of ulcers cleared) and when summarizing patients with cleared ulcers at any visit during the treatment period (with 60.0% ulcers cleared).

In general, the number of cleared ulcers increased during the treatment period in all treatment groups with the highest percentage in 20µg group at Week 4 (53.6%).

The highest proportion of patients with cleared ulcers at Week 1-3 were seen in the placebo group. Cleared ulcers in this group were all very small at Baseline. For more detailed analyses of individual ulcer areas having cleared during the study by treatment group, refer to Figure 6 of the Statistical Report in Appendix 16.1.9.

Text Table 11-22: Summary of patients with cleared ulcers (total ulcer size=0 cm^2) by visit, [FAS]

Period	20µg n /N (%)	5µg n /N (%)	1µg n /N (%)	Placebo n /N (%)
Week 1	9/30 (30.0)	10/34 (29.4)	11/39 (28.2)	12/31 (38.7)
Week 2	11/29 (37.9)	13/34 (38.2)	12/37 (32.4)	12/28 (42.9)
Week 3	11/27 (40.7)	13/33 (39.4)	10/36 (27.8)	13/27 (48.1)
Week 4	15/28 (53.6)	15/33 (45.5)	13/35 (37.1)	13/27 (48.1)
Follow-up	13/28 (46.4)	11/33 (33.3)	10/34 (29.4)	12/26 (46.2)
Last treatment	16/30 (53.3)	15/34 (44.1)	14/40 (35.0)	14/31 (45.2)
During treatment	18/30 (60.0)	20/34 (58.8)	17/40 (42.5)	18/31 (58.1)

N=number of patients in the subgroup considered or in total; n=number of patients among N; (%)=percentages are based on N¸
Last treatment = Last assessment in treatment period; During treatment: Minimum value during treatment period
Source: Table 14.2.1.8 a. Listing(s): Derived from Listing 16.2.6.1

The outcome is further visualized by histograms in Figure 14.2.1.5 a.

No statistically significant differences were found in the statistical evaluation of cleared ulcers by logistic regression (Table 14.2.1.9 a).

11.1.3.1.2 Cleared lesions

The proportion of patients with cleared lesions at each study visit over 4 weeks of treatment was exploratory endpoint #6a. A cleared lesion was defined as a total lesion area (all lesions treated with IMP of a patient) of 0 cm^2. The number of cleared lesions was assessed via the OLPClinROM at every study visit (Visit 1 to Visit 7).

Descriptive statistics by treatment group are given in Text Table 11-23. Few patients showed cleared lesions during the study, the highest proportion of patients with cleared lesions was seen in the 20µg group when summarizing patients with cleared lesions at their last assessment in the treatment period (9.7%) or when summarizing patients with cleared lesions at any visit during the treatment period (19.7%).

Text Table 11-23: Summary of patients with cleared lesions (total lesion size=0 cm^2) by visit [FAS]

Period	20µg n /N (%)	5µg n /N (%)	1µg n /N (%)	Placebo n /N (%)
Week 1	2/31 (6.5)	1/34 (2.9)	1/39 (2.6)	0/31 (0.0)
Week 2	1/30 (3.3)	0/34 (0.0)	2/37 (5.4)	2/28 (7.1)
Week 3	3/28 (10.7)	2/33 (6.1)	2/36 (5.6)	2/27 (7.4)
Week 4	3/29 (10.3)	3/33 (9.1)	3/35 (8.6)	2/27 (7.4)
Follow-up	3/29 (10.3)	1/33 (3.0)	2/34 (5.9)	1/26 (3.8)
Last treatment	3/31 (9.7)	3/34 (8.8)	3/40 (7.5)	2/31 (6.5)
During treatment	6/31 (19.4)	4/34 (11.8)	3/40 (7.5)	2/31 (6.5)

N=number of patients in the subgroup considered or in total; n=number of patients among N; (%)=percentages are based on N¸ Last treatment = Last assessment in treatment period; During treatment: minimum value during treatment
Source: Table 14.2.8.1 b. Listing(s): Derived from Listing 16.2.6.1

The outcome is further visualized by histograms in Figure 14.2.1.5 b.

No statistically significant differences were found in the statistical evaluation of cleared lesions by logistic regression. For details refer to Table 14.2.1.9 b.

11.1.3.2 Further OLPSSM Questions

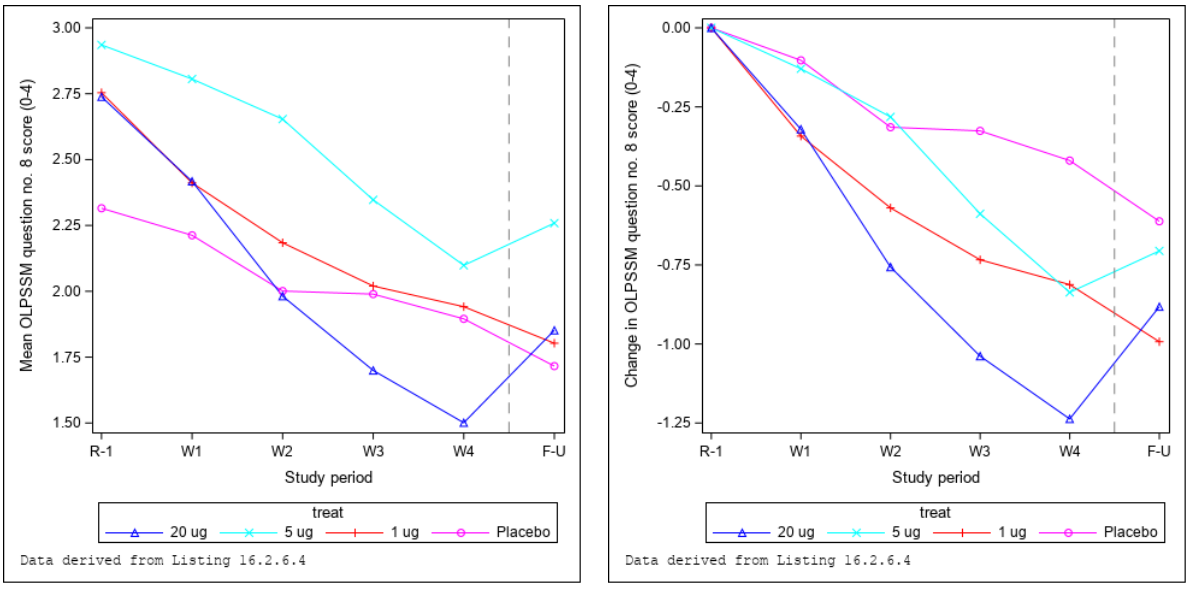
11.1.3.2.1 OLPSSM Questions 8-10

The change in OLPSSM symptom scores questions 8-10 from Baseline (run-in mean = mean of last 7 days prior to Baseline) to mean over weeks 3 and 4 was exploratory endpoint #1a.

Questions 8-10 of the OLPSSM score (regarding severity of OLP symptoms) were completed by the patients daily (Visit 1 to Visit 7) as part of the patient´s diary. They were included as anchor variables for the total sum score. Questions 8 and 9 were scored on a 0-4 scale and question 10 was scored on a 0-10 scale. Low scores indicated no or mild symptoms while high scores indicated very severe symptoms. From the daily scores, weekly means were computed and used for analysis. Baseline was the average over the last 7 days of the run-in period (Visit 1 to Visit 2).

Question 8:

Descriptive statistics of the OLPSSM score for question 8 "*How much of the time did you have OLP symptoms in the past 24 hours while you were awake*?" are given in Text Table 11-24. Text Figure 11-19 shows the OLPSSM Q8 score mean value curves based on the weekly means by treatment as absolute values and as change from Baseline. For details on daily mean value curves, refer to Figure 14.2.3.4. The result of the statistical analysis of the OLPSSM Q8 score is summarized in Text Table 11-25.



absolute values change

Text Figure 11-19: Mean OLPSSM Q8 score over time (absolute values and change from Baseline)
Source: Figure 14.2.3.5 a + b

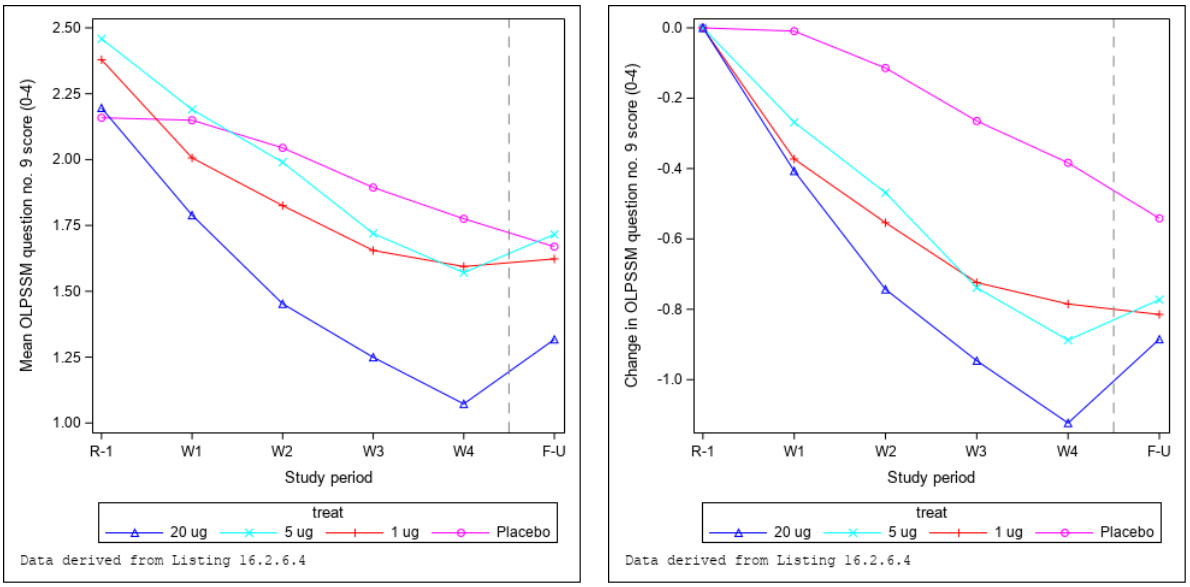
Average baseline scores ranged from 2.3 to 2.9 over the treatment groups. There was a continuous reduction in score over the 4 weeks of treatment for all treatment groups and with

the 20µg group showing the largest reduction compared to the other treatment groups from Week 2.

The difference between 20µg group and placebo reached statistical significance for the primary comparison of the change from Baseline to the average of weeks 3 and 4 and for the individual tests of Week 4 and Week 3 separately.

Question 9:

Descriptive statistics of the OLPSSM score for question 9 "*At their worst, how severe were your oral lichen planus symptoms in the past 24 hours?*" are given in Text Table 11-24. Text Figure 11-20 shows the OLPSSM Q9 score mean value curves based on the weekly means by treatment as absolute values and as change from Baseline. The result of the statistical analysis of the OLPSSM Q9 score is summarized in Text Table 11-25.



absolute values change

Text Figure 11-20: Mean OLPSSM Q9 score over time (absolute values and change from Baseline)
Source: Figure 14.2.3.5

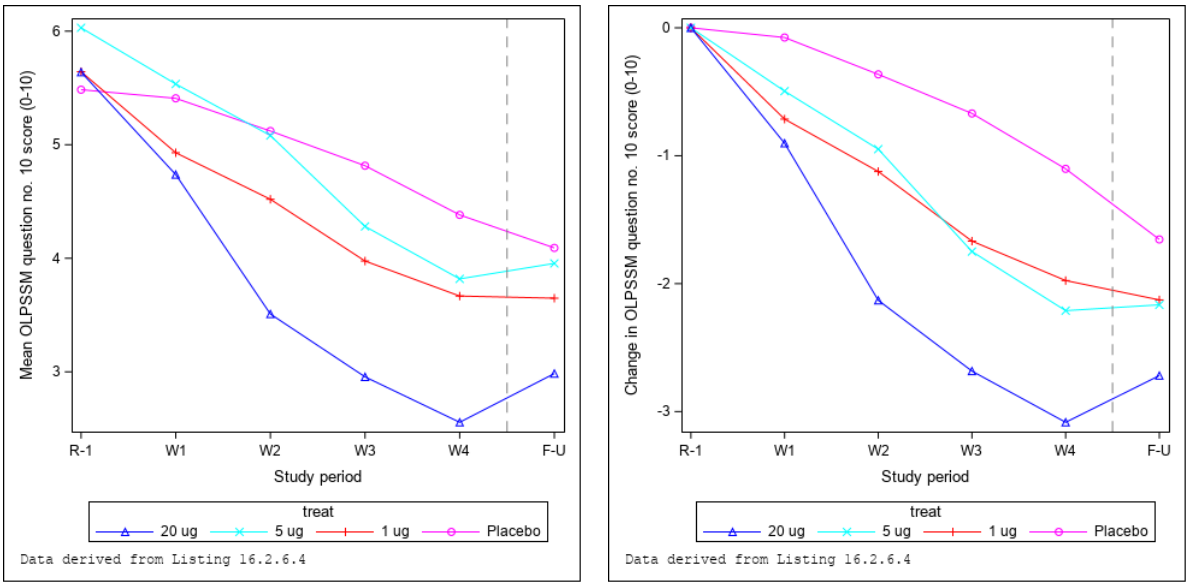
Average baseline scores ranged from 2.2 to 2.5 over the treatment groups. There was a continuous reduction in scores over the 4 weeks of treatment for all treatment groups and with the 20µg group showing the largest reduction compared to the other treatment groups from Week 2.

The difference between 20µg group and placebo reached statistical significance for the primary comparison of the change from Baseline to the average of weeks 3 and 4 and for the individual tests of Week 1-4. The difference between the 5µg group and placebo showed borderline significance (p=0.0620) for the test of average of weeks 3 and 4.

Question 10:

Descriptive statistics of the OLPSSM score for question 10 "*Overall, what was the severity of your oral lichen planus symptoms in the past 24 hours?*?" are given in Text Table 11-24. Text Figure 11-21 shows the OLPSSM Q10 score mean value curves based on the weekly

means by treatment as absolute values and as change from Baseline. The result of the statistical analysis of the OLPSSM Q10 score is summarized in Text Table 11-25.



absolute values change

Text Figure 11-21: Mean OLPSSM Q10 score over time (absolute values and change from Baseline)
Source: Figure 14.2.3.5 e + f

Average baseline scores ranged from 5.5 to 6.0 over the treatment groups. There was a continuous reduction in score over the 4 weeks of treatment for all treatment groups and with the 20µg group showing the largest reduction. The difference between 20µg group and placebo reached statistical significance for the primary comparison of the change from Baseline to the average of week 3 and 4 and for the individual tests of week 1 -4 separately. The difference between the 5µg group and placebo showed borderline significance (p=0.0707) for the test of average of weeks 3 and 4.

Text Table 11-24: Summary of OLPSSM #8 - #10 weekly means [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of OLPSSM question no. 8 score by visit	Baseline	n	31	32	40	29
		Mean(SD)	2.747 (1.17)	2.935 (0.99)	2.754 (0.99)	2.314 (0.87)
		Median	2.857	3.000	2.786	2.143
		Min, Max	1.00-4.00	1.00-4.00	1.00-4.00	1.00-4.00
	Week 1	n	29	33	40	28
		Mean(SD)	2.469 (1.31)	2.842 (0.96)	2.411 (1.04)	2.169 (0.96)
		Median	2.143	2.857	2.402	2.437
		Min, Max	0.17-4.00	1.00-4.00	0.56-4.00	0.86-4.00

Text Table 11-24: Summary of OLPSSM #8 - #10 weekly means [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Change from baseline Week 1	n	28	32	40	27
		Mean(SD)	-0.337 (0.88)	-0.129 (0.62)	-0.342 (0.71)	-0.103 (0.54)
		Median	-0.071	0.000	-0.155	-0.143
		Min, Max	-1.93-2.43	-1.60-1.71	-3.00-0.75	-1.57-1.00
	Week 2	n	29	34	34	25
		Mean(SD)	2.111 (1.33)	2.645 (1.17)	2.245 (1.06)	1.899 (0.93)
		Median	1.800	2.652	2.163	1.375
		Min, Max	0.29-4.00	0.50-4.00	0.14-4.00	1.00-3.63
	Change from baseline Week 2	n	28	32	34	24
		Mean(SD)	-0.753 (1.00)	-0.282 (1.02)	-0.580 (1.01)	-0.371 (0.68)
		Median	-0.544	0.000	-0.343	-0.402
		Min, Max	-2.86-1.53	-2.50-2.67	-3.00-1.57	-1.57-1.26
	Week 3	n	30	33	35	24
		Mean(SD)	1.785 (1.41)	2.306 (1.26)	2.046 (1.13)	1.844 (1.00)
		Median	1.083	2.000	2.000	1.429
		Min, Max	0.00-4.00	0.00-4.00	0.33-4.00	0.13-3.71
	Change from baseline Week 3	n	29	31	35	23
		Mean(SD)	-1.025 (1.04)	-0.618 (1.11)	-0.715 (1.11)	-0.426 (0.89)
		Median	-1.000	-0.214	-0.429	-0.429
		Min, Max	-3.57-0.14	-4.00-2.00	-3.00-1.29	-1.86-1.29
	Week 4	n	26	32	35	23
		Mean(SD)	1.478 (1.37)	2.098 (1.31)	1.880 (0.97)	1.777 (0.97)
		Median	1.000	1.500	1.800	1.429
		Min, Max	0.00-4.00	0.25-4.00	0.75-4.00	0.00-4.00
	Change from baseline Week 4	n	25	31	35	23
		Mean(SD)	-1.263 (1.03)	-0.875 (1.29)	-0.893 (1.12)	-0.536 (0.82)
		Median	-1.429	-0.429	-0.714	-0.571
		Min, Max	-3.14-0.14	-3.75-2.00	-3.25-1.57	-2.14-1.00

Text Table 11-24: Summary of OLPSSM #8 - #10 weekly means [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of OLPSSM question no. 9 score by visit	Baseline	n	32	32	40	29
		Mean(SD)	2.221 (0.79)	2.458 (0.60)	2.379 (0.69)	2.153 (0.58)
		Median	2.143	2.571	2.286	2.000
		Min, Max	0.86-3.83	1.00-4.00	1.29-4.00	1.14-3.14
	Week 1	n	29	33	40	28
		Mean(SD)	1.774 (0.68)	2.181 (0.63)	2.006 (0.70)	2.114 (0.71)
		Median	1.833	2.000	2.000	2.071
		Min, Max	0.17-3.00	1.00-3.43	0.56-3.25	1.00-4.00
	Change from baseline Week 1	n	29	32	40	27
		Mean(SD)	-0.435 (0.62)	-0.268 (0.55)	-0.373 (0.66)	-0.009 (0.46)
		Median	-0.500	-0.286	-0.286	0.000
		Min, Max	-1.69-1.63	-1.43-0.86	-3.00-0.57	-1.00-1.00
	Week 2	n	29	34	34	25
		Mean(SD)	1.479 (0.68)	1.961 (0.77)	1.899 (0.76)	1.934 (0.77)
		Median	1.286	1.929	1.873	1.800
		Min, Max	0.29-3.00	0.25-3.60	0.43-3.43	1.00-3.43
	Change from baseline Week 2	n	29	32	34	24
		Mean(SD)	-0.765 (0.77)	-0.469 (0.78)	-0.542 (0.74)	-0.147 (0.65)
		Median	-0.857	-0.532	-0.429	-0.143
		Min, Max	-2.40-1.29	-1.78-1.36	-2.71-0.71	-1.63-1.20
	Week 3	n	30	33	35	24
		Mean(SD)	1.253 (0.74)	1.667 (0.72)	1.683 (0.77)	1.763 (0.79)
		Median	1.155	1.571	1.714	1.619
		Min, Max	0.00-2.50	0.00-3.00	0.33-3.57	0.25-3.00
	Change from baseline Week 3	n	30	31	35	23
		Mean(SD)	-0.949 (0.65)	-0.795 (0.73)	-0.714 (0.82)	-0.399 (0.79)
		Median	-1.000	-0.857	-0.500	-0.429
		Min, Max	-2.29-0.14	-2.83-0.43	-3.00-0.91	-2.00-1.14
	Week 4	n	26	32	35	23
		Mean(SD)	1.011 (0.75)	1.539 (0.82)	1.586 (0.64)	1.657 (0.75)
		Median	1.000	1.286	1.500	1.778
		Min, Max	0.00-2.57	0.00-3.17	0.63-3.17	0.00-3.00

Text Table 11-24: Summary of OLPSSM #8 - #10 weekly means [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Change from baseline Week 4	n	26	31	35	23
		Mean(SD)	-1.162 (0.63)	-0.949 (0.96)	-0.839 (0.76)	-0.539 (0.75)
		Median	-1.131	-0.857	-0.714	-0.571
		Min, Max	-2.14-0.00	-3.57-0.79	-2.43-0.33	-2.00-0.90
Summary of OLPSSM question no. 10 score by visit	Baseline	n	32	32	40	29
		Mean(SD)	5.682 (2.47)	6.030 (2.00)	5.643 (2.33)	5.479 (1.88)
		Median	6.500	6.286	5.845	5.429
		Min, Max	1.00-9.50	1.00-9.14	1.00-9.29	1.43-8.29
	Week 1	n	29	33	40	28
		Mean(SD)	4.727 (2.25)	5.485 (1.94)	4.929 (2.19)	5.364 (1.85)
		Median	5.125	6.286	5.619	5.500
		Min, Max	0.17-8.50	1.00-8.40	1.00-8.71	1.50-9.00
	Change from baseline Week 1	n	29	32	40	27
		Mean(SD)	-0.939 (1.63)	-0.495 (1.21)	-0.714 (1.37)	-0.076 (1.00)
		Median	-0.714	-0.524	-0.298	0.000
		Min, Max	-4.93-4.13	-3.87-2.29	-5.30-1.29	-2.14-1.45
	Week 2	n	29	34	34	25
		Mean(SD)	3.643 (2.22)	4.929 (2.24)	4.736 (2.15)	4.967 (1.96)
		Median	3.400	4.845	4.917	5.000
		Min, Max	0.29-8.75	1.00-8.71	0.43-8.29	1.50-8.86
	Change from baseline Week 2	n	29	32	34	24
		Mean(SD)	-2.223 (2.02)	-0.949 (1.89)	-1.019 (1.39)	-0.479 (1.72)
		Median	-2.000	-0.940	-1.000	-0.286
		Min, Max	-6.43-3.18	-5.54-3.88	-4.49-1.71	-4.43-2.14
	Week 3	n	30	33	35	24
		Mean(SD)	2.983 (2.38)	4.051 (2.12)	4.054 (2.09)	4.663 (2.16)
		Median	2.286	3.833	4.143	4.500
		Min, Max	0.00-8.00	0.00-8.10	1.00-8.57	0.25-9.00
	Change from baseline Week 3	n	30	31	35	23
		Mean(SD)	-2.721 (1.99)	-1.885 (1.95)	-1.618 (1.90)	-0.922 (2.17)
		Median	-2.905	-1.429	-1.667	-1.286

Text Table 11-24: Summary of OLPSSM #8 - #10 weekly means [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Min, Max	-7.43-0.14	-7.67-1.50	-5.86-1.14	-4.71-2.48
	Week 4	n	26	32	35	23
		Mean(SD)	2.304 (2.16)	3.658 (2.16)	3.623 (2.02)	4.227 (2.17)
		Median	2.268	3.214	3.429	4.000
		Min, Max	0.00-7.71	0.50-7.71	0.86-7.50	0.00-8.57
	Change from baseline Week 4	n	26	31	35	23
		Mean(SD)	-3.142 (1.93)	-2.362 (2.51)	-2.131 (2.07)	-1.431 (2.32)
		Median	-3.286	-1.929	-1.714	-1.429
		Min, Max	-6.86-0.00	-8.00-2.31	-6.45-1.67	-5.86-2.76

Source: Table 14.2.3.3. Listing(s): Derived from Listing 16.2.4.1

Text Table 11-25: Statistical analysis of OLPSSM #8 - #10 weekly means [FAS]

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Analysis of OLPSSM question no. 8 score by visit, ANCOVA	Week 1	20 ug	-0.269	20 ug vs placebo	-0.125	(-0.488, 0.238)	0.4965
		5 ug	-0.057	5 ug vs placebo	0.087	(-0.275, 0.449)	0.6352
		1 ug	-0.305	1 ug vs placebo	-0.162	(-0.504, 0.181)	0.3520
		Placebo	-0.144				
	Week 2	20 ug	-0.656	20 ug vs placebo	-0.274	(-0.739, 0.191)	0.2450
		5 ug	-0.132	5 ug vs placebo	0.250	(-0.214, 0.714)	0.2888
		1 ug	-0.480	1 ug vs placebo	-0.099	(-0.537, 0.340)	0.6570
		Placebo	-0.382				
	Week 3	20 ug	-0.801	20 ug vs placebo	-0.532	(-1.050, -0.015)	0.0439
		5 ug	-0.308	5 ug vs placebo	-0.040	(-0.556, 0.477)	0.8794
		1 ug	-0.538	1 ug vs placebo	-0.269	(-0.757, 0.220)	0.2778
		Placebo	-0.269				
	Week 4	20 ug	-0.972	20 ug vs placebo	-0.600	(-1.117, -0.082)	0.0235
		5 ug	-0.523	5 ug vs placebo	-0.151	(-0.667, 0.366)	0.5643
		1 ug	-0.581	1 ug vs placebo	-0.209	(-0.697, 0.279)	0.3983
		Placebo	-0.372				
	Week 3-4	20 ug	-0.886	20 ug vs placebo	-0.566	(-1.065, -0.066)	0.0268
		5 ug	-0.415	5 ug vs placebo	-0.095	(-0.593, 0.404)	0.7073
		1 ug	-0.561	1 ug vs placebo	-0.241	(-0.712, 0.230)	0.3130
		Placebo	-0.320				

Text Table 11-25: Statistical analysis of OLPSSM #8 - #10 weekly means [FAS]

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Analysis of OLPSSM question no. 9 score by visit, ANCOVA	Week 1	20 ug	-0.439	20 ug vs placebo	-0.371	(-0.650, -0.092)	0.0096
		5 ug	-0.226	5 ug vs placebo	-0.158	(-0.439, 0.122)	0.2666
		1 ug	-0.356	1 ug vs placebo	-0.288	(-0.555, -0.022)	0.0343
		Placebo	-0.068				
	Week 2	20 ug	-0.735	20 ug vs placebo	-0.589	(-0.931, -0.247)	0.0009
		5 ug	-0.354	5 ug vs placebo	-0.208	(-0.552, 0.136)	0.2344
		1 ug	-0.473	1 ug vs placebo	-0.327	(-0.654, -0.001)	0.0497
		Placebo	-0.146				
	Week 3	20 ug	-0.827	20 ug vs placebo	-0.627	(-0.974, -0.281)	0.0005
		5 ug	-0.512	5 ug vs placebo	-0.312	(-0.661, 0.036)	0.0784
		1 ug	-0.556	1 ug vs placebo	-0.356	(-0.686, -0.025)	0.0354
		Placebo	-0.200				
	Week 4	20 ug	-0.957	20 ug vs placebo	-0.672	(-1.017, -0.327)	0.0002
		5 ug	-0.597	5 ug vs placebo	-0.311	(-0.658, 0.036)	0.0781
		1 ug	-0.555	1 ug vs placebo	-0.269	(-0.598, 0.061)	0.1088
		Placebo	-0.286				
	Week 3-4	20 ug	-0.891	20 ug vs placebo	-0.649	(-0.974, -0.324)	0.0001
		5 ug	-0.553	5 ug vs placebo	-0.311	(-0.637, 0.016)	0.0620
		1 ug	-0.558	1 ug vs placebo	-0.316	(-0.627, -0.006)	0.0456
		Placebo	-0.242				

Text Table 11-25: Statistical analysis of OLPSSM #8 - #10 weekly means [FAS]

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Analysis of OLPSSM question no. 10 score by visit, ANCOVA	Week 1	20 ug	-0.875	20 ug vs placebo	-0.759	(-1.399, -0.118)	0.0206
		5 ug	-0.456	5 ug vs placebo	-0.340	(-0.979, 0.300)	0.2950
		1 ug	-0.763	1 ug vs placebo	-0.647	(-1.255, -0.039)	0.0373
		Placebo	-0.116				
	Week 2	20 ug	-2.065	20 ug vs placebo	-1.672	(-2.521, -0.823)	0.0002
		5 ug	-0.821	5 ug vs placebo	-0.428	(-1.276, 0.420)	0.3193
		1 ug	-1.108	1 ug vs placebo	-0.715	(-1.522, 0.092)	0.0818
		Placebo	-0.393				
	Week 3	20 ug	-2.345	20 ug vs placebo	-1.865	(-2.788, -0.942)	0.0001
		5 ug	-1.345	5 ug vs placebo	-0.864	(-1.786, 0.057)	0.0658
		1 ug	-1.463	1 ug vs placebo	-0.983	(-1.859, -0.106)	0.0284
		Placebo	-0.480				
	Week 4	20 ug	-2.574	20 ug vs placebo	-1.783	(-2.760, -0.805)	0.0004
		5 ug	-1.613	5 ug vs placebo	-0.821	(-1.797, 0.155)	0.0984
		1 ug	-1.586	1 ug vs placebo	-0.794	(-1.723, 0.134)	0.0928
		Placebo	-0.792				
	Week 3-4	20 ug	-2.456	20 ug vs placebo	-1.823	(-2.737, -0.908)	0.0001
		5 ug	-1.475	5 ug vs placebo	-0.841	(-1.755, 0.072)	0.0707
		1 ug	-1.534	1 ug vs placebo	-0.900	(-1.769, -0.031)	0.0424
		Placebo	-0.633				

CI=Confidence Interval

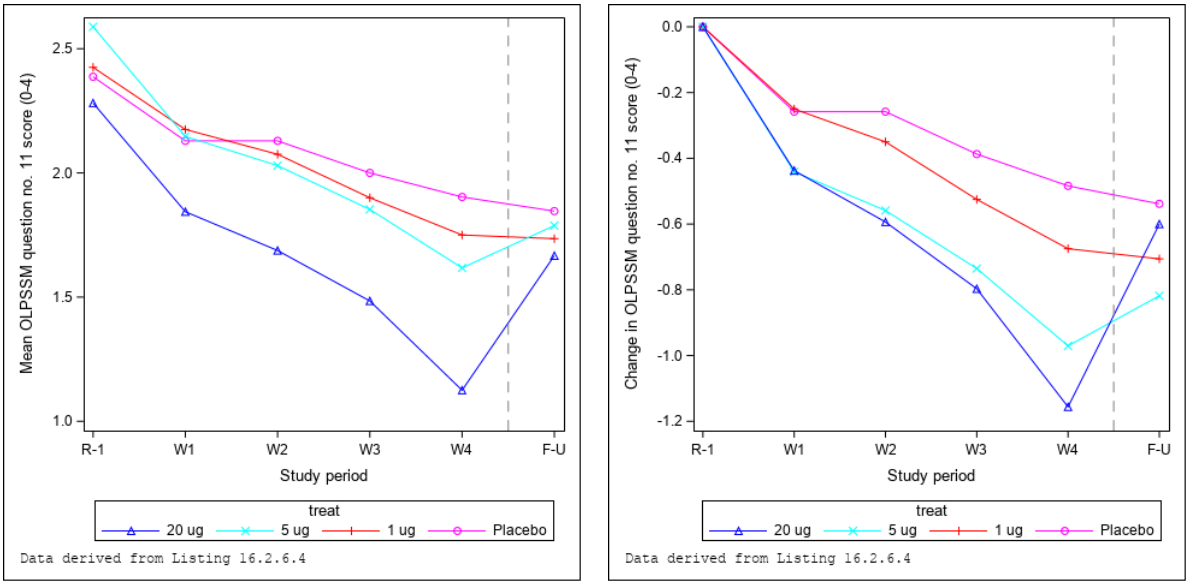
Analysis performed by PROC MIXED.
Source: Table 14.2.3.4. Listing(s): Derived from Listing 16.2.6.3

11.1.3.2.2 OLPSSM Questions 11 and 12

The change in OLPSSM weekly symptom scores Q11 from Baseline to Week 4 was exploratory endpoint 1b and the OLPSSM score Q12 at Week 4 was exploratory endpoint #1c. Both items were included as anchor variables for the OLPSSM total sum score.

Question 11:
Question 11 *("How severe were your OLP symptoms over the past week?")* was answered at every study visit (Visit 1 to Visit 7) and scored on a 0-4 scale (ranging from 'none' – 'very severe').

Descriptive statistics of the OLPSSM score for question 11 are given in Text Table 11-26. Text Figure 11-22 shows the mean value curves based on the weekly means by treatment as absolute values and as change from Baseline. The result of the statistical analysis of the OLPSSM Q11 score is summarized in Text Table 11-27.



absolute values change

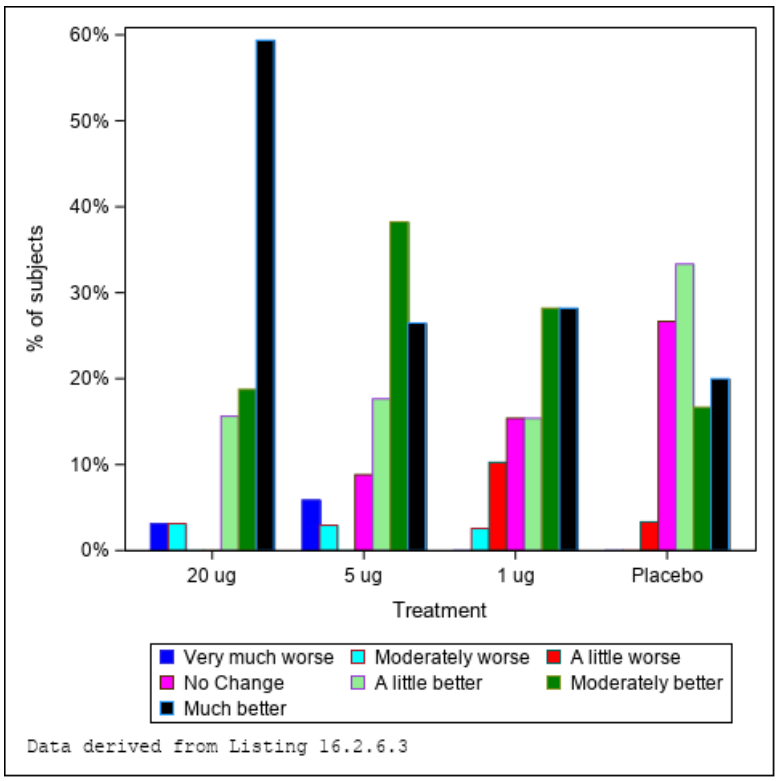
Text Figure 11-22: Mean OLPSSM Q11 score over time (absolute values and change from Baseline)
Source: Figure 14.2.3.5 g + h

Average baseline scores ranged from 2.3 to 2.6 over the treatment groups. There was a continuous reduction in scores over the 4 weeks of treatment for all treatment groups and with the 5µg and 20µg groups showing the largest reductions. The difference between 20µg group and placebo reached statistical significance for the primary comparison of the change from Baseline to the average of weeks 3 and 4 and for the individual tests of Week 2-4.

Question 12:

Question 12 ("*How did your overall OLP symptoms change since you started this study?")* was answered once at Visit 6/Week 4 (end of treatment) using a scale ranging from -3 ('very much worse') to + 3 ('very much better').

Descriptive statistics of the OLPSSM score for question 12 are given in Text Table 11-26. Text Figure 11-23 shows a histogram of OLPSSM Q12 distribution and the result of the statistical analysis is summarized in Text Table 11-27.



Text Figure 11-23: Histogram with distribution of OLPSSM Q12 scores at V6 (end of treatment)
Source: Figure 14.2.3.6

Average scores were higher in the 20µg group with almost 60% of patients answering very much better (+3). The difference between 20µg group and placebo reached statistical significance.

Text Table 11-26: Summary of OLPSSM #11 - #12 weekly means [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of OLPSSM question no. 11 score by visit	Baseline	n	33	34	40	31
		Mean(SD)	2.273 (0.76)	2.588 (0.78)	2.425 (0.75)	2.387 (0.67)
		Median	2.000	3.000	2.000	2.000
		Min, Max	1.00-4.00	1.00-4.00	1.00-4.00	1.00-4.00
	Week 1	n	32	34	39	31
		Mean(SD)	1.844 (0.85)	2.147 (0.70)	2.179 (0.76)	2.129 (0.72)
		Median	2.000	2.000	2.000	2.000
		Min, Max	0.00-4.00	1.00-3.00	1.00-4.00	1.00-4.00

Text Table 11-26: Summary of OLPSSM #11 - #12 weekly means [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Change from baseline Week 1	n	32	34	39	31
		Mean(SD)	-0.438 (0.72)	-0.441 (0.79)	-0.256 (0.72)	-0.258 (0.77)
		Median	0.000	0.000	0.000	0.000
		Min, Max	-2.00-1.00	-3.00-1.00	-2.00-1.00	-2.00-1.00
	Week 2	n	31	34	37	28
		Mean(SD)	1.613 (0.88)	2.029 (0.76)	2.000 (0.71)	2.107 (0.79)
		Median	2.000	2.000	2.000	2.000
		Min, Max	0.00-4.00	1.00-4.00	1.00-4.00	1.00-4.00
	Change from baseline Week 2	n	31	34	37	28
		Mean(SD)	-0.645 (0.98)	-0.559 (0.89)	-0.432 (0.69)	-0.286 (0.81)
		Median	-1.000	-0.500	0.000	0.000
		Min, Max	-2.00-1.00	-3.00-1.00	-2.00-1.00	-2.00-1.00
	Week 3	n	29	33	36	27
		Mean(SD)	1.448 (0.78)	1.818 (0.77)	1.806 (0.79)	1.889 (0.85)
		Median	1.000	2.000	2.000	2.000
		Min, Max	0.00-3.00	0.00-3.00	1.00-4.00	0.00-3.00
	Change from baseline Week 3	n	29	33	36	27
		Mean(SD)	-0.828 (0.93)	-0.788 (0.89)	-0.639 (0.76)	-0.481 (1.01)
		Median	-1.000	-1.000	-1.000	-1.000
		Min, Max	-2.00-1.00	-3.00-1.00	-2.00-1.00	-3.00-1.00
	Week 4	n	30	33	35	27
		Mean(SD)	1.033 (0.85)	1.576 (0.83)	1.600 (0.81)	1.778 (0.64)
		Median	1.000	1.000	2.000	2.000
		Min, Max	0.00-3.00	0.00-3.00	0.00-4.00	0.00-3.00
	Change from baseline Week 4	n	30	33	35	27
		Mean(SD)	-1.233 (0.90)	-1.030 (1.10)	-0.829 (0.98)	-0.593 (1.01)
		Median	-1.000	-1.000	-1.000	-1.000
		Min, Max	-3.00-0.00	-3.00-1.00	-3.00-1.00	-3.00-2.00
Summary of OLPSSM question no. 12 score by visit	Week 4	n	32	34	39	30
		Mean(SD)	2.156 (1.44)	1.500 (1.60)	1.410 (1.45)	1.233 (1.17)
		Median	3.000	2.000	2.000	1.000
		Min, Max	-3.00-3.00	-3.00-3.00	-2.00-3.00	-1.00-3.00

N=number of patients in the subgroup considered or in total; n=number of patients among N; SD=Standard Deviation
Source: Table 14.2.3.5. Listing(s): Derived from Listing 16.2.4.1

Text Table 11-27: Statistical analysis of OLPSSM Q11 score (Week 2-4 and average of weeks 3 and 4) by treatment group – FAS

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Analysis of OLPSSM question no. 11 score by visit, ANCOVA	Week 1	20 ug	-0.435	20 ug vs placebo	-0.225	(-0.546, 0.097)	0.1693
		5 ug	-0.300	5 ug vs placebo	-0.090	(-0.409, 0.228)	0.5763
		1 ug	-0.218	1 ug vs placebo	-0.008	(-0.314, 0.298)	0.9600
		Placebo	-0.210				
	Week 2	20 ug	-0.550	20 ug vs placebo	-0.386	(-0.756, -0.016)	0.0410
		5 ug	-0.343	5 ug vs placebo	-0.179	(-0.545, 0.187)	0.3354
		1 ug	-0.252	1 ug vs placebo	-0.088	(-0.440, 0.265)	0.6228
		Placebo	-0.164				
	Week 3	20 ug	-0.635	20 ug vs placebo	-0.434	(-0.799, -0.070)	0.0199
		5 ug	-0.404	5 ug vs placebo	-0.203	(-0.563, 0.158)	0.2687
		1 ug	-0.340	1 ug vs placebo	-0.139	(-0.486, 0.208)	0.4304
		Placebo	-0.201				
	Week 4	20 ug	-1.000	20 ug vs placebo	-0.705	(-1.109, -0.301)	0.0008
		5 ug	-0.594	5 ug vs placebo	-0.299	(-0.699, 0.101)	0.1417
		1 ug	-0.461	1 ug vs placebo	-0.165	(-0.550, 0.219)	0.3966
		Placebo	-0.295				
	Week 3-4	20 ug	-0.824	20 ug vs placebo	-0.577	(-0.920, -0.235)	0.0011
		5 ug	-0.498	5 ug vs placebo	-0.251	(-0.591, 0.088)	0.1451
		1 ug	-0.400	1 ug vs placebo	-0.153	(-0.479, 0.173)	0.3554
		Placebo	-0.247				

Text Table 11-27: Statistical analysis of OLPSSM Q11 score (Week 2-4 and average of weeks 3 and 4) by treatment group – FAS

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Analysis of OLPSSM question no. 12 score by visit, ANCOVA	Week 4	20 ug	1.928	20 ug vs placebo	0.907	(0.206, 1.608)	0.0116
		5 ug	1.254	5 ug vs placebo	0.233	(-0.460, 0.926)	0.5066
		1 ug	1.222	1 ug vs placebo	0.201	(-0.473, 0.875)	0.5560
		Placebo	1.021				
Analysis performed by PROC MIXED. CI=Confidence Interval Source: Table 14.2.3.6. Listing(s): Derived from Listing 16.2.6.3							

11.1.3.3 Guy´s 106 Oral Disease Severity score (ODSS)

Guy's 106 ODSS score divided the oral cavity in 17 anatomical sites with one site score and one activity score for each anatomical site plus an overall pain score on a 0-10 scale ('no pain' to 'most pain imaginable'). The total site score, the disease activity score (sum of the product of the site and activity scores) and the pain score constituted three sub-scores that were added into an overall, the disease severity score. Assessments of Guy´s ODSS were done at each study visit. The change in Guy's disease severity score, Guy's total site score, Guy's total disease activity score and Guy's pain score from Baseline to average of weeks 3 and 4 was exploratory endpoint 3.

Descriptive statistics of the Guy´s disease severity score and each of the three sub-scores are given in Text Table 11-28.

Baseline scores were comparable between treatment groups for the disease severity score as well as for all sub-scores. Reductions could be observed in all treatment groups and all scores, with the largest reduction in the 20µg group at Week 4 for each individual score and the overall score.

Text Table 11-28: Summary of Guy´s 106 ODSS by treatment and visits [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of Guys 106 disease severity score by visit	Baseline	n	33	34	40	31
		Mean(SD)	20.303 (9.05)	20.382 (7.31)	21.200 (7.92)	20.710 (8.34)
		Median	17.000	19.500	20.000	19.000
		Min, Max	6.000-38.000	5.000-35.000	8.000-38.000	9.000-49.000
	Week 1	n	33	34	40	31
		Mean(SD)	15.485 (9.28)	16.824 (8.45)	18.200 (8.51)	18.871 (8.89)
		Median	15.000	15.000	17.000	18.000
		Min, Max	0.000-36.000	1.000-40.000	0.000-37.000	5.000-47.000

Text Table 11-28: Summary of Guy´s 106 ODSS by treatment and visits [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Change from baseline Week 1	n	33	34	40	31
		Mean(SD)	-4.818 (6.03)	-3.559 (3.91)	-3.000 (5.78)	-1.839 (4.94)
		Median	-4.000	-2.500	-2.500	-2.000
		Min, Max	-20.000-7.000	-13.000-5.000	-21.000-13.000	-13.000-9.000
	Week 2	n	31	34	37	28
		Mean(SD)	13.419 (8.59)	17.382 (9.07)	16.892 (8.53)	18.429 (11.30)
		Median	12.000	16.500	15.000	17.000
		Min, Max	0.000-38.000	4.000-42.000	3.000-34.000	2.000-48.000
	Change from baseline Week 2	n	31	34	37	28
		Mean(SD)	-6.839 (6.34)	-3.000 (5.02)	-4.378 (6.16)	-2.286 (8.04)
		Median	-6.000	-3.000	-4.000	-2.000
		Min, Max	-20.000-6.000	-12.000-7.000	-18.000-9.000	-19.000-19.000
	Week 3	n	29	33	36	27
		Mean(SD)	12.897 (8.69)	16.091 (9.81)	15.722 (8.16)	16.111 (10.31)
		Median	14.000	13.000	14.000	15.000
		Min, Max	0.000-34.000	5.000-43.000	3.000-35.000	1.000-48.000
	Change from baseline Week 3	n	29	33	36	27
		Mean(SD)	-7.069 (7.01)	-4.576 (5.61)	-5.361 (5.95)	-4.815 (7.08)
		Median	-5.000	-5.000	-5.000	-5.000
		Min, Max	-21.000-5.000	-14.000-11.000	-20.000-7.000	-22.000-8.000
	Week 4	n	30	33	35	27
		Mean(SD)	11.200 (7.34)	15.515 (10.43)	14.886 (8.57)	16.111 (10.05)
		Median	10.000	12.000	13.000	13.000
		Min, Max	0.000-27.000	2.000-44.000	0.000-33.000	1.000-49.000
	Change from baseline Week 4	n	30	33	35	27
		Mean(SD)	-9.300 (6.74)	-5.152 (8.09)	-6.000 (7.38)	-4.815 (7.10)
		Median	-9.000	-6.000	-6.000	-5.000
		Min, Max	-24.000-3.000	-21.000-17.000	-23.000-10.000	-24.000-10.000

Text Table 11-28: Summary of Guy´s 106 ODSS by treatment and visits [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of Guys 106 total site score by visit	Baseline	n	33	34	40	31
		Mean(SD)	5.030 (3.75)	4.794 (2.50)	5.175 (3.32)	5.032 (2.77)
		Median	4.000	4.500	4.000	4.000
		Min, Max	1.000-14.000	1.000-9.000	1.000-14.000	2.000-13.000
	Week 1	n	33	34	40	31
		Mean(SD)	4.636 (3.89)	4.471 (3.00)	4.625 (3.10)	5.000 (2.72)
		Median	4.000	4.000	4.000	5.000
		Min, Max	0.000-15.000	0.000-13.000	0.000-14.000	1.000-12.000
	Change from baseline Week 1	n	33	34	40	31
		Mean(SD)	-0.394 (1.54)	-0.324 (1.43)	-0.550 (1.84)	-0.032 (1.20)
		Median	0.000	0.000	0.000	0.000
		Min, Max	-5.000-3.000	-3.000-4.000	-7.000-3.000	-2.000-3.000
	Week 2	n	31	34	37	28
		Mean(SD)	4.484 (3.56)	4.882 (2.89)	4.649 (3.14)	4.786 (3.22)
		Median	4.000	5.000	4.000	4.000
		Min, Max	0.000-14.000	1.000-12.000	0.000-13.000	0.000-12.000
	Change from baseline Week 2	n	31	34	37	28
		Mean(SD)	-0.613 (1.78)	0.088 (1.44)	-0.459 (1.35)	-0.143 (1.94)
		Median	0.000	0.000	0.000	0.000
		Min, Max	-7.000-3.000	-3.000-5.000	-4.000-3.000	-4.000-6.000
	Week 3	n	29	33	36	27
		Mean(SD)	4.000 (3.01)	4.818 (3.34)	4.417 (2.90)	4.519 (3.03)
		Median	3.000	4.000	4.000	4.000
		Min, Max	0.000-11.000	0.000-13.000	0.000-11.000	0.000-12.000
	Change from baseline Week 3	n	29	33	36	27
		Mean(SD)	-0.862 (2.00)	-0.091 (1.96)	-0.583 (1.52)	-0.481 (1.63)
		Median	0.000	0.000	0.000	-1.000
		Min, Max	-7.000-2.000	-4.000-5.000	-4.000-2.000	-4.000-4.000
	Week 4	n	30	33	35	27
		Mean(SD)	3.867 (2.97)	4.485 (2.88)	4.257 (2.93)	4.481 (2.97)
		Median	3.000	4.000	4.000	4.000
		Min, Max	0.000-11.000	1.000-12.000	0.000-10.000	0.000-12.000

Text Table 11-28: Summary of Guy´s 106 ODSS by treatment and visits [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Change from baseline Week 4	n	30	33	35	27
		Mean(SD)	-1.300 (1.95)	-0.424 (2.08)	-0.657 (1.91)	-0.519 (1.70)
		Median	-1.000	0.000	0.000	0.000
		Min, Max	-7.000-1.000	-4.000-4.000	-6.000-4.000	-4.000-4.000
Summary of Guys 106 disease activity score by visit	Baseline	n	33	34	40	31
		Mean(SD)	9.545 (5.24)	9.706 (4.45)	10.250 (5.27)	9.903 (5.17)
		Median	8.000	10.000	9.000	9.000
		Min, Max	1.000-21.000	3.000-17.000	3.000-22.000	3.000-28.000
	Week 1	n	33	34	40	31
		Mean(SD)	6.970 (4.98)	7.676 (5.00)	8.675 (5.28)	8.742 (5.51)
		Median	6.000	6.000	7.000	8.000
		Min, Max	0.000-18.000	0.000-22.000	0.000-21.000	0.000-26.000
	Change from baseline Week 1	n	33	34	40	31
		Mean(SD)	-2.576 (3.88)	-2.029 (2.95)	-1.575 (3.53)	-1.161 (3.48)
		Median	-2.000	-2.000	-1.000	-2.000
		Min, Max	-12.000-5.000	-10.000-5.000	-12.000-5.000	-8.000-6.000
	Week 2	n	31	34	37	28
		Mean(SD)	5.806 (4.29)	7.765 (5.42)	7.946 (5.35)	8.857 (7.14)
		Median	5.000	6.500	7.000	7.000
		Min, Max	0.000-19.000	0.000-21.000	0.000-21.000	0.000-28.000
	Change from baseline Week 2	n	31	34	37	28
		Mean(SD)	-3.710 (4.33)	-1.941 (3.81)	-2.514 (3.93)	-1.000 (5.06)
		Median	-3.000	-2.000	-2.000	-0.500
		Min, Max	-13.000-6.000	-10.000-7.000	-12.000-5.000	-12.000-10.000
	Week 3	n	29	33	36	27
		Mean(SD)	6.069 (4.58)	7.576 (6.00)	7.278 (4.86)	7.444 (6.31)
		Median	6.000	5.000	6.000	6.000
		Min, Max	0.000-18.000	0.000-25.000	0.000-19.000	0.000-28.000

Text Table 11-28: Summary of Guy´s 106 ODSS by treatment and visits [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Change from baseline Week 3	n	29	33	36	27
		Mean(SD)	-3.379 (4.47)	-2.333 (4.07)	-3.028 (3.81)	-2.519 (4.05)
		Median	-3.000	-3.000	-3.000	-2.000
		Min, Max	-14.000-4.000	-10.000-9.000	-12.000-4.000	-12.000-4.000
	Week 4	n	30	33	35	27
		Mean(SD)	4.833 (3.85)	7.455 (6.34)	7.200 (5.21)	7.778 (6.24)
		Median	3.500	6.000	6.000	7.000
		Min, Max	0.000-13.000	0.000-25.000	0.000-20.000	0.000-29.000
	Change from baseline Week 4	n	30	33	35	27
		Mean(SD)	-4.800 (4.30)	-2.455 (5.12)	-2.914 (4.47)	-2.185 (3.77)
		Median	-4.500	-4.000	-3.000	-2.000
		Min, Max	-13.000-3.000	-10.000-10.000	-12.000-8.000	-12.000-5.000
Summary of Guys 106 pain VAS score by visit	Baseline	n	33	34	40	31
		Mean(SD)	5.727 (2.44)	5.882 (2.32)	5.775 (2.38)	5.774 (2.22)
		Median	7.000	6.500	6.000	6.000
		Min, Max	0.000-9.000	1.000-10.000	1.000-10.000	1.000-10.000
	Week 1	n	32	34	39	31
		Mean(SD)	4.000 (2.74)	4.676 (2.21)	5.026 (2.57)	5.129 (1.93)
		Median	4.000	5.000	6.000	5.000
		Min, Max	0.000-10.000	1.000-8.000	0.000-9.000	1.000-9.000
	Change from baseline Week 1	n	32	34	39	31
		Mean(SD)	-1.688 (1.99)	-1.206 (1.95)	-0.821 (2.34)	-0.645 (1.68)
		Median	-2.000	-1.000	-1.000	-1.000
		Min, Max	-5.000-3.000	-9.000-2.000	-5.000-5.000	-4.000-2.000
	Week 2	n	31	34	37	28
		Mean(SD)	3.129 (2.58)	4.735 (2.49)	4.297 (2.32)	4.786 (2.30)
		Median	3.000	4.500	4.000	5.000
		Min, Max	0.000-10.000	0.000-9.000	0.000-9.000	0.000-8.000
	Change from baseline Week 2	n	31	34	37	28
		Mean(SD)	-2.516 (2.19)	-1.147 (1.69)	-1.405 (2.42)	-1.143 (2.26)
		Median	-2.000	-1.000	-1.000	-1.000
		Min, Max	-6.000-2.000	-7.000-2.000	-8.000-4.000	-5.000-3.000

Text Table 11-28: Summary of Guy´s 106 ODSS by treatment and visits [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Week 3	n	29	33	36	27
		Mean(SD)	2.828 (2.59)	3.697 (2.19)	4.028 (2.40)	4.148 (2.01)
		Median	2.000	3.000	4.000	4.000
		Min, Max	0.000-8.000	0.000-8.000	0.000-9.000	0.000-8.000
	Change from baseline Week 3	n	29	33	36	27
		Mean(SD)	-2.828 (2.24)	-2.152 (1.91)	-1.750 (2.56)	-1.815 (2.35)
		Median	-3.000	-2.000	-2.000	-2.000
		Min, Max	-7.000-1.000	-7.000-1.000	-8.000-6.000	-6.000-3.000
	Week 4	n	30	33	35	27
		Mean(SD)	2.500 (2.45)	3.576 (2.45)	3.429 (2.21)	3.852 (2.14)
		Median	2.000	3.000	4.000	4.000
		Min, Max	0.000-8.000	0.000-8.000	0.000-8.000	0.000-8.000
	Change from baseline Week 4	n	30	33	35	27
		Mean(SD)	-3.200 (2.61)	-2.273 (2.58)	-2.429 (2.87)	-2.111 (2.81)
		Median	-3.500	-2.000	-1.000	-2.000
		Min, Max	-8.000-2.000	-9.000-3.000	-8.000-2.000	-8.000-4.000

N=number of patients in the subgroup considered or in total; n=number of patients among N;
SD=Standard Deviation
Source: Table 14.2.6.1. Listing(s): Derived from Listing 16.2.4.1

These results are visualized by mean value curves for the overall *disease severity score* (Text Figure 11-24) and the 3 sub-scores *total site score* (Text Figure 11-25), *disease activity score* (Text Figure 11-26) and *pain score* (Text Figure 11-27).

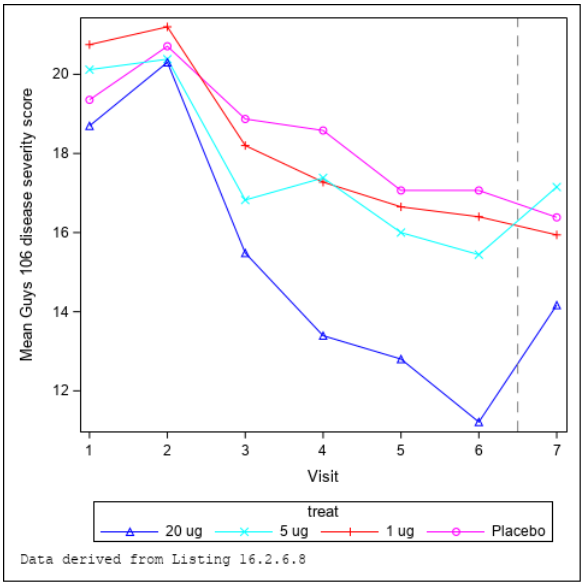
The overall *disease severity score* decreased in all treatment groups over the 4 weeks treatment, with the largest reduction in the 20µg group compared to the other treatment groups already from Week 1.

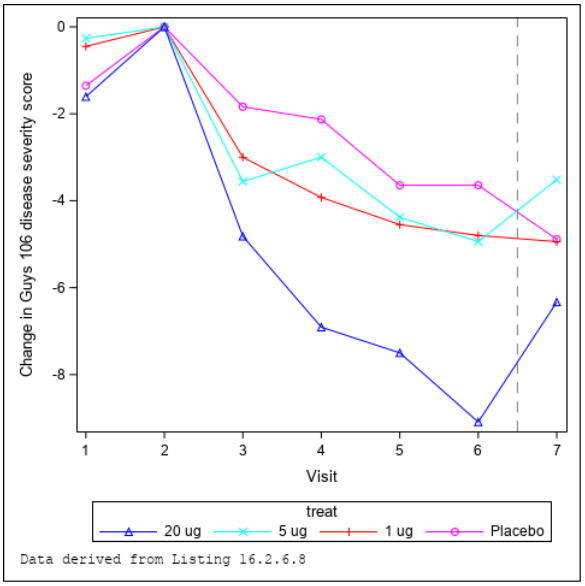
In the 20µg group the sub-scores of *total site score* and *disease activity score* decreased continuously over the 4 weeks treatment, as well (see Text Figure 11-25, Text Figure 11-26).

For the 5µg and 1µg groups, there was an initial decrease after one week in *total site score* and *disease activity score*, but curves then flattened.

Placebo curve showed only limited decrease on *total site score* but a gradual decrease on the *disease activity score*.

The *pain score* decreased in all treatment groups over the 4 weeks treatment with strongest reduction in 20 µg group (see Text Figure 11-27).



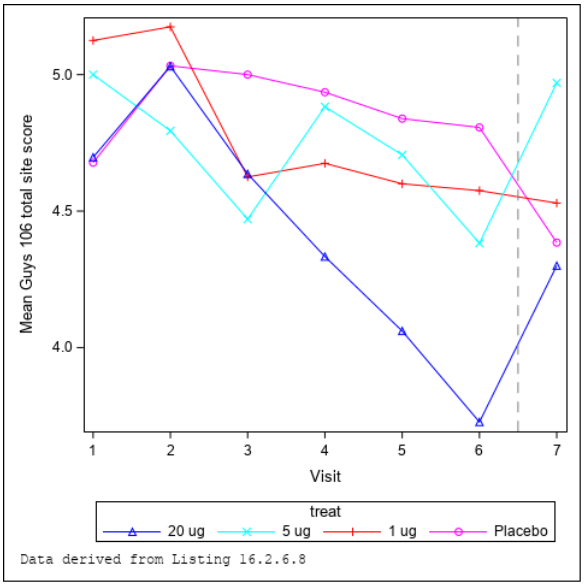


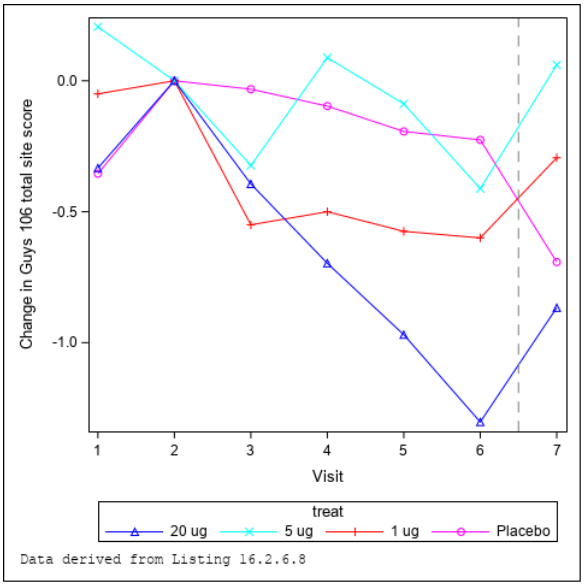
absolute values change

Text Figure 11-24: Mean Guy´s disease severity score over time (absolute values and change from Baseline)

Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up

Source: Figure 14.2.6.2 a + b



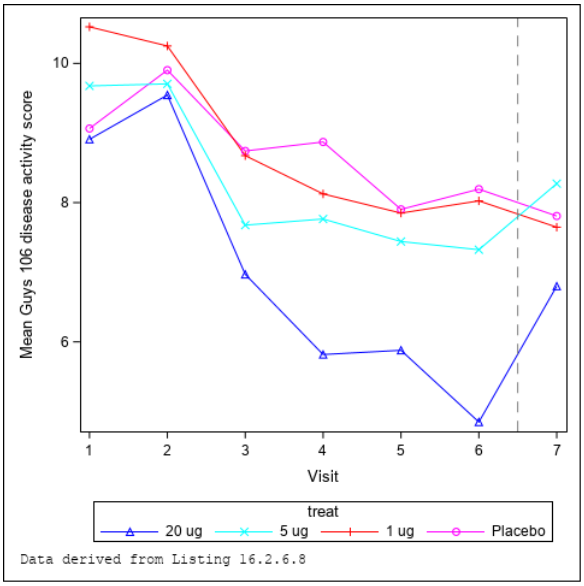


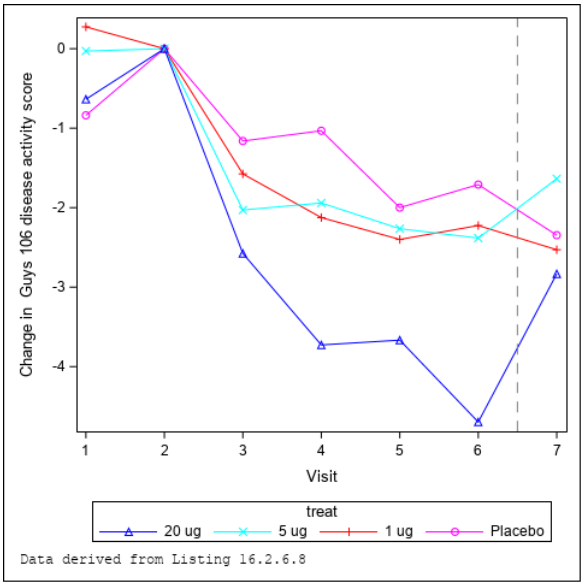
absolute values change

Text Figure 11-25: Mean Guy´s total site score over time (absolute values and change from Baseline)

Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up

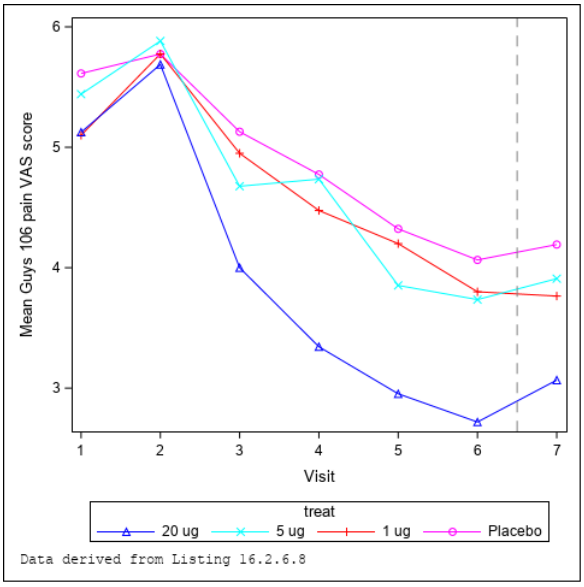
Source: Figure 14.2.6.2 c + d

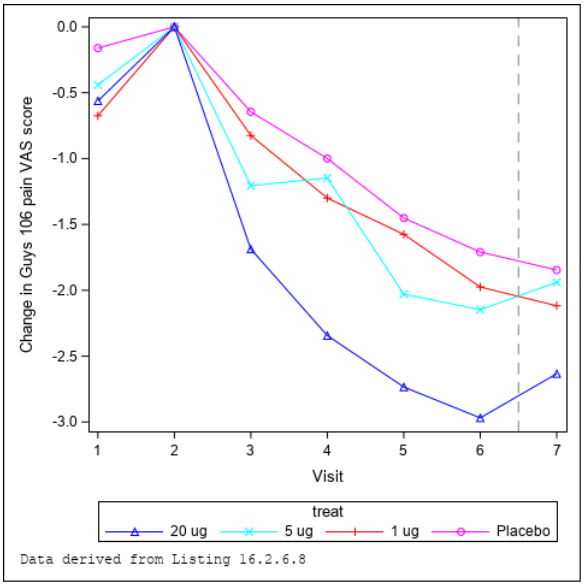




absolute values change

Text Figure 11-26: Mean Guy´s disease activity score over time (absolute values and change from Baseline)
Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up
Source: Figure 14.2.6.2 e + f





absolute values change

Text Figure 11-27: Mean Guy´s pain score over time (absolute values and change from Baseline)
Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up
Source: Figure 14.2.6.2 g + h

The result of the statistical analysis of Guy´s ODSS is summarized in Text Table 11-29.

Overall disease severity:
For the overall *disease severity score* a statistically significant difference was seen between the 20µg group and placebo (p=0.0060) for the change from Baseline to average over weeks 3 and 4. The difference between 20µg and placebo reached statistical significance also for the tests at each of Week 1 to Week 4.

No statistically significant difference to placebo was found for the other doses of the overall disease severity score.

Sub-scores:
Between 20µg group and placebo statistically significant differences were seen for the change from Baseline to the average over weeks 3 and 4 for all three sub-scores.

The difference between 20µg and placebo reached statistical significance also for the tests at Week 4 for the *total site score* and the *disease activity score* and for each of Week 1 to Week 4 for the *pain score*.

No statistically significant differences were found for the other doses in any subdomain.

Text Table 11-29: Statistical analysis of Guy's 106 ODSS [FAS]

Efficacy Variable	Period	Treat-ment	Esti-mate	Contrast	Diffe-rence	95% CI	p-value
Analysis of Guys 106 disease severity score by visit, ANCOVA	Week 1	20 ug	-4.551	20 ug vs placebo	-2.890	(-5.332, -0.447)	0.0208
		5 ug	-3.573	5 ug vs placebo	-1.912	(-4.346, 0.522)	0.1225
		1 ug	-2.960	1 ug vs placebo	-1.299	(-3.645, 1.047)	0.2754
		Placebo	-1.661				.
	Week 2	20 ug	-5.867	20 ug vs placebo	-4.633	(-7.586, -1.679)	0.0024
		5 ug	-2.304	5 ug vs placebo	-1.070	(-4.013, 1.873)	0.4732
		1 ug	-3.316	1 ug vs placebo	-2.082	(-4.919, 0.755)	0.1489
		Placebo	-1.235				.
	Week 3	20 ug	-6.110	20 ug vs placebo	-3.608	(-6.785, -0.431)	0.0263
		5 ug	-3.304	5 ug vs placebo	-0.803	(-3.968, 2.363)	0.6166
		1 ug	-3.535	1 ug vs placebo	-1.034	(-4.086, 2.017)	0.5037
		Placebo	-2.501				.
	Week 4	20 ug	-7.402	20 ug vs placebo	-5.219	(-8.747, -1.691)	0.0041
		5 ug	-3.483	5 ug vs placebo	-1.300	(-4.815, 2.215)	0.4657
		1 ug	-3.266	1 ug vs placebo	-1.083	(-4.471, 2.306)	0.5284
		Placebo	-2.184				.
	Week 3-4	20 ug	-6.786	20 ug vs placebo	-4.453	(-7.602, -1.303)	0.0060
		5 ug	-3.390	5 ug vs placebo	-1.057	(-4.195, 2.081)	0.5062
		1 ug	-3.397	1 ug vs placebo	-1.064	(-4.089, 1.961)	0.4878
		Placebo	-2.333				.

Text Table 11-29: Statistical analysis of Guy's 106 ODSS [FAS]

Efficacy Variable	Period	Treat-ment	Esti-mate	Contrast	Diffe-rence	95% CI	p-value
Analysis of Guys 106 total site score by visit, ANCOVA	Week 1	20 ug	-0.568	20 ug vs placebo	-0.369	(-1.108, 0.370)	0.3248
		5 ug	-0.544	5 ug vs placebo	-0.345	(-1.081, 0.392)	0.3559
		1 ug	-0.707	1 ug vs placebo	-0.508	(-1.218, 0.202)	0.1591
		Placebo	-0.199				.
	Week 2	20 ug	-0.555	20 ug vs placebo	-0.570	(-1.358, 0.218)	0.1546
		5 ug	0.140	5 ug vs placebo	0.125	(-0.660, 0.910)	0.7536
		1 ug	-0.414	1 ug vs placebo	-0.429	(-1.186, 0.328)	0.2644
		Placebo	0.015				.
	Week 3	20 ug	-0.774	20 ug vs placebo	-0.714	(-1.597, 0.168)	0.1115
		5 ug	-0.014	5 ug vs placebo	0.046	(-0.833, 0.925)	0.9183
		1 ug	-0.441	1 ug vs placebo	-0.381	(-1.229, 0.466)	0.3748
		Placebo	-0.059				.
	Week 4	20 ug	-1.077	20 ug vs placebo	-1.015	(-1.912, -0.118)	0.0268
		5 ug	-0.319	5 ug vs placebo	-0.258	(-1.152, 0.636)	0.5685
		1 ug	-0.417	1 ug vs placebo	-0.356	(-1.218, 0.506)	0.4153
		Placebo	-0.061				.
	Week 3-4	20 ug	-0.946	20 ug vs placebo	-0.895	(-1.725, -0.065)	0.0348
		5 ug	-0.163	5 ug vs placebo	-0.112	(-0.939, 0.715)	0.7890
		1 ug	-0.424	1 ug vs placebo	-0.373	(-1.170, 0.424)	0.3562
		Placebo	-0.051				.

Text Table 11-29: Statistical analysis of Guy's 106 ODSS [FAS]

Efficacy Variable	Period	Treat-ment	Esti-mate	Contrast	Diffe-rence	95% CI	p-value
Analysis of Guys 106 disease activity score by visit, ANCOVA	Week 1	20 ug	-2.338	20 ug vs placebo	-1.408	(-3.023, 0.208)	0.0871
		5 ug	-1.915	5 ug vs placebo	-0.985	(-2.594, 0.624)	0.2280
		1 ug	-1.401	1 ug vs placebo	-0.471	(-2.022, 1.080)	0.5491
		Placebo	-0.930				.
	Week 2	20 ug	-3.143	20 ug vs placebo	-2.653	(-4.555, -0.752)	0.0066
		5 ug	-1.557	5 ug vs placebo	-1.067	(-2.962, 0.827)	0.2670
		1 ug	-1.778	1 ug vs placebo	-1.289	(-3.115, 0.538)	0.1651
		Placebo	-0.489				.
	Week 3	20 ug	-2.966	20 ug vs placebo	-1.557	(-3.511, 0.397)	0.1173
		5 ug	-1.706	5 ug vs placebo	-0.298	(-2.244, 1.649)	0.7628
		1 ug	-1.867	1 ug vs placebo	-0.459	(-2.335, 1.418)	0.6295
		Placebo	-1.409				.
	Week 4	20 ug	-3.934	20 ug vs placebo	-2.875	(-4.971, -0.779)	0.0076
		5 ug	-1.713	5 ug vs placebo	-0.655	(-2.743, 1.434)	0.5362
		1 ug	-1.494	1 ug vs placebo	-0.435	(-2.448, 1.578)	0.6696
		Placebo	-1.059				.
	Week 3-4	20 ug	-3.450	20 ug vs placebo	-2.216	(-4.106, -0.326)	0.0219
		5 ug	-1.710	5 ug vs placebo	-0.476	(-2.359, 1.407)	0.6177
		1 ug	-1.680	1 ug vs placebo	-0.447	(-2.262, 1.368)	0.6269
		Placebo	-1.234				.

Text Table 11-29: Statistical analysis of Guy's 106 ODSS [FAS]

Efficacy Variable	Period	Treat-ment	Esti-mate	Contrast	Diffe-rence	95% CI	p-value
Analysis of Guys 106 pain VAS score by visit, ANCOVA	Week 1	20 ug	-1.600	20 ug vs placebo	-1.028	(-1.905, -0.150)	0.0221
		5 ug	-1.136	5 ug vs placebo	-0.564	(-1.430, 0.303)	0.2003
		1 ug	-0.846	1 ug vs placebo	-0.274	(-1.111, 0.563)	0.5183
		Placebo	-0.572				.
	Week 2	20 ug	-2.127	20 ug vs placebo	-1.338	(-2.326, -0.349)	0.0084
		5 ug	-0.921	5 ug vs placebo	-0.132	(-1.108, 0.845)	0.7902
		1 ug	-1.159	1 ug vs placebo	-0.370	(-1.313, 0.573)	0.4393
		Placebo	-0.789				.
	Week 3	20 ug	-2.354	20 ug vs placebo	-1.260	(-2.274, -0.246)	0.0153
		5 ug	-1.621	5 ug vs placebo	-0.527	(-1.529, 0.474)	0.2992
		1 ug	-1.295	1 ug vs placebo	-0.201	(-1.168, 0.765)	0.6809
		Placebo	-1.094				.
	Week 4	20 ug	-2.415	20 ug vs placebo	-1.247	(-2.383, -0.110)	0.0319
		5 ug	-1.493	5 ug vs placebo	-0.325	(-1.447, 0.798)	0.5683
		1 ug	-1.468	1 ug vs placebo	-0.300	(-1.384, 0.784)	0.5850
		Placebo	-1.168				.
	Week 3-4	20 ug	-2.391	20 ug vs placebo	-1.261	(-2.241, -0.281)	0.0121
		5 ug	-1.556	5 ug vs placebo	-0.426	(-1.394, 0.541)	0.3849
		1 ug	-1.381	1 ug vs placebo	-0.252	(-1.186, 0.683)	0.5951
		Placebo	-1.130				.

CI=Confidence Interval
Analysis performed by PROC MIXED.
Source: Table 14.2.6.2. Listing(s): Derived from Listing 16.2.6.3

11.1.3.4 Further Patient reported outcomes

11.1.3.4.1 Instructions for use questionnaire

The instruction for use questionnaire consisted of two questions regarding the clarity of the provided instructions for use (patch application and patch removal procedure) answered by the patient and one question about successful patch application assessed by the site staff. Questionnaire was filled in at Baseline and at Visit 3 (after 1 week of treatment). Answers have been rearranged so that the most positive outcome is presented first and the most negative outcome last. The proportion of patients with successful patch applications assessed at both time points was exploratory endpoint 5.

A Summary of the answering frequencies for the 3 questions are shown in Text Table 11-30 (patient´s part) and Text Table 11-31(site staff part). Almost all patients indicated positive responses – stating the instructions were ‘extremely clear’ or ‘moderately clear’ – for both, patch application and removal, and for both assessment days.

The percentage of successful patch applications ranged from 93.7 to 98.8%, with the highest numbers in the placebo group. Thus, patch applications at visits on site were performed correctly and successfully by almost all patients and among all treatment groups.

Text Table 11-30: Summary of answers to instructions for use questionnaire [FAS]: Patient's instruction for use questionnaire

Variable	Visit	20 ug	5 ug	1 ug	Placebo
Patch application	2	26/ 7/ 0/ 0/ 0	28/ 5/ 0/ 1/ 0	32/ 6/ 0/ 0/ 0	22/ 9/ 0/ 0/ 0
	3	25/ 4/ 2/ 0/ 0	25/ 4/ 3/ 0/ 0	26/ 6/ 1/ 1/ 1	20/ 6/ 0/ 0/ 0
Patch removal	2	30/ 3/ 0/ 0/ 0	27/ 6/ 1/ 0/ 0	32/ 5/ 1/ 0/ 0	23/ 8/ 0/ 0/ 0
	3	27/ 4/ 0/ 0/ 0	27/ 5/ 0/ 0/ 0	31/ 3/ 0/ 1/ 0	21/ 5/ 0/ 0/ 0
Frequency of categories 1-5 ordered with most favourable category first and least favourable category last Source: Table 14.2.8.1a; Listing(s): Derived from Listing 16.2.6.11					

Text Table 11-31: Summary of answers to instructions for use questionnaire [FAS]: Site assessment on correct use of instruction for use questionnaire

Visit	20 ug	5 ug	1 ug	Placebo
2	88/ 90 (97.8)	95/100 (95.0)	108/115 (93.9)	83/ 84 (98.8)
3	83/ 87 (95.4)	89/ 95 (93.7)	120/127 (94.5)	76/ 78 (97.4)
Source: Table 14.2.8.1 b. Listing(s): Derived from Listing 16.2.6.2				

Histograms on the answering frequencies for the questions on clarity of patch application and patch removal procedure are shown in Figure 14.2.8.1 a-d.

11.1.3.4.2 COMDQ

The COMDQ questionnaire consisted of 26 questions regarding quality of life, divided in 4 sub-domains (‘medication and treatment’, ‘pain and functional limitations, ‘social and emotional’, ‘patient support’) that were added to a total score. Each individual question was to be assessed by the patients on a 5-point rating scale (ranging between 0 [most positive] and 4 [most negative]), resulting in a total score of maximum 104 points. Thus, a reduction of the scores, meant an improvement of the quality of life items assessed. COMDQ was assessed at Baseline and at Week 2 and Week 4. The change from Baseline to both time points in total COMDQ score and each of the 4 sub-domain scores was exploratory endpoint 8.

Descriptive statistics of the COMDQ (total score and sub-domains) for the change from Baseline to Week 2 and Week 4 are given in Text Table 11-32.

For the total score, average baseline scores were comparable (ranging from 77.5 to 81.8) in the four treatment groups. Total scores decreased in all treatment groups continuously over the 4 weeks treatment, with the largest reduction in the 20µg group compared to other treatment groups from Week 2.

On the sub-domains, baseline scores were comparable between treatment groups. Scores for ‘pain and functional limitations’ and for ‘social and emotional’ decreased in all treatment

groups continuously over the 4 weeks treatment, with the largest decreases seen in the 20µg group.

Scores for 'medication and treatment' were unchanged or increased slightly except for larger reductions in the 20µg and 5µg groups at Week 4. 'Patient support' scores decreased in the 20µg and placebo groups and increased in the 5µg and 1µg groups.

Text Table 11-32: Summary of COMDQ scores by treatment group and visit [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of COMDQ, total score, by visit	Baseline	n	33	34	40	31
		Mean(SD)	79.33 (12.83)	78.24 (17.66)	77.53 (21.21)	81.81 (15.21)
		Median	78.00	80.50	82.00	80.00
		Min, Max	56.0-102.0	41.0-114.0	17.0-115.0	56.0-116.0
	Week 2	n	32	34	39	31
		Mean(SD)	72.66 (17.55)	75.06 (14.56)	76.51 (17.55)	77.45 (12.54)
		Median	74.50	79.50	77.00	77.00
		Min, Max	44.0-117.0	46.0-96.0	45.0-111.0	54.0-108.0
	Change from baseline Week 2	n	32	34	39	31
		Mean(SD)	-7.03 (15.12)	-3.18 (8.21)	-0.72 (14.26)	-4.35 (11.04)
		Median	-10.50	-1.50	-3.00	-5.00
		Min, Max	-32.0-25.0	-22.0-9.0	-30.0-50.0	-31.0-16.0
	Week 4	n	30	33	36	27
		Mean(SD)	63.10 (17.35)	68.85 (15.85)	72.58 (16.80)	75.44 (12.43)
		Median	63.00	68.00	70.50	72.00
		Min, Max	26.0-107.0	42.0-94.0	45.0-108.0	53.0-104.0
	Change from baseline Week 4	n	30	33	36	27
		Mean(SD)	-16.80 (14.12)	-9.48 (14.26)	-4.03 (15.96)	-7.89 (11.91)
		Median	-15.00	-6.00	-1.00	-6.00
		Min, Max	-45.0-9.0	-48.0-15.0	-40.0-37.0	-41.0-16.0

Text Table 11-32: Summary of COMDQ scores by treatment group and visit [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of COMDQ, medication and treatment domain, by visit	Baseline	n	33	34	38	31
		Mean(SD)	17.27 (4.13)	17.97 (4.32)	17.50 (4.85)	17.61 (4.92)
		Median	18.00	18.50	17.50	17.00
		Min, Max	9.0-27.0	9.0-25.0	6.0-28.0	7.0-27.0
	Week 2	n	32	34	39	31
		Mean(SD)	17.56 (4.33)	18.56 (3.40)	17.82 (4.96)	17.58 (4.02)
		Median	18.00	18.50	19.00	17.00
		Min, Max	9.0-29.0	12.0-26.0	7.0-29.0	8.0-26.0
	Change from baseline Week 2	n	32	34	37	31
		Mean(SD)	0.13 (4.70)	0.59 (2.96)	0.41 (3.52)	-0.03 (4.14)
		Median	0.50	0.00	0.00	0.00
		Min, Max	-10.0-10.0	-6.0-9.0	-6.0-10.0	-9.0-11.0
	Week 4	n	30	33	36	27
		Mean(SD)	14.90 (5.05)	17.45 (4.35)	17.92 (4.40)	18.33 (4.24)
		Median	16.50	18.00	18.50	18.00
		Min, Max	4.0-21.0	6.0-25.0	9.0-25.0	9.0-27.0
	Change from baseline Week 4	n	30	33	34	27
		Mean(SD)	-2.80 (4.97)	-0.58 (4.15)	0.53 (4.52)	0.37 (4.06)
		Median	-3.00	0.00	0.50	0.00
		Min, Max	-16.0-5.0	-14.0-6.0	-9.0-8.0	-8.0-12.0

Text Table 11-32: Summary of COMDQ scores by treatment group and visit [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of COMDQ, pain and functional limitation domain, by visit	Baseline	n	33	34	38	31
		Mean(SD)	28.24 (6.91)	27.91 (7.88)	29.13 (6.43)	29.03 (6.60)
		Median	28.00	29.50	29.00	28.00
		Min, Max	15.0-39.0	12.0-41.0	15.0-41.0	20.0-44.0
	Week 2	n	32	34	39	31
		Mean(SD)	23.53 (9.43)	25.03 (7.98)	26.38 (7.42)	26.26 (6.95)
		Median	23.00	25.50	27.00	25.00
		Min, Max	10.0-44.0	10.0-40.0	14.0-41.0	15.0-40.0
	Change from baseline Week 2	n	32	34	37	31
		Mean(SD)	-4.72 (8.46)	-2.88 (4.87)	-2.76 (5.67)	-2.77 (6.94)
		Median	-6.00	-3.00	-2.00	-2.00
		Min, Max	-22.0-14.0	-16.0-8.0	-18.0-10.0	-26.0-15.0
	Week 4	n	30	33	36	27
		Mean(SD)	19.60 (8.02)	21.82 (7.82)	24.11 (7.19)	24.37 (5.71)
		Median	18.00	22.00	23.50	24.00
		Min, Max	9.0-36.0	8.0-33.0	12.0-43.0	9.0-35.0
	Change from baseline Week 4	n	30	33	34	27
		Mean(SD)	-8.87 (8.29)	-5.88 (7.26)	-4.82 (7.21)	-5.15 (7.54)
		Median	-9.00	-3.00	-4.00	-4.00
		Min, Max	-24.0-7.0	-30.0-3.0	-22.0-13.0	-32.0-6.0

Text Table 11-32: Summary of COMDQ scores by treatment group and visit [FAS]

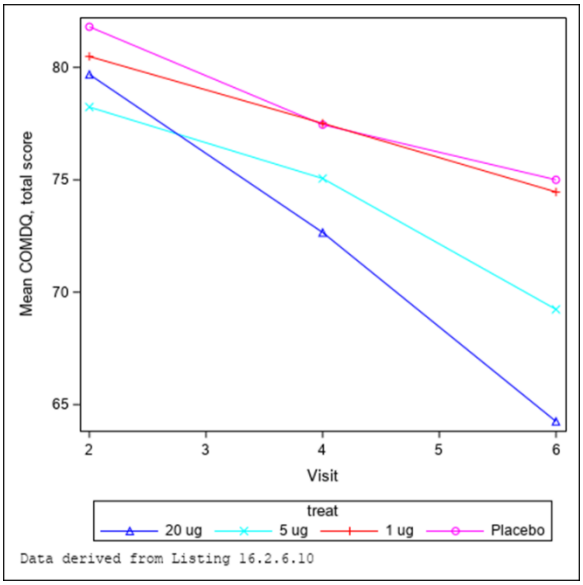
Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of COMDQ, social and emotional domain, by visit	Baseline	n	33	34	40	31
		Mean(SD)	21.39 (6.79)	20.68 (6.60)	21.10 (7.04)	22.35 (5.98)
		Median	21.00	22.00	22.00	23.00
		Min, Max	9.0-33.0	8.0-35.0	8.0-35.0	10.0-33.0
	Week 2	n	32	34	39	31
		Mean(SD)	19.38 (7.37)	19.21 (6.29)	19.97 (7.34)	20.87 (5.48)
		Median	20.00	21.00	21.00	21.00
		Min, Max	7.0-35.0	7.0-34.0	8.0-33.0	9.0-31.0
	Change from baseline Week 2	n	32	34	39	31
		Mean(SD)	-2.22 (6.23)	-1.47 (5.02)	-0.90 (3.89)	-1.48 (3.24)
		Median	-1.50	-1.00	-1.00	-2.00
		Min, Max	-16.0-11.0	-13.0-9.0	-7.0-7.0	-8.0-4.0
	Week 4	n	30	33	36	27
		Mean(SD)	17.03 (7.59)	17.00 (5.85)	18.36 (6.95)	20.22 (6.39)
		Median	15.00	16.00	18.50	21.00
		Min, Max	7.0-34.0	7.0-28.0	8.0-31.0	9.0-31.0
	Change from baseline Week 4	n	30	33	36	27
		Mean(SD)	-4.43 (6.37)	-3.82 (5.25)	-2.17 (4.48)	-2.63 (4.39)
		Median	-4.00	-3.00	-2.00	-3.00
		Min, Max	-17.0-11.0	-16.0-9.0	-11.0-6.0	-11.0-5.0

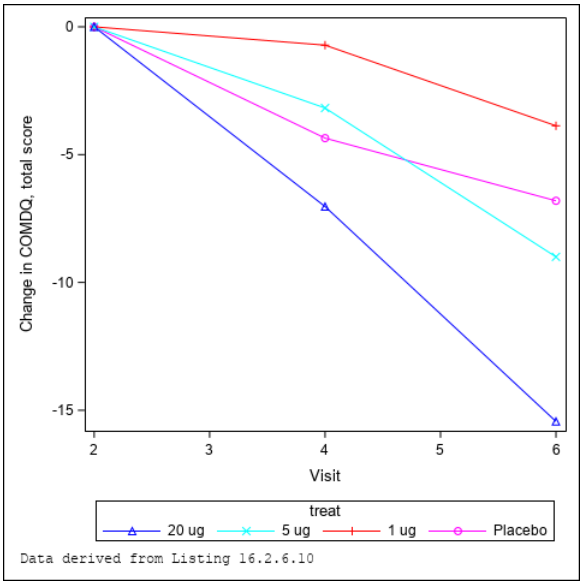
Text Table 11-32: Summary of COMDQ scores by treatment group and visit [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of COMDQ, patient support domain, by visit	Baseline	n	33	34	40	31
		Mean(SD)	12.42 (2.68)	11.68 (2.47)	12.13 (3.58)	12.81 (2.32)
		Median	13.00	12.00	12.00	13.00
		Min, Max	7.0-18.0	8.0-16.0	5.0-20.0	9.0-17.0
	Week 2	n	32	34	38	31
		Mean(SD)	12.19 (3.00)	12.26 (2.30)	12.66 (3.43)	12.74 (3.10)
		Median	13.00	12.00	13.00	13.00
		Min, Max	4.0-16.0	8.0-17.0	5.0-19.0	7.0-17.0
	Change from baseline Week 2	n	32	34	38	31
		Mean(SD)	-0.22 (2.28)	0.59 (2.12)	0.45 (2.67)	-0.06 (2.79)
		Median	0.00	0.00	0.00	0.00
		Min, Max	-7.0-6.0	-4.0-5.0	-7.0-6.0	-7.0-6.0
	Week 4	n	30	33	36	27
		Mean(SD)	11.57 (3.51)	12.58 (2.89)	12.19 (3.50)	12.52 (2.64)
		Median	12.00	12.00	12.50	12.00
		Min, Max	4.0-19.0	6.0-17.0	4.0-19.0	4.0-18.0
	Change from baseline Week 4	n	30	33	36	27
		Mean(SD)	-0.70 (2.59)	0.79 (2.34)	0.19 (2.87)	-0.48 (2.44)
		Median	-1.00	0.00	0.00	0.00
		Min, Max	-9.0-4.0	-4.0-5.0	-6.0-7.0	-8.0-5.0

N=number of patients in the subgroup considered or in total; n=number of patients among N; SD=Standard Deviation
Source: Table 14.2.7.1. Listing(s): Derived from Listing 16.2.4.1

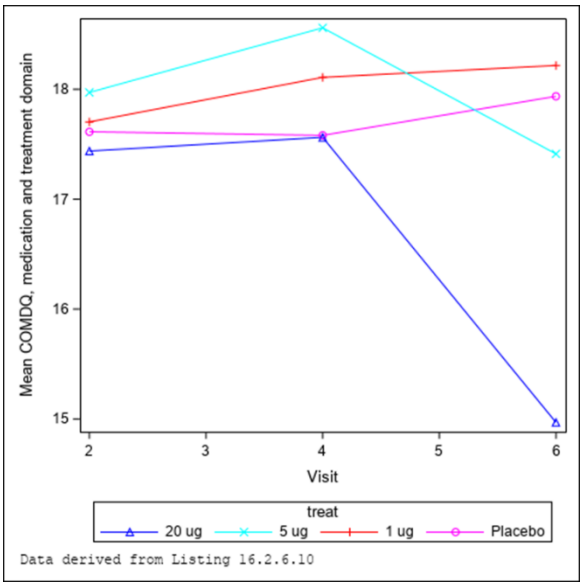
Results are further visualized in Text Figure 11-28 to Text Figure 11-32.

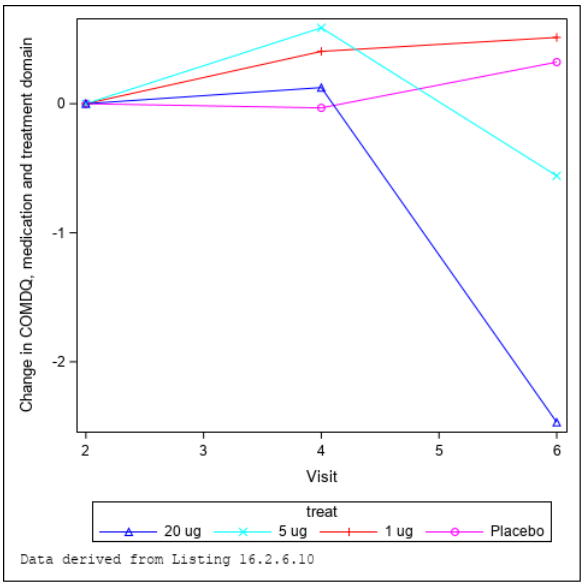




absolute values change

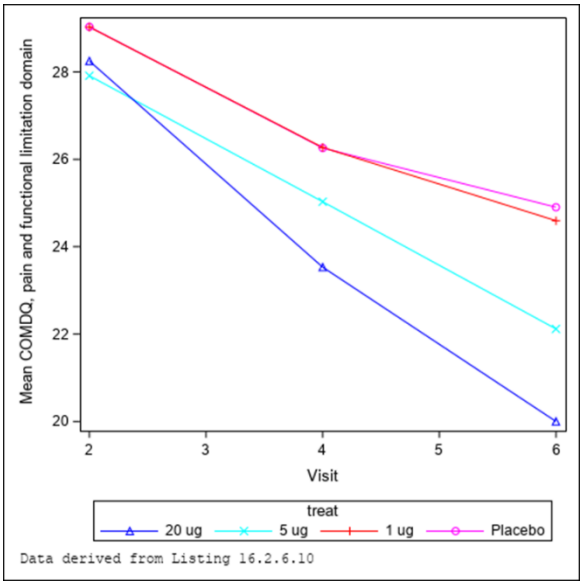
Text Figure 11-28: Mean COMDQ total score over time (absolute values and change from Baseline)
Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up
Source: Figure 14.2.7.2 a + b

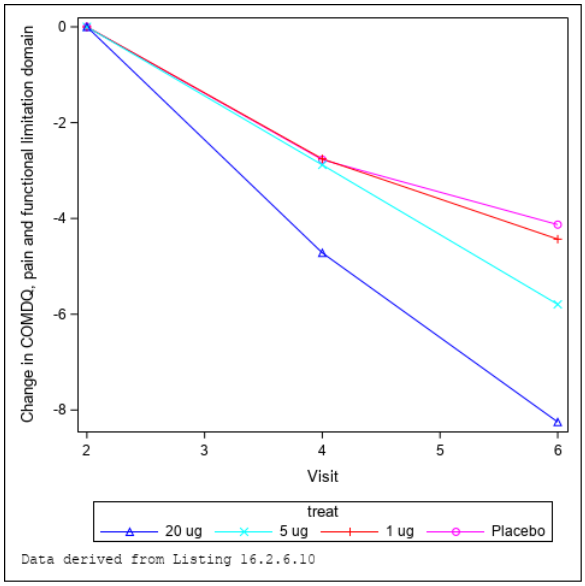




absolute values change

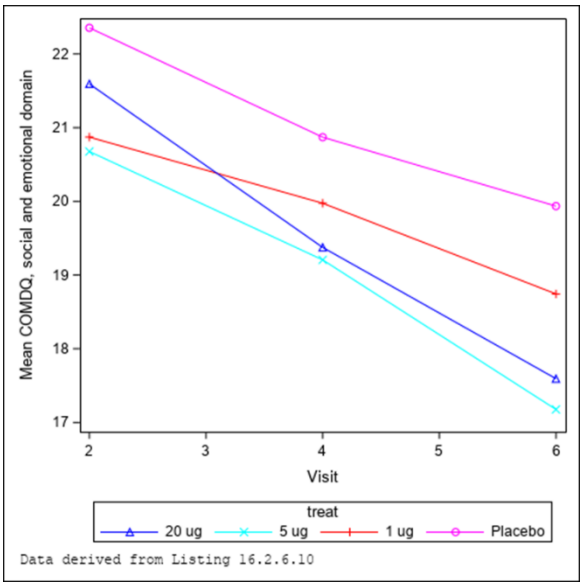
Text Figure 11-29: Mean COMDQ medication score over time (absolute values and change from Baseline)
Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up
Source: Figure 14.2.7.2 e + f

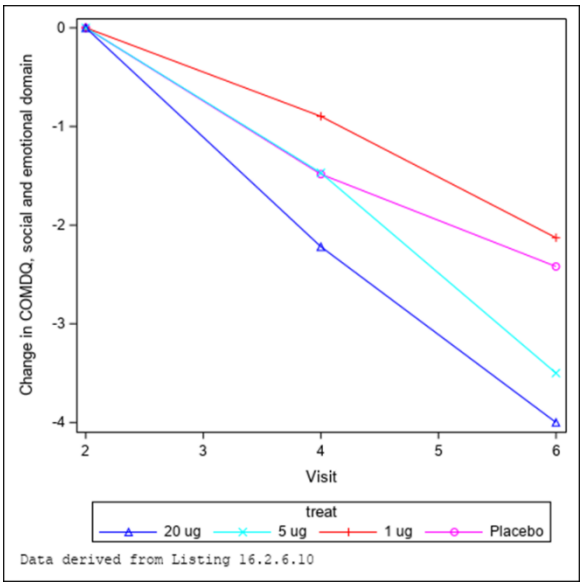




absolute values change

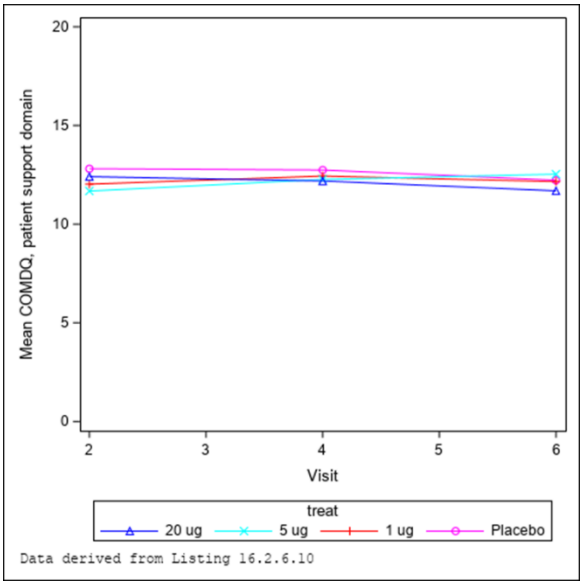
Text Figure 11-30: Mean COMDQ pain score over time (absolute values and change from Baseline)
Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up
Source: Figure 14.2.7.2 c + d

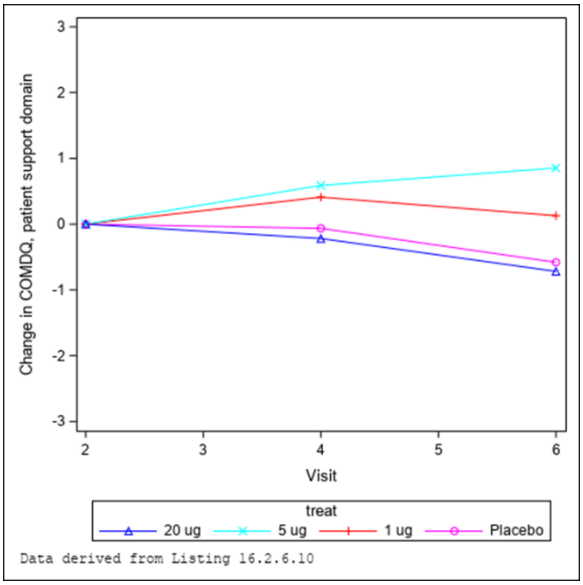




absolute values change

Text Figure 11-31: Mean COMDQ social/emotional score (absolute values and change from Baseline)
Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up
Source: Figure 14.2.7.2 g + h





absolute values change

Text Figure 11-32: Mean COMDQ patient support score over time (absolute values and change from Baseline)
Visit 2 = Baseline; Visit 3 = Week 1; Visit 4 = Week 2; Visit 5=Week 3; Visit 6=Week 4; Visit 7=Follow up
Source: Figure 14.2.7.2 i + j

The result of the statistical analysis of total score and sub-domains is summarized in Text Table 11-33. For the total score, a statistically significant difference was seen between the 20µg group and placebo (p=0.0032) at Week 4. No statistically significant differences were seen for the other doses at Week 4 or for any dose at Week 2.

On the sub-domains, statistically significant differences were seen between the 20µg group and placebo for 'pain and functional limitations' (p=0.0099) and 'medication and treatment' (p=0.0027) at Week 4.

No statistically significant differences were found for the other doses or on any other sub-domain.

Thus, overall quality of life improved significantly in the 20µg group. Also, quality of life regarding pain and the need for medication improved significantly in the 20µg group.

Text Table 11-33: Statistical analysis of COMDQ scores [FAS]

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Summary of COMDQ, total score, by visit	Week 2	20 ug	-5.311	20 ug vs placebo	-3.116	(-8.612, 2.381)	0.2641
		5 ug	-1.891	5 ug vs placebo	0.305	(-5.148, 5.757)	0.9122
		1 ug	-0.027	1 ug vs placebo	2.169	(-3.128, 7.465)	0.4193
		Placebo	-2.195				

Text Table 11-33: Statistical analysis of COMDQ scores [FAS]

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
	Week 4	20 ug	-12.062	20 ug vs placebo	-9.022	(-14.965, -3.079)	0.0032
		5 ug	-6.497	5 ug vs placebo	-3.458	(-9.354, 2.438)	0.2480
		1 ug	-1.772	1 ug vs placebo	1.268	(-4.459, 6.995)	0.6620
		Placebo	-3.040				
Summary of COMDQ, medication and treatment domain, by visit	Week 2	20 ug	0.002	20 ug vs placebo	0.100	(-1.578, 1.777)	0.9064
		5 ug	0.659	5 ug vs placebo	0.757	(-0.899, 2.413)	0.3674
		1 ug	0.397	1 ug vs placebo	0.495	(-1.131, 2.120)	0.5481
		Placebo	-0.098				
	Week 4	20 ug	-2.524	20 ug vs placebo	-2.854	(-4.695, -1.013)	0.0027
		5 ug	-0.435	5 ug vs placebo	-0.765	(-2.583, 1.053)	0.4064
		1 ug	0.579	1 ug vs placebo	0.249	(-1.535, 2.033)	0.7828
		Placebo	0.330				
Summary of COMDQ, pain and functional limitation domain, by visit	Week 2	20 ug	-3.853	20 ug vs placebo	-2.012	(-5.145, 1.121)	0.2061
		5 ug	-2.100	5 ug vs placebo	-0.259	(-3.360, 2.843)	0.8691
		1 ug	-1.659	1 ug vs placebo	0.182	(-2.851, 3.216)	0.9055
		Placebo	-1.841				
	Week 4	20 ug	-6.905	20 ug vs placebo	-4.340	(-7.620, -1.060)	0.0099
		5 ug	-4.765	5 ug vs placebo	-2.200	(-5.447, 1.047)	0.1824
		1 ug	-2.803	1 ug vs placebo	-0.238	(-3.414, 2.938)	0.8824
		Placebo	-2.565				

Text Table 11-33: Statistical analysis of COMDQ scores [FAS]

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Summary of COMDQ, social and emotional domain, by visit	Week 2	20 ug	-1.641	20 ug vs placebo	-0.790	(-3.021, 1.441)	0.4849
		5 ug	-1.101	5 ug vs placebo	-0.250	(-2.466, 1.967)	0.8240
		1 ug	-0.618	1 ug vs placebo	0.233	(-1.915, 2.381)	0.8303
		Placebo	-0.852				
	Week 4	20 ug	-2.859	20 ug vs placebo	-1.591	(-4.002, 0.820)	0.1940
		5 ug	-2.779	5 ug vs placebo	-1.511	(-3.906, 0.885)	0.2143
		1 ug	-1.346	1 ug vs placebo	-0.078	(-2.400, 2.244)	0.9470
		Placebo	-1.268				
Summary of COMDQ, patient support domain, by visit	Week 2	20 ug	-0.332	20 ug vs placebo	-0.343	(-1.523, 0.837)	0.5660
		5 ug	0.297	5 ug vs placebo	0.286	(-0.892, 1.463)	0.6322
		1 ug	0.236	1 ug vs placebo	0.224	(-0.910, 1.359)	0.6962
		Placebo	0.012				
	Week 4	20 ug	-0.417	20 ug vs placebo	-0.270	(-1.502, 0.961)	0.6646
		5 ug	0.988	5 ug vs placebo	1.135	(-0.094, 2.364)	0.0700
		1 ug	0.312	1 ug vs placebo	0.458	(-0.726, 1.642)	0.4451
		Placebo	-0.147				

CI=Confidence Interval
Analysis performed by PROC MIXED.
Source: Table 14.2.7.2. Listing(s): Derived from Listing 16.2.6.3

11.1.3.5 Rescue Analgesics

Rescue analgesics were allowed during the study (Visit 1 to Visit 7). As the type of medication was not standardized, patients were allowed to use different rescue analgesics, more than one rescue preparation or no rescue analgesic at all. Patients recorded every day with rescue analgesic use as well as the units taken. The change from Baseline (run-in mean over the last 7 days prior to Baseline) to each of the means over Week 1, 2, 3 and 4, and the follow-up period in use of rescue analgesics was exploratory endpoint 7.

The extent and type of rescue analgesics used overall during the study is summarized in Text Table 11-34. In total, 101 patients (73%) used any type of rescue analgesics during the study. The most frequent type of rescue analgesics was anilides (48%). In general, the use of rescue analgesics was highest in the placebo group (81%) and lowest in the 20µg group (64%).

Text Table 11-34: Summary of rescue analgesics use [FAS]: Summary of rescue analgesics by ATC class

Medication Class (ATC level 2 and 4)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
ANY RESCUE MEDICATION	21 (64)	27 (79)	28 (70)	25 (81)	101 (73)
ANALGESICS	12 (36)	18 (53)	21 (53)	17 (55)	68 (49)
- ANILIDES	11 (33)	17 (50)	21 (53)	17 (55)	66 (48)
- OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	1 (3)	1 (3)	0	0	2 (1)
- OTHER OPIOIDS	0	1 (3)	0	0	1 (1)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	4 (12)	8 (24)	6 (15)	5 (16)	23 (17)
- PROPIONIC ACID DERIVATIVES	4 (12)	8 (24)	6 (15)	5 (16)	23 (17)
STOMATOLOGICAL PREPARATIONS	5 (15)	6 (18)	6 (15)	6 (19)	23 (17)
- OTHER AGENTS FOR LOCAL ORAL TREATMENT	5 (15)	6 (18)	6 (15)	6 (19)	23 (17)
ANESTHETICS	4 (12)	4 (12)	3 (8)	3 (10)	14 (10)
- AMIDES	4 (12)	4 (12)	3 (8)	3 (10)	14 (10)
PSYCHOLEPTICS	0	1 (3)	0	0	1 (1)
- OTHER HYPNOTICS AND SEDATIVES	0	1 (3)	0	0	1 (1)

N=number of patients in the subgroup considered or in total; n=number of patients among N; (%)=percentages are based on N

Source: Table 14.2.9.1 a; Listing(s): Derived from Listing 16.2.4.2

Two approaches were used to analyze the use of rescue analgesics in this study. Within the first approach, weekly means of rescue analgesic units taken were summarized (total use), whereas within the second approach only days with rescue analgesic use (independent of units used) were noted and the proportion of days with rescue analgesic use was defined as the endpoint.

Descriptive statistics of the change in total rescue analgesics use are given in Text Table 11-35. Weekly mean value curves on total rescue analgesics use are shown in Figure 14.2.9.2. Average baseline values ranged from 0.39 to 0.74 units in the four treatment groups, with lowest baseline use in the placebo group. The scores decreased in all treatment groups even if the variability was high. The largest reduction was seen in the 20µg group at Week 4.

Text Table 11-35: Summary of rescue analgesics use [FAS]: Summary of total rescue analgesics use, rescue population

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	20	24	27	23
	Mean(SD)	0.634 (1.11)	0.734 (0.89)	0.744 (2.39)	0.389 (0.72)
	Median	0.000	0.343	0.000	0.000
	Min, Max	0.00-4.29	0.00-3.14	0.00-12.29	0.00-2.71
Week 1	n	19	27	24	22
	Mean(SD)	0.484 (0.91)	0.542 (0.84)	0.809 (2.29)	0.307 (0.63)
	Median	0.000	0.125	0.000	0.000
	Min, Max	0.00-3.33	0.00-3.14	0.00-11.00	0.00-2.50
Change from baseline Week 1	n	19	24	24	20
	Mean(SD)	-0.184 (0.89)	-0.125 (0.40)	-0.008 (0.48)	-0.035 (0.21)
	Median	0.000	0.000	0.000	0.000
	Min, Max	-2.29-2.08	-1.38-0.43	-1.29-1.42	-0.57-0.50
Week 2	n	18	27	20	19
	Mean(SD)	0.306 (0.62)	0.716 (1.25)	0.801 (2.13)	0.263 (0.65)
	Median	0.000	0.000	0.000	0.000
	Min, Max	0.00-2.00	0.00-5.43	0.00-9.43	0.00-2.50
Change from baseline Week 2	n	18	24	20	18
	Mean(SD)	-0.399 (0.80)	0.072 (1.12)	-0.136 (0.84)	-0.117 (0.33)
	Median	0.000	0.000	0.000	0.000
	Min, Max	-2.29-0.86	-1.71-4.60	-2.86-1.29	-1.00-0.38
Week 3	n	18	25	21	18
	Mean(SD)	0.300 (0.56)	0.366 (0.83)	0.435 (0.94)	0.111 (0.47)
	Median	0.000	0.000	0.000	0.000
	Min, Max	0.00-2.00	0.00-3.57	0.00-3.86	0.00-2.00
Change from baseline Week 3	n	18	22	21	17
	Mean(SD)	-0.404 (0.82)	-0.355 (0.64)	-0.498 (1.89)	-0.369 (0.58)
	Median	0.000	0.000	0.000	0.000
	Min, Max	-2.29-0.86	-1.86-0.43	-8.43-1.17	-1.67-0.00
Week 4	n	14	25	20	17
	Mean(SD)	0.296 (0.63)	0.436 (0.99)	0.502 (1.07)	0.261 (0.74)
	Median	0.000	0.000	0.000	0.000
	Min, Max	0.00-2.00	0.00-4.00	0.00-4.20	0.00-2.86

Text Table 11-35: Summary of rescue analgesics use [FAS]: Summary of total rescue analgesics use, rescue population

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Change from baseline Week 4	n	14	22	20	17
	Mean(SD)	-0.569 (0.94)	-0.275 (0.96)	-0.435 (2.56)	-0.226 (0.66)
	Median	-0.286	-0.143	0.000	0.000
	Min, Max	-2.29-1.14	-1.86-3.17	-10.29-4.03	-1.60-1.19
N=number of patients in the subgroup considered or in total; n=number of patients among N; SD=Standard Deviation Source: Table 14.2.9.1 b. Listing(s): Derived from Listing 16.2.6					

Descriptive statistics of days with rescue analgesics use are given in Text Table 11-36. Average Baseline values ranged from 0.16 to 0.38 in the four treatment groups, with lowest baseline use in the placebo group. The scores decreased in all treatment groups with the largest reductions in the 20µg group at Week 4.

Text Table 11-36: Summary of rescue analgesics use [FAS]: Summary of days with rescue analgesics use, rescue population

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	20	24	27	23
	Mean(SD)	0.271 (0.40)	0.375 (0.42)	0.215 (0.38)	0.158 (0.27)
	Median	0.000	0.243	0.000	0.000
	Min, Max	0.00-1.00	0.00-1.00	0.00-1.00	0.00-1.00
Week 1	n	19	27	24	22
	Mean(SD)	0.249 (0.39)	0.267 (0.37)	0.232 (0.38)	0.152 (0.26)
	Median	0.000	0.125	0.000	0.000
	Min, Max	0.00-1.00	0.00-1.00	0.00-1.00	0.00-1.00
Change from baseline Week 1	n	19	24	24	20
	Mean(SD)	-0.036 (0.30)	-0.075 (0.19)	0.011 (0.14)	-0.011 (0.13)
	Median	0.000	0.000	0.000	0.000
	Min, Max	-0.86-0.86	-0.69-0.14	-0.43-0.44	-0.21-0.33
Week 2	n	18	27	20	19
	Mean(SD)	0.188 (0.38)	0.288 (0.41)	0.251 (0.40)	0.125 (0.27)
	Median	0.000	0.000	0.000	0.000
	Min, Max	0.00-1.00	0.00-1.00	0.00-1.00	0.00-1.00
Change from baseline Week 2	n	18	24	20	18
	Mean(SD)	-0.113 (0.42)	-0.051 (0.31)	0.000 (0.26)	-0.045 (0.16)
	Median	0.000	0.000	0.000	0.000
	Min, Max	-1.00-0.86	-0.86-0.67	-0.69-0.86	-0.50-0.22

Text Table 11-36: Summary of rescue analgesics use [FAS]: Summary of days with rescue analgesics use, rescue population

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Week 3	n	18	25	21	18
	Mean(SD)	0.188 (0.35)	0.199 (0.35)	0.230 (0.39)	0.056 (0.24)
	Median	0.000	0.000	0.000	0.000
	Min, Max	0.00-1.00	0.00-1.00	0.00-1.00	0.00-1.00
Change from baseline Week 3	n	18	22	21	17
	Mean(SD)	-0.113 (0.41)	-0.168 (0.32)	-0.023 (0.28)	-0.124 (0.22)
	Median	0.000	0.000	0.000	0.000
	Min, Max	-1.00-0.86	-1.00-0.18	-0.61-1.00	-0.83-0.00
Week 4	n	14	25	20	17
	Mean(SD)	0.184 (0.38)	0.213 (0.38)	0.236 (0.40)	0.126 (0.33)
	Median	0.000	0.000	0.000	0.000
	Min, Max	0.00-1.00	0.00-1.00	0.00-1.00	0.00-1.00
Change from baseline Week 4	n	14	22	20	17
	Mean(SD)	-0.173 (0.46)	-0.152 (0.34)	-0.015 (0.35)	-0.057 (0.15)
	Median	0.000	0.000	0.000	0.000
	Min, Max	-1.00-0.86	-1.00-0.67	-0.86-0.83	-0.50-0.17

N=number of patients in the subgroup considered or in total; n=number of patients among N; SD=Standard Deviation
Source: Table 14.2.9.1 c. Listing(s): Derived from Listing 16.2.6

No statistically significant differences were found on any of the two approaches for any dose (For details please refer to Table 14.2.9.1 d and e)

11.1.4 *Post-hoc* Analyses

No post-hoc analyses were performed.

11.2 Results of Statistical Issues Encountered During the Analysis

11.2.1 Adjustments for Covariates

See section 9.7.1 or Pre-specified analyses adjusted for treatment, patch strata, country (ANCOVA type only) and baseline (if appropriate).

11.2.2 Handling of Withdrawals, Discontinuations or Missing Data

Imputation of missing data is specified in section 9.7.1.8.2.

11.2.3 Interim Analyses and Data Monitoring

The general procedures and the final outcome of the interim analysis are described in section 9.7.3.

11.2.4 Multicenter Studies

No summaries were made on the site level due to the large number of sites and varying sizes. Country was used as a factor in the ANCOVA based analyses.

11.2.5 Multiple comparison/ Multiplicity

All testing was performed using a closed test procedure as described in section 9.7.1.8.1. This is a hypothesis-generating phase II study and no adjustment was made between different secondary endpoints.

11.2.6 Use of an "Efficacy Subset" of Patients

There were no efficacy subsets pre-defined. The per-protocol set was used for sensitivity analyses of ulcer size, lesion size and 5-point erythema score.

11.2.7 Examination of Subgroups

An extensive set of subgroup analyses were performed to investigate the homogeneity of the effect across different patient groups. All results from such analyses are presented in a separate Exploratory report and not included in this CSR.

11.2.8 Tabulation of Individual Response Data

Individual subject response data are presented in listings in Appendix 16.2.

11.3 Pharmacokinetic, Pharmacodynamic and other Analyses Results

11.3.1 Plasma Clobetasol

Blood samples for analysis of plasma clobetasol were taken pre-patch application at Visit 3 (after 1 week of treatment). A few patients had their samples taken at Visit 4 (after 2 weeks of treatment) instead, but all values were included in the analysis since no difference in exposure was expected. The samples should have been taken pre-patch application between 7 and 9 in the morning and the patient should have applied the patches in the evening before the visit. This was not always adhered to; thus, summary statistics is also given for those samples taken according to protocol.

A summary of the analysis of the plasma clobetasol concentrations by treatment is shown in Text Table 11-37.

Text Table 11-37: Summary of plasma clobetasol concentrations [FAS]

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Clobetasol propionate (pg/ml)	Visit 3 (Visit 4)	n	29	33	38	28
		Below LOQ (n)	27	33	37	27
		Max	2000	.	29	24.3
Clobetasol propionate (pg/ml)*	Visit 3 (Visit 4)	n	21	26	30	22
		Below LOQ (n)	20	26	29	22
		Max	2000	.	29	.

N=number of patients in the subgroup considered or in total;

Values above ULOQ estimated to 2 x ULOQ
*Patch applied evening before + sampling between 07 and 09AM
Source: Table 14.2.10.1 – based on first analysis values. Listing(s): Derived from Listing 16.2.8.1

Of the 128 samples analyzed, only 4 samples showed clobetasol concentrations above the LOQ (20 pg/ml), 2 in the 20µg group, 1 in the 1µg group and even 1 in the placebo group.

Clobetasol traces in a sample of the placebo group cannot be explained by the treatment with placebo patches. A re-analysis of the sample was not initiated due to the blinding of the laboratory and irregularities with the sample could not be found retrospectively. The sample was taken from a 69 year old white woman, with a small ulcer, but a relatively high degree of suffering (as shown by Baseline PROs and a total lesion area of nearly 6 cm^2).The patient used clobetasol gel 0.05% as previous OLP treatment (effectiveness rated as good) until 19 days prior to Baseline and withdrew from the study after 7 days of patch treatment due to lack of efficacy. In this setting, unreported use of prohibited concomitant clobetasol preparations (e.g. in terms of reversion to the effective previous treatment) seems to be the most probable explanation.

Three samples contained concentrations just above the LOQ limit (24.3 pg/ml, placebo; 25.9 pg/ml, 20µg; 29.0 pg/ml, 1µg), whereas the fourth sample (20µg group) was reported as >1000 pg/mL after first analysis and 21470 pg/ml, 28847 pg/ml and 33511 pg/ml after re-analysis, an excess that cannot be explained by sole absorption of clobetasol from the patch. This sample was taken from a 73-year old, white woman (417004) with concomitant therapy against hypertension (oral lisinopril; 5 mg daily), no AEs, 2 small ulcerative lesions on gingivae (about 0.2-0.3 cm^2, each) and a total comparatively small lesion size of 2.4 cm^2. The patient was compliant with respect to the patch applications prior to V3. The serum morning cortisol concentration was in normal range. Advanced information on this case was not available, hence it's a moot question whether a technical failure or unreported usage of a concomitant clobetasol preparation were the reasons for this unrealistic high plasma level. The sample was re-analyzed on sponsor´s request after un-blinding.

11.3.2 Serum Morning Cortisol

Blood samples for serum morning cortisol were also taken at Visit 3 (after 1 week of treatment) and Visit 4 (after 2 weeks of treatment) for some patients. Again, all values were included into the analysis, since no difference in exposure was expected. The samples should have been taken pre-patch application between 7 and 9 in the morning and the patient should have applied the patches in the evening before the visit. This was not always adhered to; thus, summary statistics is also given for those samples taken according to protocol.

Summary statistics of serum morning cortisol by treatment group are given in Text Table 11-38. For details on scatter plots of individual and mean serum cortisol levels, refer to Figure 14.2.10.2.

Text Table 11-38: Summary of serum cortisol levels [FAS]

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Cortisol (nmol/L)	Visit 3 (Visit 4)	n	30	33	38	29
		Gmean (CV)	316.9 (46.4)	276.1 (41.9)	294.2 (26.8)	317.9 (34.6)
		Median	348.5	276.8	292.6	319.9
		Min, Max	67.60, 749.6	107.4, 589.3	178.3, 471.4	149.3, 576.3
Cortisol (nmol/L)*	Visit 3 (Visit 4)	n	22	26	30	23
		Gmean (CV)	338.1 (48.3)	271.5 (43.6)	302.6 (27.0)	334.4 (29.3)
		Median	358.4	263.9	294.1	338.1
		Min, Max	67.60, 749.6	107.4, 546.5	178.3, 471.4	170.6, 576.3

N=number of patients in the subgroup considered or in total; Gmean = geometric mean, CV = coefficient of variation
Values above upper LOQ estimated to 2 x upper LOQ
*Patch applied evening before + sampling between 07 and 09AM
Source: Table 14.2.10.2. Listing(s): Derived from Listing 16.2.8.1

Mean morning cortisol levels were at nearly comparable levels for all treatment groups, with slightly lower concentration for the 5µg and the 1µg group. Given a normal range for serum morning cortisol of 119-618 nmol/l, all values measured in the 1µg and the placebo group lay within normal range. One patient with cortisol level above normal range was observed in the 20µg group (749.6 nmol/l) and 2 patients with cortisol levels below normal range were observed in the 20µg (67.6 nmol/l) and 5µg (107.4 nmol/l) groups, each. Lowest and the highest cortisol concentrations were both measured in the 20µg group. The blood samples of all patients with values outside the normal range were taken according to protocol.

The patient with the lowest serum morning cortisol level (67.6 nmol/l) was a 64-year old white woman (411005) with no AEs, multiple concomitant diseases (including obesity, hyperglycemia, high cholesterol, hypertension, arthritis, degenerative disc disease, depression, urticaria, hypothyroid, Sjogren's syndrome, sciatica), multiple concomitant treatments (none with a potential influence on steroidal metabolism especially no systemic or topical corticosteroid preparations), with normal biochemistry and hematology results and a clobetasol level below LOQ.

The other patient with serum morning cortisol levels below normal range (107.4 nmol/l) was a 41-year old white man (601023) with no AEs, concomitant diseases anxiety, depression, sleep apnea and seasonal allergies and only vitamin preparations as concomitant treatments.

As changes of morning-cortisol from baseline were not investigated in this study, individual abnormal findings can hardly be assessed. Further samples would be necessary to interpret results in context with the patient's medical history, physiological variability or potential influence by concomitant/investigational drugs. With non-measurable clobetasol plasma level any influence of the IMP can be excluded.

11.4 Efficacy Results Summary

- Overall, Rivelin®-CLO patches 20 µg were shown to be effective in reducing OLP severity and symptoms and improving QoL as assessed by clinicians and patients. Thus, this dose strength is recommended for further clinical projects investigating Rivelin®-CLO patches from the efficacy perspective.
- Reducing OLP severity was shown in significantly reducing the total ulcer area (primary endpoint) and the Guy´s 106 ODSS. Borderline significance was observed in reducing the total lesion area on the FAS, with significant differences seen on the per protocol population.
- Reducing OLP symptoms was shown in significantly reducing the total OLPSSM Q1-7 score, single items OLPSSM Q8-11 scores, the Guy´s pain score. Borderline significance could be observed in reducing the worst symptoms at anatomical site score.
- Quality of life was shown to significantly improve measured by COMDQ and OLPSSM Q12.
- Rivelin®-CLO patches 5µg were shown to be effective in reducing total ulcer area (primary endpoint). Trends could be observed for improvement of some items of the OLPSSM questionnaire.
- For Rivelin-CLO patches 1µg only trends could be observed for improvement of some items of the OLPSSM questionnaire.
- None of the doses was able to significantly improve the erythema scores (5-point/3-point) or the Clinical Global Impression at anatomical site score. An exploratory analysis of maximum 5-point erythema score at clinical visits (see statistical report in Appendix 16.1.9) showed significant improvements for the 20µg group.
- No difference could be shown between any dose of Rivelin®-CLO and Rivelin® plain patches in reducing the use of rescue analgesics or completely clearing OLP lesions (total lesion area=0) or ulcers (total ulcer size=0).
- All doses of Rivelin®-patches were shown to be easy to handle, well tolerable and adhered very well to the oral mucosa for about 90 minutes.
- No indication for an impact of Rivelin®-CLO patches on the cortisol levels of patients and no indication for patch induced systemic availability of clobetasol propionate (as

measured by means of morning-serum sampling after 1-week IMP treatment) could be observed.

- The new OLPSSM measure showed to be sensitive in revealing change in OLP symptoms and is recommended for the detailed assessment of patient reported OLP symptoms in future clinical projects investigating OLP and/or Rivelin®-CLO patches.

12 SAFETY EVALUATION

12.1 Adverse Events

For the safety analysis all AEs occurring from first trial-related activity performed until the end of the trial had been recorded and were coded and sorted by MedDRA-System Organ Class (SOC) and preferred terms (PT). In the safety analysis all AEs in the Safety Set (N=138) are displayed by treatment group. Multiple occurrences of AEs related to a particular SOC or PT, respectively, in the same patient count as one occurrence.

A detailed listing of all AE data, including those AEs occurring during the screening phase, is given in Listing 16.2.7.1. SAEs, and AEs leading to IMP treatment discontinuation in addition are listed separately in Listing 16.2.7.2 and Listing 16.2.7.3, respectively.

The following sections display in detail the occurrence of treatment emergent adverse events (TEAE) i.e. AEs which occurred or deteriorated at or after the first application of the IMP. For unification, TEAEs are mostly named AEs in the following.

12.1.1 Summary of Adverse Events

A summary of all TEAEs is given in Text Table 12-1.

Text Table 12-1: Summary of adverse events – Safety Set

Category	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Total no. of AEs*	31	31	28	31	121
No. of subjects with at least one AE	15 (45.5)	16 (47.1)	17 (42.5)	15 (48.4)	63 (45.7)
No. of subjects with at least one SAE**	1 (3.0)	0	1 (2.5)	0	2 (1.4)
No. of subjects with at least one DAE	0	0	1 (2.5)	1 (3.2)	2 (1.4)
No. of subjects withdrawn due to AE	0	0	2 (5.0)	2 (6.5)	4 (2.9)
No. of subjects with at least one AE related to clobetasol	2 (6.1)	2 (5.9)	7 (17.5)	5 (16.1)	16 (11.6)
- at least one related AE	0	0	2 (5.0)	0	2 (1.4)
- at least one probably related AE	1 (3.0)	1 (2.9)	2 (5.0)	1 (3.2)	5 (3.6)
- at least one possibly related AE	2 (6.1)	1 (2.9)	5 (12.5)	4 (12.9)	12 (8.7)
No. of subjects with at least one AE related to patch application	2 (6.1)	6 (17.6)	5 (12.5)	3 (9.7)	16 (11.6)
- at least one related AE	0	2 (5.9)	2 (5.0)	1 (3.2)	5 (3.6)
- at least one probably related AE	2 (6.1)	2 (5.9)	1 (2.5)	0	5 (3.6)
- at least one possibly related AE	2 (6.1)	3 (8.8)	3 (7.5)	2 (6.5)	10 (7.2)
No. of subjects with at least one AE related to study procedure	0	0	0	1 (3.2)	1 (0.7)
No. of subjects with at least one mild AE	10 (30.3)	12 (35.3)	11 (27.5)	11 (35.5)	44 (31.9)

Text Table 12-1: Summary of adverse events – Safety Set

Category	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
No. of subjects with at least one moderate AE	9 (27.3)	6 (17.6)	6 (15.0)	8 (25.8)	29 (21.0)
No. of subjects with at least one severe AE	2 (6.1)	1 (2.9)	1 (2.5)	1 (3.2)	5 (3.6)
No. of subjects with AE with chronicity Continuous	9 (27.3)	7 (20.6)	12 (30.0)	9 (29.0)	37 (26.8)
No. of subjects with AE with chronicity Intermittent	4 (12.1)	7 (20.6)	5 (12.5)	7 (22.6)	23 (16.7)
No. of subjects with AE with chronicity Isolated	6 (18.2)	8 (23.5)	5 (12.5)	6 (19.4)	25 (18.1)
No. of subjects with AE in oral cavity	9 (27.3)	11 (32.4)	11 (27.5)	11 (35.5)	42 (30.4)

N=number of patients in the subgroup considered or in total; n=number of patients among N; (%)=percentages are based on N; counts reflect numbers of patients reporting any AE in the respective category;
SAE=serious adverse event; DAE=discontinuation of treatment due to AE
* Counted uniquely by preferred term within subject
** Including deaths
Source: Table 14.3.1.1, Listing(s): Data derived from Listing 16.2.7.1

Sixty-three patients (45.7%) reported a total of 121 TEAEs during the study, with only small differences between the treatment groups regarding frequencies. TEAEs in about two-thirds of all patients with any AE were TEAEs that occurred in the oral cavity.

Sixteen patients (11.6%) reported TEAEs judged to be causally related to the treatment received (namely to the active component of the IMP (ADRs)). Thereof more patients in the 1µg and the placebo group had TEAEs considered causally related to the treatment. TEAEs judged as causally related with the physical/mechanical patch properties (ADEs) were reported in 16 patients (11.6%), too, with heterogenous frequencies in the different dose groups. A *possible* relationship was the most commonly chosen causality definition of ADRs as well as of ADEs. A *probable* or *definite* relationship was assumed in fewer cases. No clustering of events could be observed here. Furthermore, causality had to be assessed with respect to *other* sources (i.e. ‘study procedure’, ‘rescue analgesics’, or ‘none’). A positive assessment was found in only one patient (411003) from the placebo group with an ‘other causality’ assessed related to ‘study procedure’ (‘application of patches’). Related TEAEs are described in detail in section 12.1.3.2

As described in further detail in section 12.2.2 two patients (1.4%), each one from the 1µg and the placebo group had TEAEs leading to permanent discontinuation of treatment and 4 patients (2.9%), again from the 1µg and the placebo group were withdrawn from study due to TEAE.

Most AEs were of mild intensity experienced by 44 patients (31.9%), followed by moderate AEs experienced by 29 patients (21%). A minority of only 5 patients (3.6%) had severe AEs, none of those assessed as ADR or ADE. Seeming clustering of moderate and severe intensities in the highest dose and placebo group is not attached any medical importance, not least due to minor amounts of severe events.

In total 2 patients (1.4%) experienced SAEs, each one from the 20µg and the 1µg treatment group and both judged as not related to the IMP. There were no deaths in the study. Further details regarding SAEs are given in section 12.2.1.

12.1.2 Frequencies of Adverse Events

In Text Table 12-2 all TEAEs are displayed by MedDRA SOCs and preferred terms (PTs), with overall frequencies and subordinated frequencies in different dose groups.

Text Table 12-2: Adverse Events by SOC and preferred term – Safety Set

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	15 (45)	16 (47)	17 (43)	15 (48)	63 (46)
GASTROINTESTINAL DISORDERS	7 (21)	9 (26)	6 (15)	8 (26)	30 (22)
- PERIODONTAL DISEASE	4 (12)	2 (6)	2 (5)	2 (6)	10 (7)
- SALIVARY HYPERSECRETION	1 (3)	3 (9)	0 (0)	1 (3)	5 (4)
- AMALGAM TATTOO	1 (3)	0 (0)	0 (0)	2 (6)	3 (2)
- DIARRHOEA	0 (0)	0 (0)	1 (3)	1 (3)	2 (1)
- GINGIVAL BLEEDING	0 (0)	1 (3)	1 (3)	0 (0)	2 (1)
- NAUSEA	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- ORAL PAIN	0 (0)	0 (0)	2 (5)	0 (0)	2 (1)
- ABDOMINAL DISCOMFORT	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- ABDOMINAL PAIN	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- GINGIVAL PAIN	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- HAEMORRHOIDAL HAEMORRHAGE	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- ORAL DISORDER	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- ORAL LICHEN PLANUS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- ORAL MUCOSA HAEMATOMA	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- SALIVA ALTERED	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- STOMATITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- TOOTHACHE	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
INFECTIONS AND INFESTATIONS	3 (9)	4 (12)	6 (15)	8 (26)	21 (15)
- NASOPHARYNGITIS	0 (0)	2 (6)	2 (5)	3 (10)	7 (5)
- APPLICATION SITE INFECTION	0 (0)	0 (0)	2 (5)	2 (6)	4 (3)
- ORAL CANDIDIASIS	0 (0)	1 (3)	1 (3)	1 (3)	3 (2)
- URINARY TRACT INFECTION	2 (6)	0 (0)	0 (0)	1 (3)	3 (2)
- CYSTITIS	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- EYE INFECTION	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- ORAL FUNGAL INFECTION	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)

Text Table 12-2: Adverse Events by SOC and preferred term – Safety Set

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
- PULPITIS DENTAL	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- VARICELLA ZOSTER VIRUS INFECTION	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- VIRAL SINUSITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- VULVOVAGINAL MYCOTIC INFECTION	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (9)	4 (12)	4 (10)	1 (3)	12 (9)
- APPLICATION SITE HAEMORRHAGE	2 (6)	1 (3)	1 (3)	0 (0)	4 (3)
- APPLICATION SITE PAIN	1 (3)	0 (0)	2 (5)	0 (0)	3 (2)
- FACIAL PAIN	1 (3)	0 (0)	0 (0)	1 (3)	2 (1)
- APPLICATION SITE HYPERSENSITIVITY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- APPLICATION SITE INJURY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- APPLICATION SITE PLAQUE	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- FATIGUE	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- MALAISE	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- PAIN	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
NERVOUS SYSTEM DISORDERS	6 (18)	1 (3)	3 (8)	0 (0)	10 (7)
- HEADACHE	4 (12)	1 (3)	0 (0)	0 (0)	5 (4)
- DIZZINESS	3 (9)	0 (0)	1 (3)	0 (0)	4 (3)
- DYSGEUSIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- EPILEPSY	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- NEUROPATHY PERIPHERAL	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (3)	4 (12)	1 (3)	2 (6)	8 (6)
- BITE	0 (0)	1 (3)	0 (0)	1 (3)	2 (1)
- CONTUSION	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- MULTIPLE FRACTURES	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- MUSCLE STRAIN	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- TOOTH FRACTURE	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- TOOTH INJURY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- TRAUMATIC ULCER	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (3)	1 (3)	0 (0)	2 (6)	4 (3)
- ASTHMA	1 (3)	0 (0)	0 (0)	1 (3)	2 (1)
- OROPHARYNGEAL PAIN	0 (0)	1 (3)	0 (0)	1 (3)	2 (1)
- COUGH	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)

Text Table 12-2: Adverse Events by SOC and preferred term – Safety Set

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
VASCULAR DISORDERS	0 (0)	2 (6)	0 (0)	2 (6)	4 (3)
- HYPERTENSION	0 (0)	1 (3)	0 (0)	2 (6)	3 (2)
- FLUSHING	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
PSYCHIATRIC DISORDERS	0 (0)	1 (3)	1 (3)	1 (3)	3 (2)
- INSOMNIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- RESTLESSNESS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- SLEEP DISORDER	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- STRESS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
EAR AND LABYRINTH DISORDERS	1 (3)	0 (0)	0 (0)	1 (3)	2 (1)
- EAR PAIN	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- INNER EAR DISORDER	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
INVESTIGATIONS	0 (0)	0 (0)	1 (3)	1 (3)	2 (1)
- HEART RATE INCREASED	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- HEPATIC ENZYME INCREASED	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (3)	0 (0)	0 (0)	1 (3)	2 (1)
- ARTHRALGIA	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- BACK PAIN	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0)	1 (3)	0 (0)	1 (3)	2 (1)
- PRURITUS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- RASH PRURITIC	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- SENSITIVE SKIN	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- LYMPHADENOPATHY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
CARDIAC DISORDERS	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- ACUTE MYOCARDIAL INFARCTION	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
IMMUNE SYSTEM DISORDERS	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- ALLERGY TO CHEMICALS	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)

Text Table 12-2: Adverse Events by SOC and preferred term – Safety Set

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
METABOLISM AND NUTRITION DISORDERS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- TYPE 2 DIABETES MELLITUS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)

N=number of patients in the subgroup considered or in total; n=number of patients among N; (%)=percentages are based on N;
Counts reflect numbers of patients reporting any AE in the respective category.
Source: Table 14.3.1.2. Listing(s): Derived from Listing 16.2.7.1

With regard to the TEAEs on SOC basis, 'gastrointestinal disorders' were the most common TEAEs (occurring in overall 30 patients [22%]), followed by 'infections/infestations' (in 21 [15%] patients), 'general disorders' (12 [9%] patients), 'nervous system disorders' (10 [7%] patients) and 'injury/poisoning and procedural complications' (8 [6%] patients). All remaining SOCs of TEAEs comprised overall less than 5 % of patients.

On PT level, the most common TEAEs were 'periodontal disease' (10 patients [7%]) in SOC 'gastrointestinal disorders' and 'nasopharyngitis' (7 patients [5%]) in SOC 'infections and infestations'. All other preferred terms of TEAEs occurred in overall less than 5% of patients.

Looking at different treatment groups on SOC basis, 'infections and infestations' were most common in the placebo group (in 8 patients [26%]), whereas 'general disorders' were more common in each of the clobetasol groups (1µg: 4 patients, 5µg: 4 patients and 20µg: 3 patients, accounting to 10.3% of all patients who received clobetasol), without any obvious clustering of TEAEs on PT basis. 'Nervous system disorders' predominately in terms of 'headache' (4 patients) and 'dizziness' (3 patients), were most frequently reported in patients of the 20µg clobetasol group (in 6 patients [18%] within this group).

12.1.3 Related Adverse Events

All TEAEs had to be assessed by the investigator for any causal relationship between the TEAE and the treatment received, in regard to the active component of the IMP (clobetasol propionate, shortly clobetasol) to account for possible adverse drug reactions (ADRs) and in regard to the mechanical/physical properties of the IMP to account for potential adverse device effects (ADEs) of the patch itself.

For reporting purposes, 'related', 'probably related' and 'possibly related' TEAEs were treated as related TEAEs.

12.1.3.1 Related Adverse Events - Drug Reactions on clobetasol

Text Table 12-3 provides an overview of TEAEs assessed as related to the active component clobetasol.

Text Table 12-3: Causally related adverse events by SOC and preferred term: related to clobetasol – Safety Set

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	2 (6)	2 (6)	7 (18)	5 (16)	16 (12)
INFECTIONS AND INFESTATIONS	0 (0)	1 (3)	4 (10)	3 (10)	8 (6)
- APPLICATION SITE INFECTION	0 (0)	0 (0)	2 (5)	2 (6)	4 (3)
- ORAL CANDIDIASIS	0 (0)	1 (3)	1 (3)	1 (3)	3 (2)
- ORAL FUNGAL INFECTION	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
GASTROINTESTINAL DISORDERS	1 (3)	1 (3)	2 (5)	1 (3)	5 (4)
- NAUSEA	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- DIARRHOEA	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- GINGIVAL BLEEDING	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- GINGIVAL PAIN	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- ORAL PAIN	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- STOMATITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (3)	1 (3)	2 (5)	0 (0)	4 (3)
- APPLICATION SITE PAIN	1 (3)	0 (0)	2 (5)	0 (0)	3 (2)
- APPLICATION SITE HYPERSENSITIVITY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- FACIAL PAIN	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
NERVOUS SYSTEM DISORDERS	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- DYSGEUSIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- HEADACHE	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
PSYCHIATRIC DISORDERS	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- SLEEP DISORDER	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)

N=number of patients in the subgroup considered or in total; n=number of patients among N; (%)=percentages are based on N;
Counts reflect numbers of patients reporting any AE in the respective category.
Source: Table 14.3.1.3 a. Listing(s): Derived from Listing 16.2.7.1

At least one ADR was reported for a total of 16 patients (12%), including 5 patients from the placebo group. As these patients did not receive any active treatment, relatedness to the active ingredient can be ruled out and TEAEs might rather be assessed as related to the patch itself, thus representing ADEs.

Taking into consideration the clobetasol treatment groups for the analysis of ADRs only, 11 of 107 patients (10%) had at least 1 TEAE judged as related to clobetasol. The highest incidence for ADRs affecting 7 patients (18%) was found in the group receiving the lowest clobetasol dose, whereas only 2 patients (6%), each had at least one within the 5µg group and the 20µg group.

Adverse drug reactions regarding the clobetasol groups only were restricted to 4 SOCs: 'Infections and infestations' in 5 patients, 'gastrointestinal disorders' and 'general disorders and application site reactions' in 4 patients each, and 'nervous system disorders' in 2 patients.

Most ADRs on PT level were local reactions, predominately infections in the oral cavity in overall 5 patients reported as 'application site infection' (pseudomembranous candidiasis in 2 patients of the 1µg group), 'oral candidiasis' (in each 1 patient of the 1µg and the 5 µg group) and 'oral fungal infection' (in 1 patient of the 1µg group) and local pain reactions reported as 'application site pain' (in a total of 3 patients, 2 patients from the 1µg group and 1 patient from the 20 µg group), 'gingival pain' (in 1 patient of the 5µg group), and 'oral pain' (in 1 patient of the 1µg group). Further ADRs comprised 'nausea' (2 patients, each 1 from the 1µg and the 20µg group), 'facial pain', 'gingival bleeding', 'stomatitis', 'application site hypersensitivity', 'dysgeusia' and 'headache' in just 1 patient, each. There was no medical reasonable clustering of ADRs in any of the treatment groups, especially not in the two highest dose groups.

If considering the placebo group also, there were 3 additional patients suffering from local infections (2 patients with 'application site infection' and 1 patient with 'oral candidiasis') even though not having received active treatment, 1 patient with 'diarrhoea' and another patient with 'sleep disorder' (in SOC 'psychiatric disorders').

The majority of ADRs (about two-thirds, see Listing 16.2.7.1) were also assessed as ADE. Events that were more often rated as *sole* ADR and *not as ADE* were the infections with candidiasis in the oral cavity or restricted to the application site(s) (in 6 of 8 patients). About two thirds of ADRs were judged as being of mild intensity. The remaining third was rated as being of moderate intensity, and no ADR was rated as being severe (see Listing 16.2.7.1).

Except for two events, all ADRs were documented as recovered until the individual end of study: One event of 'dysgeusia' in patient 301006 from the 1µg group only recovered with sequelae and another one of 'sleep disorder' in patient 600001 from the placebo group was reported to be not recovered until the individual end of study.

12.1.3.2 Related Adverse Events - Device Effects (of the patch properties)

AEs assessed as being related to the mechanical/physical properties of the patches are summarized in Text Table 12-4.

Text Table 12-4: Causally related adverse events by SOC and preferred term: related to patch application – Safety Set

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	2 (6)	6 (18)	5 (13)	3 (10)	16 (12)
GASTROINTESTINAL DISORDERS	1 (3)	4 (12)	2 (5)	2 (6)	9 (7)
- SALIVARY HYPERSECRETION	0 (0)	2 (6)	0 (0)	1 (3)	3 (2)
- GINGIVAL BLEEDING	0 (0)	1 (3)	1 (3)	0 (0)	2 (1)
- NAUSEA	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- DIARRHOEA	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- GINGIVAL PAIN	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)

Text Table 12-4: Causally related adverse events by SOC and preferred term: related to patch application – Safety Set

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
- ORAL LICHEN PLANUS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- ORAL PAIN	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- SALIVA ALTERED	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- STOMATITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (6)	2 (6)	3 (8)	0 (0)	7 (5)
- APPLICATION SITE PAIN	1 (3)	0 (0)	2 (5)	0 (0)	3 (2)
- APPLICATION SITE HAEMORRHAGE	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- APPLICATION SITE HYPERSENSITIVITY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- APPLICATION SITE INJURY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- FACIAL PAIN	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
INFECTIONS AND INFESTATIONS	0 (0)	1 (3)	0 (0)	1 (3)	2 (1)
- APPLICATION SITE INFECTION	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- ORAL CANDIDIASIS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
NERVOUS SYSTEM DISORDERS	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- DYSGEUSIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- HEADACHE	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)

Listing(s): Derived from Listing 16.2.7.1

N=number of patients in the subgroup considered or in total; n=number of patients among N; (%)=percentages are based on N;
Counts reflect numbers of patients reporting any AE in the respective category.
Source: Table 14.3.1.3 b. Listing(s): Derived from Listing 16.2.7.1

At least one ADE was reported for a total of 16 patients (12 %), with the highest incidence in the 5µg group (18 %) and the lowest incidence in the 20µg group (6%).

ADEs were reported in 4 different SOCs: ‘Gastrointestinal Infections and infestations’ in 9 patients, ‘general disorders and application site reactions’ in 7 patients and ‘infections and infestations’ and ‘nervous system disorders’ in 2 patients, each. On PT level ‘salivary hypersecretion’ and ‘application site pain’ were most frequently reported (in each 3 patients), followed by ‘gingival bleeding’, ‘application site haemorrhage’ and ‘nausea’ (in each 2 patients). All other ADEs were reported in only 1 patient, each.

The majority of ADEs (about two-thirds, see Listing 16.2.7.1) were also assessed as ADR. Those assessed as related to the patch application only (about one-third) were predominately events concerning hypersalivation or altered salivation (in 3 patients) and ‘application site hemorrhage’ (in 2 patients).

Most ADEs were judged as being of mild intensity and none of the ADEs was judged as being severe. In line with the ADRs no clustering of ADEs were observed in any of the treatment groups.

12.1.3.1 Related Adverse Events – In oral cavity

In order to compare related AEs with known side effects of topical Clobetasol preparations and inhaled corticosteroids, they were classified according to their location, which was either reported 'occurred in the oral cavity' (representative for local reactions) or 'not occurred in the oral cavity' (representative for any other/systemic reactions).

The following Text Table 12-5 displays drug reactions on clobetasol in the oral cavity.

Text Table 12-5: Summary of adverse events in oral cavity causally related to clobetasol treatment by SOC and preferred term – Safety Set

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	1 (3)	2 (6)	7 (18)	3 (10)	13 (9)
INFECTIONS AND INFESTATIONS	0 (0)	1 (3)	4 (10)	3 (10)	8 (6)
- APPLICATION SITE INFECTION	0 (0)	0 (0)	2 (5)	2 (6)	4 (3)
- ORAL CANDIDIASIS	0 (0)	1 (3)	1 (3)	1 (3)	3 (2)
- ORAL FUNGAL INFECTION	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (3)	1 (3)	2 (5)	0 (0)	4 (3)
- APPLICATION SITE PAIN	1 (3)	0 (0)	2 (5)	0 (0)	3 (2)
- APPLICATION SITE HYPERSENSITIVITY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
GASTROINTESTINAL DISORDERS	0 (0)	1 (3)	1 (3)	0 (0)	2 (1)
- GINGIVAL BLEEDING	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- GINGIVAL PAIN	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- ORAL PAIN	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- STOMATITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
NERVOUS SYSTEM DISORDERS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- DYSGEUSIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)

Source: Table 14.3.3.3. Listing(s): Derived from Listing 16.2.7.1

Overall 13 patients (9%) were reported to have at least one ADR in the oral cavity, with the highest incidence in the lowest clobetasol group (18%), a lower incidence in the placebo group (10%) and least incidences in the 5µg group (6%), and 20µg group (3%) , respectively. Most common represented SOC here was 'infections and infestations' with 3 different PTs of candidiasis infections occurring in overall 8 patients. No infection was observed in the highest dose group, only 1 infection in the 5µg group and each 3 - 4 infections were observed in the placebo- and 1µg-groups, indicating that clobetasol was not mainly responsible for increased susceptibility to fungal infection. Next common SOC was 'general disorders and

administration site conditions' in 4 patients of the clobetasol groups only, who had 'applications site pain' or 'application site hypersensitivity', suggesting that clobetasol might had contributed to these reactions, too. Within the SOC 'gastrointestinal disorders' 2 patients of the two lower dose groups had 4 events of 'gingival bleeding/ -pain', 'oral pain', or stomatitis. One patient of the 1µg dose experienced one event of 'dysgeusia'.

Text Table 12-6 displays adverse device effects of the patch properties that had occurred in the oral cavity.

Text Table 12-6: Summary of adverse events in oral cavity causally related to patch applications by SOC and preferred term – Safety Set

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	2 (6)	6 (18)	5 (13)	2 (6)	15 (11)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (6)	2 (6)	3 (8)	0 (0)	7 (5)
- APPLICATION SITE PAIN	1 (3)	0 (0)	2 (5)	0 (0)	3 (2)
- APPLICATION SITE HAEMORRHAGE	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- APPLICATION SITE HYPERSENSITIVITY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- APPLICATION SITE INJURY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
GASTROINTESTINAL DISORDERS	0 (0)	4 (12)	1 (3)	1 (3)	6 (4)
- SALIVARY HYPERSECRETION	0 (0)	2 (6)	0 (0)	1 (3)	3 (2)
- GINGIVAL BLEEDING	0 (0)	1 (3)	1 (3)	0 (0)	2 (1)
- GINGIVAL PAIN	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- ORAL LICHEN PLANUS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- ORAL PAIN	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- SALIVA ALTERED	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- STOMATITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
INFECTIONS AND INFESTATIONS	0 (0)	1 (3)	0 (0)	1 (3)	2 (1)
- APPLICATION SITE INFECTION	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- ORAL CANDIDIASIS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
NERVOUS SYSTEM DISORDERS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- DYSGEUSIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)

Source: Table 14.3.3.4. Listing(s): Derived from Listing 16.2.7.1

Slightly more ADEs than ADRs in oral cavity were reported in overall 15 patients (11%). Incidences ranged from each 6% in the 20µg- and placebo group to 13% in the 1µg group, and 18% in the 5µg group. Most frequent ADEs on SOC basis were 'general disorders and administration site conditions' in 7 patients of the clobetasol groups only, with PTs of different application site disorders (namely 'AS-pain', 'AS-hemorrhage', 'AS-hypersensitivity', and 'AS-injury'). Exceptional occurrences in the clobetasol groups suggest an involvement of clobetasol in these application site reactions, too. However, this is

speculative due to the small subpopulations of patients with ADEs. 'Gastrointestinal disorders' occurred in 6 patients of all groups except for the highest dose group with the main PTs of 'salivary hypersecretion'/'saliva altered' and 'gingival pain'/ 'hemorrhage'). Only 2 events of candidiasis infection that had occurred in each 1 patient of the 5µg group and placebo group, respectively, were assessed as ADE, too (in contrary to the other events of candidiasis infection that were solely assessed as ADR, see Text Table 12-5).

Looking to the reported terms ('verbatims') of oral ADRs/ADEs, the nature and causation of events is illustrated more accurately (see Listing 16.2.7.1): The events of 'application site pain' rather referred to procedurally limited sensations of 'stinging', than to an independent constant pain. Events of 'application site hemorrhage' referred to limited bleedings triggered by patching procedures. Most 'gingival disorders' and the one event of 'oral pain' were situationally restricted ("teeth brushing"). Most 'salivary disorders' were limited to the patch residence time. So, besides the events of infection, the majority of local reactions were limited to a triggering event (patch procedure or daily activity procedure) and did not represent a constant side effect during IMP treatment.

Text Table 12-7 displays all AEs of candidiasis infections in the oral cavity in overall 8 patients. Displayed are start/stop days relative to baseline, event intensities, causality-specifications, and actions taken.

Text Table 12-7: Summary of adverse events reported as oral candidiasis/oral fungal infection / application site infection during the study – Safety Set

Subject no./ Age (yrs)/ Sex/ Race/ Treatment	Country	Diagn. duration (yrs)	No. patch	AE symptom	Start day /Stop day	Severity	Action taken	Other action	Causality
301001/ 71/ F/ WHITE/ C	DNK	1.0	4	ORAL CANDIDOSIS	13/31	MODERATE	DOSE NOT CHANGED	Concomitant treatment	PROBABLY RELATED
301002/ 74/ F/ WHITE/ A	DNK	12.0	2	ORAL CANDIDOSIS	22/42	MILD	DOSE NOT CHANGED	Other action	POSSIBLY RELATED
301003/ 74/ F/ WHITE/ B	DNK	4.6	1	ORAL FUNGAL INFECTION	9/12	MILD	NOT APPLICABLE	Concomitant treatment	POSSIBLY RELATED
301009/ 76/ F/ WHITE/ B	DNK	12.9	3	ORAL CANDIDIASIS	29/40	MILD	DOSE NOT CHANGED	Other action	POSSIBLY RELATED
400011/ 72/ F/ WHITE/ B	USA	3.0	5	APPLICATION SITE INFECTION*	10/15	MILD	DOSE NOT CHANGED	Concomitant treatment	RELATED
400011/ 72/ F/ WHITE/ B	USA	3.0	5	APPLICATION SITE INFECTION*	29/43	MILD	DOSE NOT CHANGED	Concomitant treatment	RELATED
400012/ 57/ M/ WHITE/ B	USA	1.1	6	APPLICATION SITE INFECTION*	8/17	MILD	DOSE NOT CHANGED	Concomitant treatment	PROBABLY RELATED
400012/ 57/ M/ WHITE/ B	USA	1.1	6	APPLICATION SITE INFECTION*	22/29	MILD	DOSE NOT CHANGED	Concomitant treatment	PROBABLY RELATED

Text Table 12-7: Summary of adverse events reported as oral candidiasis/oral fungal infection / application site infection during the study – Safety Set

Subject no./ Age (yrs)/ Sex/ Race/ Treatment	Country	Diagn. duration (yrs)	No. patch	AE symptom	Start day /Stop day	Severity	Action taken	Other action	Causality
410008/ 55/ F/ WHITE/ A	USA	0.0	5	APPLICATION SITE INFECTION*	30/59	MILD	NOT APPLICABLE	Concomitant treatment	PROBABLY RELATED
411003/ 77/ F/ WHITE/ A	USA	0.4	4	APPLICATION SITE INFECTION*	37/44	MODERATE	NOT APPLICABLE	Other action	POSSIBLY RELATED

A = placebo, B = 1 ug, C = 5 ug, D = 20 ug
F = Female, M = Male, DNK = Denmark
*(pseudomembraneous) candidiasis at application site
Start-/Stop-days = relative to BL
Causality to clobetasol
Source: Table 14.3.3.2, Listing(s): Derived from Listing 16.2.4.1 and Listing 16.2.7.1

6 patients experienced each one event of candidiasis infection, and 2 patients had each 2 events of infection. Infections occurred mainly in the 1µg and placebo groups but were rated as ADRs in all cases (see Text Table 12-5). No oral (candida) infections were observed in the 20µg group. 4 patients had infections restricted to patch application areas, and in the other 4 patients infections were reported as ‘oral candidosis’ or ‘fungal oral infection’. Most of patients were female, aged between 55 – 77 years, and were treated with an average number of 3.75 patches. Infections started within 8 – 37 days after baseline, were mostly mild in intensity (6 patients), and did not require IMP withdrawal in any case. If ‘action taken’ was reported as “not applicable” respective patient had already completed the treatment phase or had dropped prematurely (e.g. pt. 303003 was prematurely withdrawn due to a protocol violation). All events of candidiasis infections had recovered completely (see Listing 16.2.7.1).

12.1.3.1 Related Adverse events – Outside the oral cavity

A minority of 6 events in 5 patients occurred outside the oral cavity or were of systemic nature, most rated as both, ADR and ADE (see Text Table 12-3 and Listing 16.2.7.1) Reactions were reported in each 1 - 2 patients of the placebo-, 1µg- and 20µg-group. On PT basis these were ‘nausea’ (1µg and 20 µg group), ‘facial pain’ (20 µg group), ‘headache’ (20µg group), ‘sleep disorder’ (placebo group), and ‘diarrhea’ (placebo group). One event of ‘nausea’ was reported to be *due to smell of patches* (pt. 301006, see verbatim in Listing 16.2.7.1).

12.2 Analysis of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.2.1 Deaths and Serious Adverse Events

Text Table 12-8 summarizes serious treatment emergent adverse events (SAEs) by system organ class and preferred terms.

Overall 2 SAEs in 2 (1.4%) patients, each one from the 1µg group and from the 20µg group, respectively were reported in the trial. None of these events were considered related to study treatment. No case of death was reported.

Text Table 12-8: Summary of serious adverse events by SOC and Preferred Terms – Safety Set

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
CARDIAC DISORDERS	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- ACUTE MYOCARDIAL INFARCTION	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- MULTIPLE FRACTURES	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)

N=number of patients in the subgroup considered or in total; n=number of patients among N; (%)=percentages are based on N; SOC=System Organ Class;
Counts reflect numbers of patients reporting any SAE in the respective category.
Source: Table 14.3.2.1. Listing(s): Derived from Listing 16.2.7.1

Each SAE is described case by case in patient SAE narratives in section 12.2.3

12.2.2 Adverse Events leading to Permanent Discontinuation of IMP

Four TEAEs in overall 2 patients (1.4%), each one from the 1µg group and the placebo group were reported to result in permanent discontinuation of IMP (see Text Table 12-9).

Text Table 12-9: Summary of discontinuations of treatment due to AEs by SOC and Preferred Terms – Safety Set

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	0 (0)	0 (0)	1 (3)	1 (3)	2 (1)
GASTROINTESTINAL DISORDERS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- ORAL PAIN*	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- STOMATITIS**	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
INFECTIONS AND INFESTATIONS	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- VARICELLA ZOSTER VIRUS INFECTION	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
PSYCHIATRIC DISORDERS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- INSOMNIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)

N=number of patients in the subgroup considered or in total; n=number of patients among N; (%)=percentages are based on N; SOC=System Organ Class; PT=preferred term
Counts reflect numbers of patients reporting at least one AE in the respective category.
*INCREASED INFLAMMATION ON LEFT SIDE ORAL CAVITY (DISTANT) LESION
**INCREASED SENSITIVITY WHEN BRUSHING TEETH (DISTANT) LESION
Source: Table 14.3.3.1 and Listing 16.2.7.3

One patient from the 1µg group (400002) experienced ‘insomnia’, ‘oral pain’ and ‘stomatitis’ leading to withdrawal of study medication. ‘Oral pain’ and ‘stomatitis’ led to premature discontinuation of treatment after 9 days of treatment, even though both events occurred distant from the patched lesions (see verbatims in Text-Table 12-9). Both were considered possibly related to study treatment (to both the active ingredient of the IMP as well as to the patch properties itself). As already outlined in section 10.3, patient 400002 switched to treatment with 20µg patches on date of Visit 3 (day 8) due to an incorrect allocation of the second treatment kit via the IWRS. Correspondingly local AEs leading to premature discontinuation of treatment occurred under the treatment with the highest dose of clobetasol (day 2) and not under treatment with 1µg patches as originally assigned at date of randomization. ‘Increased insomnia’ started on day 12 and was considered unlikely related to study treatment, it has not recovered at patient’s individual end of study on day 29 (see Listing 16.7.2.3).

One patient from the placebo group (400007) experienced ‘varicella zoster virus infection’ which led to withdrawal of study medication. The adverse event started on day 5 and was not considered related to study treatment.

12.2.3 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Narratives for serious adverse events that occurred in patient 204002 from the 20µg group and in patient 406002 from the 1µg group are provided below:

Subject identifier	204002
Year of birth	1958
Age (at Screening)	61 years
Sex	F
Race/Ethnicity	White/Not Hispanic or Latino
Investigational product	Rivelin®-Clo 20µg
Start/stop dates of trial treatment	03-Jul-2019 07-Aug-2019
Event (reported term / coded PT)	**NSTEMI – Non-ST Segment Elevation Myocardial infarction/ Myocardial infarction**
Severity (= maximum intensity)	Severe
Seriousness criterion	Patient Hospitalisation Life threatening
Start/stop date of event	23-Jul-2019 26-Jul-2019
Date of last dose of trial treatment before event	22-Jul-2019
Action taken	IP interrupted (23-Jul-2019 – 30-Jul-2019) Drug treatment
Outcome of event	Recovered/resolved with sequelae
Date of death (if applicable)	Not applicable
Relationship to trial treatment	Not related

Narrative:

This 61-year-old woman entered the study on 25-Jun-2019 showing oral lichen planus of moderate to severe intensity at left and right buccal mucosa.

Concomitant medications included:

- Oral bisoprolol, 2.5 mg daily since 2004 for hypertension
- Oral ramipril; 10 mg daily since 2017 for previous myocardial infarction
- Oral aspirin, 75 mg daily since 2017 preventive after previous myocardial infarction and stent placement

Subject identifier	204002
Year of birth	1958

- Glyceryl trinitrate spray, 400 mg as needed, since 2017 for angina pectoris
- Oral atorvastatin; 80 µg daily since 2017 for hypercholesterinaemia
- Oral metformin, 10 mg daily since 2018 for diabetes type II

The subject started to apply IP as per protocol on 03-Jul-2019.

On 23-Jul-2019, i.e 20 days after the onset of the IP, the subject was hospitalised for the event of 'myocardial infarction', which was considered as severe in intensity.

The patient was admitted to hospital with chest pain. ECG examinations and the consultation of a cardiologist revealed a myocardial infarction related to ischaemic heart disease on the background of type II diabetes.

In hospital, subject was treated with one dose of 2.5 mg subcutaneous fondaparinux and one dose of 300 mg oral clopidogrel on the 23-Jul-2019. Furthermore, dose of oral bisoprolol was increased from 2.5 mg daily dose to 5 mg daily dose on the same day. On 24-Jul-2019 ongoing treatment with oral isosorbide mononitrate 25 mg daily dose was initiated.

On 26-Jul-2019, i.e. 3 days after SAE onset, the patient was discharged from hospital and the event was assessed as recovered/resolved with sequelae.

The study drug was temporarily interrupted from 22-Jul-2019 to 30-Jul-2019.

The investigator assessed the event to be unrelated to the IP.

Subject identifier	406002
Year of birth	1946
Age (at Screening)	73 years
Sex	F
Race/Ethnicity	White/Not Hispanic or Latino
Investigational product	Rivelin®-Clo 1µg
Start/stop dates of trial treatment	03-Jan-2019 29-Jan-2019
Event (reported term / coded PT)	**Fractured left tibia, fractured right humerus / Multiple fractures**
Severity (= maximum intensity)	Severe
Seriousness criterion	Hospitalisation
Start/stop date of event	24-Jan-2019 31-May-2019
Date of last dose of trial treatment before event	24-Jan-2019

Subject identifier	406002
Year of birth	1946
Action taken	None - Dose not changed
Outcome of event	Recovered/resolved
Date of death (if applicable)	Not applicable
Relationship to trial treatment	Not related

Narrative:

This 73-year-old woman entered the study on 18-Dec-2018 showing oral lichen planus of mild to moderate intensity at left and right buccal mucosa.

Concomitant medications included:

- Oral omeprazole, 20 mg daily since Sep-2018 for esophagitis
- Oral sertraline; 50 mg daily since 2008 for depression
- Oral amlodipine; 2.5 mg daily since 2010 for hypertension
- Oral levothyroxine; 112 µg daily since 1998 for hypothyroidism

The patient started to apply IP as per protocol on 03-Jan-2019.

On 24-Jan-2019, i.e. 21 days after the onset of the IP, the patient was hospitalized for the event of 'multiple fractures', which was considered as severe in intensity.

In the evening of 24-Jan-2019, the patient was pulled down while walking her dog in the dark. The dog was frightened by a passing snow plow, jumped and pulled the owner down. The patient fell on her left knee and injured her right shoulder while trying to break her fall. She was hospitalized on the same night and X-ray imaging revealed displaced fracture of the right humerus, mildly depressed fracture of left medial tibial plateau and nondisplaced fracture of left proximal fibula.

The patient refused pain treatment during the first hours in hospital, but on 25-Jan-2019 ongoing treatment with celebrex/celecoxib 400 mg daily dose, acetaminophen 1000mg daily dose and oxycodone HCl (as needed) for pain management was initiated. All other concomitant treatments were continued unchanged.

The patient was admitted for conservative management (sling for the shoulder and brace for the knee) and was transferred to a rehabilitation facility on 28-Jan-2019.

On 31-May-2019, i.e. 127 days after SAE onset, the event was assessed as recovered/resolved, when the patient had her Visit 6 (early termination) assessments on site.

The investigator assessed the event to be unrelated to the IMP.

12.3 Clinical Laboratory Evaluation

Blood samples for hematology and serum chemistry and a urine sample were taken at Visit 1 (assessed as baseline values/prior to treatment) and at Visit 7 (End of Study) or in case of

patient's withdrawal during the treatment period at Visit 6. The blood samples for hematology and serum chemistry were analyzed centrally. The urine status was analyzed locally by using dip-stick tests.

For each female patient of childbearing potential, a serum pregnancy test was performed at Visit 1 (prior to treatment). Urine pregnancy tests were performed at Visit 0 (prior to biopsy, if a biopsy had to be taken), at Baseline and at Visit 6 (End of Treatment).

Any laboratory result outside the normal range was graded by investigator as 'abnormal, not clinically significant' or 'abnormal, clinically significant'.

Abnormal clinically significant findings as determined by the investigator were reported as medical history if detected at Visit 1. An abnormal and clinically significant laboratory value at Visit 6/Visit 7, had to be documented as an AE, if it indicated a newly developed or worsened condition.

For patients with more than one assessment prior to treatment, the last non-missing assessment has been used as the baseline value. Similar for patients with more than one follow-up value, the first non-missing value has been used, except when laboratory data was collected at both Visit 6 and 7, then values from the protocol specified Visit 7 was used.

12.3.1 Individual Laboratory Measurements by Patient and each Abnormal Laboratory Value

Individual laboratory measurements by patient and visit including normal indicator are displayed in Listing 16.2.8.1 (a) hematology; b) biochemistry and c) urinalysis). Respective data for abnormal post-dose laboratory measurements are provided in Listing 16.2.8.2 (a) hematology; b) biochemistry and c) urinalysis).

12.3.2 Evaluation of Each Laboratory Parameter

12.3.2.1 Hematology and Serum Chemistry

Summary statistics by visit with difference from Baseline (=pre-treatment) for central laboratory data are provided with Table 14.3.4.1 (a) hematology; b) biochemistry). Shift tables showing out-of-range values on laboratory data are given in Table 14.3.4.2 (a) hematology; b) biochemistry) and corresponding shift plots are provided in Figure 14.3.4.1.

Mean (SD) values of central laboratory parameters at Baseline and related changes from Baseline until the End of Study/Early Termination Visit are summarized in Text Table 12-10 for hematology and in Text Table 12-11 for serum chemistry.

Text Table 12-10: Hematology: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Hemoglobin (g/dL)	Baseline	n	33	33	40	31
		Mean(SD)	13.92 (1.34)	14.01 (1.24)	13.64 (1.13)	13.83 (0.99)
		Median	14.20	14.01	13.79	13.70
		Min, Max	11.1-16.7	10.6-16.3	11.0-16.4	12.2-16.0

Text Table 12-10: Hematology: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Follow-up	n	29	33	36	30
		Mean(SD)	13.91 (1.24)	14.00 (1.23)	13.52 (1.14)	13.64 (0.97)
		Median	14.01	14.00	13.61	13.61
		Min, Max	11.4-16.7	10.0-16.1	11.0-15.6	11.4-15.5
	Change from baseline	n	29	32	36	30
		Mean(SD)	-0.00 (0.59)	-0.05 (0.49)	-0.08 (0.47)	-0.17 (0.55)
		Median	0.00	0.00	-0.16	-0.18
		Min, Max	-0.8-1.8	-1.3-0.8	-1.1-1.3	-1.2-0.8
Platelets (10^9/L)	Baseline	n	33	33	40	31
		Mean(SD)	254.00 (73.22)	244.58 (52.33)	250.43 (62.83)	259.13 (57.42)
		Median	246.00	243.00	254.00	257.00
		Min, Max	84.0-486.0	125.0-349.0	112.0-383.0	122.0-368.0
	Follow-up	n	29	33	36	30
		Mean(SD)	247.62 (60.91)	239.36 (67.81)	247.03 (61.95)	263.70 (70.40)
		Median	240.00	241.00	254.00	241.50
		Min, Max	89.0-383.0	43.0-384.0	103.0-365.0	147.0-454.0
	Change from baseline	n	29	32	36	30
		Mean(SD)	0.00 (23.23)	-3.63 (41.69)	-4.42 (26.85)	3.13 (39.02)
		Median	0.00	0.00	-2.00	-1.50
		Min, Max	-70.0-44.0	-193.0-68.0	-119.0-56.0	-46.0-172.0
Erythrocytes (10^12/L)	Baseline	n	33	33	40	31
		Mean(SD)	4.53 (0.41)	4.65 (0.36)	4.58 (0.38)	4.57 (0.37)
		Median	4.50	4.59	4.51	4.59
		Min, Max	3.8-5.3	4.0-5.3	3.7-5.5	4.0-5.1
	Follow-up	n	29	33	36	30
		Mean(SD)	4.54 (0.38)	4.64 (0.38)	4.56 (0.42)	4.46 (0.34)
		Median	4.50	4.54	4.53	4.49
		Min, Max	3.9-5.1	3.8-5.5	3.8-5.7	3.9-5.1
	Change from baseline	n	29	32	36	30
		Mean(SD)	0.01 (0.17)	-0.02 (0.16)	-0.03 (0.20)	-0.09 (0.15)
		Median	0.00	-0.01	-0.06	-0.10
		Min, Max	-0.2-0.6	-0.4-0.3	-0.5-0.7	-0.4-0.2

Text Table 12-10: Hematology: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Leukocytes (10^9/L)	Baseline	n	33	33	40	31
		Mean(SD)	6.86 (2.69)	6.36 (1.34)	6.91 (1.65)	6.81 (1.65)
		Median	6.20	6.30	7.00	6.60
		Min, Max	3.0-18.0	3.6-10.3	2.9-10.6	3.7-10.3
	Follow-up	n	29	33	36	30
		Mean(SD)	6.64 (1.80)	6.61 (1.55)	6.67 (1.80)	6.58 (1.72)
		Median	6.50	6.40	6.65	6.20
		Min, Max	3.9-9.9	4.3-10.7	3.3-11.8	3.4-9.6
	Change from baseline	n	29	32	36	30
		Mean(SD)	-0.31 (2.00)	0.23 (1.16)	-0.15 (1.17)	-0.28 (1.06)
		Median	-0.30	0.10	-0.20	-0.25
		Min, Max	-8.6-2.6	-1.6-2.5	-2.5-3.1	-2.4-2.5
Neutrophils (10^9/L)	Baseline	n	33	33	40	31
		Mean(SD)	4.24 (2.39)	3.86 (1.20)	4.25 (1.29)	4.07 (1.38)
		Median	3.71	4.12	4.04	3.98
		Min, Max	1.0-14.9	2.0-7.5	1.5-6.7	1.3-6.6
	Follow-up	n	29	33	36	30
		Mean(SD)	4.08 (1.53)	4.09 (1.36)	3.89 (1.23)	3.93 (1.25)
		Median	3.56	3.98	3.72	3.58
		Min, Max	1.8-7.4	2.2-8.1	1.9-7.6	1.1-6.3
	Change from baseline	n	29	32	36	30
		Mean(SD)	-0.24 (1.90)	0.25 (1.05)	-0.32 (0.97)	-0.18 (0.84)
		Median	-0.17	0.03	-0.35	-0.15
		Min, Max	-8.3-3.1	-1.1-3.7	-2.7-1.7	-2.0-2.1

Text Table 12-10: Hematology: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Neutrophils/ Leukocytes (%)	Baseline	n	33	33	40	31
		Mean(SD)	59.70 (9.97)	60.06 (10.95)	60.87 (8.20)	58.47 (9.69)
		Median	59.80	61.90	61.00	59.90
		Min, Max	34.6-82.6	36.4-78.5	44.8-83.4	33.8-70.6
	Follow-up	n	29	33	36	30
		Mean(SD)	60.45 (8.94)	61.00 (8.77)	58.21 (9.15)	58.92 (7.87)
		Median	60.70	61.30	59.10	59.35
		Min, Max	41.0-77.7	41.5-78.4	36.3-74.5	32.3-72.3
	Change from baseline	n	29	32	36	30
		Mean(SD)	0.08 (7.10)	1.28 (7.44)	-2.72 (6.02)	0.39 (6.18)
		Median	0.00	0.30	-1.75	-0.45
		Min, Max	-12.6-18.7	-15.7-22.0	-15.5-6.6	-12.5-21.3
Monocytes (10^9/L)	Baseline	n	33	33	40	31
		Mean(SD)	0.43 (0.15)	0.49 (0.20)	0.51 (0.15)	0.54 (0.14)
		Median	0.39	0.47	0.49	0.52
		Min, Max	0.2-1.0	0.2-1.1	0.2-0.8	0.3-0.8
	Follow-up	n	29	33	36	30
		Mean(SD)	0.43 (0.13)	0.52 (0.16)	0.53 (0.17)	0.52 (0.16)
		Median	0.42	0.50	0.50	0.52
		Min, Max	0.3-0.8	0.2-1.1	0.3-1.0	0.3-0.9
	Change from baseline	n	29	32	36	30
		Mean(SD)	0.01 (0.11)	0.03 (0.14)	0.03 (0.09)	-0.03 (0.12)
		Median	0.03	0.02	0.04	-0.04
		Min, Max	-0.3-0.2	-0.4-0.3	-0.2-0.2	-0.3-0.3

Text Table 12-10: Hematology: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Monocytes/ Leukocytes (%)	Baseline	n	33	33	40	31
		Mean(SD)	6.48 (1.85)	7.60 (2.12)	7.47 (1.95)	8.15 (2.56)
		Median	6.10	7.30	7.60	7.90
		Min, Max	3.4-11.6	3.4-13.0	3.9-11.3	4.9-19.9
	Follow-up	n	29	33	36	30
		Mean(SD)	6.68 (1.89)	7.95 (1.84)	8.03 (1.92)	8.07 (2.40)
		Median	6.60	8.10	7.70	7.80
		Min, Max	3.8-12.6	4.3-11.7	4.9-12.8	4.9-18.4
	Change from baseline	n	29	32	36	30
		Mean(SD)	0.32 (1.62)	0.28 (1.82)	0.57 (1.43)	-0.13 (1.48)
		Median	0.40	0.35	0.25	0.20
		Min, Max	-3.9-3.5	-3.2-3.8	-1.7-3.8	-3.8-2.5
Lymphocytes (10^9/L)	Baseline	n	33	33	40	31
		Mean(SD)	1.97 (0.62)	1.77 (0.63)	1.86 (0.53)	1.94 (0.55)
		Median	1.83	1.81	1.87	1.94
		Min, Max	0.8-3.9	0.6-3.3	0.9-3.0	1.3-3.5
	Follow-up	n	29	33	36	30
		Mean(SD)	1.91 (0.53)	1.76 (0.56)	1.93 (0.75)	1.86 (0.53)
		Median	2.01	1.72	1.76	1.86
		Min, Max	0.8-2.9	0.8-3.0	1.0-4.2	1.1-3.0
	Change from baseline	n	29	32	36	30
		Mean(SD)	-0.06 (0.39)	-0.04 (0.46)	0.10 (0.38)	-0.09 (0.41)
		Median	-0.04	-0.05	0.07	-0.14
		Min, Max	-1.1-0.5	-1.0-1.0	-0.6-1.3	-1.2-0.9

Text Table 12-10: Hematology: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Lymphocytes/ Leukocytes (%)	Baseline	n	33	33	40	31
		Mean(SD)	30.26 (8.46)	28.42 (10.22)	27.73 (7.27)	29.40 (8.35)
		Median	30.30	28.00	28.55	29.90
		Min, Max	10.7-49.9	10.5-46.2	11.1-42.7	17.8-55.0
	Follow-up	n	29	33	36	30
		Mean(SD)	29.57 (7.69)	27.34 (8.52)	29.02 (8.03)	28.73 (5.81)
		Median	29.10	27.20	29.10	28.95
		Min, Max	15.2-46.9	12.1-44.4	18.2-46.6	18.0-41.7
	Change from baseline	n	29	32	36	30
		Mean(SD)	-0.12 (5.49)	-1.38 (5.81)	1.39 (4.98)	-0.54 (5.36)
		Median	1.10	-0.35	1.10	-0.30
		Min, Max	-14.1-9.2	-15.7-10.7	-11.1-10.6	-20.2-8.9
Eosinophils (10^9/L)	Baseline	n	33	33	40	31
		Mean(SD)	0.18 (0.13)	0.20 (0.12)	0.23 (0.25)	0.20 (0.13)
		Median	0.15	0.17	0.16	0.15
		Min, Max	0.0-0.6	0.0-0.6	0.0-1.3	0.1-0.5
	Follow-up	n	29	33	36	30
		Mean(SD)	0.17 (0.11)	0.19 (0.10)	0.28 (0.26)	0.21 (0.15)
		Median	0.15	0.17	0.19	0.16
		Min, Max	0.0-0.5	0.0-0.4	0.0-1.4	0.1-0.7
	Change from baseline	n	29	32	36	30
		Mean(SD)	-0.02 (0.08)	-0.01 (0.09)	0.04 (0.08)	0.00 (0.08)
		Median	-0.02	-0.01	0.02	0.00
		Min, Max	-0.3-0.1	-0.2-0.2	-0.1-0.3	-0.2-0.2

Text Table 12-10: Hematology: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Eosinophils/ Leukocytes (%)	Baseline	n	33	33	40	31
		Mean(SD)	2.95 (2.21)	3.17 (1.89)	3.18 (2.85)	3.09 (2.13)
		Median	2.30	2.90	2.25	2.60
		Min, Max	0.6-8.4	0.6-9.8	0.4-14.6	0.7-9.7
	Follow-up	n	29	33	36	30
		Mean(SD)	2.60 (1.64)	2.96 (1.63)	3.98 (3.05)	3.27 (2.55)
		Median	2.10	2.80	2.90	2.50
		Min, Max	0.6-7.0	0.4-7.4	0.5-14.3	0.7-13.1
	Change from baseline	n	29	32	36	30
		Mean(SD)	-0.36 (1.40)	-0.18 (1.39)	0.72 (1.17)	0.15 (1.24)
		Median	0.00	-0.10	0.40	0.30
		Min, Max	-3.6-1.5	-4.8-2.3	-0.8-4.4	-3.5-3.4
Basophils (10^9/L)	Baseline	n	33	33	40	31
		Mean(SD)	0.04 (0.02)	0.05 (0.03)	0.05 (0.03)	0.06 (0.03)
		Median	0.04	0.05	0.05	0.05
		Min, Max	0.0-0.1	0.0-0.1	0.0-0.1	0.0-0.1
	Follow-up	n	29	33	36	30
		Mean(SD)	0.04 (0.02)	0.05 (0.02)	0.05 (0.03)	0.07 (0.03)
		Median	0.04	0.05	0.05	0.06
		Min, Max	0.0-0.1	0.0-0.1	0.0-0.1	0.0-0.2
	Change from baseline	n	29	32	36	30
		Mean(SD)	0.00 (0.02)	-0.00 (0.03)	-0.00 (0.02)	0.01 (0.03)
		Median	0.00	0.00	0.00	0.00
		Min, Max	-0.0-0.1	-0.1-0.1	-0.1-0.1	-0.0-0.1

Text Table 12-10: Hematology: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Basophils/ Leukocytes (%)	Baseline	n	33	33	40	31
		Mean(SD)	0.606 (0.26)	0.764 (0.39)	0.770 (0.33)	0.842 (0.42)
		Median	0.500	0.700	0.700	0.900
		Min, Max	0.20-1.30	0.00-1.90	0.20-1.60	0.00-1.70
	Follow-up	n	29	32	36	30
		Mean(SD)	0.710 (0.38)	0.763 (0.29)	0.764 (0.36)	1.003 (0.47)
		Median	0.600	0.700	0.700	0.950
		Min, Max	0.10-1.60	0.20-1.60	0.00-1.40	0.10-2.00
	Change from baseline	n	29	32	36	30
		Mean(SD)	0.076 (0.33)	0.006 (0.40)	0.011 (0.43)	0.177 (0.50)
		Median	0.000	0.000	0.100	0.100
		Min, Max	-0.50-1.10	-1.50-0.90	-0.80-1.20	-0.70-1.60

SD = Standard deviation
Source: Table 14.3.4.1 a; Listing(s): Derived from Listing 16.2.8.1

Baseline mean level and mean changes of erythrocytes and hemoglobin did not show any clinically relevant abnormalities or differences between treatment groups. Platelets did not neither, besides in 3 cases: One patient of the 20µg group with concomitant ‘liver sclerosis’ (pt. 601003) with noticeably thrombopenia at Baseline (85 10^9/L) as well as end of treatment, that were both rated ‘not clinically significant’. In the 5µg group there was one substantial platelet decrease (i.e. ‘min change’) in patient 102008 to an alarming level of 43 10^9/L, that was rated not clinically significant (‘measurement error’ assumed) because control sampling 1 week later revealed normal level. The ‘max change’ in the placebo group referred to patient 410008 whose normal level at Baseline had increased to abnormal 454 10^9/L rated as not clinically significant.

White blood cells mean level at Baseline were unremarkable with respect to the clinical significance as well as mean changes within the different treatment groups, except for one case in the 20µg group (pt. 600002) with leukocytosis (18 10^9/L) including neutrophils increase at baseline. Both abnormalities were rated not clinically significant because neither corresponding TEAE nor concomitant disease were observed. Both levels had turned to normal until the end of trial.

Overall compared to baseline values, there were no clinically relevant changes in mean/median values of any hematology parameter for any of the treatment groups.

Text Table 12-11: Serum chemistry: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Albumin (g/L)	Baseline	n	33	33	40	31
		Mean(SD)	43.03 (2.91)	43.36 (2.76)	42.93 (3.25)	43.10 (2.10)
		Median	43.00	44.00	43.00	43.00
		Min, Max	36.0-48.0	38.0-49.0	31.0-48.0	39.0-47.0
	Follow-up	n	30	34	38	31
		Mean(SD)	43.00 (2.83)	43.18 (2.28)	42.45 (3.25)	42.87 (2.49)
		Median	43.00	42.50	42.50	43.00
		Min, Max	36.0-48.0	40.0-48.0	32.0-48.0	39.0-47.0
	Change from baseline	n	30	33	38	31
		Mean(SD)	-0.10 (2.20)	-0.15 (2.35)	-0.34 (2.00)	-0.23 (1.84)
		Median	0.00	0.00	0.00	0.00
		Min, Max	-4.0-6.0	-5.0-4.0	-5.0-3.0	-4.0-4.0
Alkaline Phosphatase (U/L)	Baseline	n	33	33	40	31
		Mean(SD)	76.45 (28.30)	65.91 (16.67)	74.53 (26.58)	74.23 (21.79)
		Median	74.00	68.00	70.00	71.00
		Min, Max	31.0-164.0	28.0-97.0	35.0-185.0	46.0-136.0
	Follow-up	n	30	34	38	31
		Mean(SD)	74.33 (30.57)	64.43 (19.89)	73.63 (26.94)	72.55 (21.73)
		Median	72.00	65.00	69.50	70.00
		Min, Max	27.0-190.0	2.5-112.0	33.0-174.0	44.0-144.0
	Change from baseline	n	30	33	38	31
		Mean(SD)	-0.27 (8.42)	-1.23 (14.36)	-1.21 (9.72)	-1.68 (6.42)
		Median	-1.50	2.00	-2.00	-1.00
		Min, Max	-18.0-26.0	-68.5-20.0	-24.0-26.0	-16.0-11.0
Alanine Aminotransferase (U/L)	Baseline	n	33	33	40	31
		Mean(SD)	30.61 (24.90)	26.94 (13.88)	25.30 (18.64)	22.35 (9.27)
		Median	24.00	23.00	21.00	21.00
		Min, Max	9.0-144.0	11.0-61.0	4.0-90.0	9.0-55.0
	Follow-up	n	30	34	38	31
		Mean(SD)	35.30 (32.42)	25.94 (15.11)	26.00 (27.11)	22.29 (9.69)
		Median	25.50	23.50	19.00	20.00

Text Table 12-11: Serum chemistry: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Min, Max	10.0-171.0	9.0-67.0	4.0-160.0	10.0-47.0
	Change from baseline	n	30	33	38	31
		Mean(SD)	3.90 (10.91)	-2.00 (10.45)	0.68 (14.73)	-0.06 (5.51)
		Median	0.50	-2.00	-1.00	0.00
		Min, Max	-10.0-31.0	-31.0-29.0	-20.0-74.0	-8.0-17.0
Aspartate Aminotransferase (U/L)	Baseline	n	33	33	40	31
		Mean(SD)	26.61 (16.17)	23.61 (7.81)	25.40 (14.41)	21.19 (6.84)
		Median	23.00	23.00	21.00	20.00
		Min, Max	13.0-100.0	12.0-42.0	10.0-79.0	11.0-49.0
	Follow-up	n	30	34	38	31
		Mean(SD)	29.20 (22.04)	22.97 (9.06)	24.26 (16.76)	22.35 (7.04)
		Median	23.00	21.50	19.50	21.00
		Min, Max	13.0-127.0	12.0-51.0	10.0-110.0	13.0-43.0
	Change from baseline	n	30	33	38	31
		Mean(SD)	2.07 (7.26)	-1.39 (6.95)	-1.26 (9.80)	1.16 (5.73)
		Median	0.00	-1.00	-1.00	0.00
		Min, Max	-7.0-27.0	-16.0-26.0	-40.0-31.0	-7.0-20.0
Bilirubin (mg/dL)	Baseline	n	33	33	40	31
		Mean(SD)	0.49 (0.34)	0.55 (0.30)	0.48 (0.24)	0.50 (0.27)
		Median	0.38	0.46	0.44	0.43
		Min, Max	0.1-1.8	0.2-1.4	0.1-1.3	0.1-1.2
	Follow-up	n	30	34	38	31
		Mean(SD)	0.48 (0.28)	0.54 (0.27)	0.46 (0.25)	0.52 (0.27)
		Median	0.39	0.45	0.37	0.43
		Min, Max	0.2-1.5	0.2-1.3	0.2-1.1	0.2-1.2
	Change from baseline	n	30	33	38	31
		Mean(SD)	-0.02 (0.18)	-0.02 (0.16)	-0.02 (0.16)	0.01 (0.13)
		Median	0.00	-0.02	-0.04	0.00
		Min, Max	-0.6-0.3	-0.5-0.5	-0.4-0.5	-0.2-0.5

Text Table 12-11: Serum chemistry: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Creatine Kinase (U/L)	Baseline	n	33	33	40	31
		Mean(SD)	110.52 (78.77)	118.64 (76.27)	105.33 (65.07)	97.39 (53.42)
		Median	98.00	95.00	83.50	85.00
		Min, Max	34.0-375.0	28.0-395.0	34.0-347.0	28.0-324.0
	Follow-up	n	30	34	38	31
		Mean(SD)	107.00 (76.53)	104.31 (79.55)	102.87 (46.65)	110.00 (78.53)
		Median	77.50	87.50	96.50	88.00
		Min, Max	31.0-389.0	3.5-426.0	28.0-219.0	34.0-401.0
	Change from baseline	n	30	33	38	31
		Mean(SD)	0.70 (23.84)	-14.20 (61.60)	-3.66 (42.02)	12.61 (71.50)
		Median	4.50	-11.00	2.00	1.00
		Min, Max	-51.0-66.0	-206.0-145.0	-148.0-55.0	-56.0-373.0
Creatinine (mg/dL)	Baseline	n	33	33	40	31
		Mean(SD)	0.79 (0.15)	0.86 (0.24)	0.80 (0.17)	0.83 (0.19)
		Median	0.75	0.81	0.78	0.77
		Min, Max	0.5-1.1	0.5-1.8	0.5-1.3	0.6-1.3
	Follow-up	n	30	34	38	31
		Mean(SD)	0.82 (0.17)	0.86 (0.20)	0.81 (0.19)	0.81 (0.17)
		Median	0.82	0.87	0.79	0.74
		Min, Max	0.5-1.2	0.6-1.6	0.5-1.4	0.6-1.3
	Change from baseline	n	30	33	38	31
		Mean(SD)	0.02 (0.08)	0.01 (0.08)	0.02 (0.08)	-0.02 (0.12)
		Median	0.03	0.01	0.02	-0.01
		Min, Max	-0.1-0.2	-0.2-0.2	-0.2-0.2	-0.6-0.2

Text Table 12-11: Serum chemistry: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Potassium (mmol/L)	Baseline	n	33	33	40	31
		Mean(SD)	4.27 (0.43)	4.45 (0.45)	4.37 (0.43)	4.41 (0.30)
		Median	4.20	4.40	4.40	4.40
		Min, Max	3.6-5.6	3.4-5.8	3.2-5.3	3.8-5.1
	Follow-up	n	30	34	38	31
		Mean(SD)	4.30 (0.32)	4.38 (0.42)	4.36 (0.34)	4.39 (0.35)
		Median	4.30	4.30	4.35	4.40
		Min, Max	3.7-5.0	3.4-5.3	3.7-5.1	3.6-5.3
	Change from baseline	n	30	33	38	31
		Mean(SD)	-0.02 (0.27)	-0.08 (0.47)	-0.01 (0.37)	-0.03 (0.33)
		Median	0.00	0.00	-0.05	-0.10
		Min, Max	-0.6-0.4	-1.1-0.8	-0.7-0.9	-0.6-1.0
Sodium (mmol/L)	Baseline	n	33	33	40	31
		Mean(SD)	139.52 (2.20)	139.52 (2.37)	139.68 (2.93)	138.97 (2.48)
		Median	139.00	139.00	140.00	139.00
		Min, Max	134.0-144.0	135.0-146.0	131.0-147.0	133.0-143.0
	Follow-up	n	30	34	38	31
		Mean(SD)	139.57 (2.24)	139.85 (2.06)	139.95 (2.61)	139.06 (2.13)
		Median	139.50	140.00	140.00	139.00
		Min, Max	135.0-143.0	133.0-145.0	132.0-146.0	135.0-144.0
	Change from baseline	n	30	33	38	31
		Mean(SD)	0.00 (1.74)	0.33 (2.20)	0.13 (2.47)	0.10 (2.23)
		Median	0.00	0.00	0.00	0.00
		Min, Max	-3.0-3.0	-4.0-5.0	-6.0-6.0	-4.0-6.0

SD = Standard deviation
Source: Table 14.3.4.1 b; Listing(s): Derived from Listing 16.2.8.1

Electrolyte's results (potassium, sodium) were unremarkable with no significant increases or decreases during IMP-treatment in any of the treatment groups.

The same applies to the parameters of bilirubin, albumin, and creatinine. Some fluctuations have been observed within creatine kinase levels because few patients had either abnormally elevated levels at Baseline or at end of trial. The majority of them were connected with concomitant disease or were assessed as not clinically significant. There was no clustering of events within treatment groups.

Alkaline phosphatase level decreased marginally in all treatment groups. The two highest baseline values of 164 and 185 U/L occurred in two patients (300002, 411006) and were rated

not clinically significant in one case and in the other case 'clinically significant' and related with a corresponding concomitant disease. There was a slight increase in the mean change of liver transaminases (AST and ALT) in the highest dose group, however this is not assumed having any clinical relevance because systemic availability of clobetasol was demonstrated to be negligibly low in nearly all cases. In the other treatment groups, meaningful mean changes of AST-/ALT-values could not be observed.

Highest ALT- and AST-baseline values were observed in patient 300002 (ALT '144 U/l, AST '100 U/L'). 'Maximum increase' of ALT occurred in patient 204003 (increase by "74" to '160 U/L). Both patients had concomitant diseases of "fatty liver", explaining the abnormal values.
Summarizing, compared to baseline values, there were no clinically relevant changes in mean/median values of any biochemistry parameter for any of the treatment groups.

12.3.2.2 Urinalysis

Descriptive statistics for urinalysis by visit are provided with Table 14.3.4.1 (c) urinalysis). A shift table from Baseline (=prior to treatment) to End of Study / Early Termination in regard to urinalysis and based on the investigator's assessment of clinical significance is provided with Text Table 12-12.

Text Table 12-12: Shift table of out-of range values: Summary of abnormal urinalysis values by visit – Safety Set

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Glucose	Baseline	n	3	2	5	1
		Abnormal NCS	3 (100.0)	1 (50.0)	3 (60.0)	1 (100.0)
		Abnormal CS	0 (0.0)	1 (50.0)	2 (40.0)	0 (0.0)
	Follow-up	n	1	2	2	1
		Abnormal NCS	1 (100.0)	2 (100.0)	0 (0.0)	1 (100.0)
		Abnormal CS	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)
Hemoglobin	Baseline	n	7	3	2	5
		Abnormal NCS	7 (100.0)	3 (100.0)	2 (100.0)	4 (80.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
	Follow-up	n	4	1	5	4
		Abnormal NCS	4 (100.0)	1 (100.0)	5 (100.0)	4 (100.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protein	Baseline	n	4	1	3	4
		Abnormal NCS	4 (100.0)	1 (100.0)	3 (100.0)	4 (100.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	6	3	3	4
		Abnormal NCS	6 (100.0)	3 (100.0)	3 (100.0)	4 (100.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

(N)CS=(not) clinically significant; Source: Table 14.3.4.2 c; Listing(s): Derived from Listing 16.2.8.1

All patients, who had at least one clinically significant abnormal urine parameter (either related to a concomitant disease or to a concomitant medication) at Baseline turned to normalized values or to values assessed as being not clinically significant at the End of Study/Early Termination Visit. Only 2 patients from the 1µg group (patient 411001 and 601010) showed clinically significant enhanced glucose levels in urine at the End of Study, but both patients had diabetes mellitus documented in their medical history, such that an impact of treatment with the IMP can be excluded.

12.3.2.3 Pregnancy Testing

For each female patient of childbearing potential, a serum pregnancy test had to be performed at Visit 1 (prior to treatment). Additional urine pregnancy tests had to be performed at Visit 0 (prior to biopsy and only if a biopsy had to be taken), at Baseline (Visit 2) and at End of Treatment (Visit 6).

Results from pregnancy testing at visits are provided in Table 14.3.5.4. Individual patient data are presented in Listing 16.2.9.4.

Among 7 female patients being of childbearing potential all pregnancy tests performed were negative and no pregnancies occurred during the study.

12.4 Vital Signs (Including Body Weight)

Vital signs (blood pressure, pulse, body temperature) and body weight were measured at Visit 1 (prior to treatment) and at Visit 7 (End of Study) or in case of patient's withdrawal during the treatment period at Visit 6. BMI was calculated for the same timepoints based on the height measured at Visit 1 and weights at Visit 6 or Visit 7.

Individual patient data for vital signs including body weight are displayed in Listing 16.2.9.1. Summarized results for blood pressure (systolic and diastolic), pulse, body temperature, body weight and BMI at each day of measurement and for the change from Baseline presenting the mean (SD) values only are shown in Text Table 12-13. Related shift plots for vital signs are shown in Figure 14.3.5.1.

Text Table 12-13: Vital signs and body weight: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Systolic Blood Pressure (mmHg)	Baseline	n	33	34	40	31
		Mean(SD)	131.0 (15.56)	137.5 (19.36)	137.5 (25.14)	141.5 (17.76)
		Median	130.0	132.0	130.5	146.0
		Min, Max	99.0-162.0	103.0-187.0	105.0-220.0	100.0-173.0
	Follow-up	n	33	34	40	31
		Mean(SD)	130.8 (14.64)	135.8 (16.72)	134.7 (20.40)	135.0 (16.97)
		Median	136.5	136.5	130.0	134.0
		Min, Max	104.0-154.0	103.0-171.0	107.0-184.0	111.0-180.0

Text Table 12-13: Vital signs and body weight: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Change from baseline	n	33	34	40	31
		Mean(SD)	-0.8 (13.13)	-1.6 (11.84)	-3.3 (16.02)	-5.9 (16.10)
		Median	-2.5	-1.0	-3.0	-6.0
		Min, Max	-42.0-31.0	-22.0-21.0	-45.0-32.0	-48.0-22.0
Diastolic Blood Pressure (mmHg	Baseline	n	33	34	40	31
		Mean(SD)	79.3 (12.17)	82.1 (13.45)	79.2 (12.02)	81.8 (11.58)
		Median	81.0	81.0	80.5	82.0
		Min, Max	47.0-104.0	52.0-111.0	55.0-103.0	55.0-104.0
	Follow-up	n	33	34	40	31
		Mean(SD)	77.7 (9.71)	79.5 (10.69)	77.5 (11.62)	78.8 (9.79)
		Median	79.0	78.5	80.0	79.5
		Min, Max	61.0-100.0	62.0-105.0	51.0-102.0	60.0-101.0
	Change from baseline	n	33	34	40	31
		Mean(SD)	-2.4 (9.48)	-2.6 (10.93)	-1.7 (8.45)	-2.8 (10.30)
		Median	-3.0	-2.5	-1.0	-3.0
		Min, Max	-24.0-15.0	-20.0-22.0	-23.0-16.0	-22.0-20.0
Pulse (beats/min)	Baseline	n	33	34	40	31
		Mean(SD)	71.7 (14.26)	70.3 (11.19)	67.6 (9.28)	69.4 (12.16)
		Median	73.0	69.5	67.5	69.0
		Min, Max	45.0-111.0	47.0-90.0	48.0-86.0	51.0-114.0
	Follow-up	n	33	34	40	31
		Mean(SD)	70.8 (11.86)	71.5 (11.32)	68.2 (10.36)	70.1 (11.43)
		Median	72.0	67.5	69.0	68.0
		Min, Max	43.0-94.0	51.0-92.0	44.0-92.0	51.0-100.0
	Change from baseline	n	33	34	40	31
		Mean(SD)	-1.2 (10.86)	1.2 (9.48)	1.0 (8.11)	0.9 (9.58)
		Median	-1.0	3.0	1.0	1.5
		Min, Max	-23.0-22.0	-30.0-16.0	-14.0-22.0	-37.0-16.0

Text Table 12-13: Vital signs and body weight: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Temperature (C)	Baseline	n	33	34	40	31
		Mean(SD)	36.6 (0.61)	36.6 (0.37)	36.5 (0.52)	36.6 (0.40)
		Median	36.7	36.6	36.5	36.7
		Min, Max	35.0-37.3	36.0-37.5	35.2-37.8	35.6-37.1
	Follow-up	n	33	34	40	31
		Mean(SD)	36.4 (0.57)	36.5 (0.59)	36.5 (0.47)	36.4 (0.58)
		Median	36.3	36.6	36.6	36.6
		Min, Max	35.3-37.4	35.0-37.7	35.6-37.5	35.0-37.1
	Change from baseline	n	33	34	40	31
		Mean(SD)	-0.1 (0.62)	-0.0 (0.48)	-0.0 (0.66)	-0.2 (0.66)
		Median	-0.2	-0.1	0.0	0.0
		Min, Max	-1.2-1.2	-1.2-0.9	-1.6-1.5	-2.0-0.6
Weight (kg)	Baseline	n	33	34	40	31
		Mean(SD)	83.6 (19.41)	85.1 (20.99)	81.6 (17.94)	82.3 (22.42)
		Median	82.7	81.4	81.6	77.2
		Min, Max	51.0-129.0	60.0-154.4	49.1-136.1	51.9-129.8
	Follow-up	n	33	34	40	31
		Mean(SD)	83.7 (19.78)	84.6 (20.86)	81.3 (18.69)	83.0 (22.34)
		Median	81.2	81.0	80.3	78.9
		Min, Max	52.5-129.8	57.9-158.9	48.2-139.5	52.1-130.2
	Change from baseline	n	33	34	40	31
		Mean(SD)	0.0 (1.99)	-0.5 (2.66)	-0.2 (1.66)	-0.1 (1.60)
		Median	0.5	-0.4	0.0	0.3
		Min, Max	-8.6-3.1	-11.7-5.1	-4.7-3.4	-3.6-2.4
Body Mass Index (kg/m2)	Baseline	n	33	34	40	31
		Mean(SD)	31.2 (6.93)	29.6 (5.96)	29.0 (5.32)	30.3 (7.60)
		Median	30.3	27.7	28.3	28.7
		Min, Max	18.7-46.9	18.9-48.2	17.8-42.3	21.2-50.9
	Follow-up	n	33	34	40	31
		Mean(SD)	31.2 (6.91)	29.4 (6.06)	29.0 (5.53)	30.5 (7.54)
		Median	30.0	27.8	28.2	29.3
		Min, Max	19.0-47.1	18.8-49.6	17.5-42.9	21.3-51.2

Text Table 12-13: Vital signs and body weight: Summary statistics by visit with difference from Baseline – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Change from baseline	n	33	34	40	31
		Mean(SD)	-0.0 (0.87)	-0.2 (0.86)	-0.1 (0.61)	-0.0 (0.60)
		Median	0.2	-0.1	0.0	0.1
		Min, Max	-4.1-1.0	-3.3-2.0	-1.9-1.2	-1.5-0.9

SD = Standard deviation
Source: Table 14.3.5.1; Listing(s): Derived from Listing 16.2.9.1

Both systolic and diastolic blood pressure decreased slightly in all treatment groups, for systolic blood pressure the largest decrease was seen in the placebo group (5.9 mmHg). Pulse showed only minor changes over the study, it decreased by 1.16 bpm on average in the 20 µg group. The largest weight gain in the study was 5.1 kg (5%, in patient 400013, Baseline weight 93 kg) and the largest weight loss was 11.7 kg (9%, in patient 411002, intended reduction with a Baseline weight of 129 kg), both reported in the 5 µg group. Neither weight gain nor weight loss was assessed as being of clinical significance. Hence no corresponding AE was reported.

Overall compared to Baseline (pre-treatment) values, there were no clinically relevant changes in mean or median values of any vital signs or body weight parameters for any of the treatment groups.

12.5 Examination of Oral Cavity Findings

An examination of the oral cavity including a check for oral infections was performed at every study visit. At Visit 1, this examination included also a check for normal or abnormal dental status. Results for the examination of oral cavity are summarized in Text Table 12-14. Individual patient data of all assessments of oral cavity examinations are displayed in Listing 16.2.9.2.

Text Table 12-14: Summary of examination of oral cavity – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Dental status	Visit 1	NORMAL	30/33 (90.9)	28/34 (82.4)	33/39 (84.6)	28/31 (90.3)
		ABNORMAL, not sign	3/33 (9.1)	5/34 (14.7)	6/39 (15.4)	3/31 (9.7)
		ABNORMAL, clin sign	0	1/34 (2.9)	0	0
Examination of any infection in the mouth	Visit 1	NORMAL	31/33 (93.9)	32/34 (94.1)	38/39 (97.4)	31/31 (100.0)
		ABNORMAL, not sign	2/33 (6.1)	1/34 (2.9)	0	0
		ABNORMAL, clin sign	0	1/34 (2.9)	1/39 (2.6)	0

Text Table 12-14: Summary of examination of oral cavity – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Visit 2	NORMAL	31/33 (93.9)	33/34 (97.1)	37/40 (92.5)	31/31 (100.0)
		ABNORMAL, not sign	1/33 (3.0)	1/34 (2.9)	0	0
		ABNORMAL, clin sign	1/33 (3.0)	0	3/40 (7.5)	0
	Visit 3	NORMAL	29/31 (93.5)	33/34 (97.1)	34/37 (91.9)	25/28 (89.3)
		ABNORMAL, not sign	1/31 (3.2)	1/34 (2.9)	0	1/28 (3.6)
		ABNORMAL, clin sign	1/31 (3.2)	0	3/37 (8.1)	2/28 (7.1)
	Visit 4	NORMAL	28/30 (93.3)	32/33 (97.0)	36/36 (100.0)	27/28 (96.4)
		ABNORMAL, not sign	1/30 (3.3)	0	0	0
		ABNORMAL, clin sign	1/30 (3.3)	1/33 (3.0)	0	1/28 (3.6)
	Visit 5	NORMAL	26/29 (89.7)	33/33 (100.0)	34/35 (97.1)	23/27 (85.2)
		ABNORMAL, not sign	2/29 (6.9)	0	0	0
		ABNORMAL, clin sign	1/29 (3.4)	0	1/35 (2.9)	4/27 (14.8)
	Visit 6	NORMAL	28/31 (90.3)	32/34 (94.1)	34/39 (87.2)	26/30 (86.7)
		ABNORMAL, not sign	1/31 (3.2)	0	2/39 (5.1)	1/30 (3.3)
		ABNORMAL, clin sign	2/31 (6.5)	2/34 (5.9)	3/39 (7.7)	3/30 (10.0)
	Visit 7	NORMAL	26/30 (86.7)	32/33 (97.0)	33/34 (97.1)	22/26 (84.6)
		ABNORMAL, not sign	3/30 (10.0)	1/33 (3.0)	1/34 (2.9)	2/26 (7.7)
		ABNORMAL, clin sign	1/30 (3.3)	0	0	2/26 (7.7)
Examination of oral cavity	Visit 1	NORMAL	31/33 (93.9)	29/34 (85.3)	29/39 (74.4)	26/31 (83.9)
		ABNORMAL, not sign	2/33 (6.1)	3/34 (8.8)	10/39 (25.6)	3/31 (9.7)
		ABNORMAL, clin sign	0	2/34 (5.9)	0	2/31 (6.5)
	Visit 2	NORMAL	28/33 (84.8)	29/34 (85.3)	29/40 (72.5)	26/31 (83.9)
		ABNORMAL, not sign	3/33 (9.1)	3/34 (8.8)	10/40 (25.0)	3/31 (9.7)
		ABNORMAL, clin sign	2/33 (6.1)	2/34 (5.9)	1/40 (2.5)	2/31 (6.5)

Text Table 12-14: Summary of examination of oral cavity – Safety Set

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Visit 3	NORMAL	25/31 (80.6)	30/34 (88.2)	30/37 (81.1)	21/28 (75.0)
		ABNORMAL, not sign	4/31 (12.9)	3/34 (8.8)	7/37 (18.9)	5/28 (17.9)
		ABNORMAL, clin sign	2/31 (6.5)	1/34 (2.9)	0	2/28 (7.1)
	Visit 4	NORMAL	22/30 (73.3)	23/33 (69.7)	29/36 (80.6)	20/28 (71.4)
		ABNORMAL, not sign	6/30 (20.0)	6/33 (18.2)	7/36 (19.4)	5/28 (17.9)
		ABNORMAL, clin sign	2/30 (6.7)	4/33 (12.1)	0	3/28 (10.7)
	Visit 5	NORMAL	21/29 (72.4)	27/33 (81.8)	25/35 (71.4)	19/27 (70.4)
		ABNORMAL, not sign	5/29 (17.2)	4/33 (12.1)	9/35 (25.7)	4/27 (14.8)
		ABNORMAL, clin sign	3/29 (10.3)	2/33 (6.1)	1/35 (2.9)	4/27 (14.8)
	Visit 6	NORMAL	27/31 (87.1)	26/34 (76.5)	29/39 (74.4)	23/30 (76.7)
		ABNORMAL, not sign	2/31 (6.5)	5/34 (14.7)	10/39 (25.6)	4/30 (13.3)
		ABNORMAL, clin sign	2/31 (6.5)	3/34 (8.8)	0	3/30 (10.0)
	Visit 7	NORMAL	25/30 (83.3)	29/33 (87.9)	25/34 (73.5)	19/26 (73.1)
		ABNORMAL, not sign	2/30 (6.7)	3/33 (9.1)	9/34 (26.5)	4/26 (15.4)
		ABNORMAL, clin sign	3/30 (10.0)	1/33 (3.0)	0	3/26 (11.5)

not sign =not clinically significant; clin sign= clinically significant
Source: Table 14.3.5.2; Listing(s): Derived from Listing 16.2.9.2

Only one patient had abnormal clinically significant dental status at Visit 1 (randomized to 1µg group).

At Baseline 1 patient from the 20µg group and 3 patients from the 1µg group had abnormal clinically significant findings on mouth infection. At the end of treatment (visit 6) this had increased to 10 patients (2 each in 20 and 5 µg groups and 3 each in the 1 µg and placebo groups) and at the follow-up Visit 7 this had decreased again to 3 patients (1 in the 20 µg group and 2 in the placebo group.

On oral cavity examination abnormal clinically significant findings were reported for 7 patients at Visit 2 (each 2 in the 20µg and the 5µg group, as well as in the placebo group 1 patient in the 1µg group). This increased to overall 8 patients (3 each in 5µg group and the placebo group and 2 patients in the 20µg group) at Visit 6 that had findings reported as abnormal clinically significant. At the end of study visit (Visit 7), clinically significant

findings were reported for 3 patients of the 20µg group and the placebo group, each and in 1 patient from the 5µg group.

Findings in the examination of Oral Cavity at screening visits (Visit 0 and Visit 1) had been recorded as concomitant diseases and are presented in section 10.4.3.

Any changes of clinical relevance in the examination of oral cavity compared to screening visits or new oral examination findings of clinical relevance were recorded as AEs and are described within section 12.1.

12.6 Summary Safety Results

- In total, 121 treatment emerged AEs occurred in 63 patients (45.7%). The incidence and type of events were similar between the 4 treatment groups without any increases in the two higher dose groups. On PT level, the most common AEs were 'periodontal disease' and 'nasopharyngitis'. The intensities of most AEs were mild (in 31.9% of patients) or moderate (in 21% of patients) and only 5 events (in 3.6% of patients) were severe, all assessed unrelated. ADRs and ADEs were reported for a total of each 16 patients (12%), Most of them occurred in the oral cavity, and only a minority of 6 events in 5 patients occurred outside the oral cavity or systemically.
- No safety concerns emerged from the ADR-profile: Frequencies of ADRs ranged from each only 6% in the higher 5µg- and 20µg groups, to 16% in the placebo- and 18% in the 1µg group, respectively. (Incidence of overall ADRs would decrease to 10% (11 patient), if 5 patients from the placebo group would be excluded). The most common ADRs comprised different PTs of oral candidiasis infections within the SOC 'infections and infestations' (in 8 patients [6%]) with highest occurrences in the 1µg- and placebo-groups (in each 3-4- patients), only 1 occurrence in the 5µg group and surprisingly no occurrence in the highest dose group. This indicates that clobetasol was not mainly responsible for increased susceptibility to fungal infection, but rather the physical patch properties themselves. No clustering of events could be observed within events of the next common SOC 'gastrointestinal disorders' (in 5 patients [4%]). Different sorts of 'general disorders and administration site conditions' (4 patients [3%] within this SOC) were only observed in the three clobetasol groups. Contrary to expectations of clustering of ADRs in the highest 20µg treatment arm, ADR-incidence was lowest here, suggesting that most reactions need to be interpreted rather in the context of device effects and not as 'real' clobetasol reactions. A minority of 5 patients experienced systemic ADRs (i.e. occurring outside the oral cavity) with 'nausea' being the only event that occurred twice. Systemic reactions occurred in all groups except for the medium 5µg dose and most of them were also rated ADE.
- The ADE-profile was uncritical, too: ADE-frequencies were also quite heterogenous, and ranged from 6% in the 20µg group, over 10% in the placebo group, 13% in the 1µg group, to 18% in the 5µg group. Only 2 events of candidiasis infection were assessed as ADEs. The major represented SOC here was 'gastrointestinal disorders' (9 patients of all treatment groups [7%]), with the main PTs 'salivary hypersecretion', 'altered saliva', 'nausea', and 'gingival bleeding'. The next common SOC 'General disorders and administration site conditions' (7 patients [5%]) included PTs of different application site reactions (namely 'AS-pain', 'AS-hypersensitivity', 'AS-hemorrhage', and 'AS-injury'), which were only observed in the clobetasol groups.

- Related AEs in oral cavity: 13 patients (9%) had different types of ADRs in the oral cavity, mainly *infections with candidiasis*. Slightly more patients were reported to have oral ADEs (15 patients ([11%]), mainly different types of *application site conditions (-pain, -hypersensitivity, -hemorrhage, and -injury)*. Except for the events of infection, most of local reactions were limited to a trigger like patch procedure or daily activity procedure and did not represent a constant side effect during IMP treatment. This was clarified by the evaluation of the respective verbatims of local reactions. Most events of candidiasis infections in the oral cavity were of mild intensity. Infections were treated medically and recovered completely in all cases. IMP treatment had not to be interrupted nor discontinued in any of these patients.
- AEs that led to permanent IMP-discontinuation, and SAEs: There were no death cases and only 2 SAEs in 2 patients ("myocardial infarction", "multiple fractures") - none of them was considered related to treatment. 4 AEs in 2 patients (1.4%) led to permanent discontinuation of the IMP: 2 events in one patient of the 1µg group were 'Gastrointestinal disorders' (PTs 'stomatitis' and 'oral pain'), both judged as oral reactions and both recovered after discontinuation of treatment. A third event in the same patient ('increased insomnia') was judged as unrelated. The fourth event ('Varicella zoster virus infection') occurred in the placebo group and was judged unrelated, too.
- Laboratory data on serum biochemistry, serum hematology, and urine, as well as data on pregnancy testing did not reveal any evidence for clinically relevant changes during the trial that called for attention. The same applies to the data of vital signs (blood pressure, pulse, body temperature) and body weight parameters.
- No accidental ingestion of the patches occurred during the trial and no AEs indicative for any significant influence of clobetasol on the cortisol levels of patients could be observed in any of the clobetasol groups.

13 DISCUSSION AND OVERALL CONCLUSIONS

This study was a randomized, double-blind, multi-center, four-armed, parallel group phase II study. The study evaluated the efficacy and safety of 3 doses (20µg, 5µg, 1µg) of clobetasol propionate containing Rivelin®-CLO patches compared to non-medicated Rivelin® patches (placebo patches) in a twice daily dosing regimen for 4 weeks. The study included adults with a clinical diagnosis of oral lichen planus, presenting with at least one symptomatic and ulcerative oral lesion at Baseline. The study was conducted in Europe (Denmark, Germany, Ireland, UK) and North America (USA, Canada). An interim analysis recommended a stop in enrollment ending the study at 138 patients randomized and treated according to the study protocol.

Compliance:

Median treatment compliance (based on drug account) was at 100% and study results showed that Rivelin®-CLO patches were easy to handle for the study population (mean age 61.1 years; range: 19 to 89 years), were well tolerated and adhered very well to the oral mucosa for about 90 minutes, allowing a delivery of clobetasol propionate to the symptomatic OLP lesions.

Patch taste increased by trend with clobetasol strength. This should be respected in future clinical projects, as it could affect the blinding of the study team.

Efficacy:

Rivelin®-CLO patches 20µg were found to be effective in reducing total ulcer area [cm^2] (as measured with the newly developed OLPClinROM) and overall OLP disease severity (as measured with the published Guy´s 106 ODDSS). They were also shown to be effective in reducing patient reported symptom severity (as measured with the newly developed OLPSSM questionnaire and Guy´s ODSS pain assesment) and in improving patient reported quality of life (as measured with the established COMDQ). Borderline efficacy was seen with reduction in total lesion area (OLPClinROM) and with significant difference when looking at the per protocol population, whereas the prespecified analysis of the 5 and 3-point erythema score revealed no significant findings. Exploratory analysis (see Statistical report in Appendix 16.1.9.) did indicate that applying a different analysis assessing the maximum 5-point erythema score at each visit demonstrated a difference between the 20µg and placebo.

Rivelin®-CLO patches 5µg were shown to be effective in the reduction of ulcer area and trends could be observed regarding improvement of patient reported OLP symptoms.

Overall, the study was well designed to reveal the treatment effects of Rivelin®-CLO patches in the population targeted for treatment.

Concerning clinical global impression and the worst symptoms at anatomical site score, both measures would need more harmonization across raters which will be handled in future training sessions. This will be implemented by clearer guidance on how to asses these.

For determination of lesion area, the entire visible lesion was measured at every visit and reductions were determined by comparing this total lesion area. But especially when lesions were very big and showing different levels of severity (symptomatic and asymptomatic parts) only the symptomatic (ulcerative) parts of these lesions needed to be patched. Thus, the reductions measured might have been in some cases smaller than they could have been, as untreated part of the lesions contributed to the total lesion area.

Clearance of lesions/ulcers was defined as complete lesion/ulcer area (all lesions/ulcers in a patient) = 0. Clearance of small lesions/ulcers was more probable within the 4 weeks treatment period than clearance of bigger lesions/ulcers per se. So, complete clearance was more probable in patients with small Baseline total lesions/ulcer area than in patients with bigger total lesions/ulcer areas. Maybe it might be worth looking at clearance of single lesions/ulcers of different sizes and determine their probability of complete clearance in future studies. Especially for the bigger lesions that were treated only partially, complete lesion clearance was nearly impossible in this study. Also, stratification for total ulcer area at Baseline instead of number of patches needed, would be worth considering in future studies to have comparable Baseline ulcer areas in the treatment groups and minimize the effect of size on treatment comparison.

Variability was high in the recruitment rates among sites. There were few highly recruiting sites while most of the other sites only recruited few patients. Also, one third of all screened patients were screen failures. Correspondingly, recruitment support and training for less-experienced sites can be of importance for further projects in this indication.

In general, the inclusion/exclusion criteria were well chosen and did not exclude any important patient groups that would normally receive intra-oral topical OLP treatment.

One inclusion criterion (IC#2) was hard to verify for some patients, due to technical problems with the electronic diary which was used at the beginning of the study. Non-functionality of the device hindered the patients to document the data needed for verification. This was the major cause for patients being excluded from the PPS. Thus, proper functionality of a device used for patient reported data collection should be assured, prior to using it in future studies. Paper documentation should always be possible as an alternative, especially when the study is performed in an elderly population and in regions with poor availability of internet resources.

Until the interim analysis, patients were almost evenly assigned to the different treatment groups, although deviating from the protocol an additional stratum – by site – was introduced by reserving a complete random block of all 4 treatments for a specific site, as soon as the first randomization number within a block had been assigned. After the interim analysis, sites were highly encouraged to recruit more patients to achieve recruitment goals. Many sites therefore intensified their recruitment activities, but most of them managed to enroll only one or two patients after the interim and not a complete randomization block. Also, patients already screened could not be randomized after the decision to stop enrollment. This additionally contributed to an imbalanced randomization of patients into treatment groups for the final analysis. Effects of the randomization error on the results of the study could have been marked (major skewness, reversion of study conclusion before and after the interim analysis, faulty decision on study progress at time of interim analysis), but in fact were regarded as tolerable as a comparable number of patients was randomized into the most important treatment groups of this study (20µg, 5µg and placebo) and statistically significant differences were shown. Nevertheless, the actual randomization may have had a relevant effect on the conclusion of the study.

Safety:

The safety analysis revealed no safety concerns for Rivelin®-CLO patches. Overall, the profile and incidence of related AEs were in accordance with the known safety profile already described in the Investigator's Brochure. Irrespective of this, some aspects that might be relevant for future research with the Rivelin®-CLO patches, should be discussed here.

Contrary to expectations of clustering of ADRs in the highest 20µg treatment arm, ADR-incidence was lowest here, suggesting that most reactions need to be interpreted rather in the context of device effects and not as 'real' clobetasol reactions.

Separate evaluations of ADRs and ADEs was of limited use in the setting of this study. Patch-induced reactions on OLP affected oral mucosa could not be differentiated clearly from clobetasol side effects as this can usually be done for other indications on exterior skin. In this setting and under the present small subpopulations, judgements on side effects of clobetasol (if any) and patch properties seemed to have overlapped and interfered with each other. For example, supposed ADRs of 'candidiasis infections' turned out to be more probably due to the physical patch properties than due to the active drug. For future studies it might be more practicable to have only one overall rating of relatedness (to active drug and patch properties) instead of the two separate ones.

Most common side effects were oral 'candida infections' (all assessed as ADRs) in almost 6% of patients. Unexpectedly, infections were observed in all treatment groups except for the highest 20µg dose group, indicating that clobetasol was not mainly responsible for an increased susceptibility to fungal infection, but rather the physical patch properties themselves. Further common side effects in 5% of patients were multiple 'application site reactions' ('- pain', '- hypersensitivity', '- injury', or 'hemorrhage' (all assessed as ADEs)), which were only observed in the clobetasol groups, suggesting that clobetasol might had contributed to these events, e.g. by promoting an increased mucosal vulnerability. Alternatively, 'seeming clustering' of application site reactions in the clobetasol groups might also be simply coincidentally because of small subpopulations.

It needs to be emphasized, that most local oral reactions (except for the infections) were characterized by transient sensations of stinging or hypersensitivity to trigger events (patching procedure, brushing, food intake) and did not represent a constant side effect during IMP treatment. Evaluation of verbatims contrary to the PTs alone did illustrate that.

Overall, the 20µg dose is recommended for future studies as it was shown to be effective in OLP treatment and was safe and well tolerated in this study.

Overall conclusions:

Significant efficacy in the treatment of OLP could be clearly shown for Rivelin®-CLO patches 20µg:

- for the primary endpoint: total ulcer area [cm^2]
- for the overall disease severity, as well as all sub-scores (total site, disease activity and pain) as measured with the Guy`s 106 ODSS
- for patient reported symptom severity as measured with the OLPSSM
- for overall quality of life, as well as for the sub-domains ‘pain and functional limitations’ and ‘medication and treatment’ as measured with the COMDQ questionnaire

For all these endpoints improvements with statistically significant differences compared to placebo could be observed at least for the change from Baseline to the average of weeks 3 and 4, in some cases even with earlier onsets.

Thus, Rivelin-CLO patches 20µg can be regarded as effective in the 4 weeks treatment of all important OLP symptom manifestations.

Rivelin® patches were shown to be easy to handle (even for an elderly patient population), adhered very well (even to ulcerative parts of) the oral mucosa and long enough for the clobetasol propionate to be absorbed. Even though the patches were assessed to be a quite disturbing foreign object by the patients, they were rated as rather well tolerable and non-irritable as well. Combined with the result that half of the patients assessed their OLP symptoms as much better after 4 weeks of treatment, the disturbances are most probable to be overweight by the positive treatment effects, at least for the 20µg patches.

Profiles and incidences of side effects were uncritical and revealed no safety concerns, not even in the highest clobetasol group. From the vital signs and laboratory data no safety concerns could be observed, too. The two most frequent groups of side effects (‘oral candidiasis infections’ and different types of ‘application site reactions’) were expected, reversible, mostly of mild intensity, and did not require IMP-discontinuation. Also, no significant systemic availability of clobetasol propionate or any significant influence on the cortisol levels of patients could be observed in any of the treatment groups, suggesting that even the 20µg dose was safe and well tolerated by the patients. Therefore, the application of Rivelin®-CLO patches can be regarded as safe and well tolerated in all tested dosages in patients with OLP. Further clinical development is clearly encouraged.

14 TABLES, FIGURES AND GRAPHS

All tables and figures of this section were produced and delivered by StatMind as a final version on 17-Jun-2020.
(Footer of source documents: StatMind AB 17JUN2020 Final SAS version 9.4 WIN X64_10PRO).

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14.1 Demographic Data and Basic Characteristics

14.1.1 Study Progress

Table 14.1.1.1: Subject disposition

Category	20 ug	5 ug	1 ug	Placebo	Total
Enrolled Patients					204
Randomized	33	34	40	31	138
Completers	30	33	34	25	122
Withdrawn	3	1	6	6	16
-- Withdrawal Of Consent	2	0	1	2	5
-- Lack Of Efficacy	0	1	1	2	4
-- Adverse Event	0	0	2	2	4
-- Lost To Follow-Up	0	0	1	0	1
-- Other	1	0	0	0	1
-- Protocol Deviation	0	0	1	0	1
No Emergency Unblinding	5	5	4	3	17
Re-Screened Patients	0	1	1	0	2
Safety Set	33	34	40	31	138
Full Analysis Set	33	34	40	31	138
Per Protocol Set	25	30	35	26	116
Listing(s): Derived from Listings 16.2.1.1 and 16.2.1.2					

14.1.2 Protocol Deviations

Table 14.1.2.1: Summary of protocol deviations [FAS]

Category	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Any Protocol Deviation	9 (27.3)	6 (17.6)	11 (27.5)	8 (25.8)	34 (24.6)
- Informed Consent	0 (0.0)	3 (8.8)	4 (10.0)	1 (3.2)	8 (5.8)
- Inclusion / Exclusion Criteria And Eligibility Status	6 (18.2)	2 (5.9)	1 (2.5)	4 (12.9)	13 (9.4)
- Randomization Procedures / Emergency Envelopes / Unblinding	3 (9.1)	1 (2.9)	2 (5.0)	1 (3.2)	7 (5.1)
- Administration Of Prohibited Concomitant Medication / Therapy	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (0.7)
- Handling And Application Of Ip	4 (12.1)	0 (0.0)	3 (7.5)	1 (3.2)	8 (5.8)
- Laboratory Assessments	0 (0.0)	0 (0.0)	2 (5.0)	0 (0.0)	2 (1.4)
- Study Related Assessments And Questionnaires / Diaries	2 (6.1)	0 (0.0)	0 (0.0)	1 (3.2)	3 (2.2)
- Visit Schedule/Interval	1 (3.0)	1 (2.9)	1 (2.5)	1 (3.2)	4 (2.9)
Listing(s): Derived from Listings 16.2.2.1					

Table 14.1.2.2: Summary of protocol deviations: Reason for exclusion in PPS

Category	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Any Protocol Deviation	8 (24.2)	4 (11.8)	5 (12.5)	5 (16.1)	22 (15.9)
- Inclusion / Exclusion Criteria And Eligibility Status	6 (18.2)	2 (5.9)	1 (2.5)	4 (12.9)	13 (9.4)
- Randomization Procedures / Emergency Envelopes / Unblinding	0 (0.0)	1 (2.9)	1 (2.5)	0 (0.0)	2 (1.4)
- Administration Of Prohibited Concomitant Medication / Therapy	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (0.7)
- Handling And Application Of Ip	3 (9.1)	0 (0.0)	3 (7.5)	1 (3.2)	7 (5.1)
- Study Related Assessments And Questionnaires / Diaries	2 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)
- Visit Schedule/Interval	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (0.7)

Listing(s): Derived from Listings 16.2.2.1

14.1.3 Screening / Baseline

Table 14.1.3.1: Summary of demographics and baseline characteristics

a) Safety population

		20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N = 138
Stratum	1-3 Patches	22 (66.7)	19 (55.9)	23 (57.5)	20 (64.5)	84 (60.9)
	4-6 Patches	11 (33.3)	15 (44.1)	17 (42.5)	11 (35.5)	54 (39.1)
Country	Canada	8 (24.2)	7 (20.6)	7 (17.5)	7 (22.6)	29 (21.0)
	Germany	1 (3.0)	1 (2.9)	2 (5.0)	2 (6.5)	6 (4.3)
	Denmark	3 (9.1)	3 (8.8)	5 (12.5)	3 (9.7)	14 (10.1)
	Great Britain	7 (21.2)	7 (20.6)	6 (15.0)	7 (22.6)	27 (19.6)
	Ireland	3 (9.1)	2 (5.9)	3 (7.5)	2 (6.5)	10 (7.2)
	USA	11 (33.3)	14 (41.2)	17 (42.5)	10 (32.3)	52 (37.7)
Age (yrs)	Mean	58.6	59.7	62.2	63.9	61.1
	SD	11.8	10.5	12.1	11.5	11.6
	Median	60.0	61.0	63.0	66.0	61.0
	Range	33-77	37-75	19-89	30-81	19-89
Sex	Male	9 (27.3)	13 (38.2)	12 (30.0)	5 (16.1)	39 (28.3)
	Female	24 (72.7)	21 (61.8)	28 (70.0)	26 (83.9)	99 (71.7)
Race	White	26 (78.8)	32 (94.1)	36 (90.0)	29 (93.5)	123 (89.1)
	Black	1 (3.0)	0	2 (5.0)	1 (3.2)	4 (2.9)
	Asian	4 (12.1)	1 (2.9)	2 (5.0)	1 (3.2)	8 (5.8)
	American Indian or Alaska	0	1 (2.9)	0	0	1 (0.7)

		20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N = 138
	Other	2 (6.1)	0	0	0	2 (1.4)
Ethnic origin	Hispanic or Latino	3 (9.1)	4 (11.8)	5 (12.5)	4 (12.9)	16 (11.6)
	Not hispanic or Latino	30 (90.9)	30 (88.2)	35 (87.5)	27 (87.1)	122 (88.4)
Weight (kg)	Mean	83.6	85.1	81.6	80.2	82.6
	SD	19.4	21.0	17.9	23.3	20.2
	Median	82.7	81.4	81.6	76.0	79.7
	Range	51-129	60-154	49-136	39-130	39-154
Height (cm)	Mean	163.7	169.3	167.4	162.8	165.9
	SD	9.3	10.4	10.2	14.4	11.4
	Median	162.0	167.8	165.0	162.0	164.8
	Range	145-190	153-187	141-188	105-188	105-190
BMI (kg/m^2)	Mean	31.2	29.6	29.0	30.0	29.9
	SD	6.9	6.0	5.3	7.6	6.4
	Median	30.3	27.7	28.3	28.5	28.7
	Range	18.7-46.9	18.9-48.2	17.8-42.3	21.2-50.9	17.8-50.9
Alcohol habits	Never	7 (21.2)	6 (17.6)	8 (20.0)	9 (29.0)	30 (21.7)
	Rare (seldom)	9 (27.3)	7 (20.6)	16 (40.0)	8 (25.8)	40 (29.0)
	Occasional	16 (48.5)	9 (26.5)	11 (27.5)	11 (35.5)	47 (34.1)
	Often	1 (3.0)	12 (35.3)	5 (12.5)	3 (9.7)	21 (15.2)
Smoking status	Never smoked	17 (51.5)	17 (50.0)	27 (67.5)	19 (61.3)	80 (58.0)
	Habitual	2 (6.1)	1 (2.9)	0	1 (3.2)	4 (2.9)

		20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N = 138
	Occasional	1 (3.0)	0	1 (2.5)	1 (3.2)	3 (2.2)
	Ex-smoker	13 (39.4)	16 (47.1)	12 (30.0)	10 (32.3)	51 (37.0)
Reproduc. status	No	20 (83.3)	20 (95.2)	26 (92.9)	26 (100.0)	92 (92.9)
	Yes	4 (16.7)	1 (4.8)	2 (7.1)	0 (0.0)	7 (7.1)
Time since first diagnosis	Mean	3.9	4.9	4.7	3.7	4.3
	SD	4.7	9.3	6.5	6.1	6.8
	Median	2.0	1.8	1.5	1.5	1.9
	Range	0.0-16.7	0.0-50.1	0.0-24.7	0.0-25.5	0.0-50.1
Previous OLP treatment last 12 months	No	8 (24.2)	11 (32.4)	12 (30.0)	7 (22.6)	38 (27.5)
	Yes	25 (75.8)	23 (67.6)	27 (67.5)	24 (77.4)	99 (71.7)
	Missing	0	0	1 (2.5)	0	1 (0.7)
Extra-oral manifestations of LP	No	27 (81.8)	29 (85.3)	35 (87.5)	24 (77.4)	115 (83.3)
	Yes	6 (18.2)	5 (14.7)	5 (12.5)	7 (22.6)	23 (16.7)

BMI=Body mass index;
Listing(s): Derived from Listing 16.2.4.1

Table 14.1.3.1 Summary of demographics and baseline characteristics: b) Strata 1-3 patches

		20 ug, N=22	5 ug, N=19	1 ug, N=23	Placebo, N=20	Total, N = 84
Country	Canada	7 (31.8)	6 (31.6)	6 (26.1)	7 (35.0)	26 (31.0)
	Germany	1 (4.5)	1 (5.3)	1 (4.3)	1 (5.0)	4 (4.8)
	Denmark	3 (13.6)	2 (10.5)	4 (17.4)	3 (15.0)	12 (14.3)
	Great Britain	3 (13.6)	3 (15.8)	3 (13.0)	3 (15.0)	12 (14.3)
	Ireland	2 (9.1)	1 (5.3)	2 (8.7)	1 (5.0)	6 (7.1)
	USA	6 (27.3)	6 (31.6)	7 (30.4)	5 (25.0)	24 (28.6)
Age (yrs)	Mean	60.1	58.9	64.7	62.8	61.8
	SD	12.6	10.8	9.6	12.8	11.5
	Median	60.0	59.0	66.0	59.5	61.0
	Range	33-77	39-74	47-89	30-81	30-89
Sex	Male	7 (31.8)	9 (47.4)	6 (26.1)	2 (10.0)	24 (28.6)
	Female	15 (68.2)	10 (52.6)	17 (73.9)	18 (90.0)	60 (71.4)
Race	White	18 (81.8)	18 (94.7)	21 (91.3)	20 (100.0)	77 (91.7)
	Black	1 (4.5)	0	1 (4.3)	0	2 (2.4)
	Asian	2 (9.1)	0	1 (4.3)	0	3 (3.6)
	American Indian or Alaska	0	1 (5.3)	0	0	1 (1.2)
	Other	1 (4.5)	0	0	0	1 (1.2)

		20 ug, N=22	5 ug, N=19	1 ug, N=23	Placebo, N=20	Total, N = 84
Ethnic origin	Hispanic or Latino	2 (9.1)	4 (21.1)	3 (13.0)	2 (10.0)	11 (13.1)
	Not hispanic or Latino	20 (90.9)	15 (78.9)	20 (87.0)	18 (90.0)	73 (86.9)
Weight (kg)	Mean	80.5	86.4	79.9	76.6	80.7
	SD	14.6	22.9	18.0	23.8	19.9
	Median	81.0	83.4	77.3	73.8	78.8
	Range	51-110	60-154	57-136	39-127	39-154
Height (cm)	Mean	163.3	170.7	165.8	159.5	164.7
	SD	8.8	10.6	11.7	15.1	12.2
	Median	161.8	170.1	163.0	159.8	162.5
	Range	145-180	155-185	141-188	105-182	105-188
BMI (kg/m^2)	Mean	30.2	29.6	28.9	29.8	29.6
	SD	5.3	6.9	5.0	8.4	6.3
	Median	29.9	27.7	28.1	28.0	28.5
	Range	19.4-42.6	18.9-48.2	21.1-39.8	21.2-50.9	18.9-50.9
Alcohol habits	Never	5 (22.7)	5 (26.3)	6 (26.1)	6 (30.0)	22 (26.2)
	Rare (seldom)	6 (27.3)	4 (21.1)	6 (26.1)	5 (25.0)	21 (25.0)
	Occasional	10 (45.5)	4 (21.1)	6 (26.1)	7 (35.0)	27 (32.1)
	Often	1 (4.5)	6 (31.6)	5 (21.7)	2 (10.0)	14 (16.7)
Smoking status	Never smoked	11 (50.0)	9 (47.4)	11 (47.8)	13 (65.0)	44 (52.4)
	Habitual	2 (9.1)	1 (5.3)	0	1 (5.0)	4 (4.8)

		20 ug, N=22	5 ug, N=19	1 ug, N=23	Placebo, N=20	Total, N = 84
	Occasional	0	0	1 (4.3)	1 (5.0)	2 (2.4)
	Ex-smoker	9 (40.9)	9 (47.4)	11 (47.8)	5 (25.0)	34 (40.5)
Reproduc. status	No	12 (80.0)	9 (90.0)	16 (94.1)	18 (100.0)	55 (91.7)
	Yes	3 (20.0)	1 (10.0)	1 (5.9)	0 (0.0)	5 (8.3)
Time since first diagnosis	Mean	3.2	4.5	4.5	4.6	4.2
	SD	4.1	11.3	5.8	7.2	7.3
	Median	1.9	1.6	2.6	2.1	1.8
	Range	0.0-15.0	0.0-50.1	0.0-21.0	0.1-25.5	0.0-50.1
Previous OLP treatment last 12 months	No	8 (36.4)	8 (42.1)	7 (30.4)	7 (35.0)	30 (35.7)
	Yes	14 (63.6)	11 (57.9)	15 (65.2)	13 (65.0)	53 (63.1)
	Missing	0	0	1 (4.3)	0	1 (1.2)
Extra-oral manifestations of LP	No	18 (81.8)	16 (84.2)	18 (78.3)	17 (85.0)	69 (82.1)
	Yes	4 (18.2)	3 (15.8)	5 (21.7)	3 (15.0)	15 (17.9)

BMI=Body mass index;
Listing(s): Derived from Listing 16.2.4.1

Table 14.1.3.1 Summary of demographics and baseline characteristics: c) Strata 4-6 patches

		20 ug, N=11	5 ug, N=15	1 ug, N=17	Placebo, N=11	Total, N = 54
Country	Canada	1 (9.1)	1 (6.7)	1 (5.9)	0	3 (5.6)
	Germany	0	0	1 (5.9)	1 (9.1)	2 (3.7)
	Denmark	0	1 (6.7)	1 (5.9)	0	2 (3.7)
	Great Britain	4 (36.4)	4 (26.7)	3 (17.6)	4 (36.4)	15 (27.8)
	Ireland	1 (9.1)	1 (6.7)	1 (5.9)	1 (9.1)	4 (7.4)
	USA	5 (45.5)	8 (53.3)	10 (58.8)	5 (45.5)	28 (51.9)
Age (yrs)	Mean	55.5	60.7	58.8	66.0	60.1
	SD	9.9	10.4	14.6	8.9	11.8
	Median	58.0	61.0	57.0	69.0	61.0
	Range	34-66	37-75	19-82	48-77	19-82
Sex	Male	2 (18.2)	4 (26.7)	6 (35.3)	3 (27.3)	15 (27.8)
	Female	9 (81.8)	11 (73.3)	11 (64.7)	8 (72.7)	39 (72.2)
Race	White	8 (72.7)	14 (93.3)	15 (88.2)	9 (81.8)	46 (85.2)
	Black	0	0	1 (5.9)	1 (9.1)	2 (3.7)
	Asian	2 (18.2)	1 (6.7)	1 (5.9)	1 (9.1)	5 (9.3)
	Other	1 (9.1)	0	0	0	1 (1.9)
Ethnic origin	Hispanic or Latino	1 (9.1)	0	2 (11.8)	2 (18.2)	5 (9.3)
	Not hispanic or Latino	10 (90.9)	15 (100.0)	15 (88.2)	9 (81.8)	49 (90.7)
Weight (kg)	Mean	89.8	83.3	83.9	86.8	85.5
	SD	26.4	19.0	18.1	22.1	20.6

		20 ug, N=11	5 ug, N=15	1 ug, N=17	Placebo, N=11	Total, N = 54
	Median	83.5	79.4	82.8	82.2	82.5
	Range	55-129	61-129	49-127	59-130	49-130
Height (cm)	Mean	164.5	167.6	169.5	168.7	167.8
	SD	10.7	10.2	7.7	11.5	9.8
	Median	165.0	166.7	170.0	166.5	166.3
	Range	147-190	153-187	156-187	155-188	147-190
BMI (kg/m^2)	Mean	33.3	29.5	29.2	30.3	30.3
	SD	9.4	4.8	5.9	6.2	6.6
	Median	32.6	27.6	28.4	30.6	28.7
	Range	18.7-46.9	22.0-37.3	17.8-42.3	21.7-40.2	17.8-46.9
Alcohol habits	Never	2 (18.2)	1 (6.7)	2 (11.8)	3 (27.3)	8 (14.8)
	Rare (seldom)	3 (27.3)	3 (20.0)	10 (58.8)	3 (27.3)	19 (35.2)
	Occasional	6 (54.5)	5 (33.3)	5 (29.4)	4 (36.4)	20 (37.0)
	Often	0	6 (40.0)	0	1 (9.1)	7 (13.0)
Smoking status	Never smoked	6 (54.5)	8 (53.3)	16 (94.1)	6 (54.5)	36 (66.7)
	Occasional	1 (9.1)	0	0	0	1 (1.9)
	Ex-smoker	4 (36.4)	7 (46.7)	1 (5.9)	5 (45.5)	17 (31.5)
Reproduc. status	No	8 (88.9)	11 (100.0)	10 (90.9)	8 (100.0)	37 (94.9)
	Yes	1 (11.1)	0 (0.0)	1 (9.1)	0 (0.0)	2 (5.1)
Time since first diagnosis	Mean	5.1	5.4	4.9	2.0	4.5
	SD	5.7	6.2	7.5	2.4	6.0

		20 ug, N=11	5 ug, N=15	1 ug, N=17	Placebo, N=11	Total, N = 54
	Median	2.8	2.9	1.5	0.5	2.0
	Range	0.0-16.7	0.0-18.8	0.0-24.7	0.0-6.6	0.0-24.7
Previous OLP treatment last 12 months	No	0	3 (20.0)	5 (29.4)	0	8 (14.8)
	Yes	11 (100.0)	12 (80.0)	12 (70.6)	11 (100.0)	46 (85.2)
Extra-oral manifestations of LP	No	9 (81.8)	13 (86.7)	17 (100.0)	7 (63.6)	46 (85.2)
	Yes	2 (18.2)	2 (13.3)	0	4 (36.4)	8 (14.8)

BMI=Body mass index;
Listing(s): Derived from Listing 16.2.4.1

Table 14.1.3.1 Summary of demographics and baseline characteristics: d) PPS

		20 ug, N=25	5 ug, N=30	1 ug, N=35	Placebo, N=26	Total, N = 116
Stratum	1-3 Patches	15 (60.0)	17 (56.7)	21 (60.0)	16 (61.5)	69 (59.5)
	4-6 Patches	10 (40.0)	13 (43.3)	14 (40.0)	10 (38.5)	47 (40.5)
Country	Canada	7 (28.0)	5 (16.7)	7 (20.0)	6 (23.1)	25 (21.6)
	Germany	0	1 (3.3)	1 (2.9)	2 (7.7)	4 (3.4)
	Denmark	2 (8.0)	2 (6.7)	4 (11.4)	2 (7.7)	10 (8.6)
	Great Britain	5 (20.0)	7 (23.3)	5 (14.3)	6 (23.1)	23 (19.8)
	Ireland	2 (8.0)	2 (6.7)	3 (8.6)	1 (3.8)	8 (6.9)
	USA	9 (36.0)	13 (43.3)	15 (42.9)	9 (34.6)	46 (39.7)

		20 ug, N=25	5 ug, N=30	1 ug, N=35	Placebo, N=26	Total, N = 116
Age (yrs)	Mean	59.8	60.3	62.3	63.9	61.6
	SD	11.9	10.3	12.4	12.3	11.7
	Median	61.0	61.5	64.0	67.5	62.0
	Range	33-77	37-75	19-89	30-81	19-89
Sex	Male	7 (28.0)	11 (36.7)	10 (28.6)	5 (19.2)	33 (28.4)
	Female	18 (72.0)	19 (63.3)	25 (71.4)	21 (80.8)	83 (71.6)
Race	White	19 (76.0)	29 (96.7)	32 (91.4)	24 (92.3)	104 (89.7)
	Black	1 (4.0)	0	2 (5.7)	1 (3.8)	4 (3.4)
	Asian	4 (16.0)	1 (3.3)	1 (2.9)	1 (3.8)	7 (6.0)
	Other	1 (4.0)	0	0	0	1 (0.9)
Ethnic origin	Hispanic or Latino	3 (12.0)	4 (13.3)	5 (14.3)	4 (15.4)	16 (13.8)
	Not hispanic or Latino	22 (88.0)	26 (86.7)	30 (85.7)	22 (84.6)	100 (86.2)
Weight (kg)	Mean	81.9	81.8	82.3	79.3	81.4
	SD	17.9	17.5	18.4	24.4	19.4
	Median	79.0	75.2	82.8	73.8	78.8
	Range	55-129	60-129	49-136	39-130	39-136
Height (cm)	Mean	163.0	168.6	167.3	161.8	165.5
	SD	9.9	10.8	9.9	15.2	11.7
	Median	162.0	167.2	165.0	161.0	164.5
	Range	145-190	153-187	141-188	105-188	105-190

		20 ug, N=25	5 ug, N=30	1 ug, N=35	Placebo, N=26	Total, N = 116
BMI (kg/m^2)	Mean	30.8	28.7	29.3	29.9	29.6
	SD	6.0	5.1	5.6	7.9	6.1
	Median	30.3	27.6	28.7	28.3	28.7
	Range	18.7-46.9	18.9-40.8	17.8-42.3	21.2-50.9	17.8-50.9
Alcohol habits	Never	6 (24.0)	6 (20.0)	7 (20.0)	9 (34.6)	28 (24.1)
	Rare (seldom)	6 (24.0)	5 (16.7)	13 (37.1)	6 (23.1)	30 (25.9)
	Occasional	12 (48.0)	8 (26.7)	10 (28.6)	10 (38.5)	40 (34.5)
	Often	1 (4.0)	11 (36.7)	5 (14.3)	1 (3.8)	18 (15.5)
Smoking status	Never smoked	15 (60.0)	16 (53.3)	23 (65.7)	17 (65.4)	71 (61.2)
	Habitual	1 (4.0)	1 (3.3)	0	1 (3.8)	3 (2.6)
	Occasional	1 (4.0)	0	1 (2.9)	0	2 (1.7)
	Ex-smoker	8 (32.0)	13 (43.3)	11 (31.4)	8 (30.8)	40 (34.5)
Reproduc. status	No	15 (83.3)	18 (94.7)	23 (92.0)	21 (100.0)	77 (92.8)
	Yes	3 (16.7)	1 (5.3)	2 (8.0)	0 (0.0)	6 (7.2)
Time since first diagnosis	Mean	4.2	5.4	4.1	4.0	4.5
	SD	5.2	9.8	6.3	6.5	7.1
	Median	1.9	2.4	1.2	1.8	1.8
	Range	0.0-16.7	0.0-50.1	0.0-24.7	0.0-25.5	0.0-50.1
Previous OLP treatment last 12 months	No	5 (20.0)	8 (26.7)	12 (34.3)	5 (19.2)	30 (25.9)
	Yes	20 (80.0)	22 (73.3)	22 (62.9)	21 (80.8)	85 (73.3)
	Missing	0	0	1 (2.9)	0	1 (0.9)

		20 ug, N=25	5 ug, N=30	1 ug, N=35	Placebo, N=26	Total, N = 116
Extra-oral manifestations of LP	No	21 (84.0)	25 (83.3)	31 (88.6)	19 (73.1)	96 (82.8)
	Yes	4 (16.0)	5 (16.7)	4 (11.4)	7 (26.9)	20 (17.2)

BMI=Body mass index;
Listing(s): Derived from Listing 16.2.4.1

Table 14.1.3.2: Summary of OLP prior medications

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
ANY PREVIOUS OLP MEDICATION	25 (76)	23 (68)	27 (68)	24 (77)	99 (72)
STOMATOLOGICAL PREPARATIONS	24 (73)	22 (65)	26 (65)	24 (77)	96 (70)
- CORTICOSTEROIDS FOR LOCAL ORAL TREATMENT	21 (64)	22 (65)	24 (60)	23 (74)	90 (65)
- ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREATMENT	5 (15)	4 (12)	6 (15)	4 (13)	19 (14)
- OTHER AGENTS FOR LOCAL ORAL TREATMENT	3 (9)	5 (15)	4 (10)	3 (10)	15 (11)
- STOMATOLOGICAL PREPARATIONS	0	0	0	3 (10)	3 (2)
CORTICOSTEROIDS FOR SYSTEMIC USE	3 (9)	7 (21)	3 (8)	5 (16)	18 (13)
- GLUCOCORTICOIDS	3 (9)	7 (21)	3 (8)	5 (16)	18 (13)
OTHER DERMATOLOGICAL PREPARATIONS	2 (6)	3 (9)	6 (15)	2 (6)	13 (9)
- AGENTS FOR DERMATITIS, EXCLUDING CORTICOSTEROIDS	2 (6)	3 (9)	6 (15)	2 (6)	13 (9)
ANTIBACTERIALS FOR SYSTEMIC USE	1 (3)	2 (6)	0	0	3 (2)
- TETRACYCLINES	1 (3)	1 (3)	0	0	2 (1)
- IMIDAZOLE DERIVATIVES	0	1 (3)	0	0	1 (1)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0	1 (3)	1 (3)	0	2 (1)
- OTHER ANTIINFLAMMATORY AND ANTIRHEUMATIC AGENTS, NON-STEROIDS	0	0	1 (3)	0	1 (1)
- PROPIONIC ACID DERIVATIVES	0	1 (3)	0	0	1 (1)
ALL OTHER THERAPEUTIC PRODUCTS	0	0	1 (3)	0	1 (1)
- OTHER THERAPEUTIC PRODUCTS	0	0	1 (3)	0	1 (1)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
ANESTHETICS	0	0	1 (3)	0	1 (1)
- AMIDES	0	0	1 (3)	0	1 (1)
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE	0	1 (3)	0	0	1 (1)
- OTHER ANTIBIOTICS FOR TOPICAL USE	0	1 (3)	0	0	1 (1)
ANTIMYCOTICS FOR SYSTEMIC USE	0	0	1 (3)	0	1 (1)
- TRIAZOLE DERIVATIVES	0	0	1 (3)	0	1 (1)
ANTISEPTICS AND DISINFECTANTS	0	0	0	1 (3)	1 (1)
- OTHER ANTISEPTICS AND DISINFECTANTS	0	0	0	1 (3)	1 (1)
ANTIVIRALS FOR SYSTEMIC USE	0	1 (3)	0	0	1 (1)
- NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	0	1 (3)	0	0	1 (1)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	0	1 (3)	0	0	1 (1)
- CORTICOSTEROIDS, POTENT (GROUP III)	0	1 (3)	0	0	1 (1)
IMMUNOSUPPRESSANTS	0	1 (3)	0	0	1 (1)
- SELECTIVE IMMUNOSUPPRESSANTS	0	1 (3)	0	0	1 (1)

Listing(s): Derived from Listing 16.2.4.2

Table 14.1.3.3: Summary of prior medications

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
ANY PRIOR MEDICATION	29 (88)	27 (79)	34 (85)	26 (84)	116 (84)
LIPID MODIFYING AGENTS	10 (30)	8 (24)	16 (40)	10 (32)	44 (32)
- HMG COA REDUCTASE INHIBITORS	10 (30)	7 (21)	15 (38)	10 (32)	42 (30)
- OTHER LIPID MODIFYING AGENTS	0	0	2 (5)	2 (6)	4 (3)
- FIBRATES	0	2 (6)	0	0	2 (1)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	12 (36)	6 (18)	12 (30)	10 (32)	40 (29)
- ANGIOTENSIN II ANTAGONISTS, PLAIN	5 (15)	4 (12)	7 (18)	5 (16)	21 (15)
- ACE INHIBITORS, PLAIN	7 (21)	1 (3)	5 (13)	4 (13)	17 (12)
- ANGIOTENSIN II ANTAGONISTS AND DIURETICS	0	1 (3)	0	1 (3)	2 (1)
DRUGS FOR ACID RELATED DISORDERS	8 (24)	5 (15)	18 (45)	3 (10)	34 (25)
- PROTON PUMP INHIBITORS	6 (18)	4 (12)	16 (40)	2 (6)	28 (20)
- H2-RECEPTOR ANTAGONISTS	1 (3)	1 (3)	2 (5)	1 (3)	5 (4)
- OTHER DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	2 (6)	0	0	0	2 (1)
THYROID THERAPY	6 (18)	9 (26)	7 (18)	9 (29)	31 (22)
- THYROID HORMONES	6 (18)	8 (24)	7 (18)	9 (29)	30 (22)
- SULFUR-CONTAINING IMIDAZOLE DERIVATIVES	0	1 (3)	0	0	1 (1)
VITAMINS	6 (18)	6 (18)	7 (18)	8 (26)	27 (20)
- VITAMIN D AND ANALOGUES	6 (18)	6 (18)	4 (10)	6 (19)	22 (16)
- COMBINATIONS OF VITAMINS	1 (3)	2 (6)	3 (8)	2 (6)	8 (6)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- OTHER PLAIN VITAMIN PREPARATIONS	1 (3)	0	2 (5)	1 (3)	4 (3)
- ASCORBIC ACID (VITAMIN C), PLAIN	0	1 (3)	0	0	1 (1)
- MULTIVITAMINS WITH MINERALS	1 (3)	0	0	0	1 (1)
- VITAMIN A AND D IN COMBINATION	0	1 (3)	0	0	1 (1)
- VITAMIN A, PLAIN	0	1 (3)	0	0	1 (1)
DRUGS USED IN DIABETES	7 (21)	7 (21)	8 (20)	3 (10)	25 (18)
- BIGUANIDES	6 (18)	5 (15)	7 (18)	3 (10)	21 (15)
- INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING	1 (3)	1 (3)	4 (10)	0	6 (4)
- INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	0	2 (6)	2 (5)	0	4 (3)
- SULFONYLUREAS	1 (3)	0	2 (5)	1 (3)	4 (3)
- DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS	0	1 (3)	2 (5)	0	3 (2)
- GLUCAGON-LIKE PEPTIDE-1 (GLP-1) ANALOGUES	0	0	1 (3)	2 (6)	3 (2)
- SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS	2 (6)	0	1 (3)	0	3 (2)
- COMBINATIONS OF ORAL BLOOD GLUCOSE LOWERING DRUGS	1 (3)	0	0	0	1 (1)
ANTITHROMBOTIC AGENTS	2 (6)	5 (15)	10 (25)	7 (23)	24 (17)
- PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	2 (6)	5 (15)	10 (25)	5 (16)	22 (16)
- DIRECT FACTOR XA INHIBITORS	0	0	0	3 (10)	3 (2)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	2 (6)	10 (29)	7 (18)	4 (13)	23 (17)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- PROPIONIC ACID DERIVATIVES	2 (6)	4 (12)	4 (10)	3 (10)	13 (9)
- COXIBS	0	3 (9)	2 (5)	0	5 (4)
- OXICAMS	0	3 (9)	0	0	3 (2)
- ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	0	0	1 (3)	1 (3)	2 (1)
PSYCHOANALEPTICS	5 (15)	3 (9)	9 (23)	6 (19)	23 (17)
- SELECTIVE SEROTONIN REUPTAKE INHIBITORS	3 (9)	1 (3)	4 (10)	3 (10)	11 (8)
- OTHER ANTIDEPRESSANTS	1 (3)	2 (6)	3 (8)	2 (6)	8 (6)
- NON-SELECTIVE MONOAMINE REUPTAKE INHIBITORS	0	0	2 (5)	1 (3)	3 (2)
- CENTRALLY ACTING SYMPATHOMIMETICS	1 (3)	0	0	0	1 (1)
MINERAL SUPPLEMENTS	2 (6)	3 (9)	9 (23)	5 (16)	19 (14)
- CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	0	1 (3)	5 (13)	2 (6)	8 (6)
- POTASSIUM	1 (3)	0	3 (8)	0	4 (3)
- CALCIUM	0	1 (3)	1 (3)	1 (3)	3 (2)
- FLUORIDE	1 (3)	0	0	1 (3)	2 (1)
- MAGNESIUM	0	1 (3)	0	1 (3)	2 (1)
- SELENIUM	0	0	0	1 (3)	1 (1)
ANALGESICS	6 (18)	1 (3)	8 (20)	3 (10)	18 (13)
- ANILIDES	4 (12)	0	3 (8)	1 (3)	8 (6)
- OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	2 (6)	1 (3)	2 (5)	1 (3)	6 (4)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- NATURAL OPIUM ALKALOIDS	0	0	2 (5)	0	2 (1)
- OTHER ANTIMIGRAINE PREPARATIONS	0	0	0	2 (6)	2 (1)
- OTHER OPIOIDS	1 (3)	0	1 (3)	0	2 (1)
- SELECTIVE SEROTONIN (5HT1) AGONISTS	0	0	1 (3)	1 (3)	2 (1)
- ORIPAVINE DERIVATIVES	0	0	0	1 (3)	1 (1)
- SALICYLIC ACID AND DERIVATIVES	0	0	1 (3)	0	1 (1)
CALCIUM CHANNEL BLOCKERS	5 (15)	2 (6)	5 (13)	5 (16)	17 (12)
- DIHYDROPYRIDINE DERIVATIVES	5 (15)	0	3 (8)	5 (16)	13 (9)
- BENZOTHIAZEPINE DERIVATIVES	0	2 (6)	2 (5)	0	4 (3)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	3 (9)	5 (15)	6 (15)	3 (10)	17 (12)
- SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	2 (6)	4 (12)	1 (3)	3 (10)	10 (7)
- ADRENERGICS IN COMBINATION WITH CORTICOSTEROIDS OR OTHER DRUGS, EXCL. ANTICHOLINE	1 (3)	0	4 (10)	2 (6)	7 (5)
- ANTICHOLINERGICS	1 (3)	1 (3)	2 (5)	1 (3)	5 (4)
- LEUKOTRIENE RECEPTOR ANTAGONISTS	1 (3)	1 (3)	3 (8)	0	5 (4)
- GLUCOCORTICOIDS	1 (3)	0	2 (5)	0	3 (2)
- XANTHINES	0	0	1 (3)	0	1 (1)
ANTIEPILEPTICS	5 (15)	2 (6)	2 (5)	4 (13)	13 (9)
- OTHER ANTIEPILEPTICS	4 (12)	1 (3)	2 (5)	2 (6)	9 (7)
- BENZODIAZEPINE DERIVATIVES	0	1 (3)	0	1 (3)	2 (1)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- CARBOXAMIDE DERIVATIVES	1 (3)	0	0	1 (3)	2 (1)
- HYDANTOIN DERIVATIVES	1 (3)	0	0	0	1 (1)
ANTIHISTAMINES FOR SYSTEMIC USE	1 (3)	3 (9)	4 (10)	5 (16)	13 (9)
- PIPERAZINE DERIVATIVES	0	3 (9)	2 (5)	3 (10)	8 (6)
- OTHER ANTIHISTAMINES FOR SYSTEMIC USE	1 (3)	0	1 (3)	2 (6)	4 (3)
- SUBSTITUTED ALKYLAMINES	0	0	1 (3)	0	1 (1)
BETA BLOCKING AGENTS	3 (9)	1 (3)	6 (15)	3 (10)	13 (9)
- BETA BLOCKING AGENTS, SELECTIVE	3 (9)	1 (3)	5 (13)	3 (10)	12 (9)
- ALPHA AND BETA BLOCKING AGENTS	0	0	2 (5)	0	2 (1)
DIURETICS	2 (6)	3 (9)	5 (13)	3 (10)	13 (9)
- SULFONAMIDES, PLAIN	1 (3)	0	2 (5)	2 (6)	5 (4)
- THIAZIDES, PLAIN	1 (3)	1 (3)	2 (5)	1 (3)	5 (4)
- ALDOSTERONE ANTAGONISTS	0	0	1 (3)	0	1 (1)
- HIGH-CEILING DIURETICS AND POTASSIUM-SPARING AGENTS	0	1 (3)	0	0	1 (1)
- LOW-CEILING DIURETICS AND POTASSIUM-SPARING AGENTS	0	1 (3)	0	0	1 (1)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	3 (9)	1 (3)	3 (8)	5 (16)	12 (9)
- CORTICOSTEROIDS, VERY POTENT (GROUP IV)	1 (3)	0	2 (5)	3 (10)	6 (4)
- CORTICOSTEROIDS, POTENT (GROUP III)	1 (3)	0	1 (3)	2 (6)	4 (3)
- CORTICOSTEROIDS, WEAK (GROUP I)	0	1 (3)	1 (3)	1 (3)	3 (2)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- CORTICOSTEROIDS, POTENT, COMBINATIONS WITH ANTIBIOTICS	1 (3)	0	0	1 (3)	2 (1)
ANTIANEMIC PREPARATIONS	1 (3)	3 (9)	4 (10)	3 (10)	11 (8)
- VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	0	2 (6)	3 (8)	3 (10)	8 (6)
- IRON BIVALENT, ORAL PREPARATIONS	1 (3)	1 (3)	1 (3)	0	3 (2)
- FOLIC ACID AND DERIVATIVES	0	0	1 (3)	0	1 (1)
- IRON PREPARATIONS	0	1 (3)	0	0	1 (1)
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	2 (6)	2 (6)	2 (5)	4 (13)	10 (7)
- NATURAL AND SEMISYNTHETIC ESTROGENS, PLAIN	0	2 (6)	1 (3)	3 (10)	6 (4)
- PROGESTOGENS AND ESTROGENS, FIXED COMBINATIONS	2 (6)	0	0	1 (3)	3 (2)
- OTHER ESTROGENS	0	0	1 (3)	0	1 (1)
- PREGNEN (4) DERIVATIVES	0	0	0	1 (3)	1 (1)
GENERAL NUTRIENTS	2 (6)	2 (6)	3 (8)	2 (6)	9 (7)
- OTHER COMBINATIONS OF NUTRIENTS	1 (3)	2 (6)	2 (5)	2 (6)	7 (5)
- OTHER NUTRIENTS	1 (3)	0	1 (3)	0	2 (1)
OPHTHALMOLOGICALS	2 (6)	2 (6)	2 (5)	3 (10)	9 (7)
- OTHER OPHTHALMOLOGICALS	1 (3)	2 (6)	1 (3)	2 (6)	6 (4)
- PROSTAGLANDIN ANALOGUES	1 (3)	0	1 (3)	1 (3)	3 (2)
- BETA BLOCKING AGENTS	1 (3)	0	0	0	1 (1)
- SYMPATHOMIMETICS IN GLAUCOMA THERAPY	1 (3)	0	0	0	1 (1)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
PSYCHOLEPTICS	1 (3)	4 (12)	1 (3)	3 (10)	9 (7)
- BENZODIAZEPINE DERIVATIVES	1 (3)	2 (6)	0	2 (6)	5 (4)
- BENZODIAZEPINE RELATED DRUGS	1 (3)	1 (3)	1 (3)	0	3 (2)
- OTHER ANXIOLYTICS	1 (3)	1 (3)	0	1 (3)	3 (2)
- OTHER HYPNOTICS AND SEDATIVES	0	0	0	1 (3)	1 (1)
UROLOGICALS	1 (3)	2 (6)	3 (8)	3 (10)	9 (7)
- DRUGS FOR URINARY FREQUENCY AND INCONTINENCE	1 (3)	1 (3)	2 (5)	1 (3)	5 (4)
- ALPHA-ADRENORECEPTOR ANTAGONISTS	0	0	0	2 (6)	2 (1)
- TESTOSTERONE-5-ALPHA REDUCTASE INHIBITORS	0	1 (3)	1 (3)	0	2 (1)
STOMATOLOGICAL PREPARATIONS	2 (6)	0	2 (5)	3 (10)	7 (5)
- ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREATMENT	1 (3)	0	2 (5)	1 (3)	4 (3)
- OTHER AGENTS FOR LOCAL ORAL TREATMENT	1 (3)	0	0	1 (3)	2 (1)
- CARIES PROPHYLACTIC AGENTS	0	0	0	1 (3)	1 (1)
DRUGS FOR CONSTIPATION	2 (6)	1 (3)	1 (3)	2 (6)	6 (4)
- OSMOTICALLY ACTING LAXATIVES	1 (3)	1 (3)	0	2 (6)	4 (3)
- BULK-FORMING LAXATIVES	1 (3)	0	0	0	1 (1)
- CONTACT LAXATIVES	0	0	1 (3)	0	1 (1)
- OTHER DRUGS FOR CONSTIPATION	0	0	0	1 (3)	1 (1)
NASAL PREPARATIONS	1 (3)	2 (6)	1 (3)	1 (3)	5 (4)
- ANTIALLERGIC AGENTS, EXCL. CORTICOSTEROIDS	1 (3)	0	1 (3)	0	2 (1)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- CORTICOSTEROIDS	0	1 (3)	1 (3)	0	2 (1)
- SYMPATHOMIMETICS, COMBINATIONS EXCL. CORTICOSTEROIDS	0	0	0	1 (3)	1 (1)
- SYMPATHOMIMETICS, PLAIN	0	1 (3)	0	0	1 (1)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	4 (12)	1 (3)	0	0	5 (4)
- UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	4 (12)	1 (3)	0	0	5 (4)
ANTIHYPERTENSIVES	2 (6)	0	0	2 (6)	4 (3)
- ALPHA-ADRENORECEPTOR ANTAGONISTS	1 (3)	0	0	2 (6)	3 (2)
- IMIDAZOLINE RECEPTOR AGONISTS	1 (3)	0	0	0	1 (1)
CARDIAC THERAPY	2 (6)	1 (3)	0	1 (3)	4 (3)
- ORGANIC NITRATES	2 (6)	0	0	1 (3)	3 (2)
- OTHER CARDIAC PREPARATIONS	0	1 (3)	0	0	1 (1)
DRUGS FOR TREATMENT OF BONE DISEASES	0	2 (6)	2 (5)	0	4 (3)
- BISPHOSPHONATES	0	2 (6)	2 (5)	0	4 (3)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	1 (3)	0	2 (5)	1 (3)	4 (3)
- VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS	1 (3)	0	2 (5)	1 (3)	4 (3)
ANTIBACTERIALS FOR SYSTEMIC USE	2 (6)	0	1 (3)	0	3 (2)
- NITROFURAN DERIVATIVES	2 (6)	0	0	0	2 (1)
- MACROLIDES	0	0	1 (3)	0	1 (1)
OTHER DERMATOLOGICAL PREPARATIONS	0	1 (3)	2 (5)	0	3 (2)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- AGENTS FOR DERMATITIS, EXCLUDING CORTICOSTEROIDS	0	1 (3)	1 (3)	0	2 (1)
- OTHER DERMATOLOGICALS	0	0	1 (3)	0	1 (1)
TONICS	0	2 (6)	1 (3)	0	3 (2)
- TONICS	0	2 (6)	1 (3)	0	3 (2)
ANESTHETICS	0	1 (3)	1 (3)	0	2 (1)
- AMIDES	0	1 (3)	1 (3)	0	2 (1)
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE	1 (3)	1 (3)	0	0	2 (1)
- ANTIVIRALS	0	1 (3)	0	0	1 (1)
- OTHER ANTIBIOTICS FOR TOPICAL USE	1 (3)	0	0	0	1 (1)
ANTIFUNGALS FOR DERMATOLOGICAL USE	0	1 (3)	1 (3)	0	2 (1)
- IMIDAZOLE AND TRIAZOLE DERIVATIVES	0	1 (3)	0	0	1 (1)
- OTHER ANTIFUNGALS FOR TOPICAL USE	0	0	1 (3)	0	1 (1)
ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	0	1 (3)	1 (3)	0	2 (1)
- ANESTHETICS FOR TOPICAL USE	0	1 (3)	1 (3)	0	2 (1)
CORTICOSTEROIDS FOR SYSTEMIC USE	0	0	2 (5)	0	2 (1)
- GLUCOCORTICOIDS	0	0	2 (5)	0	2 (1)
COUGH AND COLD PREPARATIONS	0	0	1 (3)	1 (3)	2 (1)
- EXPECTORANTS	0	0	0	1 (3)	1 (1)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- HERBAL DIAPHORETICS AND OTHER HERBAL COUGH AND COLD REMEDIES	0	0	0	1 (3)	1 (1)
- HERBAL EXPECTORANTS AND EMOLLIENTS	0	0	0	1 (3)	1 (1)
- MUCOLYTICS	0	0	0	1 (3)	1 (1)
- OPIUM ALKALOIDS AND DERIVATIVES	0	0	1 (3)	0	1 (1)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	0	1 (3)	1 (3)	0	2 (1)
- BELLADONNA ALKALOIDS, SEMISYNTHETIC, QUATERNARY AMMONIUM COMPOUNDS	0	0	1 (3)	0	1 (1)
- PROPULSIVES	0	1 (3)	0	0	1 (1)
EMOLLIENTS AND PROTECTIVES	0	1 (3)	1 (3)	0	2 (1)
- OTHER EMOLLIENTS AND PROTECTIVES	0	1 (3)	1 (3)	0	2 (1)
- SOFT PARAFFIN AND FAT PRODUCTS	0	1 (3)	0	0	1 (1)
MUSCLE RELAXANTS	1 (3)	1 (3)	0	0	2 (1)
- OTHER CENTRALLY ACTING AGENTS	1 (3)	1 (3)	0	0	2 (1)
OTHER NERVOUS SYSTEM DRUGS	0	0	1 (3)	1 (3)	2 (1)
- OTHER PARASYMPATHOMIMETICS	0	0	1 (3)	1 (3)	2 (1)
ALL OTHER THERAPEUTIC PRODUCTS	1 (3)	0	0	0	1 (1)
- OTHER THERAPEUTIC PRODUCTS	1 (3)	0	0	0	1 (1)
ANTI-ACNE PREPARATIONS	1 (3)	0	0	0	1 (1)
- RETINOIDS FOR TOPICAL USE IN ACNE	1 (3)	0	0	0	1 (1)
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	0	0	0	1 (3)	1 (1)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- ANTIDIARRHEAL MICROORGANISMS	0	0	0	1 (3)	1 (1)
ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS	0	0	1 (3)	0	1 (1)
- CENTRALLY ACTING ANTIOBESITY PRODUCTS	0	0	1 (3)	0	1 (1)
ANTIPSORIATICS	0	0	1 (3)	0	1 (1)
- OTHER ANTIPSORIATICS FOR TOPICAL USE	0	0	1 (3)	0	1 (1)
ANTIVIRALS FOR SYSTEMIC USE	0	1 (3)	0	0	1 (1)
- NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	0	1 (3)	0	0	1 (1)
BILE AND LIVER THERAPY	1 (3)	0	0	0	1 (1)
- LIVER THERAPY	1 (3)	0	0	0	1 (1)
DIGESTIVES, INCL. ENZYMES	1 (3)	0	0	0	1 (1)
- HERBAL DIGESTIVES, OTHER	1 (3)	0	0	0	1 (1)
ENDOCRINE THERAPY	0	0	1 (3)	0	1 (1)
- GONADOTROPIN RELEASING HORMONE ANALOGUES	0	0	1 (3)	0	1 (1)
IMMUNOSUPPRESSANTS	0	0	1 (3)	0	1 (1)
- OTHER IMMUNOSUPPRESSANTS	0	0	1 (3)	0	1 (1)
OTHER GYNECOLOGICALS	1 (3)	0	0	0	1 (1)
- INTRAUTERINE CONTRACEPTIVES	1 (3)	0	0	0	1 (1)
THROAT PREPARATIONS	0	0	0	1 (3)	1 (1)
- ANTISEPTICS	0	0	0	1 (3)	1 (1)
- THROAT PREPARATIONS	0	0	0	1 (3)	1 (1)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	0	1 (3)	0	0	1 (1)
- ANTIINFLAMMATORY PREPARATIONS, NON-STEROIDS FOR TOPICAL USE	0	1 (3)	0	0	1 (1)
Listing(s): Derived from Listing 16.2.4.2					

Table 14.1.3.4 Summary of biopsy data: Study inclusion

Category	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
In scope for biopsy[a]		27	31	35	27	120
Hist. conf. in the past	Yes	23 (85.2)	22 (71.0)	28 (80.0)	23 (85.2)	96 (80.0)
	No	4 (14.8)	9 (29.0)	7 (20.0)	4 (14.8)	24 (20.0)
Biopsy type	Existing Biopsy	23 (85.2)	22 (71.0)	28 (80.0)	23 (85.2)	96 (80.0)
	Study Biopsy	4 (14.8)	9 (29.0)	7 (20.0)	4 (14.8)	24 (20.0)
Confirmatory of OLP inflammation	Yes	26 (96.3)	31 (100)	35 (100)	27 (100)	119 (99.2)
	No	1 (3.7)	0	0	0	1 (0.8)
Existing biopsy loc.	Oral Lesion	21 (91.3)	22 (100)	28 (100)	22 (95.7)	93 (96.9)
	Cutaneous Lesion	2 (8.7)	0	0	0	2 (2.1)
	Vaginal Lesion	0	0	0	1 (4.3)	1 (1.0)
Study biopsy loc.	Oral Lesion	4 (100)	9 (100)	6 (85.7)	4 (100)	23 (95.8)

Category	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
	Cutaneous Lesion	0	0	1 (14.3)	0	1 (4.2)
-Complete healing	Yes	4 (100)	9 (100)	7 (100)	4 (100)	24 (100)
-Complete pain relief	Yes	4 (100)	9 (100)	7 (100)	4 (100)	24 (100)
-Study biopsy lesion	Erythematous/White Lesion (Without Ulceration)	1 (25.0)	0	2 (33.3)	0	3 (13.0)
	Ulcerative Lesion	3 (75.0)	9 (100)	3 (50.0)	4 (100)	19 (82.6)
	Missing	0	0	1 (16.7)	0	1 (4.3)
-Oral biopsy location	Lower Labial Mucosa	0	1 (11.1)	0	0	1 (4.3)
	Right Buccal Mucosa	1 (25.0)	4 (44.4)	3 (50.0)	2 (50.0)	10 (43.5)
	Left Buccal Mucosa	1 (25.0)	2 (22.2)	3 (50.0)	1 (25.0)	7 (30.4)
	Gingivae: Lower Right (Distal)	0	0	0	1 (25.0)	1 (4.3)
	Gingivae: Lower Left (Distal)	0	1 (11.1)	0	0	1 (4.3)
	Gingivae: Upper Left (Distal)	2 (50.0)	0	0	0	2 (8.7)
	Right Lateral Ventral Tongue	0	1 (11.1)	0	0	1 (4.3)
	Not Applicable	0	0	1 (16.7)	0	1 (4.3)

[a] included after change of inclusion criteria in protocol
Listing(s): Derived from Listing 16.2.4.3

Table 14.1.3.5 Summary of lesion characteristics at screening/baseline

a) Locations assessed at Visit 1 and Visit 2

Location	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Upper Labial Mucosa	1 (3.0)	0	0	1 (3.2)	2 (1.4)
Lower Labial Mucosa	2 (6.1)	2 (5.9)	4 (10.0)	3 (9.7)	11 (8.0)
Right Buccal Mucosa	19 (57.6)	16 (47.1)	23 (57.5)	15 (48.4)	73 (52.9)
Left Buccal Mucosa	16 (48.5)	19 (55.9)	27 (67.5)	20 (64.5)	82 (59.4)
Gingivae: Lower Right (distal)	8 (24.2)	9 (26.5)	6 (15.0)	9 (29.0)	32 (23.2)
Gingivae: Lower Central	1 (3.0)	3 (8.8)	4 (10.0)	4 (12.9)	12 (8.7)
Gingivae: Lower Left (distal)	4 (12.1)	11 (32.4)	3 (7.5)	7 (22.6)	25 (18.1)
Gingivae: Upper Right (distal)	5 (15.2)	4 (11.8)	4 (10.0)	6 (19.4)	19 (13.8)
Gingivae: Upper Central	1 (3.0)	1 (2.9)	7 (17.5)	7 (22.6)	16 (11.6)
Gingivae: Upper Left (distal)	3 (9.1)	4 (11.8)	5 (12.5)	9 (29.0)	21 (15.2)
Mandibular Lingual Gingivae: Lower Right (distal)	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Central	1 (3.0)	0	0	0	1 (0.7)
Mandibular Lingual Gingivae: Lower Left (distal)	0	0	0	1 (3.2)	1 (0.7)
Dorsum Tongue	2 (6.1)	0	3 (7.5)	5 (16.1)	10 (7.2)
Right Lateral Ventral Tongue	3 (9.1)	8 (23.5)	6 (15.0)	0	17 (12.3)
Left Lateral Ventral Tongue	3 (9.1)	3 (8.8)	8 (20.0)	3 (9.7)	17 (12.3)
Floor of Mouth	0	0	0	0	0

Location	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Hard Palate	2 (6.1)	3 (8.8)	1 (2.5)	1 (3.2)	7 (5.1)
Soft Palate	0	0	0	0	0
Numbers are n (%); location counted once within patient Listing(s): Derived from Listing 16.2.4.3					

Table 14.1.3.5 Summary of lesion characteristics at screening/baseline: b) Total number and type of lesions by location, lesions assessed at Visit 1 and Visit 2

Location	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
All sites	78/45/33	89/60/29	109/82/27	96/54/42	372/241/131
Upper Labial Mucosa	1/1/0	0	0	1/0/1	2/1/1
Lower Labial Mucosa	2/2/0	3/1/2	4/2/2	3/1/2	12/6/6
Right Buccal Mucosa	23/14/9	17/14/3	24/15/9	15/11/4	79/54/25
Left Buccal Mucosa	18/11/7	22/20/2	29/25/4	20/16/4	89/72/17
Gingivae: Lower Right (distal)	8/5/3	9/6/3	7/7/0	9/4/5	33/22/11
Gingivae: Lower Central	1/1/0	3/2/1	4/2/2	4/2/2	12/7/5
Gingivae: Lower Left (distal)	4/2/2	11/6/5	3/2/1	7/2/5	25/12/13
Gingivae: Upper Right (distal)	5/3/2	4/1/3	4/3/1	6/2/4	19/9/10
Gingivae: Upper Central	1/0/1	1/0/1	9/6/3	11/3/8	22/9/13
Gingivae: Upper Left (distal)	3/1/2	4/2/2	5/3/2	9/4/5	21/10/11
Mandibular Lingual Gingivae: Lower Right (distal)	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Central	1/0/1	0	0	0	1/0/1
Mandibular Lingual Gingivae: Lower Left (distal)	0	0	0	1/0/1	1/0/1

Location	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Dorsum Tongue	3/2/1	0	5/3/2	6/5/1	14/10/4
Right Lateral Ventral Tongue	3/2/1	8/5/3	6/6/0	0	17/13/4
Left Lateral Ventral Tongue	3/1/2	3/1/2	8/7/1	3/3/0	17/12/5
Floor of Mouth	0	0	0	0	0
Hard Palate	2/0/2	4/2/2	1/1/0	1/1/0	8/4/4
Soft Palate	0	0	0	0	0

Numbers are Total lesions/Ulcerative/Erythematous
Listing(s): Derived from Listing 16.2.4.3

Table 14.1.3.5 Summary of lesion characteristics at screening/baseline: c) Location of lesions assessed at Visit 1 and Visit 2; patients requiring 1 - 3 patches

Location	20 ug, N=22	5 ug, N=19	1 ug, N=23	Placebo, N=20	Total, N=84
Upper Labial Mucosa	1 (4.5)	0	0	1 (5.0)	2 (2.4)
Lower Labial Mucosa	2 (9.1)	2 (10.5)	4 (17.4)	3 (15.0)	11 (13.1)
Right Buccal Mucosa	19 (86.4)	16 (84.2)	23 (100)	15 (75.0)	73 (86.9)
Left Buccal Mucosa	16 (72.7)	19 (100)	27 (117)	20 (100)	82 (97.6)
Gingivae: Lower Right (distal)	8 (36.4)	9 (47.4)	6 (26.1)	9 (45.0)	32 (38.1)
Gingivae: Lower Central	1 (4.5)	3 (15.8)	4 (17.4)	4 (20.0)	12 (14.3)
Gingivae: Lower Left (distal)	4 (18.2)	11 (57.9)	3 (13.0)	7 (35.0)	25 (29.8)
Gingivae: Upper Right (distal)	5 (22.7)	4 (21.1)	4 (17.4)	6 (30.0)	19 (22.6)
Gingivae: Upper Central	1 (4.5)	1 (5.3)	7 (30.4)	7 (35.0)	16 (19.0)

Location	20 ug, N=22	5 ug, N=19	1 ug, N=23	Placebo, N=20	Total, N=84
Gingivae: Upper Left (distal)	3 (13.6)	4 (21.1)	5 (21.7)	9 (45.0)	21 (25.0)
Mandibular Lingual Gingivae: Lower Right (distal)	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Central	1 (4.5)	0	0	0	1 (1.2)
Mandibular Lingual Gingivae: Lower Left (distal)	0	0	0	1 (5.0)	1 (1.2)
Dorsum Tongue	2 (9.1)	0	3 (13.0)	5 (25.0)	10 (11.9)
Right Lateral Ventral Tongue	3 (13.6)	8 (42.1)	6 (26.1)	0	17 (20.2)
Left Lateral Ventral Tongue	3 (13.6)	3 (15.8)	8 (34.8)	3 (15.0)	17 (20.2)
Floor of Mouth	0	0	0	0	0
Hard Palate	2 (9.1)	3 (15.8)	1 (4.3)	1 (5.0)	7 (8.3)
Soft Palate	0	0	0	0	0

Numbers are n (%); location counted once within patient
Listing(s): Derived from Listing 16.2.4.3

Table 14.1.3.5 Summary of lesion characteristics at screening/baseline: d) Summary of total number and type of lesions by location, lesions assessed at Visit 1 and Visit 2; patients requiring 1 - 3 patches

Location	20 ug, N=22	5 ug, N=19	1 ug, N=23	Placebo, N=20	Total, N=84
All sites	38/25/13	27/22/5	42/35/7	42/29/13	149/111/38
Upper Labial Mucosa	1/1/0	0	0	0	1/1/0
Lower Labial Mucosa	1/1/0	2/1/1	1/1/0	1/0/1	5/3/2

Location	20 ug, N=22	5 ug, N=19	1 ug, N=23	Placebo, N=20	Total, N=84
Right Buccal Mucosa	13/9/4	5/4/1	9/5/4	7/5/2	34/23/11
Left Buccal Mucosa	10/4/6	5/5/0	14/13/1	11/10/1	40/32/8
Gingivae: Lower Right (distal)	3/3/0	3/2/1	4/4/0	5/3/2	15/12/3
Gingivae: Lower Central	1/1/0	1/1/0	1/1/0	0	3/3/0
Gingivae: Lower Left (distal)	3/2/1	4/3/1	1/1/0	5/2/3	13/8/5
Gingivae: Upper Right (distal)	2/1/1	0	1/1/0	3/1/2	6/3/3
Gingivae: Upper Central	0	0	3/2/1	2/2/0	5/4/1
Gingivae: Upper Left (distal)	0	1/1/0	1/0/1	4/3/1	6/4/2
Mandibular Lingual Gingivae: Lower Right (distal)	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Central	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Left (distal)	0	0	0	0	0
Dorsum Tongue	1/1/0	0	3/3/0	3/2/1	7/6/1
Right Lateral Ventral Tongue	1/1/0	4/4/0	1/1/0	0	6/6/0
Left Lateral Ventral Tongue	2/1/1	2/1/1	2/2/0	1/1/0	7/5/2
Floor of Mouth	0	0	0	0	0
Hard Palate	0	0	1/1/0	0	1/1/0
Soft Palate	0	0	0	0	0
Numbers are Total lesions/Ulcerative/Erythematous Listing(s): Derived from Listing 16.2.4.3					

Table 14.1.3.5 Summary of lesion characteristics at screening/baseline: e) Location of lesions assessed at Visit 1 and Visit 2; patients requiring 4-6 patches

Location	20 ug, N=11	5 ug, N=15	1 ug, N=17	Placebo, N=11	Total, N=54
Upper Labial Mucosa	1 (9.1)	0	0	1 (9.1)	2 (3.7)
Lower Labial Mucosa	2 (18.2)	2 (13.3)	4 (23.5)	3 (27.3)	11 (20.4)
Right Buccal Mucosa	19 (173)	16 (107)	23 (135)	15 (136)	73 (135)
Left Buccal Mucosa	16 (145)	19 (127)	27 (159)	20 (182)	82 (152)
Gingivae: Lower Right (distal)	8 (72.7)	9 (60.0)	6 (35.3)	9 (81.8)	32 (59.3)
Gingivae: Lower Central	1 (9.1)	3 (20.0)	4 (23.5)	4 (36.4)	12 (22.2)
Gingivae: Lower Left (distal)	4 (36.4)	11 (73.3)	3 (17.6)	7 (63.6)	25 (46.3)
Gingivae: Upper Right (distal)	5 (45.5)	4 (26.7)	4 (23.5)	6 (54.5)	19 (35.2)
Gingivae: Upper Central	1 (9.1)	1 (6.7)	7 (41.2)	7 (63.6)	16 (29.6)
Gingivae: Upper Left (distal)	3 (27.3)	4 (26.7)	5 (29.4)	9 (81.8)	21 (38.9)
Mandibular Lingual Gingivae: Lower Right (distal)	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Central	1 (9.1)	0	0	0	1 (1.9)
Mandibular Lingual Gingivae: Lower Left (distal)	0	0	0	1 (9.1)	1 (1.9)
Dorsum Tongue	2 (18.2)	0	3 (17.6)	5 (45.5)	10 (18.5)
Right Lateral Ventral Tongue	3 (27.3)	8 (53.3)	6 (35.3)	0	17 (31.5)
Left Lateral Ventral Tongue	3 (27.3)	3 (20.0)	8 (47.1)	3 (27.3)	17 (31.5)
Floor of Mouth	0	0	0	0	0
Hard Palate	2 (18.2)	3 (20.0)	1 (5.9)	1 (9.1)	7 (13.0)
Soft Palate	0	0	0	0	0

Numbers are n (%); location counted once within patient
Listing(s): Derived from Listing 16.2.4.3

Table 14.1.3.5 Summary of lesion characteristics at screening/baseline: f) Total number and type of lesions by location, lesions assessed at Visit 1 and Visit 2; patients requiring 4 - 6 patches

Location	20 ug, N=11	5 ug, N=15	1 ug, N=17	Placebo, N=11	Total, N=54
All sites	40/20/20	62/38/24	67/47/20	54/25/29	223/130/93
Upper Labial Mucosa	0	0	0	1/0/1	1/0/1
Lower Labial Mucosa	1/1/0	1/0/1	3/1/2	2/1/1	7/3/4
Right Buccal Mucosa	10/5/5	12/10/2	15/10/5	8/6/2	45/31/14
Left Buccal Mucosa	8/7/1	17/15/2	15/12/3	9/6/3	49/40/9
Gingivae: Lower Right (distal)	5/2/3	6/4/2	3/3/0	4/1/3	18/10/8
Gingivae: Lower Central	0	2/1/1	3/1/2	4/2/2	9/4/5
Gingivae: Lower Left (distal)	1/0/1	7/3/4	2/1/1	2/0/2	12/4/8
Gingivae: Upper Right (distal)	3/2/1	4/1/3	3/2/1	3/1/2	13/6/7
Gingivae: Upper Central	1/0/1	1/0/1	6/4/2	9/1/8	17/5/12
Gingivae: Upper Left (distal)	3/1/2	3/1/2	4/3/1	5/1/4	15/6/9
Mandibular Lingual Gingivae: Lower Right (distal)	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Central	1/0/1	0	0	0	1/0/1
Mandibular Lingual Gingivae: Lower Left (distal)	0	0	0	1/0/1	1/0/1
Dorsum Tongue	2/1/1	0	2/0/2	3/3/0	7/4/3
Right Lateral Ventral Tongue	2/1/1	4/1/3	5/5/0	0	11/7/4
Left Lateral Ventral Tongue	1/0/1	1/0/1	6/5/1	2/2/0	10/7/3
Floor of Mouth	0	0	0	0	0

Location	20 ug, N=11	5 ug, N=15	1 ug, N=17	Placebo, N=11	Total, N=54
Hard Palate	2/0/2	4/2/2	0	1/1/0	7/3/4
Soft Palate	0	0	0	0	0
Numbers are Total lesions/Ulcerative/Erythematous Listing(s): Derived from Listing 16.2.4.3					

Table 14.1.3.5 Summary of lesion characteristics at screening/baseline: g) summary of number of patches assigned to be used at Visit 2 and patients with changes over study period

	no. patched applied						patients with	
Treatment	1	2	3	4	5	6	reduction	increase
20 ug	5 (15.2)	13 (39.4)	4 (12.1)	4 (12.1)	6 (18.2)	1 (3.0)	2 (6.1)	7 (21.2)
5 ug	7 (20.6)	10 (29.4)	2 (5.9)	8 (23.5)	1 (2.9)	6 (17.6)	2 (5.9)	7 (20.6)
1 ug	4 (10.0)	11 (27.5)	8 (20.0)	7 (17.5)	5 (12.5)	5 (12.5)	3 (7.5)	8 (20.0)
Placebo	3 (9.7)	9 (29.0)	8 (25.8)	2 (6.5)	6 (19.4)	3 (9.7)	3 (9.7)	6 (19.4)
Total	19 (13.8)	43 (31.2)	22 (15.9)	21 (15.2)	18 (13.0)	15 (10.9)	10 (7.2)	28 (20.3)
Listing(s): Derived from 16.2.5.1								

Table 14.1.3.6 Summary of medical history

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
ANY MEDICAL HISTORY	31 (94)	28 (82)	36 (90)	29 (94)	124 (90)
VASCULAR DISORDERS	16 (48)	12 (35)	17 (43)	15 (48)	60 (43)
- HYPERTENSION	16 (48)	11 (32)	17 (43)	13 (42)	57 (41)
- AORTIC ARTERIOSCLEROSIS	0	0	1 (3)	0	1 (1)
- DEEP VEIN THROMBOSIS	0	0	0	1 (3)	1 (1)
- DIABETIC VASCULAR DISORDER	0	0	1 (3)	0	1 (1)
- ESSENTIAL HYPERTENSION	0	0	0	1 (3)	1 (1)
- HOT FLUSH	0	1 (3)	0	0	1 (1)
- PERIPHERAL VASCULAR DISORDER	0	0	1 (3)	0	1 (1)
- VARICOSE VEIN	0	0	0	1 (3)	1 (1)
METABOLISM AND NUTRITION DISORDERS	14 (42)	14 (41)	14 (35)	10 (32)	52 (38)
- OBESITY	4 (12)	6 (18)	5 (13)	3 (10)	18 (13)
- TYPE 2 DIABETES MELLITUS	6 (18)	3 (9)	5 (13)	2 (6)	16 (12)
- HYPERCHOLESTEROLAEMIA	3 (9)	1 (3)	3 (8)	3 (10)	10 (7)
- HYPERLIPIDAEMIA	0	5 (15)	4 (10)	1 (3)	10 (7)
- DIABETES MELLITUS	1 (3)	1 (3)	3 (8)	3 (10)	8 (6)
- VITAMIN D DEFICIENCY	1 (3)	1 (3)	2 (5)	0	4 (3)
- DYSLIPIDAEMIA	0	0	2 (5)	1 (3)	3 (2)
- TYPE 1 DIABETES MELLITUS	0	2 (6)	0	0	2 (1)
- VITAMIN B12 DEFICIENCY	0	1 (3)	0	1 (3)	2 (1)

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- FLUID RETENTION	0	1 (3)	0	0	1 (1)
- GLUCOSE TOLERANCE IMPAIRED	0	0	1 (3)	0	1 (1)
- GOUT	0	0	0	1 (3)	1 (1)
- HYPERGLYCAEMIA	1 (3)	0	0	0	1 (1)
- IRON DEFICIENCY	1 (3)	0	0	0	1 (1)
- OVERWEIGHT	0	1 (3)	0	0	1 (1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	7 (21)	15 (44)	15 (38)	10 (32)	47 (34)
- ARTHRITIS	4 (12)	5 (15)	3 (8)	2 (6)	14 (10)
- OSTEOPOROSIS	0	3 (9)	4 (10)	1 (3)	8 (6)
- OSTEOARTHRITIS	0	2 (6)	4 (10)	1 (3)	7 (5)
- ARTHRALGIA	0	3 (9)	0	1 (3)	4 (3)
- OSTEOPENIA	0	0	3 (8)	1 (3)	4 (3)
- BACK PAIN	1 (3)	1 (3)	1 (3)	0	3 (2)
- FIBROMYALGIA	0	0	1 (3)	2 (6)	3 (2)
- SJOGREN'S SYNDROME	1 (3)	0	2 (5)	0	3 (2)
- INTERVERTEBRAL DISC DEGENERATION	1 (3)	0	1 (3)	0	2 (1)
- PLANTAR FASCIITIS	1 (3)	0	1 (3)	0	2 (1)
- ROTATOR CUFF SYNDROME	0	1 (3)	0	1 (3)	2 (1)
- DIABETIC ARTHROPATHY	0	1 (3)	0	0	1 (1)
- LUMBAR SPINAL STENOSIS	0	0	1 (3)	0	1 (1)

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- MORPHOEA	0	1 (3)	0	0	1 (1)
- MUSCLE SPASMS	0	0	0	1 (3)	1 (1)
- MYALGIA	1 (3)	0	0	0	1 (1)
- NECK PAIN	0	1 (3)	0	0	1 (1)
- PAIN IN EXTREMITY	0	1 (3)	0	0	1 (1)
- POLYARTHRITIS	0	0	1 (3)	0	1 (1)
- POLYMYALGIA RHEUMATICA	0	0	1 (3)	0	1 (1)
- PSORIATIC ARTHROPATHY	1 (3)	0	0	0	1 (1)
- SPINAL COLUMN STENOSIS	0	1 (3)	0	0	1 (1)
- SPINAL DEFORMITY	0	1 (3)	0	0	1 (1)
- SPINAL OSTEOARTHRITIS	0	0	1 (3)	0	1 (1)
- SYNOVIAL CYST	0	0	1 (3)	0	1 (1)
- SYSTEMIC LUPUS ERYTHEMATOSUS	0	0	1 (3)	0	1 (1)
- TENDONITIS	1 (3)	0	0	0	1 (1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	11 (33)	10 (29)	10 (25)	10 (32)	41 (30)
- LICHEN PLANUS	5 (15)	2 (6)	2 (5)	4 (13)	13 (9)
- LICHEN SCLEROSUS	2 (6)	4 (12)	4 (10)	3 (10)	13 (9)
- PSORIASIS	2 (6)	1 (3)	3 (8)	3 (10)	9 (7)
- ECZEMA	2 (6)	0	1 (3)	1 (3)	4 (3)
- DRY SKIN	0	0	1 (3)	1 (3)	2 (1)
- ACNE	1 (3)	0	0	0	1 (1)

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- ACTINIC KERATOSIS	0	1 (3)	0	0	1 (1)
- GRANULOMA ANNULARE	0	1 (3)	0	0	1 (1)
- PRURITUS	0	1 (3)	0	0	1 (1)
- URTICARIA	1 (3)	0	0	0	1 (1)
- VITILIGO	0	1 (3)	0	0	1 (1)
GASTROINTESTINAL DISORDERS	8 (24)	7 (21)	18 (45)	7 (23)	40 (29)
- GASTROOESOPHAGEAL REFLUX DISEASE	6 (18)	2 (6)	12 (30)	3 (10)	23 (17)
- CONSTIPATION	1 (3)	0	0	2 (6)	3 (2)
- GASTRITIS	1 (3)	1 (3)	1 (3)	0	3 (2)
- COELIAC DISEASE	0	1 (3)	0	1 (3)	2 (1)
- DRY MOUTH	0	1 (3)	0	1 (3)	2 (1)
- DYSPEPSIA	0	1 (3)	1 (3)	0	2 (1)
- OESOPHAGITIS	0	1 (3)	1 (3)	0	2 (1)
- APTYALISM	0	0	0	1 (3)	1 (1)
- CHRONIC GASTRITIS	0	0	1 (3)	0	1 (1)
- DIAPHRAGMATIC HERNIA	0	0	1 (3)	0	1 (1)
- DIARRHOEA	0	0	0	1 (3)	1 (1)
- DIVERTICULUM	0	0	0	1 (3)	1 (1)
- HIATUS HERNIA	0	0	1 (3)	0	1 (1)
- IMPAIRED GASTRIC EMPTYING	0	1 (3)	0	0	1 (1)
- IRRITABLE BOWEL SYNDROME	0	0	1 (3)	0	1 (1)

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- LARGE INTESTINE POLYP	0	0	1 (3)	0	1 (1)
- PERIODONTAL DISEASE	0	0	1 (3)	0	1 (1)
- RECTAL PROLAPSE	0	1 (3)	0	0	1 (1)
- UPPER GASTROINTESTINAL HAEMORRHAGE	1 (3)	0	0	0	1 (1)
SURGICAL AND MEDICAL PROCEDURES	8 (24)	8 (24)	12 (30)	7 (23)	35 (25)
- HYSTERECTOMY	2 (6)	3 (9)	6 (15)	1 (3)	12 (9)
- CAESAREAN SECTION	1 (3)	0	2 (5)	1 (3)	4 (3)
- CHOLECYSTECTOMY	1 (3)	1 (3)	1 (3)	1 (3)	4 (3)
- INTERVERTEBRAL DISC OPERATION	1 (3)	1 (3)	1 (3)	0	3 (2)
- KNEE OPERATION	1 (3)	1 (3)	1 (3)	0	3 (2)
- APPENDICECTOMY	0	0	1 (3)	1 (3)	2 (1)
- HERNIA REPAIR	1 (3)	0	1 (3)	0	2 (1)
- KNEE ARTHROPLASTY	1 (3)	1 (3)	0	0	2 (1)
- TONSILLECTOMY	0	0	1 (3)	1 (3)	2 (1)
- WRIST SURGERY	1 (3)	0	1 (3)	0	2 (1)
- ANGIOPLASTY	0	0	0	1 (3)	1 (1)
- BONE LESION EXCISION	0	1 (3)	0	0	1 (1)
- BONE OPERATION	1 (3)	0	0	0	1 (1)
- BUNION OPERATION	1 (3)	0	0	0	1 (1)
- CANCER SURGERY	0	1 (3)	0	0	1 (1)
- CORONARY ARTERIAL STENT INSERTION	0	1 (3)	0	0	1 (1)

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- CORONARY ARTERY BYPASS	0	0	1 (3)	0	1 (1)
- FEMALE STERILISATION	1 (3)	0	0	0	1 (1)
- GINGIVAL GRAFT	1 (3)	0	0	0	1 (1)
- HAEMORRHOID OPERATION	0	0	0	1 (3)	1 (1)
- HIP SURGERY	0	0	0	1 (3)	1 (1)
- HYSTEROSALPINGO-OOPHORECTOMY	1 (3)	0	0	0	1 (1)
- LIMB OPERATION	1 (3)	0	0	0	1 (1)
- LIPOMA EXCISION	0	1 (3)	0	0	1 (1)
- LITHOTRIPSY	0	1 (3)	0	0	1 (1)
- MAMMOPLASTY	0	1 (3)	0	0	1 (1)
- MEDICAL DEVICE IMPLANTATION	1 (3)	0	0	0	1 (1)
- NAIL OPERATION	1 (3)	0	0	0	1 (1)
- NASAL SEPTAL OPERATION	0	0	1 (3)	0	1 (1)
- PERINEAL OPERATION	0	0	1 (3)	0	1 (1)
- ROTATOR CUFF REPAIR	0	0	1 (3)	0	1 (1)
- SHOULDER OPERATION	1 (3)	0	0	0	1 (1)
- SPINAL LAMINECTOMY	0	1 (3)	0	0	1 (1)
- STENT PLACEMENT	1 (3)	0	0	0	1 (1)
- THYROIDECTOMY	0	0	0	1 (3)	1 (1)
- TOE OPERATION	1 (3)	0	0	0	1 (1)
- URETHRAL DILATION PROCEDURE	1 (3)	0	0	0	1 (1)

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- WISDOM TEETH REMOVAL	1 (3)	0	0	0	1 (1)
ENDOCRINE DISORDERS	6 (18)	10 (29)	8 (20)	10 (32)	34 (25)
- HYPOTHYROIDISM	5 (15)	7 (21)	7 (18)	10 (32)	29 (21)
- HYPERTHYROIDISM	0	1 (3)	1 (3)	0	2 (1)
- THYROID DISORDER	0	2 (6)	0	0	2 (1)
- AUTOIMMUNE THYROIDITIS	1 (3)	0	0	0	1 (1)
INVESTIGATIONS	8 (24)	7 (21)	11 (28)	5 (16)	31 (22)
- BLOOD CHOLESTEROL INCREASED	6 (18)	3 (9)	6 (15)	4 (13)	19 (14)
- BLOOD POTASSIUM DECREASED	1 (3)	0	2 (5)	0	3 (2)
- BLOOD TRIGLYCERIDES INCREASED	0	2 (6)	0	0	2 (1)
- COLONOSCOPY	0	1 (3)	1 (3)	0	2 (1)
- HEPATIC ENZYME INCREASED	1 (3)	1 (3)	0	0	2 (1)
- ARTHROSCOPY	0	0	1 (3)	0	1 (1)
- BIOPSY BREAST	0	0	1 (3)	0	1 (1)
- BLOOD ALKALINE PHOSPHATASE INCREASED	0	0	1 (3)	0	1 (1)
- BLOOD POTASSIUM INCREASED	1 (3)	0	0	0	1 (1)
- BLOOD URINE PRESENT	0	0	0	1 (3)	1 (1)
- BONE DENSITY ABNORMAL	0	0	1 (3)	0	1 (1)
- GLUCOSE URINE PRESENT	0	1 (3)	0	0	1 (1)
- HAEMOGLOBIN DECREASED	1 (3)	0	0	0	1 (1)
- OESOPHAGOGASTRODUODENOSCOPY	0	1 (3)	0	0	1 (1)

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- PLATELET COUNT DECREASED	1 (3)	0	0	0	1 (1)
PSYCHIATRIC DISORDERS	5 (15)	8 (24)	8 (20)	6 (19)	27 (20)
- DEPRESSION	4 (12)	2 (6)	6 (15)	1 (3)	13 (9)
- ANXIETY	0	4 (12)	0	3 (10)	7 (5)
- INSOMNIA	1 (3)	2 (6)	0	1 (3)	4 (3)
- ANXIETY DISORDER	1 (3)	0	1 (3)	0	2 (1)
- ATTENTION DEFICIT/HYPERACTIVITY DISORDER	1 (3)	0	0	0	1 (1)
- MAJOR DEPRESSION	0	0	1 (3)	0	1 (1)
- MERYCISM	0	0	0	1 (3)	1 (1)
- PERSISTENT DEPRESSIVE DISORDER	0	1 (3)	0	0	1 (1)
- SLEEP DISORDER	0	0	1 (3)	0	1 (1)
NERVOUS SYSTEM DISORDERS	6 (18)	4 (12)	8 (20)	7 (23)	25 (18)
- MIGRAINE	1 (3)	0	3 (8)	2 (6)	6 (4)
- EPILEPSY	1 (3)	1 (3)	0	1 (3)	3 (2)
- HEADACHE	1 (3)	0	0	2 (6)	3 (2)
- NEUROPATHY PERIPHERAL	2 (6)	0	0	0	2 (1)
- POLYNEUROPATHY	0	0	2 (5)	0	2 (1)
- SCIATICA	1 (3)	1 (3)	0	0	2 (1)
- AUTONOMIC NEUROPATHY	0	1 (3)	0	0	1 (1)
- CAROTID ARTERY DISEASE	0	0	1 (3)	0	1 (1)
- CAUDA EQUINA SYNDROME	0	1 (3)	0	0	1 (1)

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- CEREBROVASCULAR ACCIDENT	0	0	1 (3)	0	1 (1)
- DIABETIC NEUROPATHY	0	0	1 (3)	0	1 (1)
- ORTHOSTATIC INTOLERANCE	0	1 (3)	0	0	1 (1)
- TENSION HEADACHE	0	0	0	1 (3)	1 (1)
- TRANSIENT ISCHAEMIC ATTACK	0	0	0	1 (3)	1 (1)
- VOCAL CORD PARALYSIS	0	0	1 (3)	0	1 (1)
- VOCAL CORD PARESIS	0	1 (3)	0	0	1 (1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (15)	8 (24)	8 (20)	4 (13)	25 (18)
- ASTHMA	2 (6)	4 (12)	6 (15)	4 (13)	16 (12)
- CHRONIC OBSTRUCTIVE PULMONARY DISEASE	1 (3)	1 (3)	2 (5)	0	4 (3)
- SLEEP APNOEA SYNDROME	2 (6)	1 (3)	0	0	3 (2)
- RHINITIS ALLERGIC	1 (3)	1 (3)	0	0	2 (1)
- COUGH	0	0	1 (3)	0	1 (1)
- NASAL CONGESTION	0	1 (3)	0	0	1 (1)
IMMUNE SYSTEM DISORDERS	7 (21)	3 (9)	8 (20)	6 (19)	24 (17)
- SEASONAL ALLERGY	6 (18)	2 (6)	7 (18)	5 (16)	20 (14)
- DRUG HYPERSENSITIVITY	1 (3)	1 (3)	1 (3)	1 (3)	4 (3)
- FOOD ALLERGY	0	1 (3)	0	0	1 (1)
- IODINE ALLERGY	0	0	1 (3)	0	1 (1)
CARDIAC DISORDERS	4 (12)	2 (6)	6 (15)	4 (13)	16 (12)
- MYOCARDIAL INFARCTION	2 (6)	0	2 (5)	1 (3)	5 (4)

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- CORONARY ARTERY DISEASE	0	0	2 (5)	1 (3)	3 (2)
- ANGINA PECTORIS	2 (6)	0	0	0	2 (1)
- ATRIAL FIBRILLATION	1 (3)	0	0	1 (3)	2 (1)
- BUNDLE BRANCH BLOCK	0	1 (3)	0	0	1 (1)
- CARDIAC FAILURE CHRONIC	0	0	1 (3)	0	1 (1)
- CARDIOVASCULAR DISORDER	0	0	1 (3)	0	1 (1)
- PAROXYSMAL ARRHYTHMIA	0	0	0	1 (3)	1 (1)
- PERICARDITIS	0	0	0	1 (3)	1 (1)
- SINUS TACHYCARDIA	0	1 (3)	0	0	1 (1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (6)	4 (12)	4 (10)	6 (19)	16 (12)
- VULVOVAGINAL DRYNESS	0	2 (6)	1 (3)	1 (3)	4 (3)
- BENIGN PROSTATIC HYPERPLASIA	0	0	1 (3)	2 (6)	3 (2)
- ENDOMETRIOSIS	0	0	1 (3)	1 (3)	2 (1)
- BREAST MASS	0	0	1 (3)	0	1 (1)
- ERECTILE DYSFUNCTION	0	1 (3)	0	0	1 (1)
- GENITAL DISCOMFORT	0	0	0	1 (3)	1 (1)
- HAEMATOSALPINX	1 (3)	0	0	0	1 (1)
- MENOPAUSAL SYMPTOMS	0	0	0	1 (3)	1 (1)
- PROSTATOMEGALY	0	1 (3)	0	0	1 (1)
- VAGINAL EROSION	1 (3)	0	0	0	1 (1)
EYE DISORDERS	4 (12)	1 (3)	3 (8)	4 (13)	12 (9)

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- DRY EYE	0	0	2 (5)	2 (6)	4 (3)
- GLAUCOMA	1 (3)	0	1 (3)	0	2 (1)
- BLEPHARITIS	0	1 (3)	0	0	1 (1)
- MACULAR DEGENERATION	1 (3)	0	0	0	1 (1)
- MYOPIA	1 (3)	0	0	0	1 (1)
- NORMAL TENSION GLAUCOMA	0	0	0	1 (3)	1 (1)
- OPTIC NEUROPATHY	1 (3)	0	0	0	1 (1)
- RETINAL DETACHMENT	0	0	0	1 (3)	1 (1)
- RETINAL DISORDER	0	0	1 (3)	0	1 (1)
INFECTIONS AND INFESTATIONS	3 (9)	2 (6)	3 (8)	1 (3)	9 (7)
- ORAL CANDIDIASIS	1 (3)	0	1 (3)	0	2 (1)
- ORAL HERPES	1 (3)	1 (3)	0	0	2 (1)
- GENITAL HERPES	0	1 (3)	0	0	1 (1)
- HEPATITIS A	0	0	1 (3)	0	1 (1)
- HEPATITIS C	0	0	1 (3)	0	1 (1)
- ONYCHOMYCOSIS	0	0	1 (3)	0	1 (1)
- PERIODONTITIS	0	0	0	1 (3)	1 (1)
- STAPHYLOCOCCAL INFECTION	1 (3)	0	0	0	1 (1)
- URINARY TRACT INFECTION	1 (3)	0	0	0	1 (1)
SOCIAL CIRCUMSTANCES	1 (3)	3 (9)	1 (3)	4 (13)	9 (7)
- POSTMENOPAUSE	1 (3)	3 (9)	0	3 (10)	7 (5)

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
- MENOPAUSE	0	0	1 (3)	1 (3)	2 (1)
RENAL AND URINARY DISORDERS	2 (6)	2 (6)	3 (8)	1 (3)	8 (6)
- HYPERTONIC BLADDER	0	0	2 (5)	1 (3)	3 (2)
- INCONTINENCE	1 (3)	1 (3)	0	0	2 (1)
- NEPHROLITHIASIS	1 (3)	1 (3)	0	0	2 (1)
- CHRONIC KIDNEY DISEASE	0	0	1 (3)	0	1 (1)
- MICROALBUMINURIA	0	0	1 (3)	0	1 (1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1 (3)	5 (13)	0	6 (4)
- BENIGN NEOPLASM OF THYROID GLAND	0	0	3 (8)	0	3 (2)
- BASAL CELL CARCINOMA	0	0	2 (5)	0	2 (1)
- BENIGN OVARIAN TUMOUR	0	1 (3)	0	0	1 (1)
- MALIGNANT MELANOMA	0	0	1 (3)	0	1 (1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	2 (6)	2 (5)	1 (3)	5 (4)
- ANAEMIA	0	0	1 (3)	1 (3)	2 (1)
- IRON DEFICIENCY ANAEMIA	0	2 (6)	0	0	2 (1)
- PLASMACYTOSIS	0	0	1 (3)	0	1 (1)
EAR AND LABYRINTH DISORDERS	1 (3)	1 (3)	2 (5)	1 (3)	5 (4)
- VERTIGO	0	1 (3)	1 (3)	1 (3)	3 (2)
- DEAFNESS NEUROSENSORY	1 (3)	0	0	0	1 (1)
- DEAFNESS UNILATERAL	0	0	1 (3)	0	1 (1)

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
HEPATOBILIARY DISORDERS	2 (6)	0	3 (8)	0	5 (4)
- HEPATIC STEATOSIS	1 (3)	0	2 (5)	0	3 (2)
- HEPATIC FIBROSIS	1 (3)	0	0	0	1 (1)
- NON-ALCOHOLIC FATTY LIVER	0	0	1 (3)	0	1 (1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	2 (6)	2 (5)	1 (3)	5 (4)
- CONCUSSION	0	1 (3)	0	0	1 (1)
- DENTAL RESTORATION FAILURE	0	1 (3)	0	0	1 (1)
- JAW FRACTURE	0	0	0	1 (3)	1 (1)
- JOINT DISLOCATION	0	0	1 (3)	0	1 (1)
- LIGAMENT RUPTURE	0	0	1 (3)	0	1 (1)
- LOWER LIMB FRACTURE	0	0	1 (3)	0	1 (1)
- MENISCUS INJURY	0	0	1 (3)	0	1 (1)
- POST CONCUSSION SYNDROME	0	0	1 (3)	0	1 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (3)	1 (3)	1 (3)	1 (3)	4 (3)
- CHEST PAIN	0	1 (3)	1 (3)	0	2 (1)
- PAIN	1 (3)	0	0	1 (3)	2 (1)
- ACCESSORY CARPAL BONE	0	1 (3)	0	0	1 (1)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	1 (3)	0	0	1 (1)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1 (3)	0	0	0	1 (1)
- ECTOPIC PREGNANCY	1 (3)	0	0	0	1 (1)

System Organ Class/Preferred term	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138
Listing(s): Derived from Listing 16.2.4.3					

Table 14.1.3.7 Summary of compliance

a) Drug compliance (%) based on number of patches dispensed and returned

Period	Stats	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Week 1	N	33	34	40	31	138
	Used patches, median	32	35	51	42	42
	Range	10, 108	10, 84	8 , 95	12, 108	8 , 108
	Compliance, median	100	100	100	100	100
	Range	9.3, 279	79, 179	46, 226	22, 207	9.3, 279
	Total dose, median	640	175	51	0	
	Range	200, 2160	50, 420	8 , 95	0 , 0	
	Daily dose, median	97	26	6.4	0	
	Range	2 , 223	9.3, 60	1 , 13.6	0 , 0	
Week 2	N	31	34	35	26	126
	Used patches, median	39	40	43	55	43
	Range	14, 77	11, 96	8 , 108	12, 108	8 , 108
	Compliance, median	100	103	100	106	100
	Range	22, 161	79, 133	71, 117	71, 129	22, 161

Period	Stats	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
	Total dose, median	780	188	43	0	
	Range	280, 1540	55, 480	8 , 1340	0 , 0	
	Daily dose, median	91	22	6.1	0	
	Range	34, 270	9.3, 64.3	1.8, 191	0 , 0	
Week 3	N	30	33	36	27	126
	Used patches, median	44	42	45	44	44
	Range	8 , 78	9 , 84	9 , 84	14, 108	8 , 108
	Compliance, median	100	100	100	100	100
	Range	43, 133	60, 131	64, 110	96, 147	43, 147
	Total dose, median	870	200	45	0	
	Range	160, 1560	45, 420	9 , 84	0 , 0	
	Daily dose, median	109	30	6.4	0	
	Range	23, 260	9 , 60	1.8, 12	0 , 0	
Week 4	N	28	32	35	27	122
	Used patches, median	43	40	43	41	42
	Range	9 , 84	13, 90	11, 84	14, 90	9 , 90
	Compliance, median	100	100	100	100	100
	Range	75, 257	36, 233	26, 107	43, 136	26, 257
	Total dose, median	860	178	43	0	
	Range	180, 1680	65, 450	11, 84	0 , 0	
	Daily dose, median	128	23	6.1	0	

Period	Stats	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
	Range	40, 264	10, 60	0.2, 12	0 , 0	
Total	N	33	34	40	31	138
	Used patches, median	151	162	172	163	165
	Range	10, 324	46, 342	8 , 341	12, 384	8 , 384
	Compliance, median	100	102	100	100	100
	Range	9.3, 159	71, 134	50, 143	22, 136	9.3, 159
	Total dose, median	3020	735	172	0	
	Range	200, 6480	230, 1710	8 , 1469	0 , 0	
	Daily dose, median	108	26	6.5	0	
	Range	2 , 231	10, 61.1	1 , 70	0 , 0	

Listing(s): Derived from 16.2.5.1

Table 14.1.3.7 Summary of compliance b) Diary compliance (%)

		Days recorded			Compliance (%)	
Treatment	**Period**	**N**	**Median**	**Range**	**Median**	**Range**
20 ug	Run-in	25	8	5, 14	100	82.4, 100.0
	Treatment	25	28	2, 34	96.6	2.0, 100.0
5 ug	Run-in	30	7	6, 15	100	35.0, 100.0
	Treatment	30	29	15, 35	96.8	93.1, 100.0
1 ug	Run-in	34	7	6, 18	100	90.0, 100.0
	Treatment	34	29	4, 32	96.6	44.4, 100.0
Placebo	Run-in	27	7	0, 26	100	0.0, 100.0
	Treatment	27	28	3, 33	96.6	27.6, 100.0
Total	Run-in	116	7	0, 26	100	0.0, 100.0
	Treatment	116	29	2, 35	96.7	2.0, 100.0

Listing(s): Derived from 16.2.5.1

Table 14.1.3.7 Summary of compliance c) Summary of drug compliance (%) based on number of patches used and recorded in diary

		Treatment				
Period	**Stats**	**20 ug, N=33**	**5 ug, N=34**	**1 ug, N=40**	**Placebo, N=31**	**Total**
Total study	n	33	34	40	30	137
Total study	Used patches, median	110	157.5	155	136	140
Total study	range	4, 318	38, 342	8, 341	12, 336	4, 342
Total study	Compliance, median	96.6	100	100	100	100
Total study	range	5.6, 103	35, 106	43, 102	3.7, 103	3.7, 106
Listing(s): Derived from 16.2.5.1						

14.2 Efficacy Data

14.2.1 Ulcer area, lesion area, cleared ulcers, cleared lesions, additional lesions

Table 14.2.1.1 Summary of lesion and ulcer areas by treatment group and visit, [FAS]

a) ulcer size (cm2)

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	31	34	40	31
	Mean(SD)	0.585 (0.84)	1.476 (2.69)	0.556 (0.57)	0.630 (1.29)
	Median	0.250	0.410	0.390	0.180
	Min, Max	0.02-3.21	0.01-12.02	0.01-2.55	0.03-6.17
Week 1	n	30	34	39	31
	Mean(SD)	0.340 (0.55)	1.063 (2.52)	0.466 (0.69)	0.588 (1.30)
	Median	0.080	0.090	0.240	0.120
	Min, Max	0.00-2.11	0.00-10.35	0.00-2.58	0.00-5.15
Change from baseline Week 1	n	30	34	39	31
	Mean(SD)	-0.260 (0.52)	-0.413 (1.21)	-0.104 (0.43)	-0.042 (0.53)
	Median	-0.130	-0.135	-0.090	-0.040
	Min, Max	-2.08-0.83	-6.27-1.97	-1.13-1.09	-1.94-1.31
Week 2	n	29	34	37	28
	Mean(SD)	0.270 (0.56)	0.993 (2.48)	0.447 (0.99)	0.806 (2.18)
	Median	0.030	0.060	0.070	0.045
	Min, Max	0.00-2.49	0.00-10.50	0.00-5.06	0.00-9.70

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Change from baseline Week 2	n	29	34	37	28
	Mean(SD)	-0.345 (0.52)	-0.483 (1.32)	-0.065 (0.96)	0.118 (0.85)
	Median	-0.180	-0.175	-0.180	-0.080
	Min, Max	-2.44-0.35	-6.39-2.12	-1.58-4.87	-0.52-3.53
Week 3	n	27	33	36	27
	Mean(SD)	0.222 (0.39)	0.806 (2.22)	0.438 (0.95)	0.791 (2.16)
	Median	0.020	0.050	0.100	0.010
	Min, Max	0.00-1.44	0.00-10.00	0.00-4.17	0.00-8.92
Change from baseline Week 3	n	27	33	36	27
	Mean(SD)	-0.401 (0.65)	-0.677 (1.29)	-0.084 (0.87)	0.105 (1.03)
	Median	-0.200	-0.300	-0.175	-0.100
	Min, Max	-2.71-0.31	-6.45-0.02	-1.54-3.50	-0.60-5.08
Week 4	n	28	33	35	27
	Mean(SD)	0.150 (0.29)	0.722 (1.98)	0.307 (0.72)	0.760 (1.76)
	Median	0.000	0.020	0.030	0.020
	Min, Max	0.00-1.14	0.00-9.17	0.00-3.76	0.00-7.78
Change from baseline Week 4	n	28	33	35	27
	Mean(SD)	-0.462 (0.67)	-0.761 (1.62)	-0.218 (0.78)	0.075 (0.88)
	Median	-0.230	-0.170	-0.230	-0.080
	Min, Max	-2.76-0.20	-6.45-0.79	-1.66-3.51	-1.28-3.94

Listing(s): Derived from Listing 16.2.6

Table 14.2.1.1 Summary of lesion and ulcer areas by treatment group and visit, [FAS]: b) ulcer size (% changes)

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Week 1	n	30	34	39	31
	Mean(SD)	-30.1 (124.94)	-44.4 (64.04)	-9.8 (134.45)	-4.1 (147.05)
	Median	-68.2	-43.5	-42.9	-57.1
	Min, Max	-100.00-488.24	-100.00-233.33	-100.00-573.68	-100.00-600.00
Week 2	n	29	34	37	28
	Mean(SD)	-68.7 (38.91)	-38.9 (136.74)	48.9 (463.22)	-54.7 (57.32)
	Median	-83.3	-72.8	-81.6	-78.8
	Min, Max	-100.00-52.24	-100.00-700.00	-100.00-2563.16	-100.00-77.78
Week 3	n	27	33	36	27
	Mean(SD)	-49.4 (99.29)	-69.3 (40.37)	-1.0 (256.80)	-50.2 (72.69)
	Median	-84.4	-77.8	-68.4	-95.5
	Min, Max	-100.00-300.00	-100.00-66.67	-100.00-1400.00	-100.00-150.00
Week 4	n	28	33	35	27
	Mean(SD)	-54.4 (127.75)	-75.8 (33.89)	-12.5 (257.79)	-12.3 (188.04)
	Median	-100.0	-93.5	-89.6	-93.9
	Min, Max	-100.00-500.00	-100.00-9.43	-100.00-1404.00	-100.00-800.00
Listing(s): Derived from Listing 16.2.6.1					

Table 14.2.1.1 Summary of lesion and ulcer areas by treatment group and visit, [FAS]: c) lesion size (cm2)

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	32	34	40	31
	Mean(SD)	6.472 (5.82)	7.764 (6.82)	6.846 (5.36)	8.840 (13.22)
	Median	4.780	5.560	5.010	4.710
	Min, Max	0.48-23.01	0.24-25.92	1.20-25.29	0.15-67.20
Week 1	n	31	34	39	31
	Mean(SD)	4.515 (5.42)	5.938 (6.80)	5.806 (5.30)	6.535 (8.54)
	Median	2.400	3.855	4.240	3.640
	Min, Max	0.00-21.62	0.00-31.01	0.00-22.40	0.20-37.85
Change from baseline Week 1	n	31	34	39	31
	Mean(SD)	-2.014 (2.25)	-1.826 (3.39)	-1.054 (3.38)	-2.306 (7.80)
	Median	-1.370	-1.000	-0.640	-0.290
	Min, Max	-7.30-0.10	-11.43-5.09	-17.50-6.04	-42.45-3.50
Week 2	n	30	34	37	28
	Mean(SD)	4.252 (4.69)	5.967 (5.90)	4.774 (4.62)	7.150 (12.27)
	Median	2.565	3.490	2.300	2.955
	Min, Max	0.00-15.21	0.01-26.79	0.00-16.20	0.00-58.25
Change from baseline Week 2	n	30	34	37	28
	Mean(SD)	-2.464 (2.66)	-1.797 (3.85)	-1.797 (3.58)	-1.976 (2.77)
	Median	-1.530	-1.315	-1.540	-0.980
	Min, Max	-8.61-1.91	-11.89-5.90	-17.50-5.05	-8.95-3.84

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Week 3	n	28	33	36	27
	Mean(SD)	4.206 (5.17)	5.905 (7.25)	4.482 (4.46)	7.809 (13.33)
	Median	1.715	3.380	3.100	3.000
	Min, Max	0.00-20.93	0.00-30.36	0.00-16.63	0.00-59.80
Change from baseline Week 3	n	28	33	36	27
	Mean(SD)	-2.789 (3.31)	-1.958 (3.84)	-1.965 (4.31)	-1.481 (4.46)
	Median	-1.830	-1.430	-2.235	-1.080
	Min, Max	-10.13-3.68	-13.20-7.25	-17.50-8.05	-10.27-14.94
Week 4	n	29	33	35	27
	Mean(SD)	3.342 (4.12)	5.366 (6.74)	4.571 (5.05)	7.466 (15.08)
	Median	1.420	2.880	2.660	3.000
	Min, Max	0.00-12.17	0.00-28.18	0.00-16.95	0.00-73.50
Change from baseline Week 4	n	29	33	35	27
	Mean(SD)	-3.487 (3.40)	-2.497 (4.32)	-1.880 (4.14)	-1.824 (3.96)
	Median	-2.100	-2.190	-1.700	-1.600
	Min, Max	-11.79-3.05	-14.10-12.50	-17.50-10.55	-9.31-6.76

Listing(s): Derived from Listing 16.2.6

Table 14.2.1.1 Summary of lesion and ulcer areas by treatment group and visit, [FAS]: d) lesion size (% changes)

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Week 1	n	31	34	39	31
	Mean(SD)	-35.6 (33.39)	-24.9 (36.53)	-12.8 (35.78)	-14.3 (41.05)
	Median	-31.0	-20.7	-11.4	-12.4
	Min, Max	-100.00-8.70	-100.00-56.00	-100.00-56.76	-87.79-81.35
Week 2	n	30	34	37	28
	Mean(SD)	-42.5 (34.48)	-9.7 (68.03)	-29.3 (39.20)	-26.8 (38.55)
	Median	-37.4	-33.8	-32.2	-25.3
	Min, Max	-100.00-26.90	-99.81-200.00	-100.00-81.45	-100.00-78.37
Week 3	n	28	33	36	27
	Mean(SD)	-50.4 (38.85)	-29.9 (52.16)	-23.1 (81.52)	-30.3 (54.17)
	Median	-48.4	-34.7	-48.1	-42.3
	Min, Max	-100.00-36.13	-100.00-166.67	-100.00-348.65	-100.00-127.26
Week 4	n	29	33	35	27
	Mean(SD)	-57.4 (36.27)	-33.6 (68.01)	-25.6 (68.95)	-26.5 (59.42)
	Median	-54.5	-43.7	-47.2	-42.3
	Min, Max	-100.00-42.96	-100.00-224.82	-100.00-185.81	-100.00-100.00
Listing(s): Derived from Listing 16.2.6.1					

Table 14.2.1.2 Statistical analysis of ulcer area [FAS]: ulcer size (cm2)

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-0.333	20 ug vs placebo	-0.216	(-0.569, 0.137)	0.2291
	5 ug	-0.357	5 ug vs placebo	-0.240	(-0.587, 0.107)	0.1741
	1 ug	-0.191	1 ug vs placebo	-0.073	(-0.403, 0.257)	0.6614
	Placebo	-0.118				
Week 2	20 ug	-0.403	20 ug vs placebo	-0.420	(-0.906, 0.066)	0.0894
	5 ug	-0.487	5 ug vs placebo	-0.504	(-0.982, -0.026)	0.0388
	1 ug	-0.144	1 ug vs placebo	-0.161	(-0.615, 0.293)	0.4836
	Placebo	0.017				
Week 3	20 ug	-0.367	20 ug vs placebo	-0.416	(-0.880, 0.048)	0.0786
	5 ug	-0.491	5 ug vs placebo	-0.540	(-0.997, -0.084)	0.0207
	1 ug	-0.074	1 ug vs placebo	-0.124	(-0.557, 0.310)	0.5733
	Placebo	0.049				
Week 4	20 ug	-0.509	20 ug vs placebo	-0.485	(-0.936, -0.033)	0.0356
	5 ug	-0.502	5 ug vs placebo	-0.478	(-0.922, -0.034)	0.0350
	1 ug	-0.287	1 ug vs placebo	-0.263	(-0.685, 0.159)	0.2197
	Placebo	-0.024				
Week 3-4	20 ug	-0.438	20 ug vs placebo	-0.450	(-0.894, -0.007)	0.0468
	5 ug	-0.497	5 ug vs placebo	-0.509	(-0.945, -0.073)	0.0226
	1 ug	-0.181	1 ug vs placebo	-0.193	(-0.608, 0.221)	0.3579
	Placebo	0.013				

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.1						

Table 14.2.1.3 Statistical analysis of ulcer area [PPS]: ulcer size (cm2)

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-0.289	20 ug vs placebo	-0.248	(-0.548, 0.052)	0.1040
	5 ug	-0.232	5 ug vs placebo	-0.191	(-0.479, 0.096)	0.1906
	1 ug	-0.088	1 ug vs placebo	-0.047	(-0.324, 0.230)	0.7370
	Placebo	-0.041				
Week 2	20 ug	-0.370	20 ug vs placebo	-0.493	(-0.979, -0.006)	0.0471
	5 ug	-0.326	5 ug vs placebo	-0.448	(-0.914, 0.018)	0.0595
	1 ug	-0.045	1 ug vs placebo	-0.167	(-0.616, 0.282)	0.4630
	Placebo	0.122				
Week 3	20 ug	-0.305	20 ug vs placebo	-0.446	(-0.921, 0.028)	0.0649
	5 ug	-0.351	5 ug vs placebo	-0.493	(-0.948, -0.038)	0.0341
	1 ug	0.052	1 ug vs placebo	-0.090	(-0.528, 0.349)	0.6855
	Placebo	0.142				
Week 4	20 ug	-0.483	20 ug vs placebo	-0.529	(-1.008, -0.050)	0.0308
	5 ug	-0.404	5 ug vs placebo	-0.451	(-0.911, 0.009)	0.0544
	1 ug	-0.202	1 ug vs placebo	-0.249	(-0.692, 0.194)	0.2675
	Placebo	0.047				

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 3-4	20 ug	-0.394	20 ug vs placebo	-0.488	(-0.947, -0.029)	0.0374
	5 ug	-0.378	5 ug vs placebo	-0.472	(-0.912, -0.032)	0.0359
	1 ug	-0.075	1 ug vs placebo	-0.169	(-0.593, 0.255)	0.4301
	Placebo	0.094				
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.1						

Table 14.2.1.4 Statistical analysis of ulcer area (relative changes) [FAS]: relative change in ulcer size (%)

Variable	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-26.1	20 ug vs placebo	-27.9	(-102.8, 47.0)	0.4628
	5 ug	-40.3	5 ug vs placebo	-42.0	(-115.7, 31.6)	0.2607
	1 ug	13.4	1 ug vs placebo	11.6	(-58.4, 81.5)	0.7436
	Placebo	1.8				
Week 2	20 ug	-43.1	20 ug vs placebo	1.3	(-133.3, 135.9)	0.9849
	5 ug	-32.9	5 ug vs placebo	11.5	(-120.8, 143.8)	0.8639
	1 ug	41.4	1 ug vs placebo	85.7	(-39.9, 211.4)	0.1794
	Placebo	-44.3				
Week 3	20 ug	-24.3	20 ug vs placebo	17.6	(-61.8, 97.1)	0.6610
	5 ug	-63.2	5 ug vs placebo	-21.2	(-99.3, 56.9)	0.5917
	1 ug	1.3	1 ug vs placebo	43.3	(-30.9, 117.5)	0.2504
	Placebo	-42.0				
Week 4	20 ug	-27.2	20 ug vs placebo	-22.2	(-112.5, 68.1)	0.6268

Variable	Treatment	Estimate	Contrast	Difference	95% CI	p-value
	5 ug	-63.2	5 ug vs placebo	-58.2	(-146.9, 30.6)	0.1971
	1 ug	-6.1	1 ug vs placebo	-1.1	(-85.4, 83.2)	0.9793
	Placebo	-5.0				
Week 3-4	20 ug	-25.8	20 ug vs placebo	-2.3	(-83.6, 79.0)	0.9554
	5 ug	-63.2	5 ug vs placebo	-39.7	(-119.6, 40.2)	0.3273
	1 ug	-2.4	1 ug vs placebo	21.1	(-54.8, 97.0)	0.5833
	Placebo	-23.5				
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.1						

Table 14.2.1.5 Statistical analysis of lesion area [FAS]: lesion size (cm2)

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-2.589	20 ug vs placebo	-0.552	(-2.348, 1.244)	0.5439
	5 ug	-2.150	5 ug vs placebo	-0.113	(-1.867, 1.641)	0.8986
	1 ug	-1.691	1 ug vs placebo	0.346	(-1.352, 2.044)	0.6876
	Placebo	-2.037				
Week 2	20 ug	-2.532	20 ug vs placebo	-0.956	(-2.383, 0.472)	0.1878
	5 ug	-1.698	5 ug vs placebo	-0.121	(-1.516, 1.273)	0.8634
	1 ug	-1.795	1 ug vs placebo	-0.219	(-1.569, 1.131)	0.7485
	Placebo	-1.576				
Week 3	20 ug	-2.651	20 ug vs placebo	-1.576	(-3.442, 0.290)	0.0971
	5 ug	-1.599	5 ug vs placebo	-0.524	(-2.347, 1.298)	0.5702

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
	1 ug	-1.699	1 ug vs placebo	-0.624	(-2.388, 1.140)	0.4854
	Placebo	-1.075				
Week 4	20 ug	-3.208	20 ug vs placebo	-1.794	(-3.768, 0.179)	0.0743
	5 ug	-2.074	5 ug vs placebo	-0.660	(-2.588, 1.267)	0.4991
	1 ug	-1.448	1 ug vs placebo	-0.034	(-1.900, 1.832)	0.9714
	Placebo	-1.414				
Week 3-4	20 ug	-2.931	20 ug vs placebo	-1.687	(-3.487, 0.114)	0.0661
	5 ug	-1.836	5 ug vs placebo	-0.592	(-2.351, 1.166)	0.5064
	1 ug	-1.573	1 ug vs placebo	-0.329	(-2.031, 1.373)	0.7028
	Placebo	-1.244				
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.1						

Table 14.2.1.6 Statistical analysis of lesion area [PPS]: lesion size (cm2)

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-2.374	20 ug vs placebo	-0.044	(-2.023, 1.935)	0.9651
	5 ug	-2.246	5 ug vs placebo	0.084	(-1.798, 1.967)	0.9293
	1 ug	-1.886	1 ug vs placebo	0.444	(-1.383, 2.272)	0.6308
	Placebo	-2.330				

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 2	20 ug	-2.751	20 ug vs placebo	-1.175	(-2.698, 0.348)	0.1292
	5 ug	-2.028	5 ug vs placebo	-0.452	(-1.901, 0.997)	0.5374
	1 ug	-2.175	1 ug vs placebo	-0.598	(-2.005, 0.808)	0.4008
	Placebo	-1.576				
Week 3	20 ug	-2.578	20 ug vs placebo	-1.936	(-3.923, 0.051)	0.0561
	5 ug	-1.781	5 ug vs placebo	-1.139	(-3.029, 0.751)	0.2349
	1 ug	-1.886	1 ug vs placebo	-1.244	(-3.079, 0.591)	0.1819
	Placebo	-0.642				
Week 4	20 ug	-3.438	20 ug vs placebo	-2.591	(-4.739, -0.442)	0.0186
	5 ug	-2.266	5 ug vs placebo	-1.419	(-3.462, 0.625)	0.1716
	1 ug	-1.678	1 ug vs placebo	-0.830	(-2.814, 1.154)	0.4087
	Placebo	-0.847				
Week 3-4	20 ug	-3.008	20 ug vs placebo	-2.263	(-4.185, -0.342)	0.0214
	5 ug	-2.023	5 ug vs placebo	-1.279	(-3.106, 0.549)	0.1683
	1 ug	-1.782	1 ug vs placebo	-1.037	(-2.812, 0.738)	0.2493
	Placebo	-0.745				

Analysis performed by PROC MIXED.
Listing(s): Derived from 16.2.6.1

Table 14.2.1.7 Statistical analysis of lesion area (relative changes) [FAS]: relative change in lesion size (%)

Variable	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-37.0	20 ug vs placebo	-21.6	(-39.0, -4.2)	0.0152
	5 ug	-27.9	5 ug vs placebo	-12.4	(-29.5, 4.6)	0.1499
	1 ug	-16.5	1 ug vs placebo	-1.1	(-17.5, 15.4)	0.8979
	Placebo	-15.4				
Week 2	20 ug	-36.5	20 ug vs placebo	-15.8	(-39.7, 8.1)	0.1925
	5 ug	-5.1	5 ug vs placebo	15.6	(-7.7, 38.9)	0.1878
	1 ug	-23.0	1 ug vs placebo	-2.3	(-24.9, 20.2)	0.8393
	Placebo	-20.7				
Week 3	20 ug	-33.9	20 ug vs placebo	-18.0	(-46.9, 10.9)	0.2196
	5 ug	-12.1	5 ug vs placebo	3.8	(-24.4, 32.0)	0.7910
	1 ug	-6.8	1 ug vs placebo	9.1	(-18.3, 36.4)	0.5133
	Placebo	-15.9				
Week 4	20 ug	-40.6	20 ug vs placebo	-29.6	(-59.7, 0.5)	0.0537
	5 ug	-16.1	5 ug vs placebo	-5.1	(-34.5, 24.3)	0.7310
	1 ug	-7.8	1 ug vs placebo	3.1	(-25.3, 31.6)	0.8286
	Placebo	-11.0				
Week 3-4	20 ug	-37.3	20 ug vs placebo	-23.9	(-51.5, 3.7)	0.0889
	5 ug	-14.1	5 ug vs placebo	-0.7	(-27.6, 26.3)	0.9611
	1 ug	-7.3	1 ug vs placebo	6.1	(-20.0, 32.2)	0.6454
	Placebo	-13.4				

Variable	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.1						

Table 14.2.1.8 Summary of number of cleared ulcers/lesions [FAS]

a) patients with cleared ulcers (size 0 cm2) by visit

Variable	20 ug	5 ug	1 ug	Placebo
Week 1	9/30 (30.0)	10/34 (29.4)	11/39 (28.2)	12/31 (38.7)
Week 2	11/29 (37.9)	13/34 (38.2)	12/37 (32.4)	12/28 (42.9)
Week 3	11/27 (40.7)	13/33 (39.4)	10/36 (27.8)	13/27 (48.1)
Week 4	15/28 (53.6)	15/33 (45.5)	13/35 (37.1)	13/27 (48.1)
Follow up	13/28 (46.4)	11/33 (33.3)	10/34 (29.4)	12/26 (46.2)
Last on treatmen	16/30 (53.3)	15/34 (44.1)	14/40 (35.0)	14/31 (45.2)
During treatment	18/30 (60.0)	20/34 (58.8)	17/40 (42.5)	18/31 (58.1)
Last on-treatment=Last assessment in treatment period During treatment=Minimum value during treatment period Listing(s): Derived from 16.2.6.1				

Table 14.2.1.8 Summary of number of cleared ulcers/lesions [FAS]:

b) patients with cleared lesions (size 0 cm2) by visit

Variable	20 ug	5 ug	1 ug	Placebo
Week 1	2/31 (6.5)	1/34 (2.9)	1/39 (2.6)	0/31 (0.0)
Week 2	1/30 (3.3)	0/34 (0.0)	2/37 (5.4)	2/28 (7.1)
Week 3	3/28 (10.7)	2/33 (6.1)	2/36 (5.6)	2/27 (7.4)
Week 4	3/29 (10.3)	3/33 (9.1)	3/35 (8.6)	2/27 (7.4)
Follow up	3/29 (10.3)	1/33 (3.0)	2/34 (5.9)	1/26 (3.8)
Last on treatmen	3/31 (9.7)	3/34 (8.8)	3/40 (7.5)	2/31 (6.5)
During treatment	6/31 (19.4)	4/34 (11.8)	3/40 (7.5)	2/31 (6.5)
Last on-treatment=Last assessment in treatment period During treatment=Minimum value during treatment period Listing(s): Derived from 16.2.6.1				

Table 14.2.1.9 Statistical analysis of cleared ulcers/lesions [FAS]

a) proportion of patients with cleared ulcers, logistic regression

Variable	Treatment	Estimate	Contrast	Ratio	95% CI	pval
Last on treatment	Placebo	1.06	20 ug vs placebo	1.41	(0.510, 3.890)	0.5115
		0.76	5 ug vs placebo	1.01	(0.370, 2.710)	0.9894
		0.51	1 ug vs placebo	0.68	(0.260, 1.780)	0.4276
		0.75				
Any during treatment	Placebo	1.37	20 ug vs placebo	1.10	(0.390, 3.100)	0.8616
		1.38	5 ug vs placebo	1.11	(0.400, 3.030)	0.8430
		0.69	1 ug vs placebo	0.55	(0.210, 1.450)	0.2279
		1.25				
Analysis performed by PROC GENMOD. Listing(s): Derived from 16.2.6.1						

Table 14.2.1.9 Statistical analysis of cleared ulcers/lesions [FAS]:

b) proportion of patients with cleared lesions, logistic regression

Variable	Treatment	Estimate	Contrast	Ratio	95% CI	pval
Last on treatment	Placebo	0.08	20 ug vs placebo	1.56	(0.240, 10.220)	0.6404
		0.08	5 ug vs placebo	1.54	(0.240, 10.050)	0.6529
		0.06	1 ug vs placebo	1.26	(0.190, 8.190)	0.8064
		0.05				
Any during treatment	Placebo	0.19	20 ug vs placebo	3.57	(0.650, 19.570)	0.1431
		0.11	5 ug vs placebo	2.12	(0.350, 12.680)	0.4106
		0.07	1 ug vs placebo	1.26	(0.190, 8.130)	0.8104
		0.05				
Analysis performed by PROC GENMOD. Listing(s): Derived from 16.2.6.1						

Table 14.2.1.10 Summary of additional lesions identified during visits 3 - 7 [FAS]

a) location of lesions identified at Visit 3 - 6

Location	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Upper Labial Mucosa	0	0	2 (5.0)	0	2 (1.4)
Lower Labial Mucosa	0	1 (2.9)	0	0	1 (0.7)
Right Buccal Mucosa	3 (9.1)	2 (5.9)	2 (5.0)	3 (9.7)	10 (7.2)
Left Buccal Mucosa	2 (6.1)	4 (11.8)	4 (10.0)	1 (3.2)	11 (8.0)
Gingivae: Lower Right (distal)	2 (6.1)	0	1 (2.5)	2 (6.5)	5 (3.6)
Gingivae: Lower Central	0	0	0	0	0
Gingivae: Lower Left (distal)	1 (3.0)	1 (2.9)	0	2 (6.5)	4 (2.9)
Gingivae: Upper Right (distal)	1 (3.0)	4 (11.8)	1 (2.5)	1 (3.2)	7 (5.1)
Gingivae: Upper Central	0	0	0	1 (3.2)	1 (0.7)
Gingivae: Upper Left (distal)	0	3 (8.8)	2 (5.0)	0	5 (3.6)
Mandibular Lingual Gingivae: Lower Right (distal)	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Central	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Left (distal)	0	0	0	0	0
Dorsum Tongue	0	1 (2.9)	0	1 (3.2)	2 (1.4)
Right Lateral Ventral Tongue	1 (3.0)	0	0	2 (6.5)	3 (2.2)
Left Lateral Ventral Tongue	1 (3.0)	2 (5.9)	2 (5.0)	1 (3.2)	6 (4.3)
Floor of Mouth	0	1 (2.9)	1 (2.5)	0	2 (1.4)
Hard Palate	0	1 (2.9)	0	1 (3.2)	2 (1.4)
Soft Palate	0	0	0	0	0

Location	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Numbers are n (%); location counted once within patient Listing(s): Derived from Listing 16.2.4.3					

Table 14.2.1.10 Summary of additional lesions identified during visits 3 - 7 [FAS]: b) total number and type of lesions by location, lesions identified at Visit 3 - 6

Location	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
All sites	14/10/4	21/17/4	15/13/2	15/12/3	65/52/13
Upper Labial Mucosa	0	0	2/2/0	0	2/2/0
Lower Labial Mucosa	0	1/1/0	0	0	1/1/0
Right Buccal Mucosa	3/3/0	2/2/0	2/2/0	3/2/1	10/9/1
Left Buccal Mucosa	3/2/1	5/5/0	4/2/2	1/1/0	13/10/3
Gingivae: Lower Right (distal)	2/0/2	0	1/1/0	2/2/0	5/3/2
Gingivae: Lower Central	0	0	0	0	0
Gingivae: Lower Left (distal)	1/1/0	1/1/0	0	2/1/1	4/3/1
Gingivae: Upper Right (distal)	1/1/0	4/2/2	1/1/0	1/0/1	7/4/3
Gingivae: Upper Central	0	0	0	1/1/0	1/1/0
Gingivae: Upper Left (distal)	0	3/3/0	2/2/0	0	5/5/0
Mandibular Lingual Gingivae: Lower Right (distal)	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Central	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Left (distal)	0	0	0	0	0
Dorsum Tongue	0	1/1/0	0	1/1/0	2/2/0

Location	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Right Lateral Ventral Tongue	1/0/1	0	0	2/2/0	3/2/1
Left Lateral Ventral Tongue	3/3/0	2/2/0	2/2/0	1/1/0	8/8/0
Floor of Mouth	0	1/0/1	1/1/0	0	2/1/1
Hard Palate	0	1/0/1	0	1/1/0	2/1/1
Soft Palate	0	0	0	0	0

Numbers are Total lesions/Ulcerative/Erythematous
Listing(s): Derived from Listing 16.2.4.3

Table 14.2.1.10 Summary of additional lesions identified during visits 3 - 7 [FAS]: c) location of lesions identified at Visit 7

Location	20 ug, N=30	5 ug, N=33	1 ug, N=34	Placebo, N=26	Total, N=123
Upper Labial Mucosa	0	0	0	0	0
Lower Labial Mucosa	0	0	0	0	0
Right Buccal Mucosa	0	0	1 (2.9)	1 (3.8)	2 (1.6)
Left Buccal Mucosa	0	0	0	2 (7.7)	2 (1.6)
Gingivae: Lower Right (distal)	1 (3.3)	0	0	0	1 (0.8)
Gingivae: Lower Central	2 (6.7)	0	1 (2.9)	0	3 (2.4)
Gingivae: Lower Left (distal)	0	0	1 (2.9)	0	1 (0.8)
Gingivae: Upper Right (distal)	0	0	0	0	0
Gingivae: Upper Central	0	0	0	0	0
Gingivae: Upper Left (distal)	1 (3.3)	0	0	0	1 (0.8)

Location	20 ug, N=30	5 ug, N=33	1 ug, N=34	Placebo, N=26	Total, N=123
Mandibular Lingual Gingivae: Lower Right (distal)	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Central	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Left (distal)	0	0	0	0	0
Dorsum Tongue	0	0	1 (2.9)	0	1 (0.8)
Right Lateral Ventral Tongue	0	0	0	1 (3.8)	1 (0.8)
Left Lateral Ventral Tongue	0	1 (3.0)	0	1 (3.8)	2 (1.6)
Floor of Mouth	1 (3.3)	0	0	0	1 (0.8)
Hard Palate	0	0	0	0	0
Soft Palate	0	0	0	0	0

Numbers are n (%); location counted once within patient
Listing(s): Derived from Listing 16.2.4.3

Table 14.2.1.10 Summary of additional lesions identified during visits 3 - 7 [FAS]: d) total number and type of lesions by location, lesions identified at Visit 7

Location	20 ug, N=28	5 ug, N=33	1 ug, N=34	Placebo, N=26	Total, N=121
All sites	5/3/2	1/1/0	4/3/1	5/2/3	15/9/6
Upper Labial Mucosa	0	0	0	0	0
Lower Labial Mucosa	0	0	0	0	0
Right Buccal Mucosa	0	0	1/1/0	1/0/1	2/1/1
Left Buccal Mucosa	0	0	0	2/0/2	2/0/2
Gingivae: Lower Right (distal)	1/0/1	0	0	0	1/0/1

Location	20 ug, N=28	5 ug, N=33	1 ug, N=34	Placebo, N=26	Total, N=121
Gingivae: Lower Central	2/2/0	0	1/1/0	0	3/3/0
Gingivae: Lower Left (distal)	0	0	1/1/0	0	1/1/0
Gingivae: Upper Right (distal)	0	0	0	0	0
Gingivae: Upper Central	0	0	0	0	0
Gingivae: Upper Left (distal)	1/0/1	0	0	0	1/0/1
Mandibular Lingual Gingivae: Lower Right (distal)	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Central	0	0	0	0	0
Mandibular Lingual Gingivae: Lower Left (distal)	0	0	0	0	0
Dorsum Tongue	0	0	1/0/1	0	1/0/1
Right Lateral Ventral Tongue	0	0	0	1/1/0	1/1/0
Left Lateral Ventral Tongue	0	1/1/0	0	1/1/0	2/2/0
Floor of Mouth	1/1/0	0	0	0	1/1/0
Hard Palate	0	0	0	0	0
Soft Palate	0	0	0	0	0

Numbers are Total lesions/Ulcerative/Erythematous
Listing(s): Derived from Listing 16.2.4.3

Figure 14.2.1.2 Mean value curves of ulcer area over time [FAS]

a: absolute scale

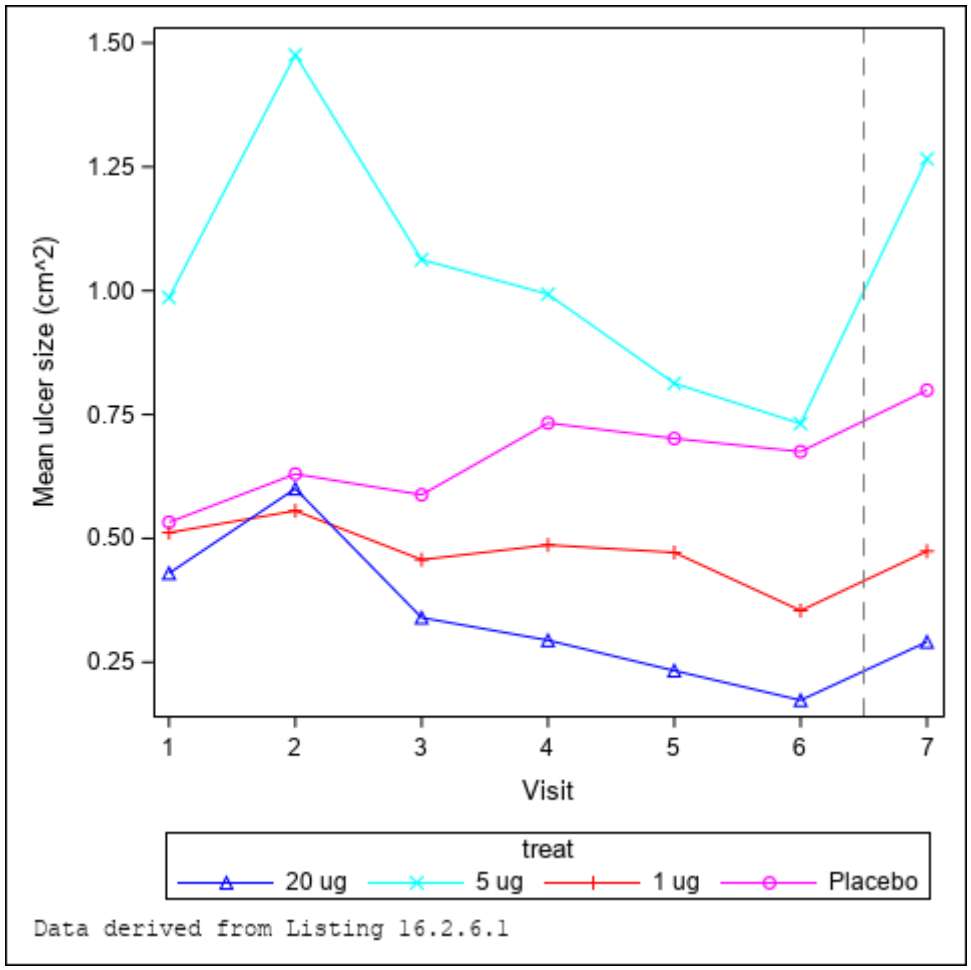


Figure 14.2.1.2 Mean value curves of ulcer area over time [FAS] b: change

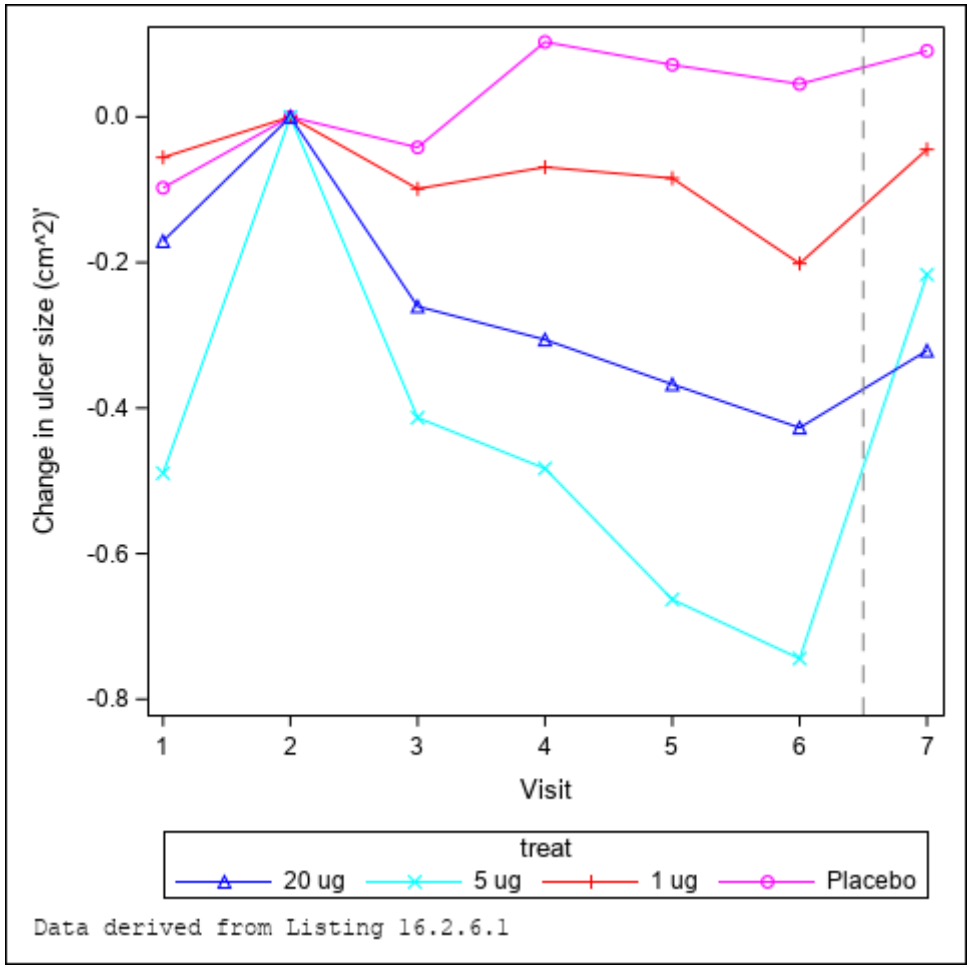


Figure 14.2.1.4 Mean value curves of lesion area over time [FAS]

a: absolute scale

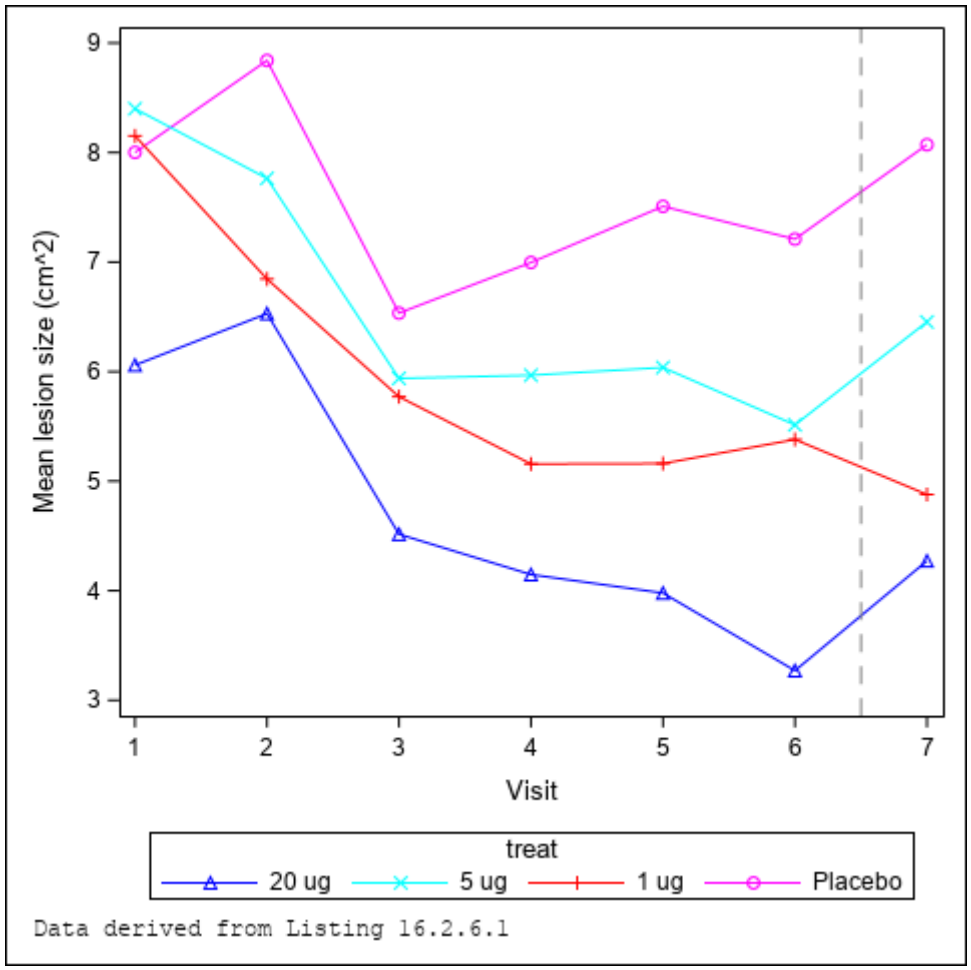


Figure 14.2.1.4 Mean value curves of lesion area over time [FAS] b: change

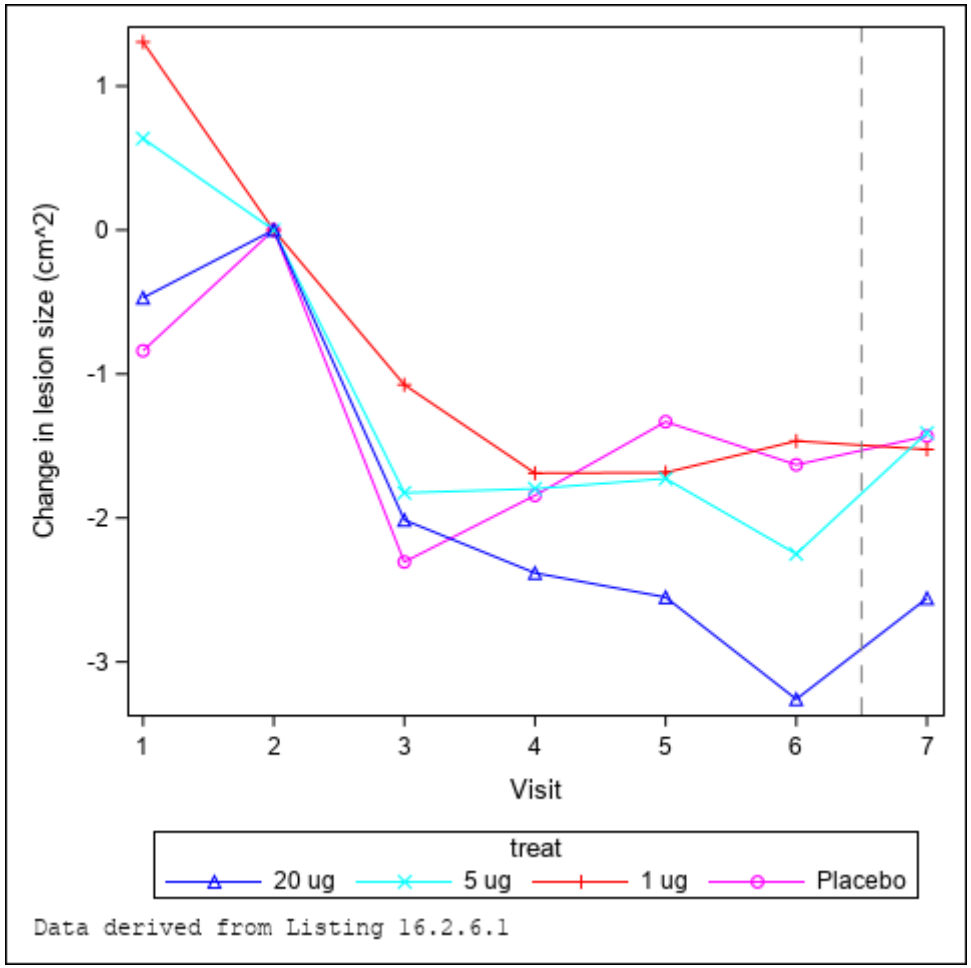


Figure 14.2.1.5 Histograms of percentage of cleared lesions and ulcers [FAS]

a: ulcers

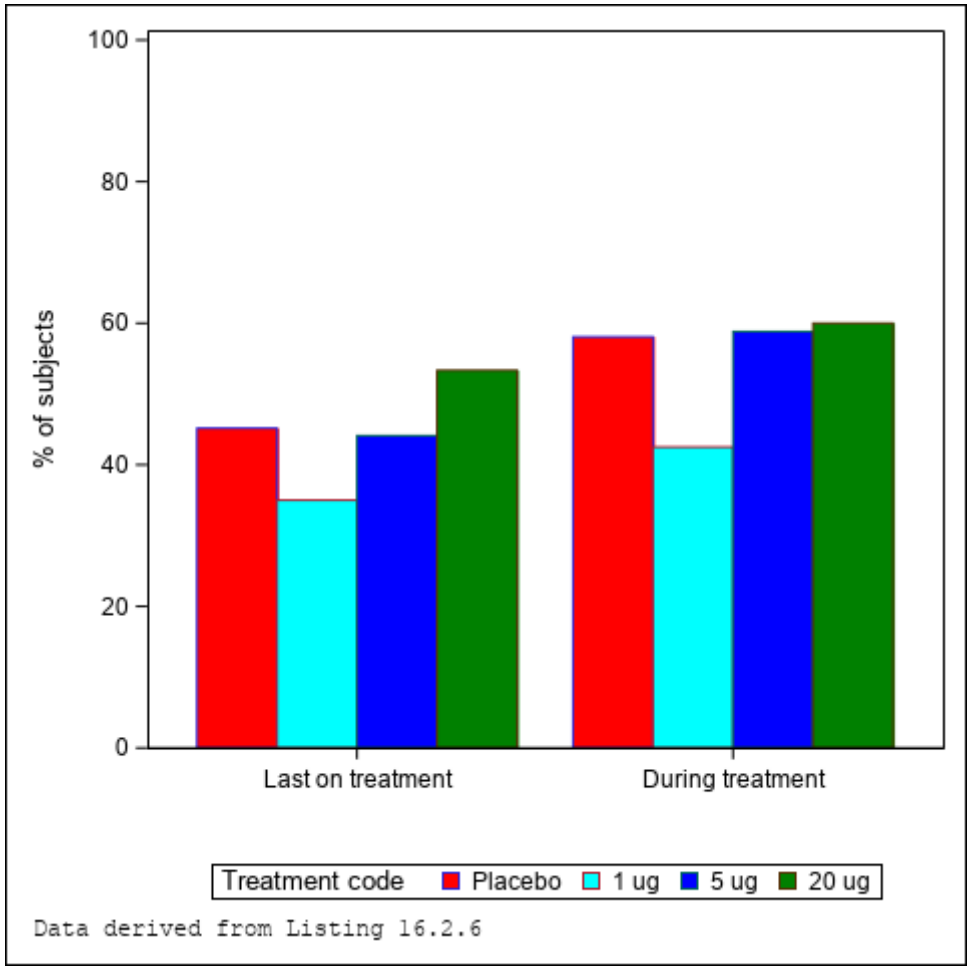
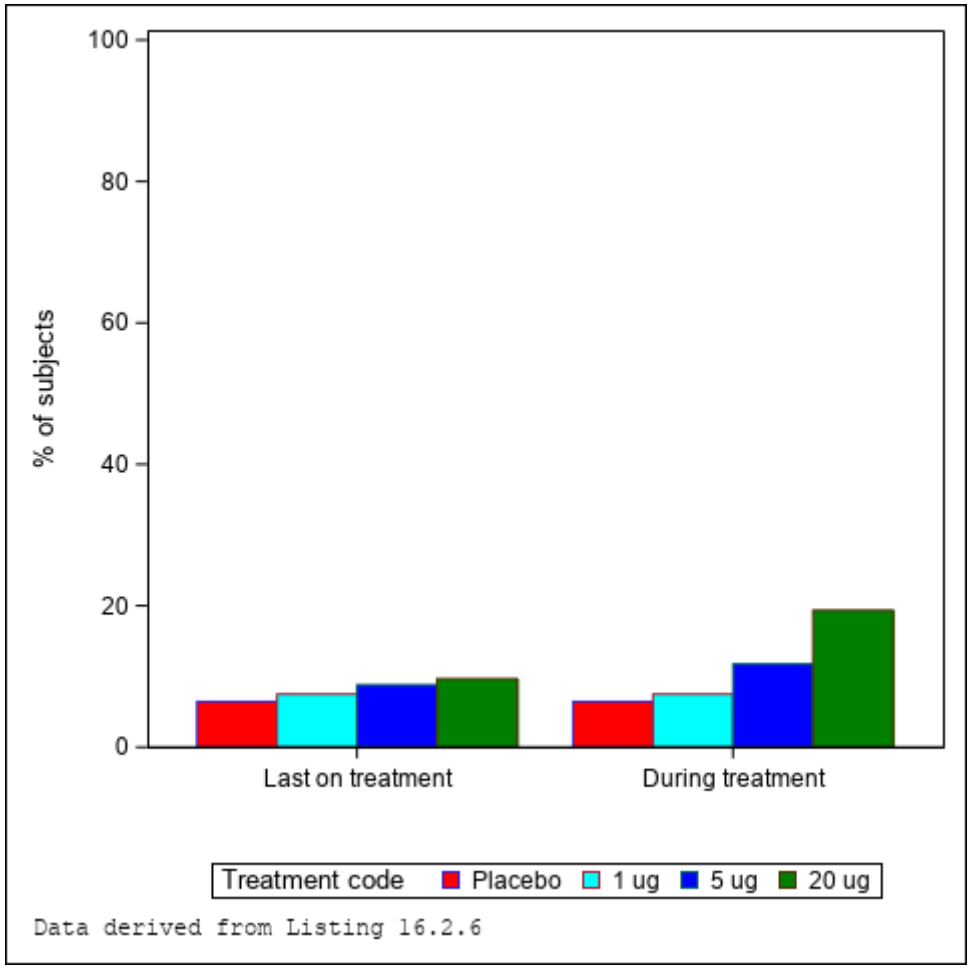


Figure 14.2.1.5 Histograms of percentage of cleared lesions and ulcers [FAS] b: lesions



14.2.2 Erythema scores, worst symptoms at anatomical site score, clinical global impression score

Table 14.2.2.1 Summary of erythema scores, worst symptoms at anatomical site and global impression of anatomical site score by treatment group and visit [FAS]

a) 5-point erythema score

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	33	34	40	31
	Mean(SD)	2.434 (0.80)	2.612 (0.82)	2.686 (0.75)	2.603 (0.81)
	Median	2.250	2.450	2.750	2.750
	Min, Max	1.00-4.00	1.00-4.00	1.00-4.00	1.00-4.00
Week 1	n	32	34	39	31
	Mean(SD)	1.820 (1.00)	1.833 (0.83)	2.138 (0.86)	2.012 (0.81)
	Median	1.667	1.708	2.000	2.000
	Min, Max	0.00-4.00	0.00-4.00	0.00-4.00	0.67-4.00
Change from baseline Week 1	n	32	34	39	31
	Mean(SD)	-0.596 (1.16)	-0.779 (0.89)	-0.579 (0.92)	-0.590 (0.86)
	Median	-0.500	-0.667	-0.333	-0.500
	Min, Max	-4.00-1.50	-4.00-1.00	-4.00-1.00	-2.67-1.00
Week 2	n	31	34	37	28
	Mean(SD)	1.489 (0.97)	1.571 (0.89)	1.713 (0.75)	1.846 (0.99)
	Median	1.250	1.333	2.000	1.750
	Min, Max	0.00-4.00	0.00-4.00	0.00-3.00	0.00-3.00
Change from baseline Week 2	n	31	34	37	28
	Mean(SD)	-0.924 (1.03)	-1.041 (1.02)	-0.979 (1.11)	-0.830 (1.14)

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Median	-0.750	-1.000	-1.000	-0.633
	Min, Max	-4.00-1.00	-4.00-0.50	-4.00-0.67	-4.00-1.00
Week 3	n	29	33	36	27
	Mean(SD)	1.305 (0.97)	1.582 (0.79)	1.725 (0.86)	1.557 (0.85)
	Median	1.000	1.333	1.500	1.667
	Min, Max	0.00-4.00	0.00-4.00	0.00-4.00	0.00-3.25
Change from baseline Week 3	n	29	33	36	27
	Mean(SD)	-1.137 (1.08)	-0.987 (0.71)	-0.978 (1.07)	-1.107 (1.12)
	Median	-1.000	-1.000	-1.000	-1.000
	Min, Max	-4.00-1.00	-2.00-0.00	-4.00-0.50	-4.00-1.00
Week 4	n	30	33	35	27
	Mean(SD)	1.077 (0.85)	1.379 (0.94)	1.537 (0.97)	1.514 (1.03)
	Median	1.000	1.000	1.333	1.333
	Min, Max	0.00-4.00	0.00-4.00	0.00-4.00	0.00-4.00
Change from baseline Week 4	n	30	33	35	27
	Mean(SD)	-1.350 (1.12)	-1.190 (0.95)	-1.169 (1.24)	-1.151 (1.29)
	Median	-1.292	-1.000	-1.000	-1.000
	Min, Max	-4.00-1.00	-3.00-0.00	-4.00-1.00	-4.00-1.00

Listing(s): Derived from Listing 16.2.6

Table 14.2.2.1 Summary of erythema scores, worst symptoms at anatomical site and global impression of anatomical site score by treatment group and visit [FAS]: b) worst symptoms at anatomical site

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	33	34	40	31
	Mean(SD)	5.375 (2.31)	5.558 (2.33)	5.580 (2.37)	5.722 (2.34)
	Median	5.333	6.000	5.875	5.250
	Min, Max	0.00-9.20	1.00-10.00	1.00-9.50	2.00-10.00
Week 1	n	32	34	39	31
	Mean(SD)	3.401 (2.59)	4.258 (2.01)	4.516 (2.48)	4.677 (2.02)
	Median	2.708	4.000	4.667	4.250
	Min, Max	0.00-10.00	1.00-8.00	1.00-9.00	1.25-8.33
Change from baseline Week 1	n	32	34	39	31
	Mean(SD)	-1.970 (1.79)	-1.300 (1.56)	-1.130 (1.68)	-1.044 (1.73)
	Median	-2.000	-1.417	-1.333	-1.000
	Min, Max	-6.00-3.00	-5.00-3.00	-5.50-3.67	-6.00-2.33
Week 2	n	31	34	37	28
	Mean(SD)	2.677 (2.37)	4.027 (2.13)	3.887 (1.97)	4.013 (2.24)
	Median	2.000	4.000	4.000	3.625
	Min, Max	0.00-8.00	0.00-9.00	1.00-8.00	0.20-8.25
Change from baseline Week 2	n	31	34	37	28
	Mean(SD)	-2.641 (1.70)	-1.531 (2.01)	-1.541 (1.93)	-1.833 (2.91)
	Median	-2.667	-1.333	-1.500	-1.500
	Min, Max	-7.00-1.00	-7.00-2.00	-5.60-1.75	-9.00-3.67

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Week 3	n	29	33	36	27
	Mean(SD)	2.494 (2.51)	3.237 (1.85)	3.297 (2.15)	3.449 (2.07)
	Median	1.500	3.000	3.167	3.333
	Min, Max	0.00-8.00	0.00-7.00	0.50-7.40	0.00-8.50
Change from baseline Week 3	n	29	33	36	27
	Mean(SD)	-2.829 (2.05)	-2.278 (2.17)	-2.222 (2.19)	-2.392 (2.75)
	Median	-3.000	-2.000	-2.250	-3.000
	Min, Max	-7.00-3.00	-7.00-3.00	-6.67-3.20	-9.00-2.33
Week 4	n	30	33	35	27
	Mean(SD)	2.020 (2.08)	2.885 (2.04)	2.963 (2.22)	3.273 (2.26)
	Median	1.375	3.000	2.800	3.000
	Min, Max	0.00-8.00	0.00-7.00	0.00-8.00	0.00-8.50
Change from baseline Week 4	n	30	33	35	27
	Mean(SD)	-3.376 (2.18)	-2.630 (2.35)	-2.593 (2.51)	-2.567 (2.77)
	Median	-3.875	-2.333	-2.000	-2.750
	Min, Max	-7.50-1.00	-7.67-1.25	-8.00-2.33	-8.50-2.00

Listing(s): Derived from Listing 16.2.6

Table 14.2.2.1 Summary of erythema scores, worst symptoms at anatomical site and global impression of anatomical site score by treatment group and visit [FAS]: c) global impression of anatomical site

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	33	34	40	31
	Mean(SD)	2.369 (0.83)	2.541 (0.89)	2.697 (0.76)	2.629 (0.74)
	Median	2.000	2.333	3.000	3.000
	Min, Max	1.00-4.00	1.00-4.00	1.33-4.00	1.33-4.00
Week 1	n	32	34	39	31
	Mean(SD)	1.841 (1.07)	1.825 (0.93)	2.165 (0.83)	1.883 (0.66)
	Median	1.667	1.667	2.000	1.833
	Min, Max	0.00-4.00	0.00-4.00	0.00-4.00	1.00-3.25
Change from baseline Week 1	n	32	34	39	31
	Mean(SD)	-0.508 (1.17)	-0.716 (0.89)	-0.562 (0.97)	-0.746 (0.79)
	Median	-0.500	-0.667	-0.200	-0.500
	Min, Max	-4.00-2.00	-4.00-1.00	-4.00-1.00	-2.67-0.50
Week 2	n	31	34	37	28
	Mean(SD)	1.444 (0.93)	1.743 (0.97)	1.727 (0.79)	1.851 (0.92)
	Median	1.000	1.417	2.000	1.875
	Min, Max	0.00-4.00	0.00-4.00	0.00-4.00	0.00-3.33
Change from baseline Week 2	n	31	34	37	28
	Mean(SD)	-0.884 (1.02)	-0.798 (1.08)	-0.963 (1.07)	-0.824 (1.10)
	Median	-1.000	-0.625	-1.000	-0.583
	Min, Max	-4.00-1.00	-4.00-1.00	-4.00-0.67	-4.00-0.67

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Week 3	n	29	33	36	27
	Mean(SD)	1.486 (1.02)	1.677 (0.82)	1.790 (0.84)	1.631 (0.93)
	Median	1.250	1.500	1.775	1.600
	Min, Max	0.00-4.00	0.00-4.00	0.00-4.00	0.00-3.50
Change from baseline Week 3	n	29	33	36	27
	Mean(SD)	-0.882 (1.17)	-0.820 (0.76)	-0.933 (1.06)	-1.033 (1.13)
	Median	-1.000	-0.750	-0.875	-1.000
	Min, Max	-4.00-2.00	-2.00-0.20	-4.00-0.50	-4.00-0.50
Week 4	n	30	33	35	27
	Mean(SD)	1.194 (0.97)	1.558 (0.96)	1.645 (1.07)	1.635 (0.99)
	Median	1.000	1.250	1.500	1.500
	Min, Max	0.00-4.00	0.00-4.00	0.00-4.00	0.00-4.00
Change from baseline Week 4	n	30	33	35	27
	Mean(SD)	-1.144 (1.19)	-0.939 (1.02)	-1.076 (1.32)	-1.028 (1.27)
	Median	-1.000	-0.833	-1.000	-0.667
	Min, Max	-4.00-2.00	-3.00-1.00	-4.00-1.00	-4.00-1.00

Listing(s): Derived from Listing 16.2.6

Table 14.2.2.1 Summary of erythema scores, worst symptoms at anatomical site and global impression of anatomical site score by treatment group and visit [FAS]: d) 3-point erythema score

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	33	34	40	31
	Mean(SD)	1.517 (0.46)	1.608 (0.43)	1.637 (0.38)	1.600 (0.46)
	Median	1.500	1.667	1.708	1.667
	Min, Max	0.50-2.00	1.00-2.00	1.00-2.00	0.33-2.00
Week 1	n	32	34	39	31
	Mean(SD)	1.143 (0.57)	1.256 (0.51)	1.368 (0.50)	1.272 (0.52)
	Median	1.000	1.000	1.400	1.333
	Min, Max	0.00-2.00	0.00-2.00	0.00-2.00	0.00-2.00
Change from baseline Week 1	n	32	34	39	31
	Mean(SD)	-0.359 (0.66)	-0.352 (0.47)	-0.286 (0.54)	-0.328 (0.50)
	Median	-0.250	-0.250	0.000	0.000
	Min, Max	-2.00-1.00	-2.00-0.25	-2.00-1.00	-1.50-0.33
Week 2	n	31	34	37	28
	Mean(SD)	0.968 (0.47)	1.140 (0.47)	1.118 (0.49)	1.173 (0.60)
	Median	1.000	1.000	1.000	1.000
	Min, Max	0.00-2.00	0.00-2.00	0.00-2.00	0.00-2.00
Change from baseline Week 2	n	31	34	37	28
	Mean(SD)	-0.518 (0.54)	-0.469 (0.60)	-0.540 (0.61)	-0.444 (0.61)
	Median	-0.500	-0.500	-0.500	-0.267
	Min, Max	-2.00-0.50	-2.00-1.00	-2.00-0.50	-2.00-0.33

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Week 3	n	29	33	36	27
	Mean(SD)	0.894 (0.63)	1.002 (0.47)	1.071 (0.53)	1.033 (0.52)
	Median	1.000	1.000	1.000	1.000
	Min, Max	0.00-2.00	0.00-2.00	0.00-2.00	0.00-2.00
Change from baseline Week 3	n	29	33	36	27
	Mean(SD)	-0.597 (0.75)	-0.594 (0.47)	-0.591 (0.56)	-0.581 (0.59)
	Median	-0.500	-0.667	-0.500	-0.500
	Min, Max	-2.00-1.00	-1.50-0.00	-2.00-0.25	-2.00-0.33
Week 4	n	30	33	35	27
	Mean(SD)	0.697 (0.51)	0.979 (0.65)	1.033 (0.60)	1.022 (0.54)
	Median	0.750	1.000	1.000	1.000
	Min, Max	0.00-2.00	0.00-2.00	0.00-2.00	0.00-2.00
Change from baseline Week 4	n	30	33	35	27
	Mean(SD)	-0.794 (0.69)	-0.617 (0.71)	-0.630 (0.61)	-0.593 (0.72)
	Median	-1.000	-0.500	-0.500	-0.500
	Min, Max	-2.00-1.00	-2.00-1.00	-2.00-0.00	-2.00-0.67

Listing(s): Derived from Listing 16.2.6

Table 14.2.2.2 Statistical analysis of 5-point erythema score [FAS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-0.733	20 ug vs placebo	-0.122	(-0.529, 0.286)	0.5549
	5 ug	-0.792	5 ug vs placebo	-0.181	(-0.581, 0.220)	0.3739
	1 ug	-0.549	1 ug vs placebo	0.062	(-0.325, 0.449)	0.7516
	Placebo	-0.611				
Week 2	20 ug	-0.914	20 ug vs placebo	-0.177	(-0.620, 0.266)	0.4315
	5 ug	-0.971	5 ug vs placebo	-0.234	(-0.669, 0.201)	0.2894
	1 ug	-0.828	1 ug vs placebo	-0.091	(-0.511, 0.330)	0.6706
	Placebo	-0.737				
Week 3	20 ug	-1.076	20 ug vs placebo	-0.131	(-0.557, 0.295)	0.5445
	5 ug	-0.902	5 ug vs placebo	0.043	(-0.376, 0.462)	0.8390
	1 ug	-0.778	1 ug vs placebo	0.168	(-0.237, 0.573)	0.4140
	Placebo	-0.945				
Week 4	20 ug	-1.288	20 ug vs placebo	-0.319	(-0.809, 0.172)	0.2013
	5 ug	-1.071	5 ug vs placebo	-0.101	(-0.584, 0.381)	0.6781
	1 ug	-0.881	1 ug vs placebo	0.089	(-0.377, 0.555)	0.7071
	Placebo	-0.969				
Week 3-4	20 ug	-1.182	20 ug vs placebo	-0.225	(-0.649, 0.200)	0.2968
	5 ug	-0.987	5 ug vs placebo	-0.029	(-0.446, 0.388)	0.8903
	1 ug	-0.829	1 ug vs placebo	0.128	(-0.275, 0.532)	0.5303
	Placebo	-0.957				

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.2						

Table 14.2.2.3 Statistical analysis of 5-point erythema score [PPS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-0.714	20 ug vs placebo	0.073	(-0.381, 0.527)	0.7502
	5 ug	-0.841	5 ug vs placebo	-0.054	(-0.485, 0.376)	0.8025
	1 ug	-0.593	1 ug vs placebo	0.194	(-0.223, 0.611)	0.3582
	Placebo	-0.787				
Week 2	20 ug	-0.938	20 ug vs placebo	0.012	(-0.479, 0.503)	0.9621
	5 ug	-1.103	5 ug vs placebo	-0.153	(-0.618, 0.312)	0.5153
	1 ug	-0.970	1 ug vs placebo	-0.020	(-0.471, 0.431)	0.9311
	Placebo	-0.950				
Week 3	20 ug	-1.090	20 ug vs placebo	-0.011	(-0.493, 0.471)	0.9638
	5 ug	-1.017	5 ug vs placebo	0.062	(-0.395, 0.518)	0.7896
	1 ug	-0.839	1 ug vs placebo	0.240	(-0.203, 0.682)	0.2847
	Placebo	-1.079				
Week 4	20 ug	-1.282	20 ug vs placebo	-0.292	(-0.826, 0.242)	0.2805
	5 ug	-1.178	5 ug vs placebo	-0.189	(-0.694, 0.317)	0.4613
	1 ug	-0.940	1 ug vs placebo	0.050	(-0.440, 0.540)	0.8402
	Placebo	-0.990				
Week 3-4	20 ug	-1.186	20 ug vs placebo	-0.152	(-0.621, 0.318)	0.5238

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
	5 ug	-1.098	5 ug vs placebo	-0.064	(-0.509, 0.382)	0.7778
	1 ug	-0.889	1 ug vs placebo	0.145	(-0.286, 0.576)	0.5067
	Placebo	-1.034				
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.2						

Table 14.2.2.4 Statistical analysis of worst symptoms at anatomical site [FAS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-1.889	20 ug vs placebo	-1.012	(-1.783, -0.242)	0.0105
	5 ug	-1.211	5 ug vs placebo	-0.334	(-1.095, 0.427)	0.3869
	1 ug	-1.049	1 ug vs placebo	-0.172	(-0.906, 0.563)	0.6441
	Placebo	-0.877				
Week 2	20 ug	-2.293	20 ug vs placebo	-0.878	(-1.804, 0.049)	0.0631
	5 ug	-1.266	5 ug vs placebo	0.149	(-0.765, 1.064)	0.7475
	1 ug	-1.300	1 ug vs placebo	0.115	(-0.768, 0.998)	0.7969
	Placebo	-1.415				
Week 3	20 ug	-2.507	20 ug vs placebo	-0.763	(-1.749, 0.224)	0.1285
	5 ug	-1.866	5 ug vs placebo	-0.122	(-1.096, 0.851)	0.8041
	1 ug	-1.835	1 ug vs placebo	-0.091	(-1.032, 0.849)	0.8478
	Placebo	-1.744				
Week 4	20 ug	-2.748	20 ug vs placebo	-0.995	(-2.038, 0.048)	0.0614
	5 ug	-2.035	5 ug vs placebo	-0.282	(-1.311, 0.748)	0.5890

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
	1 ug	-1.852	1 ug vs placebo	-0.099	(-1.092, 0.895)	0.8447
	Placebo	-1.753				
Week 3-4	20 ug	-2.634	20 ug vs placebo	-0.887	(-1.841, 0.068)	0.0684
	5 ug	-1.950	5 ug vs placebo	-0.203	(-1.145, 0.739)	0.6710
	1 ug	-1.843	1 ug vs placebo	-0.096	(-1.006, 0.814)	0.8348
	Placebo	-1.747				
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.2						

Table 14.2.2.5 Statistical analysis of global impression of anatomical site score [FAS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-0.688	20 ug vs placebo	0.066	(-0.351, 0.483)	0.7550
	5 ug	-0.782	5 ug vs placebo	-0.027	(-0.436, 0.381)	0.8946
	1 ug	-0.529	1 ug vs placebo	0.225	(-0.169, 0.619)	0.2610
	Placebo	-0.754				
Week 2	20 ug	-0.883	20 ug vs placebo	-0.169	(-0.612, 0.274)	0.4522
	5 ug	-0.746	5 ug vs placebo	-0.033	(-0.467, 0.401)	0.8812
	1 ug	-0.779	1 ug vs placebo	-0.065	(-0.484, 0.354)	0.7586
	Placebo	-0.714				
Week 3	20 ug	-0.879	20 ug vs placebo	0.014	(-0.438, 0.465)	0.9524
	5 ug	-0.752	5 ug vs placebo	0.140	(-0.302, 0.582)	0.5314
	1 ug	-0.712	1 ug vs placebo	0.180	(-0.247, 0.607)	0.4049

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
	Placebo	-0.893				
Week 4	20 ug	-1.093	20 ug vs placebo	-0.289	(-0.802, 0.223)	0.2662
	5 ug	-0.777	5 ug vs placebo	0.027	(-0.475, 0.529)	0.9149
	1 ug	-0.724	1 ug vs placebo	0.080	(-0.404, 0.565)	0.7440
	Placebo	-0.804				
Week 3-4	20 ug	-0.986	20 ug vs placebo	-0.138	(-0.596, 0.321)	0.5532
	5 ug	-0.765	5 ug vs placebo	0.084	(-0.365, 0.533)	0.7129
	1 ug	-0.718	1 ug vs placebo	0.130	(-0.303, 0.564)	0.5534
	Placebo	-0.848				
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.2						

Table 14.2.2.6 Statistical analysis of 3-point erythema score [FAS]

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-0.456	20 ug vs placebo	-0.096	(-0.342, 0.151)	0.4447
	5 ug	-0.373	5 ug vs placebo	-0.013	(-0.255, 0.230)	0.9178
	1 ug	-0.278	1 ug vs placebo	0.082	(-0.152, 0.317)	0.4878
	Placebo	-0.360				
Week 2	20 ug	-0.500	20 ug vs placebo	-0.114	(-0.355, 0.126)	0.3484
	5 ug	-0.388	5 ug vs placebo	-0.002	(-0.238, 0.234)	0.9868
	1 ug	-0.416	1 ug vs placebo	-0.030	(-0.258, 0.198)	0.7953
	Placebo	-0.386				

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 3	20 ug	-0.550	20 ug vs placebo	-0.055	(-0.318, 0.209)	0.6828
	5 ug	-0.492	5 ug vs placebo	0.003	(-0.256, 0.262)	0.9819
	1 ug	-0.431	1 ug vs placebo	0.064	(-0.186, 0.315)	0.6121
	Placebo	-0.495				
Week 4	20 ug	-0.768	20 ug vs placebo	-0.255	(-0.549, 0.040)	0.0893
	5 ug	-0.525	5 ug vs placebo	-0.012	(-0.301, 0.278)	0.9362
	1 ug	-0.469	1 ug vs placebo	0.045	(-0.235, 0.324)	0.7532
	Placebo	-0.514				
Week 3-4	20 ug	-0.659	20 ug vs placebo	-0.155	(-0.401, 0.092)	0.2173
	5 ug	-0.509	5 ug vs placebo	-0.004	(-0.247, 0.238)	0.9716
	1 ug	-0.450	1 ug vs placebo	0.054	(-0.180, 0.289)	0.6468
	Placebo	-0.504				

Analysis performed by PROC MIXED.
Listing(s): Derived from 16.2.6.2

Figure 14.2.2.1 Mean value curves of 5-point erythema score over time [FAS]

a: absolute scale

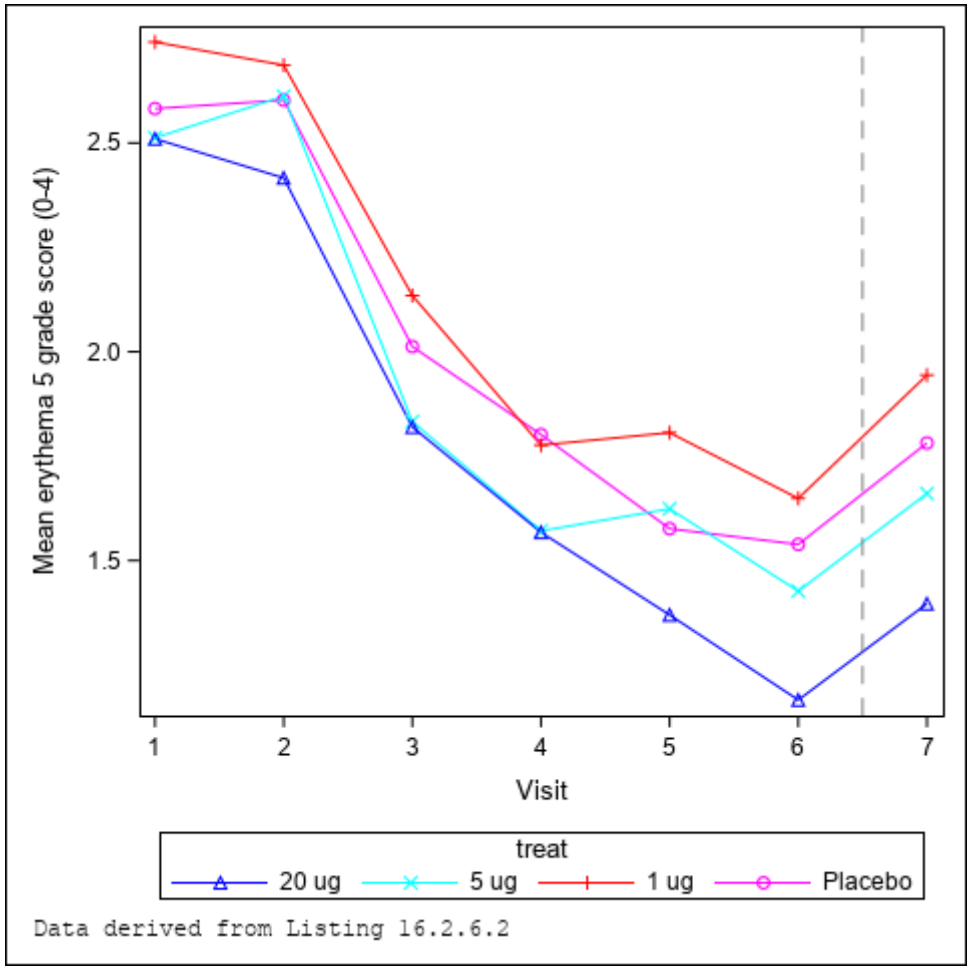


Figure 14.2.2.1 Mean value curves of 5-point erythema score over time [FAS]

b: change

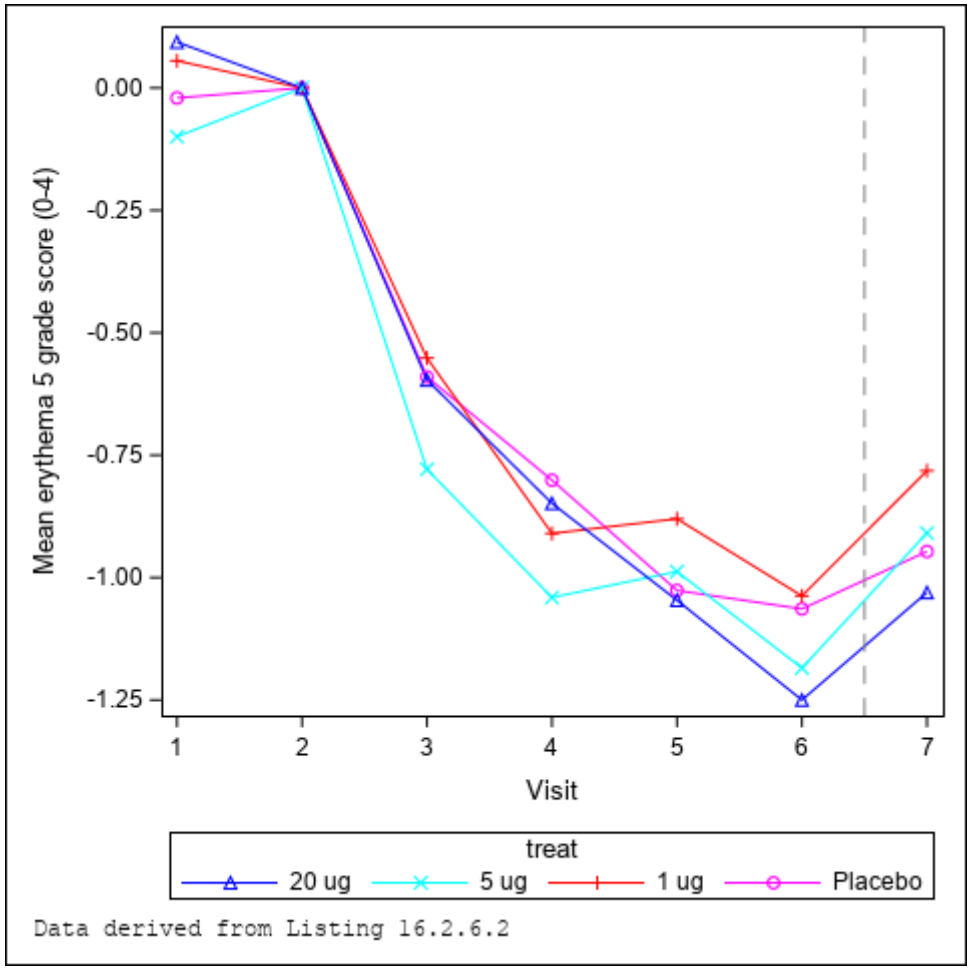


Figure 14.2.2.2 Mean value curves of worst symptom at anatomical site over time [FAS]

a: absolute scale

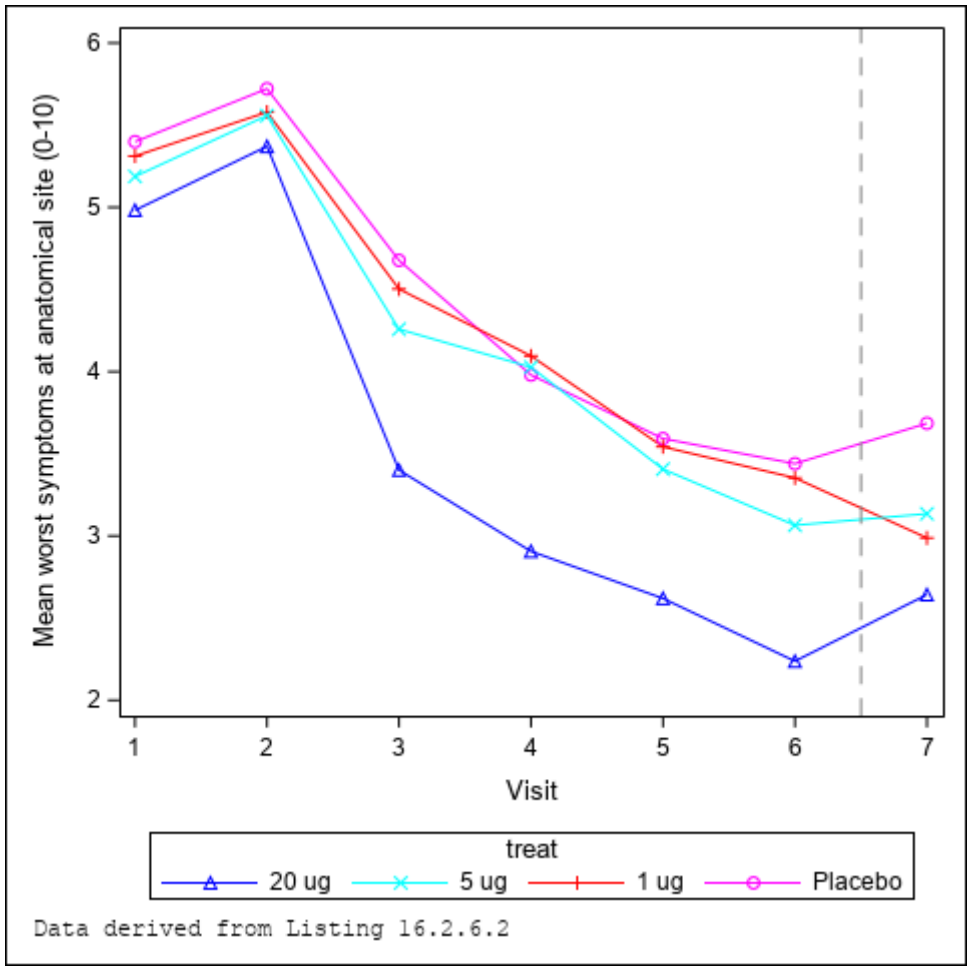


Figure 14.2.2.2 Mean value curves of worst symptom at anatomical site over time [FAS]

b: change

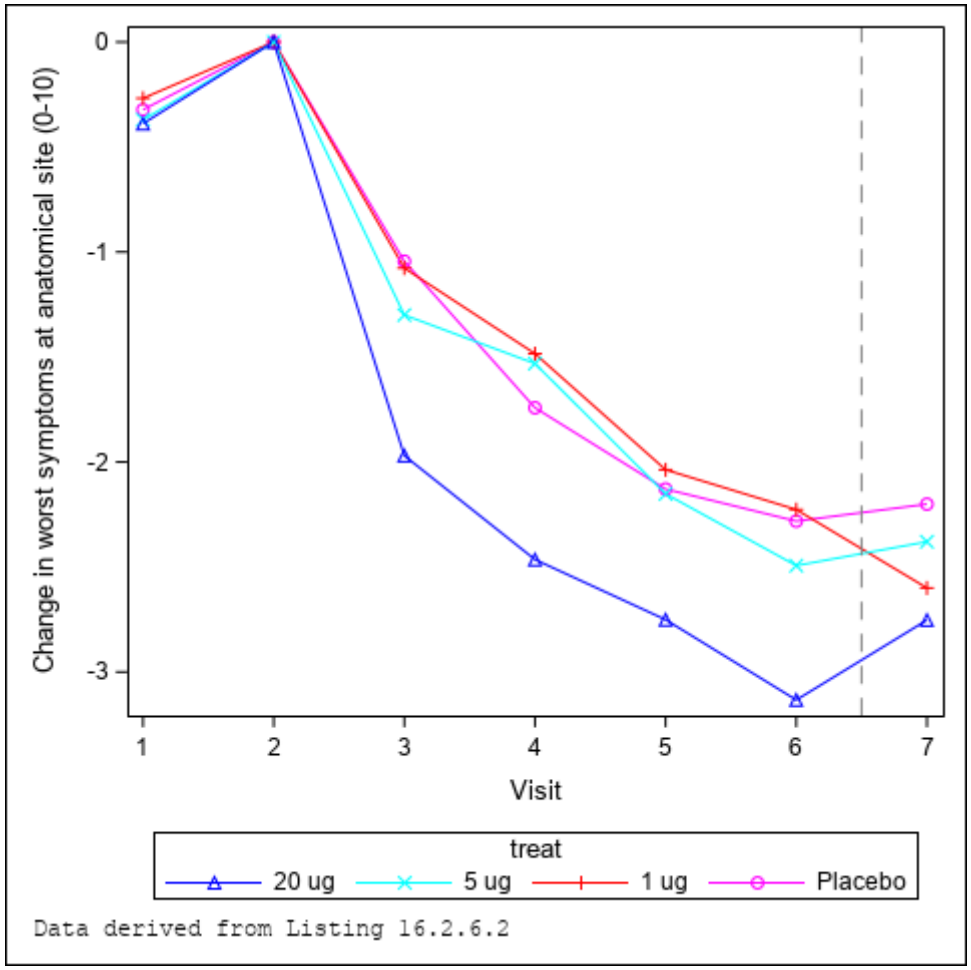


Figure 14.2.2.3 Mean value curves of global impression of anatomical site score over time [FAS]

a: absolute scale

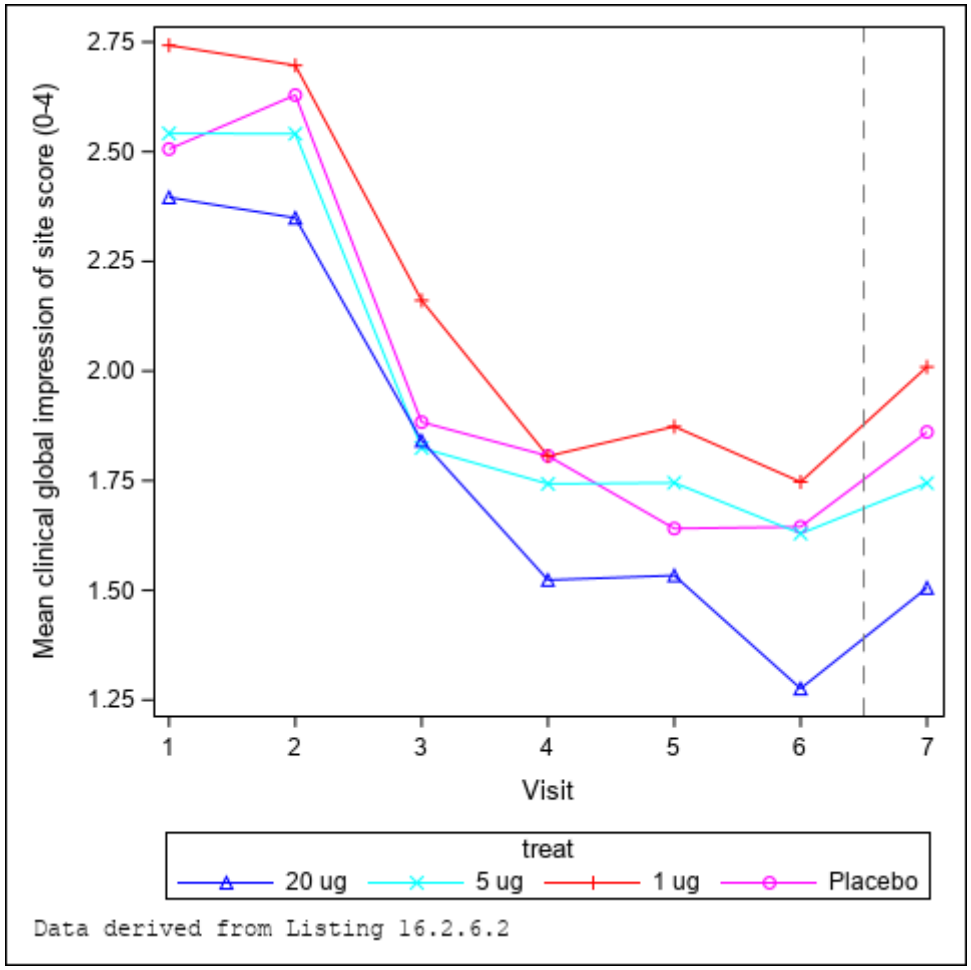


Figure 14.2.2.3 Mean value curves of global impression of anatomical site score over time [FAS]

b: change

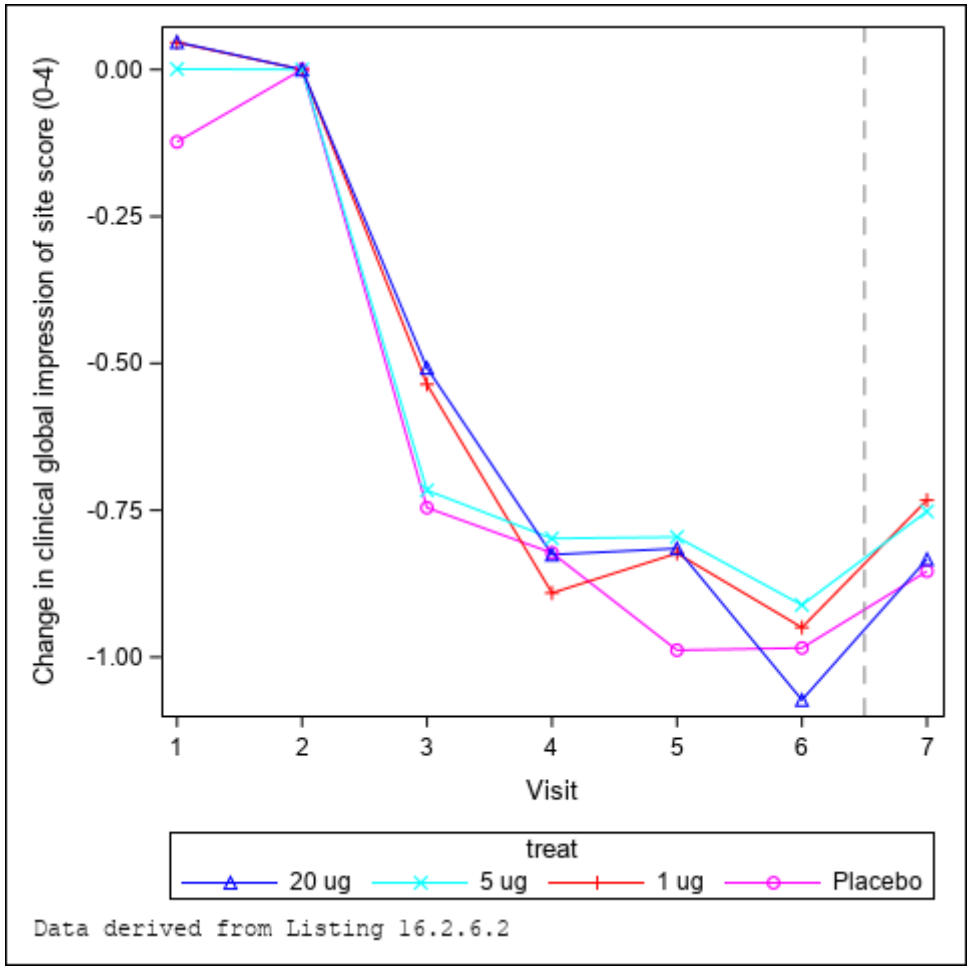


Figure 14.2.2.4 Mean value curves of 3-point erythema score over time [FAS]

a: absolute scale

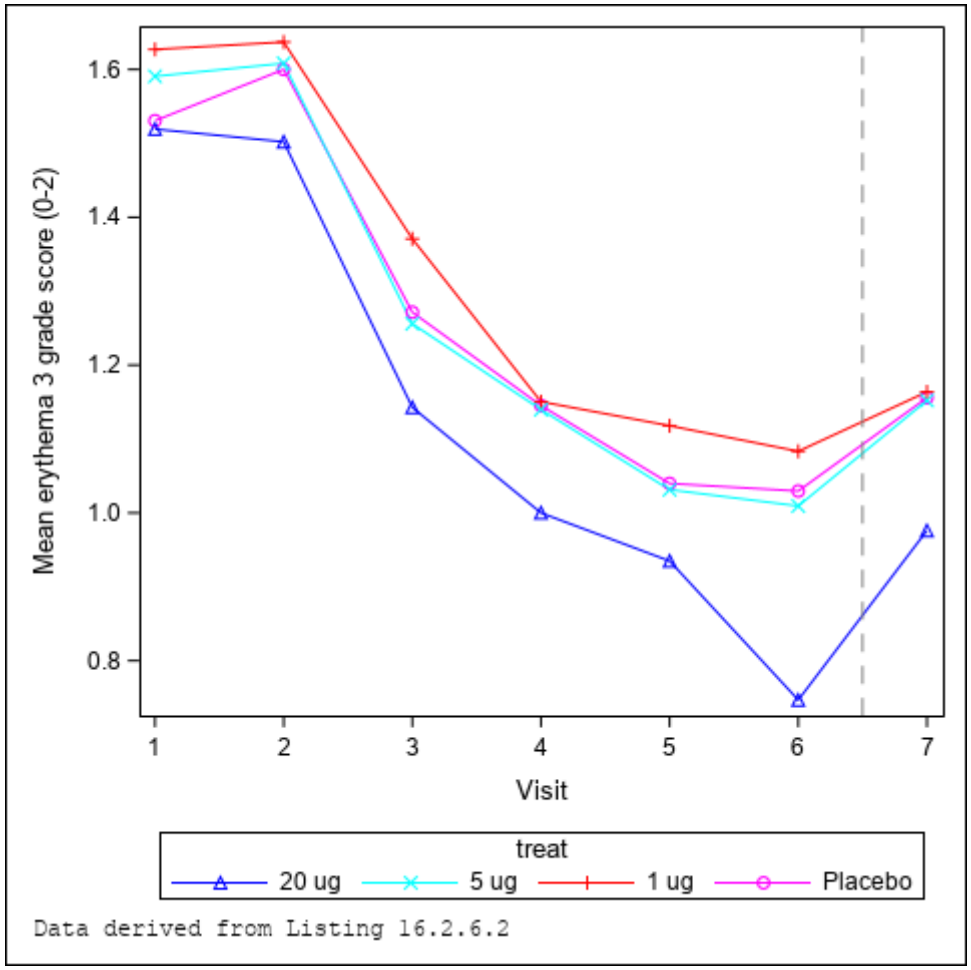
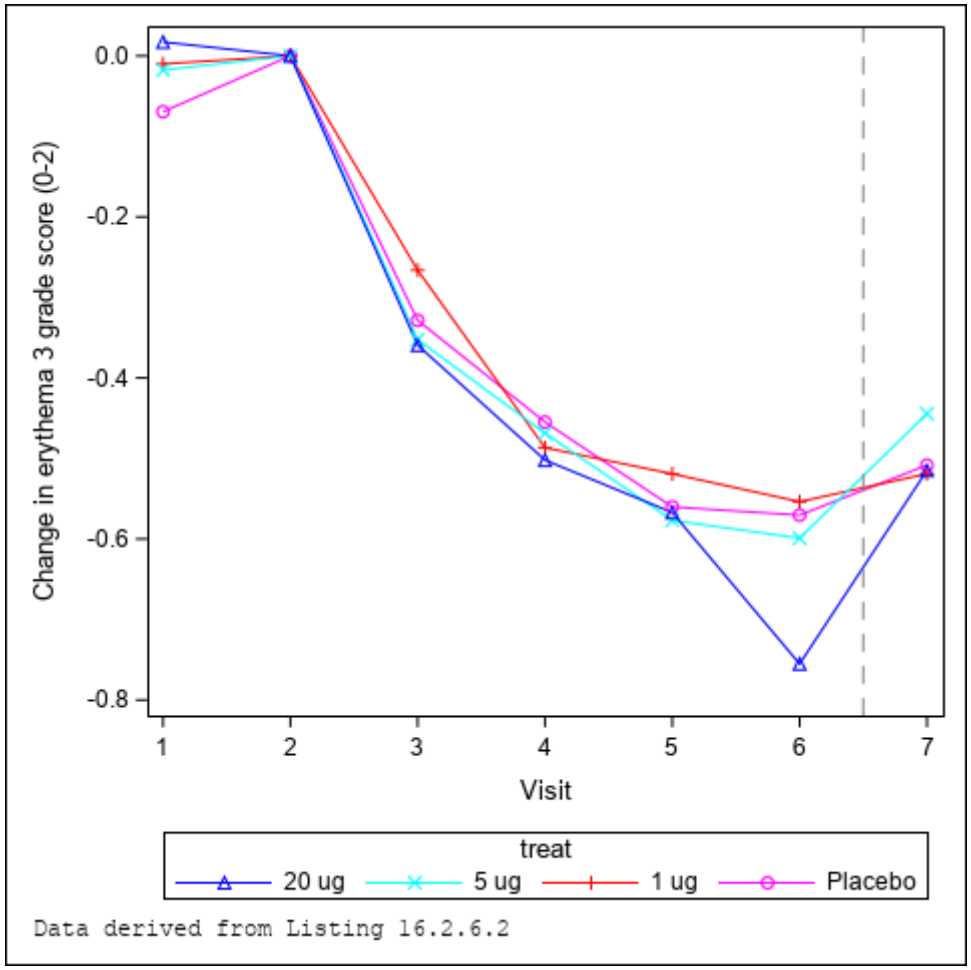


Figure 14.2.2.4 Mean value curves of 3-point erythema score over time [FAS]

b: change



14.2.3 OLPSSM

Table 14.2.3.1 Summary of OLPSSM sum score and #1 - #7 weekly means [FAS]

a) OLPSSM 1-7 Sum score

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	31	32	40	29
	Mean(SD)	10.532 (4.55)	11.165 (4.77)	11.316 (4.53)	9.822 (3.50)
	Median	11.000	10.821	10.488	9.714
	Min, Max	1.86-23.86	4.57-20.14	5.00-21.57	3.86-18.43
Week 1	n	28	33	40	28
	Mean(SD)	8.380 (4.33)	9.820 (4.44)	8.885 (4.10)	8.602 (3.62)
	Median	7.929	10.000	8.200	8.429
	Min, Max	0.17-18.33	2.29-21.00	1.44-19.67	2.88-16.80
Change from baseline Week 1	n	28	32	40	27
	Mean(SD)	-2.142 (3.96)	-1.350 (3.03)	-2.431 (3.69)	-0.832 (2.54)
	Median	-2.593	-1.452	-2.000	-0.500
	Min, Max	-11.43-7.86	-9.60-8.43	-18.86-1.86	-10.14-4.17
Week 2	n	28	34	34	25
	Mean(SD)	6.299 (4.06)	8.760 (4.60)	8.231 (4.22)	7.682 (3.62)
	Median	6.244	8.071	8.183	7.333
	Min, Max	0.29-15.57	1.25-18.57	0.71-16.29	2.00-14.20
Change from baseline Week 2	n	28	32	34	24
	Mean(SD)	-4.372 (4.49)	-2.280 (4.28)	-3.301 (4.04)	-1.435 (3.19)

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Median	-4.000	-2.586	-2.664	-1.699
	Min, Max	-14.02-4.88	-12.00-7.40	-19.00-3.00	-6.71-6.20
Week 3	n	29	33	35	24
	Mean(SD)	5.045 (4.52)	7.266 (4.28)	6.968 (3.82)	7.062 (3.96)
	Median	4.000	7.000	6.571	6.714
	Min, Max	0.00-20.17	0.00-18.80	0.43-18.14	0.63-15.67
Change from baseline Week 3	n	29	31	35	23
	Mean(SD)	-5.401 (3.89)	-3.870 (4.57)	-4.271 (4.39)	-2.536 (4.02)
	Median	-4.714	-3.524	-3.857	-2.857
	Min, Max	-13.71-0.14	-18.00-6.23	-16.57-2.86	-10.43-5.00
Week 4	n	25	32	35	23
	Mean(SD)	3.952 (3.97)	6.334 (4.60)	6.724 (3.45)	6.800 (3.90)
	Median	2.714	5.429	6.429	7.500
	Min, Max	0.00-16.43	0.00-19.50	0.75-13.00	0.00-14.14
Change from baseline Week 4	n	25	31	35	23
	Mean(SD)	-6.347 (3.66)	-4.938 (5.77)	-4.555 (3.27)	-3.012 (3.95)
	Median	-6.000	-4.243	-4.286	-3.714
	Min, Max	-13.00-0.00	-18.86-6.93	-13.86-0.73	-11.00-3.17

Listing(s): Derived from Listing 16.2.6

Table 14.2.3.1 Summary of OLPSSM sum score and #1 - #7 weekly means [FAS]: b) Summary to #1 to #7

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of OLPSSM question no. 1 score by visit	Baseline	n	31	32	40	29
		Mean(SD)	2.037 (0.96)	2.289 (0.81)	2.333 (0.83)	2.227 (0.81)
		Median	2.143	2.143	2.298	2.143
		Min, Max	0.000-4.000	0.000-4.000	1.000-4.000	0.286-4.000
	Week 1	n	28	33	40	28
		Mean(SD)	1.767 (0.90)	2.096 (0.82)	1.995 (0.89)	1.993 (0.88)
		Median	1.792	2.143	2.000	2.268
		Min, Max	0.000-3.667	0.143-4.000	0.000-4.000	0.167-3.000
	Change from baseline Week 1	n	28	32	40	27
		Mean(SD)	-0.274 (0.63)	-0.193 (0.57)	-0.338 (0.64)	-0.183 (0.44)
		Median	-0.333	-0.274	-0.174	0.000
		Min, Max	-1.381-1.143	-1.367-1.000	-3.000-0.429	-1.393-0.429
	Week 2	n	28	34	34	25
		Mean(SD)	1.366 (0.91)	1.802 (0.84)	1.845 (0.86)	1.778 (0.89)
		Median	1.286	1.708	1.845	1.800
		Min, Max	0.000-3.250	0.000-3.286	0.143-3.375	0.000-3.000
	Change from baseline Week 2	n	28	32	34	24
		Mean(SD)	-0.706 (0.76)	-0.463 (0.75)	-0.543 (0.71)	-0.327 (0.64)
		Median	-0.690	-0.348	-0.405	-0.333
		Min, Max	-2.381-0.641	-2.333-1.000	-2.714-0.571	-1.333-0.714

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Week 3	n	29	33	35	24
		Mean(SD)	1.120 (0.88)	1.567 (0.78)	1.616 (0.92)	1.650 (0.94)
		Median	1.000	1.571	1.333	1.500
		Min, Max	0.000-3.429	0.000-3.100	0.125-3.714	0.000-3.143
	Change from baseline Week 3	n	29	31	35	23
		Mean(SD)	-0.880 (0.72)	-0.727 (0.75)	-0.684 (0.85)	-0.519 (0.74)
		Median	-0.857	-0.714	-0.714	-0.571
		Min, Max	-2.286-0.286	-3.167-0.700	-2.446-1.321	-2.167-1.000
	Week 4	n	25	32	35	23
		Mean(SD)	0.917 (0.85)	1.405 (0.87)	1.648 (0.86)	1.518 (0.83)
		Median	1.000	1.000	1.429	1.667
		Min, Max	0.000-3.429	0.000-3.000	0.000-3.333	0.000-3.000
	Change from baseline Week 4	n	25	31	35	23
		Mean(SD)	-1.066 (0.68)	-0.913 (1.01)	-0.688 (0.85)	-0.717 (0.73)
		Median	-1.000	-1.000	-0.857	-0.857
		Min, Max	-2.286-0.000	-3.571-1.000	-2.714-1.571	-2.167-0.571
Summary of OLPSSM question no. 2 score by visit	Baseline	n	32	32	40	29
		Mean(SD)	1.993 (0.69)	2.177 (0.80)	2.203 (0.81)	1.972 (0.69)
		Median	2.000	2.183	2.000	2.000
		Min, Max	1.000-3.571	0.571-4.000	1.000-4.000	1.000-4.000
	Week 1	n	29	33	40	28

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Mean(SD)	1.533 (0.75)	1.877 (0.78)	1.787 (0.85)	1.701 (0.79)
		Median	1.667	2.000	1.815	1.732
		Min, Max	0.000-2.833	0.000-3.143	0.286-4.000	0.571-4.000
	Change from baseline Week 1	n	29	32	40	27
		Mean(SD)	-0.465 (0.68)	-0.305 (0.54)	-0.416 (0.72)	-0.243 (0.45)
		Median	-0.429	-0.286	-0.286	-0.143
		Min, Max	-1.857-1.143	-1.600-1.167	-2.857-1.000	-1.571-0.619
	Week 2	n	29	34	34	25
		Mean(SD)	1.084 (0.66)	1.704 (0.77)	1.588 (0.83)	1.608 (0.93)
		Median	1.000	1.571	1.586	1.500
		Min, Max	0.000-2.250	0.000-3.286	0.000-3.667	0.000-4.000
	Change from baseline Week 2	n	29	32	34	24
		Mean(SD)	-0.932 (0.79)	-0.459 (0.89)	-0.630 (0.78)	-0.280 (0.69)
		Median	-1.000	-0.464	-0.429	-0.134
		Min, Max	-2.800-0.654	-2.333-1.786	-2.857-0.571	-1.333-1.486
	Week 3	n	30	33	35	24
		Mean(SD)	0.964 (0.80)	1.415 (0.74)	1.318 (0.77)	1.414 (0.93)
		Median	1.000	1.429	1.143	1.205
		Min, Max	0.000-3.143	0.000-3.000	0.000-3.500	0.000-4.000
	Change from baseline Week 3	n	30	31	35	23
		Mean(SD)	-1.037 (0.73)	-0.785 (0.78)	-0.841 (0.84)	-0.572 (0.82)

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Median	-1.127	-0.714	-0.833	-0.571
		Min, Max	-3.000-0.143	-3.000-0.857	-2.446-0.629	-2.167-0.857
	Week 4	n	26	32	35	23
		Mean(SD)	0.742 (0.70)	1.194 (0.76)	1.323 (0.71)	1.312 (0.77)
		Median	0.619	1.000	1.167	1.286
		Min, Max	0.000-2.286	0.000-3.000	0.000-2.833	0.000-2.429
	Change from baseline Week 4	n	26	31	35	23
		Mean(SD)	-1.250 (0.68)	-1.026 (0.98)	-0.890 (0.77)	-0.692 (0.87)
		Median	-1.286	-1.000	-0.714	-0.746
		Min, Max	-2.625-0.000	-3.714-0.857	-2.714-0.405	-2.167-0.667
Summary of OLPSSM question no. 3 score by visit	Baseline	n	32	32	40	29
		Mean(SD)	1.265 (0.67)	1.592 (0.82)	1.571 (0.77)	1.411 (0.82)
		Median	1.268	1.571	1.690	1.286
		Min, Max	0.000-3.000	0.000-3.714	0.000-4.000	0.000-4.000
	Week 1	n	29	33	40	28
		Mean(SD)	0.989 (0.71)	1.322 (0.72)	1.163 (0.82)	1.164 (0.83)
		Median	1.000	1.429	1.183	1.042
		Min, Max	0.000-2.333	0.000-2.857	0.000-3.000	0.000-4.000
	Change from baseline Week 1	n	29	32	40	27
		Mean(SD)	-0.278 (0.66)	-0.284 (0.54)	-0.408 (0.71)	-0.199 (0.57)
		Median	-0.250	-0.286	-0.333	0.000

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Min, Max	-1.857-1.700	-1.089-1.571	-2.714-0.905	-1.714-0.714
	Week 2	n	29	34	34	25
		Mean(SD)	0.655 (0.62)	1.149 (0.74)	1.035 (0.79)	1.069 (0.74)
		Median	0.667	1.000	1.000	1.000
		Min, Max	0.000-2.000	0.000-2.571	0.000-3.000	0.000-2.400
	Change from baseline Week 2	n	29	32	34	24
		Mean(SD)	-0.612 (0.70)	-0.458 (0.69)	-0.489 (0.79)	-0.306 (0.75)
		Median	-0.429	-0.310	-0.489	-0.125
		Min, Max	-2.000-0.885	-2.048-0.914	-2.571-1.571	-2.000-1.114
	Week 3	n	30	33	35	24
		Mean(SD)	0.546 (0.65)	1.031 (0.73)	0.863 (0.68)	0.952 (0.82)
		Median	0.243	1.000	1.000	1.000
		Min, Max	0.000-2.429	0.000-2.700	0.000-2.286	0.000-2.500
	Change from baseline Week 3	n	30	31	35	23
		Mean(SD)	-0.703 (0.61)	-0.600 (0.76)	-0.626 (0.84)	-0.418 (0.77)
		Median	-0.545	-0.375	-0.571	-0.143
		Min, Max	-2.000-0.024	-2.589-1.014	-2.571-1.229	-2.000-0.857
	Week 4	n	26	32	35	23
		Mean(SD)	0.389 (0.55)	0.806 (0.67)	0.884 (0.64)	1.000 (0.81)
		Median	0.143	1.000	1.000	1.000
		Min, Max	0.000-1.857	0.000-2.167	0.000-2.167	0.000-3.000

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Change from baseline Week 4	n	26	31	35	23
		Mean(SD)	-0.871 (0.63)	-0.832 (0.95)	-0.613 (0.66)	-0.411 (0.55)
		Median	-1.000	-0.857	-0.714	-0.286
		Min, Max	-2.000-0.143	-3.571-0.881	-2.000-0.929	-1.667-0.482
Summary of OLPSSM question no. 4 score by visit	Baseline	n	32	32	40	29
		Mean(SD)	1.196 (0.79)	1.110 (0.77)	1.111 (0.73)	0.735 (0.81)
		Median	1.000	1.071	1.000	0.714
		Min, Max	0.000-3.000	0.000-2.333	0.000-2.429	0.000-3.000
	Week 1	n	29	33	40	28
		Mean(SD)	0.797 (0.71)	0.926 (0.80)	0.800 (0.67)	0.640 (0.62)
		Median	1.000	1.000	0.690	0.524
		Min, Max	0.000-2.222	0.000-3.143	0.000-2.143	0.000-2.000
	Change from baseline Week 1	n	29	32	40	27
		Mean(SD)	-0.393 (0.64)	-0.190 (0.60)	-0.311 (0.51)	-0.023 (0.62)
		Median	-0.286	0.000	-0.232	0.000
		Min, Max	-1.857-0.900	-1.933-1.286	-2.286-0.571	-1.714-2.000
	Week 2	n	29	34	34	25
		Mean(SD)	0.587 (0.59)	0.811 (0.76)	0.649 (0.62)	0.479 (0.56)
		Median	0.600	1.000	0.563	0.143
		Min, Max	0.000-2.000	0.000-2.400	0.000-2.143	0.000-1.500
		n	29	32	34	24

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Change from baseline Week 2	Mean(SD)	-0.629 (0.76)	-0.279 (0.64)	-0.493 (0.64)	-0.141 (0.45)
		Median	-0.500	-0.071	-0.417	0.000
		Min, Max	-2.400-0.577	-2.083-1.286	-2.429-0.571	-1.286-0.857
	Week 3	n	30	33	35	24
		Mean(SD)	0.347 (0.56)	0.663 (0.74)	0.576 (0.59)	0.504 (0.59)
		Median	0.000	0.571	0.400	0.000
		Min, Max	0.000-2.143	0.000-2.714	0.000-1.857	0.000-1.667
	Change from baseline Week 3	n	30	31	35	23
		Mean(SD)	-0.828 (0.71)	-0.413 (0.78)	-0.586 (0.68)	-0.224 (0.60)
		Median	-0.804	-0.429	-0.571	0.000
		Min, Max	-3.000-0.143	-2.333-1.714	-2.429-0.571	-1.857-0.857
	Week 4	n	26	32	35	23
		Mean(SD)	0.259 (0.49)	0.572 (0.77)	0.490 (0.53)	0.507 (0.63)
		Median	0.000	0.261	0.429	0.111
		Min, Max	0.000-1.857	0.000-3.000	0.000-2.000	0.000-2.167
	Change from baseline Week 4	n	26	31	35	23
		Mean(SD)	-0.876 (0.71)	-0.528 (0.90)	-0.652 (0.60)	-0.242 (0.61)
		Median	-0.857	-0.429	-0.571	0.000
		Min, Max	-3.000-0.143	-2.083-2.000	-2.143-0.214	-1.714-0.738
Summary of OLPSSM question no. 5 score by visit	Baseline	n	32	32	40	29
		Mean(SD)	0.784 (0.90)	0.861 (0.84)	0.652 (0.76)	0.525 (0.59)

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Median	0.464	0.929	0.214	0.200
		Min, Max	0.000-3.167	0.000-2.286	0.000-2.714	0.000-1.800
	Week 1	n	29	33	40	28
		Mean(SD)	0.561 (0.65)	0.682 (0.71)	0.434 (0.61)	0.395 (0.54)
		Median	0.286	0.667	0.000	0.071
		Min, Max	0.000-2.000	0.000-2.571	0.000-2.000	0.000-1.833
	Change from baseline Week 1	n	29	32	40	27
		Mean(SD)	-0.213 (0.54)	-0.189 (0.50)	-0.219 (0.56)	-0.052 (0.37)
		Median	0.000	0.000	0.000	0.000
		Min, Max	-1.857-1.000	-1.800-1.286	-2.714-1.000	-1.429-0.833
	Week 2	n	29	34	34	25
		Mean(SD)	0.387 (0.53)	0.640 (0.81)	0.456 (0.63)	0.327 (0.48)
		Median	0.143	0.063	0.056	0.143
		Min, Max	0.000-2.000	0.000-3.000	0.000-2.857	0.000-1.375
	Change from baseline Week 2	n	29	32	34	24
		Mean(SD)	-0.404 (0.76)	-0.212 (0.66)	-0.252 (0.63)	-0.105 (0.35)
		Median	-0.143	0.000	0.000	0.000
		Min, Max	-3.024-0.556	-1.875-1.500	-2.714-0.690	-1.000-0.548
	Week 3	n	30	33	35	24
		Mean(SD)	0.276 (0.59)	0.451 (0.61)	0.313 (0.48)	0.324 (0.51)
		Median	0.000	0.000	0.000	0.000

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Min, Max	0.000-2.143	0.000-2.300	0.000-1.571	0.000-1.500
	Change from baseline Week 3	n	30	31	35	23
		Mean(SD)	-0.494 (0.66)	-0.409 (0.66)	-0.371 (0.70)	-0.138 (0.53)
		Median	-0.143	0.000	-0.018	0.000
		Min, Max	-2.310-0.429	-2.000-1.014	-2.714-1.143	-1.429-1.000
	Week 4	n	26	32	35	23
		Mean(SD)	0.231 (0.46)	0.423 (0.64)	0.247 (0.48)	0.287 (0.47)
		Median	0.000	0.000	0.000	0.000
		Min, Max	0.000-1.714	0.000-2.333	0.000-1.857	0.000-1.333
	Change from baseline Week 4	n	26	31	35	23
		Mean(SD)	-0.550 (0.72)	-0.452 (0.83)	-0.413 (0.66)	-0.190 (0.46)
		Median	-0.143	0.000	-0.143	0.000
		Min, Max	-2.452-0.429	-2.286-1.357	-2.429-0.571	-1.571-0.589
Summary of OLPSSM question no. 6 score by visit	Baseline	n	32	32	40	29
		Mean(SD)	1.142 (0.75)	1.044 (0.89)	1.106 (0.82)	0.802 (0.81)
		Median	1.000	1.000	1.000	0.667
		Min, Max	0.000-3.429	0.000-2.500	0.000-2.714	0.000-3.000
	Week 1	n	29	33	40	28
		Mean(SD)	0.845 (0.64)	0.966 (0.82)	0.780 (0.67)	0.599 (0.70)
		Median	1.000	1.000	0.917	0.292
		Min, Max	0.000-2.000	0.000-3.143	0.000-2.667	0.000-2.667

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Change from baseline Week 1	n	29	32	40	27
		Mean(SD)	-0.311 (0.65)	-0.079 (0.57)	-0.326 (0.59)	-0.130 (0.46)
		Median	-0.167	0.000	-0.155	0.000
		Min, Max	-1.857-1.000	-1.429-1.286	-2.429-0.429	-1.857-0.833
	Week 2	n	29	34	34	25
		Mean(SD)	0.673 (0.67)	0.924 (0.90)	0.725 (0.65)	0.556 (0.52)
		Median	0.667	0.938	0.690	0.500
		Min, Max	0.000-2.143	0.000-3.000	0.000-2.143	0.000-1.375
	Change from baseline Week 2	n	29	32	34	24
		Mean(SD)	-0.493 (0.76)	-0.094 (0.71)	-0.421 (0.69)	-0.110 (0.52)
		Median	-0.286	0.000	-0.268	-0.071
		Min, Max	-2.143-1.000	-1.625-1.833	-2.714-0.429	-1.000-1.000
	Week 3	n	30	33	35	24
		Mean(SD)	0.424 (0.66)	0.724 (0.79)	0.619 (0.59)	0.511 (0.65)
		Median	0.063	0.571	0.571	0.071
		Min, Max	0.000-2.833	0.000-2.900	0.000-2.286	0.000-2.429
	Change from baseline Week 3	n	30	31	35	23
		Mean(SD)	-0.704 (0.66)	-0.281 (0.72)	-0.535 (0.68)	-0.261 (0.58)
		Median	-0.583	0.000	-0.286	-0.143
		Min, Max	-2.143-0.000	-2.500-1.043	-2.429-0.429	-1.333-1.000
	Week 4	n	26	32	35	23

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Mean(SD)	0.292 (0.59)	0.656 (0.86)	0.506 (0.53)	0.532 (0.69)
		Median	0.000	0.196	0.400	0.111
		Min, Max	0.000-2.429	0.000-3.000	0.000-1.857	0.000-2.143
	Change from baseline Week 4	n	26	31	35	23
		Mean(SD)	-0.789 (0.67)	-0.374 (0.92)	-0.616 (0.68)	-0.262 (0.60)
		Median	-0.714	-0.033	-0.500	-0.143
		Min, Max	-2.143-0.000	-2.286-1.143	-2.429-0.333	-1.333-1.000
Summary of OLPSSM question no. 7 score by visit	Baseline	n	32	32	40	29
		Mean(SD)	2.209 (0.95)	2.079 (0.94)	2.344 (1.00)	2.157 (0.70)
		Median	2.071	2.000	2.083	2.143
		Min, Max	0.143-4.000	0.000-4.000	0.000-4.000	0.286-3.571
	Week 1	n	29	33	40	28
		Mean(SD)	1.893 (0.86)	1.951 (0.86)	1.924 (0.96)	2.111 (0.66)
		Median	2.000	2.000	1.929	2.000
		Min, Max	0.000-3.500	0.143-3.400	0.000-4.000	1.000-3.800
	Change from baseline Week 1	n	29	32	40	27
		Mean(SD)	-0.304 (0.73)	-0.098 (0.69)	-0.421 (0.78)	-0.010 (0.67)
		Median	-0.286	-0.190	-0.357	0.000
		Min, Max	-1.571-1.714	-1.167-2.250	-3.143-0.714	-1.429-1.714
	Week 2	n	29	34	34	25
		Mean(SD)	1.463 (0.85)	1.729 (0.84)	1.930 (1.03)	1.865 (0.71)

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Median	1.333	1.714	1.944	1.800
		Min, Max	0.000-3.143	0.000-3.000	0.143-4.000	1.000-3.400
	Change from baseline Week 2	n	29	32	34	24
		Mean(SD)	-0.777 (0.87)	-0.304 (0.82)	-0.481 (0.88)	-0.173 (0.79)
		Median	-0.800	-0.286	-0.250	0.000
		Min, Max	-2.571-1.026	-1.778-1.714	-3.000-0.857	-1.444-1.714
	Week 3	n	30	33	35	24
		Mean(SD)	1.272 (0.99)	1.417 (0.86)	1.663 (0.96)	1.700 (0.78)
		Median	1.071	1.333	1.286	1.571
		Min, Max	0.000-4.000	0.000-3.000	0.000-3.857	0.625-3.000
	Change from baseline Week 3	n	30	31	35	23
		Mean(SD)	-0.951 (0.94)	-0.643 (0.84)	-0.634 (0.79)	-0.420 (0.94)
		Median	-0.714	-0.571	-0.429	-0.429
		Min, Max	-3.000-0.286	-3.000-1.143	-2.476-0.500	-1.571-1.464
	Week 4	n	26	32	35	23
		Mean(SD)	1.038 (1.02)	1.278 (0.87)	1.621 (0.99)	1.638 (0.77)
		Median	0.929	1.000	1.286	1.429
		Min, Max	0.000-3.714	0.000-3.000	0.000-4.000	0.000-3.000
	Change from baseline Week 4	n	26	31	35	23
		Mean(SD)	-1.149 (0.93)	-0.800 (0.99)	-0.696 (0.83)	-0.513 (1.03)
		Median	-1.286	-0.714	-0.600	-0.857

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Min, Max	-2.600-0.286	-3.571-0.857	-2.310-0.833	-2.000-1.548
Listing(s): Derived from Listing 16.2.4.1						

Table 14.2.3.2 Statistical analysis of OLPSSM sum score and #1 - #7 weekly means [FAS]

a) OLPSSM 1-7 Sum score

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-1.927	20 ug vs placebo	-0.853	(-2.424, 0.718)	0.2845
	5 ug	-1.122	5 ug vs placebo	-0.048	(-1.608, 1.512)	0.9517
	1 ug	-2.180	1 ug vs placebo	-1.106	(-2.598, 0.385)	0.1445
	Placebo	-1.074				
Week 2	20 ug	-4.268	20 ug vs placebo	-2.304	(-4.104, -0.504)	0.0126
	5 ug	-2.064	5 ug vs placebo	-0.100	(-1.887, 1.687)	0.9121
	1 ug	-2.867	1 ug vs placebo	-0.903	(-2.613, 0.806)	0.2973
	Placebo	-1.964				
Week 3	20 ug	-4.788	20 ug vs placebo	-2.712	(-4.545, -0.879)	0.0041
	5 ug	-2.876	5 ug vs placebo	-0.799	(-2.619, 1.020)	0.3862
	1 ug	-3.336	1 ug vs placebo	-1.260	(-3.000, 0.480)	0.1543
	Placebo	-2.077				
Week 4	20 ug	-5.561	20 ug vs placebo	-3.224	(-4.974, -1.474)	0.0004
	5 ug	-3.607	5 ug vs placebo	-1.270	(-3.008, 0.467)	0.1504
	1 ug	-3.155	1 ug vs placebo	-0.818	(-2.480, 0.843)	0.3315

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
	Placebo	-2.337				
Week 3-4	20 ug	-5.170	20 ug vs placebo	-2.967	(-4.643, -1.292)	0.0006
	5 ug	-3.237	5 ug vs placebo	-1.034	(-2.699, 0.630)	0.2208
	1 ug	-3.256	1 ug vs placebo	-1.054	(-2.645, 0.538)	0.1923
	Placebo	-2.203				
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.3						

Table 14.2.3.2 Statistical analysis of OLPSSM sum score and #1 - #7 weekly means [FAS]: b) #1 - #7

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Analysis of OLPSSM question no. 1 score by visit, ANCOVA	Week 1	20 ug	-0.293	20 ug vs placebo	-0.108	(-0.404, 0.188)	0.4720
		5 ug	-0.196	5 ug vs placebo	-0.011	(-0.302, 0.281)	0.9432
		1 ug	-0.329	1 ug vs placebo	-0.144	(-0.421, 0.134)	0.3084
		Placebo	-0.186				
	Week 2	20 ug	-0.750	20 ug vs placebo	-0.441	(-0.783, -0.099)	0.0119
		5 ug	-0.439	5 ug vs placebo	-0.130	(-0.466, 0.207)	0.4466
		1 ug	-0.478	1 ug vs placebo	-0.169	(-0.490, 0.152)	0.2980
		Placebo	-0.309				
	Week 3	20 ug	-0.828	20 ug vs placebo	-0.492	(-0.856, -0.128)	0.0085
		5 ug	-0.533	5 ug vs placebo	-0.196	(-0.554, 0.162)	0.2806
		1 ug	-0.526	1 ug vs placebo	-0.189	(-0.530, 0.153)	0.2760
		Placebo	-0.337				

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
	Week 4	20 ug	-0.964	20 ug vs placebo	-0.502	(-0.880, -0.124)	0.0097
		5 ug	-0.660	5 ug vs placebo	-0.198	(-0.571, 0.174)	0.2935
		1 ug	-0.440	1 ug vs placebo	0.022	(-0.333, 0.377)	0.9033
		Placebo	-0.462				
	Week 3-4	20 ug	-0.895	20 ug vs placebo	-0.498	(-0.846, -0.150)	0.0055
		5 ug	-0.594	5 ug vs placebo	-0.197	(-0.540, 0.146)	0.2573
		1 ug	-0.489	1 ug vs placebo	-0.092	(-0.419, 0.235)	0.5778
		Placebo	-0.397				
Analysis of OLPSSM question no. 2 score by visit, ANCOVA	Week 1	20 ug	-0.443	20 ug vs placebo	-0.176	(-0.476, 0.124)	0.2483
		5 ug	-0.282	5 ug vs placebo	-0.015	(-0.315, 0.285)	0.9220
		1 ug	-0.385	1 ug vs placebo	-0.117	(-0.404, 0.170)	0.4206
		Placebo	-0.267				
	Week 2	20 ug	-0.908	20 ug vs placebo	-0.584	(-0.942, -0.225)	0.0016
		5 ug	-0.397	5 ug vs placebo	-0.072	(-0.431, 0.286)	0.6896
		1 ug	-0.515	1 ug vs placebo	-0.191	(-0.533, 0.152)	0.2730
		Placebo	-0.325				
	Week 3	20 ug	-0.943	20 ug vs placebo	-0.522	(-0.898, -0.146)	0.0069
		5 ug	-0.581	5 ug vs placebo	-0.160	(-0.536, 0.216)	0.4010
		1 ug	-0.669	1 ug vs placebo	-0.248	(-0.607, 0.111)	0.1738
		Placebo	-0.421				
	Week 4	20 ug	-1.062	20 ug vs placebo	-0.577	(-0.932, -0.222)	0.0016
		5 ug	-0.729	5 ug vs placebo	-0.244	(-0.599, 0.111)	0.1755

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
		1 ug	-0.584	1 ug vs placebo	-0.100	(-0.439, 0.239)	0.5618
		Placebo	-0.485				
	Week 3-4	20 ug	-1.002	20 ug vs placebo	-0.549	(-0.888, -0.211)	0.0017
		5 ug	-0.654	5 ug vs placebo	-0.201	(-0.540, 0.137)	0.2415
		1 ug	-0.629	1 ug vs placebo	-0.177	(-0.501, 0.147)	0.2815
		Placebo	-0.452				
Analysis of OLPSSM question no. 3 score by visit, ANCOVA	Week 1	20 ug	-0.294	20 ug vs placebo	-0.130	(-0.430, 0.171)	0.3940
		5 ug	-0.199	5 ug vs placebo	-0.036	(-0.335, 0.264)	0.8149
		1 ug	-0.342	1 ug vs placebo	-0.178	(-0.464, 0.108)	0.2202
		Placebo	-0.164				
	Week 2	20 ug	-0.607	20 ug vs placebo	-0.362	(-0.678, -0.046)	0.0253
		5 ug	-0.322	5 ug vs placebo	-0.077	(-0.392, 0.239)	0.6317
		1 ug	-0.367	1 ug vs placebo	-0.121	(-0.422, 0.180)	0.4266
		Placebo	-0.245				
	Week 3	20 ug	-0.612	20 ug vs placebo	-0.411	(-0.714, -0.108)	0.0083
		5 ug	-0.389	5 ug vs placebo	-0.188	(-0.490, 0.115)	0.2214
		1 ug	-0.443	1 ug vs placebo	-0.241	(-0.530, 0.047)	0.1001
		Placebo	-0.201				
	Week 4	20 ug	-0.792	20 ug vs placebo	-0.591	(-0.869, -0.313)	<.0001
		5 ug	-0.594	5 ug vs placebo	-0.393	(-0.670, -0.115)	0.0059
		1 ug	-0.398	1 ug vs placebo	-0.197	(-0.461, 0.068)	0.1432
		Placebo	-0.202				

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
	Week 3-4	20 ug	-0.702	20 ug vs placebo	-0.501	(-0.767, -0.235)	0.0003
		5 ug	-0.491	5 ug vs placebo	-0.290	(-0.556, -0.025)	0.0325
		1 ug	-0.421	1 ug vs placebo	-0.220	(-0.473, 0.033)	0.0875
		Placebo	-0.201				
Analysis of OLPSSM question no. 4 score by visit, ANCOVA	Week 1	20 ug	-0.304	20 ug vs placebo	-0.157	(-0.431, 0.116)	0.2570
		5 ug	-0.161	5 ug vs placebo	-0.014	(-0.285, 0.257)	0.9164
		1 ug	-0.292	1 ug vs placebo	-0.145	(-0.404, 0.114)	0.2692
		Placebo	-0.146				
	Week 2	20 ug	-0.541	20 ug vs placebo	-0.165	(-0.434, 0.105)	0.2278
		5 ug	-0.258	5 ug vs placebo	0.118	(-0.149, 0.385)	0.3820
		1 ug	-0.446	1 ug vs placebo	-0.070	(-0.325, 0.185)	0.5885
		Placebo	-0.376				
	Week 3	20 ug	-0.694	20 ug vs placebo	-0.336	(-0.623, -0.049)	0.0221
		5 ug	-0.310	5 ug vs placebo	0.047	(-0.237, 0.331)	0.7435
		1 ug	-0.459	1 ug vs placebo	-0.101	(-0.373, 0.170)	0.4607
		Placebo	-0.358				
	Week 4	20 ug	-0.751	20 ug vs placebo	-0.383	(-0.667, -0.098)	0.0088
		5 ug	-0.401	5 ug vs placebo	-0.032	(-0.314, 0.249)	0.8201
		1 ug	-0.499	1 ug vs placebo	-0.130	(-0.399, 0.138)	0.3387
		Placebo	-0.368				
	Week 3-4	20 ug	-0.723	20 ug vs placebo	-0.359	(-0.629, -0.089)	0.0095
		5 ug	-0.356	5 ug vs placebo	0.007	(-0.260, 0.275)	0.9562

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
		1 ug	-0.479	1 ug vs placebo	-0.115	(-0.370, 0.140)	0.3734
		Placebo	-0.363				
Analysis of OLPSSM question no. 5 score by visit, ANCOVA	Week 1	20 ug	-0.167	20 ug vs placebo	-0.048	(-0.262, 0.167)	0.6597
		5 ug	-0.108	5 ug vs placebo	0.011	(-0.204, 0.227)	0.9174
		1 ug	-0.226	1 ug vs placebo	-0.107	(-0.310, 0.096)	0.3003
		Placebo	-0.120				
	Week 2	20 ug	-0.405	20 ug vs placebo	-0.153	(-0.410, 0.103)	0.2390
		5 ug	-0.177	5 ug vs placebo	0.075	(-0.183, 0.332)	0.5669
		1 ug	-0.317	1 ug vs placebo	-0.065	(-0.308, 0.177)	0.5958
		Placebo	-0.252				
	Week 3	20 ug	-0.422	20 ug vs placebo	-0.171	(-0.400, 0.058)	0.1418
		5 ug	-0.294	5 ug vs placebo	-0.043	(-0.272, 0.187)	0.7143
		1 ug	-0.373	1 ug vs placebo	-0.122	(-0.338, 0.095)	0.2674
		Placebo	-0.251				
	Week 4	20 ug	-0.486	20 ug vs placebo	-0.183	(-0.407, 0.041)	0.1093
		5 ug	-0.302	5 ug vs placebo	0.000	(-0.225, 0.226)	0.9967
		1 ug	-0.385	1 ug vs placebo	-0.082	(-0.294, 0.130)	0.4438
		Placebo	-0.303				
	Week 3-4	20 ug	-0.453	20 ug vs placebo	-0.177	(-0.389, 0.035)	0.1015
		5 ug	-0.298	5 ug vs placebo	-0.021	(-0.234, 0.192)	0.8438
		1 ug	-0.380	1 ug vs placebo	-0.104	(-0.304, 0.097)	0.3091
		Placebo	-0.277				

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Analysis of OLPSSM question no. 6 score by visit, ANCOVA	Week 1	20 ug	-0.199	20 ug vs placebo	0.026	(-0.234, 0.286)	0.8450
		5 ug	-0.064	5 ug vs placebo	0.160	(-0.097, 0.418)	0.2205
		1 ug	-0.301	1 ug vs placebo	-0.077	(-0.324, 0.170)	0.5384
		Placebo	-0.224				
	Week 2	20 ug	-0.460	20 ug vs placebo	-0.177	(-0.476, 0.122)	0.2436
		5 ug	-0.127	5 ug vs placebo	0.155	(-0.142, 0.452)	0.3027
		1 ug	-0.407	1 ug vs placebo	-0.124	(-0.409, 0.161)	0.3897
		Placebo	-0.282				
	Week 3	20 ug	-0.587	20 ug vs placebo	-0.281	(-0.561, -0.001)	0.0488
		5 ug	-0.211	5 ug vs placebo	0.095	(-0.183, 0.372)	0.5009
		1 ug	-0.427	1 ug vs placebo	-0.121	(-0.388, 0.145)	0.3683
		Placebo	-0.306				
	Week 4	20 ug	-0.673	20 ug vs placebo	-0.354	(-0.651, -0.056)	0.0203
		5 ug	-0.278	5 ug vs placebo	0.041	(-0.254, 0.337)	0.7822
		1 ug	-0.479	1 ug vs placebo	-0.160	(-0.443, 0.124)	0.2667
		Placebo	-0.319				
	Week 3-4	20 ug	-0.630	20 ug vs placebo	-0.317	(-0.590, -0.045)	0.0228
		5 ug	-0.244	5 ug vs placebo	0.068	(-0.203, 0.338)	0.6199
		1 ug	-0.453	1 ug vs placebo	-0.141	(-0.401, 0.118)	0.2839
		Placebo	-0.312				
Analysis of OLPSSM question no. 7 score by visit, ANCOVA	Week 1	20 ug	-0.203	20 ug vs placebo	-0.230	(-0.558, 0.097)	0.1661
		5 ug	-0.121	5 ug vs placebo	-0.148	(-0.475, 0.178)	0.3697

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
		1 ug	-0.330	1 ug vs placebo	-0.358	(-0.669, -0.046)	0.0248
		Placebo	0.028				
	Week 2	20 ug	-0.666	20 ug vs placebo	-0.503	(-0.873, -0.132)	0.0083
		5 ug	-0.327	5 ug vs placebo	-0.164	(-0.533, 0.206)	0.3822
		1 ug	-0.356	1 ug vs placebo	-0.192	(-0.545, 0.161)	0.2837
		Placebo	-0.164				
	Week 3	20 ug	-0.761	20 ug vs placebo	-0.552	(-0.938, -0.166)	0.0054
		5 ug	-0.532	5 ug vs placebo	-0.323	(-0.708, 0.061)	0.0987
		1 ug	-0.470	1 ug vs placebo	-0.261	(-0.628, 0.107)	0.1624
		Placebo	-0.209				
	Week 4	20 ug	-0.899	20 ug vs placebo	-0.660	(-1.051, -0.269)	0.0011
		5 ug	-0.616	5 ug vs placebo	-0.377	(-0.766, 0.013)	0.0582
		1 ug	-0.400	1 ug vs placebo	-0.160	(-0.532, 0.212)	0.3953
		Placebo	-0.239				
	Week 3-4	20 ug	-0.830	20 ug vs placebo	-0.606	(-0.977, -0.235)	0.0016
		5 ug	-0.574	5 ug vs placebo	-0.350	(-0.720, 0.020)	0.0637
		1 ug	-0.434	1 ug vs placebo	-0.210	(-0.564, 0.143)	0.2408
		Placebo	-0.224				
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.3							

Table 14.2.3.3 Summary of OLPSSM #8 - #10 weekly means [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of OLPSSM question no. 8 score by visit	Baseline	n	31	32	40	29
		Mean(SD)	2.747 (1.17)	2.935 (0.99)	2.754 (0.99)	2.314 (0.87)
		Median	2.857	3.000	2.786	2.143
		Min, Max	1.00-4.00	1.00-4.00	1.00-4.00	1.00-4.00
	Week 1	n	29	33	40	28
		Mean(SD)	2.469 (1.31)	2.842 (0.96)	2.411 (1.04)	2.169 (0.96)
		Median	2.143	2.857	2.402	2.437
		Min, Max	0.17-4.00	1.00-4.00	0.56-4.00	0.86-4.00
	Change from baseline Week 1	n	28	32	40	27
		Mean(SD)	-0.337 (0.88)	-0.129 (0.62)	-0.342 (0.71)	-0.103 (0.54)
		Median	-0.071	0.000	-0.155	-0.143
		Min, Max	-1.93-2.43	-1.60-1.71	-3.00-0.75	-1.57-1.00
	Week 2	n	29	34	34	25
		Mean(SD)	2.111 (1.33)	2.645 (1.17)	2.245 (1.06)	1.899 (0.93)
		Median	1.800	2.652	2.163	1.375
		Min, Max	0.29-4.00	0.50-4.00	0.14-4.00	1.00-3.63
	Change from baseline Week 2	n	28	32	34	24
		Mean(SD)	-0.753 (1.00)	-0.282 (1.02)	-0.580 (1.01)	-0.371 (0.68)
		Median	-0.544	0.000	-0.343	-0.402
		Min, Max	-2.86-1.53	-2.50-2.67	-3.00-1.57	-1.57-1.26

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Week 3	n	30	33	35	24
		Mean(SD)	1.785 (1.41)	2.306 (1.26)	2.046 (1.13)	1.844 (1.00)
		Median	1.083	2.000	2.000	1.429
		Min, Max	0.00-4.00	0.00-4.00	0.33-4.00	0.13-3.71
	Change from baseline Week 3	n	29	31	35	23
		Mean(SD)	-1.025 (1.04)	-0.618 (1.11)	-0.715 (1.11)	-0.426 (0.89)
		Median	-1.000	-0.214	-0.429	-0.429
		Min, Max	-3.57-0.14	-4.00-2.00	-3.00-1.29	-1.86-1.29
	Week 4	n	26	32	35	23
		Mean(SD)	1.478 (1.37)	2.098 (1.31)	1.880 (0.97)	1.777 (0.97)
		Median	1.000	1.500	1.800	1.429
		Min, Max	0.00-4.00	0.25-4.00	0.75-4.00	0.00-4.00
	Change from baseline Week 4	n	25	31	35	23
		Mean(SD)	-1.263 (1.03)	-0.875 (1.29)	-0.893 (1.12)	-0.536 (0.82)
		Median	-1.429	-0.429	-0.714	-0.571
		Min, Max	-3.14-0.14	-3.75-2.00	-3.25-1.57	-2.14-1.00
Summary of OLPSSM question no. 9 score by visit	Baseline	n	32	32	40	29
		Mean(SD)	2.221 (0.79)	2.458 (0.60)	2.379 (0.69)	2.153 (0.58)
		Median	2.143	2.571	2.286	2.000
		Min, Max	0.86-3.83	1.00-4.00	1.29-4.00	1.14-3.14
	Week 1	n	29	33	40	28

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Mean(SD)	1.774 (0.68)	2.181 (0.63)	2.006 (0.70)	2.114 (0.71)
		Median	1.833	2.000	2.000	2.071
		Min, Max	0.17-3.00	1.00-3.43	0.56-3.25	1.00-4.00
	Change from baseline Week 1	n	29	32	40	27
		Mean(SD)	-0.435 (0.62)	-0.268 (0.55)	-0.373 (0.66)	-0.009 (0.46)
		Median	-0.500	-0.286	-0.286	0.000
		Min, Max	-1.69-1.63	-1.43-0.86	-3.00-0.57	-1.00-1.00
	Week 2	n	29	34	34	25
		Mean(SD)	1.479 (0.68)	1.961 (0.77)	1.899 (0.76)	1.934 (0.77)
		Median	1.286	1.929	1.873	1.800
		Min, Max	0.29-3.00	0.25-3.60	0.43-3.43	1.00-3.43
	Change from baseline Week 2	n	29	32	34	24
		Mean(SD)	-0.765 (0.77)	-0.469 (0.78)	-0.542 (0.74)	-0.147 (0.65)
		Median	-0.857	-0.532	-0.429	-0.143
		Min, Max	-2.40-1.29	-1.78-1.36	-2.71-0.71	-1.63-1.20
	Week 3	n	30	33	35	24
		Mean(SD)	1.253 (0.74)	1.667 (0.72)	1.683 (0.77)	1.763 (0.79)
		Median	1.155	1.571	1.714	1.619
		Min, Max	0.00-2.50	0.00-3.00	0.33-3.57	0.25-3.00
	Change from baseline Week 3	n	30	31	35	23
		Mean(SD)	-0.949 (0.65)	-0.795 (0.73)	-0.714 (0.82)	-0.399 (0.79)

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Median	-1.000	-0.857	-0.500	-0.429
		Min, Max	-2.29-0.14	-2.83-0.43	-3.00-0.91	-2.00-1.14
	Week 4	n	26	32	35	23
		Mean(SD)	1.011 (0.75)	1.539 (0.82)	1.586 (0.64)	1.657 (0.75)
		Median	1.000	1.286	1.500	1.778
		Min, Max	0.00-2.57	0.00-3.17	0.63-3.17	0.00-3.00
	Change from baseline Week 4	n	26	31	35	23
		Mean(SD)	-1.162 (0.63)	-0.949 (0.96)	-0.839 (0.76)	-0.539 (0.75)
		Median	-1.131	-0.857	-0.714	-0.571
		Min, Max	-2.14-0.00	-3.57-0.79	-2.43-0.33	-2.00-0.90
Summary of OLPSSM question no. 10 score by visit	Baseline	n	32	32	40	29
		Mean(SD)	5.682 (2.47)	6.030 (2.00)	5.643 (2.33)	5.479 (1.88)
		Median	6.500	6.286	5.845	5.429
		Min, Max	1.00-9.50	1.00-9.14	1.00-9.29	1.43-8.29
	Week 1	n	29	33	40	28
		Mean(SD)	4.727 (2.25)	5.485 (1.94)	4.929 (2.19)	5.364 (1.85)
		Median	5.125	6.286	5.619	5.500
		Min, Max	0.17-8.50	1.00-8.40	1.00-8.71	1.50-9.00
	Change from baseline Week 1	n	29	32	40	27
		Mean(SD)	-0.939 (1.63)	-0.495 (1.21)	-0.714 (1.37)	-0.076 (1.00)
		Median	-0.714	-0.524	-0.298	0.000

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Min, Max	-4.93-4.13	-3.87-2.29	-5.30-1.29	-2.14-1.45
	Week 2	n	29	34	34	25
		Mean(SD)	3.643 (2.22)	4.929 (2.24)	4.736 (2.15)	4.967 (1.96)
		Median	3.400	4.845	4.917	5.000
		Min, Max	0.29-8.75	1.00-8.71	0.43-8.29	1.50-8.86
	Change from baseline Week 2	n	29	32	34	24
		Mean(SD)	-2.223 (2.02)	-0.949 (1.89)	-1.019 (1.39)	-0.479 (1.72)
		Median	-2.000	-0.940	-1.000	-0.286
		Min, Max	-6.43-3.18	-5.54-3.88	-4.49-1.71	-4.43-2.14
	Week 3	n	30	33	35	24
		Mean(SD)	2.983 (2.38)	4.051 (2.12)	4.054 (2.09)	4.663 (2.16)
		Median	2.286	3.833	4.143	4.500
		Min, Max	0.00-8.00	0.00-8.10	1.00-8.57	0.25-9.00
	Change from baseline Week 3	n	30	31	35	23
		Mean(SD)	-2.721 (1.99)	-1.885 (1.95)	-1.618 (1.90)	-0.922 (2.17)
		Median	-2.905	-1.429	-1.667	-1.286
		Min, Max	-7.43-0.14	-7.67-1.50	-5.86-1.14	-4.71-2.48
	Week 4	n	26	32	35	23
		Mean(SD)	2.304 (2.16)	3.658 (2.16)	3.623 (2.02)	4.227 (2.17)
		Median	2.268	3.214	3.429	4.000
		Min, Max	0.00-7.71	0.50-7.71	0.86-7.50	0.00-8.57

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Change from baseline Week 4	n	26	31	35	23
		Mean(SD)	-3.142 (1.93)	-2.362 (2.51)	-2.131 (2.07)	-1.431 (2.32)
		Median	-3.286	-1.929	-1.714	-1.429
		Min, Max	-6.86-0.00	-8.00-2.31	-6.45-1.67	-5.86-2.76
Listing(s): Derived from Listing 16.2.4.1						

Table 14.2.3.4 Statistical analysis of OLPSSM #8 - #10 weekly means [FAS]

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Analysis of OLPSSM question no. 8 score by visit, ANCOVA	Week 1	20 ug	-0.269	20 ug vs placebo	-0.125	(-0.488, 0.238)	0.4965
		5 ug	-0.057	5 ug vs placebo	0.087	(-0.275, 0.449)	0.6352
		1 ug	-0.305	1 ug vs placebo	-0.162	(-0.504, 0.181)	0.3520
		Placebo	-0.144				
	Week 2	20 ug	-0.656	20 ug vs placebo	-0.274	(-0.739, 0.191)	0.2450
		5 ug	-0.132	5 ug vs placebo	0.250	(-0.214, 0.714)	0.2888
		1 ug	-0.480	1 ug vs placebo	-0.099	(-0.537, 0.340)	0.6570
		Placebo	-0.382				
	Week 3	20 ug	-0.801	20 ug vs placebo	-0.532	(-1.050, -0.015)	0.0439
		5 ug	-0.308	5 ug vs placebo	-0.040	(-0.556, 0.477)	0.8794
		1 ug	-0.538	1 ug vs placebo	-0.269	(-0.757, 0.220)	0.2778
		Placebo	-0.269				
	Week 4	20 ug	-0.972	20 ug vs placebo	-0.600	(-1.117, -0.082)	0.0235

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
		5 ug	-0.523	5 ug vs placebo	-0.151	(-0.667, 0.366)	0.5643
		1 ug	-0.581	1 ug vs placebo	-0.209	(-0.697, 0.279)	0.3983
		Placebo	-0.372				
	Week 3-4	20 ug	-0.886	20 ug vs placebo	-0.566	(-1.065, -0.066)	0.0268
		5 ug	-0.415	5 ug vs placebo	-0.095	(-0.593, 0.404)	0.7073
		1 ug	-0.561	1 ug vs placebo	-0.241	(-0.712, 0.230)	0.3130
		Placebo	-0.320				
Analysis of OLPSSM question no. 9 score by visit, ANCOVA	Week 1	20 ug	-0.439	20 ug vs placebo	-0.371	(-0.650, -0.092)	0.0096
		5 ug	-0.226	5 ug vs placebo	-0.158	(-0.439, 0.122)	0.2666
		1 ug	-0.356	1 ug vs placebo	-0.288	(-0.555, -0.022)	0.0343
		Placebo	-0.068				
	Week 2	20 ug	-0.735	20 ug vs placebo	-0.589	(-0.931, -0.247)	0.0009
		5 ug	-0.354	5 ug vs placebo	-0.208	(-0.552, 0.136)	0.2344
		1 ug	-0.473	1 ug vs placebo	-0.327	(-0.654, -0.001)	0.0497
		Placebo	-0.146				
	Week 3	20 ug	-0.827	20 ug vs placebo	-0.627	(-0.974, -0.281)	0.0005
		5 ug	-0.512	5 ug vs placebo	-0.312	(-0.661, 0.036)	0.0784
		1 ug	-0.556	1 ug vs placebo	-0.356	(-0.686, -0.025)	0.0354
		Placebo	-0.200				
	Week 4	20 ug	-0.957	20 ug vs placebo	-0.672	(-1.017, -0.327)	0.0002
		5 ug	-0.597	5 ug vs placebo	-0.311	(-0.658, 0.036)	0.0781
		1 ug	-0.555	1 ug vs placebo	-0.269	(-0.598, 0.061)	0.1088

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
		Placebo	-0.286				
	Week 3-4	20 ug	-0.891	20 ug vs placebo	-0.649	(-0.974, -0.324)	0.0001
		5 ug	-0.553	5 ug vs placebo	-0.311	(-0.637, 0.016)	0.0620
		1 ug	-0.558	1 ug vs placebo	-0.316	(-0.627, -0.006)	0.0456
		Placebo	-0.242				
Analysis of OLPSSM question no. 10 score by visit, ANCOVA	Week 1	20 ug	-0.875	20 ug vs placebo	-0.759	(-1.399, -0.118)	0.0206
		5 ug	-0.456	5 ug vs placebo	-0.340	(-0.979, 0.300)	0.2950
		1 ug	-0.763	1 ug vs placebo	-0.647	(-1.255, -0.039)	0.0373
		Placebo	-0.116				
	Week 2	20 ug	-2.065	20 ug vs placebo	-1.672	(-2.521, -0.823)	0.0002
		5 ug	-0.821	5 ug vs placebo	-0.428	(-1.276, 0.420)	0.3193
		1 ug	-1.108	1 ug vs placebo	-0.715	(-1.522, 0.092)	0.0818
		Placebo	-0.393				
	Week 3	20 ug	-2.345	20 ug vs placebo	-1.865	(-2.788, -0.942)	0.0001
		5 ug	-1.345	5 ug vs placebo	-0.864	(-1.786, 0.057)	0.0658
		1 ug	-1.463	1 ug vs placebo	-0.983	(-1.859, -0.106)	0.0284
		Placebo	-0.480				
	Week 4	20 ug	-2.574	20 ug vs placebo	-1.783	(-2.760, -0.805)	0.0004
		5 ug	-1.613	5 ug vs placebo	-0.821	(-1.797, 0.155)	0.0984
		1 ug	-1.586	1 ug vs placebo	-0.794	(-1.723, 0.134)	0.0928
		Placebo	-0.792				
	Week 3-4	20 ug	-2.456	20 ug vs placebo	-1.823	(-2.737, -0.908)	0.0001

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
		5 ug	-1.475	5 ug vs placebo	-0.841	(-1.755, 0.072)	0.0707
		1 ug	-1.534	1 ug vs placebo	-0.900	(-1.769, -0.031)	0.0424
		Placebo	-0.633				
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.3							

Table 14.2.3.5 Summary of OLPSSM #11 - #12 weekly means [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of OLPSSM question no. 11 score by visit	Baseline	n	33	34	40	31
		Mean(SD)	2.273 (0.76)	2.588 (0.78)	2.425 (0.75)	2.387 (0.67)
		Median	2.000	3.000	2.000	2.000
		Min, Max	1.00-4.00	1.00-4.00	1.00-4.00	1.00-4.00
	Week 1	n	32	34	39	31
		Mean(SD)	1.844 (0.85)	2.147 (0.70)	2.179 (0.76)	2.129 (0.72)
		Median	2.000	2.000	2.000	2.000
		Min, Max	0.00-4.00	1.00-3.00	1.00-4.00	1.00-4.00
	Change from baseline Week 1	n	32	34	39	31
		Mean(SD)	-0.438 (0.72)	-0.441 (0.79)	-0.256 (0.72)	-0.258 (0.77)
		Median	0.000	0.000	0.000	0.000
		Min, Max	-2.00-1.00	-3.00-1.00	-2.00-1.00	-2.00-1.00
	Week 2	n	31	34	37	28
		Mean(SD)	1.613 (0.88)	2.029 (0.76)	2.000 (0.71)	2.107 (0.79)

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Median	2.000	2.000	2.000	2.000
		Min, Max	0.00-4.00	1.00-4.00	1.00-4.00	1.00-4.00
	Change from baseline Week 2	n	31	34	37	28
		Mean(SD)	-0.645 (0.98)	-0.559 (0.89)	-0.432 (0.69)	-0.286 (0.81)
		Median	-1.000	-0.500	0.000	0.000
		Min, Max	-2.00-1.00	-3.00-1.00	-2.00-1.00	-2.00-1.00
	Week 3	n	29	33	36	27
		Mean(SD)	1.448 (0.78)	1.818 (0.77)	1.806 (0.79)	1.889 (0.85)
		Median	1.000	2.000	2.000	2.000
		Min, Max	0.00-3.00	0.00-3.00	1.00-4.00	0.00-3.00
	Change from baseline Week 3	n	29	33	36	27
		Mean(SD)	-0.828 (0.93)	-0.788 (0.89)	-0.639 (0.76)	-0.481 (1.01)
		Median	-1.000	-1.000	-1.000	-1.000
		Min, Max	-2.00-1.00	-3.00-1.00	-2.00-1.00	-3.00-1.00
	Week 4	n	30	33	35	27
		Mean(SD)	1.033 (0.85)	1.576 (0.83)	1.600 (0.81)	1.778 (0.64)
		Median	1.000	1.000	2.000	2.000
		Min, Max	0.00-3.00	0.00-3.00	0.00-4.00	0.00-3.00
	Change from baseline Week 4	n	30	33	35	27
		Mean(SD)	-1.233 (0.90)	-1.030 (1.10)	-0.829 (0.98)	-0.593 (1.01)
		Median	-1.000	-1.000	-1.000	-1.000

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Min, Max	-3.00-0.00	-3.00-1.00	-3.00-1.00	-3.00-2.00
Summary of OLPSSM question no. 12 score by visit	Week 4	n	32	34	39	30
		Mean(SD)	2.156 (1.44)	1.500 (1.60)	1.410 (1.45)	1.233 (1.17)
		Median	3.000	2.000	2.000	1.000
		Min, Max	-3.00-3.00	-3.00-3.00	-2.00-3.00	-1.00-3.00
Listing(s): Derived from Listing 16.2.4.1						

Table 14.2.3.6 Statistical analysis of OLPSSM #11 - #12 weekly means [FAS]

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Analysis of OLPSSM question no. 11 score by visit, ANCOVA	Week 1	20 ug	-0.435	20 ug vs placebo	-0.225	(-0.546, 0.097)	0.1693
		5 ug	-0.300	5 ug vs placebo	-0.090	(-0.409, 0.228)	0.5763
		1 ug	-0.218	1 ug vs placebo	-0.008	(-0.314, 0.298)	0.9600
		Placebo	-0.210				
	Week 2	20 ug	-0.550	20 ug vs placebo	-0.386	(-0.756, -0.016)	0.0410
		5 ug	-0.343	5 ug vs placebo	-0.179	(-0.545, 0.187)	0.3354
		1 ug	-0.252	1 ug vs placebo	-0.088	(-0.440, 0.265)	0.6228
		Placebo	-0.164				
	Week 3	20 ug	-0.635	20 ug vs placebo	-0.434	(-0.799, -0.070)	0.0199
		5 ug	-0.404	5 ug vs placebo	-0.203	(-0.563, 0.158)	0.2687
		1 ug	-0.340	1 ug vs placebo	-0.139	(-0.486, 0.208)	0.4304
		Placebo	-0.201				

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
	Week 4	20 ug	-1.000	20 ug vs placebo	-0.705	(-1.109, -0.301)	0.0008
		5 ug	-0.594	5 ug vs placebo	-0.299	(-0.699, 0.101)	0.1417
		1 ug	-0.461	1 ug vs placebo	-0.165	(-0.550, 0.219)	0.3966
		Placebo	-0.295				
	Week 3-4	20 ug	-0.824	20 ug vs placebo	-0.577	(-0.920, -0.235)	0.0011
		5 ug	-0.498	5 ug vs placebo	-0.251	(-0.591, 0.088)	0.1451
		1 ug	-0.400	1 ug vs placebo	-0.153	(-0.479, 0.173)	0.3554
		Placebo	-0.247				
Analysis of OLPSSM question no. 12 score by visit, ANCOVA	Week 4	20 ug	1.928	20 ug vs placebo	0.907	(0.206, 1.608)	0.0116
		5 ug	1.254	5 ug vs placebo	0.233	(-0.460, 0.926)	0.5066
		1 ug	1.222	1 ug vs placebo	0.201	(-0.473, 0.875)	0.5560
		Placebo	1.021				
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.3							

Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS]

a: sum score 1 - 7 - absolute scale

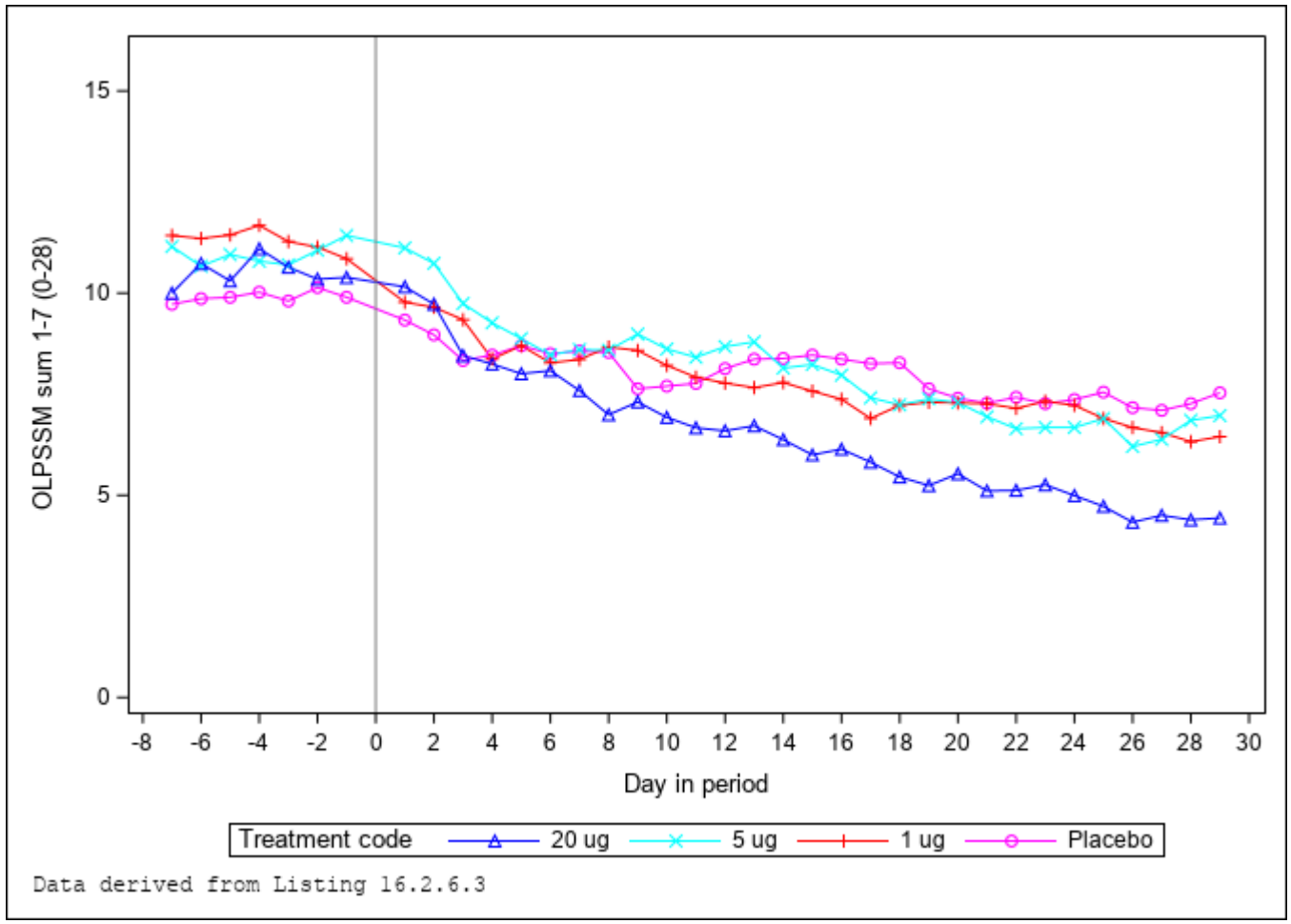


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] b: sum score 1 - 7 - change

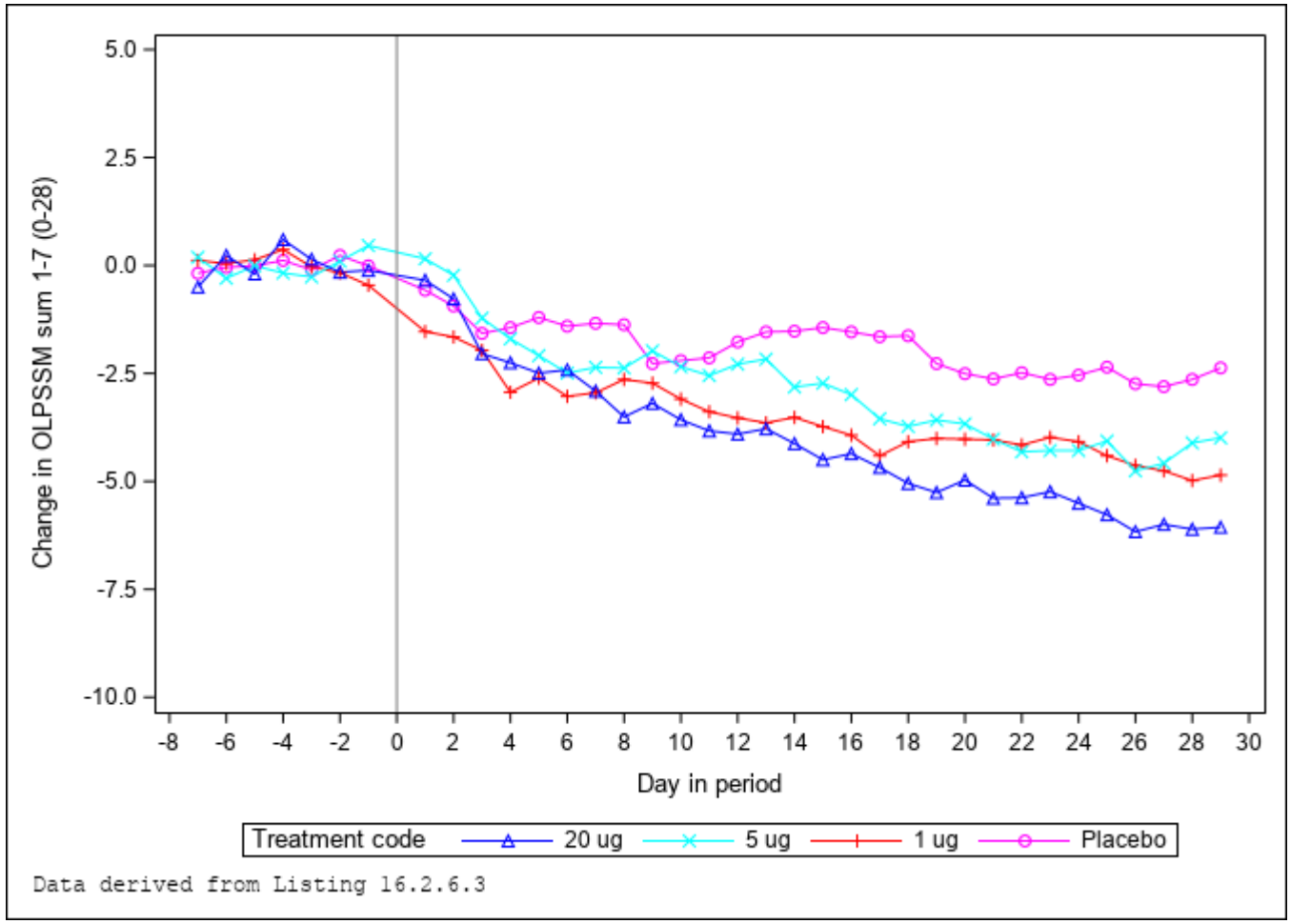


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] c: score no. 1 - absolute scale

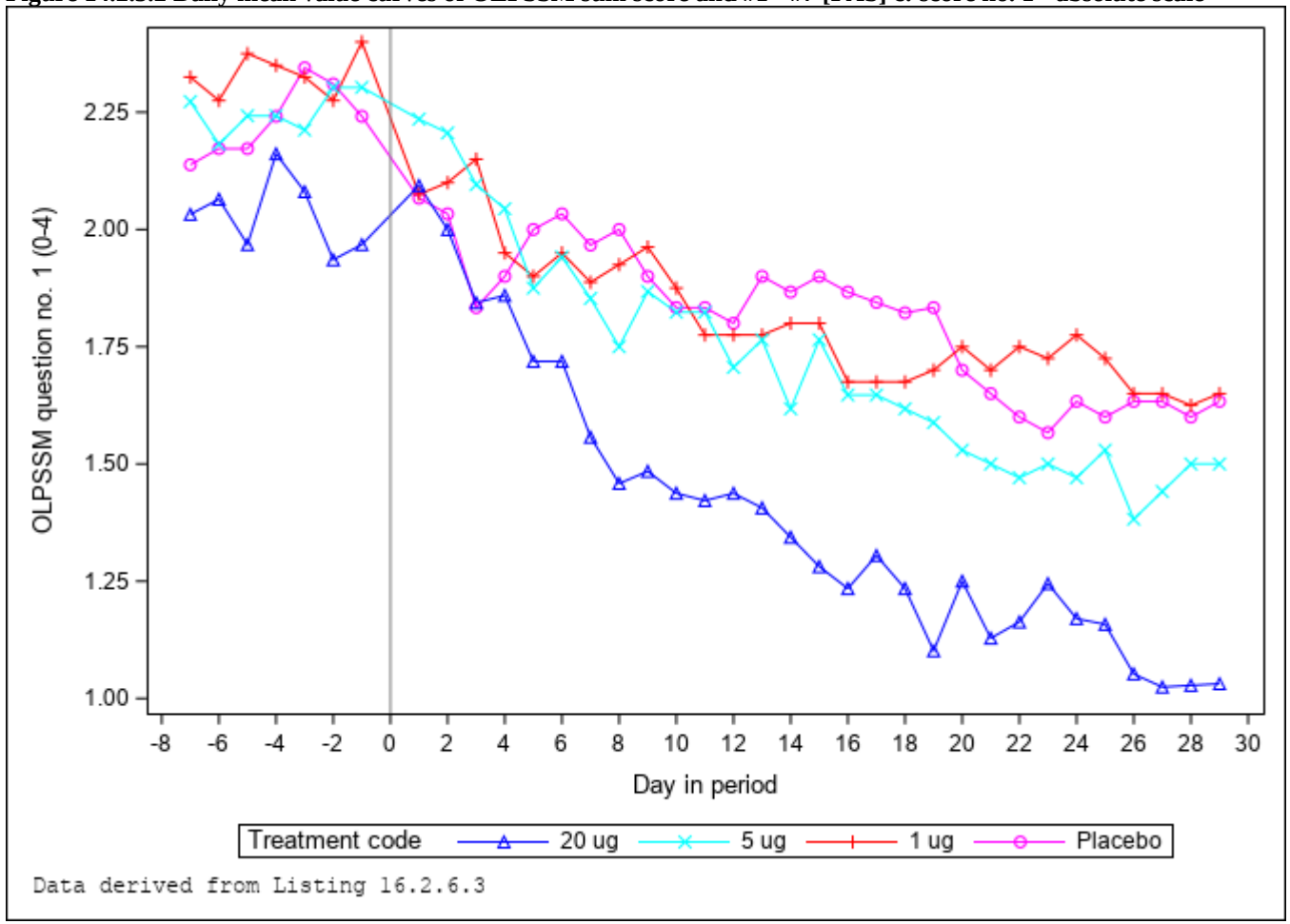


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] d: score no. 1 - change

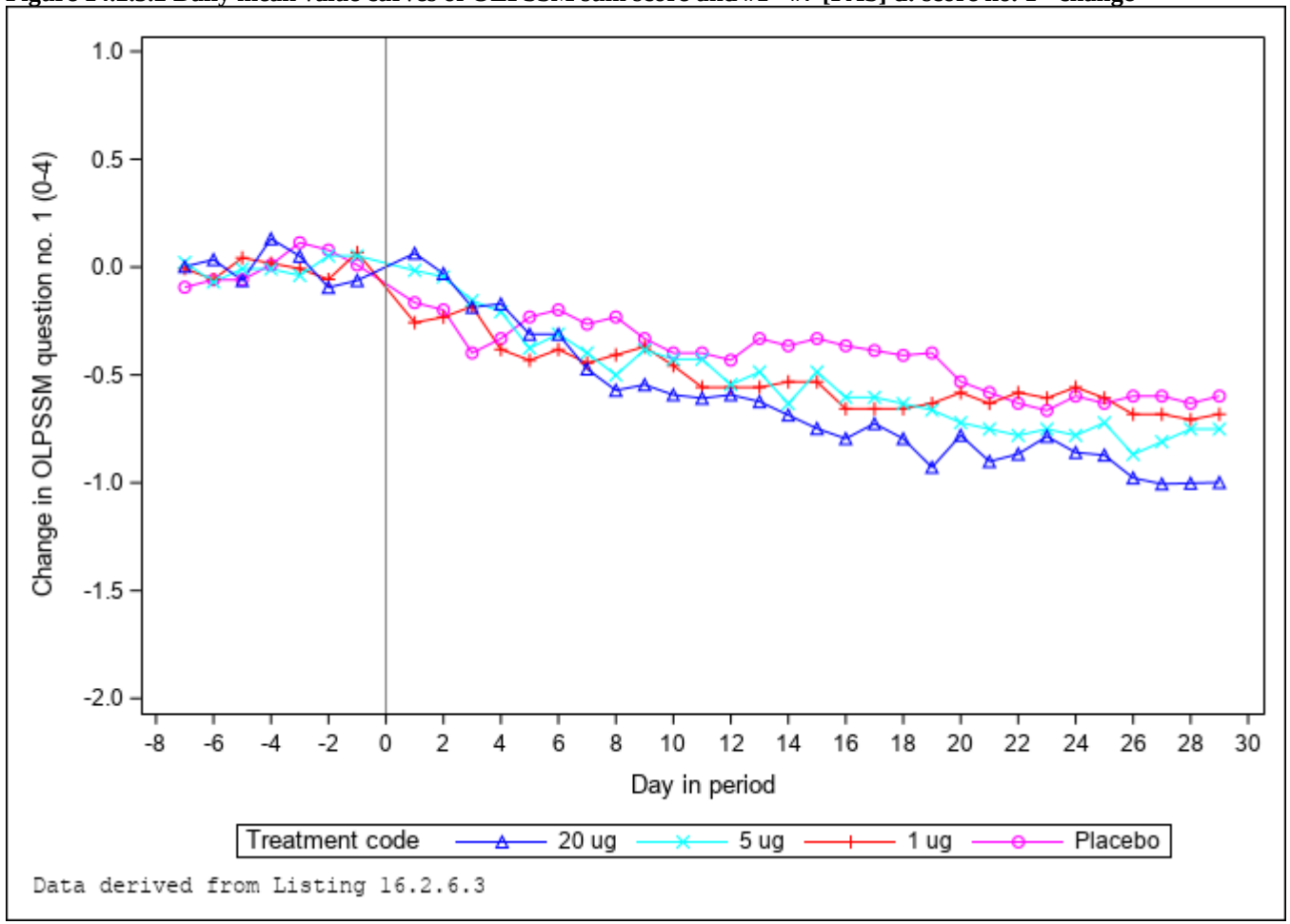


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] e: score no. 2 - absolute scale

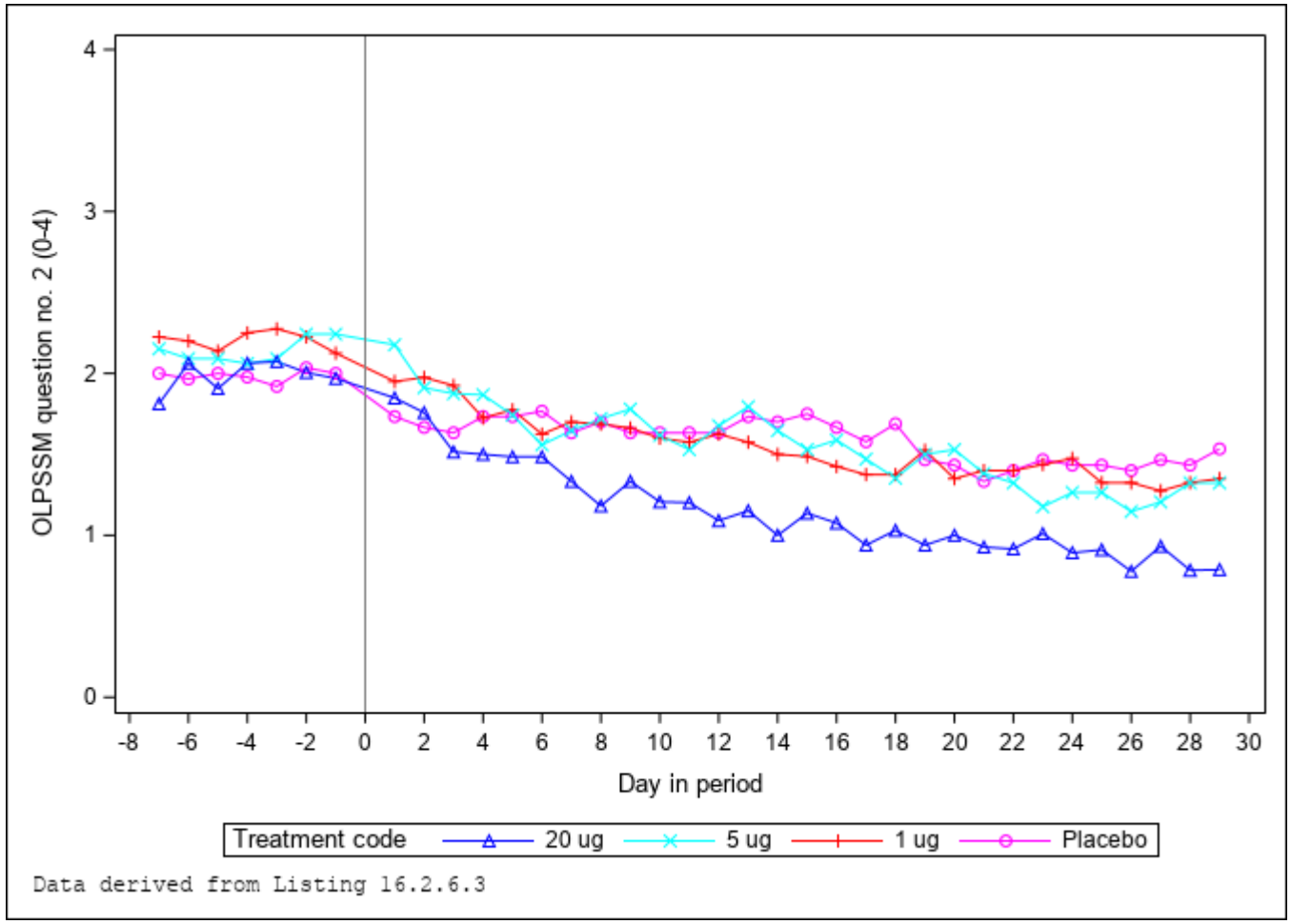


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] f: score no. 2 - change

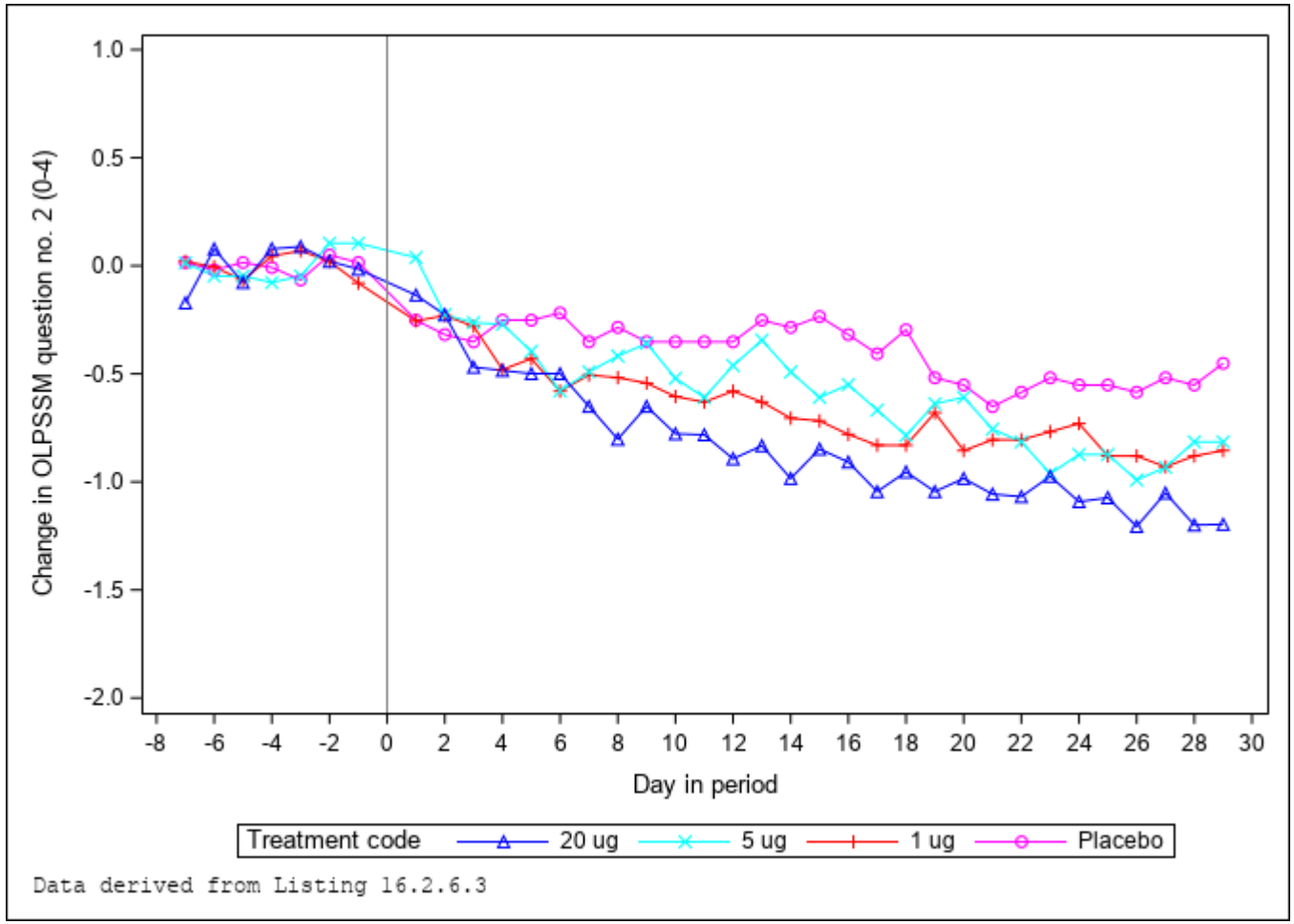


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] g: score no. 3 - absolute scale

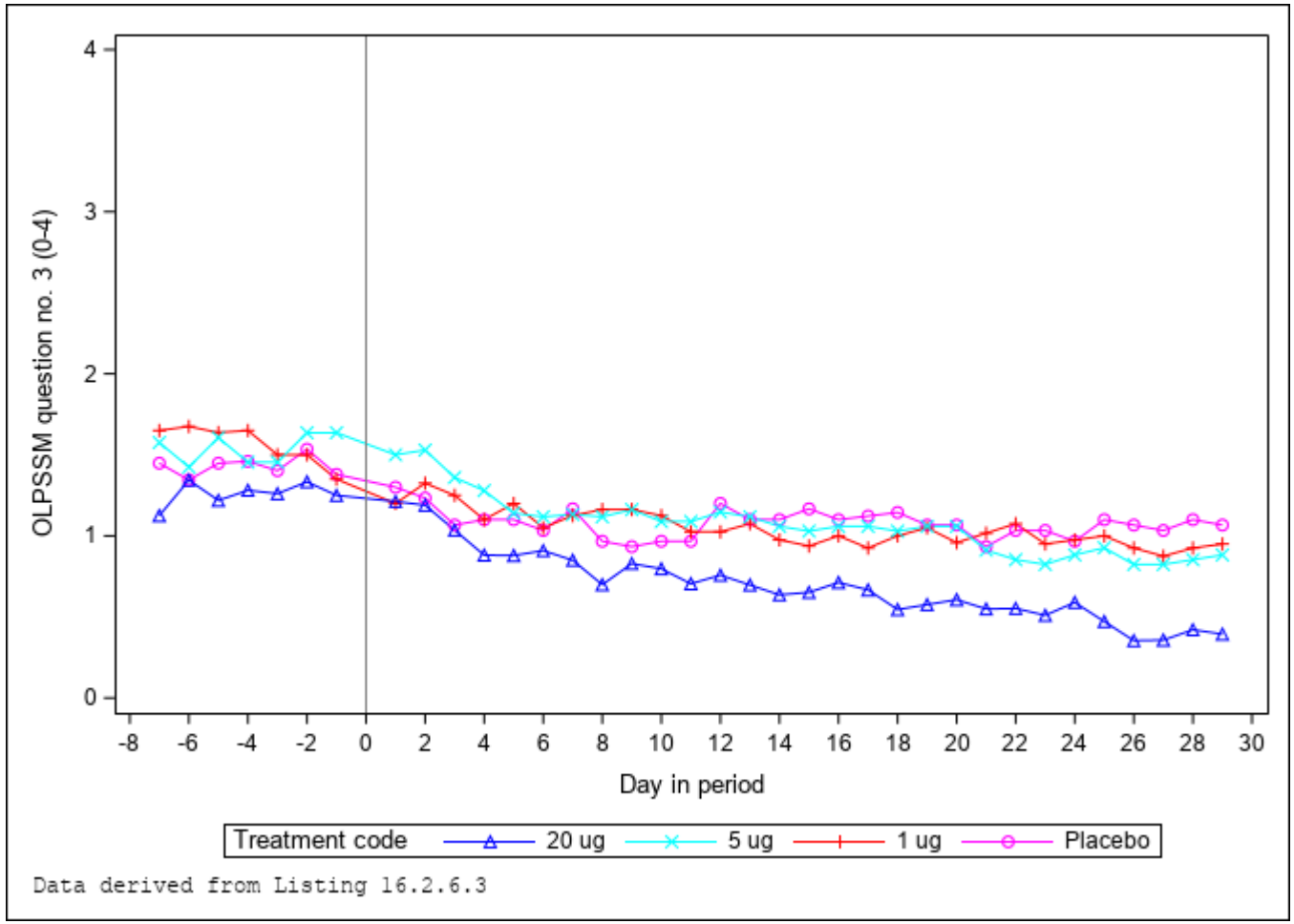


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] h: score no. 3 - change

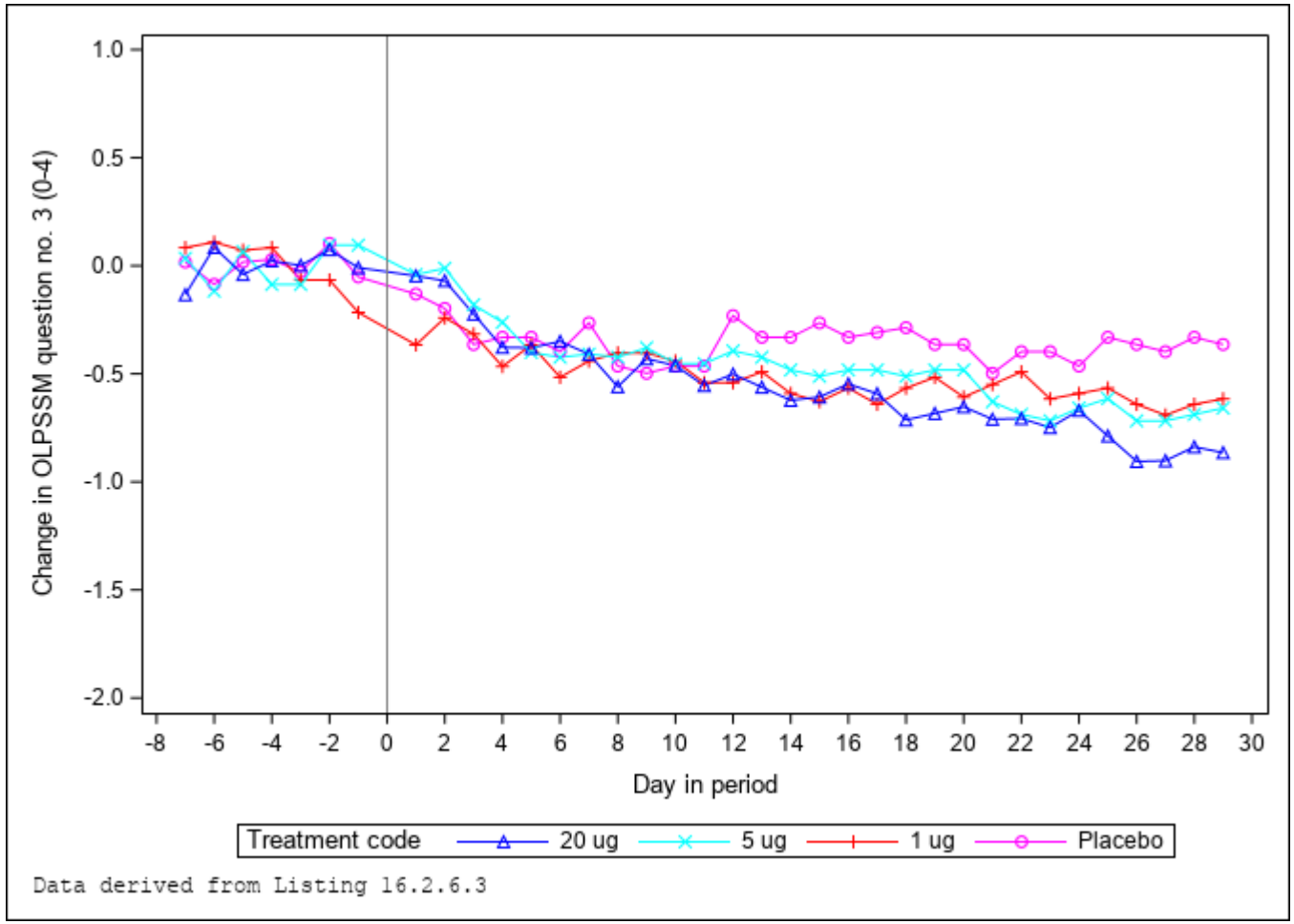


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] i: score no. 4 - absolute scale

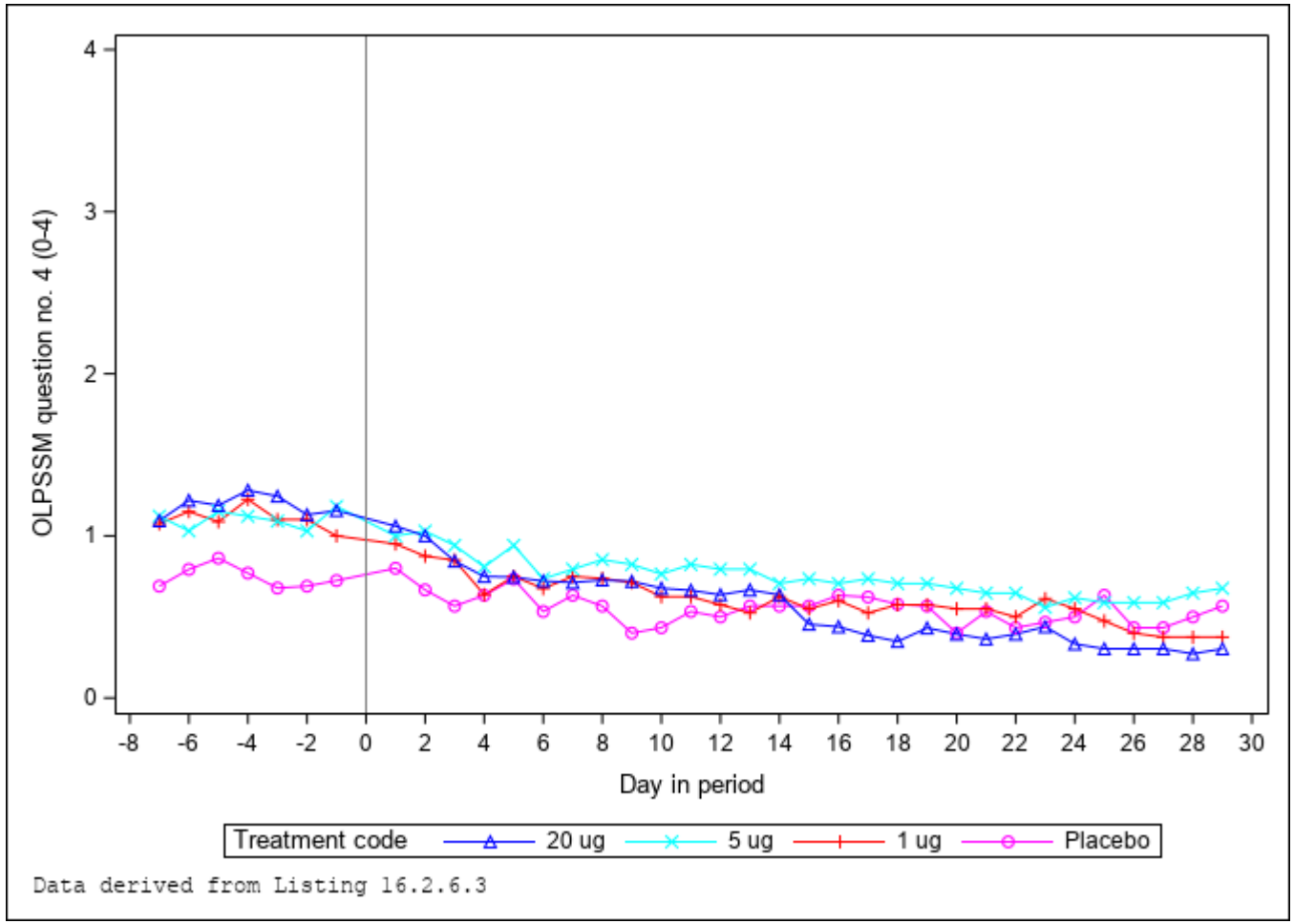


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] j: score no. 4 - change

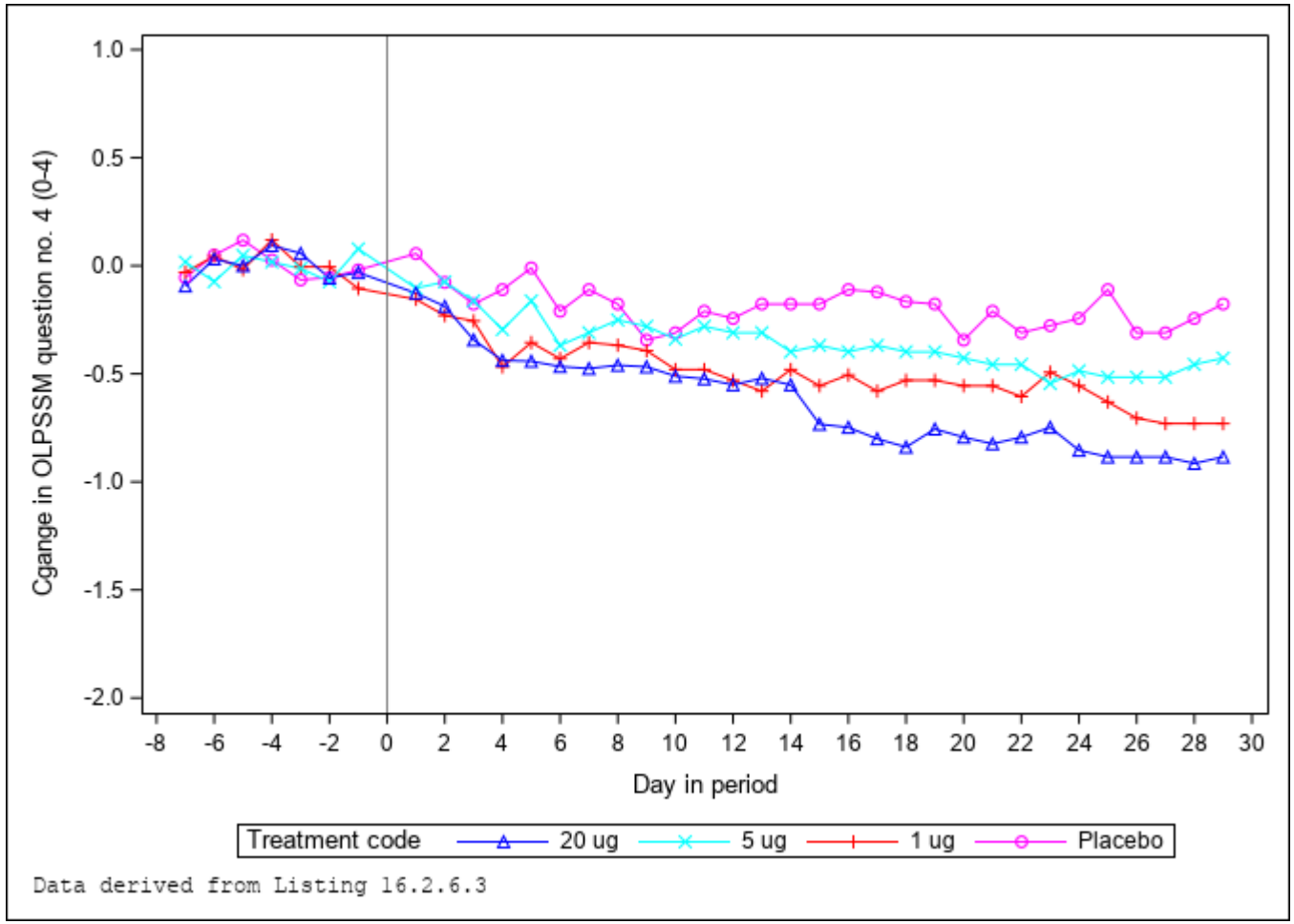


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] k: score no. 5 - absolute scale

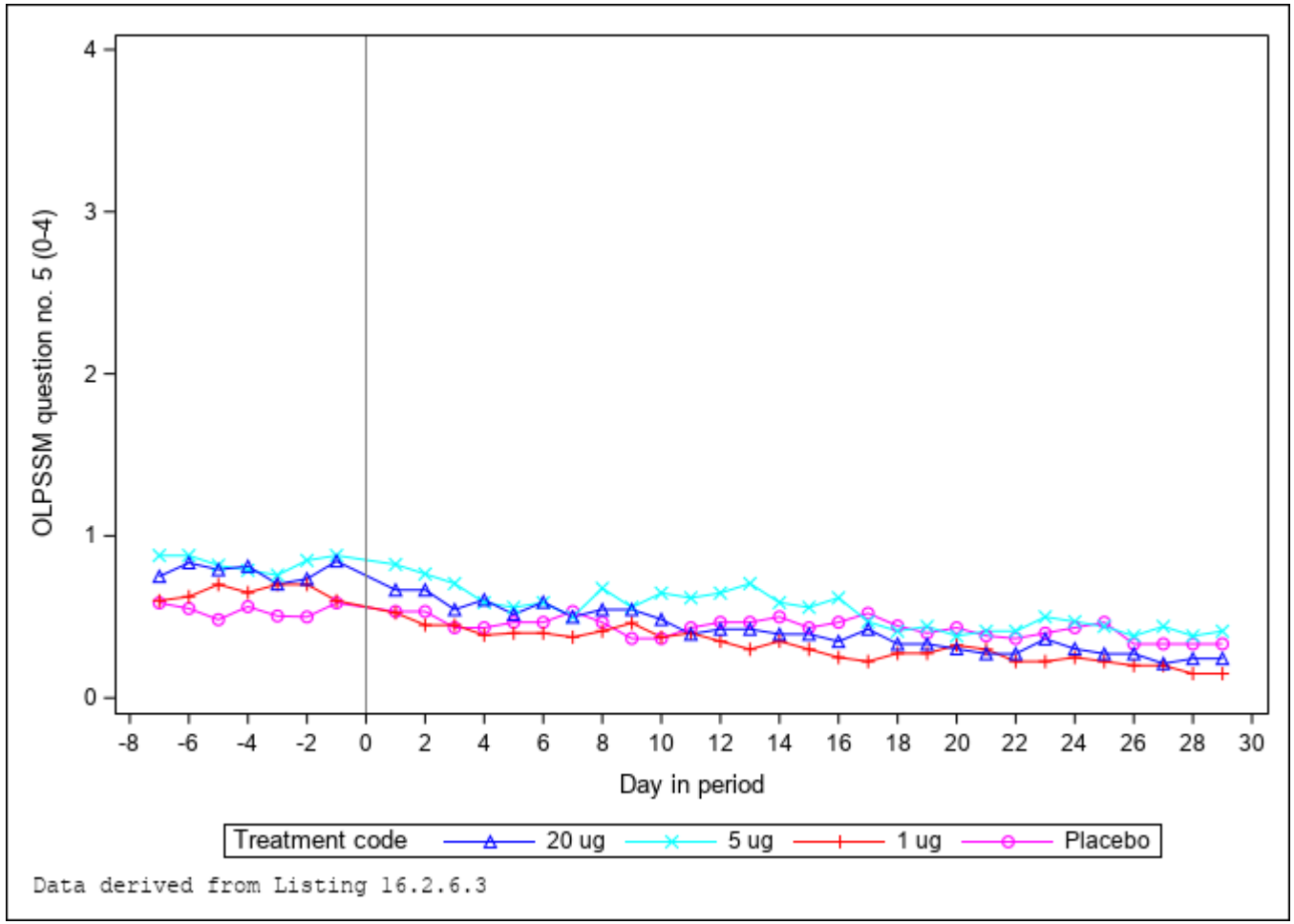


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] l: score no. 5 - change

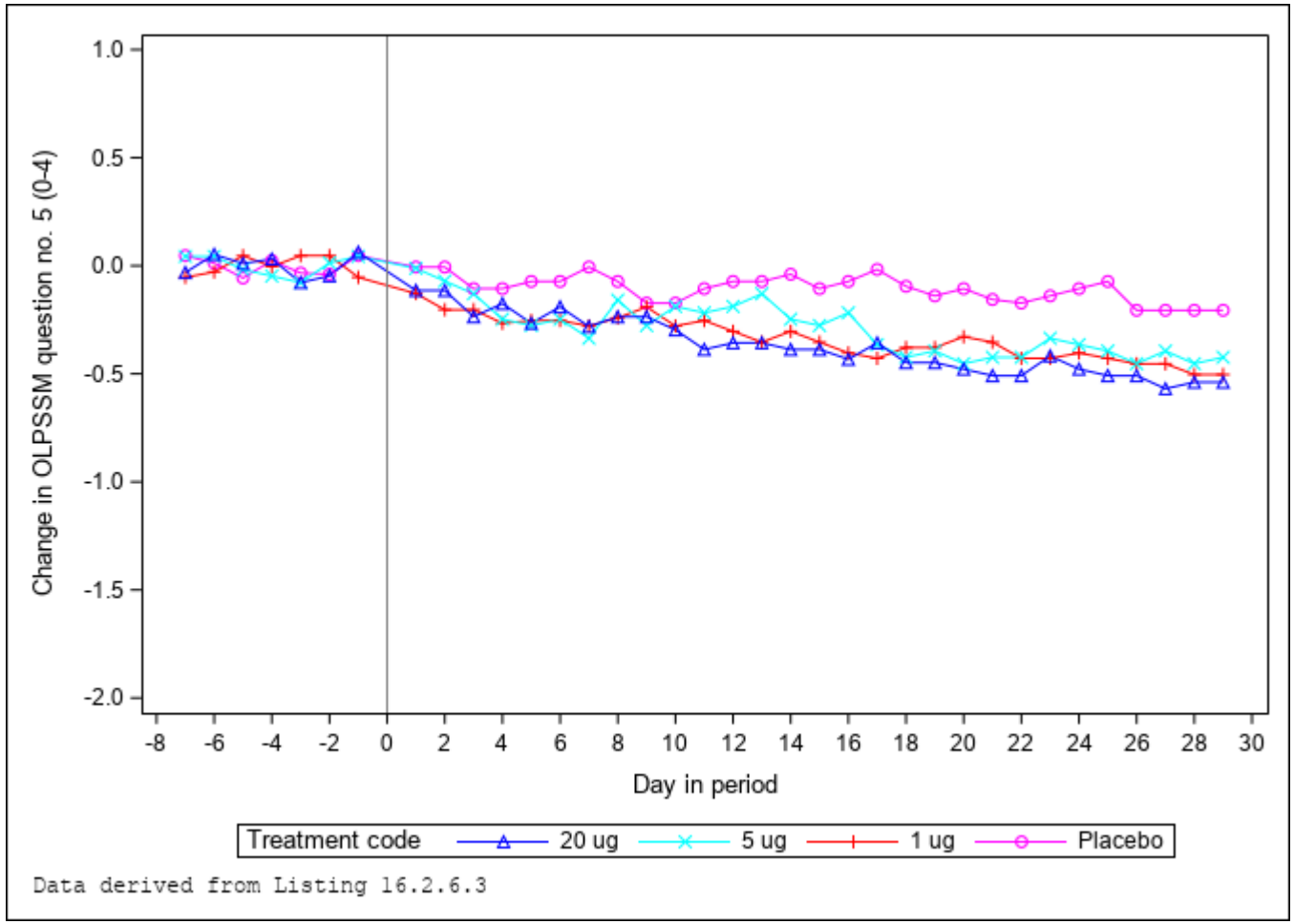


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] m: score no. 6 - absolute scale

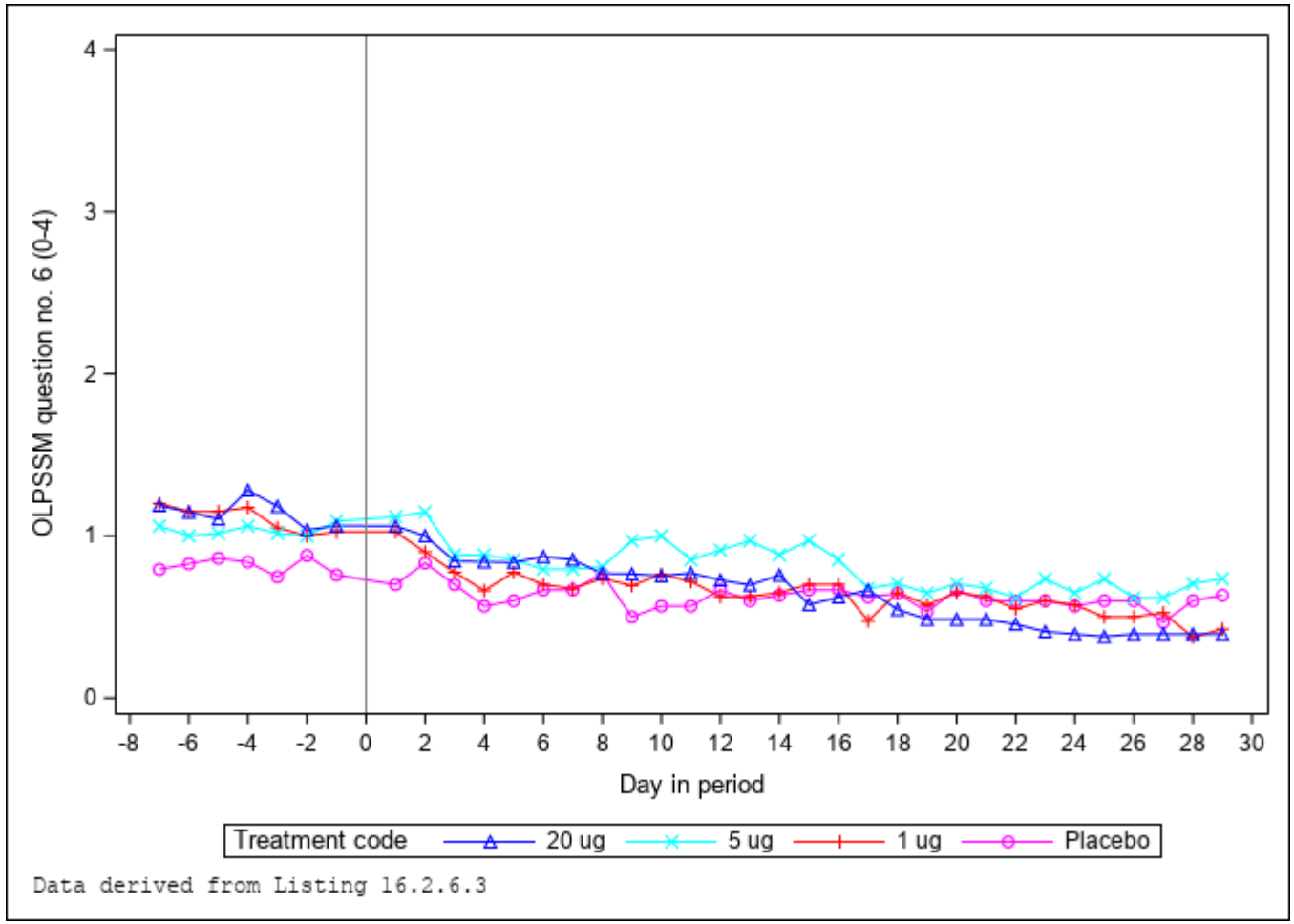


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] n: score no. 6 - change

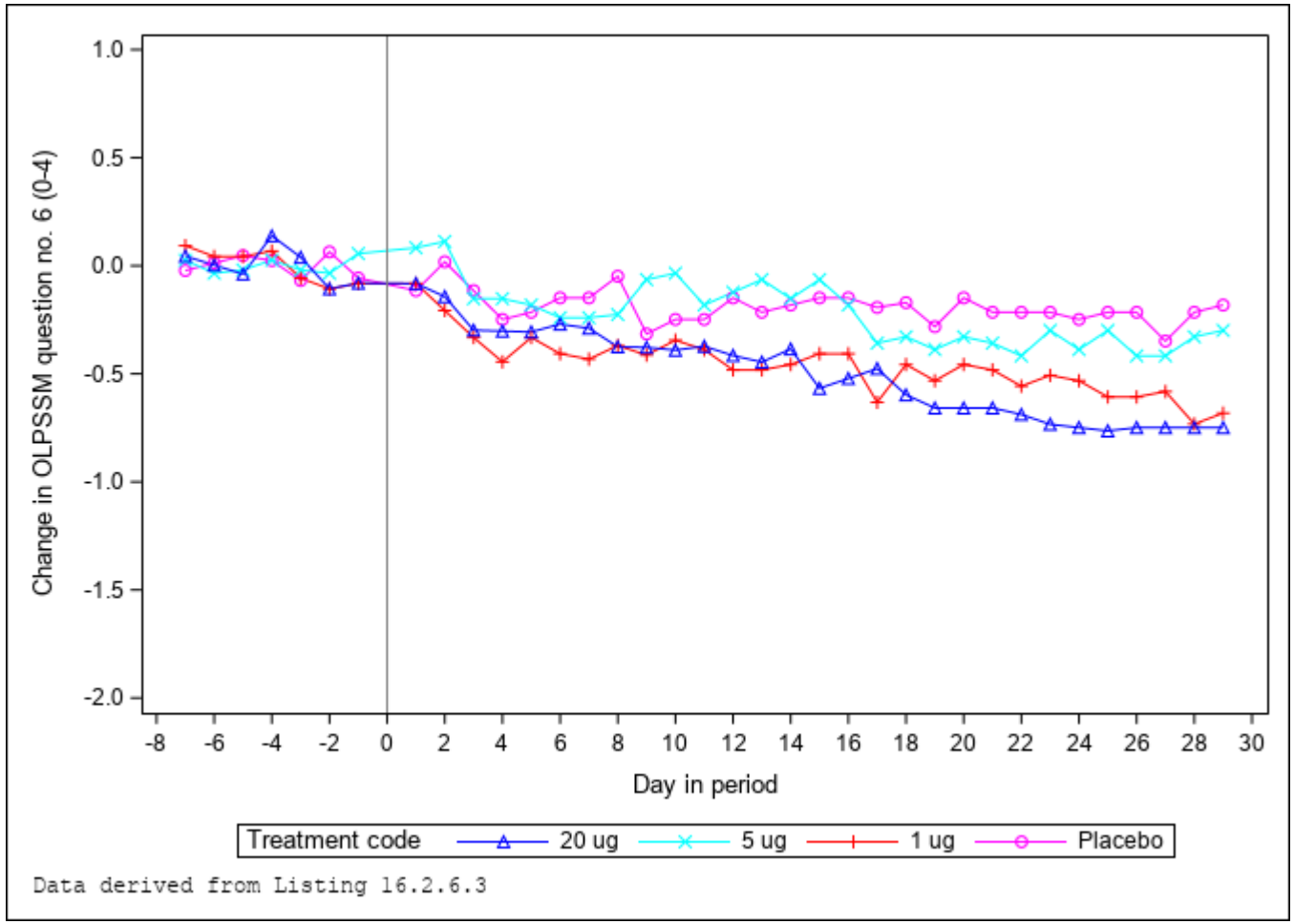


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] o: score no. 7 - absolute scale

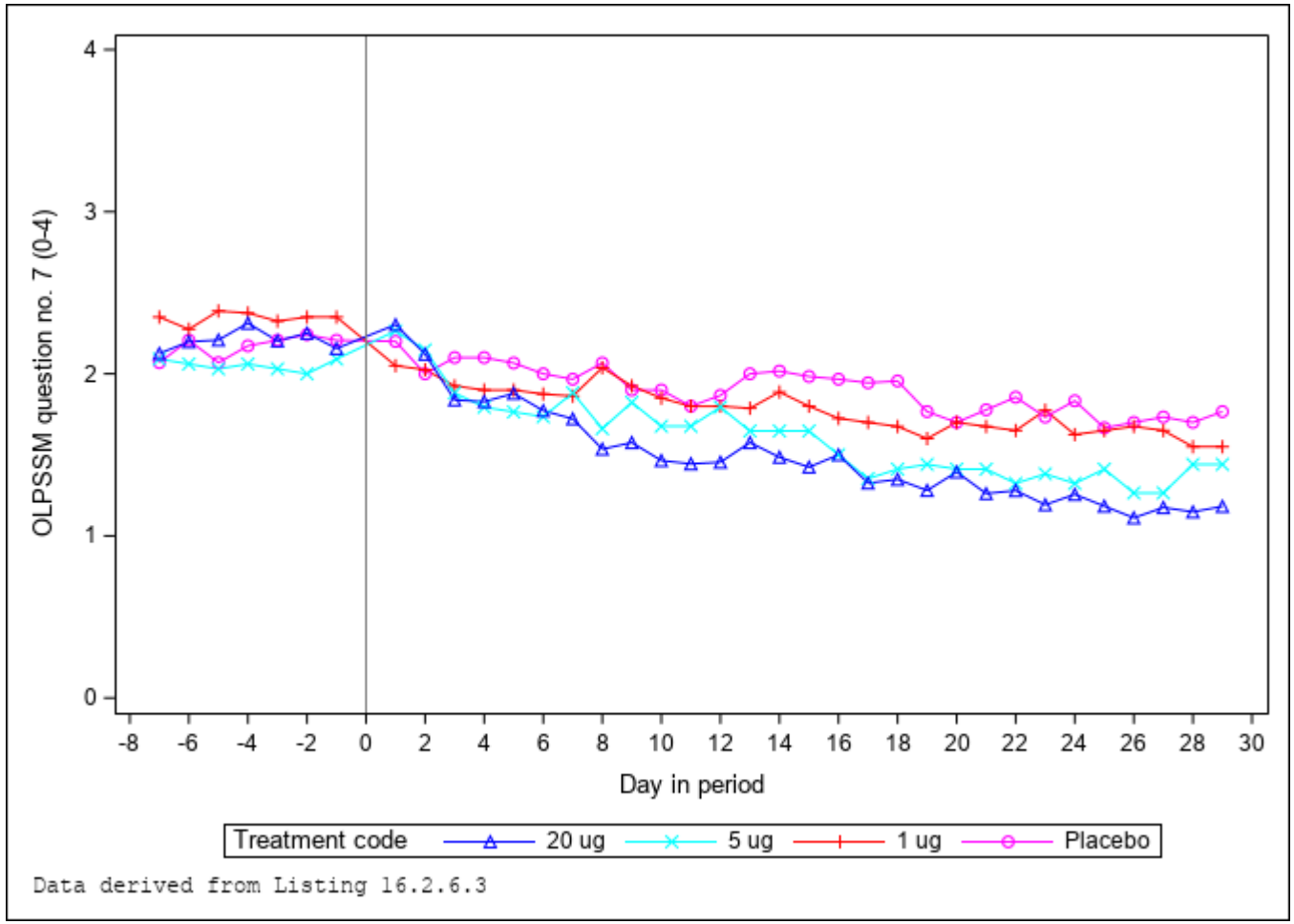


Figure 14.2.3.2 Daily mean value curves of OLPSSM sum score and #1 - #7 [FAS] p: score no. 7 - change

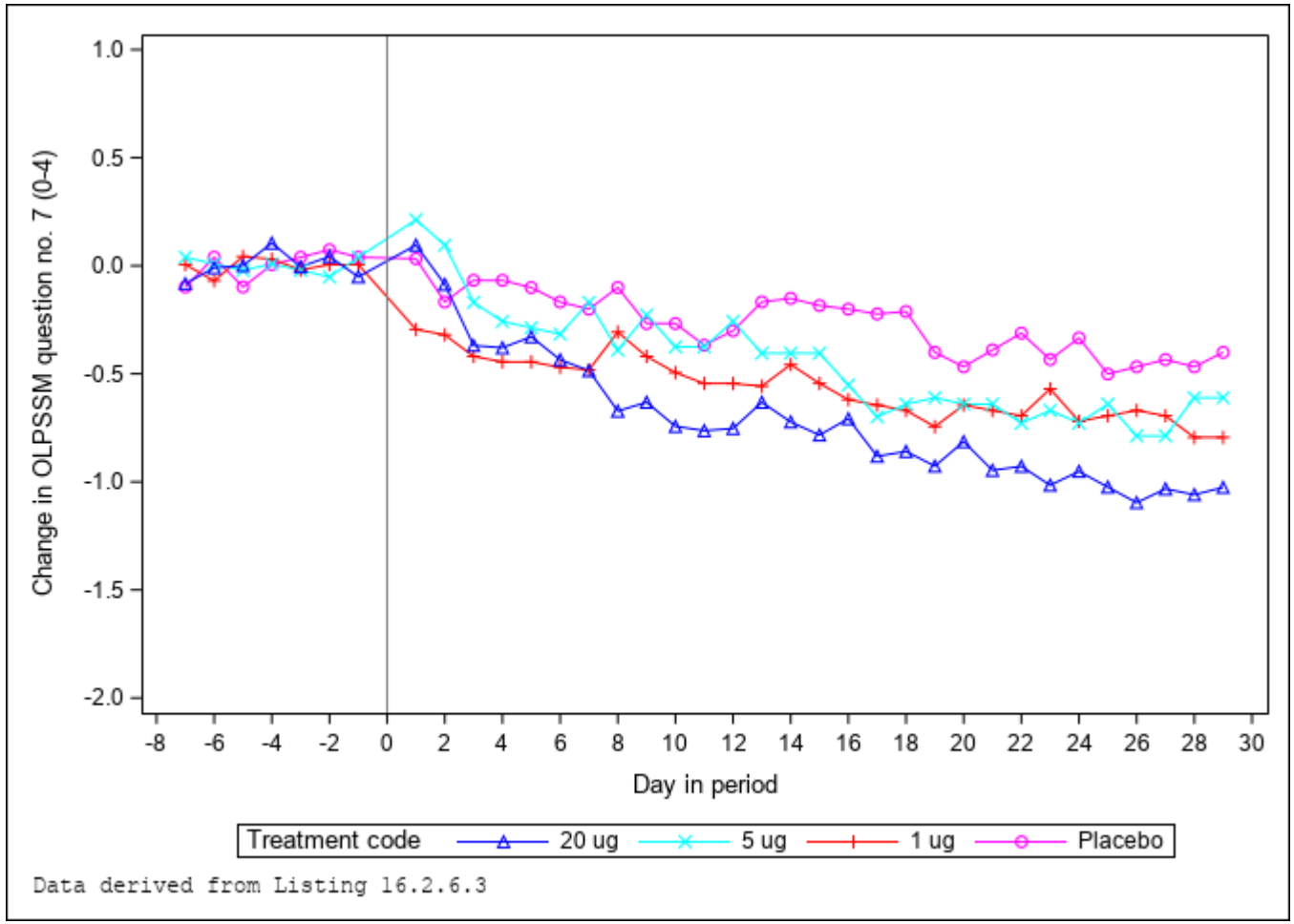


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS]

a: sum score 1 - 7 - absolute scale

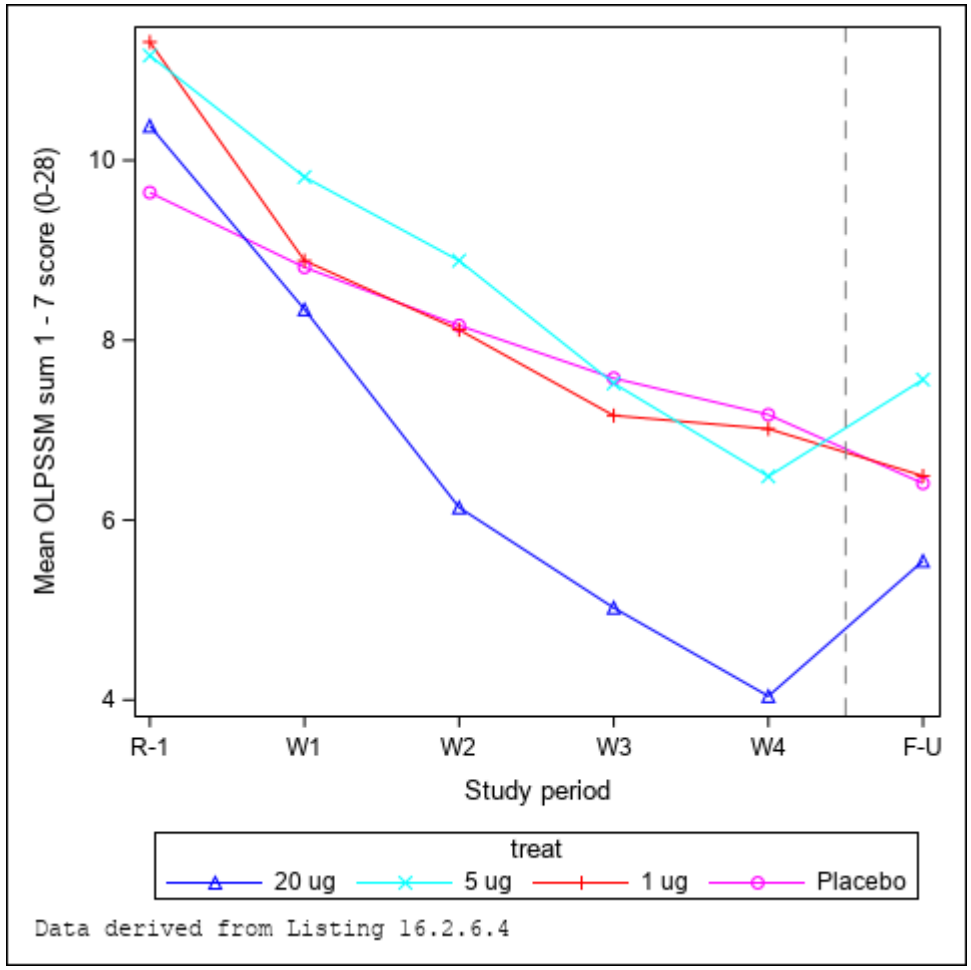


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] b: sum score 1 - 7 - change

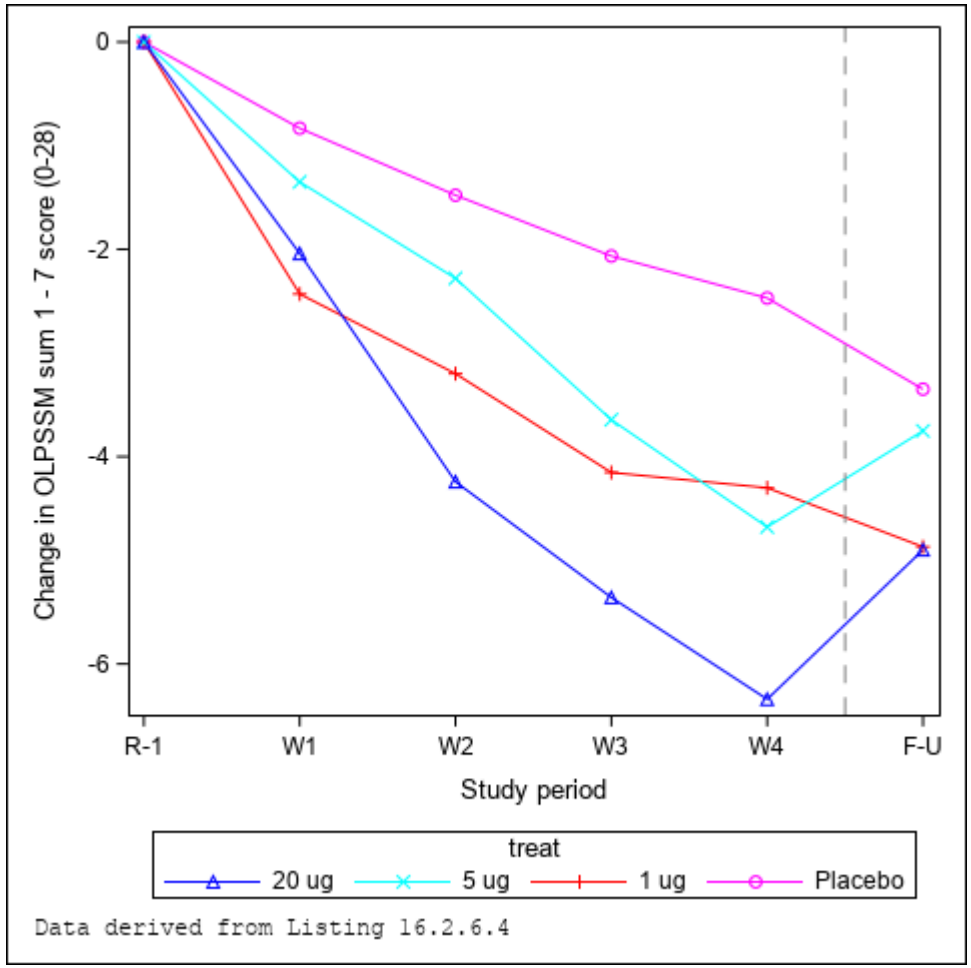


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] c: score no. 1 - absolute scale

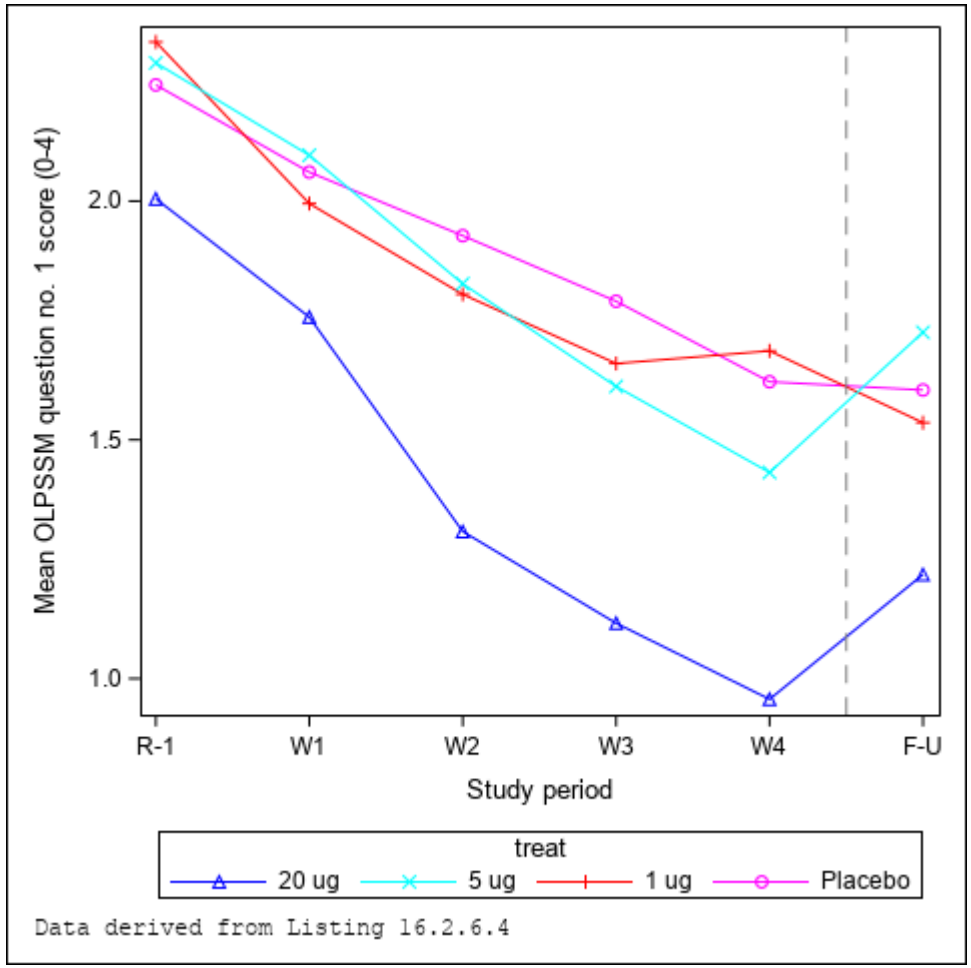


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] d: score no. 1 - change

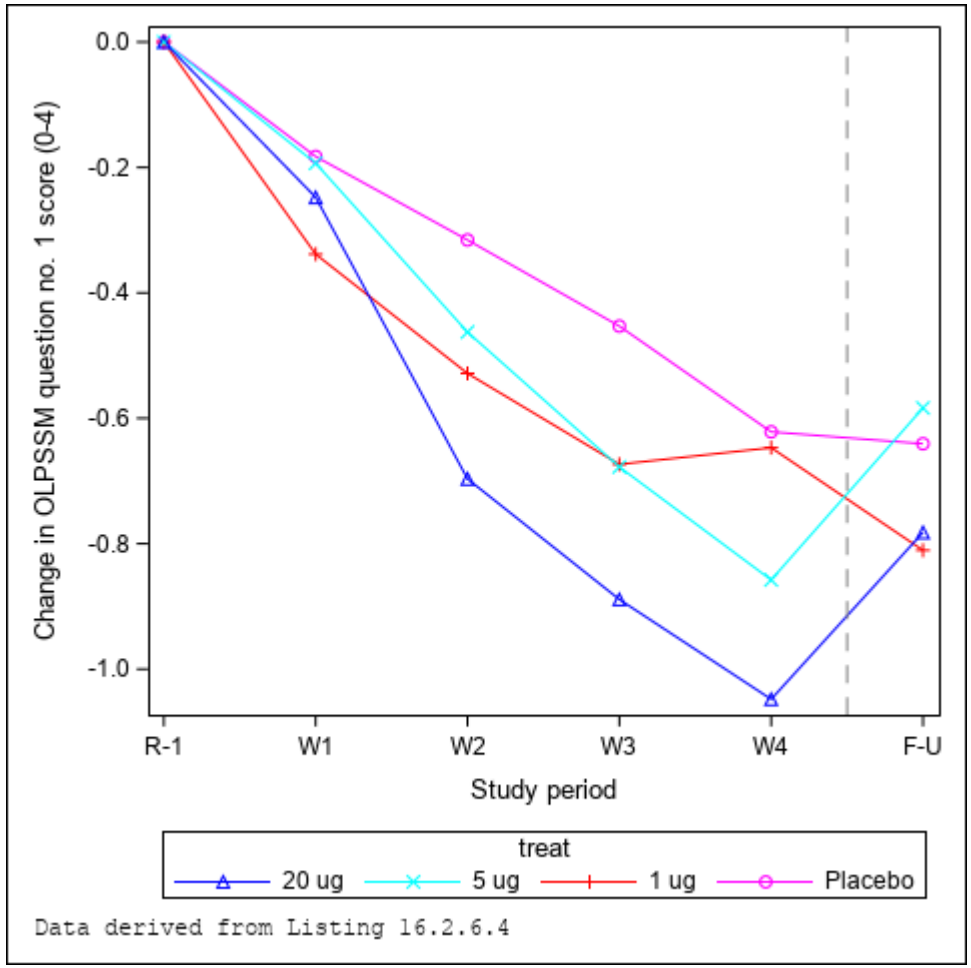


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] e: score no. 2 - absolute scale

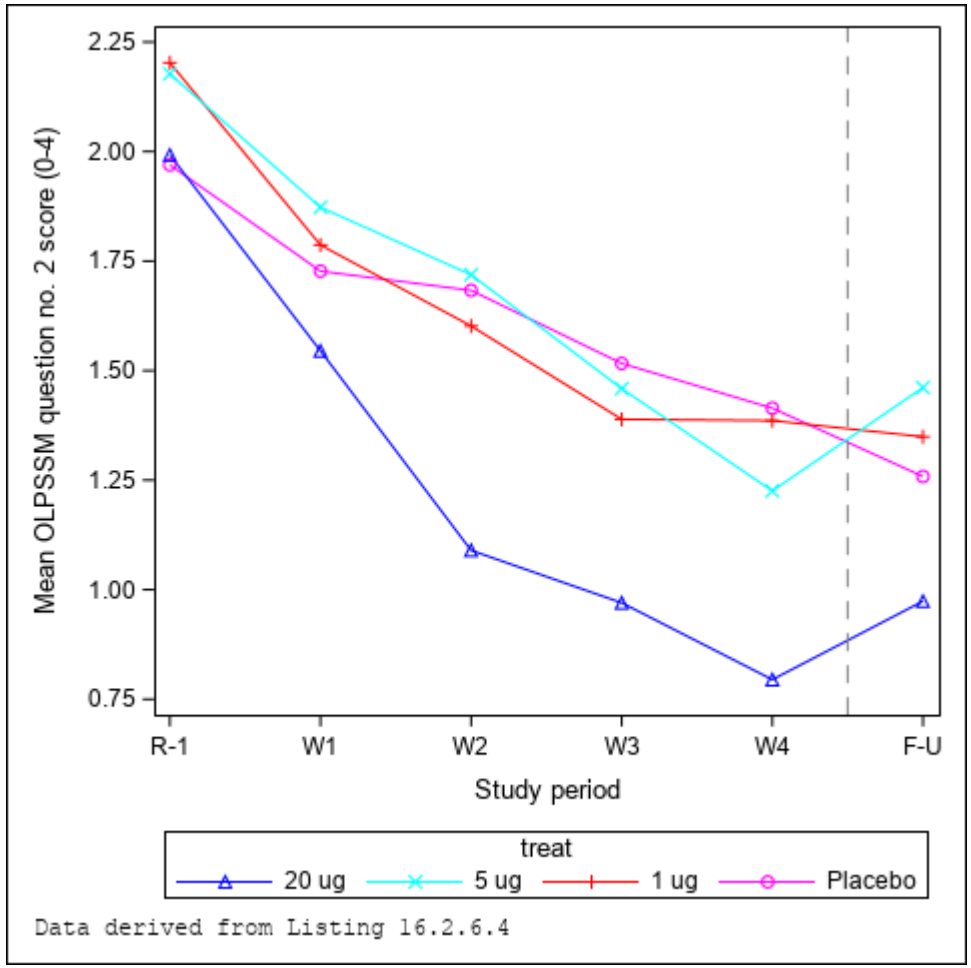


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] f: score no. 2 - change

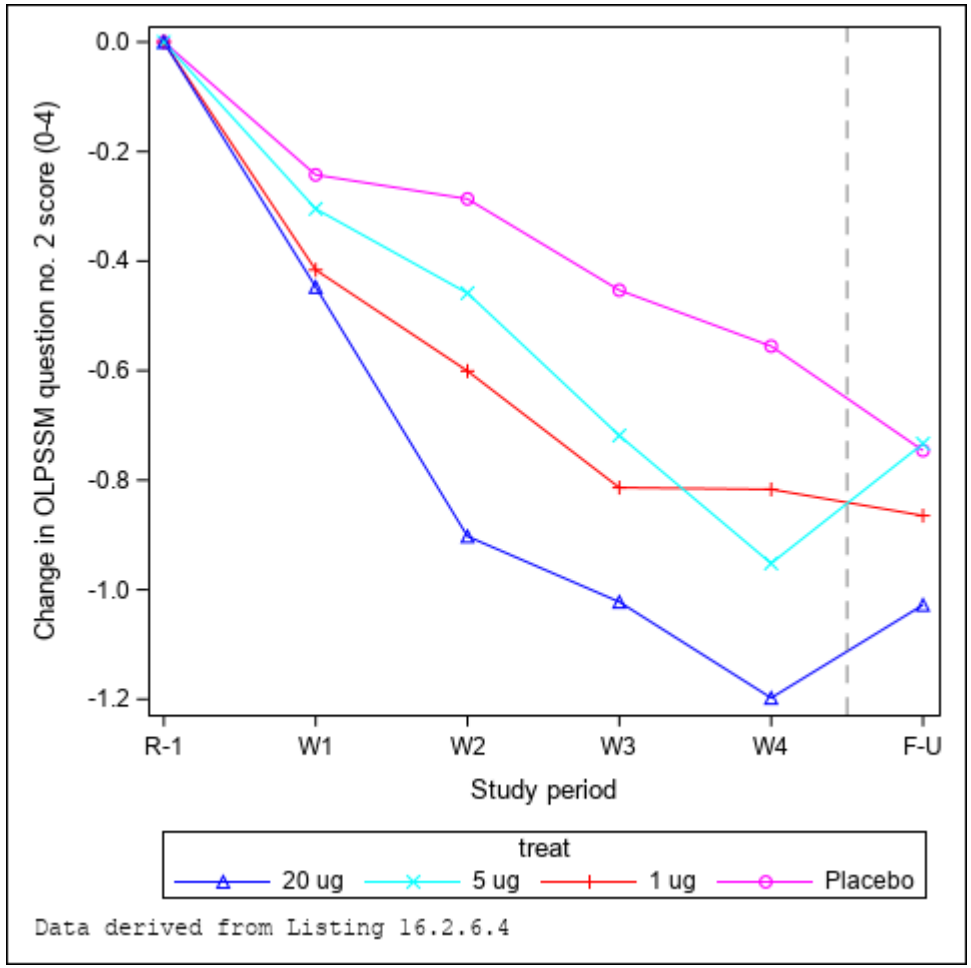


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] g: score no. 3 - absolute scale

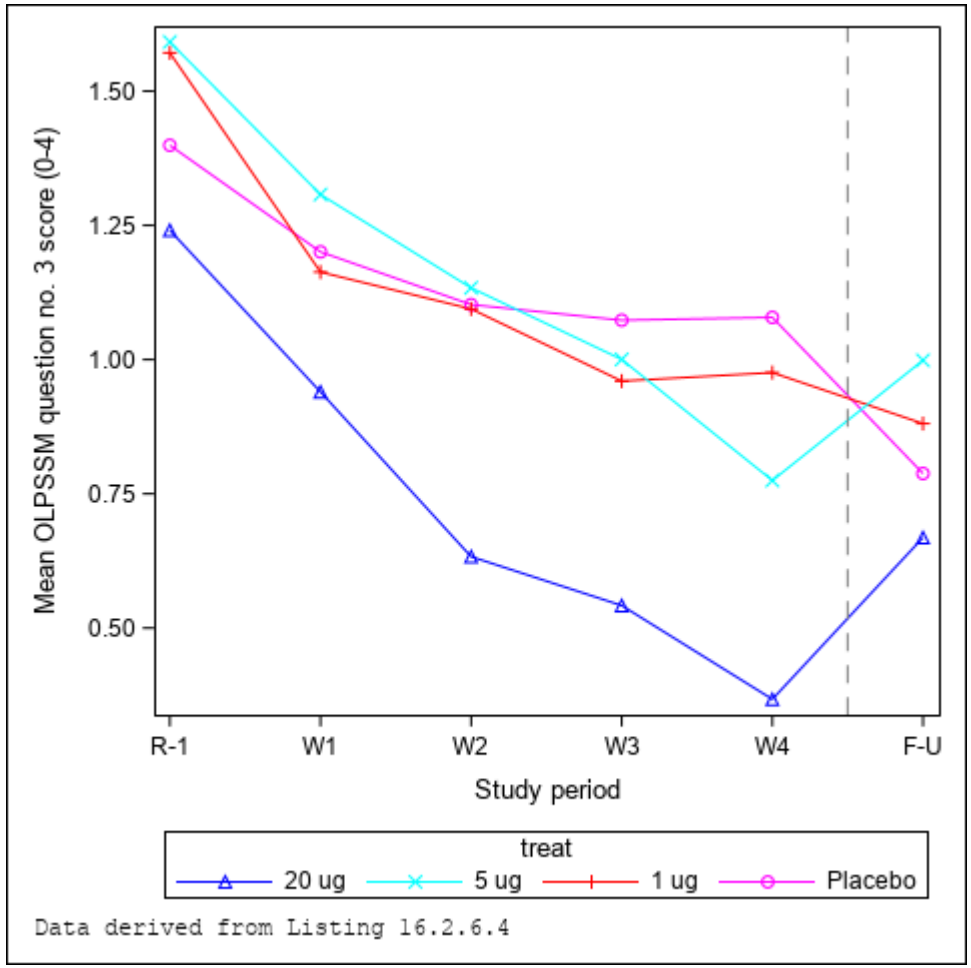


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] h: score no. 3 - change

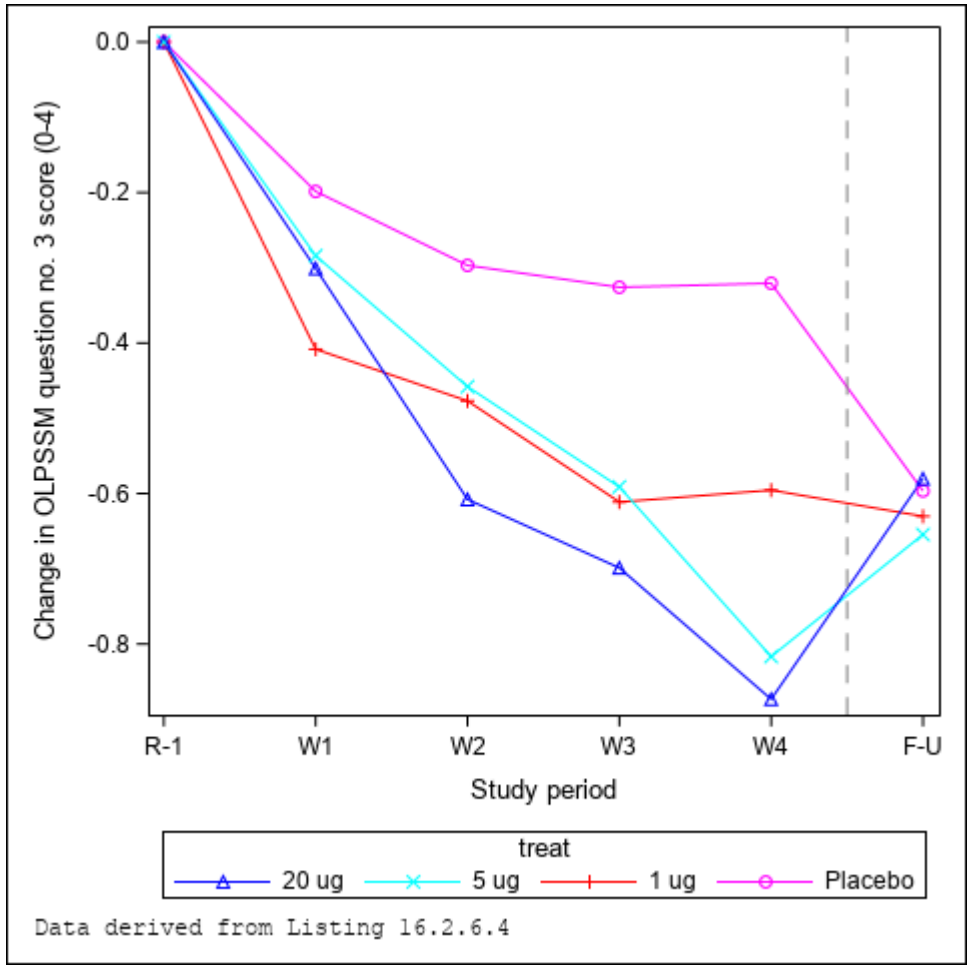


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] i: score no. 4 - absolute scale

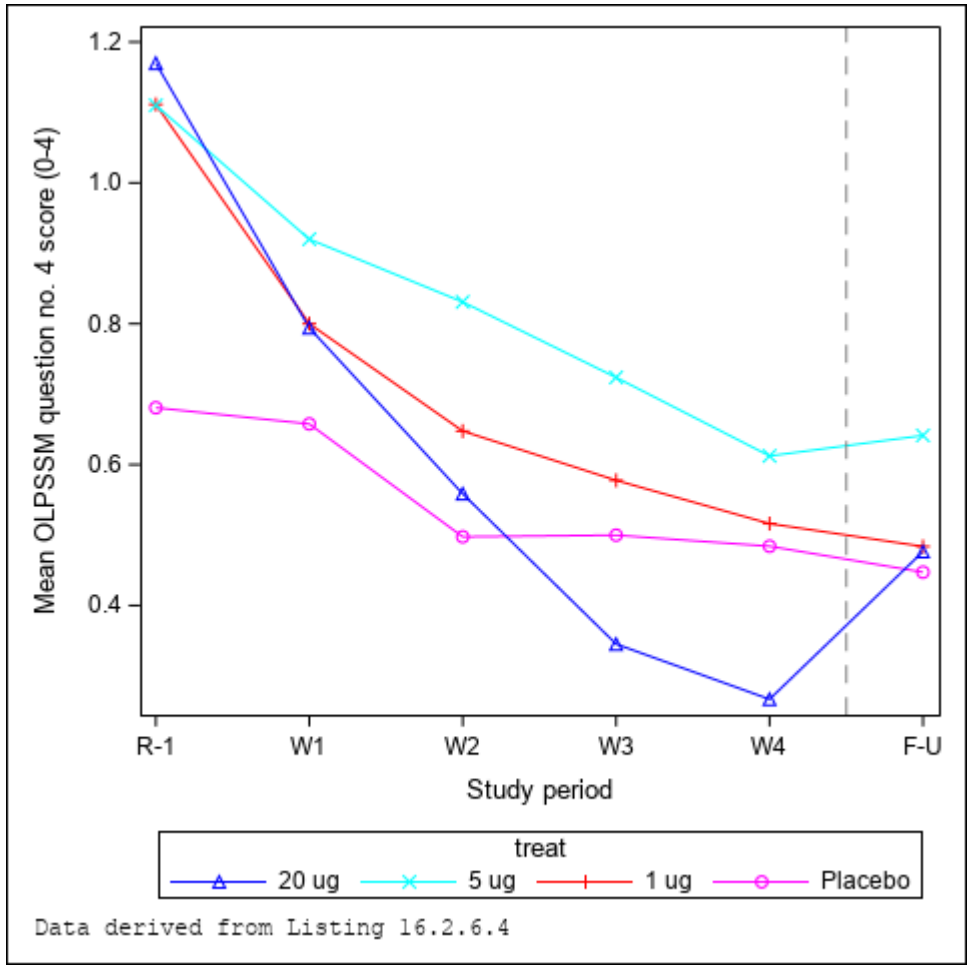


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] j: score no. 4 - change

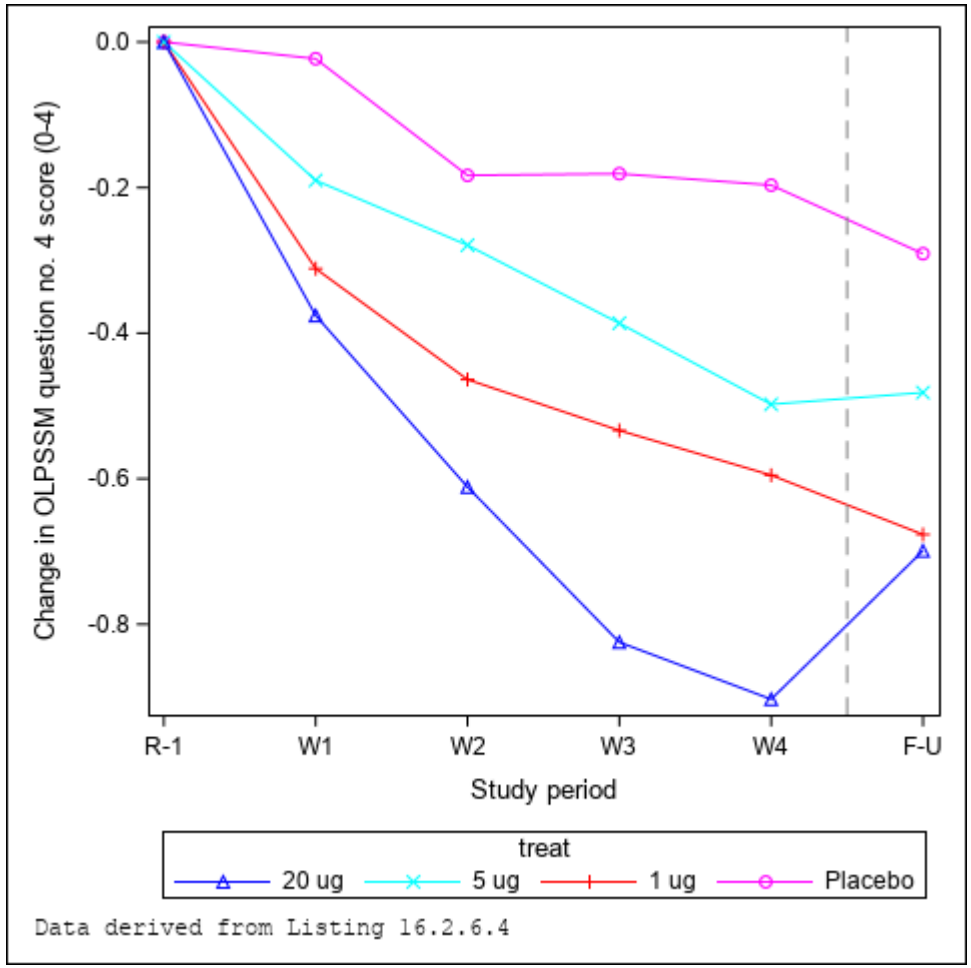


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] k: score no. 5 - absolute scale

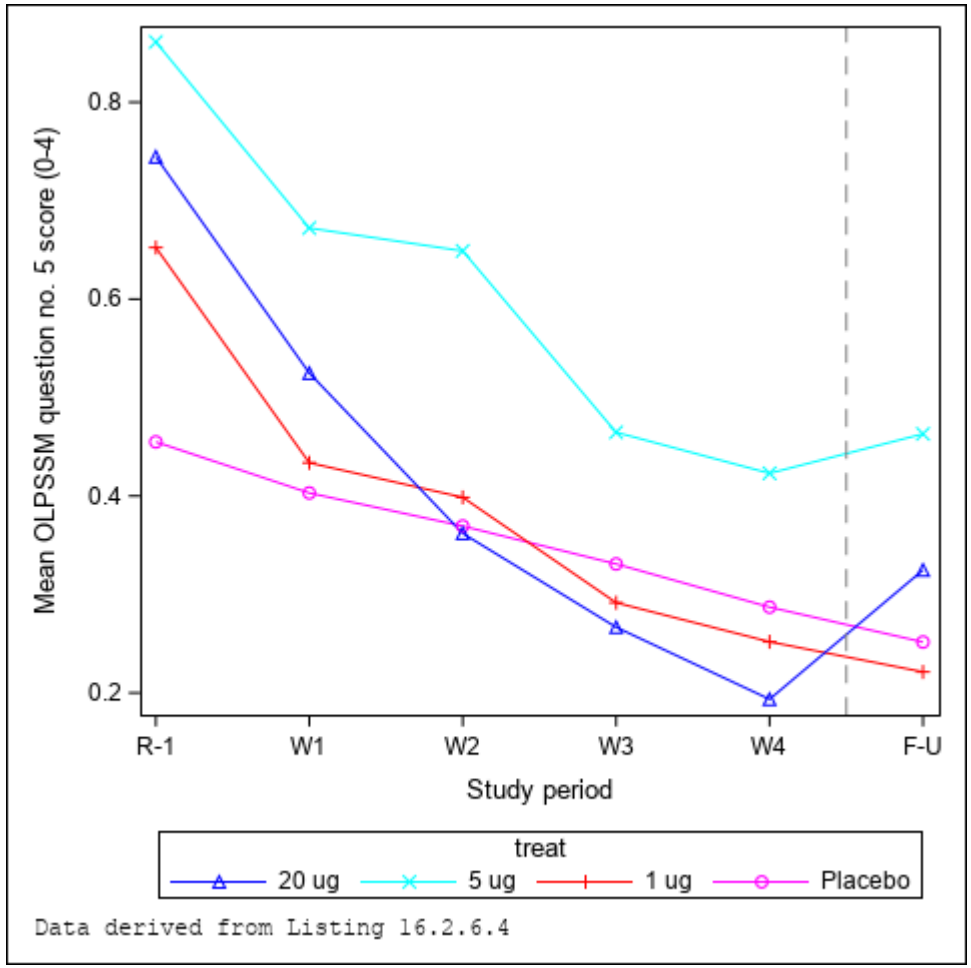


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] l: score no. 5 - change

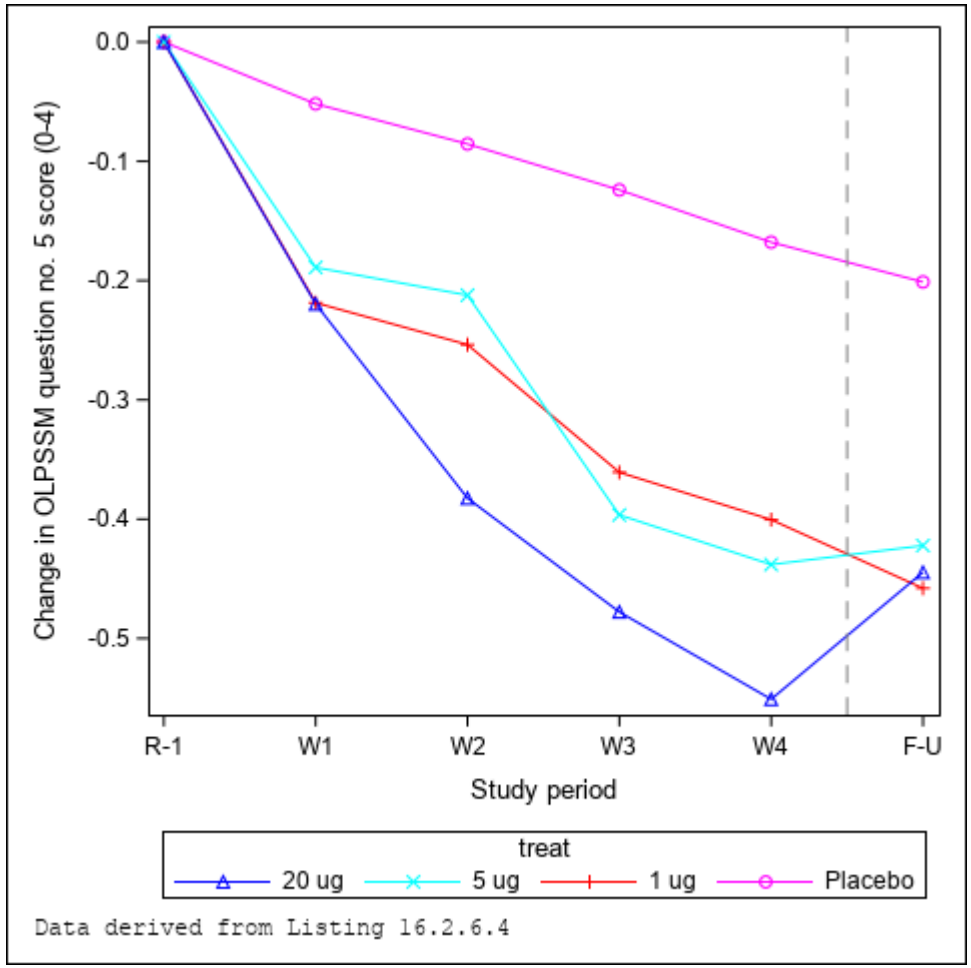


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] m: score no. 6 - absolute scale

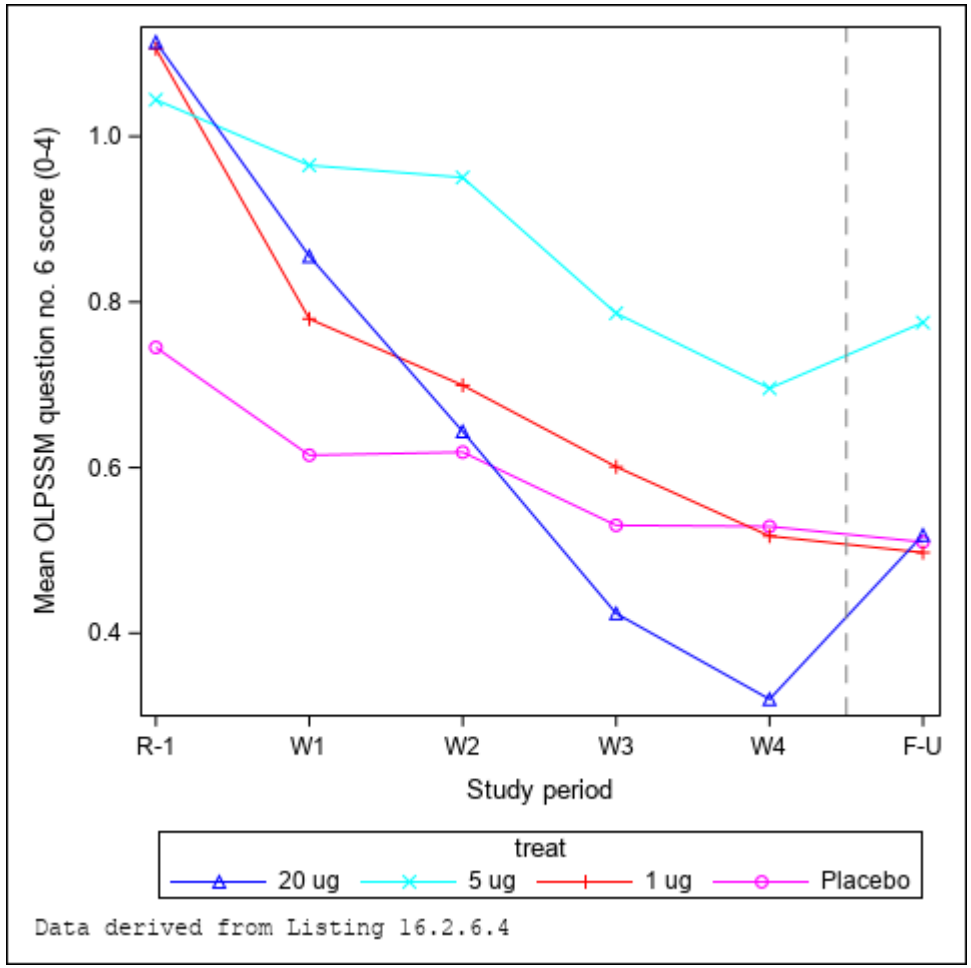


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] n: score no. 6 - change

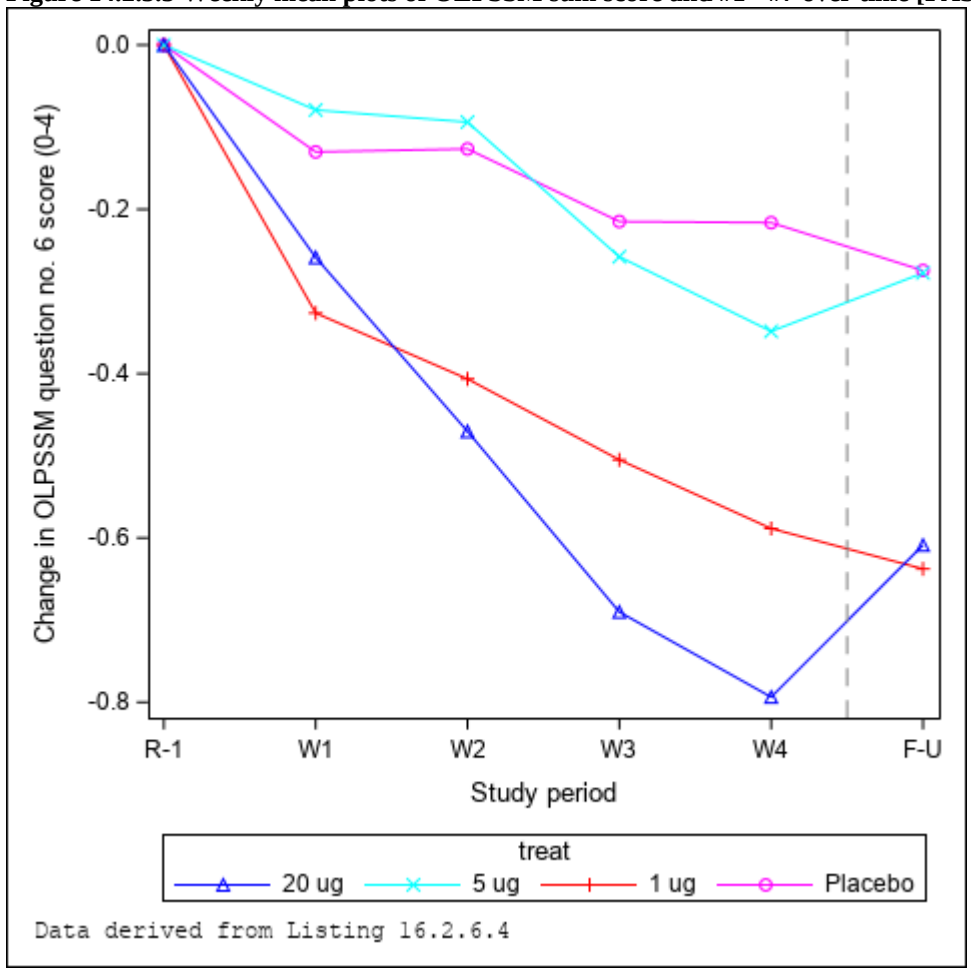


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] o: score no. 7 - absolute scale

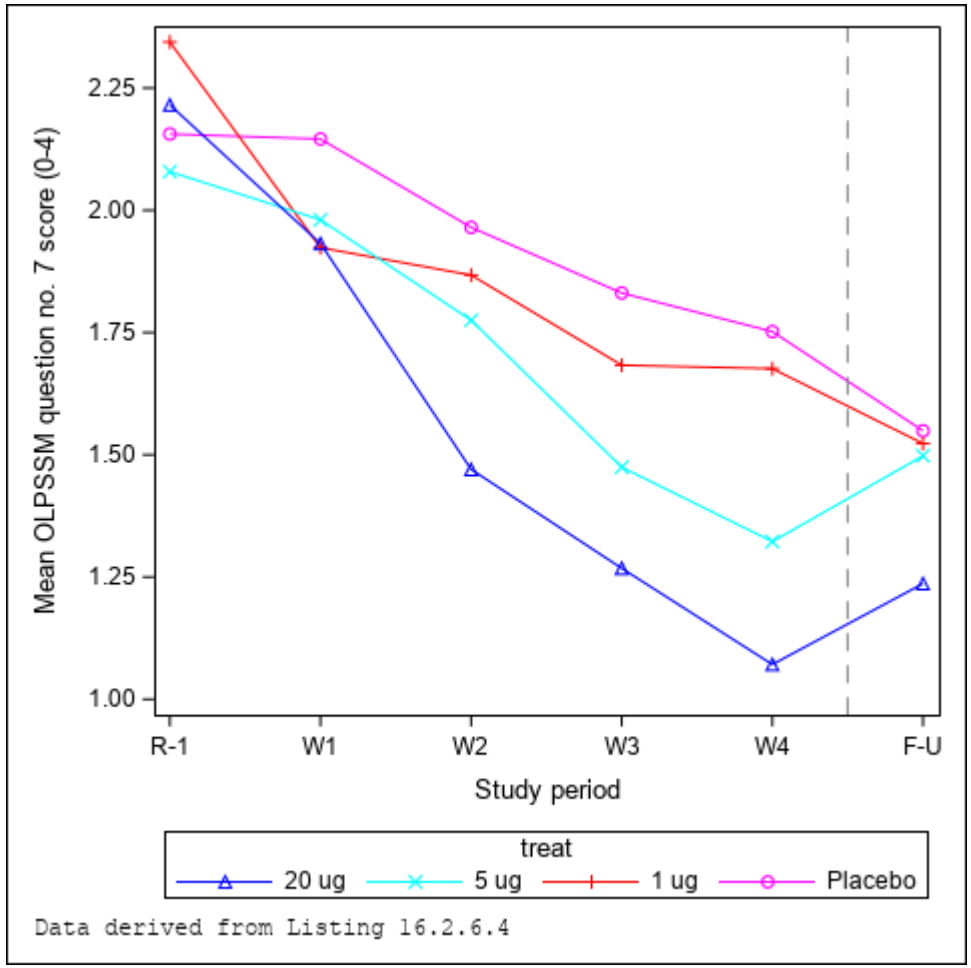


Figure 14.2.3.3 Weekly mean plots of OLPSSM sum score and #1 - #7 over time [FAS] p: score no. 7 - change

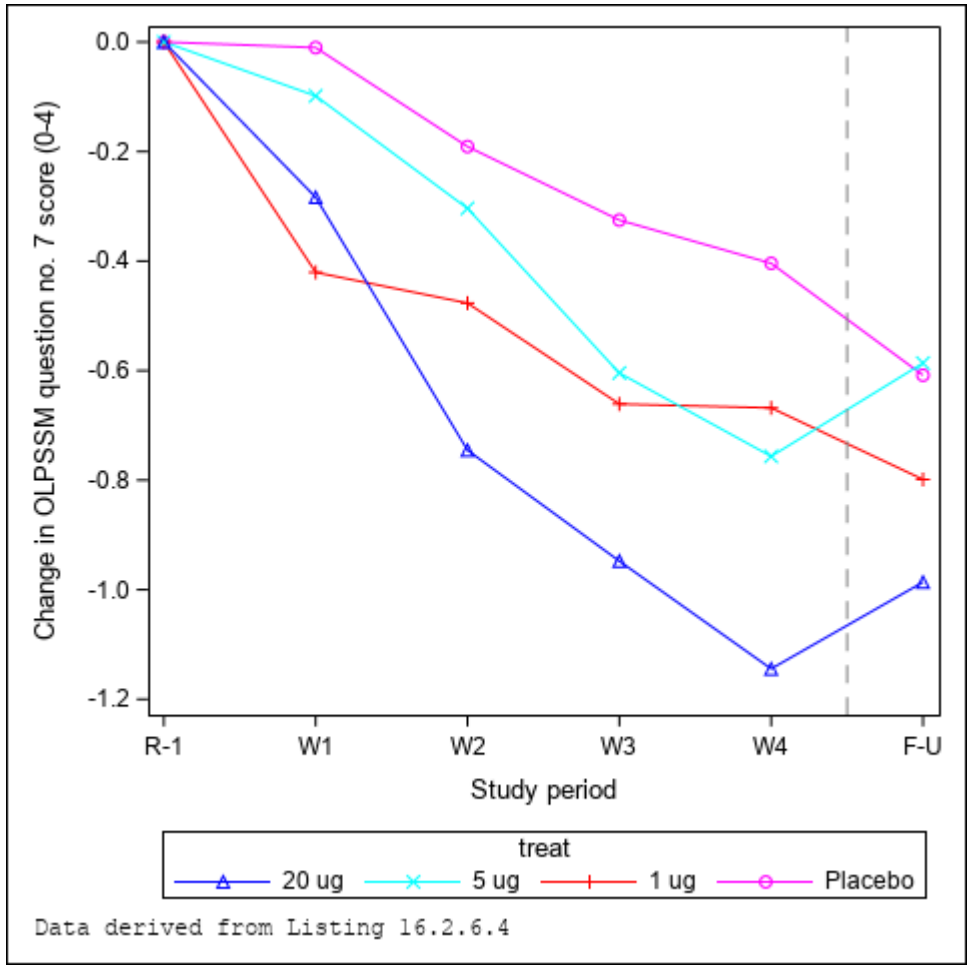


Figure 14.2.3.4 Daily mean value curves of OLPSSM #8 - #10

a: score no. 8 - absolute scale

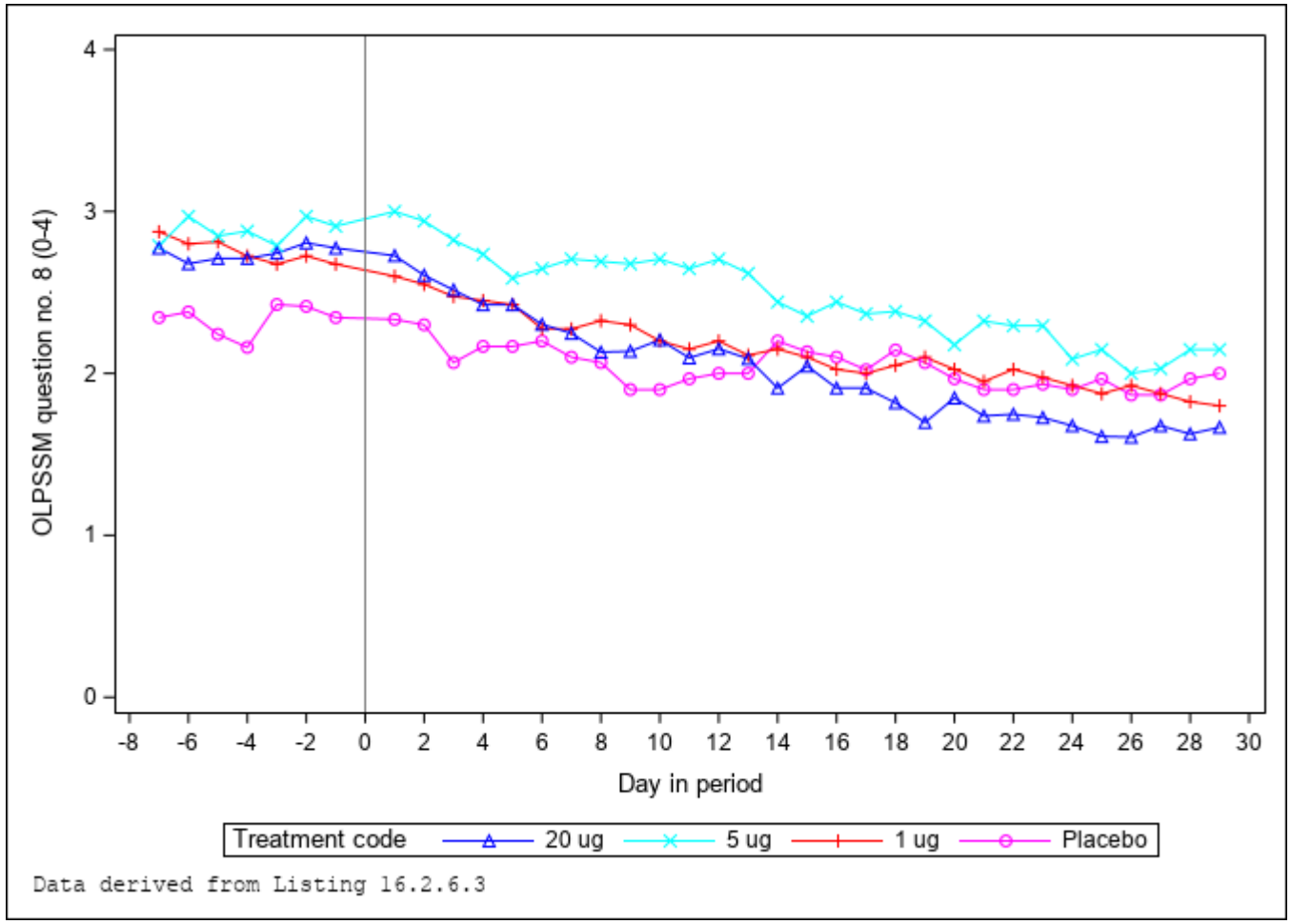


Figure 14.2.3.4 Daily mean value curves of OLPSSM #8 - #10 b: score no. 8 - change

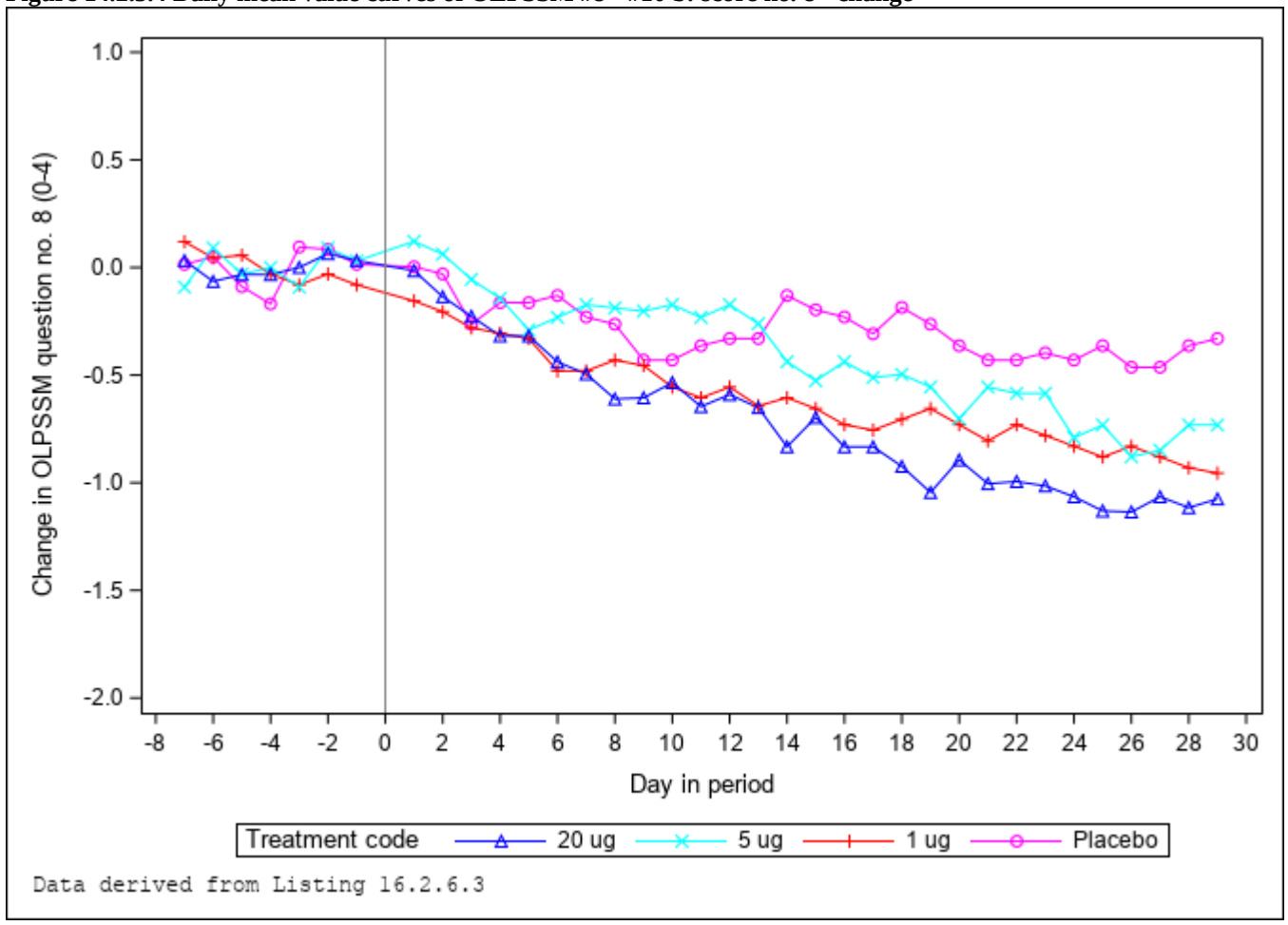


Figure 14.2.3.4 Daily mean value curves of OLPSSM #8 - #10 c: score no. 9 - absolute scale

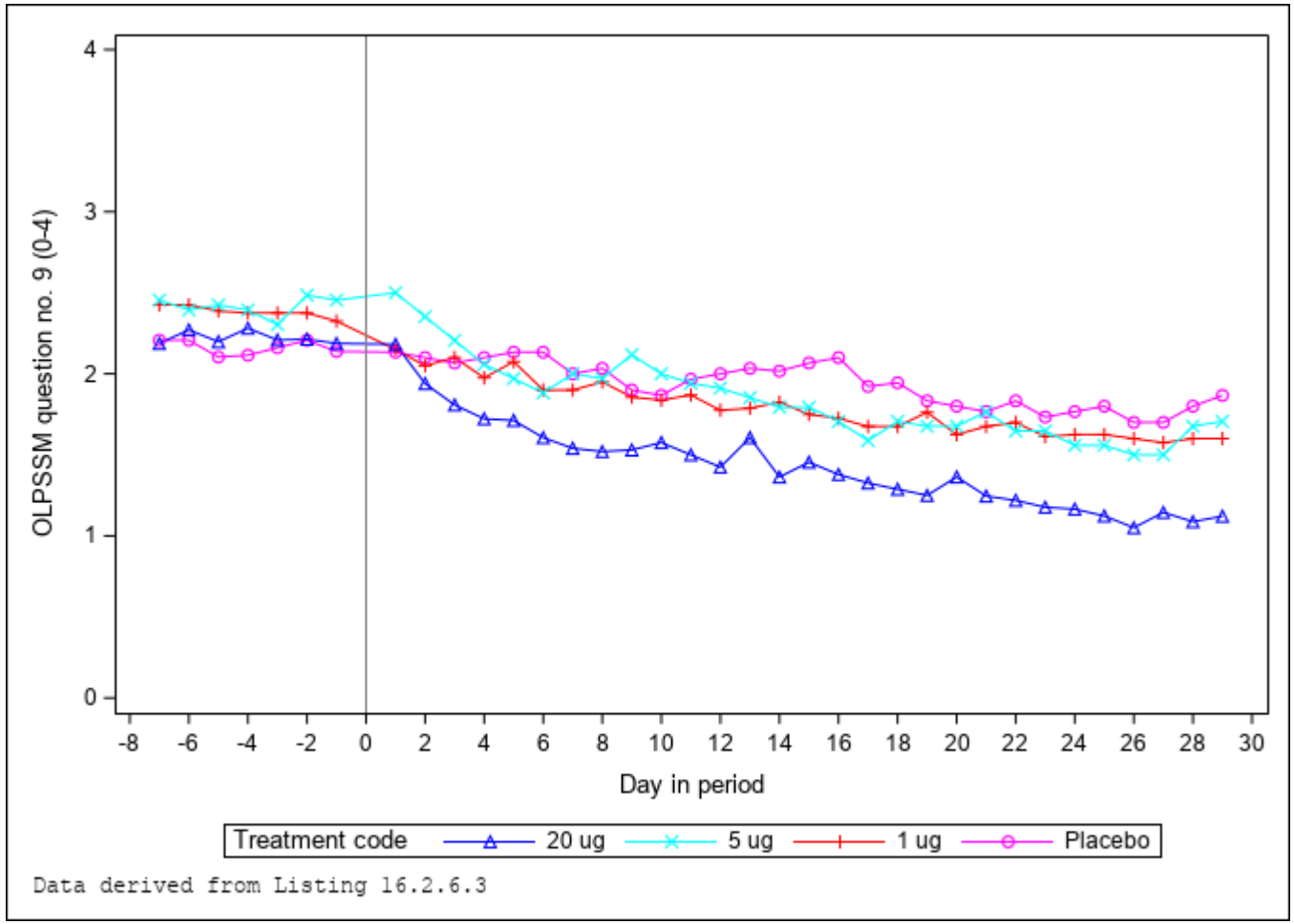


Figure 14.2.3.4 Daily mean value curves of OLPSSM #8 - #10 d: score no. 9 - change

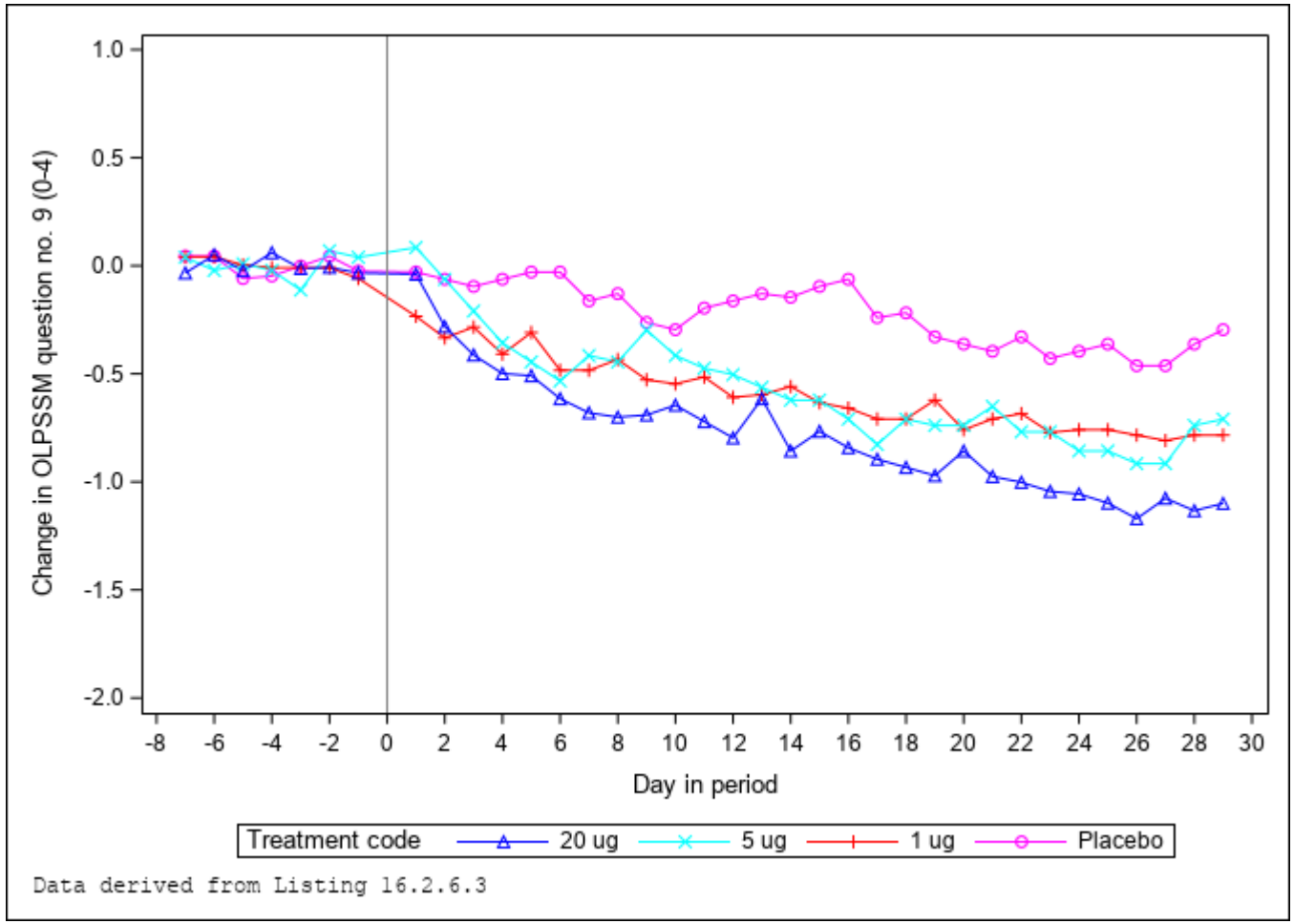


Figure 14.2.3.4 Daily mean value curves of OLPSSM #8 - #10 e: score no. 10 - absolute scale

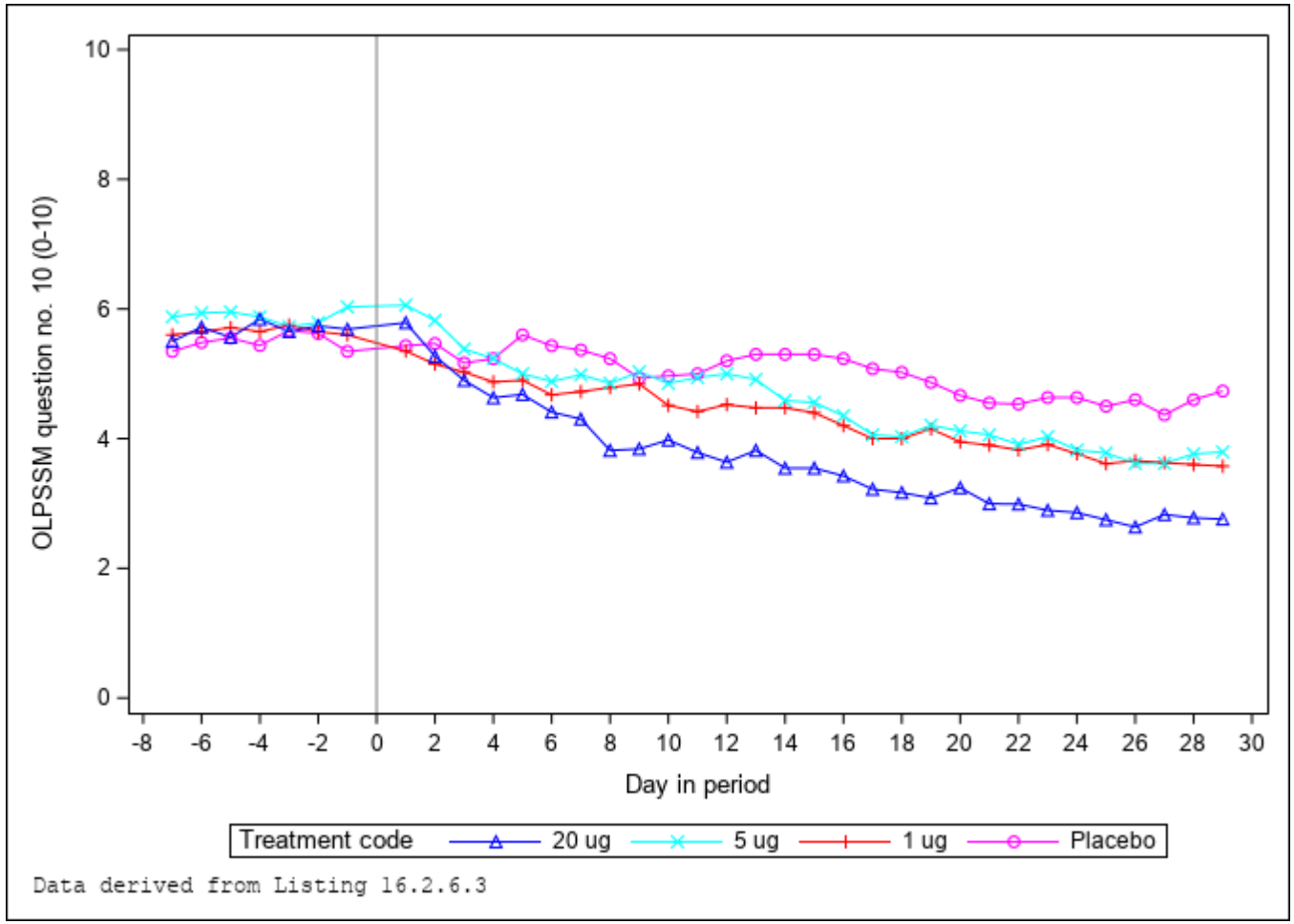


Figure 14.2.3.4 Daily mean value curves of OLPSSM #8 - #10 f: score no. 10 - change

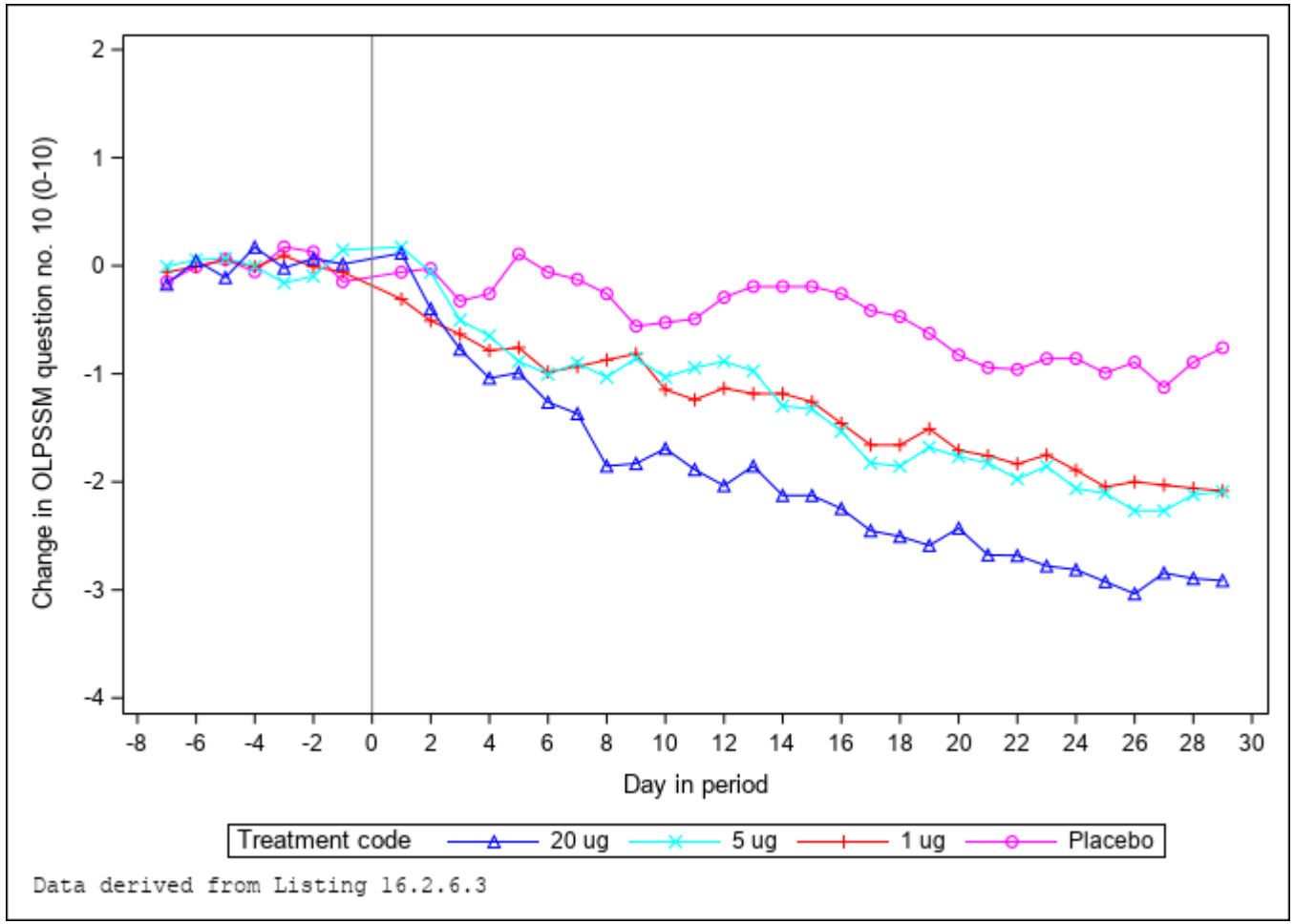


Figure 14.2.3.5 Weekly mean plots of OLPSSM #8 - #11

a: score no. 8 - absolute scale

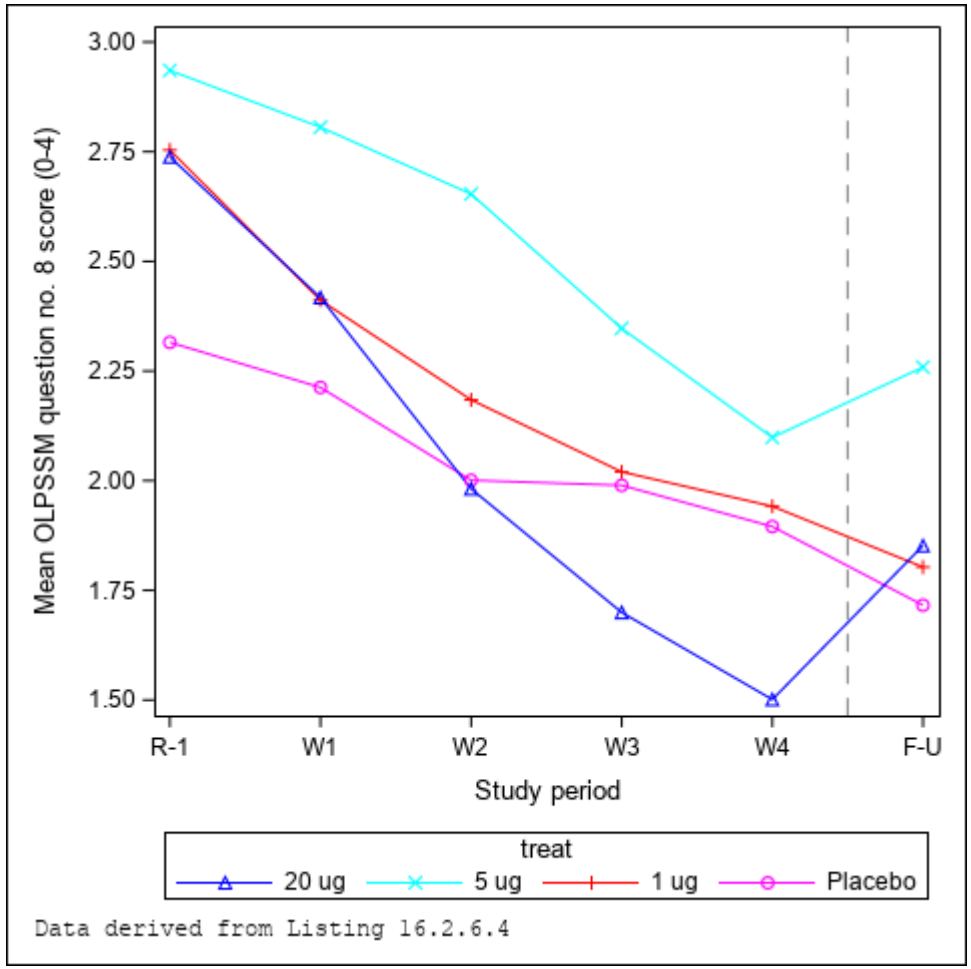


Figure 14.2.3.5 Weekly mean plots of OLPSSM #8 - #11 b: score no. 8 - change

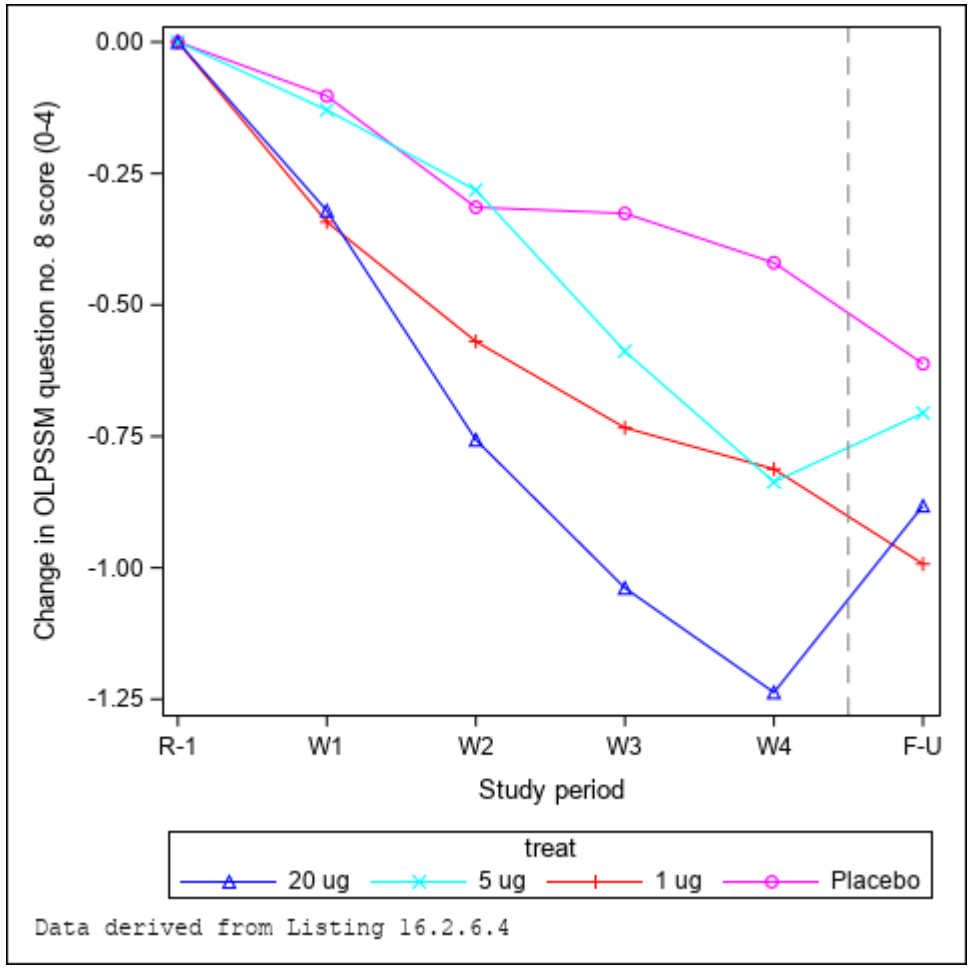


Figure 14.2.3.5 Weekly mean plots of OLPSSM #8 - #11 c: score no. 9 - absolute scale

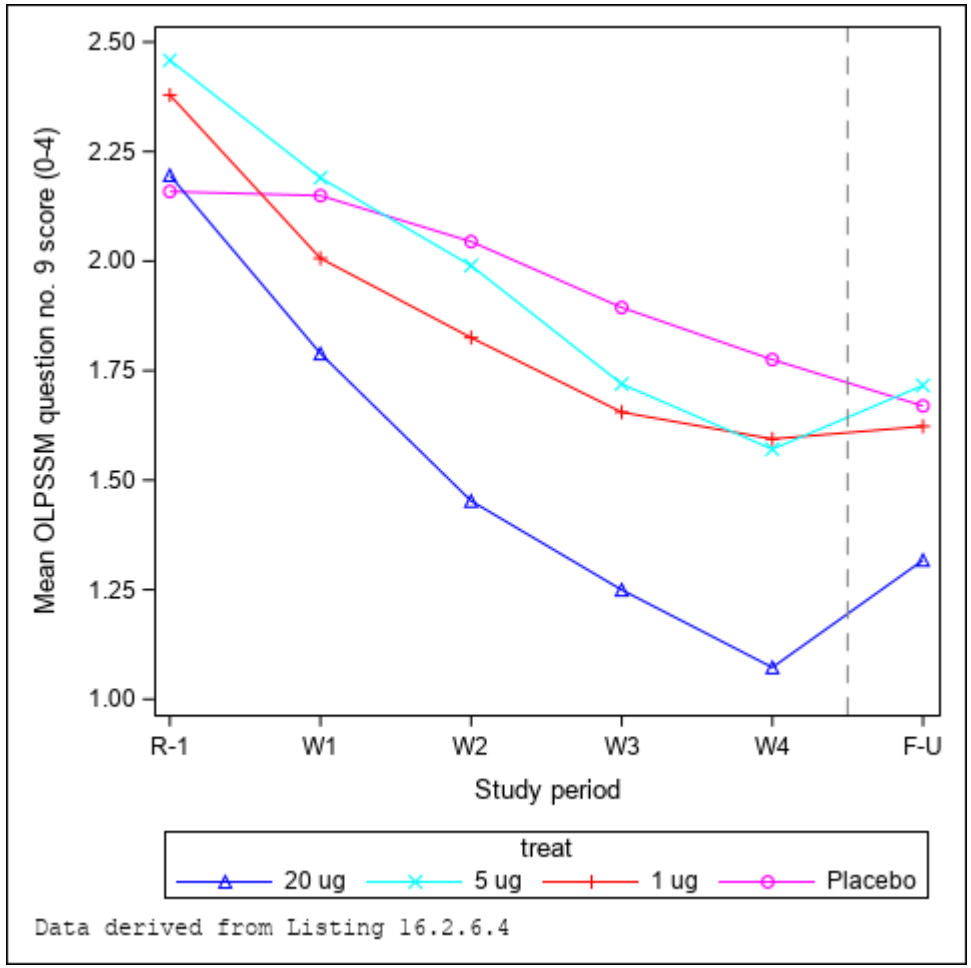


Figure 14.2.3.5 Weekly mean plots of OLPSSM #8 - #11 d: score no. 9 - change

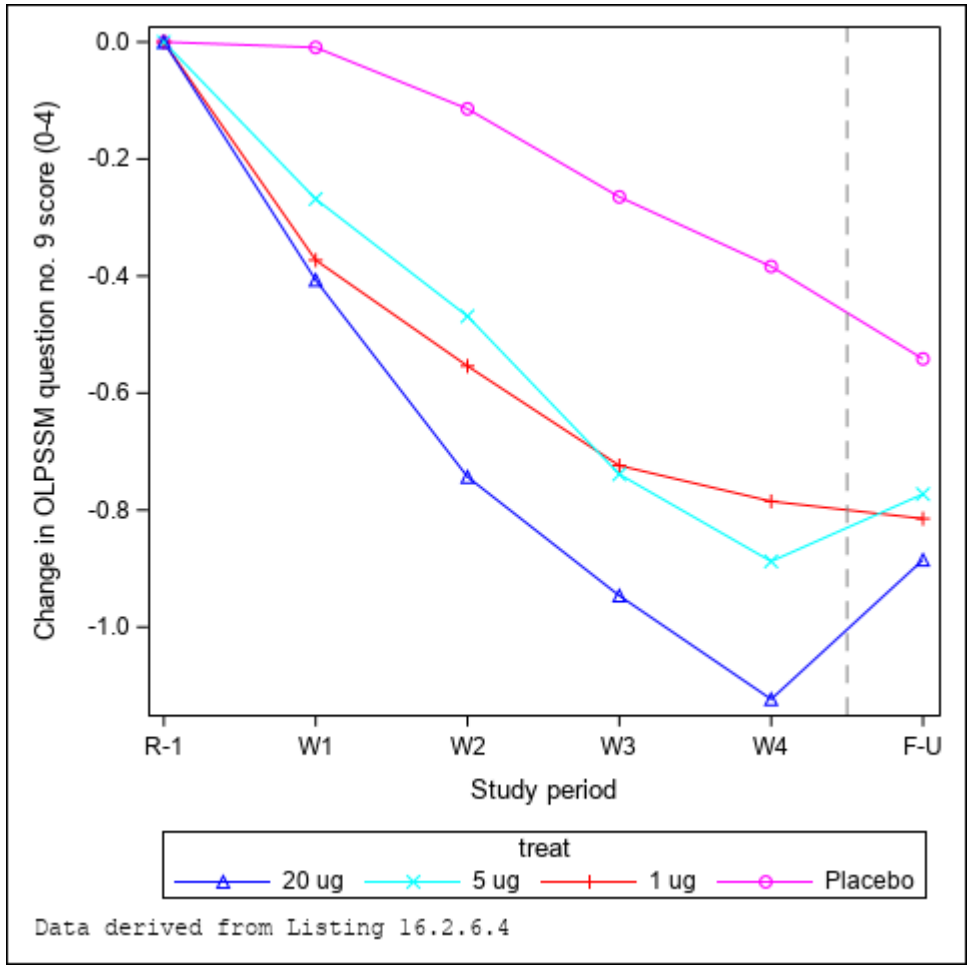


Figure 14.2.3.5 Weekly mean plots of OLPSSM #8 - #11 e: score no. 10 - absolute scale

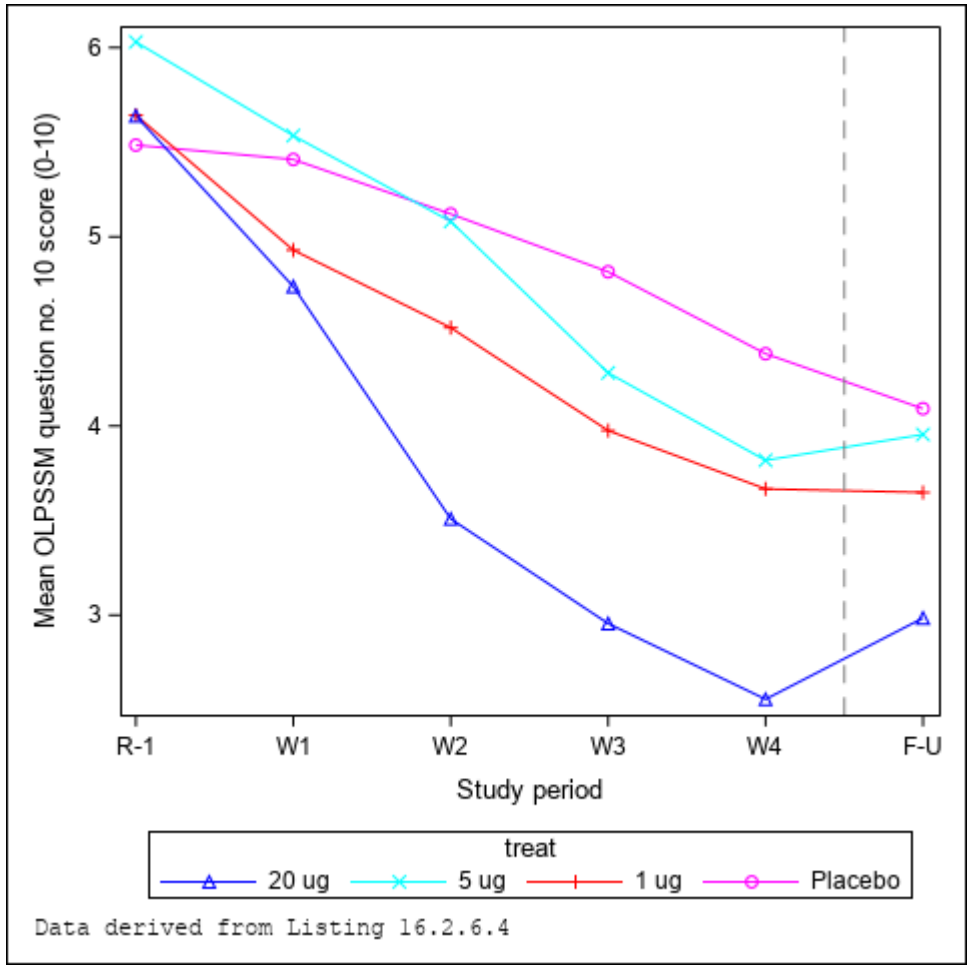


Figure 14.2.3.5 Weekly mean plots of OLPSSM #8 - #11 f: score no. 10 - change

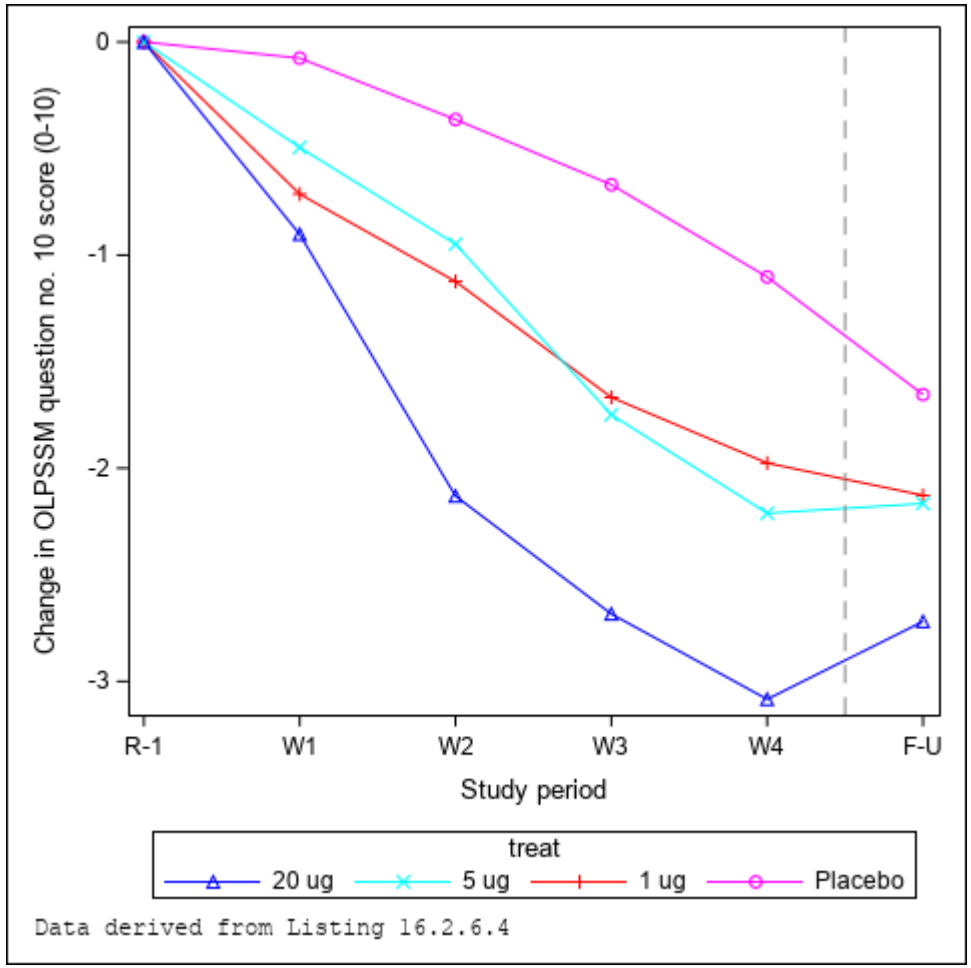


Figure 14.2.3.5 Weekly mean plots of OLPSSM #8 - #11 g: score no. 11 - absolute scale

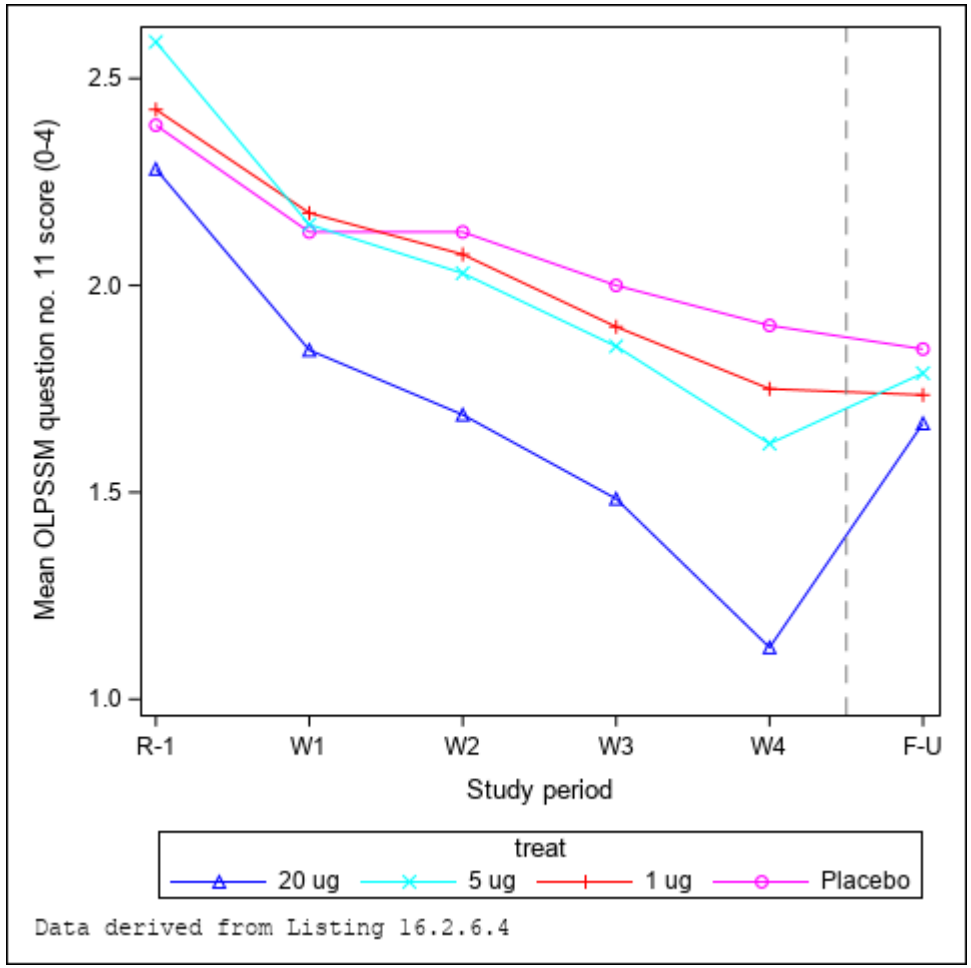


Figure 14.2.3.5 Weekly mean plots of OLPSSM #8 - #11 h: score no. 11 - change

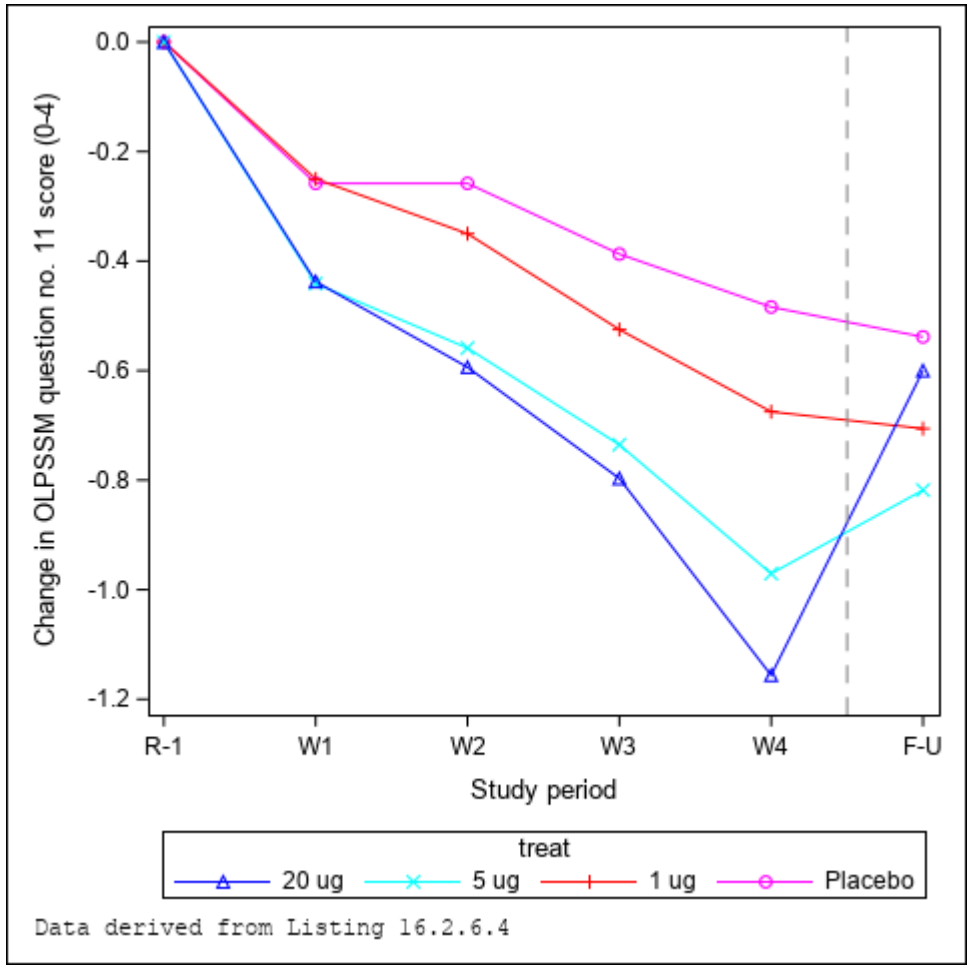
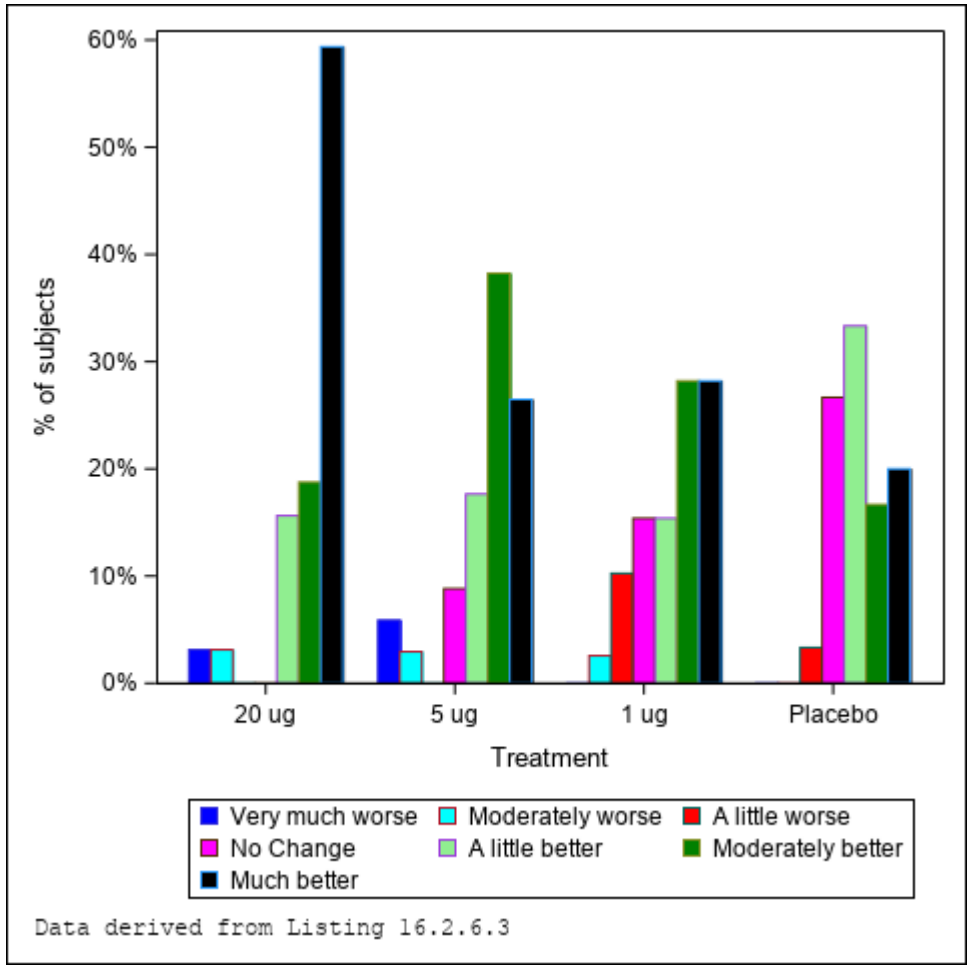


Figure 14.2.3.6 Histograms with distribution of OLPSSM #12 scores



14.2.4 Patch Sensation Questionnaire

Table 14.2.4.1 Summary of answers to the Patch Sensation Questionnaire [FAS]

Variable	Visit	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Irritation	2	22/ 0/ 7/ 3/ 0	23/ 0/ 5/ 4/ 2	21/ 0/14/ 3/ 1	21/ 0/ 3/ 4/ 1
	4	17/ 0/ 7/ 6/ 0	9/ 0/11/11/ 2	17/ 0/ 6/11/ 2	9/ 0/ 9/ 6/ 4
Adhesion	2	11/11/ 5/ 1/ 4	10/ 9/ 6/ 1/ 8	11/13/ 6/ 1/ 8	6/ 9/ 7/ 1/ 6
	4	7/ 4/11/ 4/ 4	12/ 7/ 8/ 3/ 3	6/16/ 8/ 1/ 5	5/11/ 4/ 5/ 3
Taste	2	0/13/13/ 3/ 3	0/15/15/ 2/ 2	1/19/13/ 4/ 2	0/17/12/ 0/ 0
	4	1/10/13/ 5/ 1	1/13/13/ 6/ 0	1/16/10/ 8/ 1	0/17/11/ 0/ 0
Application	2	10/13/ 9/ 0/ 0	14/10/10/ 0/ 0	12/14/12/ 1/ 0	9/ 8/11/ 1/ 0
	4	6/13/10/ 1/ 0	11/11/11/ 0/ 0	10/10/16/ 0/ 0	6/13/ 9/ 0/ 0
Speech	2	0/13/15/ 4/ 0	0/13/16/ 4/ 1	0/10/25/ 3/ 1	0/11/16/ 2/ 0
	4	0/ 8/18/ 2/ 2	0/ 7/18/ 6/ 2	0/10/14/ 6/ 6	0/ 6/14/ 4/ 4
Swallowing	2	0/21/10/ 1/ 0	0/24/ 8/ 1/ 1	0/25/12/ 1/ 1	0/20/ 9/ 0/ 0
	4	0/18/12/ 0/ 0	0/16/13/ 3/ 1	0/16/13/ 5/ 2	0/14/ 9/ 3/ 2
Saliva production	2	0/20/ 8/ 3/ 1	0/16/17/ 1/ 0	0/16/16/ 6/ 0	0/13/14/ 1/ 1
	4	0/11/15/ 1/ 3	0/11/16/ 6/ 0	0/11/15/ 7/ 3	0/ 6/13/ 5/ 4
Bothersome	2	0/11/19/ 2/ 0	0/14/16/ 3/ 1	0/ 8/26/ 4/ 0	0/ 7/14/ 8/ 0
	4	0/ 9/17/ 3/ 1	0/ 6/19/ 8/ 0	0/ 6/21/ 7/ 2	0/ 4/17/ 5/ 2
Comfortable	2	4/ 6/20/ 2/ 0	11/ 8/15/ 0/ 0	4/17/16/ 1/ 0	5/ 5/16/ 3/ 0
	4	3/13/14/ 0/ 0	4/12/16/ 1/ 0	1/15/17/ 3/ 0	2/ 9/13/ 4/ 0
Removal	2	16/10/ 6/ 0/ 0	24/ 5/ 1/ 2/ 1	24/ 9/ 4/ 1/ 0	16/ 9/ 3/ 1/ 0

Variable	Visit	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	4	15/11/ 4/ 0/ 0	25/ 6/ 2/ 0/ 0	18/ 9/ 7/ 2/ 0	15/13/ 0/ 0/ 0
Residue	2	0/12/16/ 3/ 1	0/16/12/ 2/ 3	0/17/18/ 2/ 1	0/14/11/ 4/ 0
	4	0/ 2/21/ 5/ 2	0/ 7/21/ 2/ 3	0/ 8/18/ 7/ 3	0/ 5/18/ 2/ 3
Ordered with most favourable category first and least favourable category last Listing(s): Derived from Listing 16.2.6.5					

Table 14.2.4.2 Statistical analysis of the Patch Sensation Questionnaire [FAS]

a) Visit 2; logistic regression on positive responses
b)

Variable	Treatment	Estimate	Contrast	Ratio	95% CI	pval
Irritation	20 ug	2.17	20 ug vs placebo	0.84	(0.280, 2.530)	0.7540
	5 ug	2.08	5 ug vs placebo	0.80	(0.270, 2.380)	0.6923
	1 ug	1.16	1 ug vs placebo	0.45	(0.160, 1.250)	0.1253
	Placebo	2.59				
Adhesion	20 ug	2.16	20 ug vs placebo	2.05	(0.720, 5.840)	0.1766
	5 ug	1.26	5 ug vs placebo	1.20	(0.440, 3.250)	0.7236
	1 ug	1.58	1 ug vs placebo	1.51	(0.570, 3.990)	0.4099
	Placebo	1.05				
Taste	20 ug	0.62	20 ug vs placebo	0.48	(0.170, 1.340)	0.1591
	5 ug	0.76	5 ug vs placebo	0.58	(0.210, 1.600)	0.2936
	1 ug	1.00	1 ug vs placebo	0.77	(0.290, 2.040)	0.5939
	Placebo	1.31				

Variable	Treatment	Estimate	Contrast	Ratio	95% CI	pval
Application	20 ug	2.41	20 ug vs placebo	1.81	(0.620, 5.300)	0.2769
	5 ug	2.36	5 ug vs placebo	1.78	(0.620, 5.100)	0.2845
	1 ug	1.94	1 ug vs placebo	1.46	(0.540, 3.970)	0.4602
	Placebo	1.33				
Speech	20 ug	0.60	20 ug vs placebo	1.12	(0.390, 3.190)	0.8285
	5 ug	0.58	5 ug vs placebo	1.09	(0.390, 3.080)	0.8720
	1 ug	0.31	1 ug vs placebo	0.58	(0.200, 1.670)	0.3152
	Placebo	0.53				
Swallowing	20 ug	1.71	20 ug vs placebo	0.85	(0.290, 2.550)	0.7760
	5 ug	2.37	5 ug vs placebo	1.18	(0.390, 3.550)	0.7678
	1 ug	1.69	1 ug vs placebo	0.84	(0.300, 2.400)	0.7513
	Placebo	2.00				
Saliva production	20 ug	1.61	20 ug vs placebo	2.06	(0.740, 5.730)	0.1685
	5 ug	0.88	5 ug vs placebo	1.12	(0.410, 3.040)	0.8259
	1 ug	0.71	1 ug vs placebo	0.91	(0.340, 2.400)	0.8413
	Placebo	0.78				
Bothersome	20 ug	0.40	20 ug vs placebo	1.70	(0.530, 5.400)	0.3693
	5 ug	0.62	5 ug vs placebo	2.65	(0.850, 8.310)	0.0940
	1 ug	0.21	1 ug vs placebo	0.88	(0.270, 2.880)	0.8338
	Placebo	0.23				

Variable	Treatment	Estimate	Contrast	Ratio	95% CI	pval
Comfortable	20 ug	0.40	20 ug vs placebo	0.86	(0.290, 2.530)	0.7855
	5 ug	1.23	5 ug vs placebo	2.61	(0.920, 7.390)	0.0705
	1 ug	1.16	1 ug vs placebo	2.47	(0.900, 6.790)	0.0798
	Placebo	0.47				
Removal	20 ug	4.02	20 ug vs placebo	0.69	(0.170, 2.770)	0.5988
	5 ug	7.36	5 ug vs placebo	1.26	(0.280, 5.650)	0.7626
	1 ug	6.41	1 ug vs placebo	1.10	(0.260, 4.560)	0.8986
	Placebo	5.84				
Residue	20 ug	0.58	20 ug vs placebo	0.64	(0.230, 1.780)	0.3953
	5 ug	0.93	5 ug vs placebo	1.04	(0.380, 2.830)	0.9432
	1 ug	0.79	1 ug vs placebo	0.88	(0.330, 2.320)	0.7930
	Placebo	0.90				

Listing(s): Derived from 16.2.6.5

14.2.4.2 Statistical analysis of the Patch Sensation Questionnaire [FAS]: b) Visit 4; logistic regression on positive responses

Variable	Treatment	Estimate	Contrast	Ratio	95% CI	pval
Irritation	20 ug	1.23	20 ug vs placebo	2.76	(0.940, 8.090)	0.0648
	5 ug	0.37	5 ug vs placebo	0.82	(0.270, 2.480)	0.7258
	1 ug	0.86	1 ug vs placebo	1.92	(0.680, 5.400)	0.2153
	Placebo	0.45				
Adhesion	20 ug	0.54	20 ug vs placebo	0.43	(0.150, 1.230)	0.1161
	5 ug	1.34	5 ug vs placebo	1.05	(0.380, 2.940)	0.9188
	1 ug	1.51	1 ug vs placebo	1.19	(0.440, 3.270)	0.7308
	Placebo	1.27				
Taste	20 ug	0.51	20 ug vs placebo	0.36	(0.120, 1.060)	0.0628
	5 ug	0.71	5 ug vs placebo	0.50	(0.180, 1.410)	0.1903
	1 ug	0.83	1 ug vs placebo	0.58	(0.210, 1.610)	0.2975
	Placebo	1.42				
Application	20 ug	1.59	20 ug vs placebo	0.80	(0.270, 2.410)	0.6967
	5 ug	1.97	5 ug vs placebo	1.00	(0.340, 2.960)	0.9982
	1 ug	1.18	1 ug vs placebo	0.60	(0.210, 1.690)	0.3312
	Placebo	1.97				
Speech	20 ug	0.31	20 ug vs placebo	1.32	(0.390, 4.490)	0.6579
	5 ug	0.25	5 ug vs placebo	1.06	(0.310, 3.680)	0.9280
	1 ug	0.34	1 ug vs placebo	1.45	(0.450, 4.700)	0.5320
	Placebo	0.24				

Variable	Treatment	Estimate	Contrast	Ratio	95% CI	pval
Swallowing	20 ug	1.26	20 ug vs placebo	1.50	(0.510, 4.440)	0.4592
	5 ug	0.88	5 ug vs placebo	1.06	(0.370, 3.030)	0.9172
	1 ug	0.68	1 ug vs placebo	0.82	(0.290, 2.290)	0.7003
	Placebo	0.84				
Saliva production	20 ug	0.51	20 ug vs placebo	2.12	(0.650, 6.900)	0.2117
	5 ug	0.48	5 ug vs placebo	1.98	(0.610, 6.400)	0.2536
	1 ug	0.40	1 ug vs placebo	1.66	(0.520, 5.300)	0.3903
	Placebo	0.24				
Bothersome	20 ug	0.23	20 ug vs placebo	2.72	(0.690, 10.780)	0.1547
	5 ug	0.14	5 ug vs placebo	1.63	(0.380, 6.880)	0.5095
	1 ug	0.11	1 ug vs placebo	1.28	(0.310, 5.340)	0.7322
	Placebo	0.08				
Comfortable	20 ug	1.03	20 ug vs placebo	1.76	(0.610, 5.070)	0.2930
	5 ug	0.91	5 ug vs placebo	1.57	(0.560, 4.420)	0.3966
	1 ug	0.74	1 ug vs placebo	1.27	(0.460, 3.510)	0.6460
	Placebo	0.58				
Removal	20 ug	6.00	20 ug vs placebo			
	5 ug	16.87	5 ug vs placebo			
	1 ug	2.85	1 ug vs placebo			
	Placebo					

Variable	Treatment	Estimate	Contrast	Ratio	95% CI	pval
Residue	20 ug	0.07	20 ug vs placebo	0.32	(0.060, 1.830)	0.2026
	5 ug	0.26	5 ug vs placebo	1.29	(0.360, 4.670)	0.6961
	1 ug	0.27	1 ug vs placebo	1.33	(0.380, 4.660)	0.6514
	Placebo	0.20				
For removal placebo had only successes, thus odds and associated ratios, CIs and p-values are not shown Listing(s): Derived from 16.2.6.5						

Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire

a: Q1 irritation - visit 2

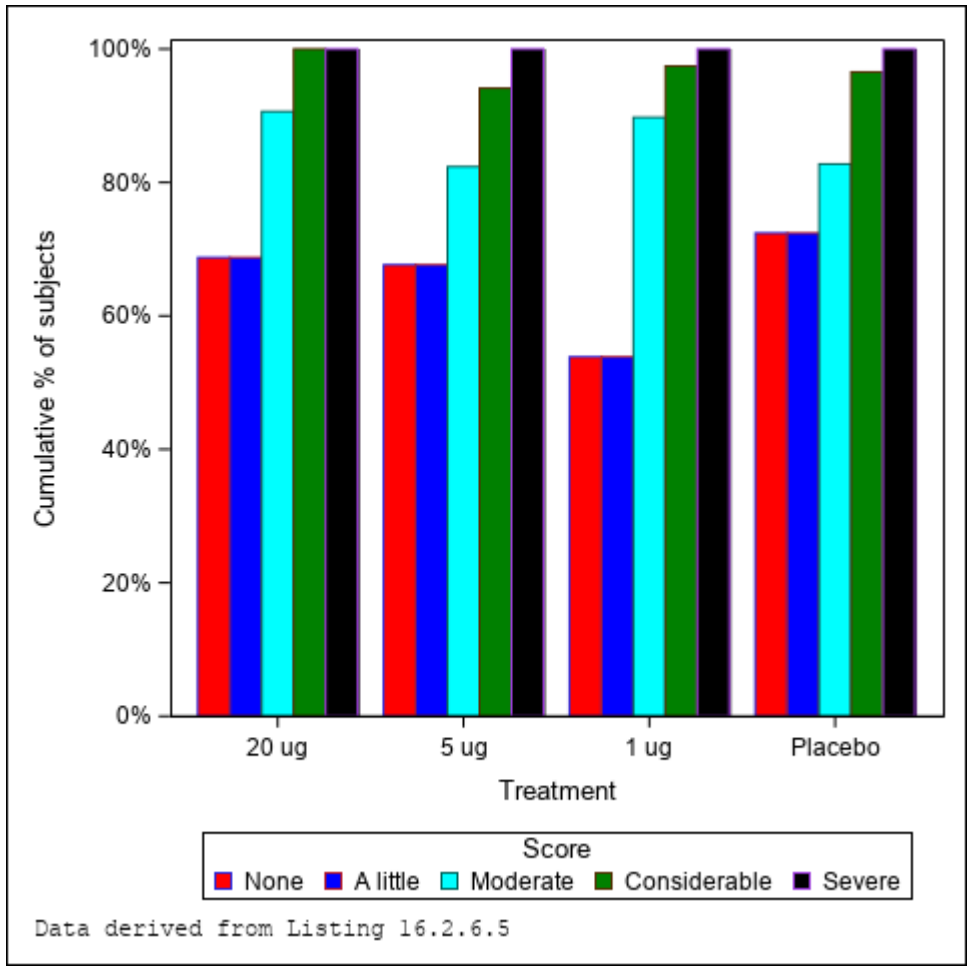


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: b: Q1 irritation - visit 4

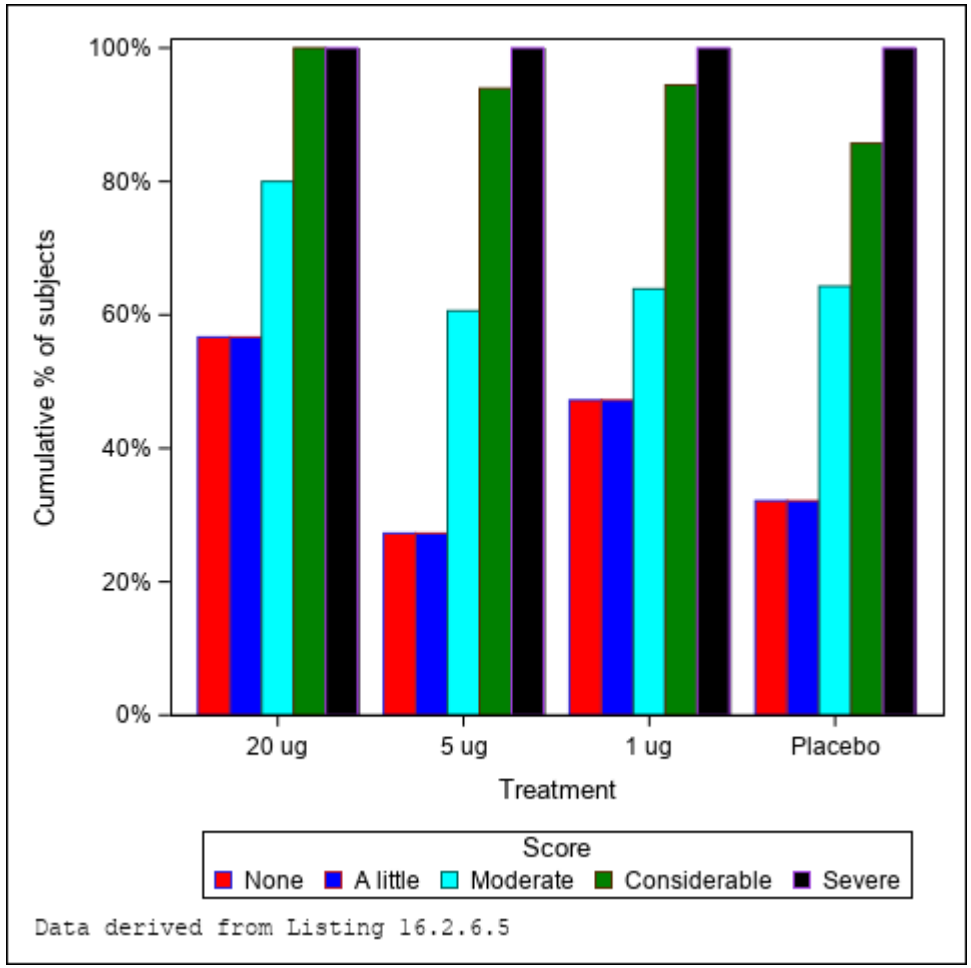


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: c: Q2 adhesion - visit 2

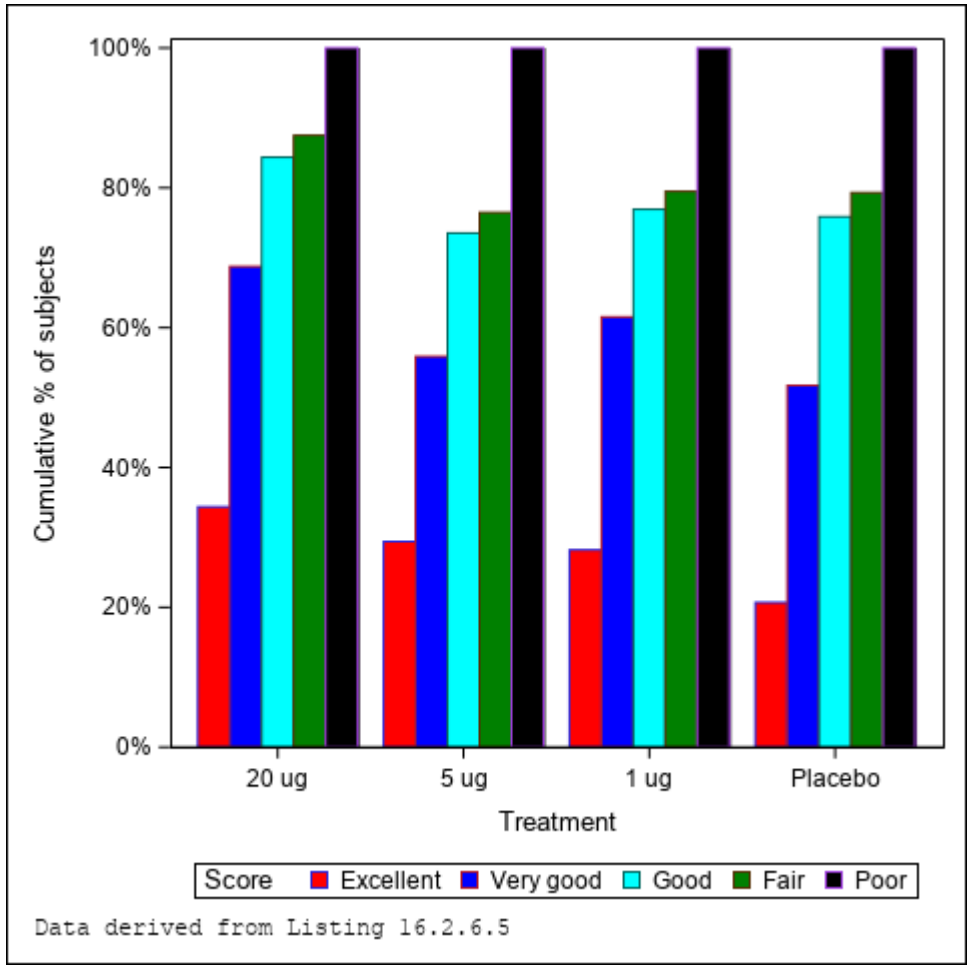


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: d: Q2 adhesion- visit 4

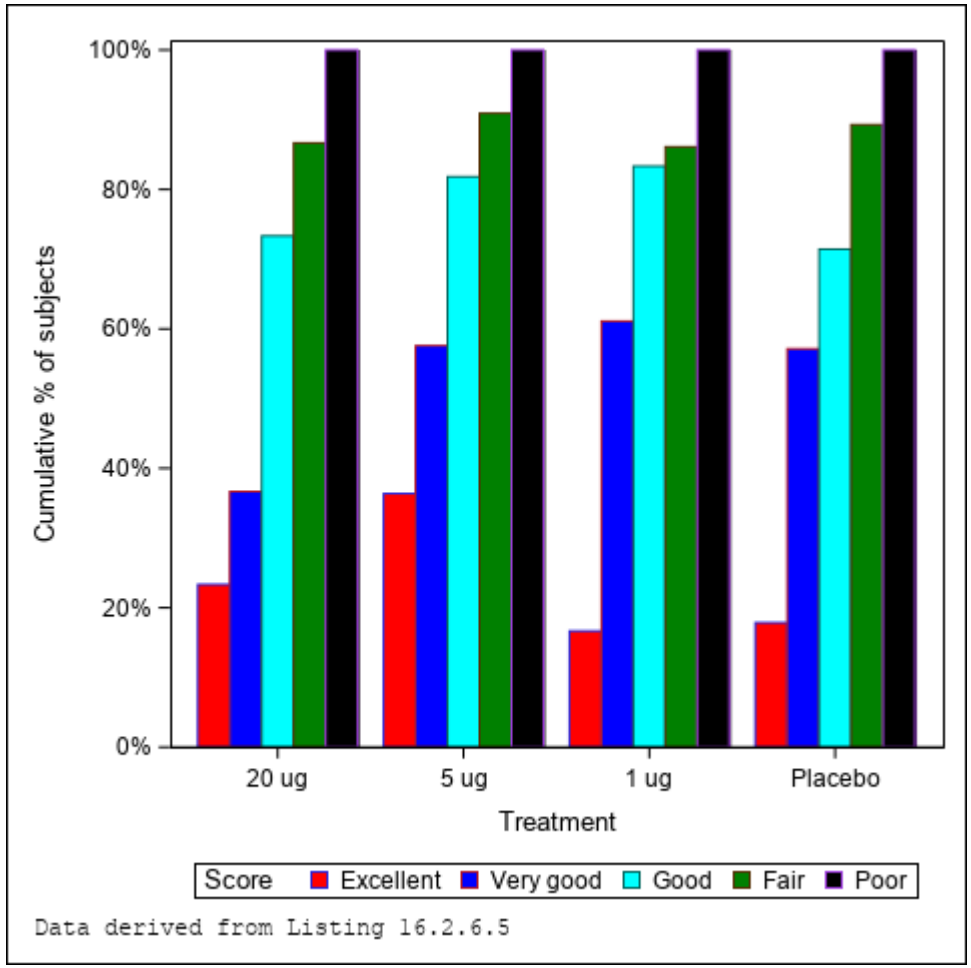


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: e: Q3 taste - visit 2

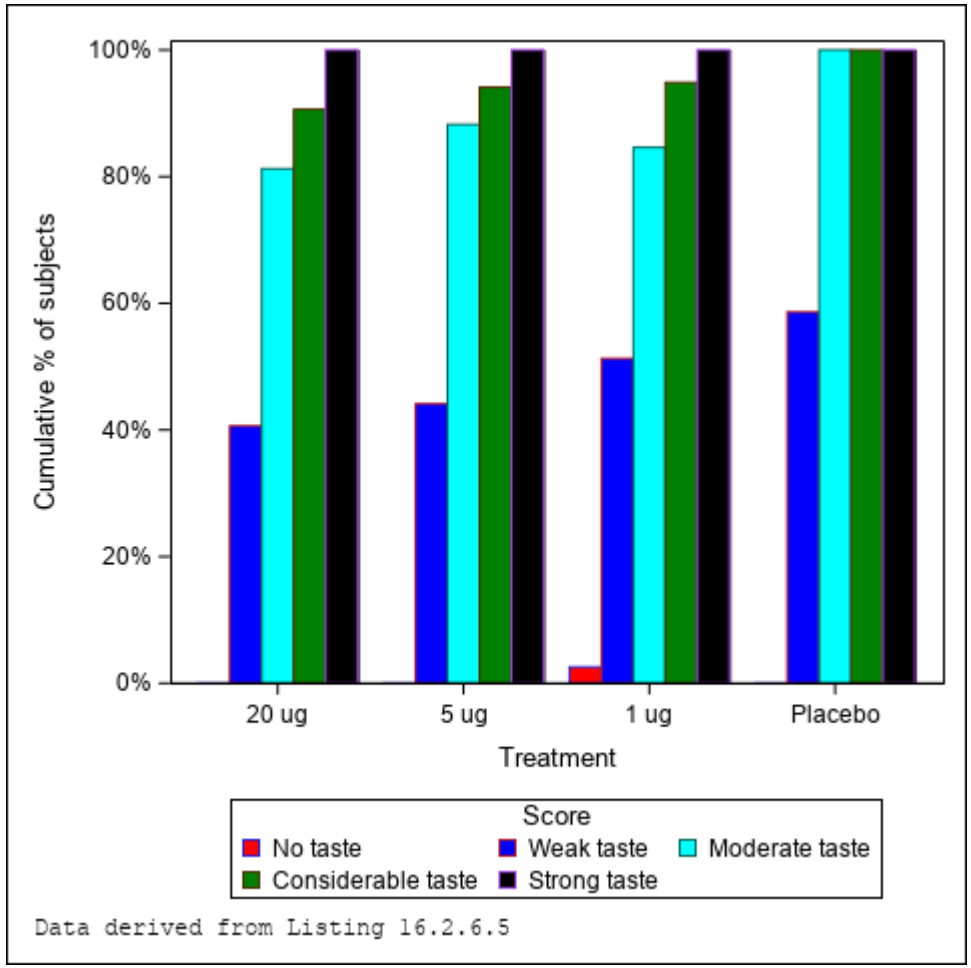


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: f: Q3 taste- visit 4

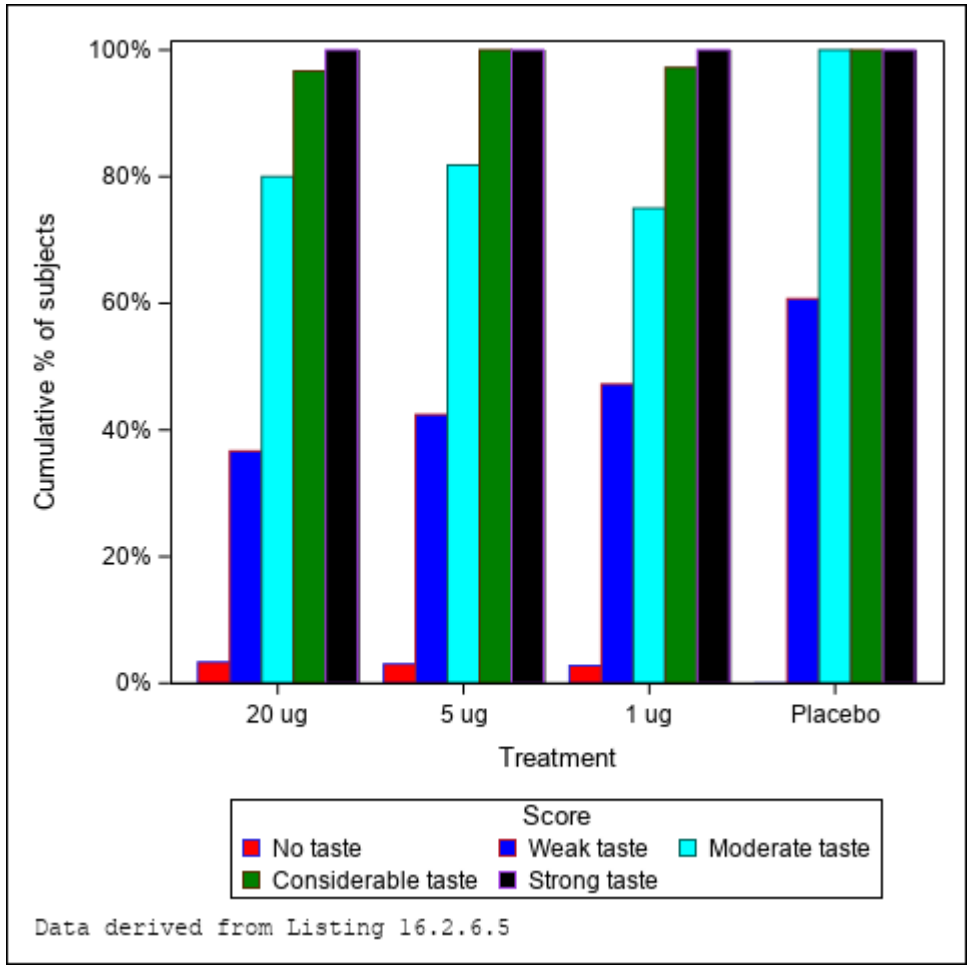


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: g: Q4 application - visit 2

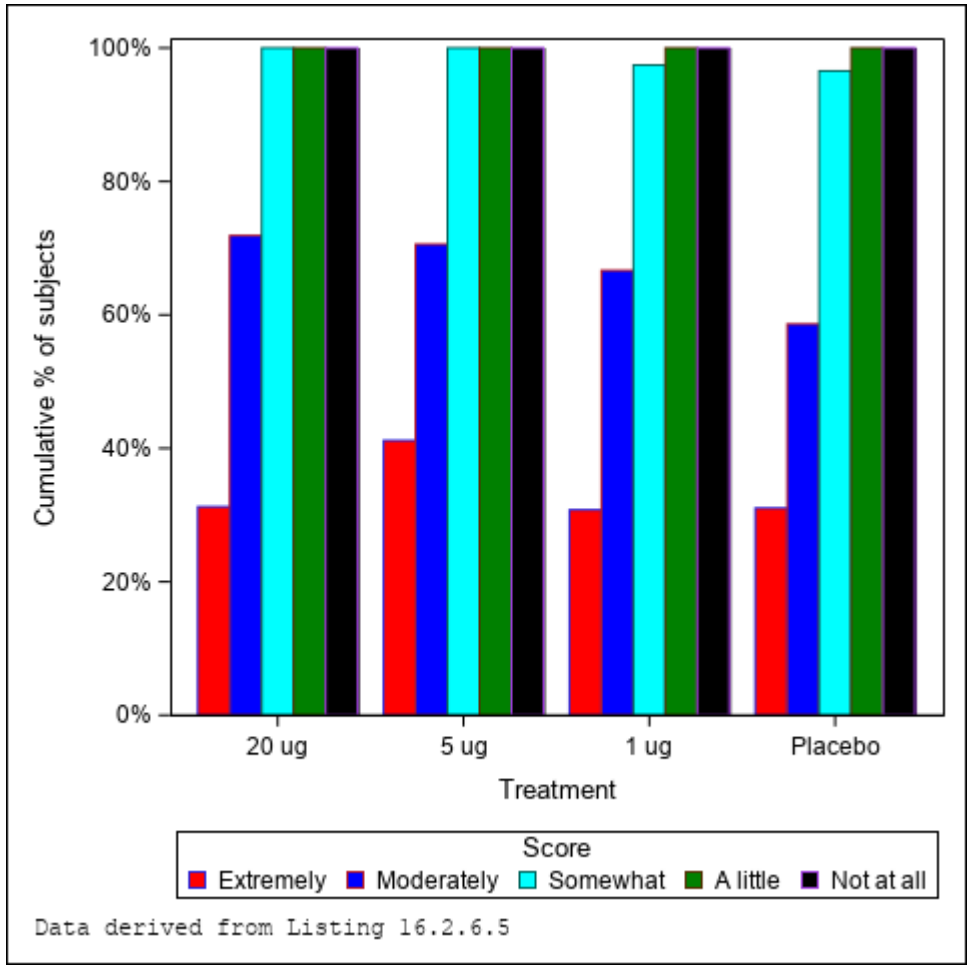


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: h: Q4 application- visit 4

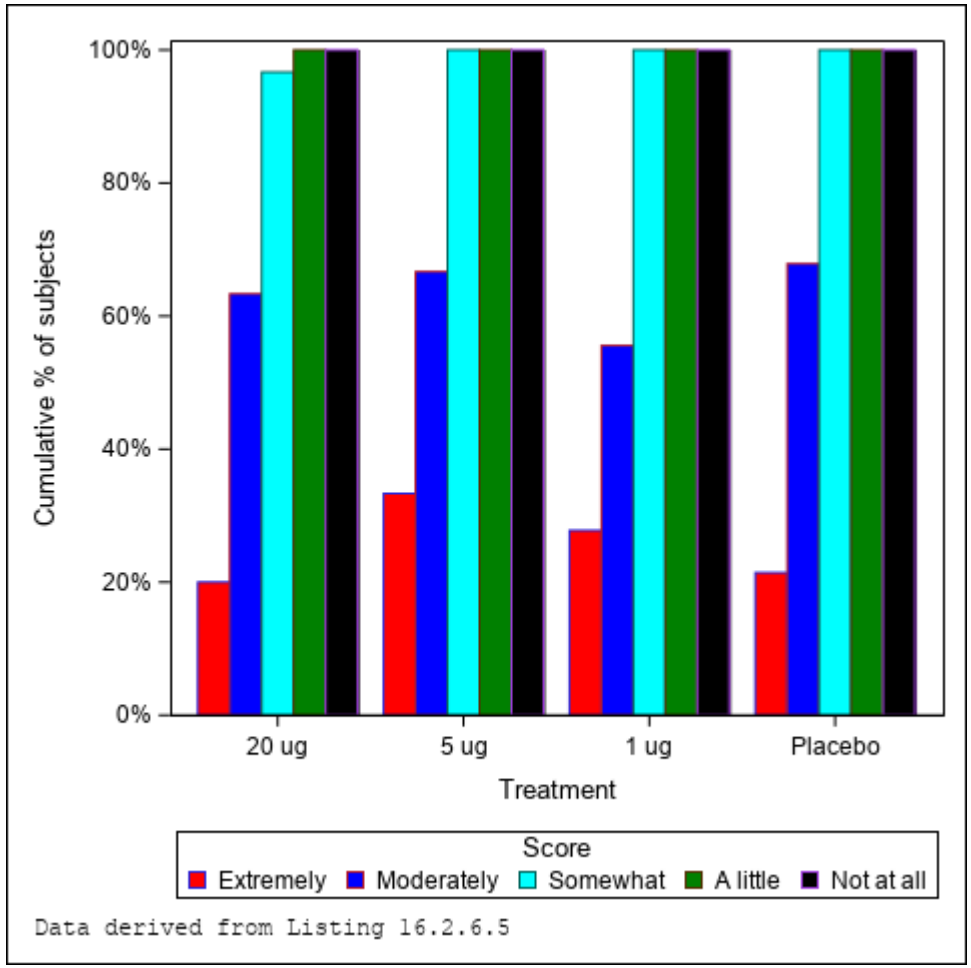


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: i: Q5 speech - visit 2

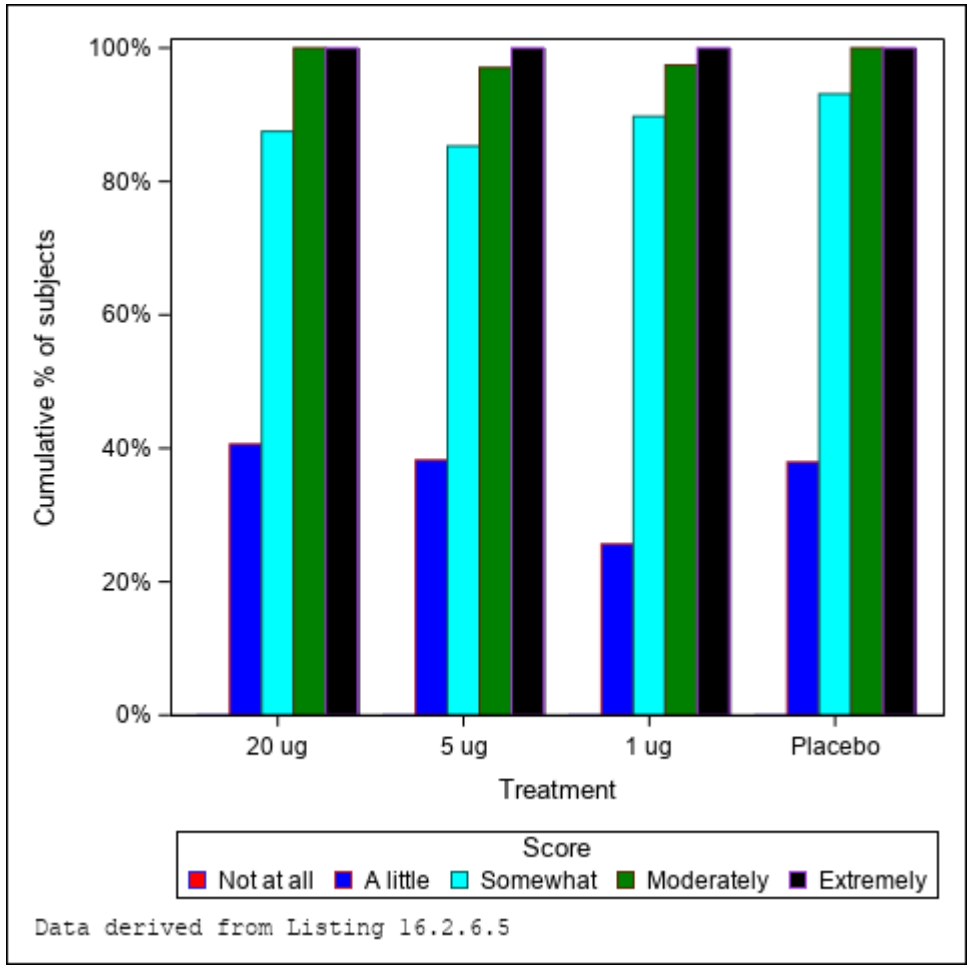


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: j: Q5 speech- visit 4

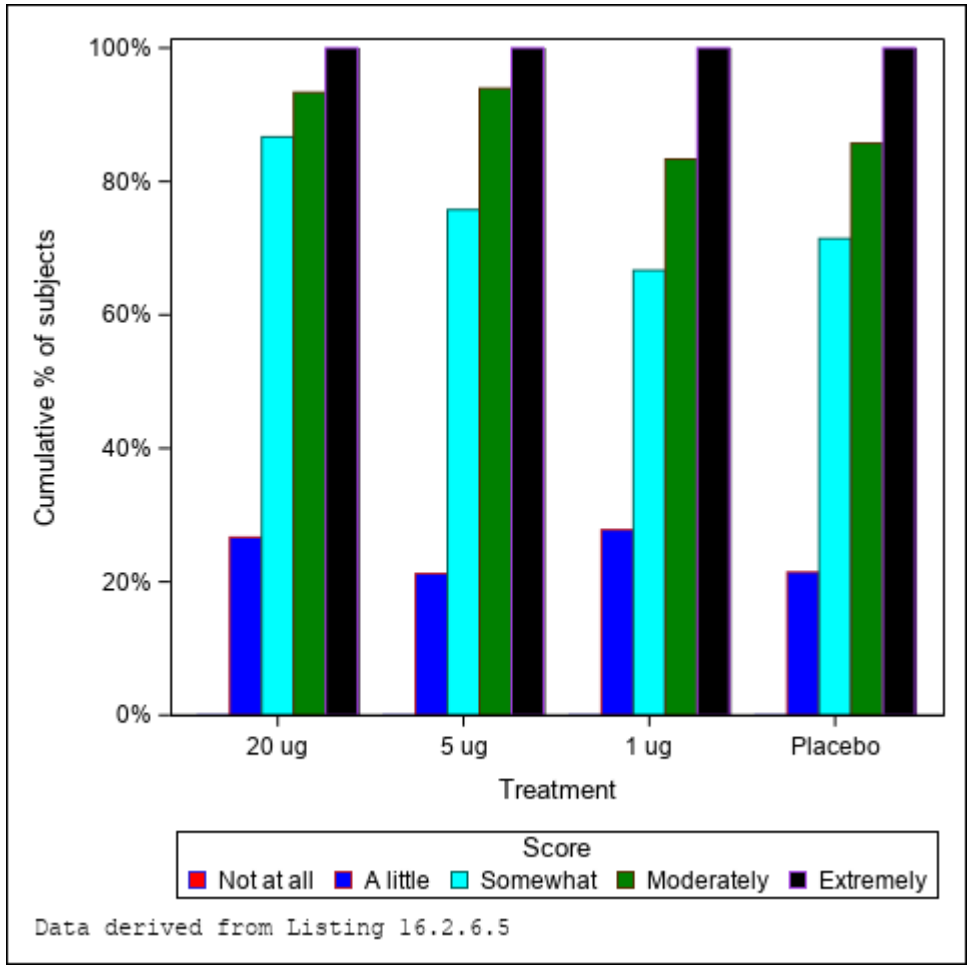


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: k: Q6 swallowing - visit 2

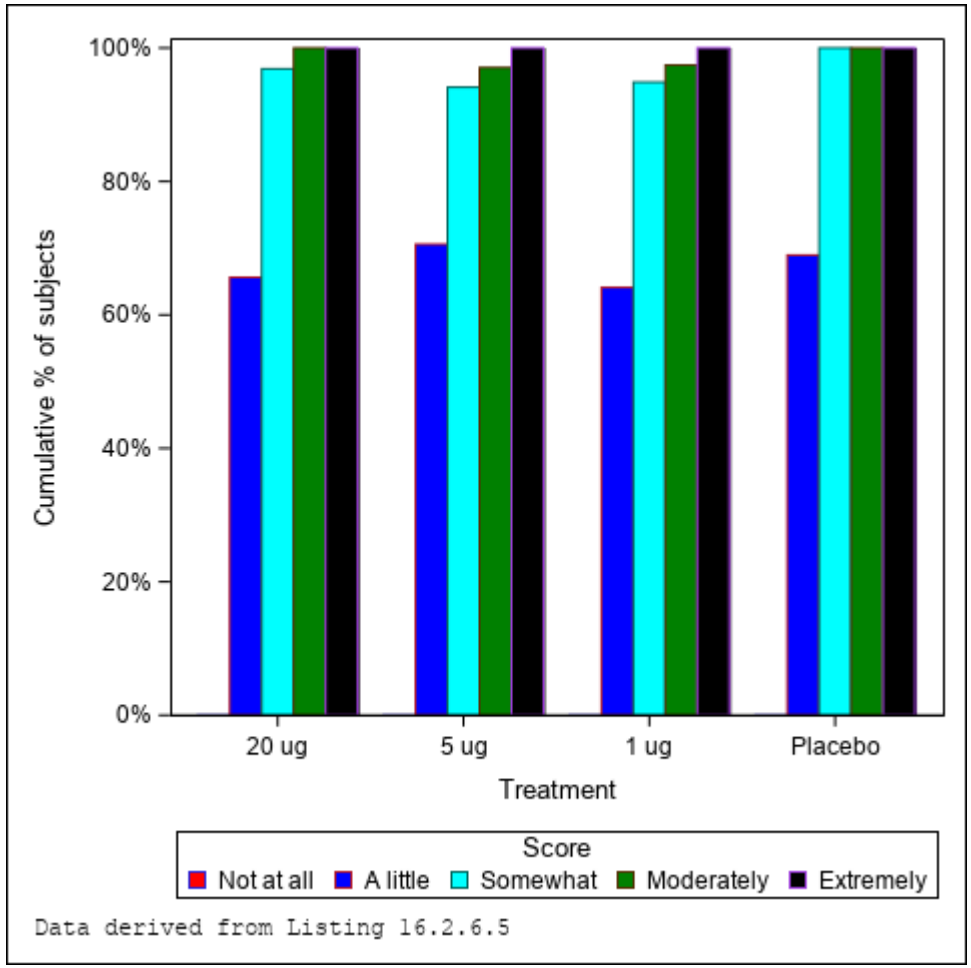


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: l: Q6 swallowing- visit 4

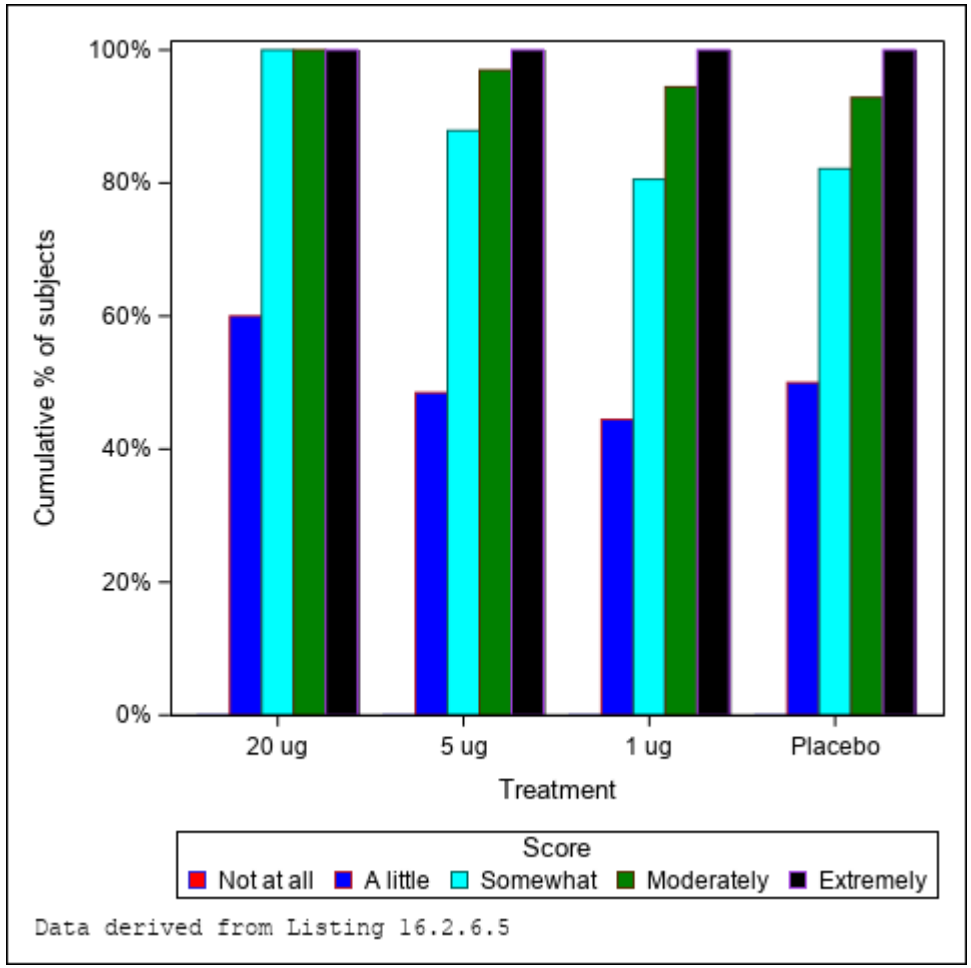


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: m: Q7 saliva production - visit 2

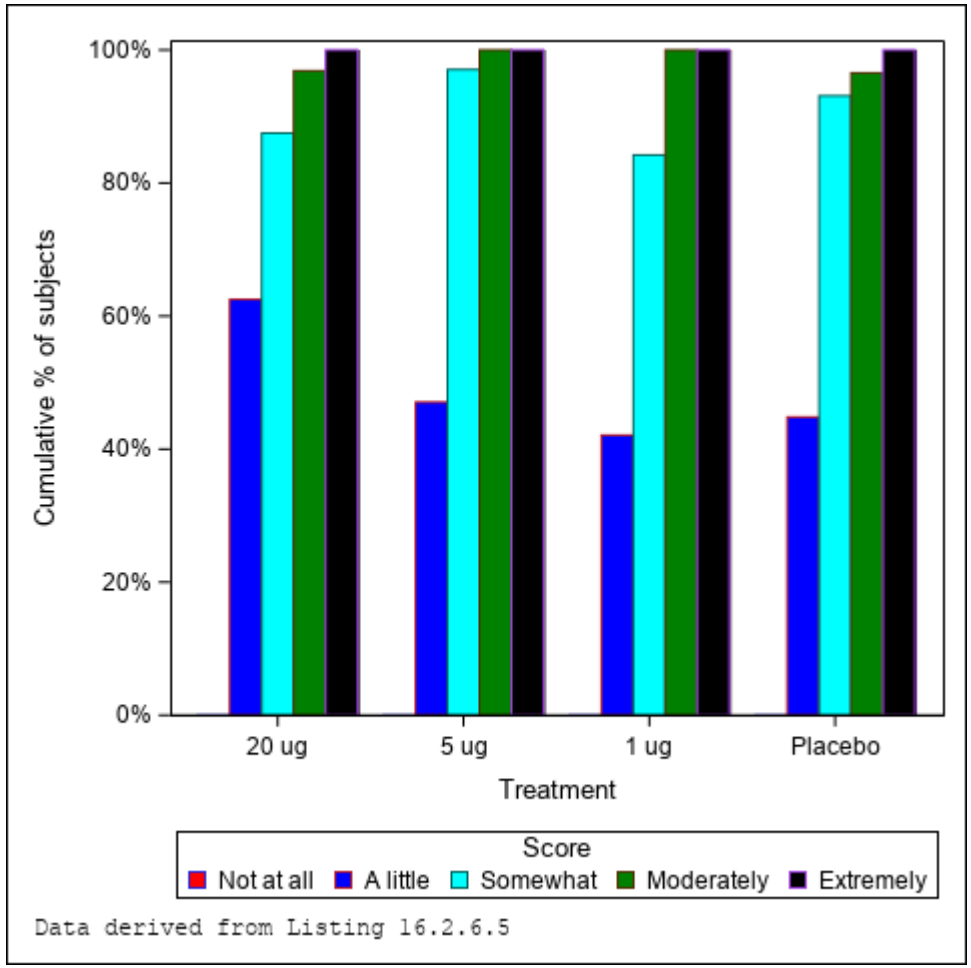


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: n: Q7 saliva production- visit 4

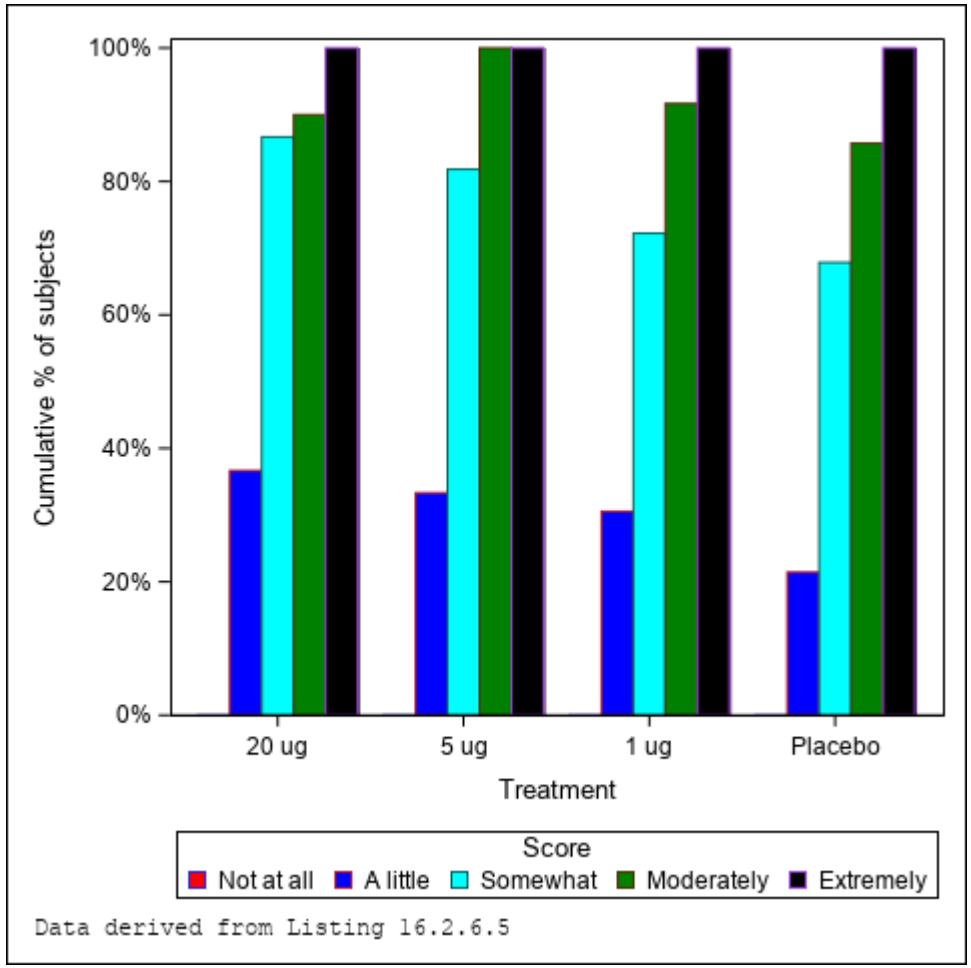


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: o: Q8 bothersome - visit 2

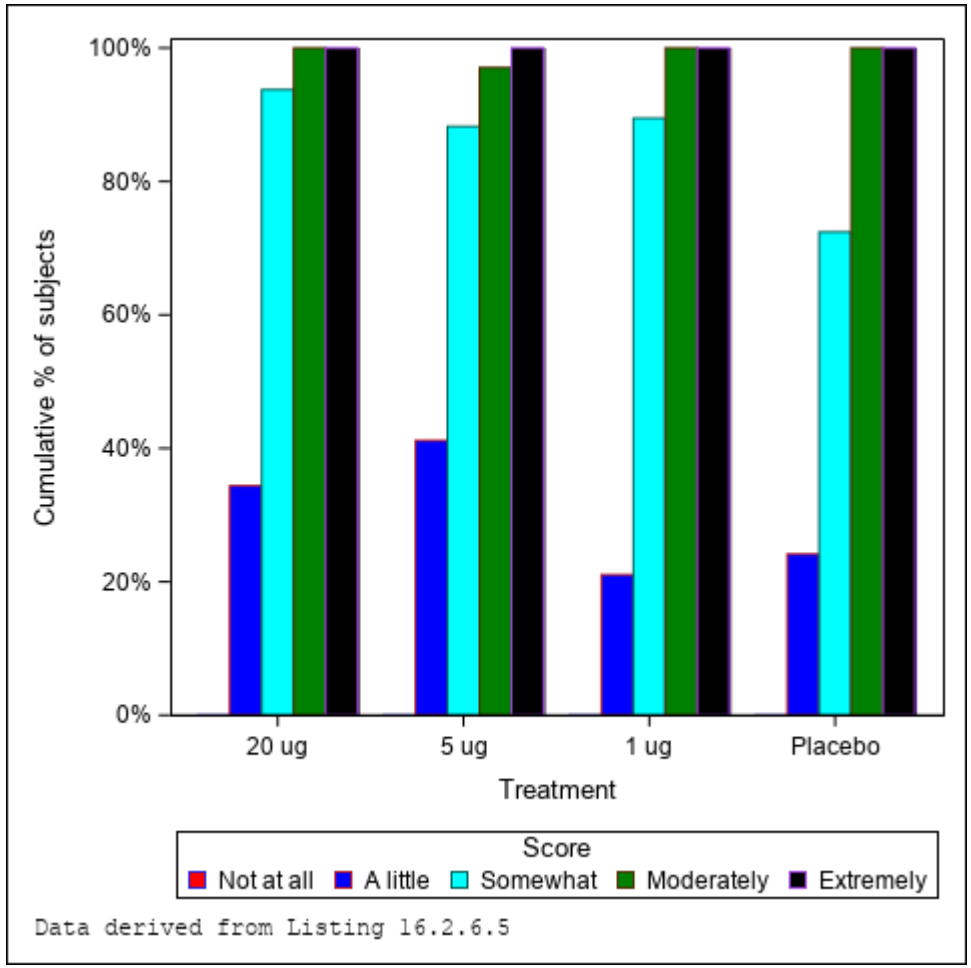


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: p: Q8 bothersome- visit 4

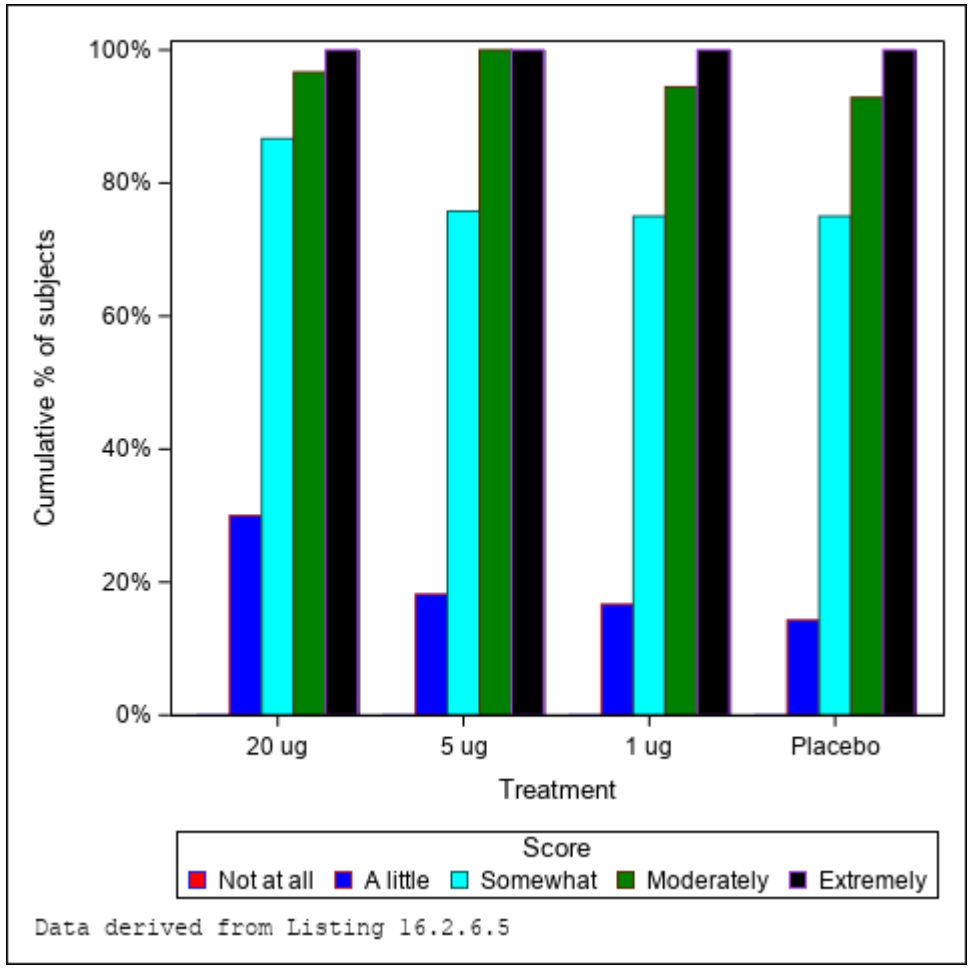


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: q: Q9 comfortable - visit 2

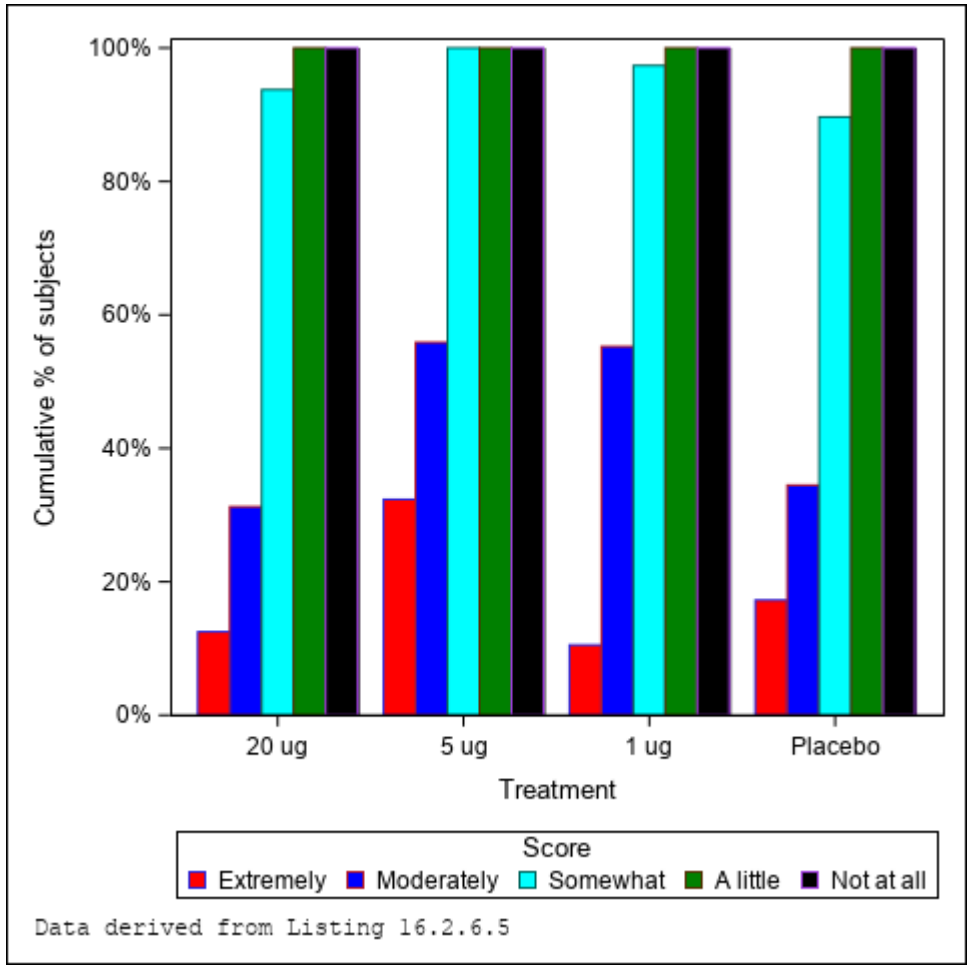


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: r: Q9 comfortable- visit 4

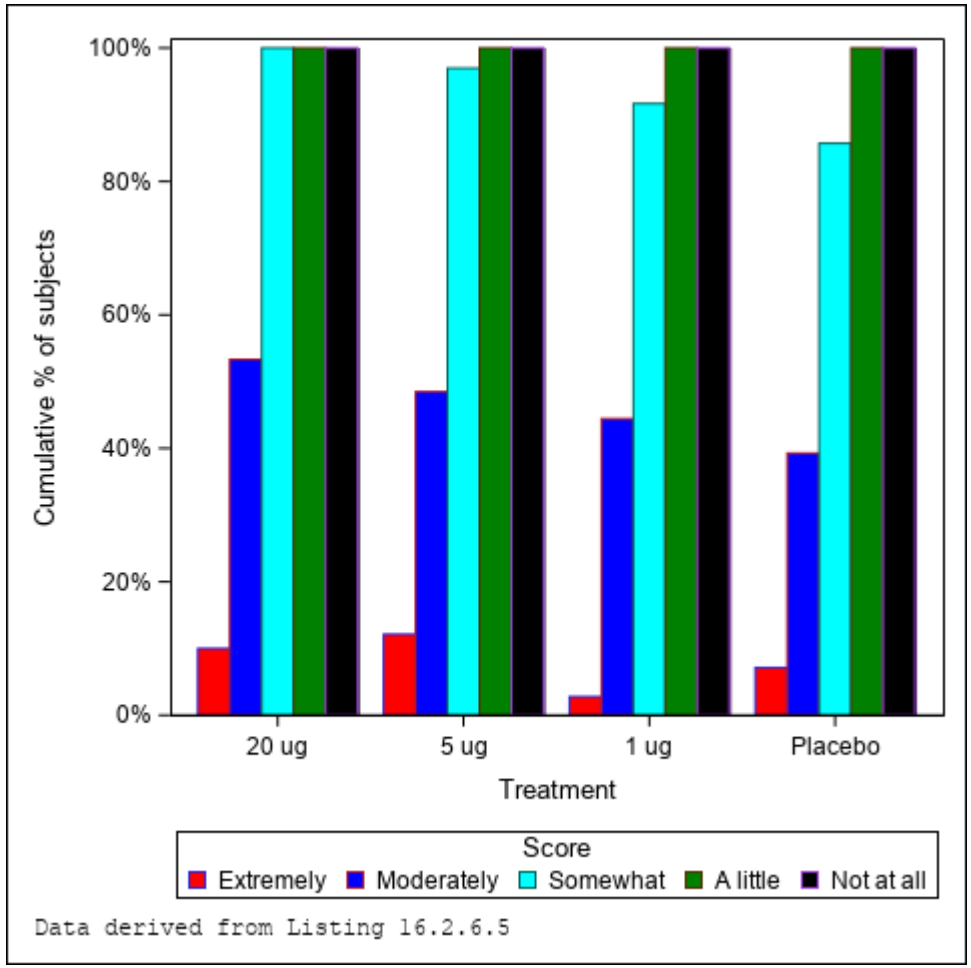


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: s: Q10 removal - visit 2

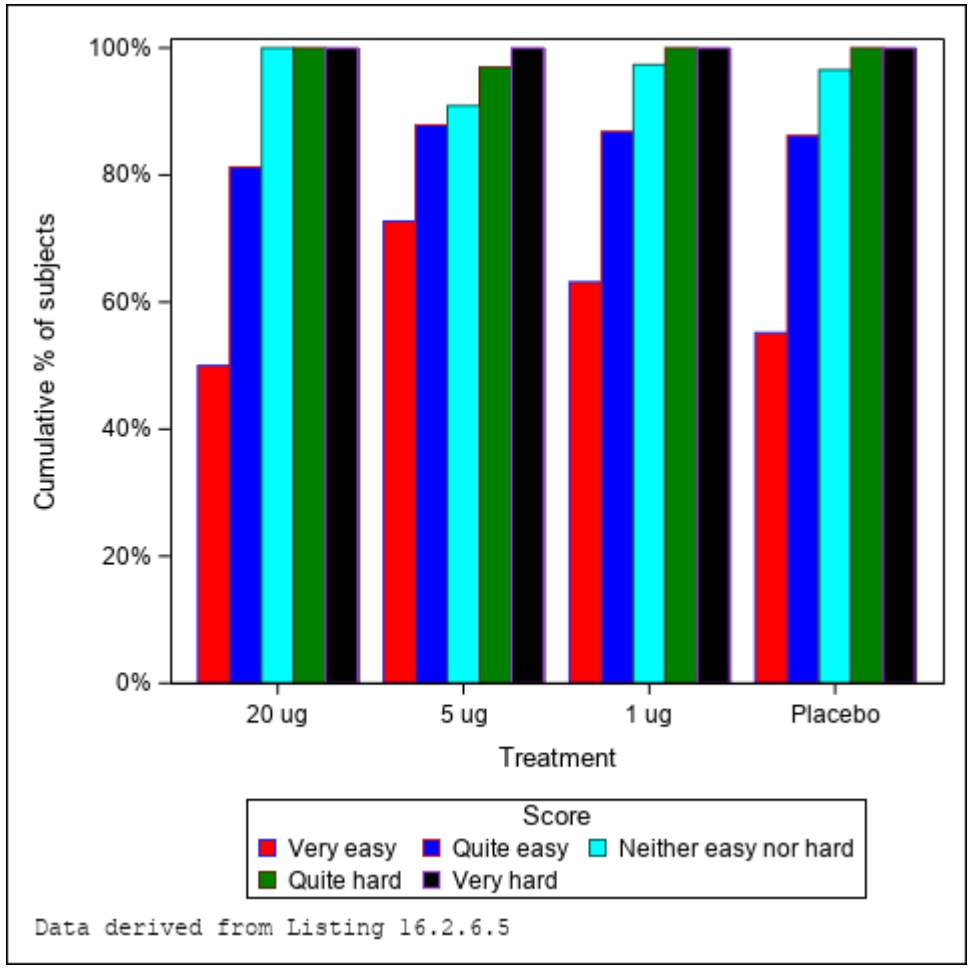


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: t: Q10 removal- visit 4

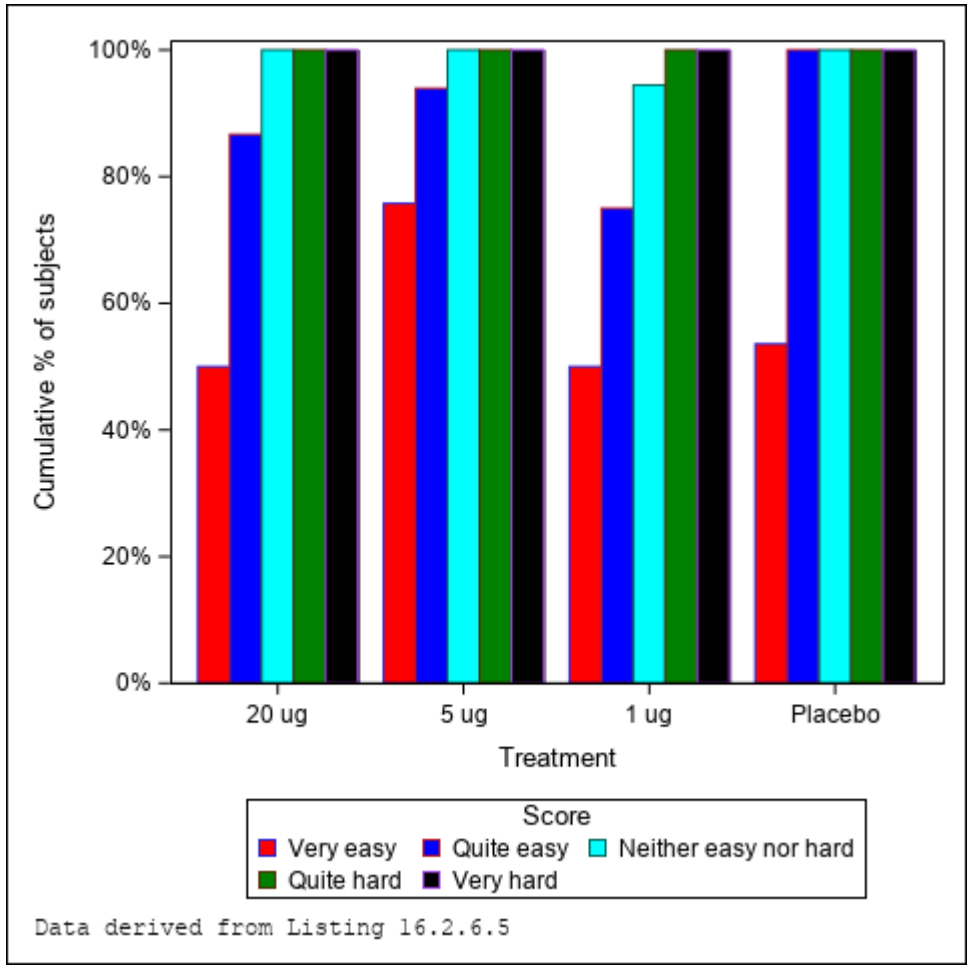


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: u: Q11 residue - visit 2

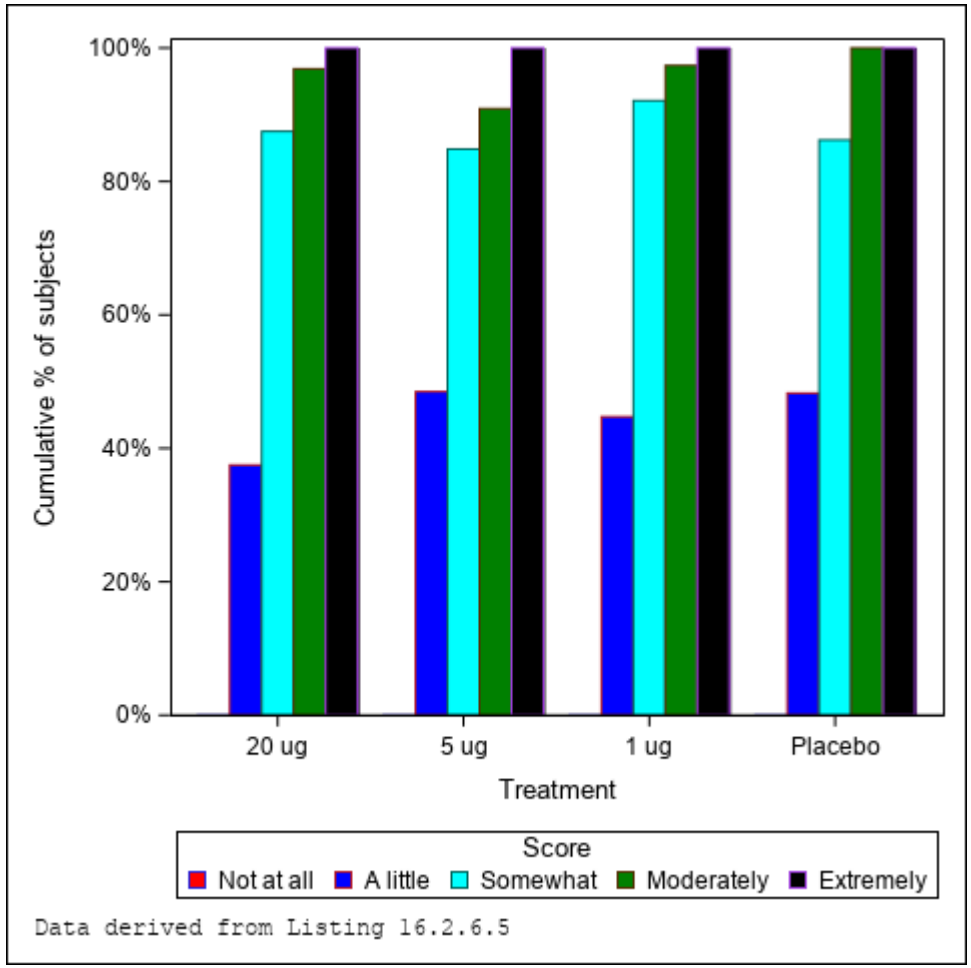
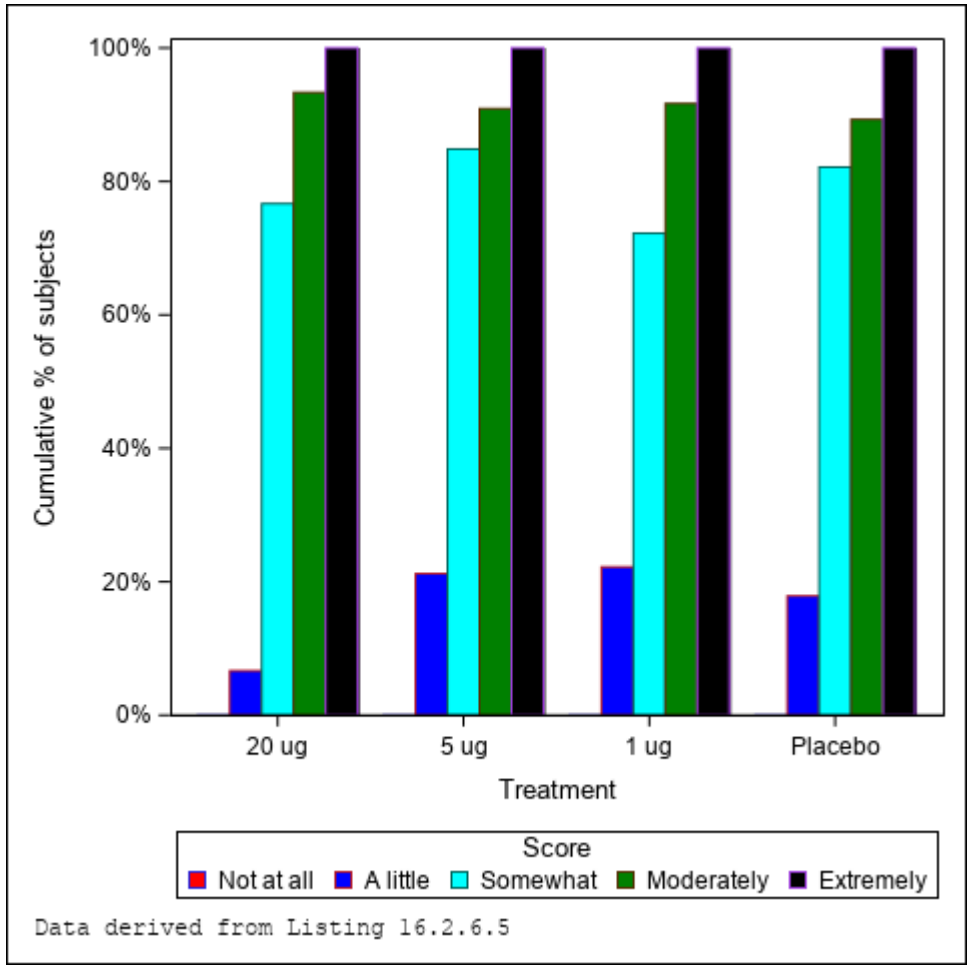


Figure 14.2.4.1 Histograms on outcomes from the patch sensation questionnaire: v: Q11 residue- visit 4



14.2.5 Patch application data

Table 14.2.5.1 Summary of patch application data [FAS]

Time	Variable	Stat	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Morning Application	Days recorded	N	33	34	40	30
		median	27	28	28	28
		range	1 - 34	11 - 34	1 - 32	1 - 33
	Patches applied	mean	68	87	79	76
		median	56	79	77	68
		range	2 - 174	22 - 174	4 - 174	6 - 168
	% adhering at 5 min	mean	96.6	98.1	98.4	96.5
		median	100.0	100.0	100.0	100.0
		range	48 - 100	73 - 100	80 - 100	67 - 100
	% adhering at 2 h	N	33	34	40	30
		mean	37.9	40.0	39.2	47.3
		median	21	26	23	44
		range	0.0 - 100	0.0 - 100	0.0 - 100	0.0 - 100
	Target adh. time (min)	mean	85.2	83.0	84.6	90.1
		median	90	90	93	105
		range	22 - 125	0 - 122	20 - 125	20 - 125
Evening Application	Days recorded	N	33	34	40	30
		median	27	28	27	28
		range	1 - 33	8 - 35	3 - 32	1 - 32

Time	Variable	Stat	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Patches applied	mean	67	86	80	76
		median	56	79	78	69
		range	2 - 145	16 - 168	4 - 168	3 - 168
	% adhering at 5 min	mean	93.4	95.4	96.0	97.3
		median	100.0	100.0	100.0	100.0
		range	23 - 100	64 - 100	0.0 - 100	77 - 100
For Target adhesion times the median times was calculated on the subject level. Listing(s): Derived from 16.2.6.5						

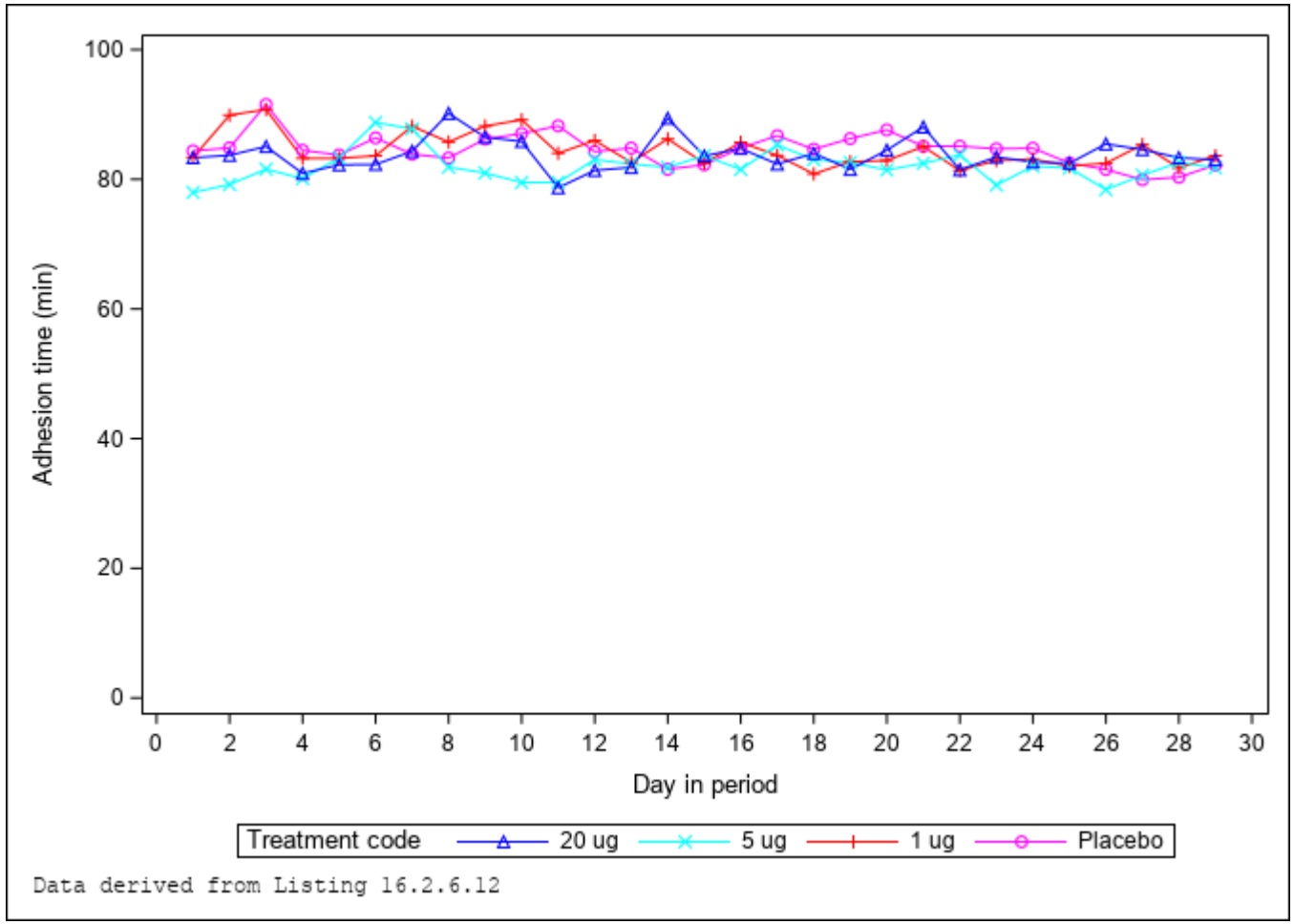
Table 14.2.5.2 Statistical analysis of successful patch applications (logistic) [FAS]

Variable	Treatment	Odds	Contrast	Ratio	95% CI	pval
Morning target	20 ug	5.15	20 ug vs placebo	0.60	(0.130, 2.770)	0.5121
	5 ug	4.65	5 ug vs placebo	0.54	(0.120, 2.400)	0.4193
	1 ug	5.47	1 ug vs placebo	0.64	(0.150, 2.800)	0.5504
	Placebo	8.59				
Analysis performed by PROC GENMOD Succesful application: >= 30 min on >=80% of days in treatment period Listing(s): Derived from 16.2.6.5						

Table 14.2.5.3 Statistical analysis of successful patch applications (ANOVA) [FAS]

Variable	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Morning target (%)	20 ug	92.7	20 ug vs placebo	-2.1	(-12.6, 8.3)	0.6845
	5 ug	90.3	5 ug vs placebo	-4.5	(-14.7, 5.7)	0.3849
	1 ug	94.9	1 ug vs placebo	0.1	(-9.8, 10.0)	0.9850
	Placebo	94.8				.
Analysis performed by PROC MIXED. Succes rate: % of days in treatment period with >= 30 min adhesion Listing(s): Derived from 16.2.6.5						

Figure 14.2.5.1 Daily mean value graphs of adhesion time (morning) [FAS]



14.2.6 Guy`s 106 ODSS

Table 14.2.6.1 Summary of Guy's 106 ODSS by treatment and visit [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of Guys 106 disease severity score by visit	Baseline	n	33	34	40	31
		Mean(SD)	20.303 (9.05)	20.382 (7.31)	21.200 (7.92)	20.710 (8.34)
		Median	17.000	19.500	20.000	19.000
		Min, Max	6.000-38.000	5.000-35.000	8.000-38.000	9.000-49.000
	Week 1	n	33	34	40	31
		Mean(SD)	15.485 (9.28)	16.824 (8.45)	18.200 (8.51)	18.871 (8.89)
		Median	15.000	15.000	17.000	18.000
		Min, Max	0.000-36.000	1.000-40.000	0.000-37.000	5.000-47.000
	Change from baseline Week 1	n	33	34	40	31
		Mean(SD)	-4.818 (6.03)	-3.559 (3.91)	-3.000 (5.78)	-1.839 (4.94)
		Median	-4.000	-2.500	-2.500	-2.000
		Min, Max	-20.000-7.000	-13.000-5.000	-21.000-13.000	-13.000-9.000
	Week 2	n	31	34	37	28
		Mean(SD)	13.419 (8.59)	17.382 (9.07)	16.892 (8.53)	18.429 (11.30)
		Median	12.000	16.500	15.000	17.000
		Min, Max	0.000-38.000	4.000-42.000	3.000-34.000	2.000-48.000
	Change from baseline Week 2	n	31	34	37	28
		Mean(SD)	-6.839 (6.34)	-3.000 (5.02)	-4.378 (6.16)	-2.286 (8.04)
		Median	-6.000	-3.000	-4.000	-2.000

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Min, Max	-20.000-6.000	-12.000-7.000	-18.000-9.000	-19.000-19.000
	Week 3	n	29	33	36	27
		Mean(SD)	12.897 (8.69)	16.091 (9.81)	15.722 (8.16)	16.111 (10.31)
		Median	14.000	13.000	14.000	15.000
		Min, Max	0.000-34.000	5.000-43.000	3.000-35.000	1.000-48.000
	Change from baseline Week 3	n	29	33	36	27
		Mean(SD)	-7.069 (7.01)	-4.576 (5.61)	-5.361 (5.95)	-4.815 (7.08)
		Median	-5.000	-5.000	-5.000	-5.000
		Min, Max	-21.000-5.000	-14.000-11.000	-20.000-7.000	-22.000-8.000
	Week 4	n	30	33	35	27
		Mean(SD)	11.200 (7.34)	15.515 (10.43)	14.886 (8.57)	16.111 (10.05)
		Median	10.000	12.000	13.000	13.000
		Min, Max	0.000-27.000	2.000-44.000	0.000-33.000	1.000-49.000
	Change from baseline Week 4	n	30	33	35	27
		Mean(SD)	-9.300 (6.74)	-5.152 (8.09)	-6.000 (7.38)	-4.815 (7.10)
		Median	-9.000	-6.000	-6.000	-5.000
		Min, Max	-24.000-3.000	-21.000-17.000	-23.000-10.000	-24.000-10.000
Summary of Guys 106 total site score by visit	Baseline	n	33	34	40	31
		Mean(SD)	5.030 (3.75)	4.794 (2.50)	5.175 (3.32)	5.032 (2.77)
		Median	4.000	4.500	4.000	4.000
		Min, Max	1.000-14.000	1.000-9.000	1.000-14.000	2.000-13.000

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Week 1	n	33	34	40	31
		Mean(SD)	4.636 (3.89)	4.471 (3.00)	4.625 (3.10)	5.000 (2.72)
		Median	4.000	4.000	4.000	5.000
		Min, Max	0.000-15.000	0.000-13.000	0.000-14.000	1.000-12.000
	Change from baseline Week 1	n	33	34	40	31
		Mean(SD)	-0.394 (1.54)	-0.324 (1.43)	-0.550 (1.84)	-0.032 (1.20)
		Median	0.000	0.000	0.000	0.000
		Min, Max	-5.000-3.000	-3.000-4.000	-7.000-3.000	-2.000-3.000
	Week 2	n	31	34	37	28
		Mean(SD)	4.484 (3.56)	4.882 (2.89)	4.649 (3.14)	4.786 (3.22)
		Median	4.000	5.000	4.000	4.000
		Min, Max	0.000-14.000	1.000-12.000	0.000-13.000	0.000-12.000
	Change from baseline Week 2	n	31	34	37	28
		Mean(SD)	-0.613 (1.78)	0.088 (1.44)	-0.459 (1.35)	-0.143 (1.94)
		Median	0.000	0.000	0.000	0.000
		Min, Max	-7.000-3.000	-3.000-5.000	-4.000-3.000	-4.000-6.000
	Week 3	n	29	33	36	27
		Mean(SD)	4.000 (3.01)	4.818 (3.34)	4.417 (2.90)	4.519 (3.03)
		Median	3.000	4.000	4.000	4.000
		Min, Max	0.000-11.000	0.000-13.000	0.000-11.000	0.000-12.000
		n	29	33	36	27

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Change from baseline Week 3	Mean(SD)	-0.862 (2.00)	-0.091 (1.96)	-0.583 (1.52)	-0.481 (1.63)
		Median	0.000	0.000	0.000	-1.000
		Min, Max	-7.000-2.000	-4.000-5.000	-4.000-2.000	-4.000-4.000
	Week 4	n	30	33	35	27
		Mean(SD)	3.867 (2.97)	4.485 (2.88)	4.257 (2.93)	4.481 (2.97)
		Median	3.000	4.000	4.000	4.000
		Min, Max	0.000-11.000	1.000-12.000	0.000-10.000	0.000-12.000
	Change from baseline Week 4	n	30	33	35	27
		Mean(SD)	-1.300 (1.95)	-0.424 (2.08)	-0.657 (1.91)	-0.519 (1.70)
		Median	-1.000	0.000	0.000	0.000
		Min, Max	-7.000-1.000	-4.000-4.000	-6.000-4.000	-4.000-4.000
Summary of Guys 106 disease activity score by visit	Baseline	n	33	34	40	31
		Mean(SD)	9.545 (5.24)	9.706 (4.45)	10.250 (5.27)	9.903 (5.17)
		Median	8.000	10.000	9.000	9.000
		Min, Max	1.000-21.000	3.000-17.000	3.000-22.000	3.000-28.000
	Week 1	n	33	34	40	31
		Mean(SD)	6.970 (4.98)	7.676 (5.00)	8.675 (5.28)	8.742 (5.51)
		Median	6.000	6.000	7.000	8.000
		Min, Max	0.000-18.000	0.000-22.000	0.000-21.000	0.000-26.000
	Change from baseline Week 1	n	33	34	40	31
		Mean(SD)	-2.576 (3.88)	-2.029 (2.95)	-1.575 (3.53)	-1.161 (3.48)

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Median	-2.000	-2.000	-1.000	-2.000
		Min, Max	-12.000-5.000	-10.000-5.000	-12.000-5.000	-8.000-6.000
	Week 2	n	31	34	37	28
		Mean(SD)	5.806 (4.29)	7.765 (5.42)	7.946 (5.35)	8.857 (7.14)
		Median	5.000	6.500	7.000	7.000
		Min, Max	0.000-19.000	0.000-21.000	0.000-21.000	0.000-28.000
	Change from baseline Week 2	n	31	34	37	28
		Mean(SD)	-3.710 (4.33)	-1.941 (3.81)	-2.514 (3.93)	-1.000 (5.06)
		Median	-3.000	-2.000	-2.000	-0.500
		Min, Max	-13.000-6.000	-10.000-7.000	-12.000-5.000	-12.000-10.000
	Week 3	n	29	33	36	27
		Mean(SD)	6.069 (4.58)	7.576 (6.00)	7.278 (4.86)	7.444 (6.31)
		Median	6.000	5.000	6.000	6.000
		Min, Max	0.000-18.000	0.000-25.000	0.000-19.000	0.000-28.000
	Change from baseline Week 3	n	29	33	36	27
		Mean(SD)	-3.379 (4.47)	-2.333 (4.07)	-3.028 (3.81)	-2.519 (4.05)
		Median	-3.000	-3.000	-3.000	-2.000
		Min, Max	-14.000-4.000	-10.000-9.000	-12.000-4.000	-12.000-4.000
	Week 4	n	30	33	35	27
		Mean(SD)	4.833 (3.85)	7.455 (6.34)	7.200 (5.21)	7.778 (6.24)
		Median	3.500	6.000	6.000	7.000

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Min, Max	0.000-13.000	0.000-25.000	0.000-20.000	0.000-29.000
	Change from baseline Week 4	n	30	33	35	27
		Mean(SD)	-4.800 (4.30)	-2.455 (5.12)	-2.914 (4.47)	-2.185 (3.77)
		Median	-4.500	-4.000	-3.000	-2.000
		Min, Max	-13.000-3.000	-10.000-10.000	-12.000-8.000	-12.000-5.000
Summary of Guys 106 pain VAS score by visit	Baseline	n	33	34	40	31
		Mean(SD)	5.727 (2.44)	5.882 (2.32)	5.775 (2.38)	5.774 (2.22)
		Median	7.000	6.500	6.000	6.000
		Min, Max	0.000-9.000	1.000-10.000	1.000-10.000	1.000-10.000
	Week 1	n	32	34	39	31
		Mean(SD)	4.000 (2.74)	4.676 (2.21)	5.026 (2.57)	5.129 (1.93)
		Median	4.000	5.000	6.000	5.000
		Min, Max	0.000-10.000	1.000-8.000	0.000-9.000	1.000-9.000
	Change from baseline Week 1	n	32	34	39	31
		Mean(SD)	-1.688 (1.99)	-1.206 (1.95)	-0.821 (2.34)	-0.645 (1.68)
		Median	-2.000	-1.000	-1.000	-1.000
		Min, Max	-5.000-3.000	-9.000-2.000	-5.000-5.000	-4.000-2.000
	Week 2	n	31	34	37	28
		Mean(SD)	3.129 (2.58)	4.735 (2.49)	4.297 (2.32)	4.786 (2.30)
		Median	3.000	4.500	4.000	5.000
		Min, Max	0.000-10.000	0.000-9.000	0.000-9.000	0.000-8.000

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Change from baseline Week 2	n	31	34	37	28
		Mean(SD)	-2.516 (2.19)	-1.147 (1.69)	-1.405 (2.42)	-1.143 (2.26)
		Median	-2.000	-1.000	-1.000	-1.000
		Min, Max	-6.000-2.000	-7.000-2.000	-8.000-4.000	-5.000-3.000
	Week 3	n	29	33	36	27
		Mean(SD)	2.828 (2.59)	3.697 (2.19)	4.028 (2.40)	4.148 (2.01)
		Median	2.000	3.000	4.000	4.000
		Min, Max	0.000-8.000	0.000-8.000	0.000-9.000	0.000-8.000
	Change from baseline Week 3	n	29	33	36	27
		Mean(SD)	-2.828 (2.24)	-2.152 (1.91)	-1.750 (2.56)	-1.815 (2.35)
		Median	-3.000	-2.000	-2.000	-2.000
		Min, Max	-7.000-1.000	-7.000-1.000	-8.000-6.000	-6.000-3.000
	Week 4	n	30	33	35	27
		Mean(SD)	2.500 (2.45)	3.576 (2.45)	3.429 (2.21)	3.852 (2.14)
		Median	2.000	3.000	4.000	4.000
		Min, Max	0.000-8.000	0.000-8.000	0.000-8.000	0.000-8.000
	Change from baseline Week 4	n	30	33	35	27
		Mean(SD)	-3.200 (2.61)	-2.273 (2.58)	-2.429 (2.87)	-2.111 (2.81)
		Median	-3.500	-2.000	-1.000	-2.000
		Min, Max	-8.000-2.000	-9.000-3.000	-8.000-2.000	-8.000-4.000

Listing(s): Derived from Listing 16.2.4.1

Table 14.2.6.2 Statistical analysis of Guy's 106 ODSS [FAS]

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Analysis of Guys 106 disease severity score by visit, ANCOVA	Week 1	20 ug	-4.551	20 ug vs placebo	-2.890	(-5.332, -0.447)	0.0208
		5 ug	-3.573	5 ug vs placebo	-1.912	(-4.346, 0.522)	0.1225
		1 ug	-2.960	1 ug vs placebo	-1.299	(-3.645, 1.047)	0.2754
		Placebo	-1.661				.
	Week 2	20 ug	-5.867	20 ug vs placebo	-4.633	(-7.586, -1.679)	0.0024
		5 ug	-2.304	5 ug vs placebo	-1.070	(-4.013, 1.873)	0.4732
		1 ug	-3.316	1 ug vs placebo	-2.082	(-4.919, 0.755)	0.1489
		Placebo	-1.235				.
	Week 3	20 ug	-6.110	20 ug vs placebo	-3.608	(-6.785, -0.431)	0.0263
		5 ug	-3.304	5 ug vs placebo	-0.803	(-3.968, 2.363)	0.6166
		1 ug	-3.535	1 ug vs placebo	-1.034	(-4.086, 2.017)	0.5037
		Placebo	-2.501				.
	Week 4	20 ug	-7.402	20 ug vs placebo	-5.219	(-8.747, -1.691)	0.0041
		5 ug	-3.483	5 ug vs placebo	-1.300	(-4.815, 2.215)	0.4657

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
		1 ug	-3.266	1 ug vs placebo	-1.083	(-4.471, 2.306)	0.5284
		Placebo	-2.184				.
	Week 3-4	20 ug	-6.786	20 ug vs placebo	-4.453	(-7.602, -1.303)	0.0060
		5 ug	-3.390	5 ug vs placebo	-1.057	(-4.195, 2.081)	0.5062
		1 ug	-3.397	1 ug vs placebo	-1.064	(-4.089, 1.961)	0.4878
		Placebo	-2.333				.
Analysis of Guys 106 total site score by visit, ANCOVA	Week 1	20 ug	-0.568	20 ug vs placebo	-0.369	(-1.108, 0.370)	0.3248
		5 ug	-0.544	5 ug vs placebo	-0.345	(-1.081, 0.392)	0.3559
		1 ug	-0.707	1 ug vs placebo	-0.508	(-1.218, 0.202)	0.1591
		Placebo	-0.199				.
	Week 2	20 ug	-0.555	20 ug vs placebo	-0.570	(-1.358, 0.218)	0.1546
		5 ug	0.140	5 ug vs placebo	0.125	(-0.660, 0.910)	0.7536
		1 ug	-0.414	1 ug vs placebo	-0.429	(-1.186, 0.328)	0.2644
		Placebo	0.015				.
	Week 3	20 ug	-0.774	20 ug vs placebo	-0.714	(-1.597, 0.168)	0.1115

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
		5 ug	-0.014	5 ug vs placebo	0.046	(-0.833, 0.925)	0.9183
		1 ug	-0.441	1 ug vs placebo	-0.381	(-1.229, 0.466)	0.3748
		Placebo	-0.059				.
	Week 4	20 ug	-1.077	20 ug vs placebo	-1.015	(-1.912, -0.118)	0.0268
		5 ug	-0.319	5 ug vs placebo	-0.258	(-1.152, 0.636)	0.5685
		1 ug	-0.417	1 ug vs placebo	-0.356	(-1.218, 0.506)	0.4153
		Placebo	-0.061				.
	Week 3-4	20 ug	-0.946	20 ug vs placebo	-0.895	(-1.725, -0.065)	0.0348
		5 ug	-0.163	5 ug vs placebo	-0.112	(-0.939, 0.715)	0.7890
		1 ug	-0.424	1 ug vs placebo	-0.373	(-1.170, 0.424)	0.3562
		Placebo	-0.051				.
Analysis of Guys 106 disease activity score by visit, ANCOVA	Week 1	20 ug	-2.338	20 ug vs placebo	-1.408	(-3.023, 0.208)	0.0871
		5 ug	-1.915	5 ug vs placebo	-0.985	(-2.594, 0.624)	0.2280
		1 ug	-1.401	1 ug vs placebo	-0.471	(-2.022, 1.080)	0.5491
		Placebo	-0.930				.

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
	Week 2	20 ug	-3.143	20 ug vs placebo	-2.653	(-4.555, -0.752)	0.0066
		5 ug	-1.557	5 ug vs placebo	-1.067	(-2.962, 0.827)	0.2670
		1 ug	-1.778	1 ug vs placebo	-1.289	(-3.115, 0.538)	0.1651
		Placebo	-0.489				.
	Week 3	20 ug	-2.966	20 ug vs placebo	-1.557	(-3.511, 0.397)	0.1173
		5 ug	-1.706	5 ug vs placebo	-0.298	(-2.244, 1.649)	0.7628
		1 ug	-1.867	1 ug vs placebo	-0.459	(-2.335, 1.418)	0.6295
		Placebo	-1.409				.
	Week 4	20 ug	-3.934	20 ug vs placebo	-2.875	(-4.971, -0.779)	0.0076
		5 ug	-1.713	5 ug vs placebo	-0.655	(-2.743, 1.434)	0.5362
		1 ug	-1.494	1 ug vs placebo	-0.435	(-2.448, 1.578)	0.6696
		Placebo	-1.059				.
	Week 3-4	20 ug	-3.450	20 ug vs placebo	-2.216	(-4.106, -0.326)	0.0219
		5 ug	-1.710	5 ug vs placebo	-0.476	(-2.359, 1.407)	0.6177

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
		1 ug	-1.680	1 ug vs placebo	-0.447	(-2.262, 1.368)	0.6269
		Placebo	-1.234				.
Analysis of Guys 106 pain VAS score by visit, ANCOVA	Week 1	20 ug	-1.600	20 ug vs placebo	-1.028	(-1.905, -0.150)	0.0221
		5 ug	-1.136	5 ug vs placebo	-0.564	(-1.430, 0.303)	0.2003
		1 ug	-0.846	1 ug vs placebo	-0.274	(-1.111, 0.563)	0.5183
		Placebo	-0.572				.
	Week 2	20 ug	-2.127	20 ug vs placebo	-1.338	(-2.326, -0.349)	0.0084
		5 ug	-0.921	5 ug vs placebo	-0.132	(-1.108, 0.845)	0.7902
		1 ug	-1.159	1 ug vs placebo	-0.370	(-1.313, 0.573)	0.4393
		Placebo	-0.789				.
	Week 3	20 ug	-2.354	20 ug vs placebo	-1.260	(-2.274, -0.246)	0.0153
		5 ug	-1.621	5 ug vs placebo	-0.527	(-1.529, 0.474)	0.2992
		1 ug	-1.295	1 ug vs placebo	-0.201	(-1.168, 0.765)	0.6809
		Placebo	-1.094				.
	Week 4	20 ug	-2.415	20 ug vs placebo	-1.247	(-2.383, -0.110)	0.0319

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
		5 ug	-1.493	5 ug vs placebo	-0.325	(-1.447, 0.798)	0.5683
		1 ug	-1.468	1 ug vs placebo	-0.300	(-1.384, 0.784)	0.5850
		Placebo	-1.168				.
	Week 3-4	20 ug	-2.391	20 ug vs placebo	-1.261	(-2.241, -0.281)	0.0121
		5 ug	-1.556	5 ug vs placebo	-0.426	(-1.394, 0.541)	0.3849
		1 ug	-1.381	1 ug vs placebo	-0.252	(-1.186, 0.683)	0.5951
		Placebo	-1.130				.
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.3							

Figure 14.2.6.2 Mean value curves of Guy's 106 ODSS over time

a: disease severity score - absolute scale

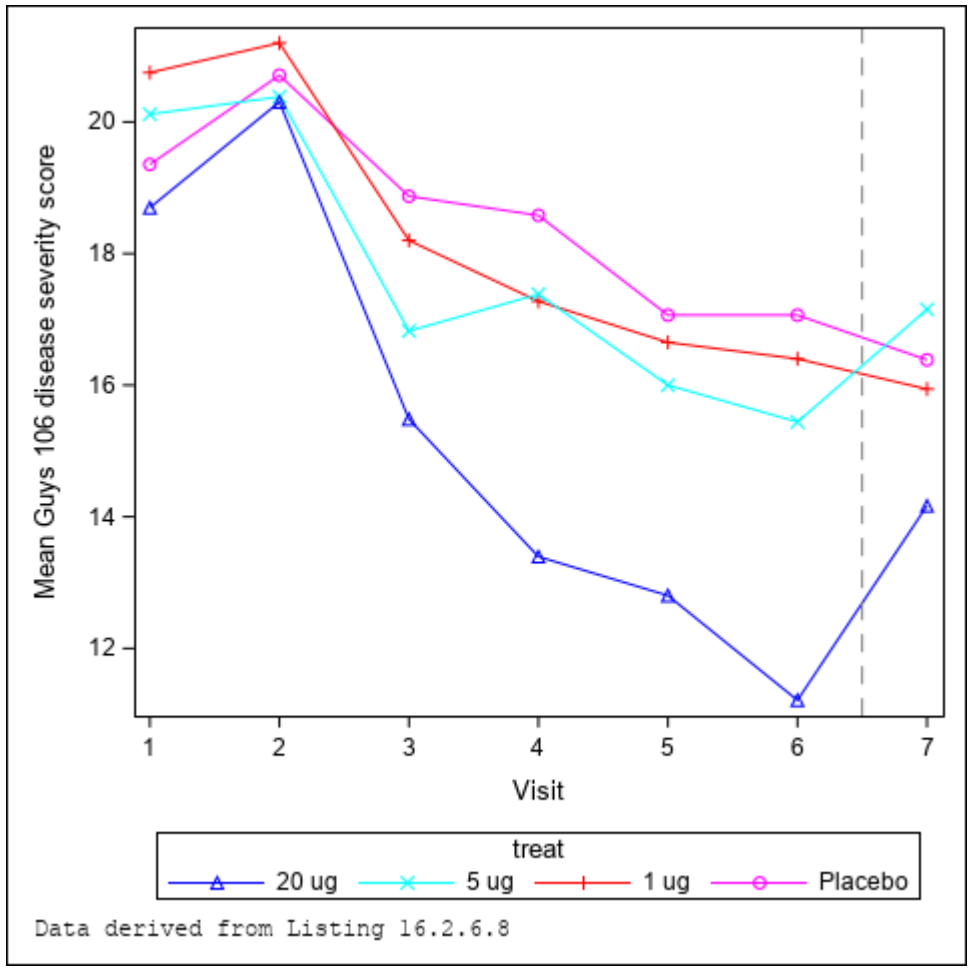


Figure 14.2.6.2 Mean value curves of Guy's 106 ODSS over time b: disease severity score - change

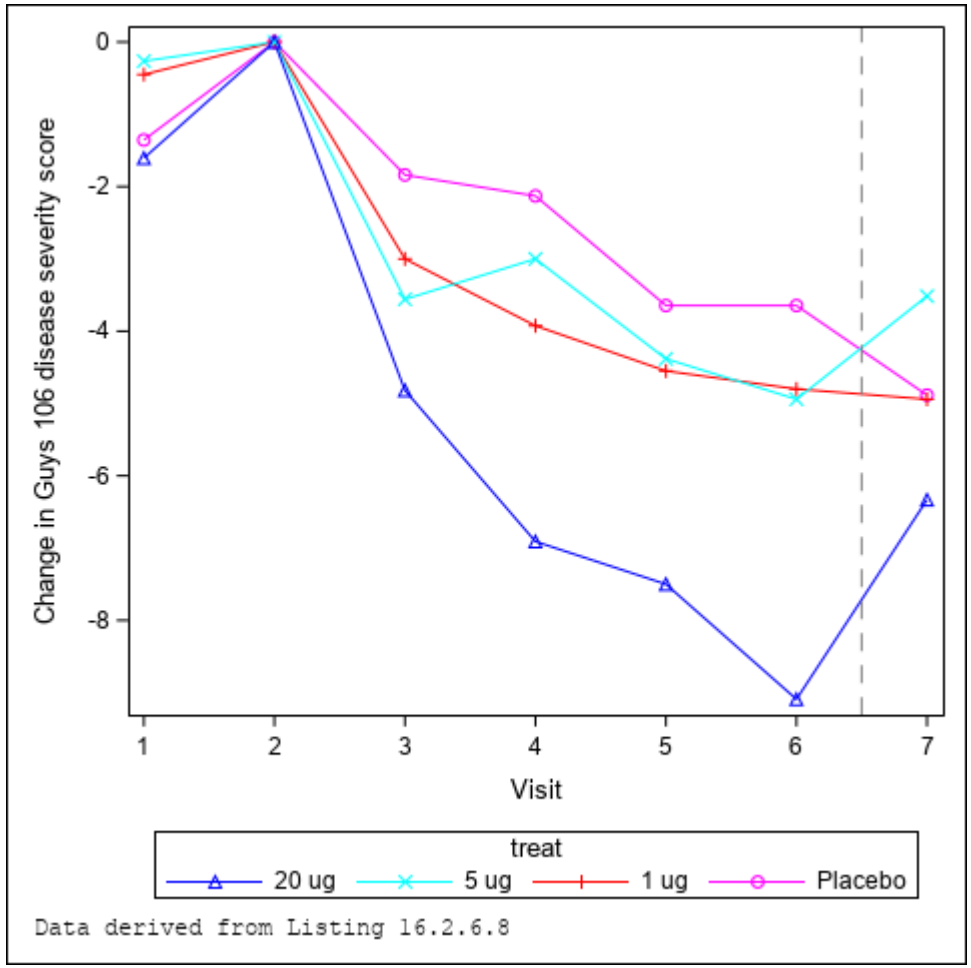


Figure 14.2.6.2 Mean value curves of Guy's 106 ODSS over time c: total site score - absolute scale

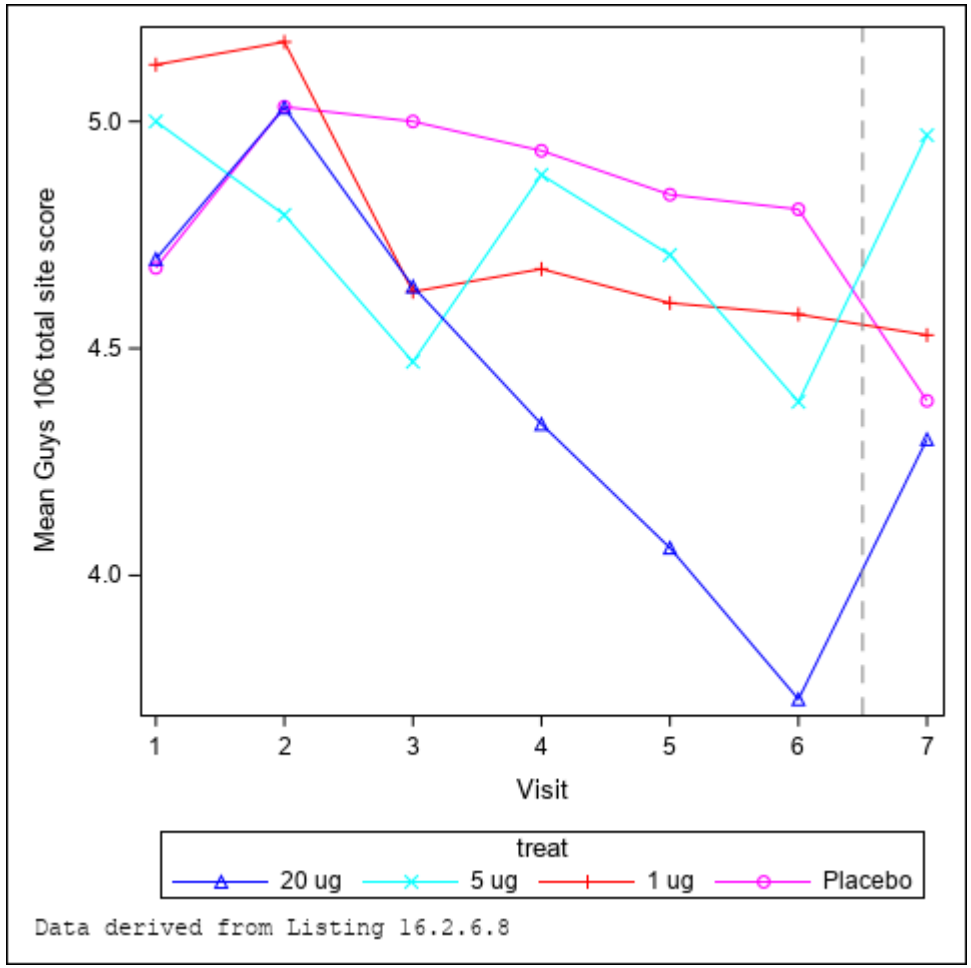


Figure 14.2.6.2 Mean value curves of Guy's 106 ODSS over time d: total site score - change

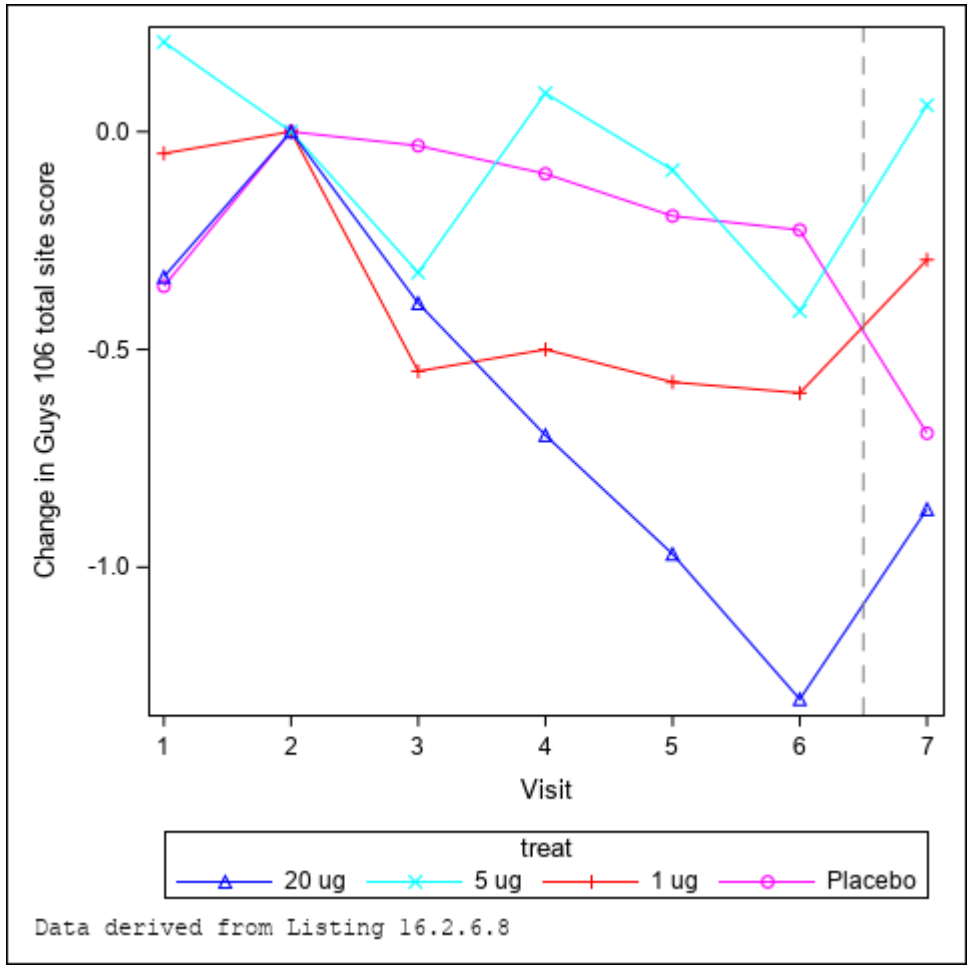


Figure 14.2.6.2 Mean value curves of Guy's 106 ODSS over time e: disease activity score - absolute scale

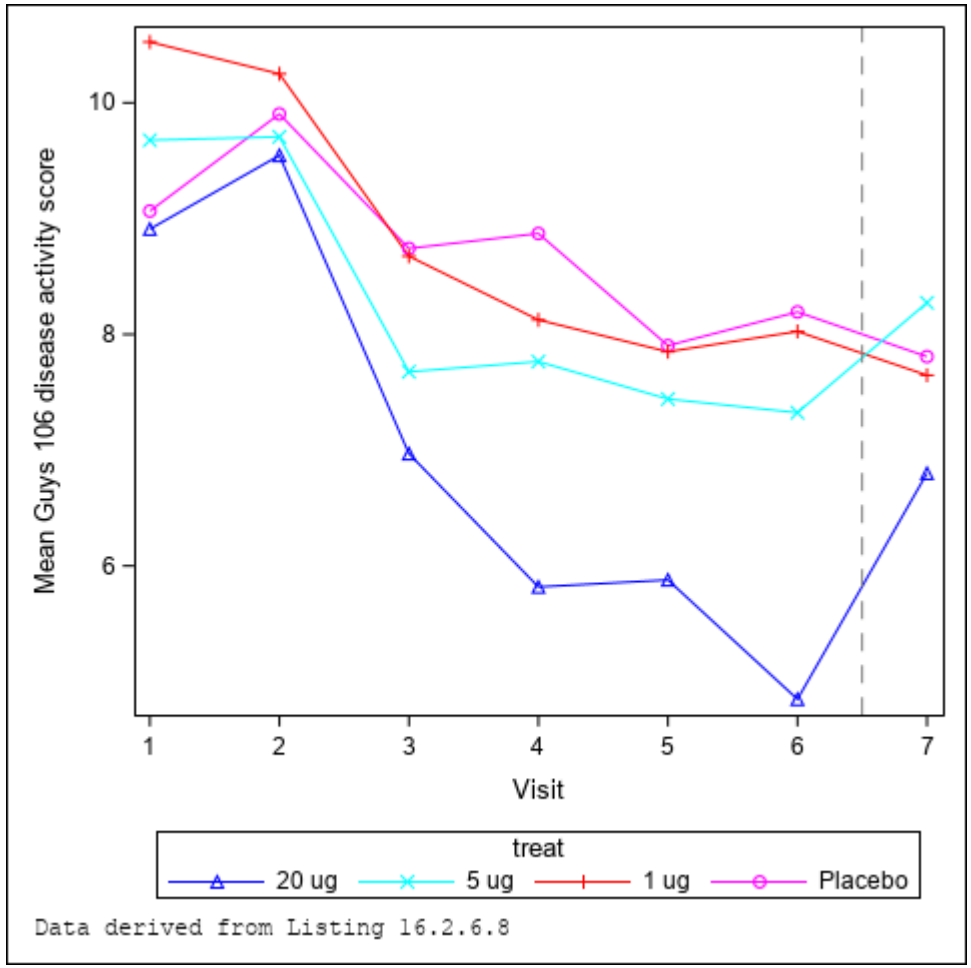


Figure 14.2.6.2 Mean value curves of Guy's 106 ODSS over time f: disease activity score - change

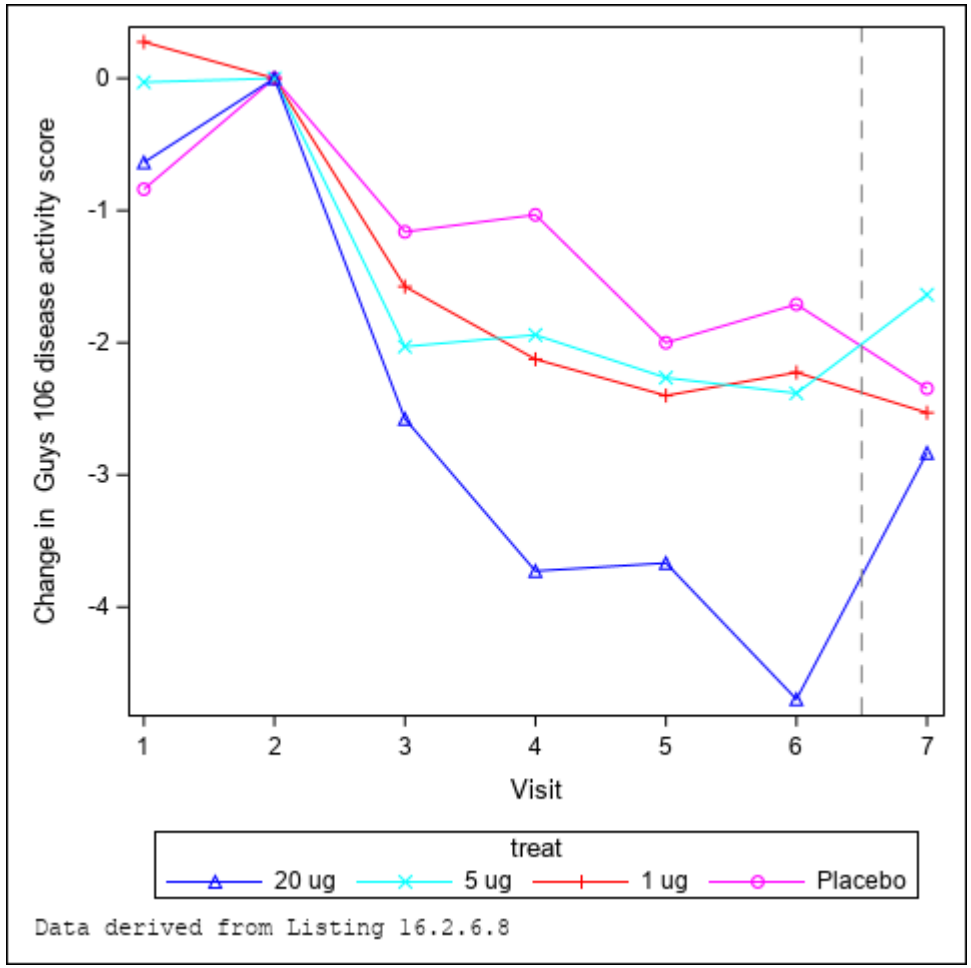


Figure 14.2.6.2 Mean value curves of Guy's 106 ODSS over time g: pain VAS score - absolute scale

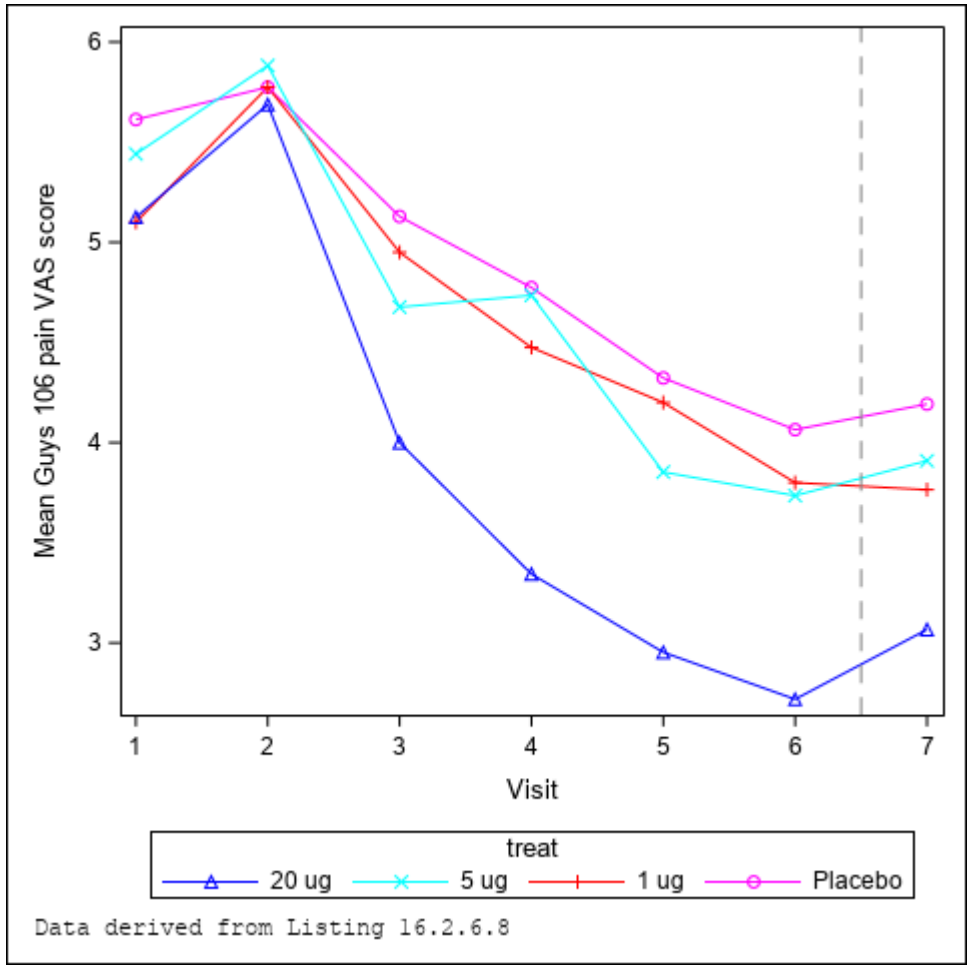
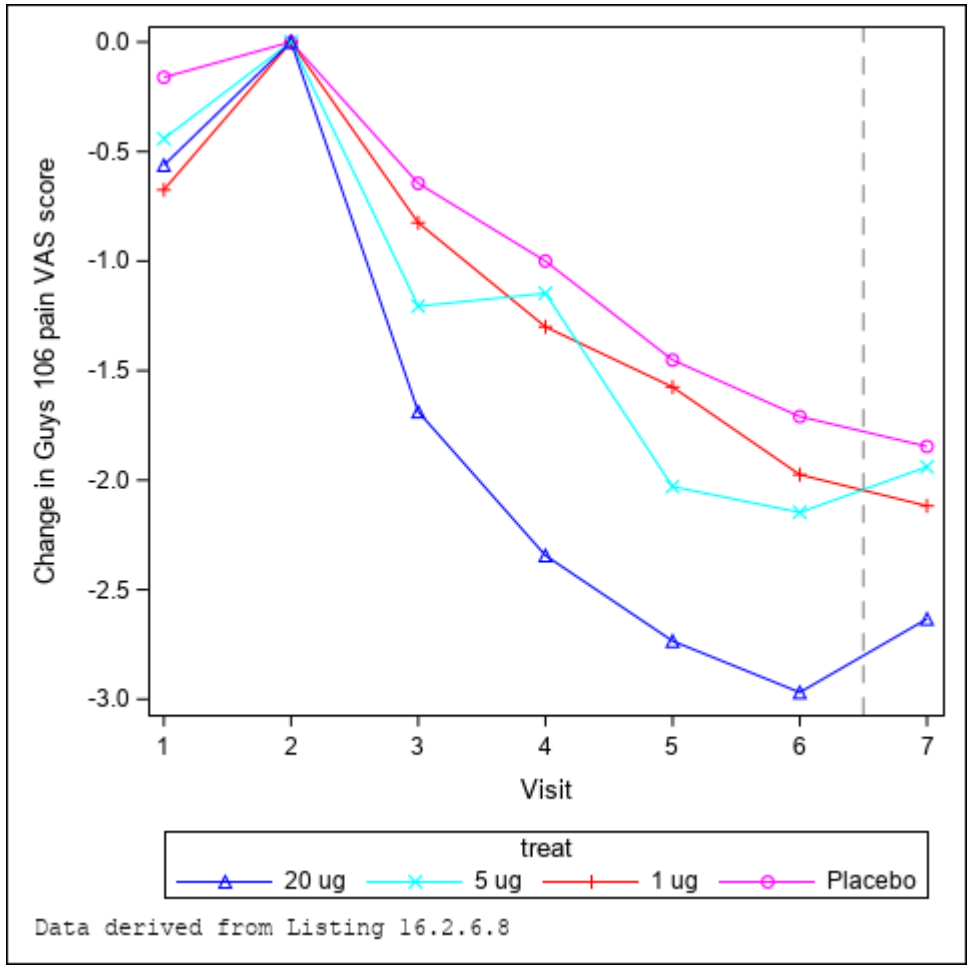


Figure 14.2.6.2 Mean value curves of Guy's 106 ODSS over time h: pain VAS score - change



14.2.7 COMDQ

Table 14.2.7.1 Summary of COMDQ scores by treatment group and visit [FAS]

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of COMDQ, total score, by visit	Baseline	n	33	34	40	31
		Mean(SD)	79.33 (12.83)	78.24 (17.66)	77.53 (21.21)	81.81 (15.21)
		Median	78.00	80.50	82.00	80.00
		Min, Max	56.0-102.0	41.0-114.0	17.0-115.0	56.0-116.0
	Week 2	n	32	34	39	31
		Mean(SD)	72.66 (17.55)	75.06 (14.56)	76.51 (17.55)	77.45 (12.54)
		Median	74.50	79.50	77.00	77.00
		Min, Max	44.0-117.0	46.0-96.0	45.0-111.0	54.0-108.0
	Change from baseline Week 2	n	32	34	39	31
		Mean(SD)	-7.03 (15.12)	-3.18 (8.21)	-0.72 (14.26)	-4.35 (11.04)
		Median	-10.50	-1.50	-3.00	-5.00
		Min, Max	-32.0-25.0	-22.0-9.0	-30.0-50.0	-31.0-16.0
	Week 4	n	30	33	36	27
		Mean(SD)	63.10 (17.35)	68.85 (15.85)	72.58 (16.80)	75.44 (12.43)
		Median	63.00	68.00	70.50	72.00
		Min, Max	26.0-107.0	42.0-94.0	45.0-108.0	53.0-104.0
	Change from baseline Week 4	n	30	33	36	27
		Mean(SD)	-16.80 (14.12)	-9.48 (14.26)	-4.03 (15.96)	-7.89 (11.91)
		Median	-15.00	-6.00	-1.00	-6.00

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Min, Max	-45.0-9.0	-48.0-15.0	-40.0-37.0	-41.0-16.0
Summary of COMDQ, medication and treatment domain, by visit	Baseline	n	33	34	38	31
		Mean(SD)	17.27 (4.13)	17.97 (4.32)	17.50 (4.85)	17.61 (4.92)
		Median	18.00	18.50	17.50	17.00
		Min, Max	9.0-27.0	9.0-25.0	6.0-28.0	7.0-27.0
	Week 2	n	32	34	39	31
		Mean(SD)	17.56 (4.33)	18.56 (3.40)	17.82 (4.96)	17.58 (4.02)
		Median	18.00	18.50	19.00	17.00
		Min, Max	9.0-29.0	12.0-26.0	7.0-29.0	8.0-26.0
	Change from baseline Week 2	n	32	34	37	31
		Mean(SD)	0.13 (4.70)	0.59 (2.96)	0.41 (3.52)	-0.03 (4.14)
		Median	0.50	0.00	0.00	0.00
		Min, Max	-10.0-10.0	-6.0-9.0	-6.0-10.0	-9.0-11.0
	Week 4	n	30	33	36	27
		Mean(SD)	14.90 (5.05)	17.45 (4.35)	17.92 (4.40)	18.33 (4.24)
		Median	16.50	18.00	18.50	18.00
		Min, Max	4.0-21.0	6.0-25.0	9.0-25.0	9.0-27.0
	Change from baseline Week 4	n	30	33	34	27
		Mean(SD)	-2.80 (4.97)	-0.58 (4.15)	0.53 (4.52)	0.37 (4.06)
		Median	-3.00	0.00	0.50	0.00
		Min, Max	-16.0-5.0	-14.0-6.0	-9.0-8.0	-8.0-12.0

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of COMDQ, pain and functional limitation domain, by visit	Baseline	n	33	34	38	31
		Mean(SD)	28.24 (6.91)	27.91 (7.88)	29.13 (6.43)	29.03 (6.60)
		Median	28.00	29.50	29.00	28.00
		Min, Max	15.0-39.0	12.0-41.0	15.0-41.0	20.0-44.0
	Week 2	n	32	34	39	31
		Mean(SD)	23.53 (9.43)	25.03 (7.98)	26.38 (7.42)	26.26 (6.95)
		Median	23.00	25.50	27.00	25.00
		Min, Max	10.0-44.0	10.0-40.0	14.0-41.0	15.0-40.0
	Change from baseline Week 2	n	32	34	37	31
		Mean(SD)	-4.72 (8.46)	-2.88 (4.87)	-2.76 (5.67)	-2.77 (6.94)
		Median	-6.00	-3.00	-2.00	-2.00
		Min, Max	-22.0-14.0	-16.0-8.0	-18.0-10.0	-26.0-15.0
	Week 4	n	30	33	36	27
		Mean(SD)	19.60 (8.02)	21.82 (7.82)	24.11 (7.19)	24.37 (5.71)
		Median	18.00	22.00	23.50	24.00
		Min, Max	9.0-36.0	8.0-33.0	12.0-43.0	9.0-35.0
	Change from baseline Week 4	n	30	33	34	27
		Mean(SD)	-8.87 (8.29)	-5.88 (7.26)	-4.82 (7.21)	-5.15 (7.54)
		Median	-9.00	-3.00	-4.00	-4.00
		Min, Max	-24.0-7.0	-30.0-3.0	-22.0-13.0	-32.0-6.0
	Baseline	n	33	34	40	31

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Summary of COMDQ, social and emotional domain, by visit		Mean(SD)	21.39 (6.79)	20.68 (6.60)	21.10 (7.04)	22.35 (5.98)
		Median	21.00	22.00	22.00	23.00
		Min, Max	9.0-33.0	8.0-35.0	8.0-35.0	10.0-33.0
	Week 2	n	32	34	39	31
		Mean(SD)	19.38 (7.37)	19.21 (6.29)	19.97 (7.34)	20.87 (5.48)
		Median	20.00	21.00	21.00	21.00
		Min, Max	7.0-35.0	7.0-34.0	8.0-33.0	9.0-31.0
	Change from baseline Week 2	n	32	34	39	31
		Mean(SD)	-2.22 (6.23)	-1.47 (5.02)	-0.90 (3.89)	-1.48 (3.24)
		Median	-1.50	-1.00	-1.00	-2.00
		Min, Max	-16.0-11.0	-13.0-9.0	-7.0-7.0	-8.0-4.0
	Week 4	n	30	33	36	27
		Mean(SD)	17.03 (7.59)	17.00 (5.85)	18.36 (6.95)	20.22 (6.39)
		Median	15.00	16.00	18.50	21.00
		Min, Max	7.0-34.0	7.0-28.0	8.0-31.0	9.0-31.0
	Change from baseline Week 4	n	30	33	36	27
		Mean(SD)	-4.43 (6.37)	-3.82 (5.25)	-2.17 (4.48)	-2.63 (4.39)
		Median	-4.00	-3.00	-2.00	-3.00
		Min, Max	-17.0-11.0	-16.0-9.0	-11.0-6.0	-11.0-5.0
Summary of COMDQ, patient support domain, by visit	Baseline	n	33	34	40	31
		Mean(SD)	12.42 (2.68)	11.68 (2.47)	12.13 (3.58)	12.81 (2.32)

Efficacy variable	Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Median	13.00	12.00	12.00	13.00
		Min, Max	7.0-18.0	8.0-16.0	5.0-20.0	9.0-17.0
	Week 2	n	32	34	38	31
		Mean(SD)	12.19 (3.00)	12.26 (2.30)	12.66 (3.43)	12.74 (3.10)
		Median	13.00	12.00	13.00	13.00
		Min, Max	4.0-16.0	8.0-17.0	5.0-19.0	7.0-17.0
	Change from baseline Week 2	n	32	34	38	31
		Mean(SD)	-0.22 (2.28)	0.59 (2.12)	0.45 (2.67)	-0.06 (2.79)
		Median	0.00	0.00	0.00	0.00
		Min, Max	-7.0-6.0	-4.0-5.0	-7.0-6.0	-7.0-6.0
	Week 4	n	30	33	36	27
		Mean(SD)	11.57 (3.51)	12.58 (2.89)	12.19 (3.50)	12.52 (2.64)
		Median	12.00	12.00	12.50	12.00
		Min, Max	4.0-19.0	6.0-17.0	4.0-19.0	4.0-18.0
	Change from baseline Week 4	n	30	33	36	27
		Mean(SD)	-0.70 (2.59)	0.79 (2.34)	0.19 (2.87)	-0.48 (2.44)
		Median	-1.00	0.00	0.00	0.00
		Min, Max	-9.0-4.0	-4.0-5.0	-6.0-7.0	-8.0-5.0

Listing(s): Derived from Listing 16.2.4.1

Table 14.2.7.2 Statistical analysis of COMDQ scores [FAS]

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Summary of COMDQ, total score, by visit	Week 2	20 ug	-5.311	20 ug vs placebo	-3.116	(-8.612, 2.381)	0.2641
		5 ug	-1.891	5 ug vs placebo	0.305	(-5.148, 5.757)	0.9122
		1 ug	-0.027	1 ug vs placebo	2.169	(-3.128, 7.465)	0.4193
		Placebo	-2.195				
	Week 4	20 ug	-12.062	20 ug vs placebo	-9.022	(-14.965, -3.079)	0.0032
		5 ug	-6.497	5 ug vs placebo	-3.458	(-9.354, 2.438)	0.2480
		1 ug	-1.772	1 ug vs placebo	1.268	(-4.459, 6.995)	0.6620
		Placebo	-3.040				
Summary of COMDQ, medication and treatment domain, by visit	Week 2	20 ug	0.002	20 ug vs placebo	0.100	(-1.578, 1.777)	0.9064
		5 ug	0.659	5 ug vs placebo	0.757	(-0.899, 2.413)	0.3674
		1 ug	0.397	1 ug vs placebo	0.495	(-1.131, 2.120)	0.5481
		Placebo	-0.098				
	Week 4	20 ug	-2.524	20 ug vs placebo	-2.854	(-4.695, -1.013)	0.0027
		5 ug	-0.435	5 ug vs placebo	-0.765	(-2.583, 1.053)	0.4064
		1 ug	0.579	1 ug vs placebo	0.249	(-1.535, 2.033)	0.7828
		Placebo	0.330				
Summary of COMDQ, pain and functional limitation domain, by visit	Week 2	20 ug	-3.853	20 ug vs placebo	-2.012	(-5.145, 1.121)	0.2061
		5 ug	-2.100	5 ug vs placebo	-0.259	(-3.360, 2.843)	0.8691
		1 ug	-1.659	1 ug vs placebo	0.182	(-2.851, 3.216)	0.9055
		Placebo	-1.841				
	Week 4	20 ug	-6.905	20 ug vs placebo	-4.340	(-7.620, -1.060)	0.0099

Efficacy Variable	Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
		5 ug	-4.765	5 ug vs placebo	-2.200	(-5.447, 1.047)	0.1824
		1 ug	-2.803	1 ug vs placebo	-0.238	(-3.414, 2.938)	0.8824
		Placebo	-2.565				
Summary of COMDQ, social and emotional domain, by visit	Week 2	20 ug	-1.641	20 ug vs placebo	-0.790	(-3.021, 1.441)	0.4849
		5 ug	-1.101	5 ug vs placebo	-0.250	(-2.466, 1.967)	0.8240
		1 ug	-0.618	1 ug vs placebo	0.233	(-1.915, 2.381)	0.8303
		Placebo	-0.852				
	Week 4	20 ug	-2.859	20 ug vs placebo	-1.591	(-4.002, 0.820)	0.1940
		5 ug	-2.779	5 ug vs placebo	-1.511	(-3.906, 0.885)	0.2143
		1 ug	-1.346	1 ug vs placebo	-0.078	(-2.400, 2.244)	0.9470
		Placebo	-1.268				
Summary of COMDQ, patient support domain, by visit	Week 2	20 ug	-0.332	20 ug vs placebo	-0.343	(-1.523, 0.837)	0.5660
		5 ug	0.297	5 ug vs placebo	0.286	(-0.892, 1.463)	0.6322
		1 ug	0.236	1 ug vs placebo	0.224	(-0.910, 1.359)	0.6962
		Placebo	0.012				
	Week 4	20 ug	-0.417	20 ug vs placebo	-0.270	(-1.502, 0.961)	0.6646
		5 ug	0.988	5 ug vs placebo	1.135	(-0.094, 2.364)	0.0700
		1 ug	0.312	1 ug vs placebo	0.458	(-0.726, 1.642)	0.4451
		Placebo	-0.147				
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.3							

Figure 14.2.7.2 Mean value curves of COMDQ scores over time [FAS]

a: total score - absolute scale

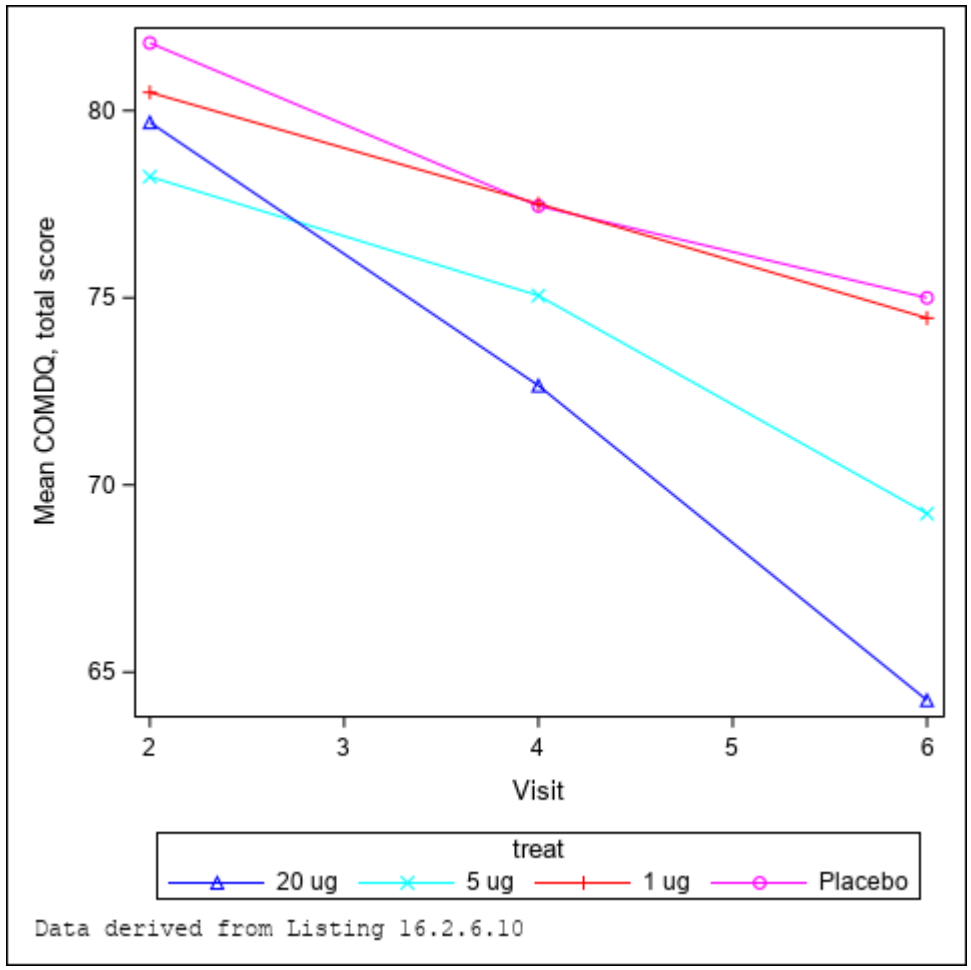


Figure 14.2.7.2 Mean value curves of COMDQ scores over time [FAS] b: total score - change

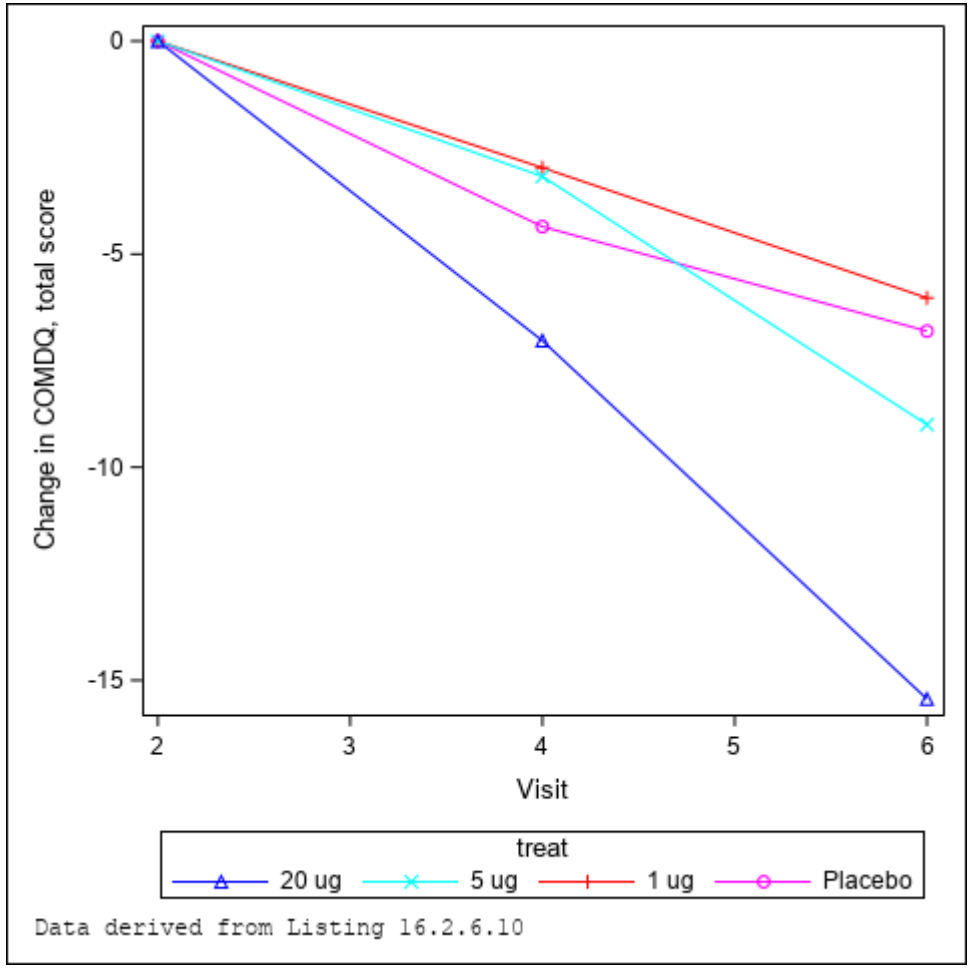


Figure 14.2.7.2 Mean value curves of COMDQ scores over time [FAS] c: pain and functional limitation - absolut

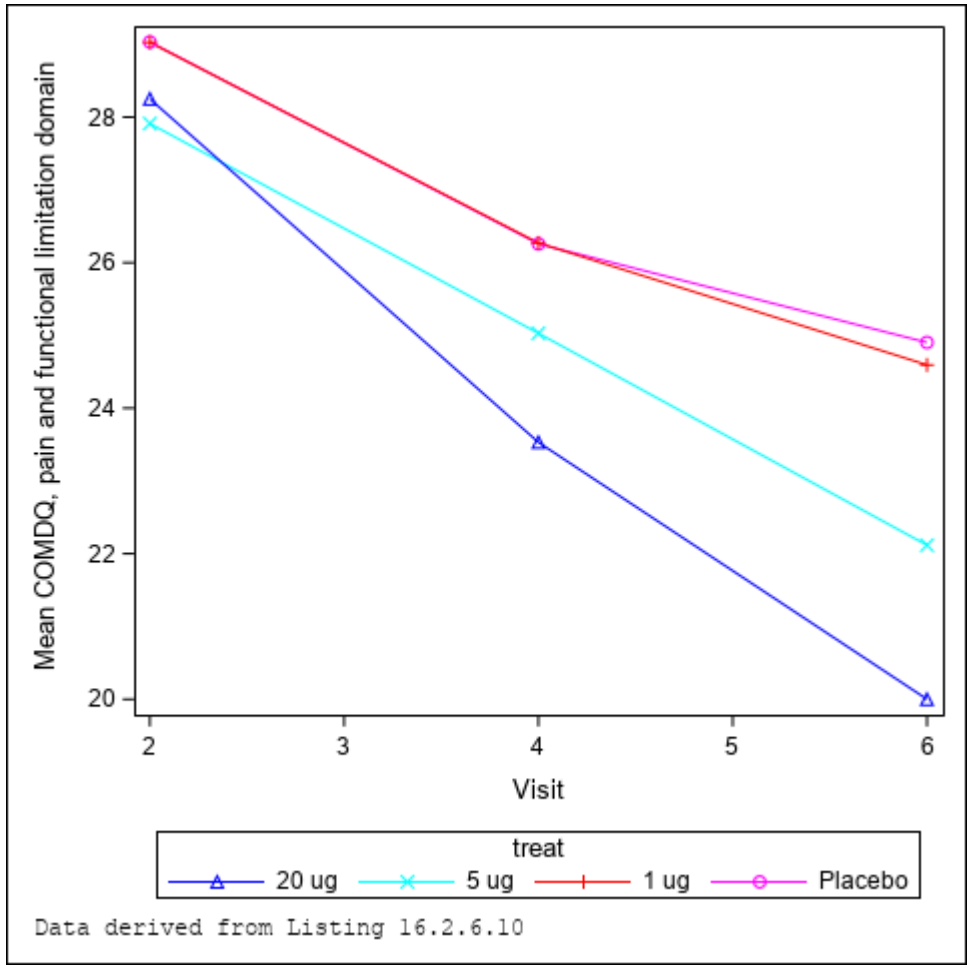


Figure 14.2.7.2 Mean value curves of COMDQ scores over time [FAS] d: pain and functional limitation - change

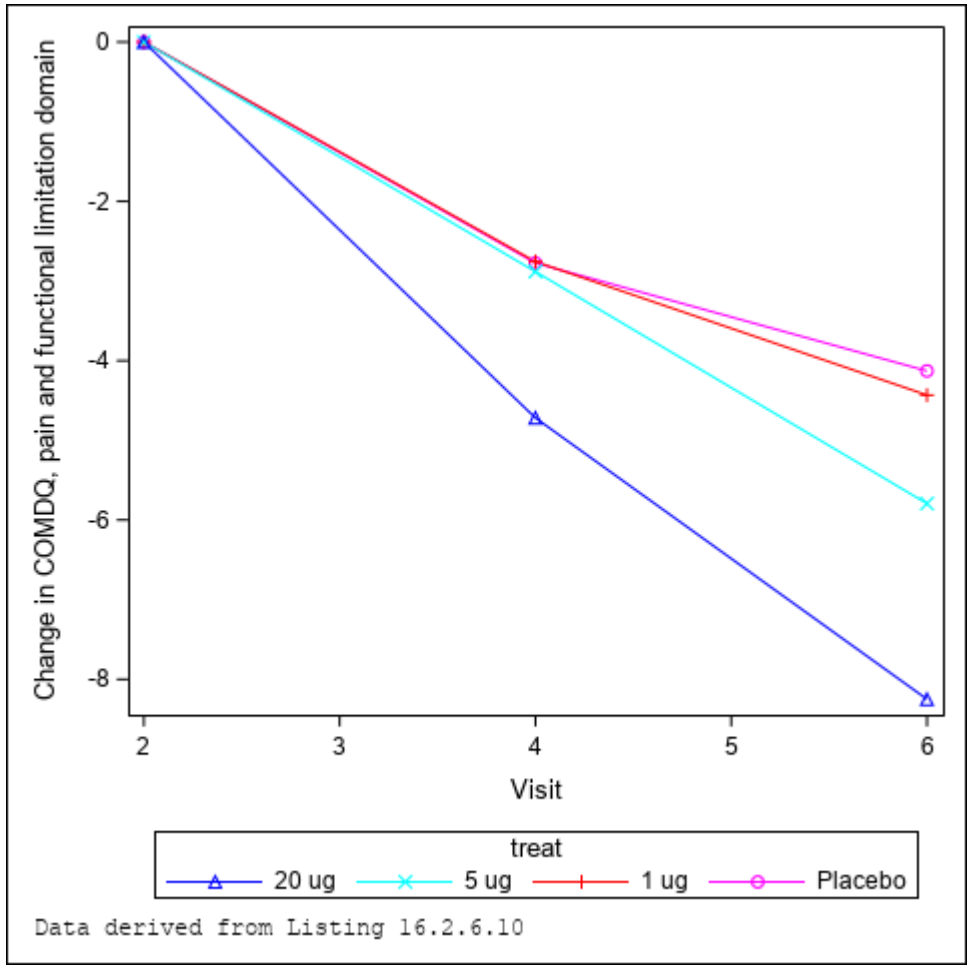


Figure 14.2.7.2 Mean value curves of COMDQ scores over time [FAS] e: medication and treatment - absolute scale

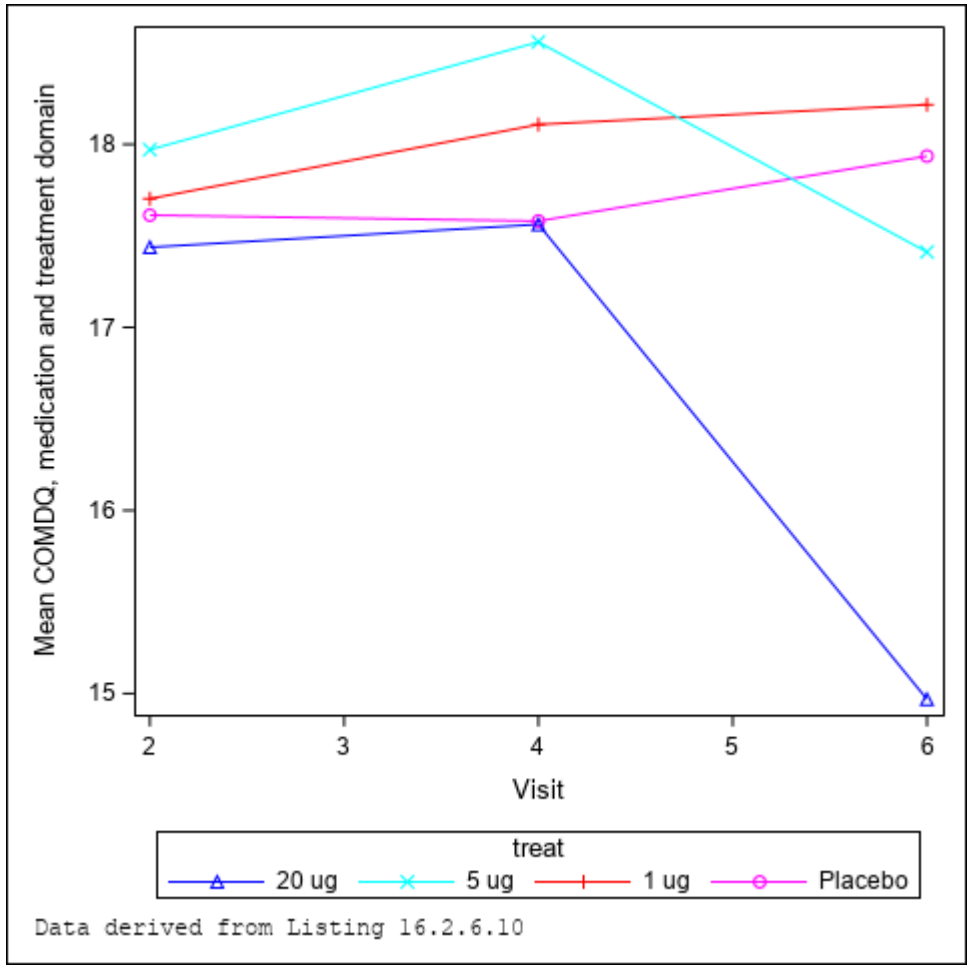


Figure 14.2.7.2 Mean value curves of COMDQ scores over time [FAS] f: medication and treatment - change

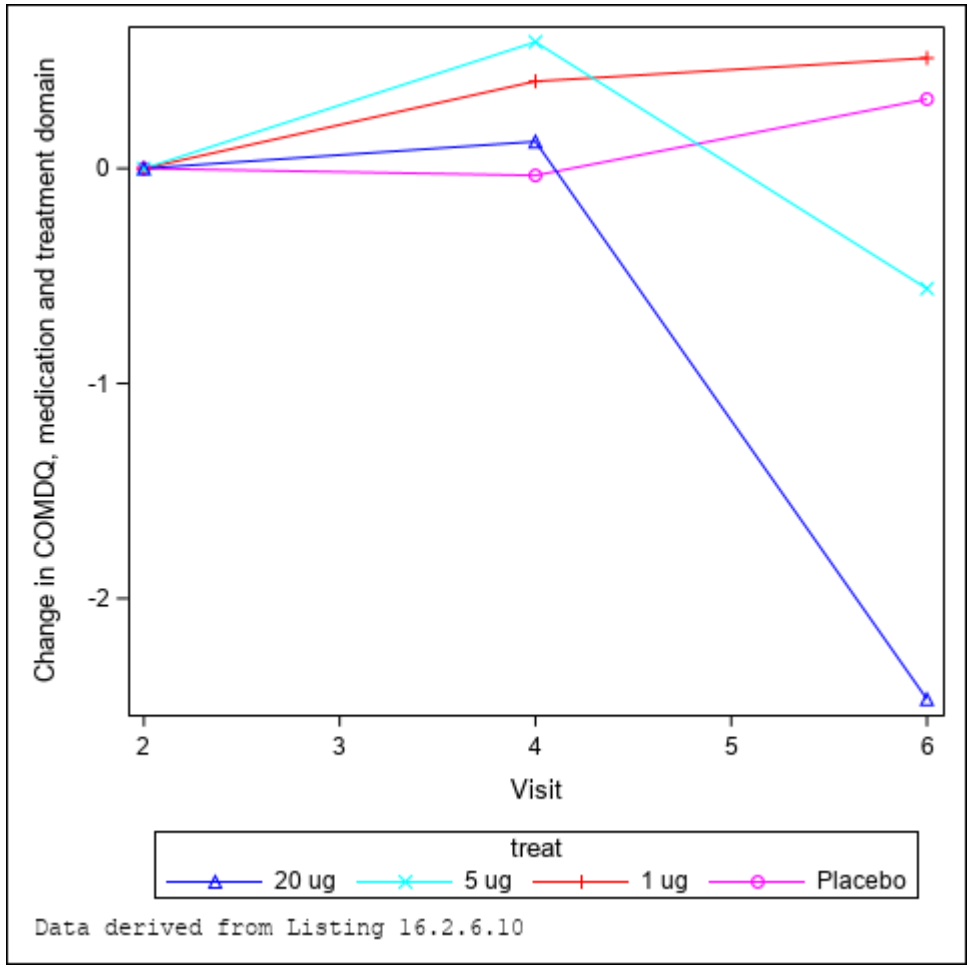


Figure 14.2.7.2 Mean value curves of COMDQ scores over time [FAS] g: social and emotional - absolute scale

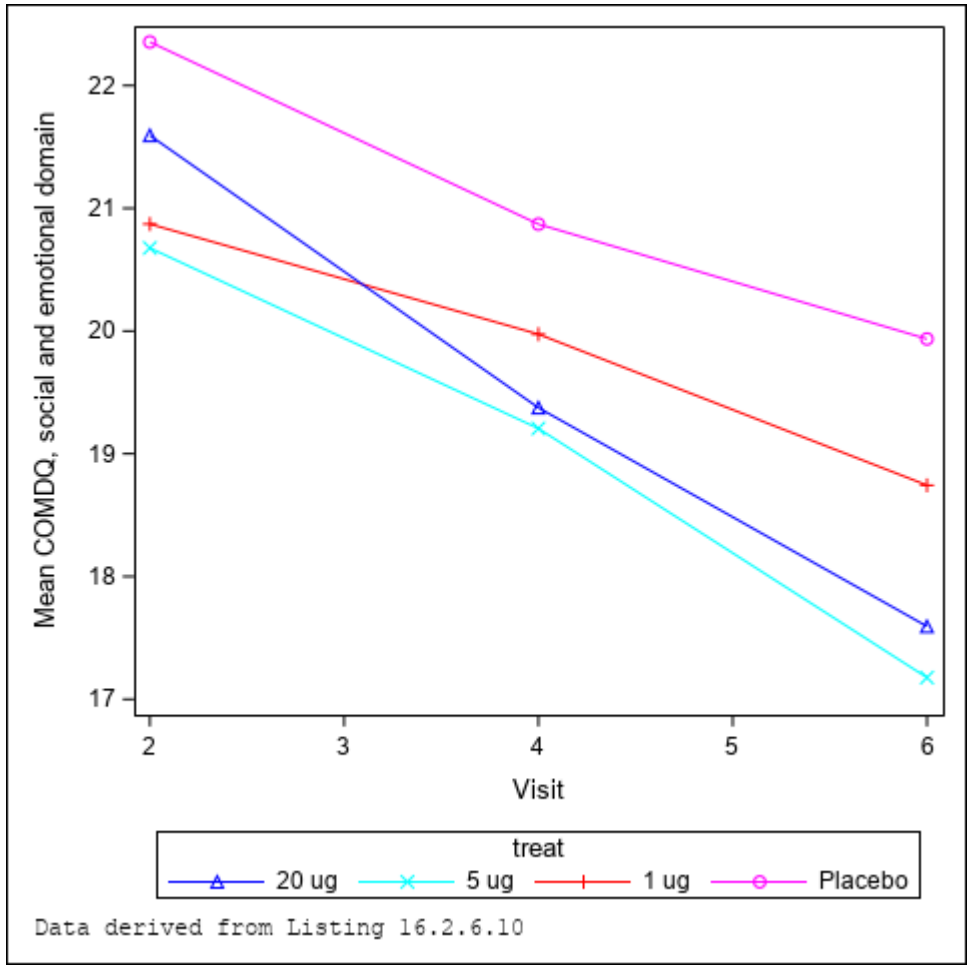


Figure 14.2.7.2 Mean value curves of COMDQ scores over time [FAS] h: social and emotional - change

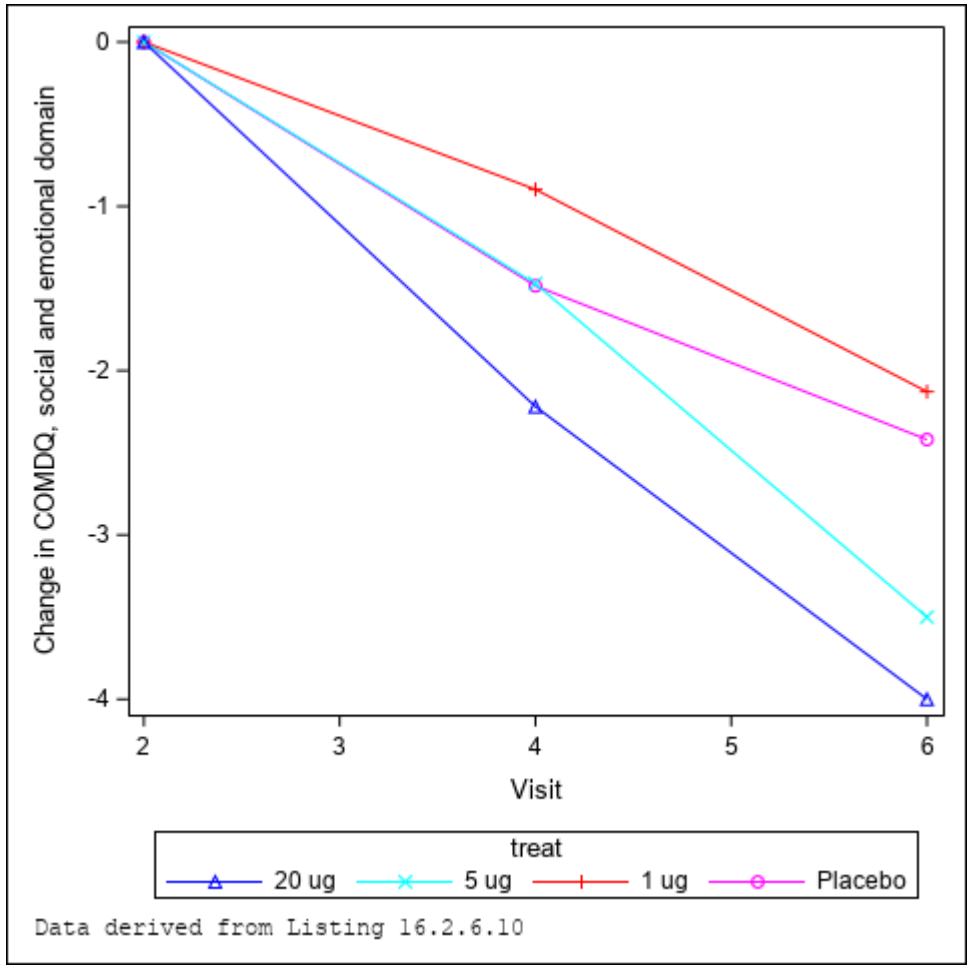


Figure 14.2.7.2 Mean value curves of COMDQ scores over time [FAS] i: patient support - absolute scale

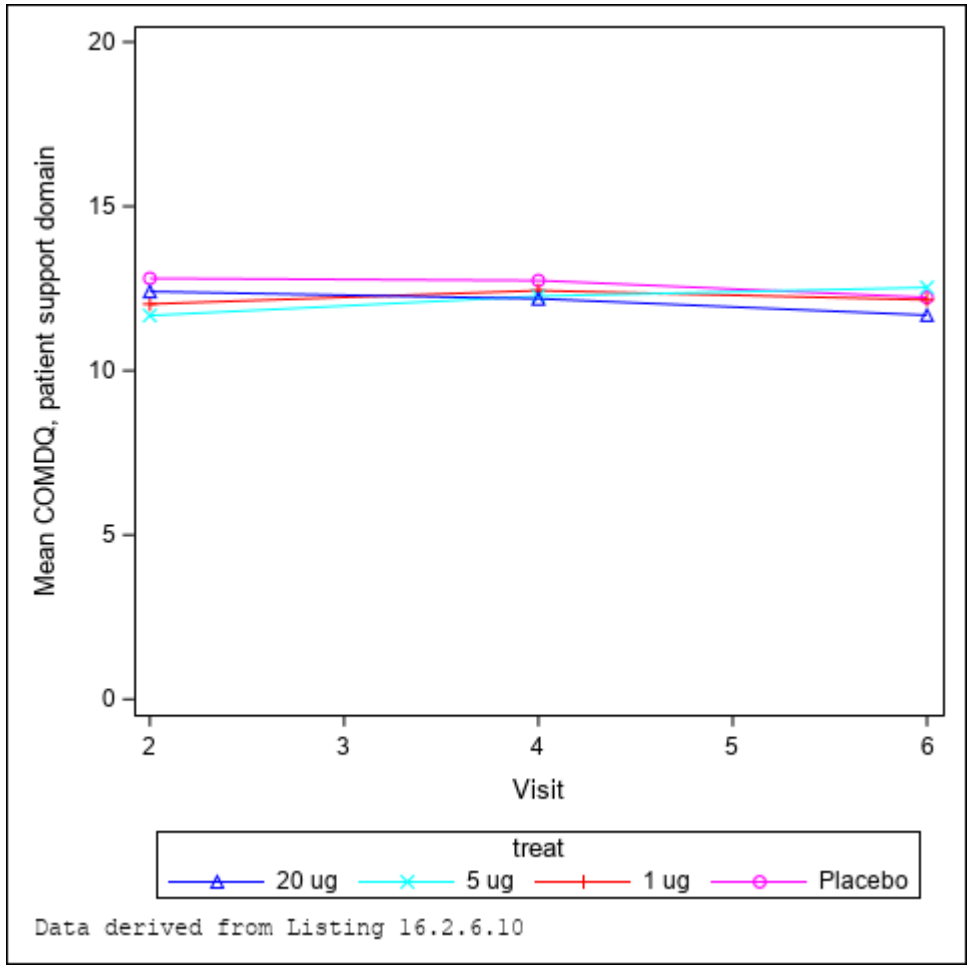
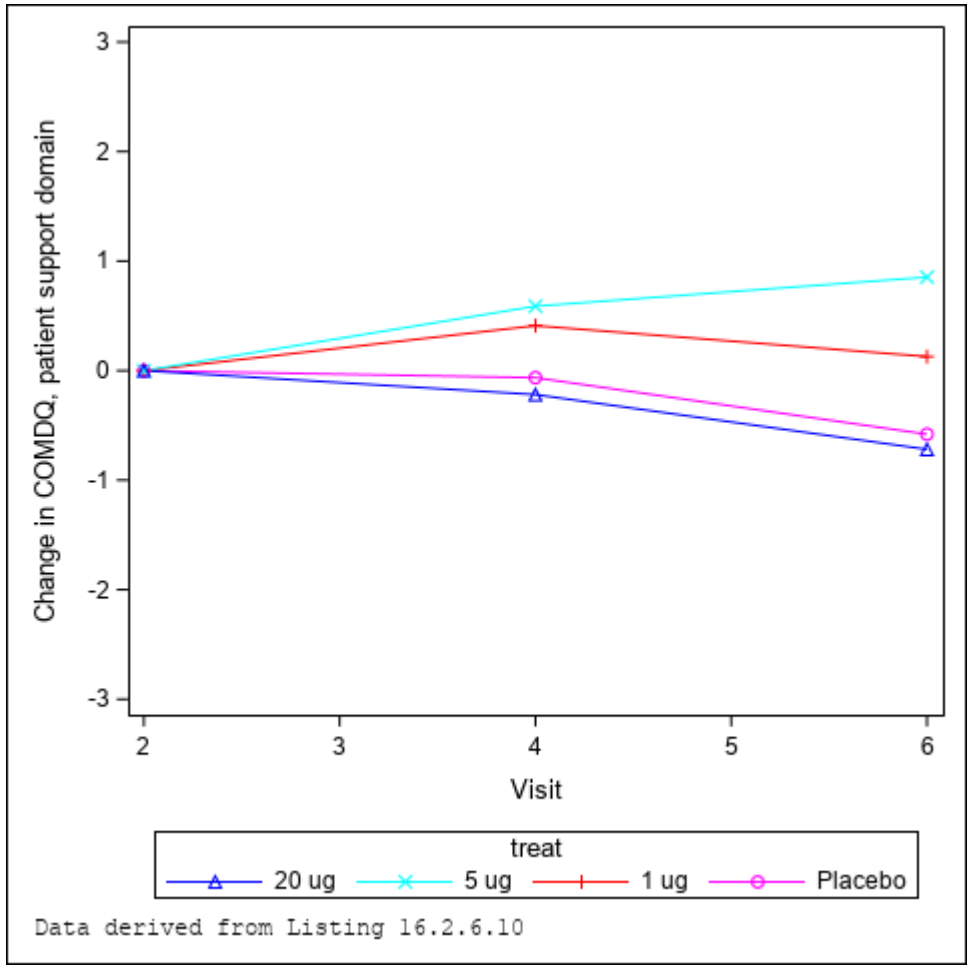


Figure 14.2.7.2 Mean value curves of COMDQ scores over time [FAS] j: patient support - change



14.2.8 IFU questionnaire

Table 14.2.8.1 Summary of answers to the IFU questionnaire [FAS]

a) Patient's instruction for use questionnaire

Variable	Visit	20 ug	5 ug	1 ug	Placebo
Patch application	2	26/ 7/ 0/ 0/ 0	28/ 5/ 0/ 1/ 0	32/ 6/ 0/ 0/ 0	22/ 9/ 0/ 0/ 0
	3	25/ 4/ 2/ 0/ 0	25/ 4/ 3/ 0/ 0	26/ 6/ 1/ 1/ 1	20/ 6/ 0/ 0/ 0
Patch removal	2	30/ 3/ 0/ 0/ 0	27/ 6/ 1/ 0/ 0	32/ 5/ 1/ 0/ 0	23/ 8/ 0/ 0/ 0
	3	27/ 4/ 0/ 0/ 0	27/ 5/ 0/ 0/ 0	31/ 3/ 0/ 1/ 0	21/ 5/ 0/ 0/ 0
Frequncy of categories 1-5 ordered with most favourable category first and least favourable category last Listing(s): Derived from 16.2.6.11					

Table 14.2.8.1 Summary of answers to the IFU questionnaire [FAS]

b) Site assessment on correct use of instruction for use questionnaire

Visit	20 ug	5 ug	1 ug	Placebo
2	88/ 90 (97.8)	95/100 (95.0)	108/115 (93.9)	83/ 84 (98.8)
3	83/ 87 (95.4)	89/ 95 (93.7)	120/127 (94.5)	76/ 78 (97.4)
Listing(s): Derived from 16.2.6.2				

Figure 14.2.8.1 Histograms on outcomes from the instruction to use questionnaire

a: Q1 application procedure (Visit 2)

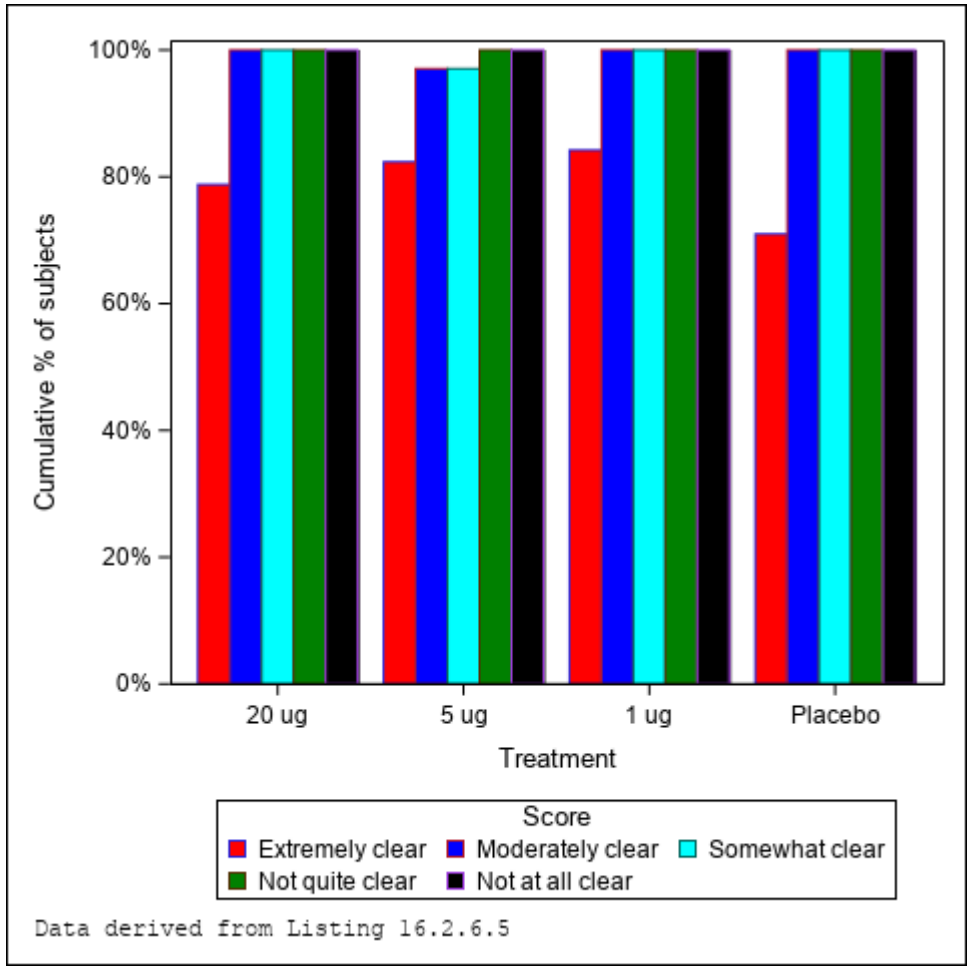


Figure 14.2.8.1 Histograms on outcomes from the instruction to use questionnaire b: Q1 application procedure (Visit 3)

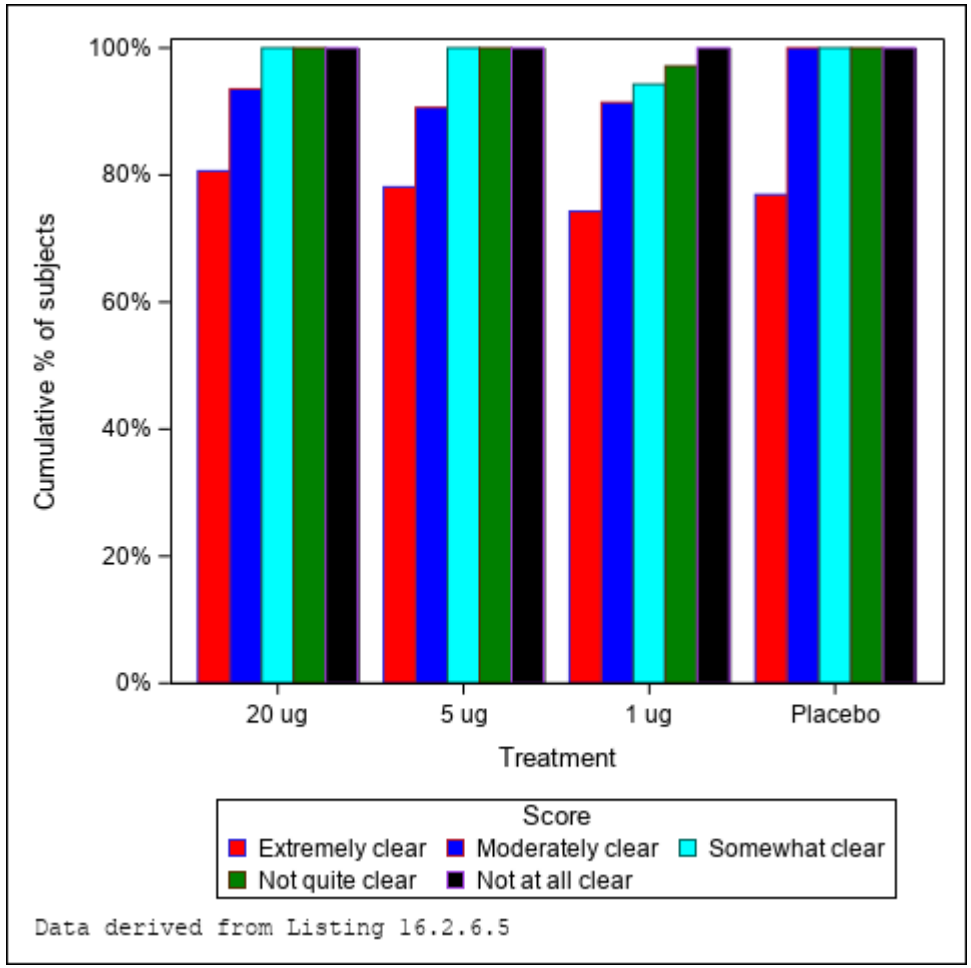


Figure 14.2.8.1 Histograms on outcomes from the instruction to use questionnaire c: Q2 removal procedure (Visit 2)

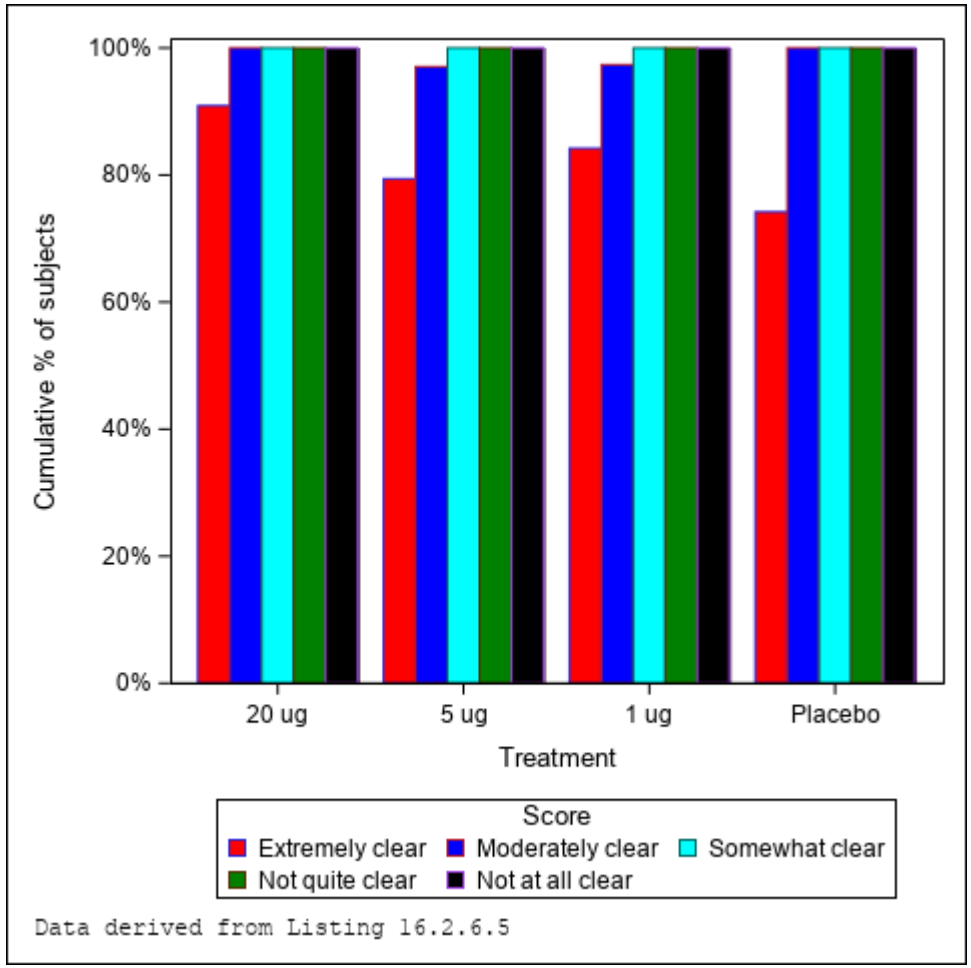
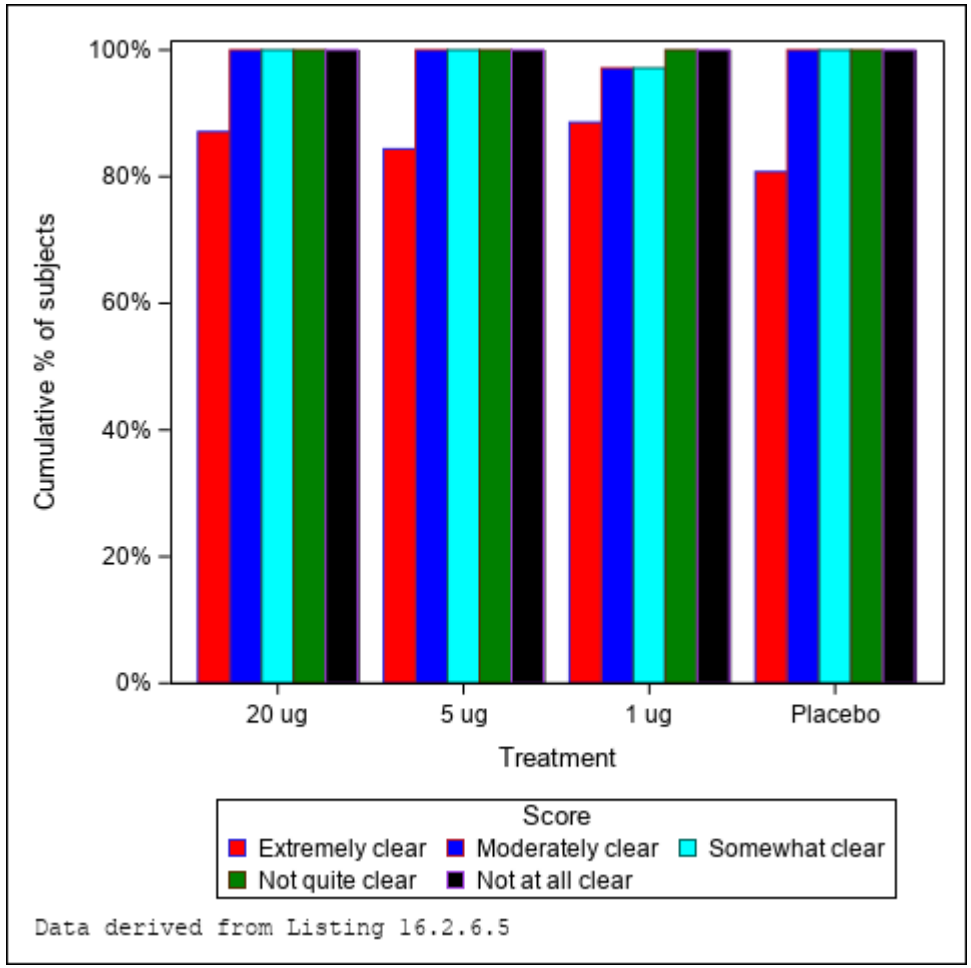


Figure 14.2.8.1 Histograms on outcomes from the instruction to use questionnaire d: Q2 removal procedure (Visit 3)



14.2.9 Rescue Analgesics

Table 14.2.9.1 Summary of rescue analgesics use [FAS]

a) Summary of rescue analgesics by ATC class

Medication Class (ATC level 2 and 4)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
ANY RESCUE MEDICATION	21 (64)	27 (79)	28 (70)	25 (81)	101 (73)
ANALGESICS	12 (36)	18 (53)	21 (53)	17 (55)	68 (49)
- ANILIDES	11 (33)	17 (50)	21 (53)	17 (55)	66 (48)
- OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	1 (3)	1 (3)	0	0	2 (1)
- OTHER OPIOIDS	0	1 (3)	0	0	1 (1)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	4 (12)	8 (24)	6 (15)	5 (16)	23 (17)
- PROPIONIC ACID DERIVATIVES	4 (12)	8 (24)	6 (15)	5 (16)	23 (17)
STOMATOLOGICAL PREPARATIONS	5 (15)	6 (18)	6 (15)	6 (19)	23 (17)
- OTHER AGENTS FOR LOCAL ORAL TREATMENT	5 (15)	6 (18)	6 (15)	6 (19)	23 (17)
ANESTHETICS	4 (12)	4 (12)	3 (8)	3 (10)	14 (10)
- AMIDES	4 (12)	4 (12)	3 (8)	3 (10)	14 (10)
PSYCHOLEPTICS	0	1 (3)	0	0	1 (1)
- OTHER HYPNOTICS AND SEDATIVES	0	1 (3)	0	0	1 (1)

Listing(s): Derived from Listing 16.2.4.2

Table 14.2.9.1 Summary of rescue analgesics use [FAS]: b) Summary of total rescue analgesics use, rescue population

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	20	24	27	23
	Mean(SD)	0.634 (1.11)	0.734 (0.89)	0.744 (2.39)	0.389 (0.72)
	Median	0.000	0.343	0.000	0.000
	Min, Max	0.00-4.29	0.00-3.14	0.00-12.29	0.00-2.71
Week 1	n	19	27	24	22
	Mean(SD)	0.484 (0.91)	0.542 (0.84)	0.809 (2.29)	0.307 (0.63)
	Median	0.000	0.125	0.000	0.000
	Min, Max	0.00-3.33	0.00-3.14	0.00-11.00	0.00-2.50
Change from baseline Week 1	n	19	24	24	20
	Mean(SD)	-0.184 (0.89)	-0.125 (0.40)	-0.008 (0.48)	-0.035 (0.21)
	Median	0.000	0.000	0.000	0.000
	Min, Max	-2.29-2.08	-1.38-0.43	-1.29-1.42	-0.57-0.50
Week 2	n	18	27	20	19
	Mean(SD)	0.306 (0.62)	0.716 (1.25)	0.801 (2.13)	0.263 (0.65)
	Median	0.000	0.000	0.000	0.000
	Min, Max	0.00-2.00	0.00-5.43	0.00-9.43	0.00-2.50
Change from baseline Week 2	n	18	24	20	18
	Mean(SD)	-0.399 (0.80)	0.072 (1.12)	-0.136 (0.84)	-0.117 (0.33)
	Median	0.000	0.000	0.000	0.000

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Min, Max	-2.29-0.86	-1.71-4.60	-2.86-1.29	-1.00-0.38
Week 3	n	18	25	21	18
	Mean(SD)	0.300 (0.56)	0.366 (0.83)	0.435 (0.94)	0.111 (0.47)
	Median	0.000	0.000	0.000	0.000
	Min, Max	0.00-2.00	0.00-3.57	0.00-3.86	0.00-2.00
Change from baseline Week 3	n	18	22	21	17
	Mean(SD)	-0.404 (0.82)	-0.355 (0.64)	-0.498 (1.89)	-0.369 (0.58)
	Median	0.000	0.000	0.000	0.000
	Min, Max	-2.29-0.86	-1.86-0.43	-8.43-1.17	-1.67-0.00
Week 4	n	14	25	20	17
	Mean(SD)	0.296 (0.63)	0.436 (0.99)	0.502 (1.07)	0.261 (0.74)
	Median	0.000	0.000	0.000	0.000
	Min, Max	0.00-2.00	0.00-4.00	0.00-4.20	0.00-2.86
Change from baseline Week 4	n	14	22	20	17
	Mean(SD)	-0.569 (0.94)	-0.275 (0.96)	-0.435 (2.56)	-0.226 (0.66)
	Median	-0.286	-0.143	0.000	0.000
	Min, Max	-2.29-1.14	-1.86-3.17	-10.29-4.03	-1.60-1.19

Listing(s): Derived from Listing 16.2.6

Table 14.2.9.1 Summary of rescue analgesics use [FAS]: c) Summary of days with rescue analgesics use, rescue population

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Baseline	n	20	24	27	23
	Mean(SD)	0.271 (0.40)	0.375 (0.42)	0.215 (0.38)	0.158 (0.27)
	Median	0.000	0.243	0.000	0.000
	Min, Max	0.00-1.00	0.00-1.00	0.00-1.00	0.00-1.00
Week 1	n	19	27	24	22
	Mean(SD)	0.249 (0.39)	0.267 (0.37)	0.232 (0.38)	0.152 (0.26)
	Median	0.000	0.125	0.000	0.000
	Min, Max	0.00-1.00	0.00-1.00	0.00-1.00	0.00-1.00
Change from baseline Week 1	n	19	24	24	20
	Mean(SD)	-0.036 (0.30)	-0.075 (0.19)	0.011 (0.14)	-0.011 (0.13)
	Median	0.000	0.000	0.000	0.000
	Min, Max	-0.86-0.86	-0.69-0.14	-0.43-0.44	-0.21-0.33
Week 2	n	18	27	20	19
	Mean(SD)	0.188 (0.38)	0.288 (0.41)	0.251 (0.40)	0.125 (0.27)
	Median	0.000	0.000	0.000	0.000
	Min, Max	0.00-1.00	0.00-1.00	0.00-1.00	0.00-1.00
Change from baseline Week 2	n	18	24	20	18
	Mean(SD)	-0.113 (0.42)	-0.051 (0.31)	0.000 (0.26)	-0.045 (0.16)
	Median	0.000	0.000	0.000	0.000
	Min, Max	-1.00-0.86	-0.86-0.67	-0.69-0.86	-0.50-0.22

Variable	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Week 3	n	18	25	21	18
	Mean(SD)	0.188 (0.35)	0.199 (0.35)	0.230 (0.39)	0.056 (0.24)
	Median	0.000	0.000	0.000	0.000
	Min, Max	0.00-1.00	0.00-1.00	0.00-1.00	0.00-1.00
Change from baseline Week 3	n	18	22	21	17
	Mean(SD)	-0.113 (0.41)	-0.168 (0.32)	-0.023 (0.28)	-0.124 (0.22)
	Median	0.000	0.000	0.000	0.000
	Min, Max	-1.00-0.86	-1.00-0.18	-0.61-1.00	-0.83-0.00
Week 4	n	14	25	20	17
	Mean(SD)	0.184 (0.38)	0.213 (0.38)	0.236 (0.40)	0.126 (0.33)
	Median	0.000	0.000	0.000	0.000
	Min, Max	0.00-1.00	0.00-1.00	0.00-1.00	0.00-1.00
Change from baseline Week 4	n	14	22	20	17
	Mean(SD)	-0.173 (0.46)	-0.152 (0.34)	-0.015 (0.35)	-0.057 (0.15)
	Median	0.000	0.000	0.000	0.000
	Min, Max	-1.00-0.86	-1.00-0.67	-0.86-0.83	-0.50-0.17

Listing(s): Derived from Listing 16.2.6

Table 14.2.9.1 Summary of rescue analgesics use [FAS]: d) Analysis of total rescue analgesics use, rescue population

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-0.159	20 ug vs placebo	0.043	(-0.280, 0.365)	0.7926
	5 ug	-0.156	5 ug vs placebo	0.046	(-0.259, 0.351)	0.7657
	1 ug	-0.033	1 ug vs placebo	0.169	(-0.136, 0.473)	0.2731
	Placebo	-0.202				
Week 2	20 ug	-0.358	20 ug vs placebo	-0.036	(-0.472, 0.400)	0.8690
	5 ug	0.036	5 ug vs placebo	0.358	(-0.054, 0.770)	0.0878
	1 ug	-0.114	1 ug vs placebo	0.208	(-0.203, 0.620)	0.3158
	Placebo	-0.322				
Week 3	20 ug	-0.295	20 ug vs placebo	0.048	(-0.237, 0.333)	0.7366
	5 ug	-0.166	5 ug vs placebo	0.177	(-0.093, 0.446)	0.1960
	1 ug	-0.281	1 ug vs placebo	0.062	(-0.207, 0.331)	0.6470
	Placebo	-0.343				
Week 4	20 ug	-0.408	20 ug vs placebo	-0.017	(-0.508, 0.473)	0.9436
	5 ug	-0.198	5 ug vs placebo	0.192	(-0.272, 0.656)	0.4124
	1 ug	-0.311	1 ug vs placebo	0.079	(-0.384, 0.542)	0.7341
	Placebo	-0.390				
Week 3-4	20 ug	-0.351	20 ug vs placebo	0.015	(-0.314, 0.345)	0.9260
	5 ug	-0.182	5 ug vs placebo	0.184	(-0.128, 0.496)	0.2428
	1 ug	-0.296	1 ug vs placebo	0.071	(-0.240, 0.382)	0.6523
	Placebo	-0.367				

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.12						

Table 14.2.9.1 Summary of rescue analgesics use [FAS]: e) Analysis of days with rescue analgesics use, rescue population

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 1	20 ug	-0.024	20 ug vs placebo	0.045	(-0.071, 0.161)	0.4423
	5 ug	-0.077	5 ug vs placebo	-0.008	(-0.119, 0.102)	0.8818
	1 ug	-0.023	1 ug vs placebo	0.046	(-0.063, 0.154)	0.4062
	Placebo	-0.068				
Week 2	20 ug	-0.096	20 ug vs placebo	0.018	(-0.143, 0.180)	0.8221
	5 ug	-0.042	5 ug vs placebo	0.072	(-0.083, 0.227)	0.3588
	1 ug	-0.037	1 ug vs placebo	0.077	(-0.074, 0.229)	0.3131
	Placebo	-0.114				
Week 3	20 ug	-0.082	20 ug vs placebo	0.055	(-0.107, 0.217)	0.5016
	5 ug	-0.091	5 ug vs placebo	0.046	(-0.110, 0.202)	0.5581
	1 ug	-0.044	1 ug vs placebo	0.093	(-0.059, 0.246)	0.2269
	Placebo	-0.137				
Week 4	20 ug	-0.122	20 ug vs placebo	-0.015	(-0.186, 0.157)	0.8653
	5 ug	-0.102	5 ug vs placebo	0.006	(-0.158, 0.170)	0.9422
	1 ug	-0.059	1 ug vs placebo	0.049	(-0.112, 0.210)	0.5452
	Placebo	-0.108				

Period	Treatment	Estimate	Contrast	Difference	95% CI	p-value
Week 3-4	20 ug	-0.102	20 ug vs placebo	0.020	(-0.134, 0.175)	0.7956
	5 ug	-0.096	5 ug vs placebo	0.026	(-0.122, 0.174)	0.7279
	1 ug	-0.051	1 ug vs placebo	0.071	(-0.074, 0.216)	0.3317
	Placebo	-0.122				
Analysis performed by PROC MIXED. Listing(s): Derived from 16.2.6.12						

Figure 14.2.9.2 Weekly mean value curves on use of rescue analgesics over time [FAS]

a: absolute scale

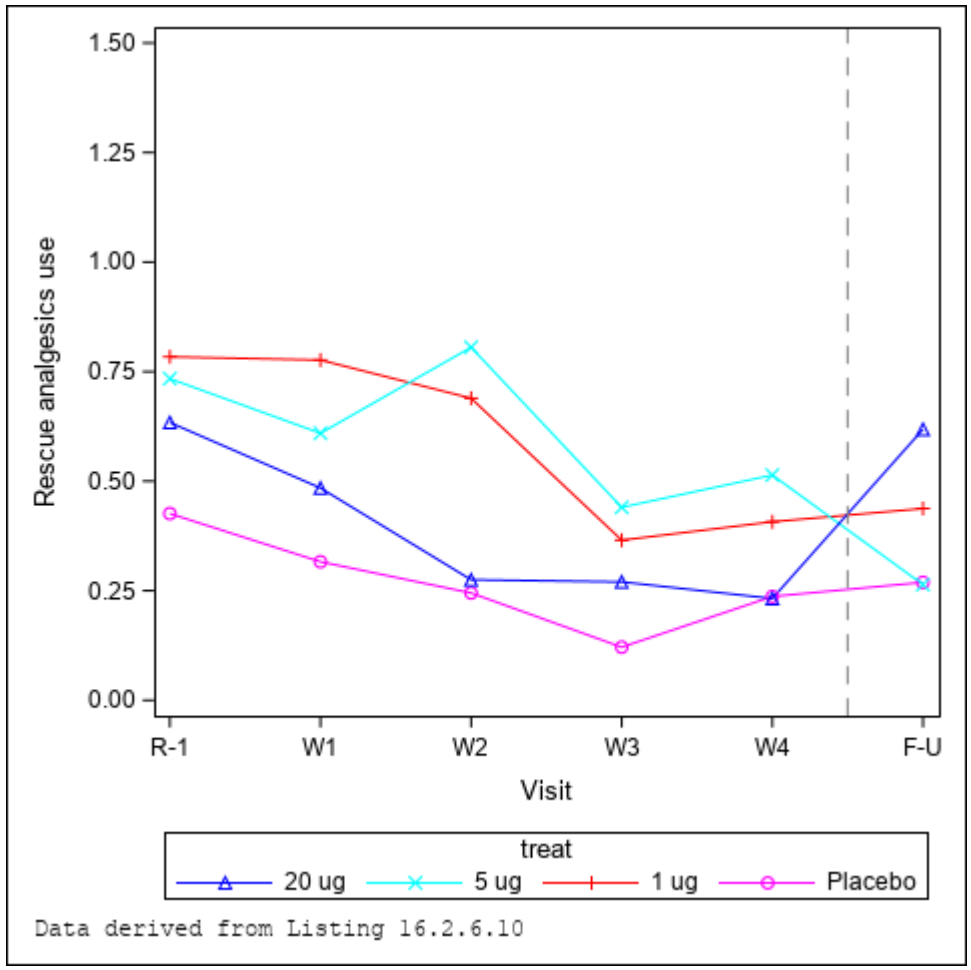
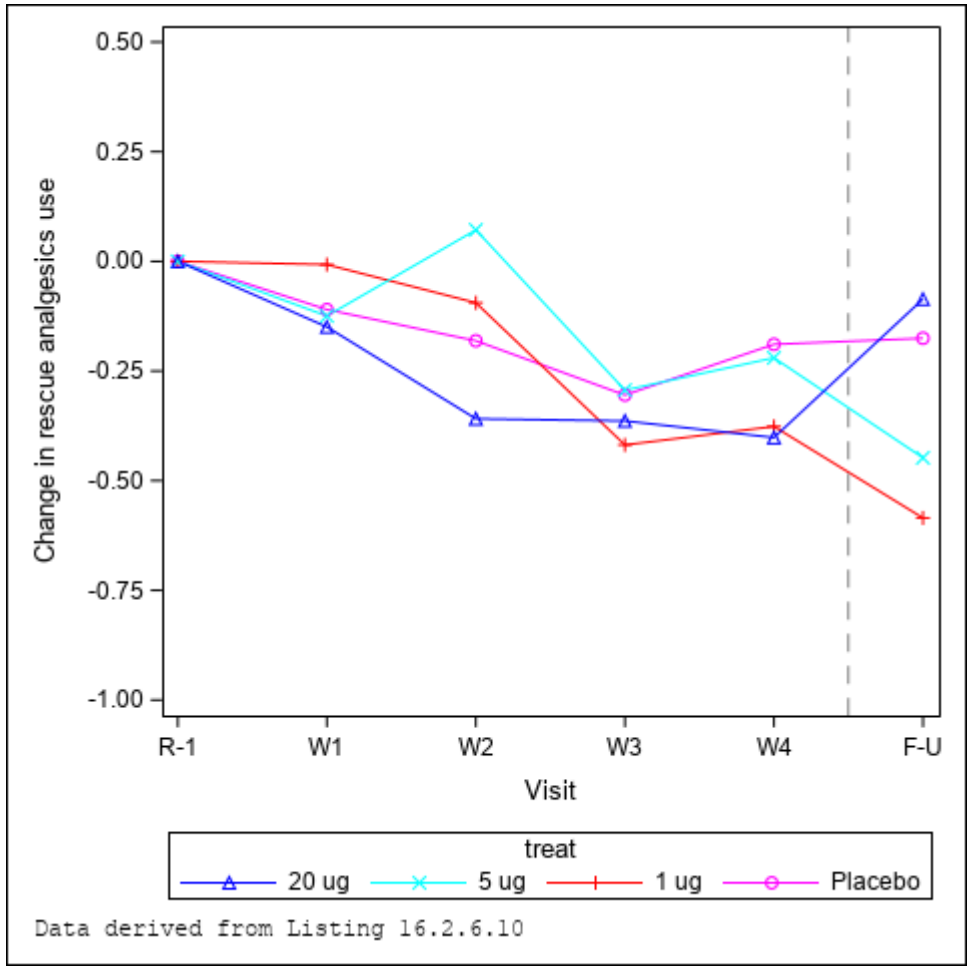


Figure 14.2.9.2 Weekly mean value curves on use of rescue analgesics over time [FAS]

b: change



14.2.10 Clobetasol and Cortisol

Table 14.2.10.1 Summary of plasma clobetasol concentrations

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Clobetasol propionate (pg/ml)	Visit 3 (Visit 4)	n	29	33	38	28
		Below LOQ (n)	27	33	37	27
		Max	2000	.	29	24.3
Clobetasol propionate (pg/ml)*	Visit 3 (Visit 4)	n	21	26	30	22
		Below LOQ (n)	20	26	29	22
		Max	2000	.	29	.
Values above ULOQ estimated to 2 x ULOQ *Patch applied evening before + sampling between 07 and 09 Listing(s): Derived from Listing 16.2.8.1						

Table 14.2.10.2 Summary of serum cortisol levels

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Cortisol (nmol/L)	Visit 3 (Visit 4)	n	30	33	38	29
		Gmean (CV)	316.9 (46.4)	276.1 (41.9)	294.2 (26.8)	317.9 (34.6)
		Median	348.5	276.8	292.6	319.9
		Min, Max	67.60, 749.6	107.4, 589.3	178.3, 471.4	149.3, 576.3

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Cortisol (nmol/L)*	Visit 3 (Visit 4)	n	22	26	30	23
		Gmean (CV)	338.1 (48.3)	271.5 (43.6)	302.6 (27.0)	334.4 (29.3)
		Median	358.4	263.9	294.1	338.1
		Min, Max	67.60, 749.6	107.4, 546.5	178.3, 471.4	170.6, 576.3

Gmean = geometric mean, CV = coefficient of variation
Values above ULOQ estimated to 2 x ULOQ
*Patch applied evening before + sampling between 07 and 09
Listing(s): Derived from Listing 16.2.8.1

Figure 14.2.10.2 Scatter plots of individual and mean serum cortisol levels by treatment group [FAS]

a: All values analyzed (pre-dose Week 1)

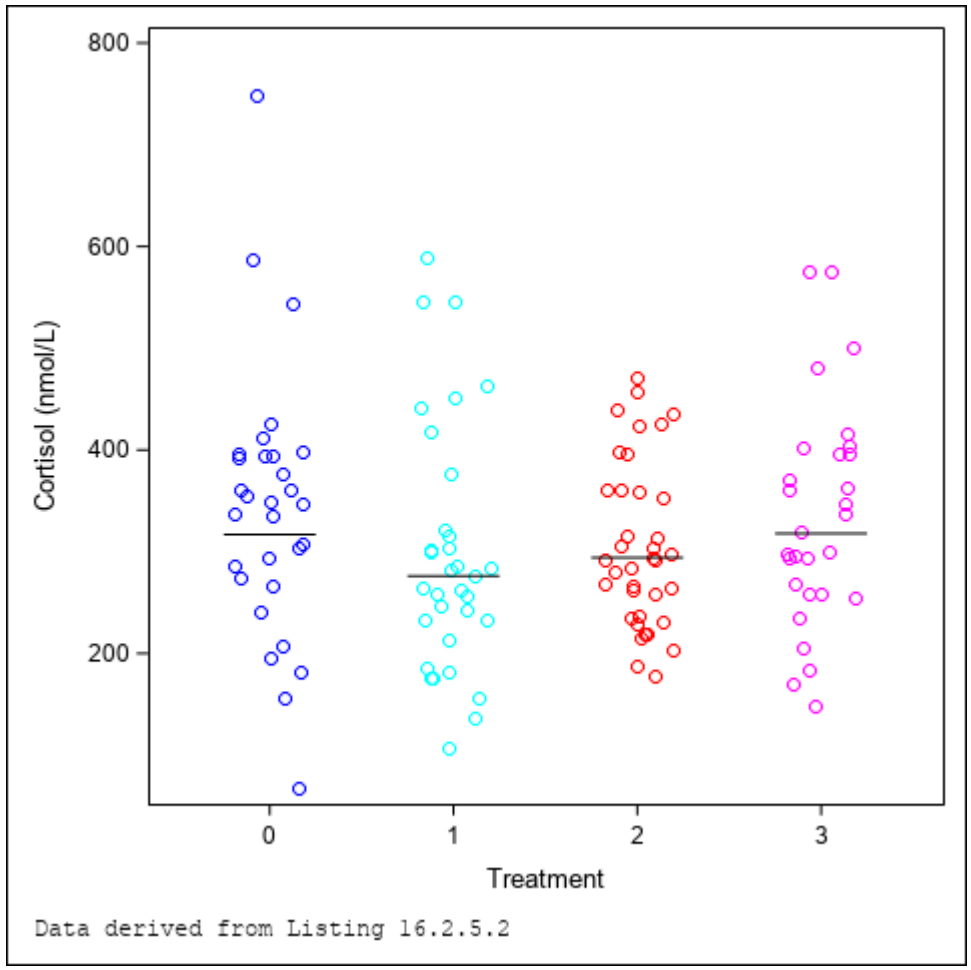
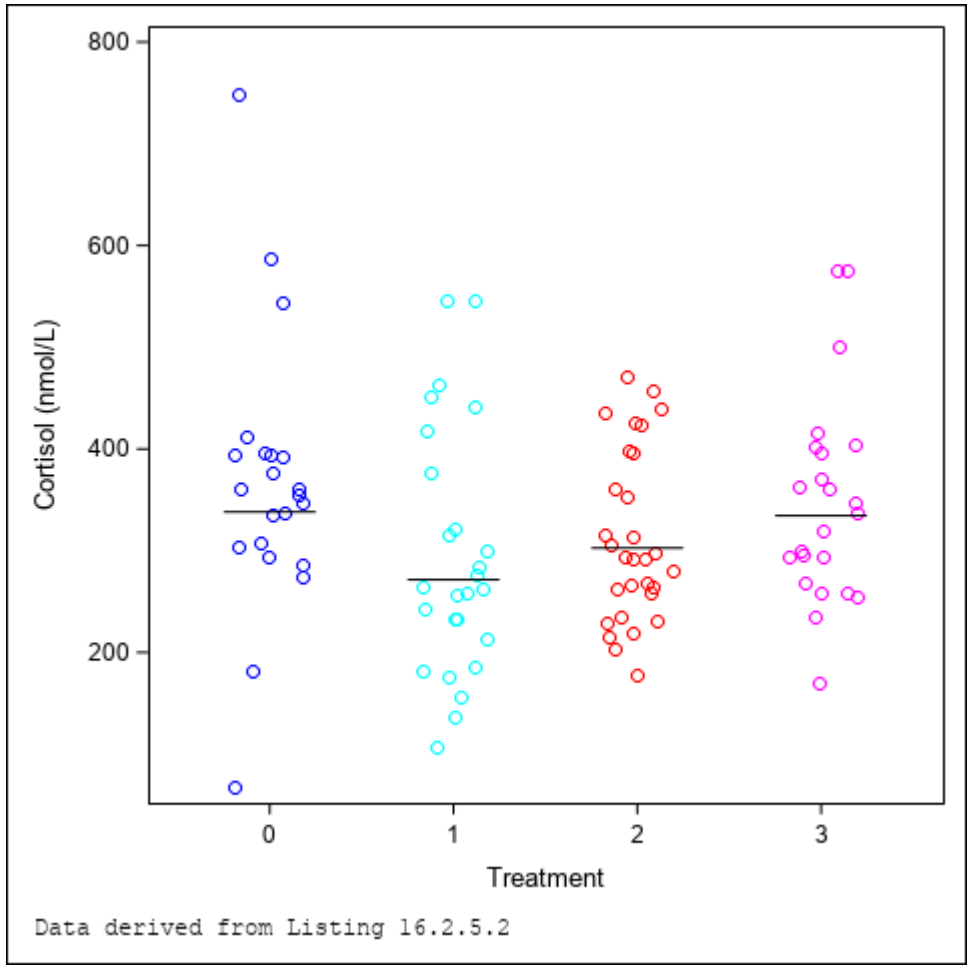


Figure 14.2.10.2 Scatter plots of individual and mean serum cortisol levels by treatment group [FAS]: b: Evening patch applied and assessment between 07 and 09 in the morning (pre-dose Week 1)



14.3 Safety Data

14.3.1 Display of Adverse Events

Table 14.3.1.1 Summary of adverse events

Category	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
Total no. of AEs*	31	31	28	31	121
No. of subjects with at least one AE	15 (45.5)	16 (47.1)	17 (42.5)	15 (48.4)	63 (45.7)
No. of subjects with at least one SAE**	1 (3.0)	0	1 (2.5)	0	2 (1.4)
No. of subjects with at least one DAE	0	0	1 (2.5)	1 (3.2)	2 (1.4)
No. of subjects withdrawn due to AE	0	0	2 (5.0)	2 (6.5)	4 (2.9)
No. of subjects with at least one AE related to clobetasol	2 (6.1)	2 (5.9)	7 (17.5)	5 (16.1)	16 (11.6)
- at least one related AE	0	0	2 (5.0)	0	2 (1.4)
- at least one probably related AE	1 (3.0)	1 (2.9)	2 (5.0)	1 (3.2)	5 (3.6)
- at least one possibly related AE	2 (6.1)	1 (2.9)	5 (12.5)	4 (12.9)	12 (8.7)
No. of subjects with at least one AE related to patch application	2 (6.1)	6 (17.6)	5 (12.5)	3 (9.7)	16 (11.6)
- at least one related AE	0	2 (5.9)	2 (5.0)	1 (3.2)	5 (3.6)
- at least one probably related AE	2 (6.1)	2 (5.9)	1 (2.5)	0	5 (3.6)
- at least one possibly related AE	2 (6.1)	3 (8.8)	3 (7.5)	2 (6.5)	10 (7.2)
No. of subjects with at least one AE related to study procedure	0	0	0	1 (3.2)	1 (0.7)
No. of subjects with at least one mild AE	10 (30.3)	12 (35.3)	11 (27.5)	11 (35.5)	44 (31.9)
No. of subjects with at least one moderate AE	9 (27.3)	6 (17.6)	6 (15.0)	8 (25.8)	29 (21.0)
No. of subjects with at least one severe AE	2 (6.1)	1 (2.9)	1 (2.5)	1 (3.2)	5 (3.6)
No. of subjects with AE with chronicity Continuous	9 (27.3)	7 (20.6)	12 (30.0)	9 (29.0)	37 (26.8)

Category	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
No. of subjects with AE with chronicity Intermittent	4 (12.1)	7 (20.6)	5 (12.5)	7 (22.6)	23 (16.7)
No. of subjects with AE with chronicity Isolated	6 (18.2)	8 (23.5)	5 (12.5)	6 (19.4)	25 (18.1)
No. of subjects with AE in oral cavity	9 (27.3)	11 (32.4)	11 (27.5)	11 (35.5)	42 (30.4)

*Counted uniquely by preferred term within subject; **Including deaths
SAE=serious adverse event; DAE=discontinuation of treatment due to AE

Listing(s): Data derived from Listing 16.2.7.1

Table 14.3.1.2 Adverse events by SOC and preferred term

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	15 (45)	16 (47)	17 (43)	15 (48)	63 (46)
GASTROINTESTINAL DISORDERS	7 (21)	9 (26)	6 (15)	8 (26)	30 (22)
- PERIODONTAL DISEASE	4 (12)	2 (6)	2 (5)	2 (6)	10 (7)
- SALIVARY HYPERSECRETION	1 (3)	3 (9)	0 (0)	1 (3)	5 (4)
- AMALGAM TATTOO	1 (3)	0 (0)	0 (0)	2 (6)	3 (2)
- DIARRHOEA	0 (0)	0 (0)	1 (3)	1 (3)	2 (1)
- GINGIVAL BLEEDING	0 (0)	1 (3)	1 (3)	0 (0)	2 (1)
- NAUSEA	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- ORAL PAIN	0 (0)	0 (0)	2 (5)	0 (0)	2 (1)
- ABDOMINAL DISCOMFORT	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- ABDOMINAL PAIN	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- GINGIVAL PAIN	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
- HAEMORRHOIDAL HAEMORRHAGE	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- ORAL DISORDER	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- ORAL LICHEN PLANUS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- ORAL MUCOSA HAEMATOMA	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- SALIVA ALTERED	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- STOMATITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- TOOTHACHE	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
INFECTIONS AND INFESTATIONS	3 (9)	4 (12)	6 (15)	8 (26)	21 (15)
- NASOPHARYNGITIS	0 (0)	2 (6)	2 (5)	3 (10)	7 (5)
- APPLICATION SITE INFECTION	0 (0)	0 (0)	2 (5)	2 (6)	4 (3)
- ORAL CANDIDIASIS	0 (0)	1 (3)	1 (3)	1 (3)	3 (2)
- URINARY TRACT INFECTION	2 (6)	0 (0)	0 (0)	1 (3)	3 (2)
- CYSTITIS	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- EYE INFECTION	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- ORAL FUNGAL INFECTION	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- PULPITIS DENTAL	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- VARICELLA ZOSTER VIRUS INFECTION	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- VIRAL SINUSITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- VULVOVAGINAL MYCOTIC INFECTION	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (9)	4 (12)	4 (10)	1 (3)	12 (9)
- APPLICATION SITE HAEMORRHAGE	2 (6)	1 (3)	1 (3)	0 (0)	4 (3)

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
- APPLICATION SITE PAIN	1 (3)	0 (0)	2 (5)	0 (0)	3 (2)
- FACIAL PAIN	1 (3)	0 (0)	0 (0)	1 (3)	2 (1)
- APPLICATION SITE HYPERSENSITIVITY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- APPLICATION SITE INJURY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- APPLICATION SITE PLAQUE	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- FATIGUE	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- MALAISE	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- PAIN	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
NERVOUS SYSTEM DISORDERS	6 (18)	1 (3)	3 (8)	0 (0)	10 (7)
- HEADACHE	4 (12)	1 (3)	0 (0)	0 (0)	5 (4)
- DIZZINESS	3 (9)	0 (0)	1 (3)	0 (0)	4 (3)
- DYSGEUSIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- EPILEPSY	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- NEUROPATHY PERIPHERAL	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (3)	4 (12)	1 (3)	2 (6)	8 (6)
- BITE	0 (0)	1 (3)	0 (0)	1 (3)	2 (1)
- CONTUSION	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- MULTIPLE FRACTURES	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- MUSCLE STRAIN	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- TOOTH FRACTURE	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- TOOTH INJURY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
- TRAUMATIC ULCER	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (3)	1 (3)	0 (0)	2 (6)	4 (3)
- ASTHMA	1 (3)	0 (0)	0 (0)	1 (3)	2 (1)
- OROPHARYNGEAL PAIN	0 (0)	1 (3)	0 (0)	1 (3)	2 (1)
- COUGH	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
VASCULAR DISORDERS	0 (0)	2 (6)	0 (0)	2 (6)	4 (3)
- HYPERTENSION	0 (0)	1 (3)	0 (0)	2 (6)	3 (2)
- FLUSHING	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
PSYCHIATRIC DISORDERS	0 (0)	1 (3)	1 (3)	1 (3)	3 (2)
- INSOMNIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- RESTLESSNESS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- SLEEP DISORDER	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- STRESS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
EAR AND LABYRINTH DISORDERS	1 (3)	0 (0)	0 (0)	1 (3)	2 (1)
- EAR PAIN	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- INNER EAR DISORDER	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
INVESTIGATIONS	0 (0)	0 (0)	1 (3)	1 (3)	2 (1)
- HEART RATE INCREASED	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- HEPATIC ENZYME INCREASED	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (3)	0 (0)	0 (0)	1 (3)	2 (1)
- ARTHRALGIA	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
- BACK PAIN	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0)	1 (3)	0 (0)	1 (3)	2 (1)
- PRURITUS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- RASH PRURITIC	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- SENSITIVE SKIN	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- LYMPHADENOPATHY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
CARDIAC DISORDERS	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- ACUTE MYOCARDIAL INFARCTION	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
IMMUNE SYSTEM DISORDERS	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- ALLERGY TO CHEMICALS	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
METABOLISM AND NUTRITION DISORDERS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- TYPE 2 DIABETES MELLITUS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)

Listing(s): Derived from Listing 16.2.7.1

Table 14.3.1.3 Causally related adverse events by SOC and preferred term

a) related to clobetasol

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	2 (6)	2 (6)	7 (18)	5 (16)	16 (12)
INFECTIONS AND INFESTATIONS	0 (0)	1 (3)	4 (10)	3 (10)	8 (6)
- APPLICATION SITE INFECTION	0 (0)	0 (0)	2 (5)	2 (6)	4 (3)
- ORAL CANDIDIASIS	0 (0)	1 (3)	1 (3)	1 (3)	3 (2)
- ORAL FUNGAL INFECTION	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
GASTROINTESTINAL DISORDERS	1 (3)	1 (3)	2 (5)	1 (3)	5 (4)
- NAUSEA	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- DIARRHOEA	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- GINGIVAL BLEEDING	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- GINGIVAL PAIN	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- ORAL PAIN	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- STOMATITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (3)	1 (3)	2 (5)	0 (0)	4 (3)
- APPLICATION SITE PAIN	1 (3)	0 (0)	2 (5)	0 (0)	3 (2)
- APPLICATION SITE HYPERSENSITIVITY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- FACIAL PAIN	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
NERVOUS SYSTEM DISORDERS	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- DYSGEUSIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- HEADACHE	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
PSYCHIATRIC DISORDERS	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- SLEEP DISORDER	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
Listing(s): Derived from Listing 16.2.7.1					

Table 14.3.1.3 Causally related adverse events by SOC and preferred term: b) related to patch application

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	2 (6)	6 (18)	5 (13)	3 (10)	16 (12)
GASTROINTESTINAL DISORDERS	1 (3)	4 (12)	2 (5)	2 (6)	9 (7)
- SALIVARY HYPERSECRETION	0 (0)	2 (6)	0 (0)	1 (3)	3 (2)
- GINGIVAL BLEEDING	0 (0)	1 (3)	1 (3)	0 (0)	2 (1)
- NAUSEA	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- DIARRHOEA	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- GINGIVAL PAIN	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- ORAL LICHEN PLANUS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- ORAL PAIN	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- SALIVA ALTERED	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- STOMATITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (6)	2 (6)	3 (8)	0 (0)	7 (5)
- APPLICATION SITE PAIN	1 (3)	0 (0)	2 (5)	0 (0)	3 (2)

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
- APPLICATION SITE HAEMORRHAGE	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- APPLICATION SITE HYPERSENSITIVITY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- APPLICATION SITE INJURY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- FACIAL PAIN	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
INFECTIONS AND INFESTATIONS	0 (0)	1 (3)	0 (0)	1 (3)	2 (1)
- APPLICATION SITE INFECTION	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- ORAL CANDIDIASIS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
NERVOUS SYSTEM DISORDERS	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- DYSGEUSIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- HEADACHE	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)

Listing(s): Derived from Listing 16.2.7.1

Table 14.3.1.4 Adverse events for each intensity by SOC and preferred term

a) AEs with severe intensity

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	2 (6)	1 (3)	1 (3)	1 (3)	5 (4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0)	1 (3)	1 (3)	0 (0)	2 (1)
- MULTIPLE FRACTURES	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- TOOTH INJURY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
CARDIAC DISORDERS	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- ACUTE MYOCARDIAL INFARCTION	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
GASTROINTESTINAL DISORDERS	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- PERIODONTAL DISEASE	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
VASCULAR DISORDERS	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- HYPERTENSION	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
Listing(s): Derived from Listing 16.2.7.2					

14.3.1.4 Adverse events for each intensity by SOC and preferred term: b) AEs with moderate intensity

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	9 (27)	6 (18)	6 (15)	8 (26)	29 (21)
GASTROINTESTINAL DISORDERS	3 (9)	4 (12)	3 (8)	3 (10)	13 (9)
- PERIODONTAL DISEASE	3 (9)	2 (6)	2 (5)	2 (6)	9 (7)
- SALIVARY HYPERSECRETION	1 (3)	2 (6)	0 (0)	0 (0)	3 (2)
- GINGIVAL BLEEDING	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- ORAL PAIN	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- STOMATITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- TOOTHACHE	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
INFECTIONS AND INFESTATIONS	2 (6)	2 (6)	2 (5)	4 (13)	10 (7)
- NASOPHARYNGITIS	0 (0)	0 (0)	1 (3)	2 (6)	3 (2)
- APPLICATION SITE INFECTION	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- CYSTITIS	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- ORAL CANDIDIASIS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- PULPITIS DENTAL	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- VARICELLA ZOSTER VIRUS INFECTION	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- VIRAL SINUSITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- VULVOVAGINAL MYCOTIC INFECTION	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (6)	2 (6)	0 (0)	0 (0)	4 (3)
- APPLICATION SITE HAEMORRHAGE	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
- APPLICATION SITE HYPERSENSITIVITY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- APPLICATION SITE INJURY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- FACIAL PAIN	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- FATIGUE	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
NERVOUS SYSTEM DISORDERS	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- DIZZINESS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- HEADACHE	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
IMMUNE SYSTEM DISORDERS	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- ALLERGY TO CHEMICALS	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- ARTHRALGIA	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
PSYCHIATRIC DISORDERS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- INSOMNIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- STRESS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- ASTHMA	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- PRURITUS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)

Listing(s): Derived from Listing 16.2.7.1

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

Table 14.3.2.1 Summary of serious adverse events by SOC and preferred term

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
CARDIAC DISORDERS	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
- ACUTE MYOCARDIAL INFARCTION	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- MULTIPLE FRACTURES	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
Listing(s): Derived from Listing 16.2.7.1					

14.3.3 Other clinically meaningful adverse events

Table 14.3.3.1 Summary of discontinuations of treatment due to AEs by SOC and preferred term

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	0 (0)	0 (0)	1 (3)	1 (3)	2 (1)
GASTROINTESTINAL DISORDERS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- ORAL PAIN	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- STOMATITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
INFECTIONS AND INFESTATIONS	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- VARICELLA ZOSTER VIRUS INFECTION	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
PSYCHIATRIC DISORDERS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- INSOMNIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
Listing(s): Derived from Listing 16.2.7.3					

Table 14.3.3.2 Summary of adverse events reported as oral candidiasis/oral fungal infection / application site infection during the study

Subject no./ Age (yrs)/ Sex/ Race/ Treatment	Country	Diagn. duration (yrs)	No. patch	AE symptom	Start day/ Stop day	Severity	Action taken	Other action	Causality
301001/ 71/ F/ WHITE/ C	DNK	1.0	4	ORAL CANDIDOSIS	13/31	MODERATE	DOSE NOT CHANGED	Concomitant treatment	PROBABLY RELATED
301002/ 74/ F/ WHITE/ A	DNK	12.0	2	ORAL CANDIDOSIS	22/42	MILD	DOSE NOT CHANGED	Other action	POSSIBLY RELATED
301003/ 74/ F/ WHITE/ B	DNK	4.6	1	ORAL FUNGAL INFECTION	9/12	MILD	NOT APPLICABLE	Concomitant treatment	POSSIBLY RELATED
301009/ 76/ F/ WHITE/ B	DNK	12.9	3	ORAL CANDIDIASIS	29/40	MILD	DOSE NOT CHANGED	Other action	POSSIBLY RELATED
400011/ 72/ F/ WHITE/ B	USA	3.0	5	APPLICATION SITE INFECTION*	10/15	MILD	DOSE NOT CHANGED	Concomitant treatment	RELATED
400011/ 72/ F/ WHITE/ B	USA	3.0	5	APPLICATION SITE INFECTION*	29/43	MILD	DOSE NOT CHANGED	Concomitant treatment	RELATED
400012/ 57/ M/ WHITE/ B	USA	1.1	6	APPLICATION SITE INFECTION*	8/17	MILD	DOSE NOT CHANGED	Concomitant treatment	PROBABLY RELATED
400012/ 57/ M/ WHITE/ B	USA	1.1	6	APPLICATION SITE INFECTION*	22/29	MILD	DOSE NOT CHANGED	Concomitant treatment	PROBABLY RELATED
410008/ 55/ F/ WHITE/ A	USA	0.0	5	APPLICATION SITE INFECTION*	30/59	MILD	NOT APPLICABLE	Concomitant treatment	PROBABLY RELATED

Subject no./ Age (yrs)/ Sex/ Race/ Treatment	Country	Diagn. duration (yrs)	No. patch	AE symptom	Start day/ Stop day	Severity	Action taken	Other action	Causality
411003/ 77/ F/ WHITE/ A	USA	0.4	4	APPLICATION SITE INFECTION*	37/44	MODERATE	NOT APPLICABLE	Other action	POSSIBLY RELATED

A = placebo, B = 1 ug, C = 5 ug, D = 20 ug
F = Female, M = Male, DNK = Denmark
*(pseudomembraneous) candidiasis at application site

Table 14.3.3.3 Summary of adverse events in oral cavity causally related to clobetasol treatment by SOC and preferred term

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	1 (3)	2 (6)	7 (18)	3 (10)	13 (9)
INFECTIONS AND INFESTATIONS	0 (0)	1 (3)	4 (10)	3 (10)	8 (6)
- APPLICATION SITE INFECTION	0 (0)	0 (0)	2 (5)	2 (6)	4 (3)
- ORAL CANDIDIASIS	0 (0)	1 (3)	1 (3)	1 (3)	3 (2)
- ORAL FUNGAL INFECTION	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (3)	1 (3)	2 (5)	0 (0)	4 (3)
- APPLICATION SITE PAIN	1 (3)	0 (0)	2 (5)	0 (0)	3 (2)
- APPLICATION SITE HYPERSENSITIVITY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
GASTROINTESTINAL DISORDERS	0 (0)	1 (3)	1 (3)	0 (0)	2 (1)
- GINGIVAL BLEEDING	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- GINGIVAL PAIN	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
- ORAL PAIN	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- STOMATITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
NERVOUS SYSTEM DISORDERS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- DYSGEUSIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
Listing(s): Derived from Listing 16.2.7.1					

Table 14.3.3.4 Summary of adverse events in oral cavity causally related to patch applications by SOC and preferred term

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
ANY ADVERSE EVENT	2 (6)	6 (18)	5 (13)	2 (6)	15 (11)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (6)	2 (6)	3 (8)	0 (0)	7 (5)
- APPLICATION SITE PAIN	1 (3)	0 (0)	2 (5)	0 (0)	3 (2)
- APPLICATION SITE HAEMORRHAGE	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
- APPLICATION SITE HYPERSENSITIVITY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- APPLICATION SITE INJURY	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
GASTROINTESTINAL DISORDERS	0 (0)	4 (12)	1 (3)	1 (3)	6 (4)
- SALIVARY HYPERSECRETION	0 (0)	2 (6)	0 (0)	1 (3)	3 (2)
- GINGIVAL BLEEDING	0 (0)	1 (3)	1 (3)	0 (0)	2 (1)
- GINGIVAL PAIN	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- ORAL LICHEN PLANUS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)

System Organ Class/Preferred term	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31	Total, N=138
- ORAL PAIN	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- SALIVA ALTERED	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
- STOMATITIS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
INFECTIONS AND INFESTATIONS	0 (0)	1 (3)	0 (0)	1 (3)	2 (1)
- APPLICATION SITE INFECTION	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
- ORAL CANDIDIASIS	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
NERVOUS SYSTEM DISORDERS	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
- DYSGEUSIA	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
Listing(s): Derived from Listing 16.2.7.1					

14.3.4 Laboratory values

Table 14.3.4.1 Summary statistics by visit with difference from baseline for laboratory data

a) Haematology

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Hemoglobin (g/dL)	Baseline	n	33	33	40	31
		Mean(SD)	13.92 (1.34)	14.01 (1.24)	13.64 (1.13)	13.83 (0.99)
		Median	14.20	14.01	13.79	13.70
		Min, Max	11.1-16.7	10.6-16.3	11.0-16.4	12.2-16.0
	Follow-up	n	29	33	36	30
		Mean(SD)	13.91 (1.24)	14.00 (1.23)	13.52 (1.14)	13.64 (0.97)
		Median	14.01	14.00	13.61	13.61
		Min, Max	11.4-16.7	10.0-16.1	11.0-15.6	11.4-15.5
	Change from baseline	n	29	32	36	30
		Mean(SD)	-0.00 (0.59)	-0.05 (0.49)	-0.08 (0.47)	-0.17 (0.55)
		Median	0.00	0.00	-0.16	-0.18
		Min, Max	-0.8-1.8	-1.3-0.8	-1.1-1.3	-1.2-0.8
Platelets (10^9/L)	Baseline	n	33	33	40	31
		Mean(SD)	254.00 (73.22)	244.58 (52.33)	250.43 (62.83)	259.13 (57.42)
		Median	246.00	243.00	254.00	257.00
		Min, Max	84.0-486.0	125.0-349.0	112.0-383.0	122.0-368.0
	Follow-up	n	29	33	36	30
		Mean(SD)	247.62 (60.91)	239.36 (67.81)	247.03 (61.95)	263.70 (70.40)

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Median	240.00	241.00	254.00	241.50
		Min, Max	89.0-383.0	43.0-384.0	103.0-365.0	147.0-454.0
	Change from baseline	n	29	32	36	30
		Mean(SD)	0.00 (23.23)	-3.63 (41.69)	-4.42 (26.85)	3.13 (39.02)
		Median	0.00	0.00	-2.00	-1.50
		Min, Max	-70.0-44.0	-193.0-68.0	-119.0-56.0	-46.0-172.0
Erythrocytes (10^12/L)	Baseline	n	33	33	40	31
		Mean(SD)	4.53 (0.41)	4.65 (0.36)	4.58 (0.38)	4.57 (0.37)
		Median	4.50	4.59	4.51	4.59
		Min, Max	3.8-5.3	4.0-5.3	3.7-5.5	4.0-5.1
	Follow-up	n	29	33	36	30
		Mean(SD)	4.54 (0.38)	4.64 (0.38)	4.56 (0.42)	4.46 (0.34)
		Median	4.50	4.54	4.53	4.49
		Min, Max	3.9-5.1	3.8-5.5	3.8-5.7	3.9-5.1
	Change from baseline	n	29	32	36	30
		Mean(SD)	0.01 (0.17)	-0.02 (0.16)	-0.03 (0.20)	-0.09 (0.15)
		Median	0.00	-0.01	-0.06	-0.10
		Min, Max	-0.2-0.6	-0.4-0.3	-0.5-0.7	-0.4-0.2
Leukocytes (10^9/L)	Baseline	n	33	33	40	31
		Mean(SD)	6.86 (2.69)	6.36 (1.34)	6.91 (1.65)	6.81 (1.65)
		Median	6.20	6.30	7.00	6.60

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Min, Max	3.0-18.0	3.6-10.3	2.9-10.6	3.7-10.3
	Follow-up	n	29	33	36	30
		Mean(SD)	6.64 (1.80)	6.61 (1.55)	6.67 (1.80)	6.58 (1.72)
		Median	6.50	6.40	6.65	6.20
		Min, Max	3.9-9.9	4.3-10.7	3.3-11.8	3.4-9.6
	Change from baseline	n	29	32	36	30
		Mean(SD)	-0.31 (2.00)	0.23 (1.16)	-0.15 (1.17)	-0.28 (1.06)
		Median	-0.30	0.10	-0.20	-0.25
		Min, Max	-8.6-2.6	-1.6-2.5	-2.5-3.1	-2.4-2.5
Neutrophils (10^9/L)	Baseline	n	33	33	40	31
		Mean(SD)	4.24 (2.39)	3.86 (1.20)	4.25 (1.29)	4.07 (1.38)
		Median	3.71	4.12	4.04	3.98
		Min, Max	1.0-14.9	2.0-7.5	1.5-6.7	1.3-6.6
	Follow-up	n	29	33	36	30
		Mean(SD)	4.08 (1.53)	4.09 (1.36)	3.89 (1.23)	3.93 (1.25)
		Median	3.56	3.98	3.72	3.58
		Min, Max	1.8-7.4	2.2-8.1	1.9-7.6	1.1-6.3
	Change from baseline	n	29	32	36	30
		Mean(SD)	-0.24 (1.90)	0.25 (1.05)	-0.32 (0.97)	-0.18 (0.84)
		Median	-0.17	0.03	-0.35	-0.15
		Min, Max	-8.3-3.1	-1.1-3.7	-2.7-1.7	-2.0-2.1

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Neutrophils/Leukocytes (%)	Baseline	n	33	33	40	31
		Mean(SD)	59.70 (9.97)	60.06 (10.95)	60.87 (8.20)	58.47 (9.69)
		Median	59.80	61.90	61.00	59.90
		Min, Max	34.6-82.6	36.4-78.5	44.8-83.4	33.8-70.6
	Follow-up	n	29	33	36	30
		Mean(SD)	60.45 (8.94)	61.00 (8.77)	58.21 (9.15)	58.92 (7.87)
		Median	60.70	61.30	59.10	59.35
		Min, Max	41.0-77.7	41.5-78.4	36.3-74.5	32.3-72.3
	Change from baseline	n	29	32	36	30
		Mean(SD)	0.08 (7.10)	1.28 (7.44)	-2.72 (6.02)	0.39 (6.18)
		Median	0.00	0.30	-1.75	-0.45
		Min, Max	-12.6-18.7	-15.7-22.0	-15.5-6.6	-12.5-21.3
Monocytes (10^9/L)	Baseline	n	33	33	40	31
		Mean(SD)	0.43 (0.15)	0.49 (0.20)	0.51 (0.15)	0.54 (0.14)
		Median	0.39	0.47	0.49	0.52
		Min, Max	0.2-1.0	0.2-1.1	0.2-0.8	0.3-0.8
	Follow-up	n	29	33	36	30
		Mean(SD)	0.43 (0.13)	0.52 (0.16)	0.53 (0.17)	0.52 (0.16)
		Median	0.42	0.50	0.50	0.52
		Min, Max	0.3-0.8	0.2-1.1	0.3-1.0	0.3-0.9
	Change from baseline	n	29	32	36	30

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Mean(SD)	0.01 (0.11)	0.03 (0.14)	0.03 (0.09)	-0.03 (0.12)
		Median	0.03	0.02	0.04	-0.04
		Min, Max	-0.3-0.2	-0.4-0.3	-0.2-0.2	-0.3-0.3
Monocytes/Leukocytes (%)	Baseline	n	33	33	40	31
		Mean(SD)	6.48 (1.85)	7.60 (2.12)	7.47 (1.95)	8.15 (2.56)
		Median	6.10	7.30	7.60	7.90
		Min, Max	3.4-11.6	3.4-13.0	3.9-11.3	4.9-19.9
	Follow-up	n	29	33	36	30
		Mean(SD)	6.68 (1.89)	7.95 (1.84)	8.03 (1.92)	8.07 (2.40)
		Median	6.60	8.10	7.70	7.80
		Min, Max	3.8-12.6	4.3-11.7	4.9-12.8	4.9-18.4
	Change from baseline	n	29	32	36	30
		Mean(SD)	0.32 (1.62)	0.28 (1.82)	0.57 (1.43)	-0.13 (1.48)
		Median	0.40	0.35	0.25	0.20
		Min, Max	-3.9-3.5	-3.2-3.8	-1.7-3.8	-3.8-2.5
Lymphocytes (10^9/L)	Baseline	n	33	33	40	31
		Mean(SD)	1.97 (0.62)	1.77 (0.63)	1.86 (0.53)	1.94 (0.55)
		Median	1.83	1.81	1.87	1.94
		Min, Max	0.8-3.9	0.6-3.3	0.9-3.0	1.3-3.5
	Follow-up	n	29	33	36	30
		Mean(SD)	1.91 (0.53)	1.76 (0.56)	1.93 (0.75)	1.86 (0.53)

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Median	2.01	1.72	1.76	1.86
		Min, Max	0.8-2.9	0.8-3.0	1.0-4.2	1.1-3.0
	Change from baseline	n	29	32	36	30
		Mean(SD)	-0.06 (0.39)	-0.04 (0.46)	0.10 (0.38)	-0.09 (0.41)
		Median	-0.04	-0.05	0.07	-0.14
		Min, Max	-1.1-0.5	-1.0-1.0	-0.6-1.3	-1.2-0.9
Lymphocytes/Leukocytes (%)	Baseline	n	33	33	40	31
		Mean(SD)	30.26 (8.46)	28.42 (10.22)	27.73 (7.27)	29.40 (8.35)
		Median	30.30	28.00	28.55	29.90
		Min, Max	10.7-49.9	10.5-46.2	11.1-42.7	17.8-55.0
	Follow-up	n	29	33	36	30
		Mean(SD)	29.57 (7.69)	27.34 (8.52)	29.02 (8.03)	28.73 (5.81)
		Median	29.10	27.20	29.10	28.95
		Min, Max	15.2-46.9	12.1-44.4	18.2-46.6	18.0-41.7
	Change from baseline	n	29	32	36	30
		Mean(SD)	-0.12 (5.49)	-1.38 (5.81)	1.39 (4.98)	-0.54 (5.36)
		Median	1.10	-0.35	1.10	-0.30
		Min, Max	-14.1-9.2	-15.7-10.7	-11.1-10.6	-20.2-8.9
Eosinophils (10^9/L)	Baseline	n	33	33	40	31
		Mean(SD)	0.18 (0.13)	0.20 (0.12)	0.23 (0.25)	0.20 (0.13)
		Median	0.15	0.17	0.16	0.15

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Min, Max	0.0-0.6	0.0-0.6	0.0-1.3	0.1-0.5
	Follow-up	n	29	33	36	30
		Mean(SD)	0.17 (0.11)	0.19 (0.10)	0.28 (0.26)	0.21 (0.15)
		Median	0.15	0.17	0.19	0.16
		Min, Max	0.0-0.5	0.0-0.4	0.0-1.4	0.1-0.7
	Change from baseline	n	29	32	36	30
		Mean(SD)	-0.02 (0.08)	-0.01 (0.09)	0.04 (0.08)	0.00 (0.08)
		Median	-0.02	-0.01	0.02	0.00
		Min, Max	-0.3-0.1	-0.2-0.2	-0.1-0.3	-0.2-0.2
Eosinophils/Leukocytes (%)	Baseline	n	33	33	40	31
		Mean(SD)	2.95 (2.21)	3.17 (1.89)	3.18 (2.85)	3.09 (2.13)
		Median	2.30	2.90	2.25	2.60
		Min, Max	0.6-8.4	0.6-9.8	0.4-14.6	0.7-9.7
	Follow-up	n	29	33	36	30
		Mean(SD)	2.60 (1.64)	2.96 (1.63)	3.98 (3.05)	3.27 (2.55)
		Median	2.10	2.80	2.90	2.50
		Min, Max	0.6-7.0	0.4-7.4	0.5-14.3	0.7-13.1
	Change from baseline	n	29	32	36	30
		Mean(SD)	-0.36 (1.40)	-0.18 (1.39)	0.72 (1.17)	0.15 (1.24)
		Median	0.00	-0.10	0.40	0.30
		Min, Max	-3.6-1.5	-4.8-2.3	-0.8-4.4	-3.5-3.4

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Basophils (10^9/L)	Baseline	n	33	33	40	31
		Mean(SD)	0.04 (0.02)	0.05 (0.03)	0.05 (0.03)	0.06 (0.03)
		Median	0.04	0.05	0.05	0.05
		Min, Max	0.0-0.1	0.0-0.1	0.0-0.1	0.0-0.1
	Follow-up	n	29	33	36	30
		Mean(SD)	0.04 (0.02)	0.05 (0.02)	0.05 (0.03)	0.07 (0.03)
		Median	0.04	0.05	0.05	0.06
		Min, Max	0.0-0.1	0.0-0.1	0.0-0.1	0.0-0.2
	Change from baseline	n	29	32	36	30
		Mean(SD)	0.00 (0.02)	-0.00 (0.03)	-0.00 (0.02)	0.01 (0.03)
		Median	0.00	0.00	0.00	0.00
		Min, Max	-0.0-0.1	-0.1-0.1	-0.1-0.1	-0.0-0.1
Basophils/Leukocytes (%)	Baseline	n	33	33	40	31
		Mean(SD)	0.606 (0.26)	0.764 (0.39)	0.770 (0.33)	0.842 (0.42)
		Median	0.500	0.700	0.700	0.900
		Min, Max	0.20-1.30	0.00-1.90	0.20-1.60	0.00-1.70
	Follow-up	n	29	32	36	30
		Mean(SD)	0.710 (0.38)	0.763 (0.29)	0.764 (0.36)	1.003 (0.47)
		Median	0.600	0.700	0.700	0.950
		Min, Max	0.10-1.60	0.20-1.60	0.00-1.40	0.10-2.00
	Change from baseline	n	29	32	36	30

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Mean(SD)	0.076 (0.33)	0.006 (0.40)	0.011 (0.43)	0.177 (0.50)
		Median	0.000	0.000	0.100	0.100
		Min, Max	-0.50-1.10	-1.50-0.90	-0.80-1.20	-0.70-1.60

BMI=Body mass index;
Listing(s): Derived from Listing 16.2.8.1

14.3.4.1 Summary statistics by visit with difference from baseline for laboratory data: b) Clinical chemistry

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Albumin (g/L)	Baseline	n	33	33	40	31
		Mean(SD)	43.03 (2.91)	43.36 (2.76)	42.93 (3.25)	43.10 (2.10)
		Median	43.00	44.00	43.00	43.00
		Min, Max	36.0-48.0	38.0-49.0	31.0-48.0	39.0-47.0
	Follow-up	n	30	34	38	31
		Mean(SD)	43.00 (2.83)	43.18 (2.28)	42.45 (3.25)	42.87 (2.49)
		Median	43.00	42.50	42.50	43.00
		Min, Max	36.0-48.0	40.0-48.0	32.0-48.0	39.0-47.0
	Change from baseline	n	30	33	38	31
		Mean(SD)	-0.10 (2.20)	-0.15 (2.35)	-0.34 (2.00)	-0.23 (1.84)
		Median	0.00	0.00	0.00	0.00
		Min, Max	-4.0-6.0	-5.0-4.0	-5.0-3.0	-4.0-4.0

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Alkaline Phosphatase (U/L)	Baseline	n	33	33	40	31
		Mean(SD)	76.45 (28.30)	65.91 (16.67)	74.53 (26.58)	74.23 (21.79)
		Median	74.00	68.00	70.00	71.00
		Min, Max	31.0-164.0	28.0-97.0	35.0-185.0	46.0-136.0
	Follow-up	n	30	34	38	31
		Mean(SD)	74.33 (30.57)	64.43 (19.89)	73.63 (26.94)	72.55 (21.73)
		Median	72.00	65.00	69.50	70.00
		Min, Max	27.0-190.0	2.5-112.0	33.0-174.0	44.0-144.0
	Change from baseline	n	30	33	38	31
		Mean(SD)	-0.27 (8.42)	-1.23 (14.36)	-1.21 (9.72)	-1.68 (6.42)
		Median	-1.50	2.00	-2.00	-1.00
		Min, Max	-18.0-26.0	-68.5-20.0	-24.0-26.0	-16.0-11.0
Alanine Aminotransferase (U/L)	Baseline	n	33	33	40	31
		Mean(SD)	30.61 (24.90)	26.94 (13.88)	25.30 (18.64)	22.35 (9.27)
		Median	24.00	23.00	21.00	21.00
		Min, Max	9.0-144.0	11.0-61.0	4.0-90.0	9.0-55.0
	Follow-up	n	30	34	38	31
		Mean(SD)	35.30 (32.42)	25.94 (15.11)	26.00 (27.11)	22.29 (9.69)
		Median	25.50	23.50	19.00	20.00
		Min, Max	10.0-171.0	9.0-67.0	4.0-160.0	10.0-47.0
	Change from baseline	n	30	33	38	31

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Mean(SD)	3.90 (10.91)	-2.00 (10.45)	0.68 (14.73)	-0.06 (5.51)
		Median	0.50	-2.00	-1.00	0.00
		Min, Max	-10.0-31.0	-31.0-29.0	-20.0-74.0	-8.0-17.0
Aspartate Aminotransferase (U/L)	Baseline	n	33	33	40	31
		Mean(SD)	26.61 (16.17)	23.61 (7.81)	25.40 (14.41)	21.19 (6.84)
		Median	23.00	23.00	21.00	20.00
		Min, Max	13.0-100.0	12.0-42.0	10.0-79.0	11.0-49.0
	Follow-up	n	30	34	38	31
		Mean(SD)	29.20 (22.04)	22.97 (9.06)	24.26 (16.76)	22.35 (7.04)
		Median	23.00	21.50	19.50	21.00
		Min, Max	13.0-127.0	12.0-51.0	10.0-110.0	13.0-43.0
	Change from baseline	n	30	33	38	31
		Mean(SD)	2.07 (7.26)	-1.39 (6.95)	-1.26 (9.80)	1.16 (5.73)
		Median	0.00	-1.00	-1.00	0.00
		Min, Max	-7.0-27.0	-16.0-26.0	-40.0-31.0	-7.0-20.0
Bilirubin (mg/dL)	Baseline	n	33	33	40	31
		Mean(SD)	0.49 (0.34)	0.55 (0.30)	0.48 (0.24)	0.50 (0.27)
		Median	0.38	0.46	0.44	0.43
		Min, Max	0.1-1.8	0.2-1.4	0.1-1.3	0.1-1.2
	Follow-up	n	30	34	38	31
		Mean(SD)	0.48 (0.28)	0.54 (0.27)	0.46 (0.25)	0.52 (0.27)

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Median	0.39	0.45	0.37	0.43
		Min, Max	0.2-1.5	0.2-1.3	0.2-1.1	0.2-1.2
	Change from baseline	n	30	33	38	31
		Mean(SD)	-0.02 (0.18)	-0.02 (0.16)	-0.02 (0.16)	0.01 (0.13)
		Median	0.00	-0.02	-0.04	0.00
		Min, Max	-0.6-0.3	-0.5-0.5	-0.4-0.5	-0.2-0.5
Creatine Kinase (U/L)	Baseline	n	33	33	40	31
		Mean(SD)	110.52 (78.77)	118.64 (76.27)	105.33 (65.07)	97.39 (53.42)
		Median	98.00	95.00	83.50	85.00
		Min, Max	34.0-375.0	28.0-395.0	34.0-347.0	28.0-324.0
	Follow-up	n	30	34	38	31
		Mean(SD)	107.00 (76.53)	104.31 (79.55)	102.87 (46.65)	110.00 (78.53)
		Median	77.50	87.50	96.50	88.00
		Min, Max	31.0-389.0	3.5-426.0	28.0-219.0	34.0-401.0
	Change from baseline	n	30	33	38	31
		Mean(SD)	0.70 (23.84)	-14.20 (61.60)	-3.66 (42.02)	12.61 (71.50)
		Median	4.50	-11.00	2.00	1.00
		Min, Max	-51.0-66.0	-206.0-145.0	-148.0-55.0	-56.0-373.0
Creatinine (mg/dL)	Baseline	n	33	33	40	31
		Mean(SD)	0.79 (0.15)	0.86 (0.24)	0.80 (0.17)	0.83 (0.19)
		Median	0.75	0.81	0.78	0.77

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Min, Max	0.5-1.1	0.5-1.8	0.5-1.3	0.6-1.3
	Follow-up	n	30	34	38	31
		Mean(SD)	0.82 (0.17)	0.86 (0.20)	0.81 (0.19)	0.81 (0.17)
		Median	0.82	0.87	0.79	0.74
		Min, Max	0.5-1.2	0.6-1.6	0.5-1.4	0.6-1.3
	Change from baseline	n	30	33	38	31
		Mean(SD)	0.02 (0.08)	0.01 (0.08)	0.02 (0.08)	-0.02 (0.12)
		Median	0.03	0.01	0.02	-0.01
		Min, Max	-0.1-0.2	-0.2-0.2	-0.2-0.2	-0.6-0.2
Potassium (mmol/L)	Baseline	n	33	33	40	31
		Mean(SD)	4.27 (0.43)	4.45 (0.45)	4.37 (0.43)	4.41 (0.30)
		Median	4.20	4.40	4.40	4.40
		Min, Max	3.6-5.6	3.4-5.8	3.2-5.3	3.8-5.1
	Follow-up	n	30	34	38	31
		Mean(SD)	4.30 (0.32)	4.38 (0.42)	4.36 (0.34)	4.39 (0.35)
		Median	4.30	4.30	4.35	4.40
		Min, Max	3.7-5.0	3.4-5.3	3.7-5.1	3.6-5.3
	Change from baseline	n	30	33	38	31
		Mean(SD)	-0.02 (0.27)	-0.08 (0.47)	-0.01 (0.37)	-0.03 (0.33)
		Median	0.00	0.00	-0.05	-0.10
		Min, Max	-0.6-0.4	-1.1-0.8	-0.7-0.9	-0.6-1.0

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Sodium (mmol/L)	Baseline	n	33	33	40	31
		Mean(SD)	139.52 (2.20)	139.52 (2.37)	139.68 (2.93)	138.97 (2.48)
		Median	139.00	139.00	140.00	139.00
		Min, Max	134.0-144.0	135.0-146.0	131.0-147.0	133.0-143.0
	Follow-up	n	30	34	38	31
		Mean(SD)	139.57 (2.24)	139.85 (2.06)	139.95 (2.61)	139.06 (2.13)
		Median	139.50	140.00	140.00	139.00
		Min, Max	135.0-143.0	133.0-145.0	132.0-146.0	135.0-144.0
	Change from baseline	n	30	33	38	31
		Mean(SD)	0.00 (1.74)	0.33 (2.20)	0.13 (2.47)	0.10 (2.23)
		Median	0.00	0.00	0.00	0.00
		Min, Max	-3.0-3.0	-4.0-5.0	-6.0-6.0	-4.0-6.0
Listing(s): Derived from Listing 16.2.8.1						

14.3.4.1 Summary statistics by visit with difference from baseline for laboratory data: c) Urinalysis

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
§ Glucose	Baseline	NEGATIVE	30 (90.9)	31 (93.9)	34 (87.2)	30 (96.8)
		1+	2 (6.1)	0 (0.0)	2 (5.1)	0 (0.0)
		2+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		3+	0 (0.0)	2 (6.1)	1 (2.6)	1 (3.2)

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		4+	1 (3.0)	0 (0.0)	2 (5.1)	0 (0.0)
	Follow-up	NEGATIVE	31 (96.9)	32 (94.1)	36 (94.7)	29 (96.7)
		1+	1 (3.1)	2 (5.9)	0 (0.0)	0 (0.0)
		2+	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
		3+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		4+	0 (0.0)	0 (0.0)	2 (5.3)	0 (0.0)
Hemoglobin	Baseline	NORMAL	26 (78.8)	30 (90.9)	37 (94.9)	26 (83.9)
		1+	5 (15.2)	2 (6.1)	0 (0.0)	4 (12.9)
		2+	2 (6.1)	1 (3.0)	1 (2.6)	0 (0.0)
		3+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		4+	0 (0.0)	0 (0.0)	1 (2.6)	1 (3.2)
	Follow-up	NORMAL	28 (87.5)	33 (97.1)	33 (86.8)	26 (86.7)
		1+	3 (9.4)	1 (2.9)	3 (7.9)	4 (13.3)
		2+	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
		3+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		4+	0 (0.0)	0 (0.0)	2 (5.3)	0 (0.0)
Protein	Baseline	NORMAL	29 (87.9)	32 (97.0)	36 (92.3)	27 (87.1)
		1+	4 (12.1)	1 (3.0)	3 (7.7)	4 (12.9)
		2+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		3+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		4+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Follow-up	NORMAL	26 (81.3)	31 (91.2)	35 (92.1)	26 (86.7)
		1+	6 (18.8)	3 (8.8)	3 (7.9)	3 (10.0)
		2+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		3+	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
		4+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

BMI=Body mass index;
Listing(s): Derived from Listing 16.2.8.1

Table 14.3.4.2 Shift table of out-of range values on laboratory data

a) Summary of abnormal haematology values by visit

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Basophils (10^9/L)	Baseline	n	33	33	40	31
		Normal	32 (97.0)	30 (90.9)	35 (87.5)	24 (77.4)
		Abnormal NCS	1 (3.0)	3 (9.1)	5 (12.5)	7 (22.6)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	29	33	36	30
		Normal	28 (96.6)	32 (97.0)	31 (86.1)	21 (70.0)
		Abnormal NCS	1 (3.4)	1 (3.0)	5 (13.9)	9 (30.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Basophils/Leukocytes (%)	Baseline	n	33	33	40	31

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Normal	33 (100.0)	31 (93.9)	39 (97.5)	30 (96.8)
		Abnormal NCS	0 (0.0)	2 (6.1)	1 (2.5)	1 (3.2)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	29	33	36	30
		Normal	28 (96.6)	32 (97.0)	36 (100.0)	25 (83.3)
		Abnormal NCS	1 (3.4)	1 (3.0)	0 (0.0)	5 (16.7)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eosinophils (10^9/L)	Baseline	n	33	33	40	31
		Normal	30 (90.9)	31 (93.9)	35 (87.5)	27 (87.1)
		Abnormal NCS	3 (9.1)	2 (6.1)	5 (12.5)	4 (12.9)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	29	33	36	30
		Normal	28 (96.6)	30 (90.9)	28 (77.8)	26 (86.7)
		Abnormal NCS	1 (3.4)	3 (9.1)	8 (22.2)	4 (13.3)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eosinophils/Leukocytes (%)	Baseline	n	33	33	40	31
		Normal	29 (87.9)	32 (97.0)	35 (87.5)	28 (90.3)
		Abnormal NCS	4 (12.1)	1 (3.0)	5 (12.5)	3 (9.7)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	29	33	36	30
		Normal	29 (100.0)	30 (90.9)	30 (83.3)	27 (90.0)

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Abnormal NCS	0 (0.0)	3 (9.1)	6 (16.7)	3 (10.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Erythrocytes (10^12/L)	Baseline	n	33	33	40	31
		Normal	29 (87.9)	32 (97.0)	39 (97.5)	30 (96.8)
		Abnormal NCS	4 (12.1)	1 (3.0)	1 (2.5)	1 (3.2)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	29	33	36	30
		Normal	26 (89.7)	30 (90.9)	32 (88.9)	28 (93.3)
		Abnormal NCS	3 (10.3)	3 (9.1)	4 (11.1)	2 (6.7)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin (g/dL)	Baseline	n	33	33	40	31
		Normal	30 (90.9)	32 (97.0)	39 (97.5)	31 (100.0)
		Abnormal NCS	2 (6.1)	1 (3.0)	1 (2.5)	0 (0.0)
		Abnormal CS	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	29	33	36	30
		Normal	28 (96.6)	31 (93.9)	33 (91.7)	29 (96.7)
		Abnormal NCS	1 (3.4)	2 (6.1)	3 (8.3)	1 (3.3)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leukocytes (10^9/L)	Baseline	n	33	33	40	31
		Normal	29 (87.9)	31 (93.9)	37 (92.5)	29 (93.5)
		Abnormal NCS	4 (12.1)	2 (6.1)	3 (7.5)	2 (6.5)

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	29	33	36	30
		Normal	28 (96.6)	32 (97.0)	34 (94.4)	29 (96.7)
		Abnormal NCS	1 (3.4)	1 (3.0)	2 (5.6)	1 (3.3)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocytes (10^9/L)	Baseline	n	33	33	40	31
		Normal	32 (97.0)	30 (90.9)	38 (95.0)	29 (93.5)
		Abnormal NCS	1 (3.0)	3 (9.1)	2 (5.0)	2 (6.5)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	29	33	36	30
		Normal	28 (96.6)	30 (90.9)	32 (88.9)	27 (90.0)
		Abnormal NCS	1 (3.4)	3 (9.1)	4 (11.1)	3 (10.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocytes/Leukocytes (%)	Baseline	n	33	33	40	31
		Normal	30 (90.9)	30 (90.9)	39 (97.5)	30 (96.8)
		Abnormal NCS	3 (9.1)	3 (9.1)	1 (2.5)	1 (3.2)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	29	33	36	30
		Normal	29 (100.0)	30 (90.9)	36 (100.0)	30 (100.0)
		Abnormal NCS	0 (0.0)	3 (9.1)	0 (0.0)	0 (0.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Monocytes (10^9/L)	Baseline	n	33	33	40	31
		Normal	32 (97.0)	31 (93.9)	38 (95.0)	30 (96.8)
		Abnormal NCS	1 (3.0)	2 (6.1)	2 (5.0)	1 (3.2)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	29	33	36	30
		Normal	29 (100.0)	30 (90.9)	34 (94.4)	28 (93.3)
		Abnormal NCS	0 (0.0)	3 (9.1)	2 (5.6)	2 (6.7)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Monocytes/Leukocytes (%)	Baseline	n	33	33	40	31
		Normal	33 (100.0)	32 (97.0)	40 (100.0)	30 (96.8)
		Abnormal NCS	0 (0.0)	1 (3.0)	0 (0.0)	1 (3.2)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	29	33	36	30
		Normal	28 (96.6)	33 (100.0)	35 (97.2)	29 (96.7)
		Abnormal NCS	1 (3.4)	0 (0.0)	1 (2.8)	1 (3.3)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophils (10^9/L)	Baseline	n	33	33	40	31
		Normal	28 (84.8)	32 (97.0)	39 (97.5)	30 (96.8)
		Abnormal NCS	5 (15.2)	1 (3.0)	1 (2.5)	1 (3.2)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	29	33	36	30

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Normal	27 (93.1)	31 (93.9)	35 (97.2)	29 (96.7)
		Abnormal NCS	2 (6.9)	2 (6.1)	1 (2.8)	1 (3.3)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophils/Leukocytes (%)	Baseline	n	33	33	40	31
		Normal	29 (87.9)	30 (90.9)	39 (97.5)	29 (93.5)
		Abnormal NCS	4 (12.1)	3 (9.1)	1 (2.5)	2 (6.5)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	29	33	36	30
		Normal	28 (96.6)	31 (93.9)	34 (94.4)	29 (96.7)
		Abnormal NCS	1 (3.4)	2 (6.1)	2 (5.6)	1 (3.3)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Platelets (10^9/L)	Baseline	n	33	33	40	31
		Normal	28 (84.8)	31 (93.9)	37 (92.5)	29 (93.5)
		Abnormal NCS	4 (12.1)	2 (6.1)	3 (7.5)	2 (6.5)
		Abnormal CS	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	29	33	36	30
		Normal	27 (93.1)	31 (93.9)	34 (94.4)	27 (90.0)
		Abnormal NCS	2 (6.9)	2 (6.1)	2 (5.6)	3 (10.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

BMI=Body mass index;
Listing(s): Derived from Listing 16.2.8.1

14.3.4.2 Shift table of out-of range values on laboratory data: b) Summary of abnormal clinical chemistry values by visit

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Alanine Aminotransferase (U/L)	Baseline	n	33	33	40	31
		Normal	27 (81.8)	28 (84.8)	36 (90.0)	30 (96.8)
		Abnormal NCS	5 (15.2)	5 (15.2)	3 (7.5)	1 (3.2)
		Abnormal CS	1 (3.0)	0 (0.0)	1 (2.5)	0 (0.0)
	Follow-up	n	30	34	38	31
		Normal	21 (70.0)	29 (85.3)	33 (86.8)	30 (96.8)
		Abnormal NCS	8 (26.7)	5 (14.7)	2 (5.3)	1 (3.2)
		Abnormal CS	1 (3.3)	0 (0.0)	3 (7.9)	0 (0.0)
Albumin (g/L)	Baseline	n	33	33	40	31
		Normal	32 (97.0)	33 (100.0)	38 (95.0)	31 (100.0)
		Abnormal NCS	1 (3.0)	0 (0.0)	2 (5.0)	0 (0.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	30	34	38	31
		Normal	29 (96.7)	34 (100.0)	35 (92.1)	31 (100.0)
		Abnormal NCS	1 (3.3)	0 (0.0)	3 (7.9)	0 (0.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alkaline Phosphatase (U/L)	Baseline	n	33	33	40	31
		Normal	31 (93.9)	33 (100.0)	37 (92.5)	30 (96.8)

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Abnormal NCS	2 (6.1)	0 (0.0)	2 (5.0)	1 (3.2)
		Abnormal CS	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)
	Follow-up	n	30	34	38	31
		Normal	28 (93.3)	33 (97.1)	36 (94.7)	30 (96.8)
		Abnormal NCS	2 (6.7)	1 (2.9)	1 (2.6)	1 (3.2)
		Abnormal CS	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)
Aspartate Aminotransferase (U/L)	Baseline	n	33	33	40	31
		Normal	30 (90.9)	32 (97.0)	36 (90.0)	30 (96.8)
		Abnormal NCS	2 (6.1)	1 (3.0)	3 (7.5)	1 (3.2)
		Abnormal CS	1 (3.0)	0 (0.0)	1 (2.5)	0 (0.0)
	Follow-up	n	30	34	38	31
		Normal	24 (80.0)	32 (94.1)	34 (89.5)	30 (96.8)
		Abnormal NCS	5 (16.7)	2 (5.9)	1 (2.6)	1 (3.2)
		Abnormal CS	1 (3.3)	0 (0.0)	3 (7.9)	0 (0.0)
Bilirubin (mg/dL)	Baseline	n	33	33	40	31
		Normal	32 (97.0)	31 (93.9)	40 (100.0)	31 (100.0)
		Abnormal NCS	1 (3.0)	2 (6.1)	0 (0.0)	0 (0.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	30	34	38	31
		Normal	30 (100.0)	33 (97.1)	38 (100.0)	31 (100.0)
		Abnormal NCS	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatine Kinase (U/L)	Baseline	n	33	33	40	31
		Normal	30 (90.9)	30 (90.9)	38 (95.0)	31 (100.0)
		Abnormal NCS	3 (9.1)	3 (9.1)	1 (2.5)	0 (0.0)
		Abnormal CS	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)
	Follow-up	n	30	34	38	31
		Normal	27 (90.0)	33 (97.1)	37 (97.4)	30 (96.8)
		Abnormal NCS	2 (6.7)	1 (2.9)	1 (2.6)	1 (3.2)
		Abnormal CS	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine (mg/dL)	Baseline	n	33	33	40	31
		Normal	32 (97.0)	32 (97.0)	37 (92.5)	29 (93.5)
		Abnormal NCS	0 (0.0)	1 (3.0)	3 (7.5)	2 (6.5)
		Abnormal CS	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	30	34	38	31
		Normal	28 (93.3)	32 (94.1)	36 (94.7)	28 (90.3)
		Abnormal NCS	1 (3.3)	2 (5.9)	2 (5.3)	3 (9.7)
		Abnormal CS	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
Potassium (mmol/L)	Baseline	n	33	33	40	31
		Normal	32 (97.0)	29 (87.9)	37 (92.5)	31 (100.0)
		Abnormal NCS	0 (0.0)	4 (12.1)	2 (5.0)	0 (0.0)
		Abnormal CS	1 (3.0)	0 (0.0)	1 (2.5)	0 (0.0)

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Follow-up	n	30	34	38	31
		Normal	30 (100.0)	31 (91.2)	37 (97.4)	30 (96.8)
		Abnormal NCS	0 (0.0)	3 (8.8)	1 (2.6)	1 (3.2)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sodium (mmol/L)	Baseline	n	33	33	40	31
		Normal	33 (100.0)	32 (97.0)	38 (95.0)	30 (96.8)
		Abnormal NCS	0 (0.0)	1 (3.0)	2 (5.0)	1 (3.2)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	30	34	38	31
		Normal	29 (96.7)	33 (97.1)	35 (92.1)	31 (100.0)
		Abnormal NCS	1 (3.3)	1 (2.9)	3 (7.9)	0 (0.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Listing(s): Derived from Listing 16.2.8.1						

14.3.4.2 Shift table of out-of range values on laboratory data: c) Summary of abnormal urinalysis values by visit

Variable	Visit	Statistics	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Glucose	Baseline	n	3	2	5	1
		Abnormal NCS	3 (100.0)	1 (50.0)	3 (60.0)	1 (100.0)
		Abnormal CS	0 (0.0)	1 (50.0)	2 (40.0)	0 (0.0)
	Follow-up	n	1	2	2	1
		Abnormal NCS	1 (100.0)	2 (100.0)	0 (0.0)	1 (100.0)
		Abnormal CS	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)
Hemoglobin	Baseline	n	7	3	2	5
		Abnormal NCS	7 (100.0)	3 (100.0)	2 (100.0)	4 (80.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
	Follow-up	n	4	1	5	4
		Abnormal NCS	4 (100.0)	1 (100.0)	5 (100.0)	4 (100.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protein	Baseline	n	4	1	3	4
		Abnormal NCS	4 (100.0)	1 (100.0)	3 (100.0)	4 (100.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up	n	6	3	3	4
		Abnormal NCS	6 (100.0)	3 (100.0)	3 (100.0)	4 (100.0)
		Abnormal CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Listing(s): Derived from Listing 16.2.8.1						

Figure 14.3.4.1 Shift plots for laboratory data

a: Hemoglobin (g/dL)

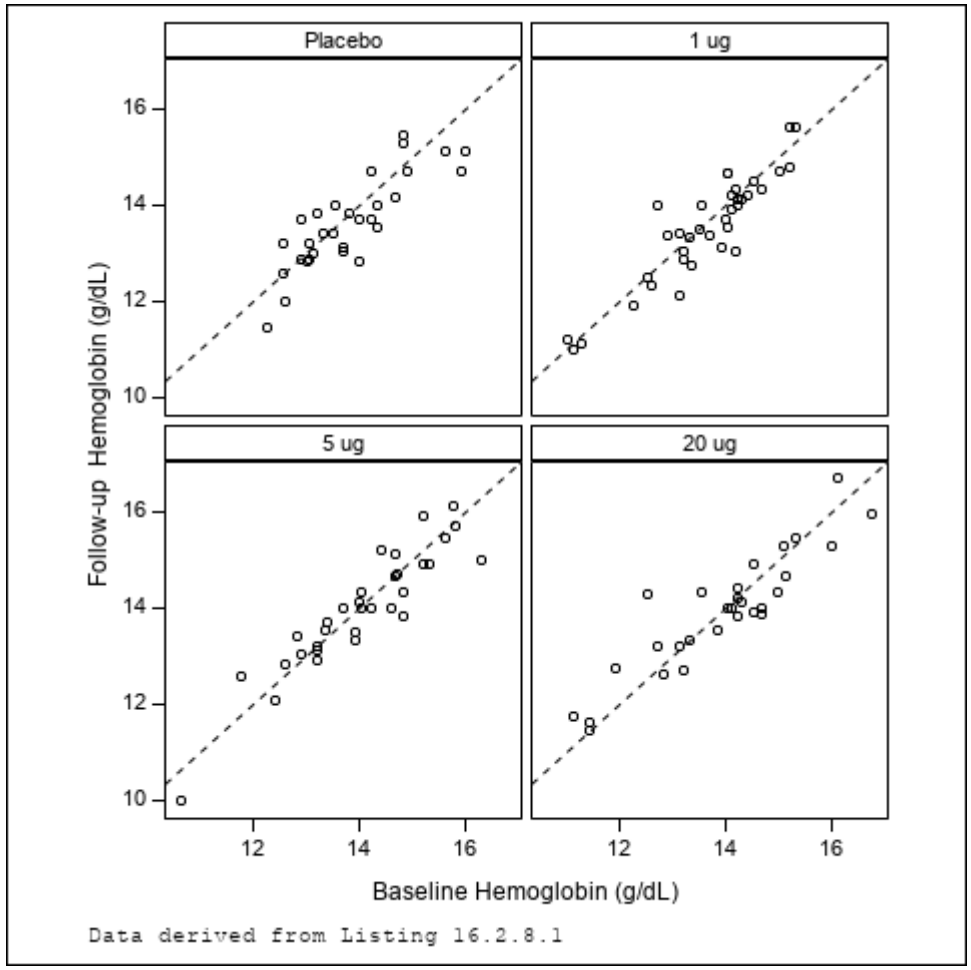


Figure 14.3.4.1 Shift plots for laboratory data: b: Platelets (10^9/L)

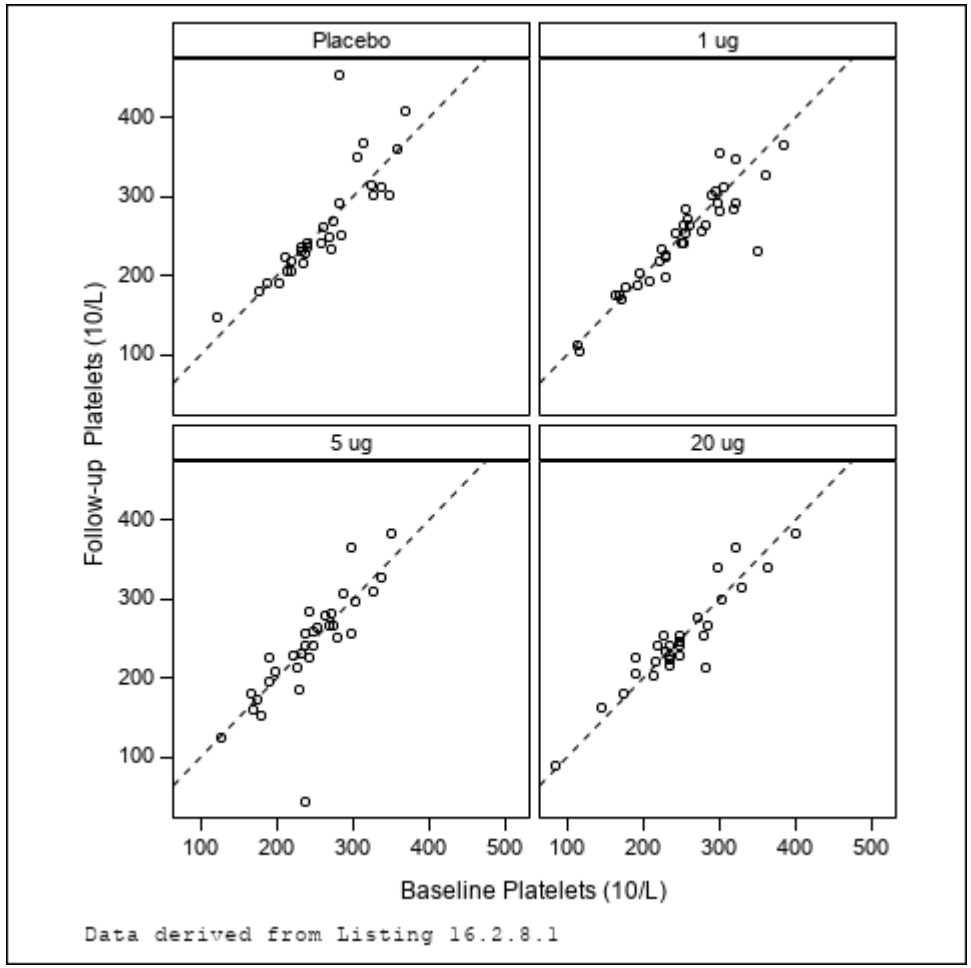


Figure 14.3.4.1 Shift plots for laboratory data: c: Erythrocytes (10^12/L)

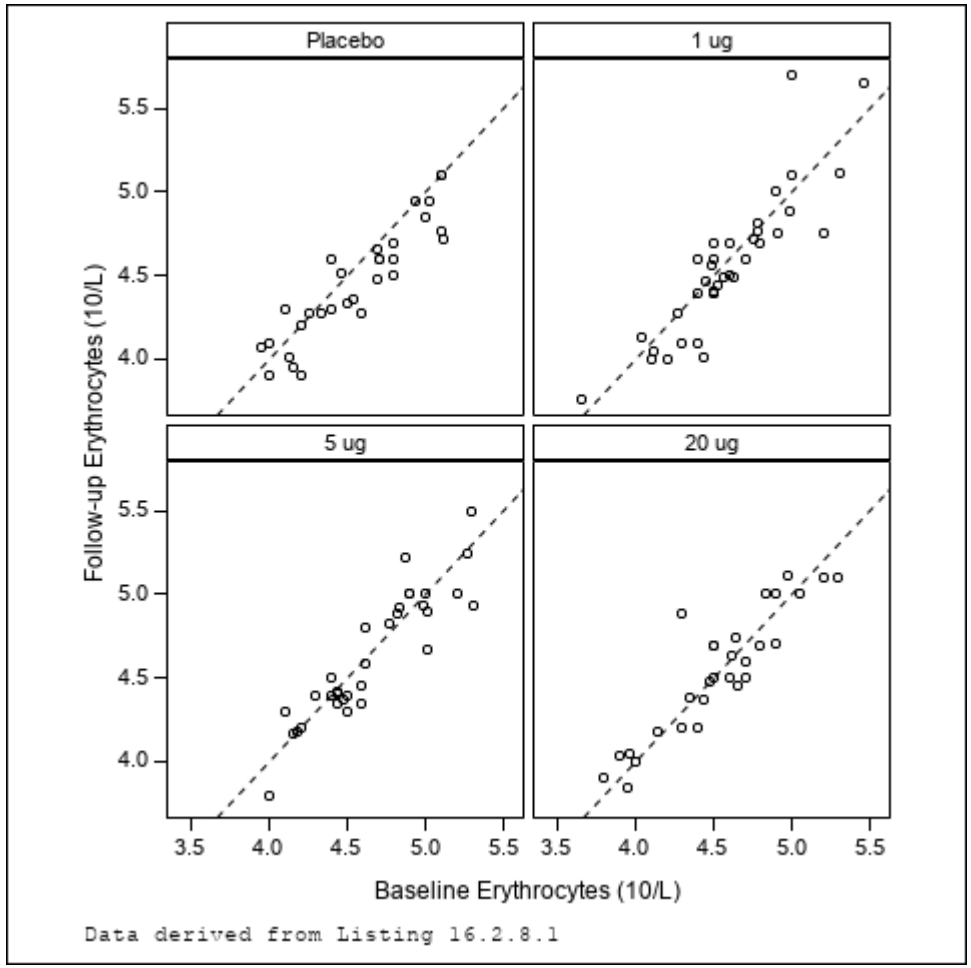


Figure 14.3.4.1 Shift plots for laboratory data: d: Leukocytes (10^9/L)

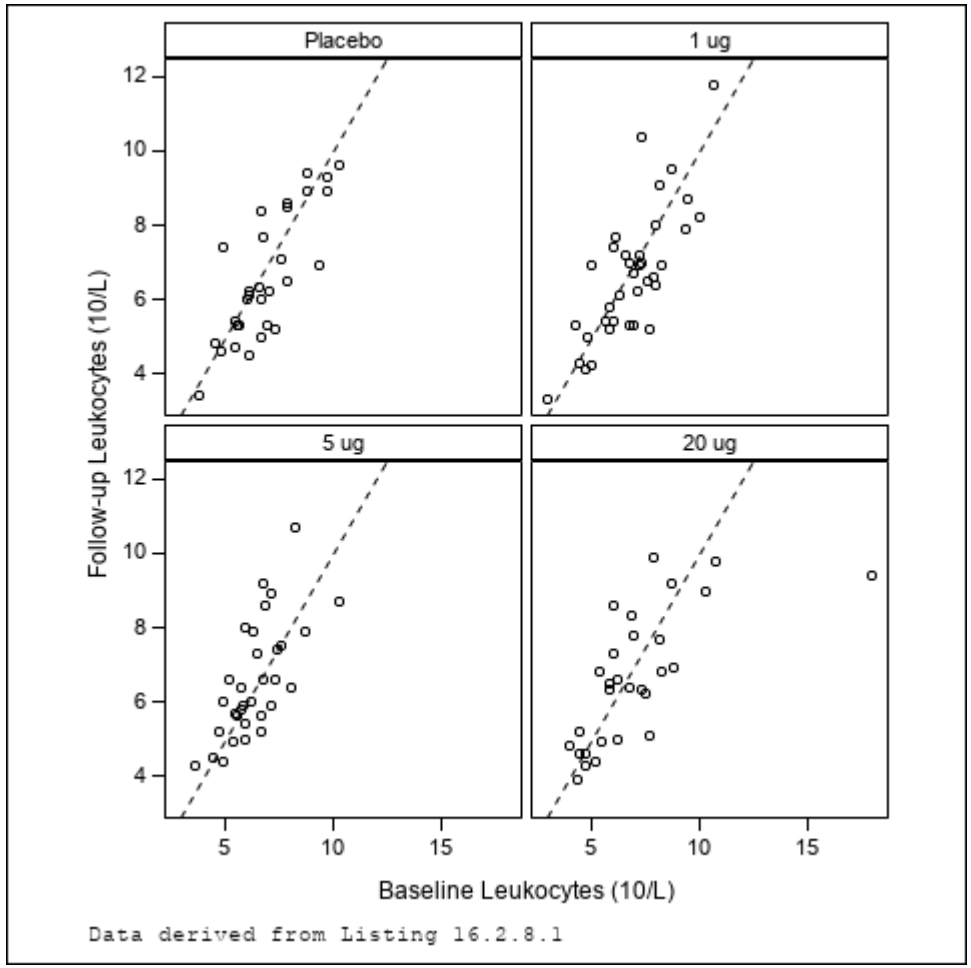


Figure 14.3.4.1 Shift plots for laboratory data: e: Neutrophils (10^9/L)

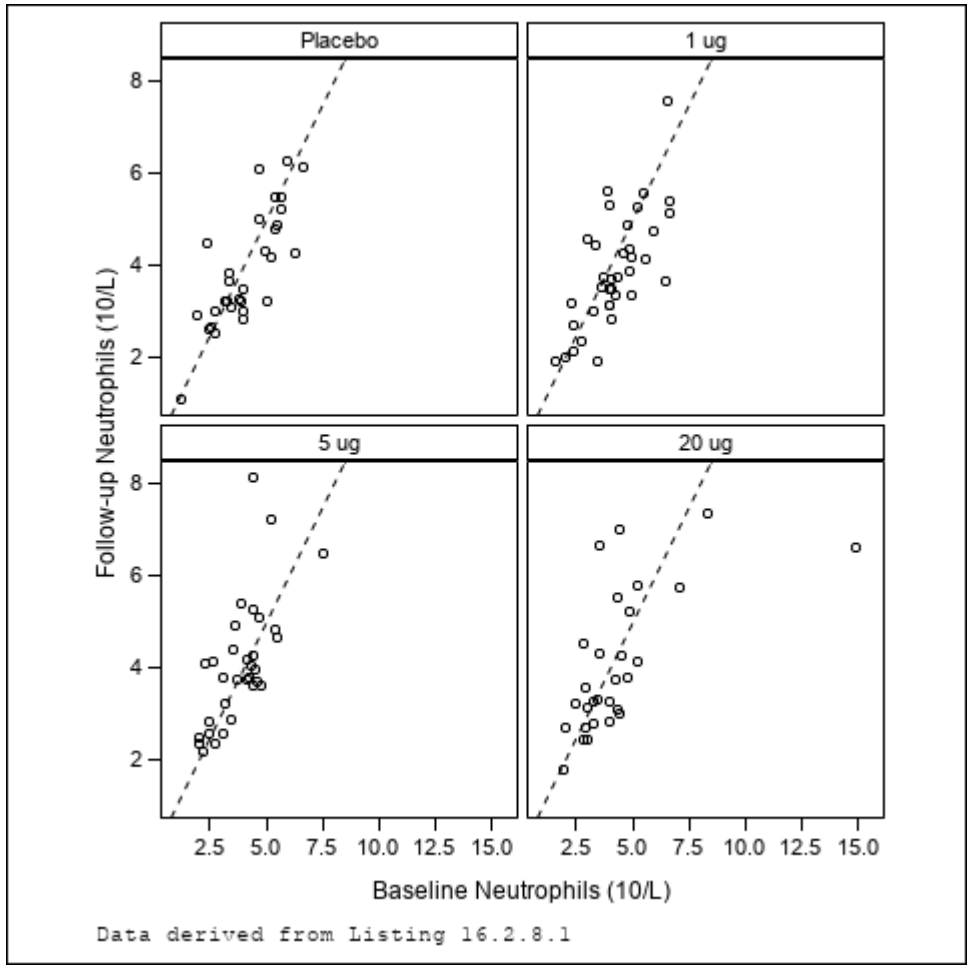


Figure 14.3.4.1 Shift plots for laboratory data: f: Neutrophils/Leukocytes (%)

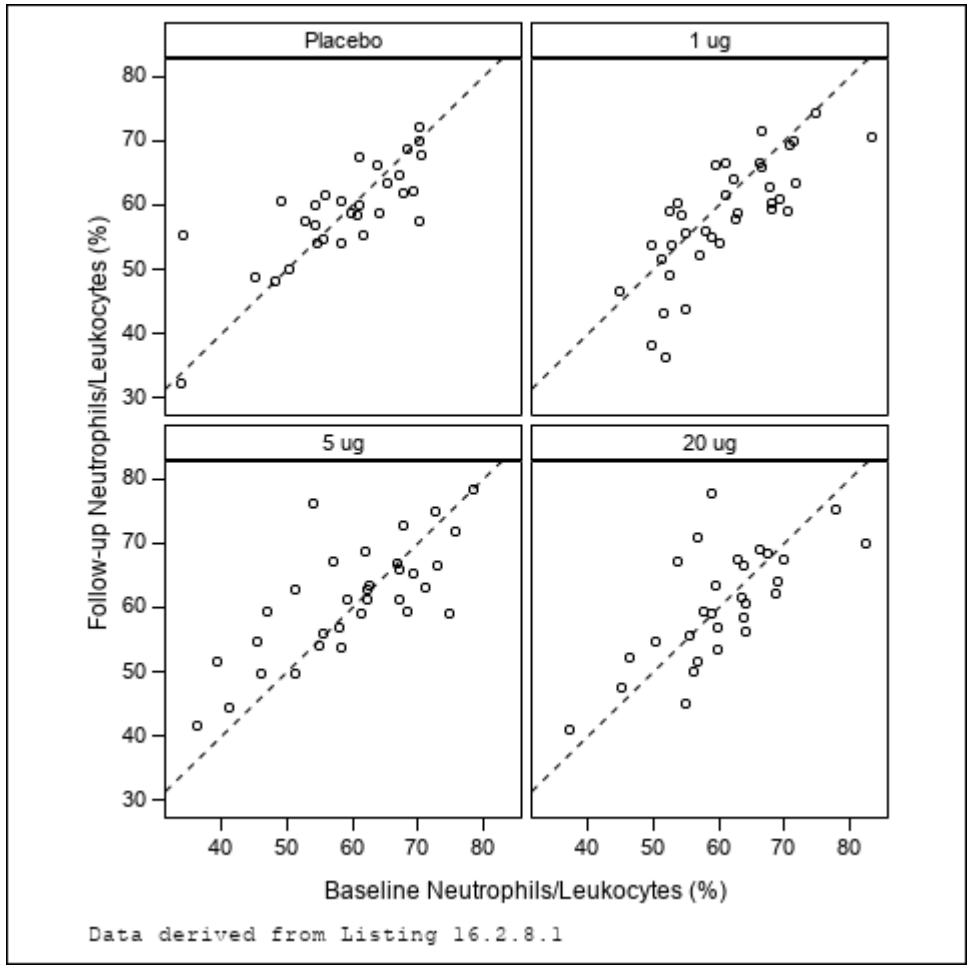


Figure 14.3.4.1 Shift plots for laboratory data: g: Monocytes (10^9/L)

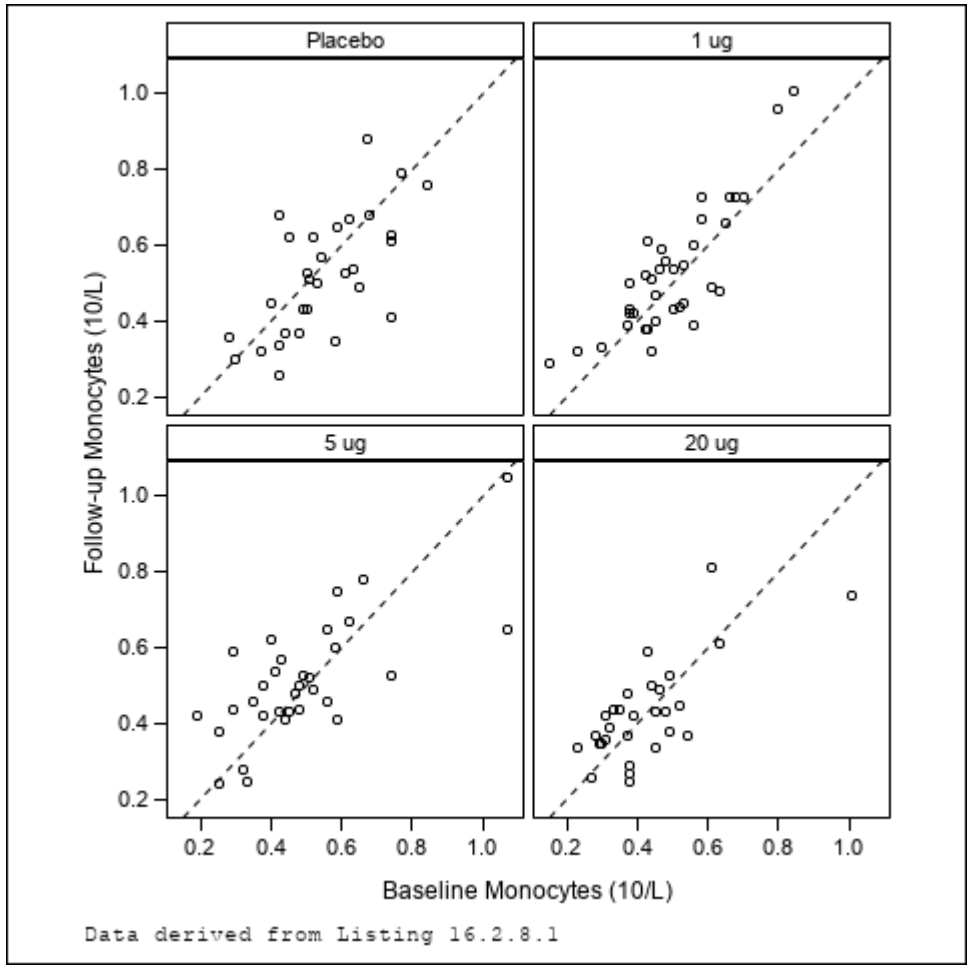


Figure 14.3.4.1 Shift plots for laboratory data: h: Monocytes/Leukocytes (%)

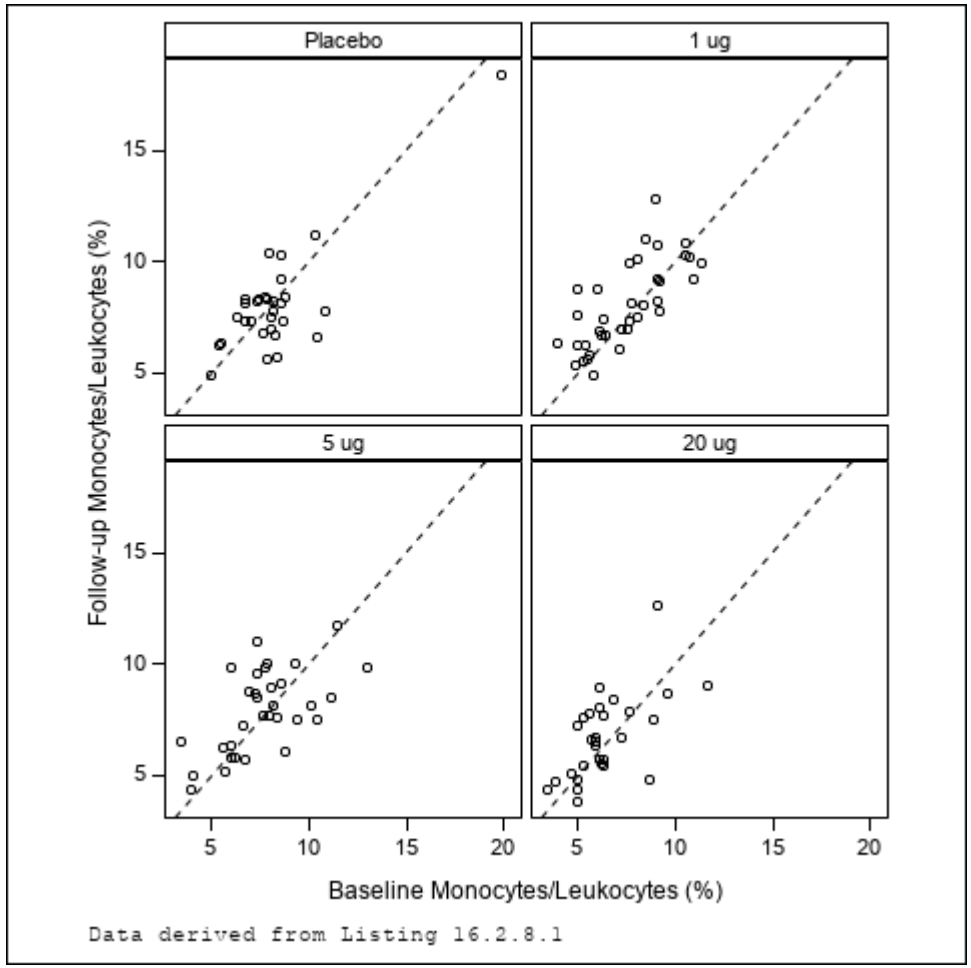


Figure 14.3.4.1 Shift plots for laboratory data: i: Lymphocytes (10^9/L)

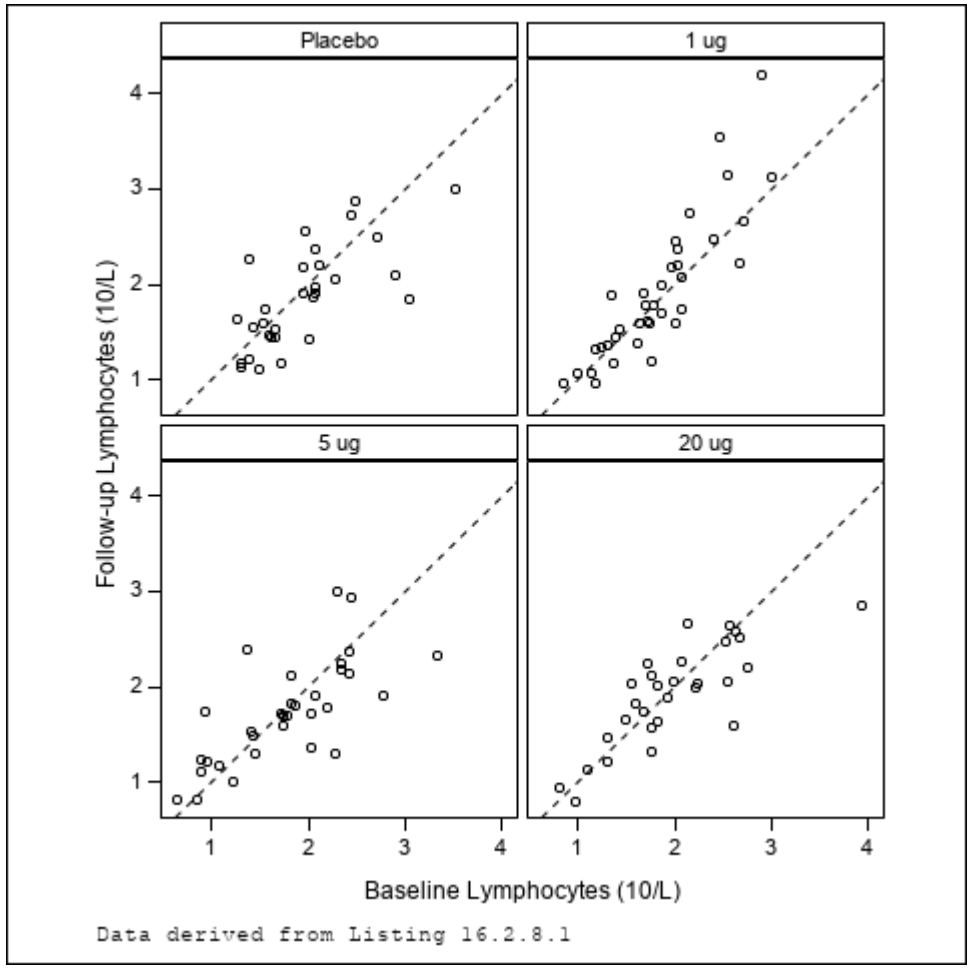


Figure 14.3.4.1 Shift plots for laboratory data: j: Lymphocytes/Leukocytes (%)

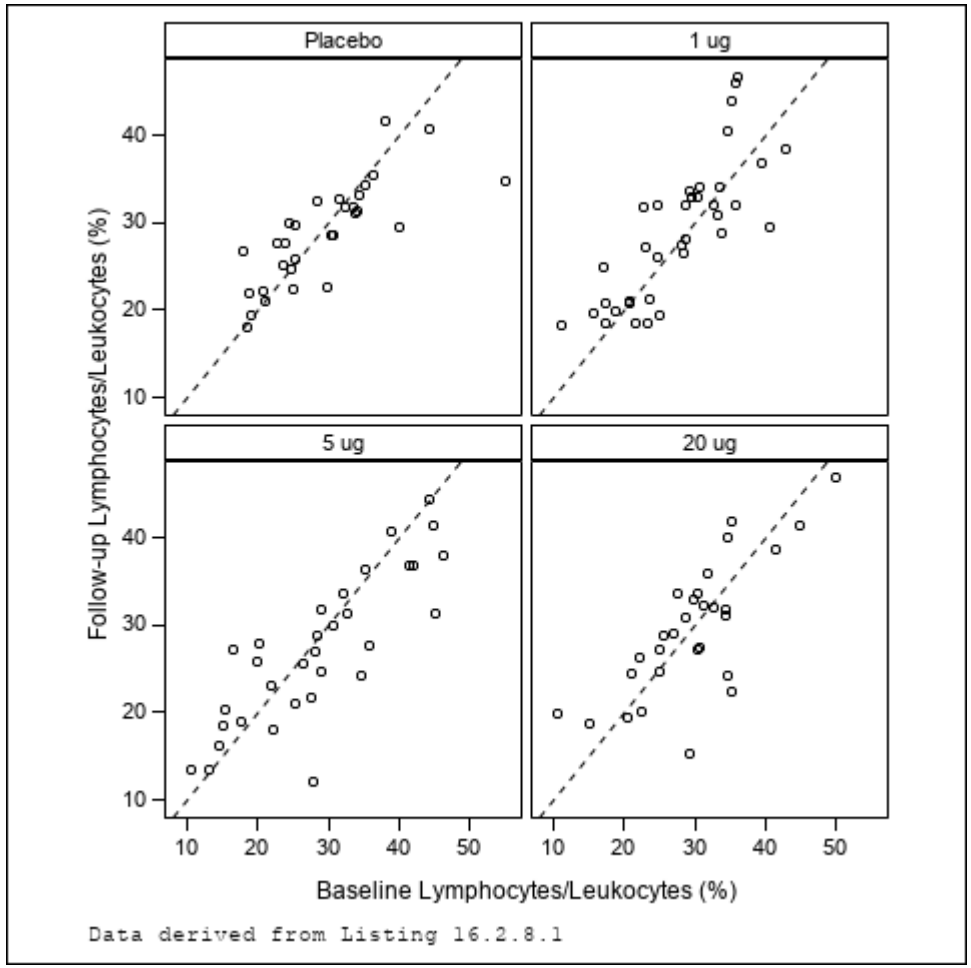


Figure 14.3.4.1 Shift plots for laboratory data: k: Eosinophils (10^9/L)

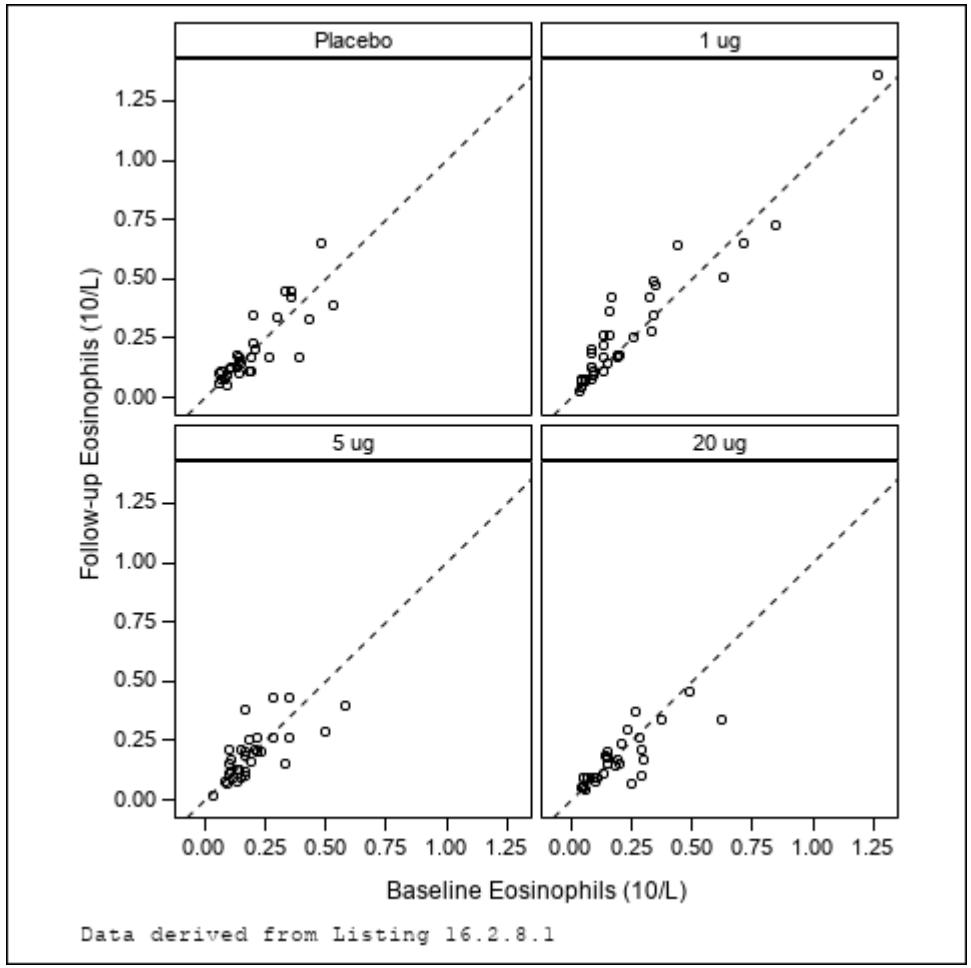


Figure 14.3.4.1 Shift plots for laboratory data: l: Eosinophils/Leukocytes (%)

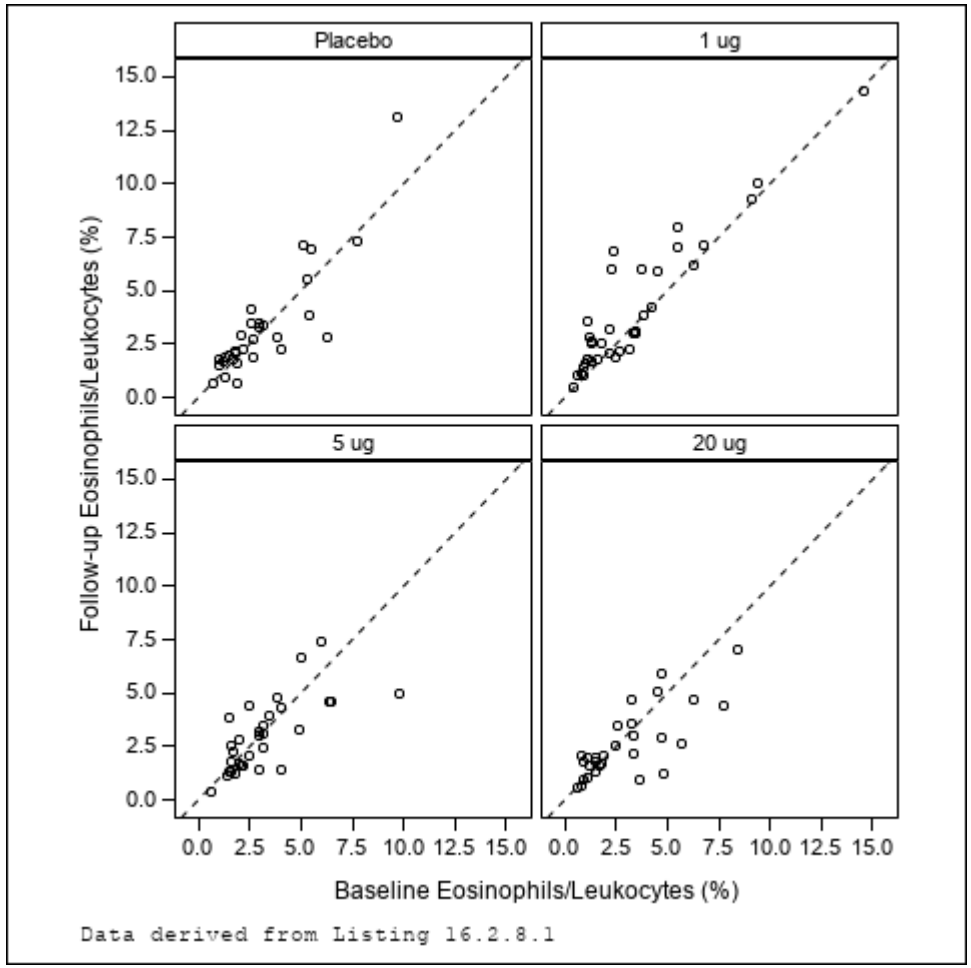


Figure 14.3.4.1 Shift plots for laboratory data: m: Basophils (10^9/L)

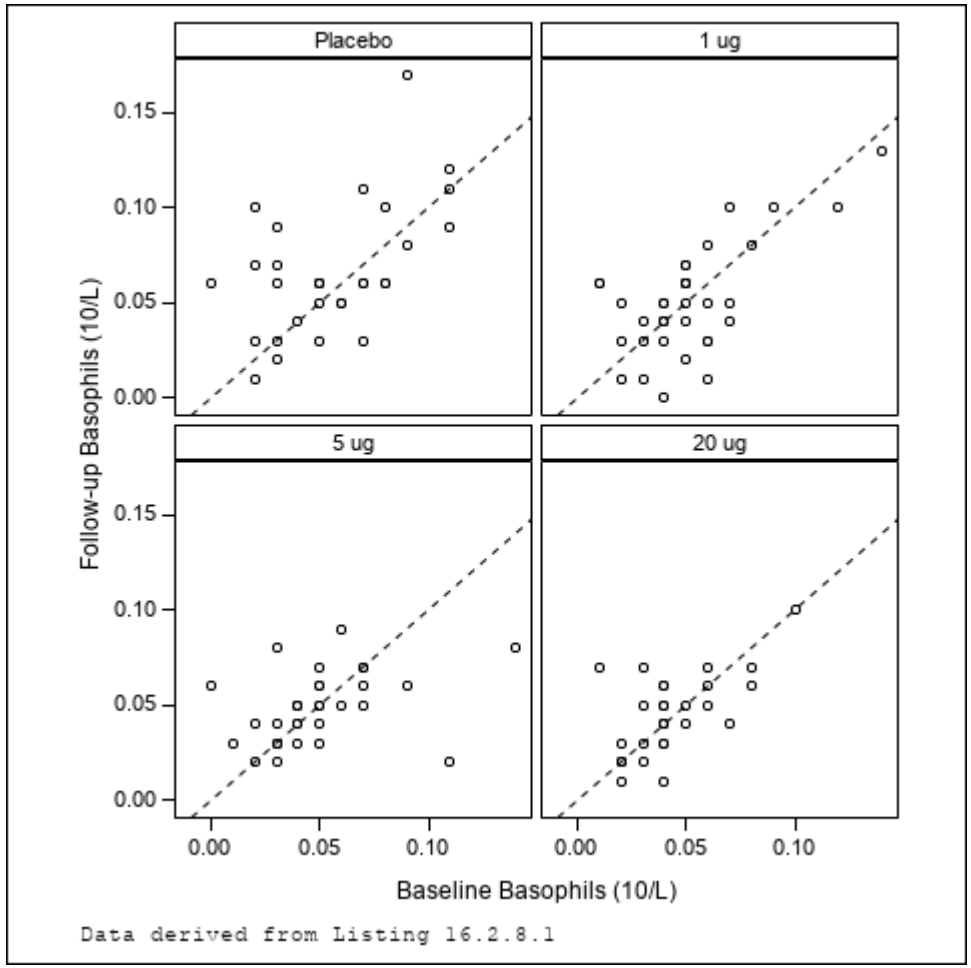


Figure 14.3.4.1 Shift plots for laboratory data: n: Basophils/Leukocytes (%)

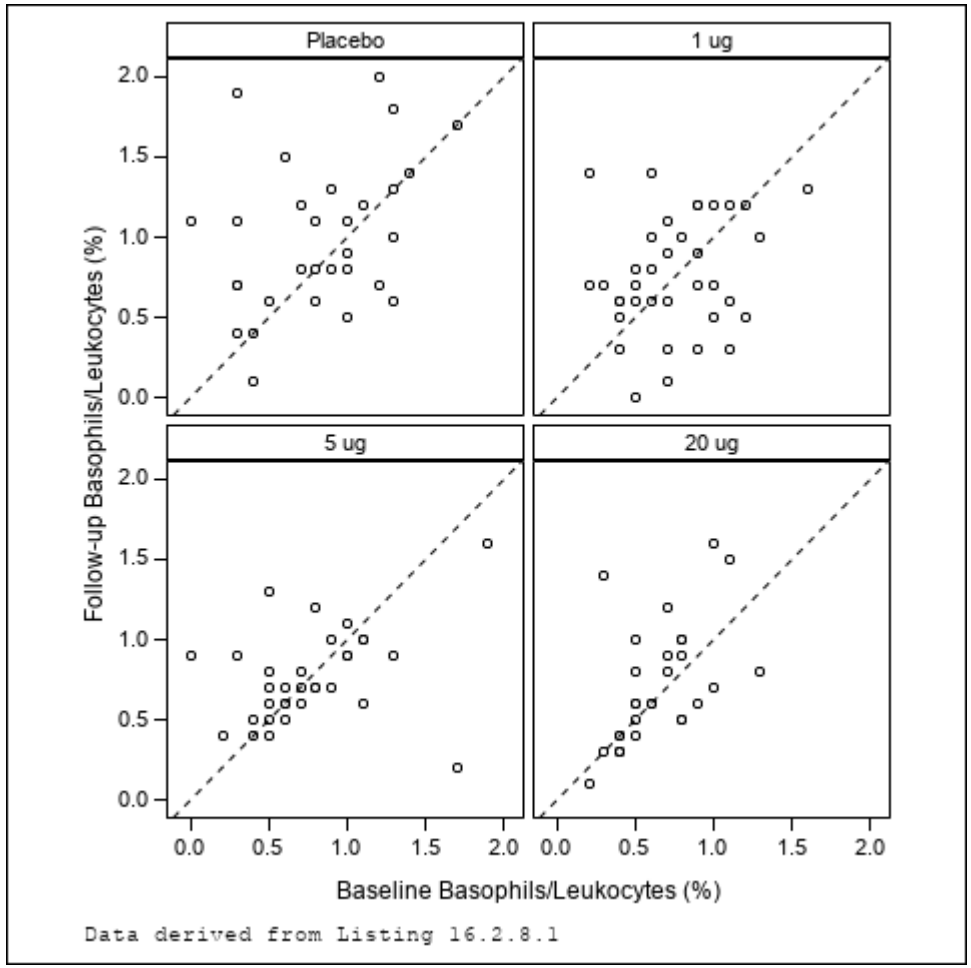


Figure 14.3.4.1 Shift plots for laboratory data: o: Albumin (g/L)

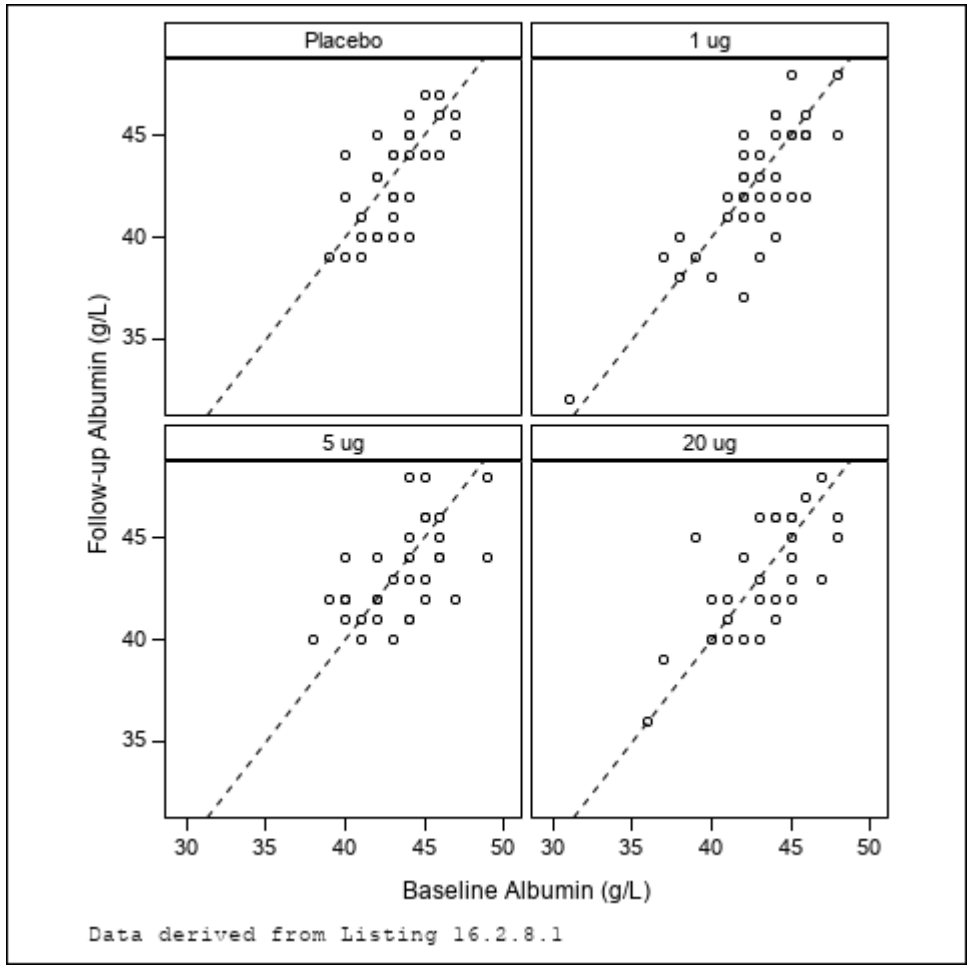


Figure 14.3.4.1 Shift plots for laboratory data: p: Alanine Aminotransferase (U/L)

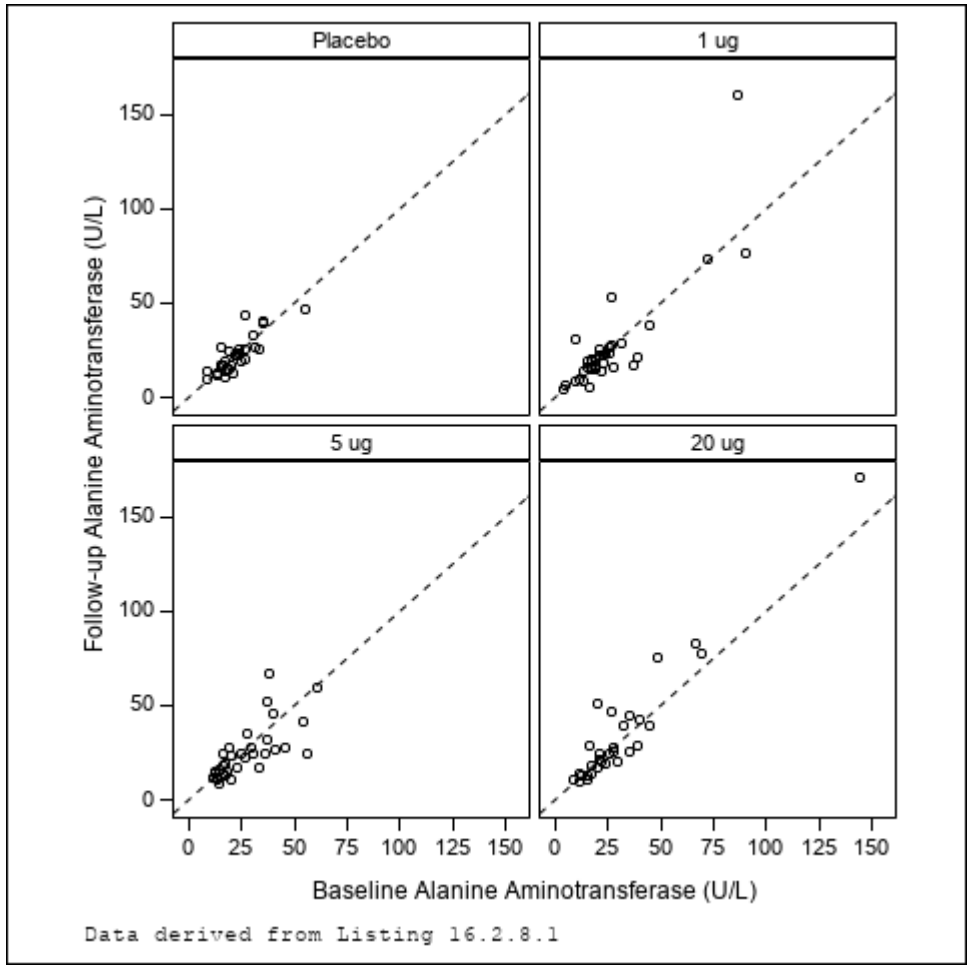


Figure 14.3.4.1 Shift plots for laboratory data: q: Alkaline Phosphatase (U/L)

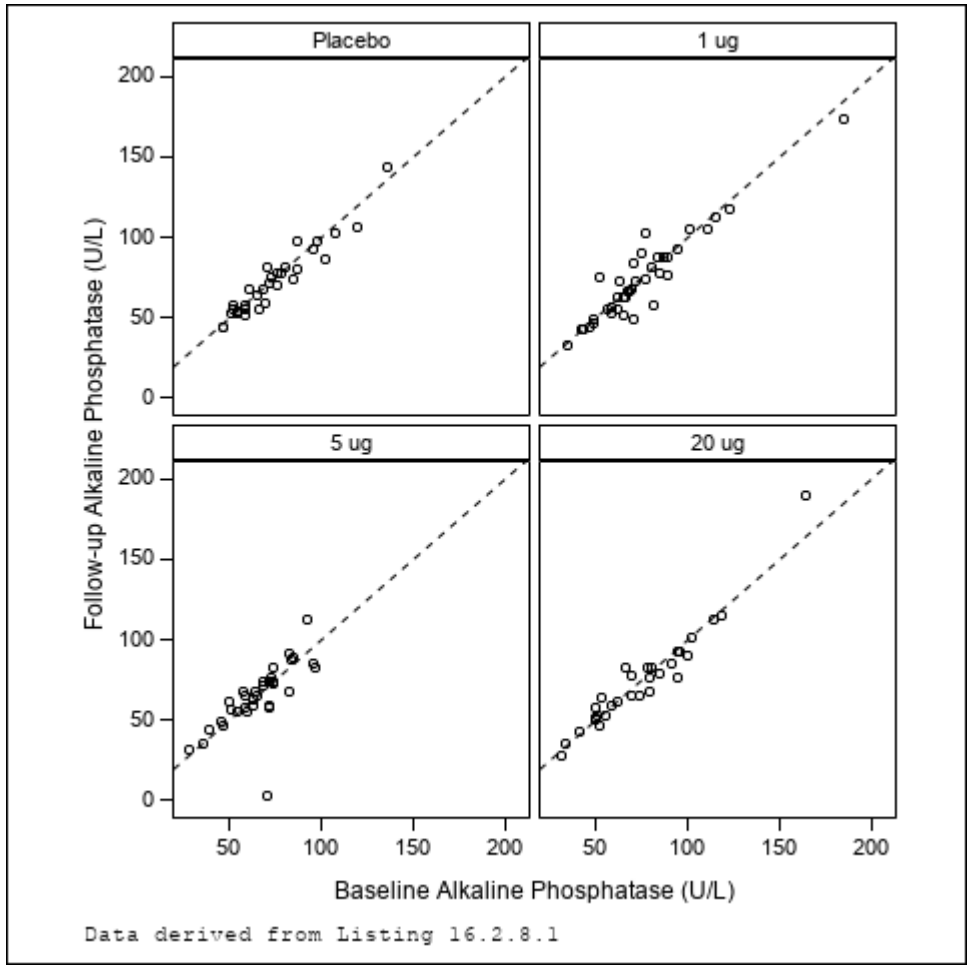


Figure 14.3.4.1 Shift plots for laboratory data: r: Aspartate Aminotransferase (U/L)

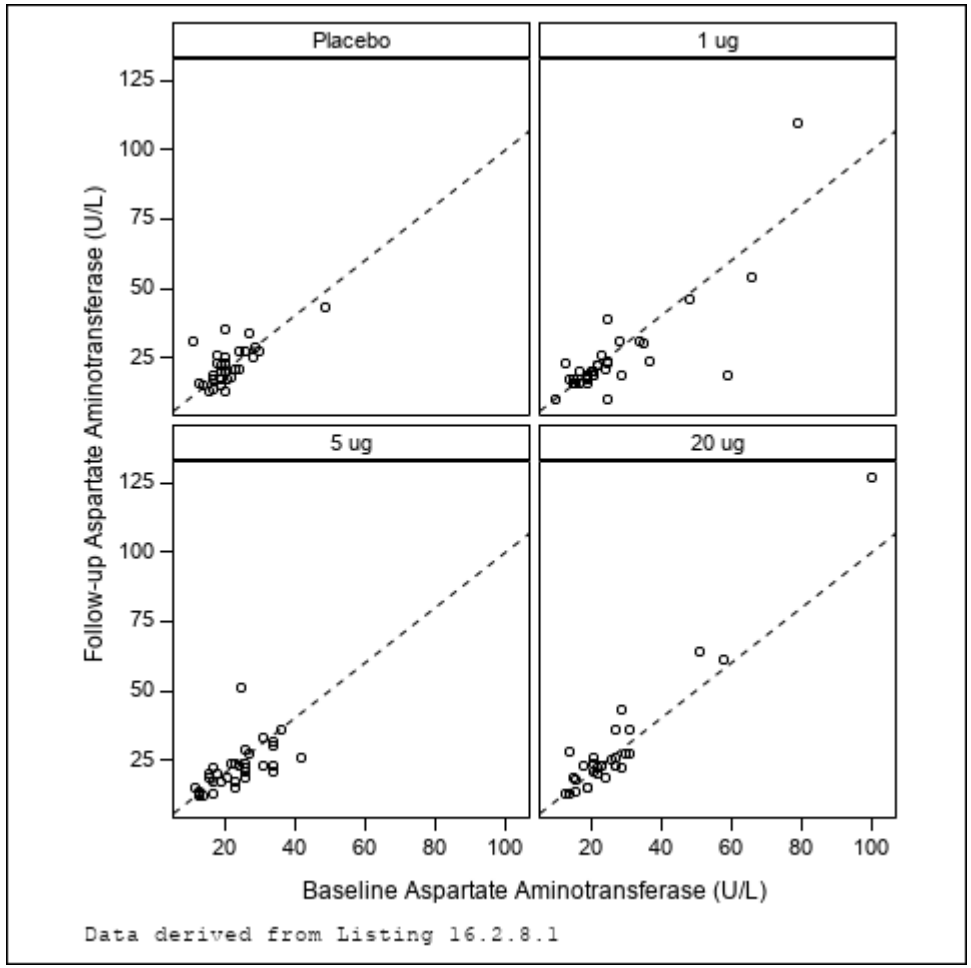


Figure 14.3.4.1 Shift plots for laboratory data: s: Bilirubin (mg/dL)

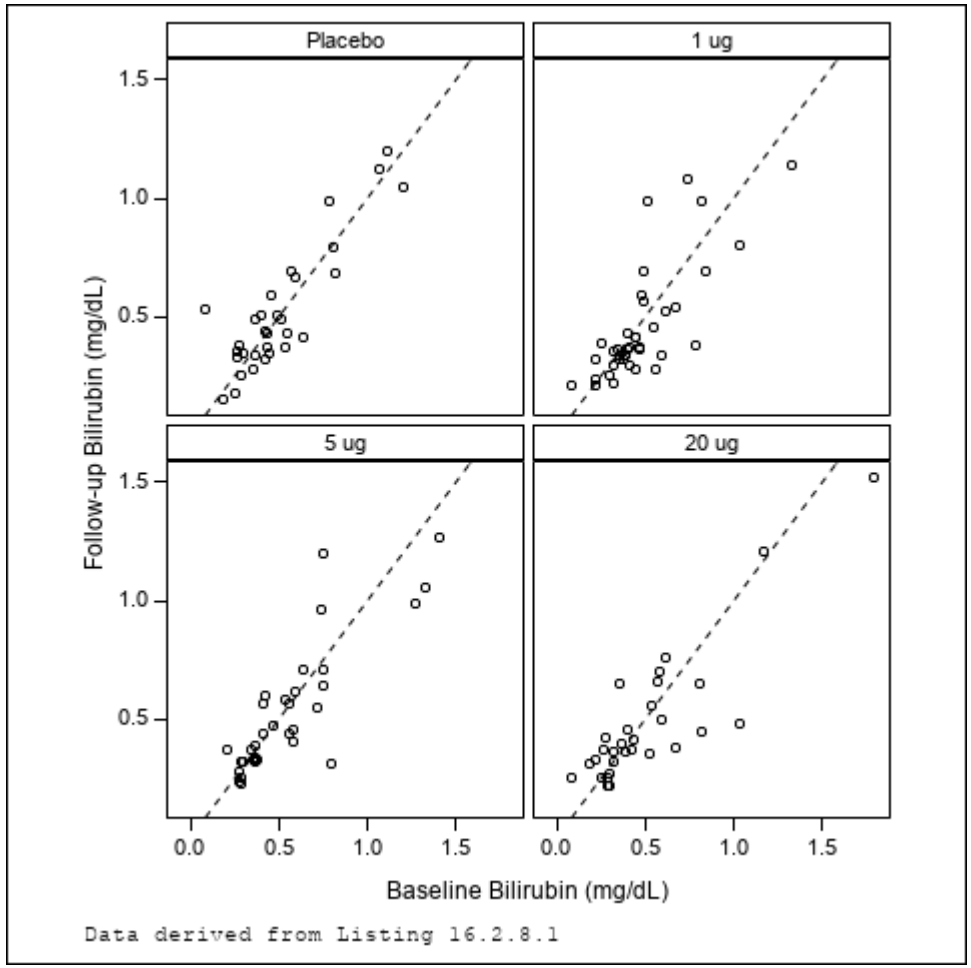


Figure 14.3.4.1 Shift plots for laboratory data: t: Creatine Kinase (U/L)

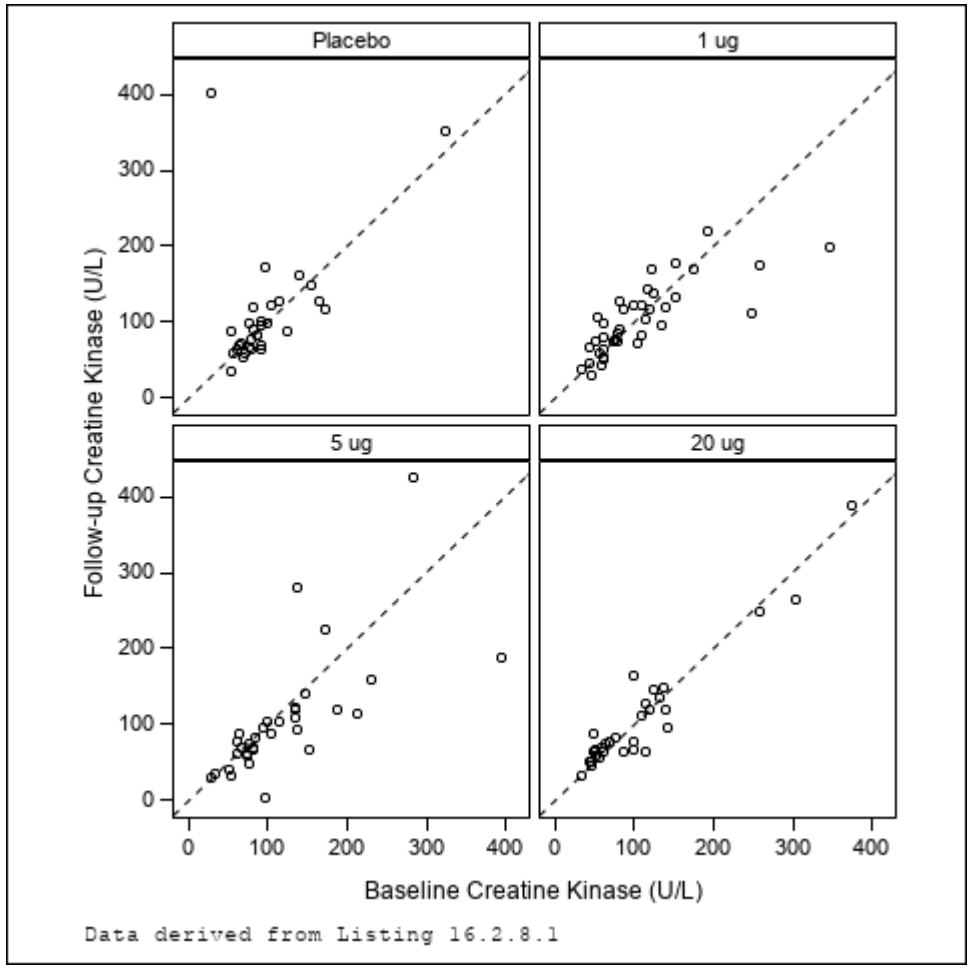


Figure 14.3.4.1 Shift plots for laboratory data: u: Creatinine (mg/dL)

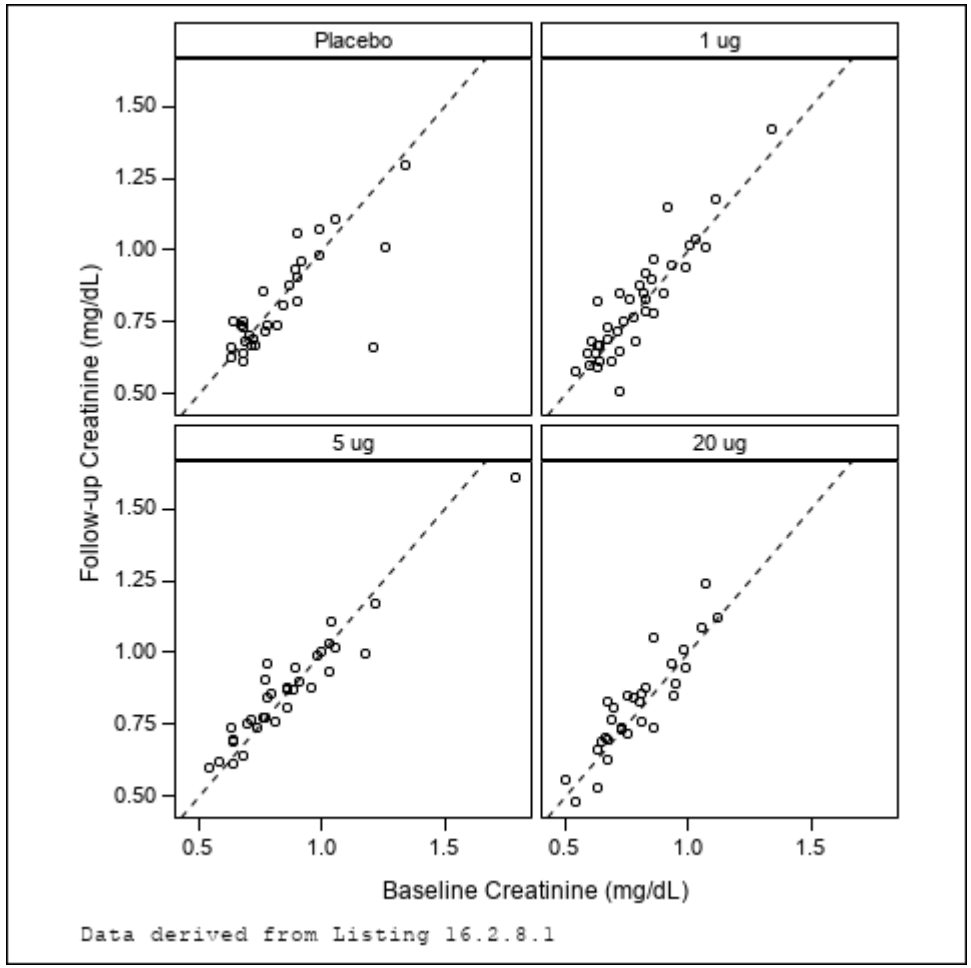


Figure 14.3.4.1 Shift plots for laboratory data: v: Potassium (mmol/L)

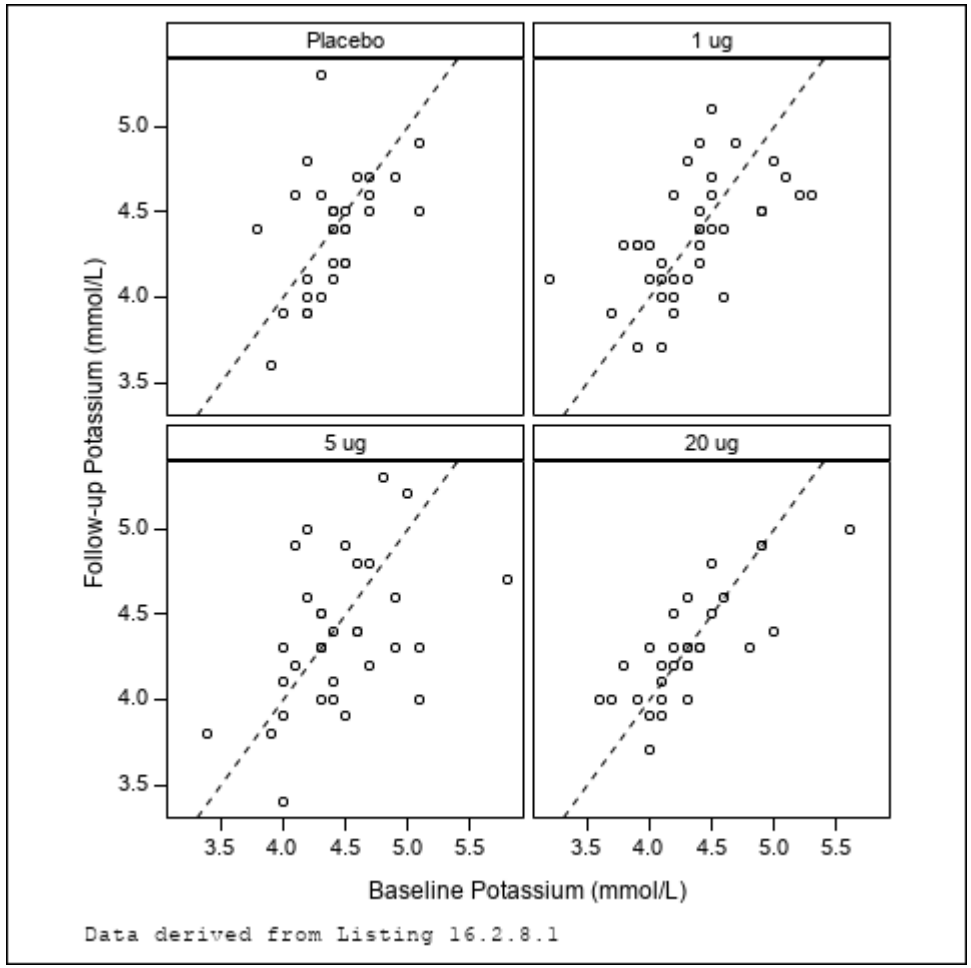
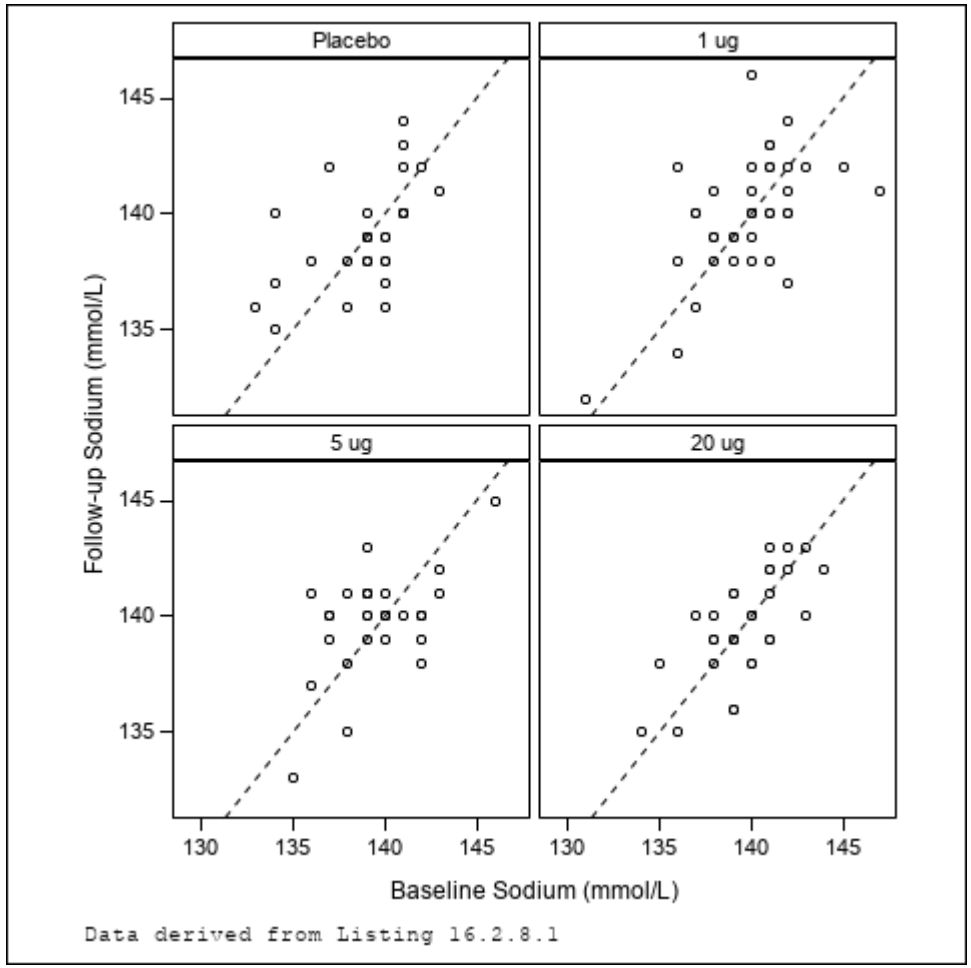


Figure 14.3.4.1 Shift plots for laboratory data: w: Sodium (mmol/L)



14.3.5 Vital signs, oral examination and other observations related to Safety

Table 14.3.5.1 Summary statistics by visit with difference from baseline for vital signs and body weight

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Systolic Blood Pressure (mmHg)	Baseline	n	33	34	40	31
		Mean(SD)	131.0 (15.56)	137.5 (19.36)	137.5 (25.14)	141.5 (17.76)
		Median	130.0	132.0	130.5	146.0
		Min, Max	99.0-162.0	103.0-187.0	105.0-220.0	100.0-173.0
	Follow-up	n	33	34	40	31
		Mean(SD)	130.8 (14.64)	135.8 (16.72)	134.7 (20.40)	135.0 (16.97)
		Median	136.5	136.5	130.0	134.0
		Min, Max	104.0-154.0	103.0-171.0	107.0-184.0	111.0-180.0
	Change from baseline	n	33	34	40	31
		Mean(SD)	-0.8 (13.13)	-1.6 (11.84)	-3.3 (16.02)	-5.9 (16.10)
		Median	-2.5	-1.0	-3.0	-6.0
		Min, Max	-42.0-31.0	-22.0-21.0	-45.0-32.0	-48.0-22.0
Diastolic Blood Pressure (mmHg	Baseline	n	33	34	40	31
		Mean(SD)	79.3 (12.17)	82.1 (13.45)	79.2 (12.02)	81.8 (11.58)
		Median	81.0	81.0	80.5	82.0
		Min, Max	47.0-104.0	52.0-111.0	55.0-103.0	55.0-104.0
	Follow-up	n	33	34	40	31
		Mean(SD)	77.7 (9.71)	79.5 (10.69)	77.5 (11.62)	78.8 (9.79)
		Median	79.0	78.5	80.0	79.5

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Min, Max	61.0-100.0	62.0-105.0	51.0-102.0	60.0-101.0
	Change from baseline	n	33	34	40	31
		Mean(SD)	-2.4 (9.48)	-2.6 (10.93)	-1.7 (8.45)	-2.8 (10.30)
		Median	-3.0	-2.5	-1.0	-3.0
		Min, Max	-24.0-15.0	-20.0-22.0	-23.0-16.0	-22.0-20.0
Pulse (beats/min)	Baseline	n	33	34	40	31
		Mean(SD)	71.7 (14.26)	70.3 (11.19)	67.6 (9.28)	69.4 (12.16)
		Median	73.0	69.5	67.5	69.0
		Min, Max	45.0-111.0	47.0-90.0	48.0-86.0	51.0-114.0
	Follow-up	n	33	34	40	31
		Mean(SD)	70.8 (11.86)	71.5 (11.32)	68.2 (10.36)	70.1 (11.43)
		Median	72.0	67.5	69.0	68.0
		Min, Max	43.0-94.0	51.0-92.0	44.0-92.0	51.0-100.0
	Change from baseline	n	33	34	40	31
		Mean(SD)	-1.2 (10.86)	1.2 (9.48)	1.0 (8.11)	0.9 (9.58)
		Median	-1.0	3.0	1.0	1.5
		Min, Max	-23.0-22.0	-30.0-16.0	-14.0-22.0	-37.0-16.0
Temperature (C)	Baseline	n	33	34	40	31
		Mean(SD)	36.6 (0.61)	36.6 (0.37)	36.5 (0.52)	36.6 (0.40)
		Median	36.7	36.6	36.5	36.7
		Min, Max	35.0-37.3	36.0-37.5	35.2-37.8	35.6-37.1

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
	Follow-up	n	33	34	40	31
		Mean(SD)	36.4 (0.57)	36.5 (0.59)	36.5 (0.47)	36.4 (0.58)
		Median	36.3	36.6	36.6	36.6
		Min, Max	35.3-37.4	35.0-37.7	35.6-37.5	35.0-37.1
	Change from baseline	n	33	34	40	31
		Mean(SD)	-0.1 (0.62)	-0.0 (0.48)	-0.0 (0.66)	-0.2 (0.66)
		Median	-0.2	-0.1	0.0	0.0
		Min, Max	-1.2-1.2	-1.2-0.9	-1.6-1.5	-2.0-0.6
Weight (kg)	Baseline	n	33	34	40	31
		Mean(SD)	83.6 (19.41)	85.1 (20.99)	81.6 (17.94)	82.3 (22.42)
		Median	82.7	81.4	81.6	77.2
		Min, Max	51.0-129.0	60.0-154.4	49.1-136.1	51.9-129.8
	Follow-up	n	33	34	40	31
		Mean(SD)	83.7 (19.78)	84.6 (20.86)	81.3 (18.69)	83.0 (22.34)
		Median	81.2	81.0	80.3	78.9
		Min, Max	52.5-129.8	57.9-158.9	48.2-139.5	52.1-130.2
	Change from baseline	n	33	34	40	31
		Mean(SD)	0.0 (1.99)	-0.5 (2.66)	-0.2 (1.66)	-0.1 (1.60)
		Median	0.5	-0.4	0.0	0.3
		Min, Max	-8.6-3.1	-11.7-5.1	-4.7-3.4	-3.6-2.4
Body Mass Index (kg/m2)	Baseline	n	33	34	40	31

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		Mean(SD)	31.2 (6.93)	29.6 (5.96)	29.0 (5.32)	30.3 (7.60)
		Median	30.3	27.7	28.3	28.7
		Min, Max	18.7-46.9	18.9-48.2	17.8-42.3	21.2-50.9
	Follow-up	n	33	34	40	31
		Mean(SD)	31.2 (6.91)	29.4 (6.06)	29.0 (5.53)	30.5 (7.54)
		Median	30.0	27.8	28.2	29.3
		Min, Max	19.0-47.1	18.8-49.6	17.5-42.9	21.3-51.2
	Change from baseline	n	33	34	40	31
		Mean(SD)	-0.0 (0.87)	-0.2 (0.86)	-0.1 (0.61)	-0.0 (0.60)
		Median	0.2	-0.1	0.0	0.1
		Min, Max	-4.1-1.0	-3.3-2.0	-1.9-1.2	-1.5-0.9
Listing(s): Derived from Listing 16.2.9.1						

Table 14.3.5.2 Summary of examination of oral cavity

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Dental status	Visit 1	NORMAL	30/33 (90.9)	28/34 (82.4)	33/39 (84.6)	28/31 (90.3)
		ABNORMAL, not sign	3/33 (9.1)	5/34 (14.7)	6/39 (15.4)	3/31 (9.7)
		ABNORMAL, clin sign	0	1/34 (2.9)	0	0
Examination of any infection in the mouth	Visit 1	NORMAL	31/33 (93.9)	32/34 (94.1)	38/39 (97.4)	31/31 (100.0)
		ABNORMAL, not sign	2/33 (6.1)	1/34 (2.9)	0	0
		ABNORMAL, clin sign	0	1/34 (2.9)	1/39 (2.6)	0
	Visit 2	NORMAL	31/33 (93.9)	33/34 (97.1)	37/40 (92.5)	31/31 (100.0)
		ABNORMAL, not sign	1/33 (3.0)	1/34 (2.9)	0	0
		ABNORMAL, clin sign	1/33 (3.0)	0	3/40 (7.5)	0
	Visit 3	NORMAL	29/31 (93.5)	33/34 (97.1)	34/37 (91.9)	25/28 (89.3)
		ABNORMAL, not sign	1/31 (3.2)	1/34 (2.9)	0	1/28 (3.6)
		ABNORMAL, clin sign	1/31 (3.2)	0	3/37 (8.1)	2/28 (7.1)
	Visit 4	NORMAL	28/30 (93.3)	32/33 (97.0)	36/36 (100.0)	27/28 (96.4)
		ABNORMAL, not sign	1/30 (3.3)	0	0	0
		ABNORMAL, clin sign	1/30 (3.3)	1/33 (3.0)	0	1/28 (3.6)
	Visit 5	NORMAL	26/29 (89.7)	33/33 (100.0)	34/35 (97.1)	23/27 (85.2)
		ABNORMAL, not sign	2/29 (6.9)	0	0	0
		ABNORMAL, clin sign	1/29 (3.4)	0	1/35 (2.9)	4/27 (14.8)
	Visit 6	NORMAL	28/31 (90.3)	32/34 (94.1)	34/39 (87.2)	26/30 (86.7)
		ABNORMAL, not sign	1/31 (3.2)	0	2/39 (5.1)	1/30 (3.3)

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		ABNORMAL, clin sign	2/31 (6.5)	2/34 (5.9)	3/39 (7.7)	3/30 (10.0)
	Visit 7	NORMAL	26/30 (86.7)	32/33 (97.0)	33/34 (97.1)	22/26 (84.6)
		ABNORMAL, not sign	3/30 (10.0)	1/33 (3.0)	1/34 (2.9)	2/26 (7.7)
		ABNORMAL, clin sign	1/30 (3.3)	0	0	2/26 (7.7)
Examination of oral cavity	Visit 1	NORMAL	31/33 (93.9)	29/34 (85.3)	29/39 (74.4)	26/31 (83.9)
		ABNORMAL, not sign	2/33 (6.1)	3/34 (8.8)	10/39 (25.6)	3/31 (9.7)
		ABNORMAL, clin sign	0	2/34 (5.9)	0	2/31 (6.5)
	Visit 2	NORMAL	28/33 (84.8)	29/34 (85.3)	29/40 (72.5)	26/31 (83.9)
		ABNORMAL, not sign	3/33 (9.1)	3/34 (8.8)	10/40 (25.0)	3/31 (9.7)
		ABNORMAL, clin sign	2/33 (6.1)	2/34 (5.9)	1/40 (2.5)	2/31 (6.5)
	Visit 3	NORMAL	25/31 (80.6)	30/34 (88.2)	30/37 (81.1)	21/28 (75.0)
		ABNORMAL, not sign	4/31 (12.9)	3/34 (8.8)	7/37 (18.9)	5/28 (17.9)
		ABNORMAL, clin sign	2/31 (6.5)	1/34 (2.9)	0	2/28 (7.1)
	Visit 4	NORMAL	22/30 (73.3)	23/33 (69.7)	29/36 (80.6)	20/28 (71.4)
		ABNORMAL, not sign	6/30 (20.0)	6/33 (18.2)	7/36 (19.4)	5/28 (17.9)
		ABNORMAL, clin sign	2/30 (6.7)	4/33 (12.1)	0	3/28 (10.7)
	Visit 5	NORMAL	21/29 (72.4)	27/33 (81.8)	25/35 (71.4)	19/27 (70.4)
		ABNORMAL, not sign	5/29 (17.2)	4/33 (12.1)	9/35 (25.7)	4/27 (14.8)
		ABNORMAL, clin sign	3/29 (10.3)	2/33 (6.1)	1/35 (2.9)	4/27 (14.8)
	Visit 6	NORMAL	27/31 (87.1)	26/34 (76.5)	29/39 (74.4)	23/30 (76.7)
		ABNORMAL, not sign	2/31 (6.5)	5/34 (14.7)	10/39 (25.6)	4/30 (13.3)

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
		ABNORMAL, clin sign	2/31 (6.5)	3/34 (8.8)	0	3/30 (10.0)
	Visit 7	NORMAL	25/30 (83.3)	29/33 (87.9)	25/34 (73.5)	19/26 (73.1)
		ABNORMAL, not sign	2/30 (6.7)	3/33 (9.1)	9/34 (26.5)	4/26 (15.4)
		ABNORMAL, clin sign	3/30 (10.0)	1/33 (3.0)	0	3/26 (11.5)
Listing(s): Derived from Listing 16.2.9.3						

Table 14.3.5.3 Summary of concomitant medications

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
ANY MEDICATION	30 (91)	26 (76)	35 (88)	27 (87)	118 (86)
LIPID MODIFYING AGENTS	10 (30)	8 (24)	16 (40)	10 (32)	44 (32)
- HMG COA REDUCTASE INHIBITORS	10 (30)	7 (21)	15 (38)	10 (32)	42 (30)
- OTHER LIPID MODIFYING AGENTS	0	0	2 (5)	2 (6)	4 (3)
- FIBRATES	0	2 (6)	0	0	2 (1)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	11 (33)	6 (18)	12 (30)	10 (32)	39 (28)
- ANGIOTENSIN II ANTAGONISTS, PLAIN	5 (15)	4 (12)	7 (18)	5 (16)	21 (15)
- ACE INHIBITORS, PLAIN	6 (18)	1 (3)	5 (13)	4 (13)	16 (12)
- ANGIOTENSIN II ANTAGONISTS AND DIURETICS	0	1 (3)	0	1 (3)	2 (1)
DRUGS FOR ACID RELATED DISORDERS	8 (24)	5 (15)	18 (45)	3 (10)	34 (25)
- PROTON PUMP INHIBITORS	6 (18)	4 (12)	16 (40)	3 (10)	29 (21)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- H2-RECEPTOR ANTAGONISTS	1 (3)	1 (3)	2 (5)	1 (3)	5 (4)
- OTHER DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	2 (6)	0	0	0	2 (1)
THYROID THERAPY	6 (18)	9 (26)	7 (18)	9 (29)	31 (22)
- THYROID HORMONES	6 (18)	8 (24)	7 (18)	9 (29)	30 (22)
- SULFUR-CONTAINING IMIDAZOLE DERIVATIVES	0	1 (3)	0	0	1 (1)
ANTITHROMBOTIC AGENTS	2 (6)	5 (15)	10 (25)	8 (26)	25 (18)
- PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	2 (6)	5 (15)	10 (25)	5 (16)	22 (16)
- DIRECT FACTOR XA INHIBITORS	0	0	0	3 (10)	3 (2)
- HEPARIN GROUP	0	0	0	1 (3)	1 (1)
- OTHER ANTITHROMBOTIC AGENTS	1 (3)	0	0	0	1 (1)
DRUGS USED IN DIABETES	7 (21)	7 (21)	8 (20)	3 (10)	25 (18)
- BIGUANIDES	6 (18)	5 (15)	7 (18)	3 (10)	21 (15)
- INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING	1 (3)	1 (3)	4 (10)	0	6 (4)
- INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	0	2 (6)	2 (5)	0	4 (3)
- SULFONYLUREAS	1 (3)	0	2 (5)	1 (3)	4 (3)
- DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS	0	1 (3)	2 (5)	0	3 (2)
- GLUCAGON-LIKE PEPTIDE-1 (GLP-1) ANALOGUES	0	0	1 (3)	2 (6)	3 (2)
- SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS	2 (6)	0	1 (3)	0	3 (2)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- COMBINATIONS OF ORAL BLOOD GLUCOSE LOWERING DRUGS	1 (3)	0	0	0	1 (1)
VITAMINS	6 (18)	4 (12)	7 (18)	8 (26)	25 (18)
- VITAMIN D AND ANALOGUES	6 (18)	4 (12)	4 (10)	6 (19)	20 (14)
- COMBINATIONS OF VITAMINS	1 (3)	2 (6)	3 (8)	2 (6)	8 (6)
- OTHER PLAIN VITAMIN PREPARATIONS	1 (3)	0	2 (5)	1 (3)	4 (3)
- ASCORBIC ACID (VITAMIN C), PLAIN	0	1 (3)	0	0	1 (1)
- MULTIVITAMINS WITH MINERALS	1 (3)	0	0	0	1 (1)
- VITAMIN A AND D IN COMBINATION	0	1 (3)	0	0	1 (1)
- VITAMIN A, PLAIN	0	1 (3)	0	0	1 (1)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	4 (12)	10 (29)	6 (15)	4 (13)	24 (17)
- PROPIONIC ACID DERIVATIVES	4 (12)	4 (12)	3 (8)	2 (6)	13 (9)
- COXIBS	0	3 (9)	2 (5)	0	5 (4)
- ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	0	0	1 (3)	2 (6)	3 (2)
- OXICAMS	0	3 (9)	0	0	3 (2)
PSYCHOANALEPTICS	5 (15)	3 (9)	9 (23)	6 (19)	23 (17)
- SELECTIVE SEROTONIN REUPTAKE INHIBITORS	3 (9)	1 (3)	4 (10)	3 (10)	11 (8)
- OTHER ANTIDEPRESSANTS	1 (3)	2 (6)	3 (8)	2 (6)	8 (6)
- NON-SELECTIVE MONOAMINE REUPTAKE INHIBITORS	0	0	2 (5)	1 (3)	3 (2)
- CENTRALLY ACTING SYMPATHOMIMETICS	1 (3)	0	0	0	1 (1)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
ANALGESICS	7 (21)	1 (3)	7 (18)	6 (19)	21 (15)
- ANILIDES	5 (15)	0	2 (5)	4 (13)	11 (8)
- OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	2 (6)	1 (3)	2 (5)	1 (3)	6 (4)
- OTHER OPIOIDS	2 (6)	0	1 (3)	1 (3)	4 (3)
- NATURAL OPIUM ALKALOIDS	0	0	2 (5)	1 (3)	3 (2)
- OTHER ANTIMIGRAINE PREPARATIONS	0	0	0	2 (6)	2 (1)
- SELECTIVE SEROTONIN (5HT1) AGONISTS	0	0	1 (3)	1 (3)	2 (1)
- ORIPAVINE DERIVATIVES	0	0	0	1 (3)	1 (1)
- SALICYLIC ACID AND DERIVATIVES	0	0	1 (3)	0	1 (1)
MINERAL SUPPLEMENTS	2 (6)	3 (9)	9 (23)	6 (19)	20 (14)
- CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	0	1 (3)	5 (13)	2 (6)	8 (6)
- POTASSIUM	1 (3)	0	3 (8)	0	4 (3)
- CALCIUM	0	1 (3)	1 (3)	1 (3)	3 (2)
- MAGNESIUM	0	1 (3)	0	2 (6)	3 (2)
- FLUORIDE	1 (3)	0	0	1 (3)	2 (1)
- SELENIUM	0	0	0	1 (3)	1 (1)
CALCIUM CHANNEL BLOCKERS	5 (15)	2 (6)	5 (13)	5 (16)	17 (12)
- DIHYDROPYRIDINE DERIVATIVES	5 (15)	0	3 (8)	5 (16)	13 (9)
- BENZOTHIAZEPINE DERIVATIVES	0	2 (6)	2 (5)	0	4 (3)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	4 (12)	4 (12)	6 (15)	3 (10)	17 (12)
- SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	3 (9)	3 (9)	1 (3)	3 (10)	10 (7)
- ADRENERGICS IN COMBINATION WITH CORTICOSTEROIDS OR OTHER DRUGS, EXCL. ANTICHOLINE	1 (3)	0	4 (10)	2 (6)	7 (5)
- LEUKOTRIENE RECEPTOR ANTAGONISTS	1 (3)	1 (3)	3 (8)	0	5 (4)
- ANTICHOLINERGICS	1 (3)	1 (3)	1 (3)	1 (3)	4 (3)
- GLUCOCORTICOIDS	1 (3)	0	2 (5)	0	3 (2)
- XANTHINES	0	0	1 (3)	0	1 (1)
ANTIHISTAMINES FOR SYSTEMIC USE	1 (3)	4 (12)	4 (10)	5 (16)	14 (10)
- PIPERAZINE DERIVATIVES	0	3 (9)	2 (5)	3 (10)	8 (6)
- OTHER ANTIHISTAMINES FOR SYSTEMIC USE	1 (3)	0	1 (3)	2 (6)	4 (3)
- AMINOALKYL ETHERS	0	1 (3)	0	0	1 (1)
- SUBSTITUTED ALKYLAMINES	0	0	1 (3)	0	1 (1)
ANTIEPILEPTICS	5 (15)	2 (6)	2 (5)	4 (13)	13 (9)
- OTHER ANTIEPILEPTICS	4 (12)	1 (3)	2 (5)	2 (6)	9 (7)
- BENZODIAZEPINE DERIVATIVES	0	1 (3)	0	1 (3)	2 (1)
- CARBOXAMIDE DERIVATIVES	1 (3)	0	0	1 (3)	2 (1)
- HYDANTOIN DERIVATIVES	1 (3)	0	0	0	1 (1)
BETA BLOCKING AGENTS	3 (9)	1 (3)	6 (15)	3 (10)	13 (9)
- BETA BLOCKING AGENTS, SELECTIVE	3 (9)	1 (3)	5 (13)	3 (10)	12 (9)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- ALPHA AND BETA BLOCKING AGENTS	0	0	2 (5)	0	2 (1)
DIURETICS	2 (6)	3 (9)	5 (13)	3 (10)	13 (9)
- SULFONAMIDES, PLAIN	1 (3)	0	2 (5)	2 (6)	5 (4)
- THIAZIDES, PLAIN	1 (3)	1 (3)	2 (5)	1 (3)	5 (4)
- ALDOSTERONE ANTAGONISTS	0	0	1 (3)	0	1 (1)
- HIGH-CEILING DIURETICS AND POTASSIUM-SPARING AGENTS	0	1 (3)	0	0	1 (1)
- LOW-CEILING DIURETICS AND POTASSIUM-SPARING AGENTS	0	1 (3)	0	0	1 (1)
ANTIANEMIC PREPARATIONS	1 (3)	3 (9)	4 (10)	3 (10)	11 (8)
- VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	0	2 (6)	3 (8)	3 (10)	8 (6)
- IRON BIVALENT, ORAL PREPARATIONS	1 (3)	1 (3)	1 (3)	0	3 (2)
- FOLIC ACID AND DERIVATIVES	0	0	1 (3)	0	1 (1)
- IRON PREPARATIONS	0	1 (3)	0	0	1 (1)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	3 (9)	0	3 (8)	4 (13)	10 (7)
- CORTICOSTEROIDS, VERY POTENT (GROUP IV)	1 (3)	0	2 (5)	2 (6)	5 (4)
- CORTICOSTEROIDS, POTENT (GROUP III)	1 (3)	0	1 (3)	2 (6)	4 (3)
- CORTICOSTEROIDS, POTENT, COMBINATIONS WITH ANTIBIOTICS	1 (3)	0	0	1 (3)	2 (1)
- CORTICOSTEROIDS, WEAK (GROUP I)	0	0	1 (3)	0	1 (1)
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	2 (6)	2 (6)	2 (5)	4 (13)	10 (7)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- NATURAL AND SEMISYNTHETIC ESTROGENS, PLAIN	0	2 (6)	1 (3)	3 (10)	6 (4)
- PROGESTOGENS AND ESTROGENS, FIXED COMBINATIONS	2 (6)	0	0	1 (3)	3 (2)
- OTHER ESTROGENS	0	0	1 (3)	0	1 (1)
- PREGNEN (4) DERIVATIVES	0	0	0	1 (3)	1 (1)
GENERAL NUTRIENTS	2 (6)	2 (6)	3 (8)	2 (6)	9 (7)
- OTHER COMBINATIONS OF NUTRIENTS	1 (3)	2 (6)	2 (5)	2 (6)	7 (5)
- OTHER NUTRIENTS	1 (3)	0	1 (3)	0	2 (1)
OPHTHALMOLOGICALS	2 (6)	1 (3)	2 (5)	4 (13)	9 (7)
- OTHER OPHTHALMOLOGICALS	1 (3)	1 (3)	1 (3)	2 (6)	5 (4)
- PROSTAGLANDIN ANALOGUES	1 (3)	0	1 (3)	1 (3)	3 (2)
- ANTIBIOTICS	0	0	0	1 (3)	1 (1)
- BETA BLOCKING AGENTS	1 (3)	0	0	0	1 (1)
- SYMPATHOMIMETICS IN GLAUCOMA THERAPY	1 (3)	0	0	0	1 (1)
PSYCHOLEPTICS	1 (3)	4 (12)	1 (3)	3 (10)	9 (7)
- BENZODIAZEPINE DERIVATIVES	1 (3)	2 (6)	0	2 (6)	5 (4)
- BENZODIAZEPINE RELATED DRUGS	1 (3)	1 (3)	1 (3)	0	3 (2)
- OTHER ANXIOLYTICS	1 (3)	1 (3)	0	1 (3)	3 (2)
- OTHER HYPNOTICS AND SEDATIVES	0	0	0	1 (3)	1 (1)
STOMATOLOGICAL PREPARATIONS	1 (3)	0	4 (10)	3 (10)	8 (6)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREATMENT	0	0	3 (8)	1 (3)	4 (3)
- OTHER AGENTS FOR LOCAL ORAL TREATMENT	1 (3)	0	1 (3)	1 (3)	3 (2)
- CARIES PROPHYLACTIC AGENTS	0	0	0	1 (3)	1 (1)
UROLOGICALS	1 (3)	2 (6)	3 (8)	2 (6)	8 (6)
- DRUGS FOR URINARY FREQUENCY AND INCONTINENCE	1 (3)	1 (3)	2 (5)	0	4 (3)
- ALPHA-ADRENORECEPTOR ANTAGONISTS	0	0	0	2 (6)	2 (1)
- TESTOSTERONE-5-ALPHA REDUCTASE INHIBITORS	0	1 (3)	1 (3)	0	2 (1)
DRUGS FOR CONSTIPATION	2 (6)	1 (3)	1 (3)	3 (10)	7 (5)
- OSMOTICALLY ACTING LAXATIVES	1 (3)	1 (3)	0	2 (6)	4 (3)
- BULK-FORMING LAXATIVES	1 (3)	0	0	0	1 (1)
- CONTACT LAXATIVES	0	0	1 (3)	0	1 (1)
- ENEMAS	0	0	0	1 (3)	1 (1)
- OTHER DRUGS FOR CONSTIPATION	0	0	0	1 (3)	1 (1)
- SOFTENERS, EMOLLIENTS	0	0	0	1 (3)	1 (1)
NASAL PREPARATIONS	1 (3)	2 (6)	1 (3)	1 (3)	5 (4)
- ANTIALLERGIC AGENTS, EXCL. CORTICOSTEROIDS	1 (3)	0	1 (3)	0	2 (1)
- CORTICOSTEROIDS	0	1 (3)	1 (3)	0	2 (1)
- SYMPATHOMIMETICS, COMBINATIONS EXCL. CORTICOSTEROIDS	0	0	0	1 (3)	1 (1)
- SYMPATHOMIMETICS, PLAIN	0	1 (3)	0	0	1 (1)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	3 (9)	1 (3)	0	1 (3)	5 (4)
- UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	3 (9)	1 (3)	0	1 (3)	5 (4)
ANTIBACTERIALS FOR SYSTEMIC USE	2 (6)	0	0	2 (6)	4 (3)
- COMBINATIONS OF SULFONAMIDES AND TRIMETHOPRIM, INCL. DERIVATIVES	1 (3)	0	0	0	1 (1)
- FIRST-GENERATION CEPHALOSPORINS	0	0	0	1 (3)	1 (1)
- FLUOROQUINOLONES	0	0	0	1 (3)	1 (1)
- NITROFURAN DERIVATIVES	1 (3)	0	0	0	1 (1)
ANTIHYPERTENSIVES	2 (6)	0	0	2 (6)	4 (3)
- ALPHA-ADRENORECEPTOR ANTAGONISTS	1 (3)	0	0	2 (6)	3 (2)
- IMIDAZOLINE RECEPTOR AGONISTS	1 (3)	0	0	0	1 (1)
CARDIAC THERAPY	2 (6)	1 (3)	0	1 (3)	4 (3)
- ORGANIC NITRATES	2 (6)	0	0	1 (3)	3 (2)
- OTHER CARDIAC PREPARATIONS	0	1 (3)	0	0	1 (1)
DRUGS FOR TREATMENT OF BONE DISEASES	0	2 (6)	2 (5)	0	4 (3)
- BISPHOSPHONATES	0	2 (6)	2 (5)	0	4 (3)
MUSCLE RELAXANTS	2 (6)	1 (3)	0	1 (3)	4 (3)
- OTHER CENTRALLY ACTING AGENTS	2 (6)	1 (3)	0	1 (3)	4 (3)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	1 (3)	0	2 (5)	1 (3)	4 (3)
- VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS	1 (3)	0	2 (5)	1 (3)	4 (3)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE	1 (3)	1 (3)	0	1 (3)	3 (2)
- OTHER ANTIBIOTICS FOR TOPICAL USE	1 (3)	0	0	1 (3)	2 (1)
- ANTIVIRALS	0	1 (3)	0	0	1 (1)
ANTIFUNGALS FOR DERMATOLOGICAL USE	0	2 (6)	1 (3)	0	3 (2)
- IMIDAZOLE AND TRIAZOLE DERIVATIVES	0	2 (6)	0	0	2 (1)
- OTHER ANTIFUNGALS FOR TOPICAL USE	0	0	1 (3)	0	1 (1)
CORTICOSTEROIDS FOR SYSTEMIC USE	0	2 (6)	1 (3)	0	3 (2)
- GLUCOCORTICOIDS	0	2 (6)	1 (3)	0	3 (2)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	0	2 (6)	1 (3)	0	3 (2)
- PROPULSIVES	0	2 (6)	0	0	2 (1)
- BELLADONNA ALKALOIDS, SEMISYNTHETIC, QUATERNARY AMMONIUM COMPOUNDS	0	0	1 (3)	0	1 (1)
OTHER DERMATOLOGICAL PREPARATIONS	0	1 (3)	2 (5)	0	3 (2)
- AGENTS FOR DERMATITIS, EXCLUDING CORTICOSTEROIDS	0	1 (3)	1 (3)	0	2 (1)
- OTHER DERMATOLOGICALS	0	0	1 (3)	0	1 (1)
TONICS	0	2 (6)	1 (3)	0	3 (2)
- TONICS	0	2 (6)	1 (3)	0	3 (2)
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	0	0	1 (3)	1 (3)	2 (1)
- ANTIDIARRHEAL MICROORGANISMS	0	0	0	1 (3)	1 (1)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- BISMUTH PREPARATIONS	0	0	1 (3)	0	1 (1)
ANTIMYCOTICS FOR SYSTEMIC USE	0	1 (3)	1 (3)	0	2 (1)
- TRIAZOLE DERIVATIVES	0	1 (3)	1 (3)	0	2 (1)
ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	0	2 (6)	0	0	2 (1)
- ANESTHETICS FOR TOPICAL USE	0	1 (3)	0	0	1 (1)
- OTHER ANTIPRURITICS	0	1 (3)	0	0	1 (1)
COUGH AND COLD PREPARATIONS	0	0	1 (3)	1 (3)	2 (1)
- EXPECTORANTS	0	0	0	1 (3)	1 (1)
- HERBAL DIAPHORETICS AND OTHER HERBAL COUGH AND COLD REMEDIES	0	0	0	1 (3)	1 (1)
- HERBAL EXPECTORANTS AND EMOLLIENTS	0	0	0	1 (3)	1 (1)
- MUCOLYTICS	0	0	0	1 (3)	1 (1)
- OPIUM ALKALOIDS AND DERIVATIVES	0	0	1 (3)	0	1 (1)
EMOLLIENTS AND PROTECTIVES	0	1 (3)	1 (3)	0	2 (1)
- OTHER EMOLLIENTS AND PROTECTIVES	0	1 (3)	1 (3)	0	2 (1)
- SOFT PARAFFIN AND FAT PRODUCTS	0	1 (3)	0	0	1 (1)
OTHER NERVOUS SYSTEM DRUGS	0	0	1 (3)	1 (3)	2 (1)
- OTHER PARASYMPATHOMIMETICS	0	0	1 (3)	1 (3)	2 (1)
ALL OTHER THERAPEUTIC PRODUCTS	1 (3)	0	0	0	1 (1)
- OTHER THERAPEUTIC PRODUCTS	1 (3)	0	0	0	1 (1)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
ANESTHETICS	0	0	0	1 (3)	1 (1)
- AMIDES	0	0	0	1 (3)	1 (1)
ANTI-ACNE PREPARATIONS	1 (3)	0	0	0	1 (1)
- RETINOIDS FOR TOPICAL USE IN ACNE	1 (3)	0	0	0	1 (1)
ANTIEMETICS AND ANTINAUSEANTS	0	0	0	1 (3)	1 (1)
- SEROTONIN (5HT3) ANTAGONISTS	0	0	0	1 (3)	1 (1)
ANTIHEMORRHAGICS	0	0	0	1 (3)	1 (1)
- AMINO ACIDS	0	0	0	1 (3)	1 (1)
ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS	0	0	1 (3)	0	1 (1)
- CENTRALLY ACTING ANTIOBESITY PRODUCTS	0	0	1 (3)	0	1 (1)
ANTIPSORIATICS	0	0	1 (3)	0	1 (1)
- OTHER ANTIPSORIATICS FOR TOPICAL USE	0	0	1 (3)	0	1 (1)
ANTIVIRALS FOR SYSTEMIC USE	0	1 (3)	0	0	1 (1)
- NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	0	1 (3)	0	0	1 (1)
BILE AND LIVER THERAPY	1 (3)	0	0	0	1 (1)
- LIVER THERAPY	1 (3)	0	0	0	1 (1)
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	0	0	0	1 (3)	1 (1)
- ELECTROLYTE SOLUTIONS	0	0	0	1 (3)	1 (1)
- SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	0	0	0	1 (3)	1 (1)
DIGESTIVES, INCL. ENZYMES	1 (3)	0	0	0	1 (1)

Medication Class (ATC code)	20 ug, N=33 n (%)	5 ug, N=34 n (%)	1 ug, N=40 n (%)	Placebo, N=31 n (%)	Total, N=138 n (%)
- HERBAL DIGESTIVES, OTHER	1 (3)	0	0	0	1 (1)
ENDOCRINE THERAPY	0	0	1 (3)	0	1 (1)
- GONADOTROPIN RELEASING HORMONE ANALOGUES	0	0	1 (3)	0	1 (1)
IMMUNOSUPPRESSANTS	0	0	1 (3)	0	1 (1)
- OTHER IMMUNOSUPPRESSANTS	0	0	1 (3)	0	1 (1)
OTHER GYNECOLOGICALS	1 (3)	0	0	0	1 (1)
- INTRAUTERINE CONTRACEPTIVES	1 (3)	0	0	0	1 (1)
THROAT PREPARATIONS	0	0	0	1 (3)	1 (1)
- ANTISEPTICS	0	0	0	1 (3)	1 (1)
- THROAT PREPARATIONS	0	0	0	1 (3)	1 (1)
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	0	1 (3)	0	0	1 (1)
- ANTIINFLAMMATORY PREPARATIONS, NON-STEROIDS FOR TOPICAL USE	0	1 (3)	0	0	1 (1)
VACCINES	0	0	1 (3)	0	1 (1)
- INFLUENZA VACCINES	0	0	1 (3)	0	1 (1)

Listing(s): Derived from Listing 16.2.4.2

Table 14.3.5.4 Summary of pregnancy test outcomes

a) Outcome at Visit 1, Visit 2 and Visit 6

Visit	Category	20 mg	5 mg	1 mg	Placebo
VISIT 1	n	4	1	2	0
	Negative	4	1	2	0
	Positive	0	0	0	0
	Not Done	0	0	0	0
VISIT 2	n	4	1	2	0
	Negative	4	1	2	0
	Positive	0	0	0	0
	Not Done	0	0	0	0
VISIT 6	n	4	1	2	0
	Negative	4	1	0	0
	Positive	0	0	0	0
	Not Done	0	0	2	0

Visit 1: serum test; Visits 2 and 6: urine tests
Listing(s): Derived from Listing 16.2.8.1

14.3.5.4 Summary of pregnancy test outcomes: b) Summary of HCG test at Visit 1

Variable	Visit	Statistic	20 ug, N=33	5 ug, N=34	1 ug, N=40	Placebo, N=31
Choriogonadotropin Beta (U/L)	Visit 1	n	9	9	7	9
		Mean (SD)	1.8 (1.2)	2.2 (2.2)	2.4 (2.8)	2.3 (1.4)
		Median	2.50	1.50	1.30	2.50
		Min, Max	0.05, 3.20	0.05, 6.60	0.05, 7.70	0.30, 4.10
Values below ULOQ estimated to 2 x ULOQ Visit 1: serum test Listing(s): Derived from Listing 16.2.8.1						

Figure 14.3.5.1 Shift plots for vital signs

a: Systolic Blood Pressure (mmHg)

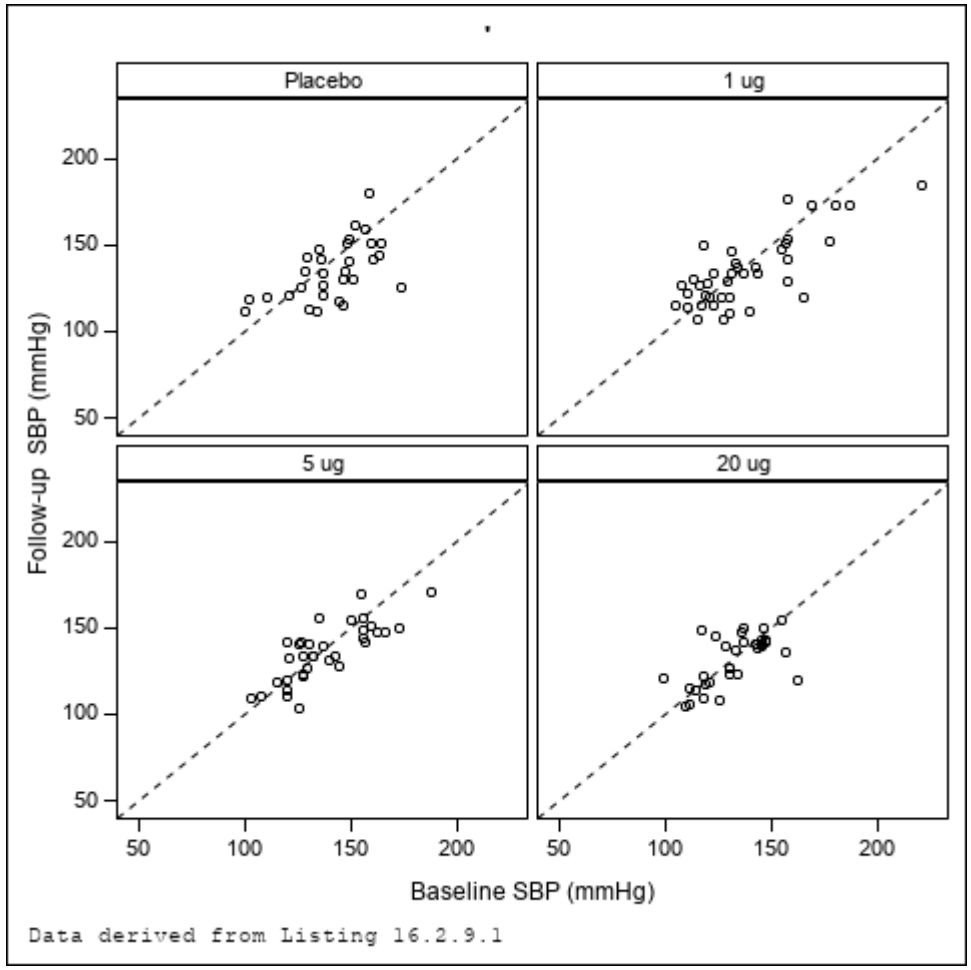


Figure 14.3.5.1 Shift plots for vital signs: b: Diastolic Blood Pressure (mmHg)

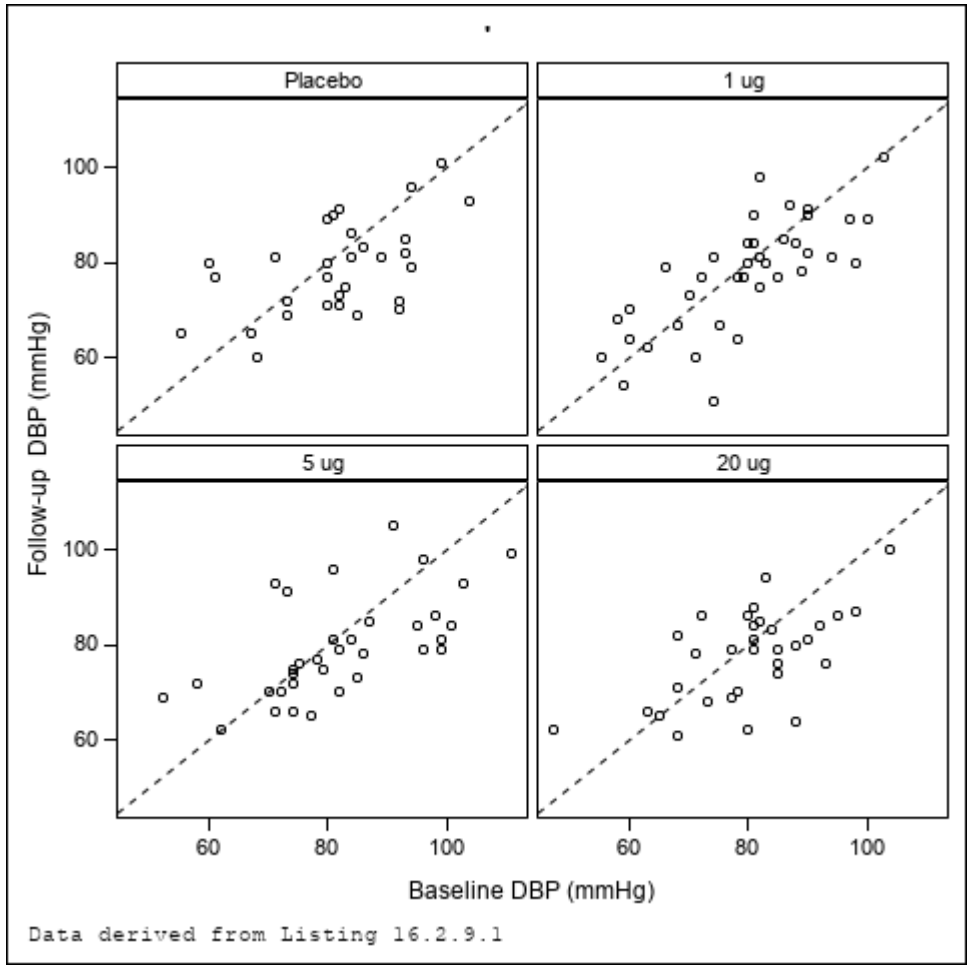


Figure 14.3.5.1 Shift plots for vital signs: c: Pulse (beats/min)

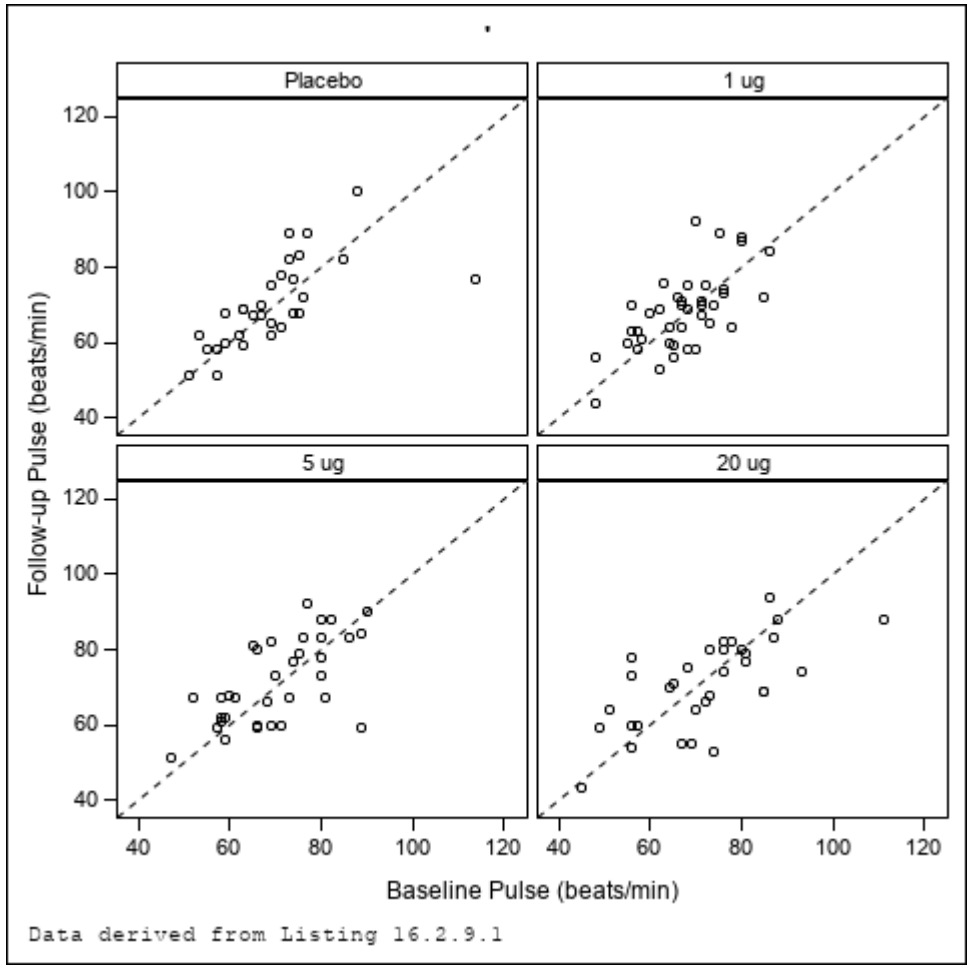


Figure 14.3.5.1 Shift plots for vital signs: d: Oral temperature (C)

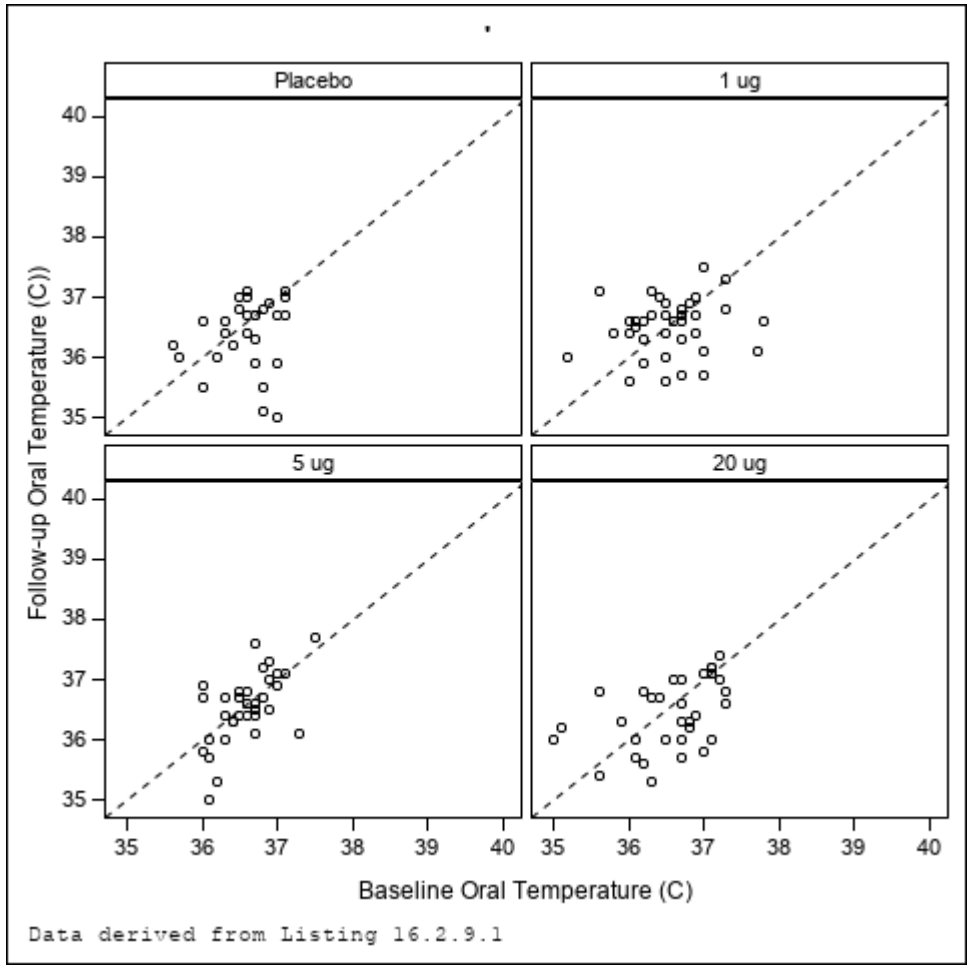


Figure 14.3.5.1 Shift plots for vital signs: e: Weight (kg)

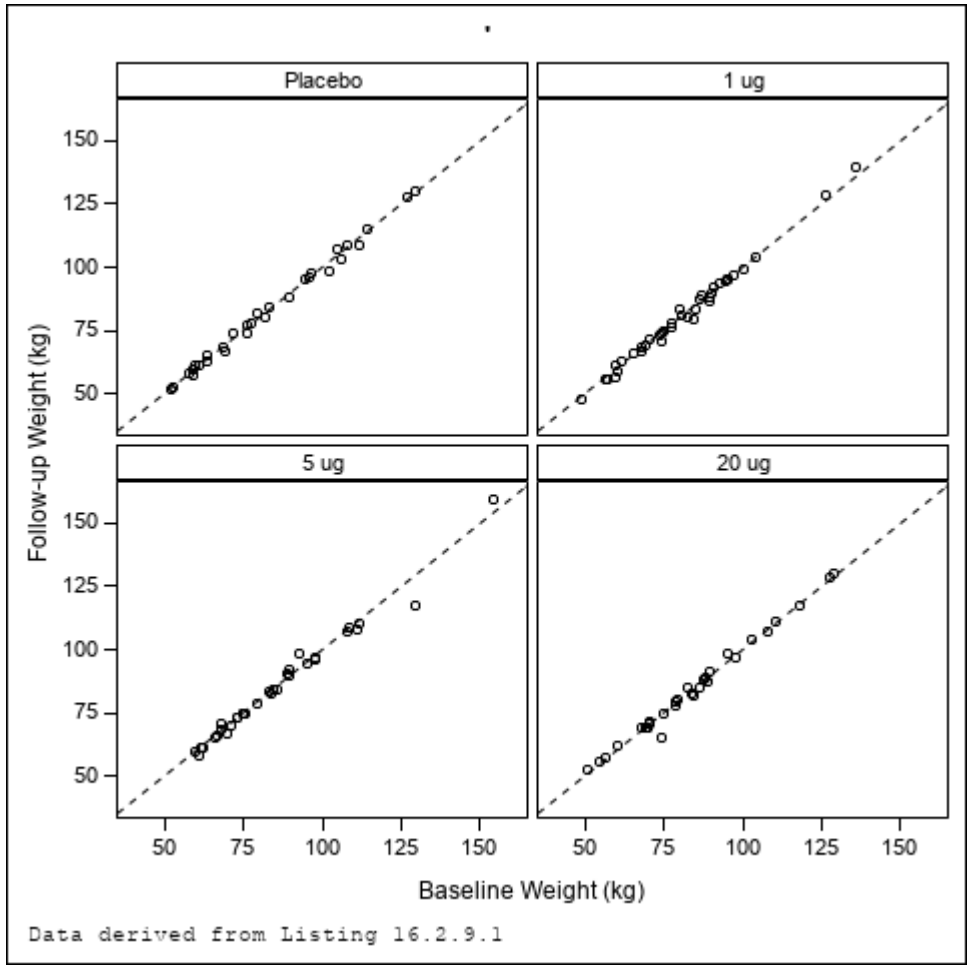
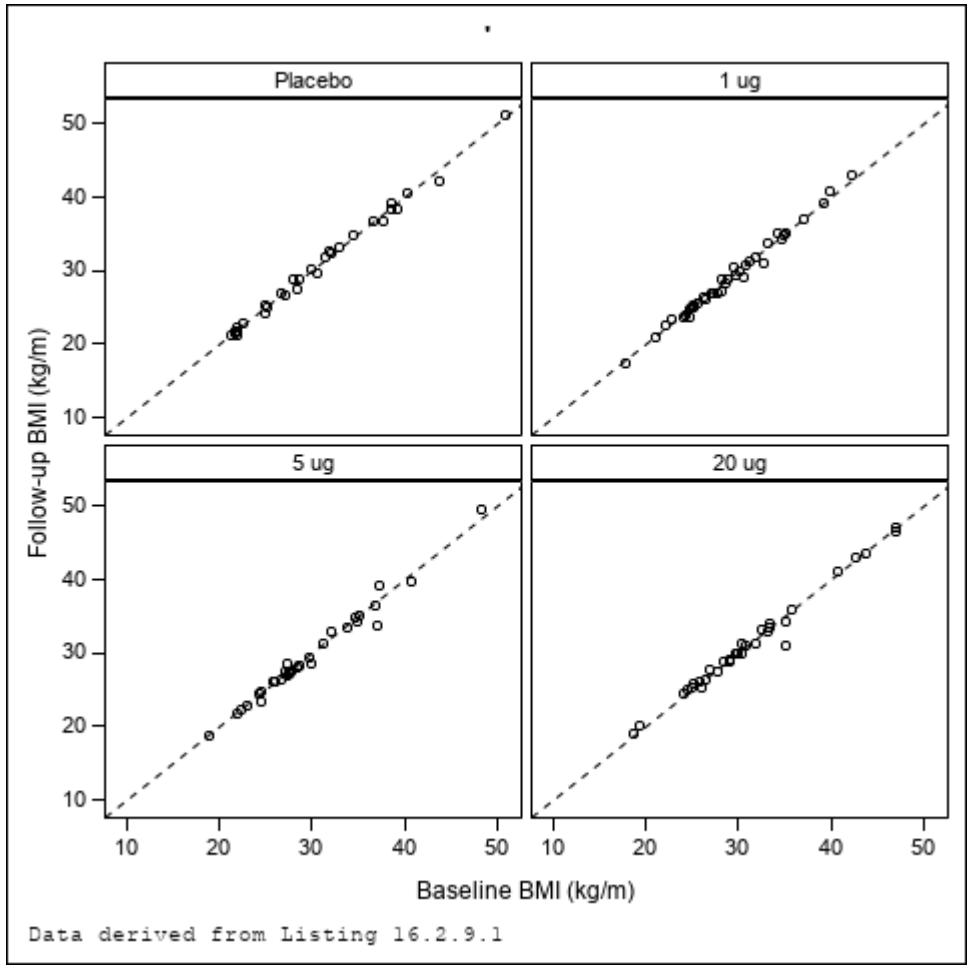


Figure 14.3.5.1 Shift plots for vital signs: f: Body Mass Index (kg/m2)



15 REFERENCE LIST

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16 APPENDICES - LIST OF APPENDICES

16.1	**Study information**
16.1.1	Protocol and protocol amendments
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