CLINICAL STUDY REPORT

According to ICH-E6 (GCP), chapter 5.22 and ICH-E3 (Study Reports)

Study Title:	**THE EFFECT OF AZELAIC ACID ON SYMPTOMS OF ACNE IN FEMALE PATIENTS AGE 20-45 WITH MILD TO MODERATE PAPULOPUSTULAR ACNE (ACNE TARDA)**
Investigational Product:	Azelaic acid 15% (Skinoren® 15% Gel)
Indication:	Mild to moderate papulopustular acne
Sponsor:	**Department of Dermatology and Allergy** Prof. Dr. med. Ulrike Blume-Peytavi, MD Clinical Research Center for Hair and Skin Science Charité-Universitätsmedizin Berlin Charité Campus Mitte Charitéplatz 1 10117 Berlin-GERMANY Tel.: + 49 30 450 518 229 Fax: + 49 30 450 512 952 E-mail: ulrike.blume-peytavi@charite.de
Protocol Code:	CRC-ACNE-A-05
EudraCT-Number:	2013-000416-24
Study Phase:	Exploratory cohort study
Date First Patient in:	9th of August 2013
Study Completion Date (Date Last Patient Out):	4th of September 2014
Name/ Affiliation of Principal Investigator:	Prof. Dr. med. Ulrike Blume-Peytavi, MD Department of Dermatology, Venereology and Allergy Clinical Research Center for Hair and Skin Science Charité-Universitätsmedizin Berlin Charité Campus Mitte Charitéplatz 1 10117 Berlin, GERMANY

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GCP and Archiving Statement:	This study was conducted in accordance with local law ("Deutsches Arzneimittelgesetz" and "GCP-Verordnung"), the Declaration of Helsinki, ICH-GCP and the study protocol as presented in this report. The study documents will be archived for 10 years: according to protocol version 1.3 reflecting GCP-Verordnung (§13, paragraph 10)
Date of the Report:	February 10, 2015

1. Report Synopsis of Study CRC-ACNE-A-05

Name of Sponsor/ Company: Prof. Dr. med. Ulrike Blume-Peytavi, MD, PhD Department of Dermatology, Venerology and Allergology Clinical Research Center for Hair and Skin Science Charité-Universitätsmedizin Berlin	Individual Study Table Referring to Part of the Dossier: n.a. Volume: n.a. Page: n.a.	(*For National Authority only*)
Name of Finished Products: • Skinoren® 15% Gel		
Name of Active Ingredients: • Azelaic acid 15%		
Title of the Study: The effect of Azelaic acid on symptoms of Acne in female patients aged 20-45 with mild to moderate papulopustular Acne (Acne tarda) (protocol version 1.2, date: 11.06.2013)		
Investigators: Principal Investigator and Sponsor: Prof. Dr. med. Ulrike Blume-Peytavi, MD, PhD Deputy principal investigator: Dr. med. Kathrin Hillmann, MD		
Study center: Clinical Research Center for Hair and Skin Science Department for Dermatology and Allergy Charité-Universitätsmedizin Berlin Charité Campus Mitte Charitéplatz 1 10117 Berlin – GERMANY		
Publication (reference): No publications at the date of the report.		

Name of Sponsor/ Company: Prof. Dr. med. Ulrike Blume-Peytavi, MD, PhD **Department of Dermatology, Venerology and Allergology** Clinical Research Center for Hair and Skin Science Charité-Universitätsmedizin Berlin	Individual Study Table Referring to Part of the Dossier: na Volume: na Page: na	(*For National Authority only*)
Name of Finished Products: • Skinoren® 15% Gel		
Name of Active Ingredients: • Azelaic acid 15%		

Studied period (years): 2013 - 2014 **Date of first enrolment:** 9th of August 2013 **Date of last subject completed:** 4th of September 2014	**Phase of development:** Exploratory cohort Study

Objectives:

The aim of this prospective study was to evaluate, whether the treatment with Skinoren® 15% gel leads to a measurable softer and smoother skin besides the improvement of acne symptoms.

Variables:

- Investigator's Static Global Assessment (ISGA) (0 to 5)
- Skin surface parameters: smoothness (SEsm), scaling (SEsc), mean roughness (Rz) measured by Visioscan® VC98
- Skin elasticity parameters: maximum extension (mm) , biological elasticity (mm) measured by Cutometer® MPA 580
- Course of intensity and spreading of the pigmentation (brightness- (L*), red- (a*) and yellow chrominance (b*) measured by broadband spectrophotometry)
- Quality of life (Dermatology Life Quality Index (DLQI)) assessment
- Safety evaluation by assessing the tolerability (local intolerance assessment) and by recording of adverse events

Number of patients (planned and analyzed):

Planned volunteers: 53

Analyzed volunteers: 53, loss to follow-up n = 12

Diagnosis and main criteria for inclusion: Mild to moderate facial papulopustular acne

Main criteria for inclusion:

- Female volunteers
- Age 20 - 45
- Acne papulopustulosa of the face (acne tarda)
- ISGA Score 2 (some non-inflammatory lesions, with few inflammatory lesions) or 3 (non-inflammatory lesions predominate, with multiple inflammatory lesions)
- Good general condition and good state of health

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- Written informed consent
- Use of a highly effective method of birth control1, if use of a hormonal method, the same drug has to be used since at least 6 month prior to inclusion in the study
- Nonsmokers or smokers of maximum 5 cigarettes/day
- BMI between 20 and 28 kg/m²

[1] Defined as a method that results in a low failure rate (i.e., less than 1% per year (Pearlindex ≤1)) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence, or vasectomized partner.

Test product, dose and mode of administration, batch number:

Skinoren® 15% Gel (Azelaic acid 15%)
Dose: Product was applied in a thin layer on the affected facial skin areas according to product information.
Mode of administration: topical, twice daily (in the morning and in the evening)
Batch numbers: **24515C** (expiry date: 10/ 2015); **34618A** (expiry date: 10/ 2016)

Duration of Treatment: 24 weeks

The overall duration of treatment with Skinoren® 15% gel was 6 months. The gel was applied topically in the morning and evening on the facial skin areas affected by acne by the patient herself.

Criteria for evaluation:

- Change of the parameters (variables / outcome/ methodology) between Baseline and End of study (Visit 4).
- Trend of the change in parameters (variables / outcome/ methodology) during the course of the study (Visit 1, 2, 3, 4)

Security:

- Local intolerance
- AEs local and systemic
- SAEs local and systemic

Assessments were performed at baseline on Day 0, at Visit 2 (week 4), at Visit 3 (week 12) and at Visit 4 (week 24)/end of trial.

Statistical methods:

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- Data analysis was conducted exploratory. All available data per measurement time point was described excluding the losses to follow-up. No imputation was used.
- The metric variables smoothness (SEsm), scaliness (SEsc), mean roughness (Rz), maximal extension (mm), biological elasticity (%), brightness- (L*), red- (a*), yellow chrominance values (b*) and DLQI scores were described using means and standard deviations
- In a second step a trend-analysis was performed using a Repeated Measures ANOVA. Only those patients were included who completed all study visits (n = 41).
- An alpha-error of 0.05 was applied for all tests.

Summary – Conclusions:

Results:

- Skinoren® 15% Gel improved acne symptoms
- The mean ISGA scores decreased
- Quality of life improved during the course of the study
- Results of skin smoothness, skin scaliness, skin elasticity and skin color measured by broadband spectrophotometry were different at the 4 measuring points (forehead – right facial side; inner cheek – right facial side; chin – center; outer cheek – right facial side.[1]
- Skin smoothness, scaliness, elastic properties and color did not change.

Safety results:

Skinoren® 15% Gel is a safe and well tolerable topical acne treatment. Local intolerances (itching, burning, stinging, scaling sensations) decreased with increasing duration of application time

There was one SAE which was not product related.

Conclusion:

Overall, it can be concluded that the test product is an effective and safe topical monotherapy for the treatment of mild to moderate acne papulopustulosa, especially acne

[1] See Figure 5.

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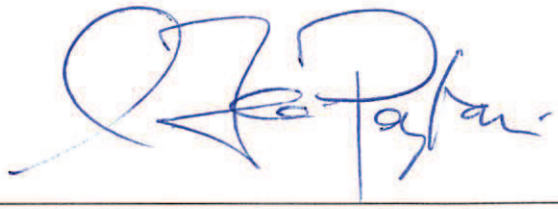
tarda. There was no overall change of the skin characteristics smoothness, colour and elasticity observed during the course of the study.

Skinoren® 15% Gel is a safe, good tolerable topical monotherapy for successfully treating mild to moderate acne papulopustulosa.

I hereby confirm that the data in the results report were collected properly and are correct.

Date of the report: February 12th, 2015

Print Name: Prof. Dr. Ulrike Blume-Peytavi

Signature: 

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3. List of Figures and Tables

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4. List of Abbreviations and Definition of Terms

Abbreviations

a	Red chrominance
AE	Adverse Event
AEF	Adverse Event Form
AFA	Adult Female Acne
AMG	Arzneimittelgesetz (German Drug Law)
AzA	Azelaic Acid
b	Yellow chrominance
BfArM	Bundesinstitut fuer Arzneimittel und Medizinprodukte
BMI	Body Mass Index
CA	Competent Authority/ ies
CI	Confidence Interval
CRC	Clinical Research Center for Hair and Skin Science
CRF	Case Report Form
CRO	Contract Research Organization
DC	Discontinued
EMA	European Medicines Agency
EoS	End of Study
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCP-V	GCP Verordnung
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IIT	Investigator Initiated Trial
IMP/ IP	Investigational Medicinal Product
INN	International Nonproprietary Names
ISF	Investigator Site File
ISGA	Investigator´s Static Global Assessment
ITT	Intent to Treat
IUD	Intra-uterine device
L	Brightness
LAGeSo	Landesamt fuer Gesundheit und Soziales
LAGeSo-IEC	Independent Ethics Committee at LAGeSo

LI	Local Intolerance
N (n)	Number
n.a.	Not applicable
n.k.	Not known
NR	Not Related
OTC	Over-the-Counter
PP	Per protocol population
QoL	Quality of Life
R	Related
R0	Structural extensibility of skin
R7	Relative elastic recovery of skin
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SN	Subject Number
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TP	Technical Procedure
UK	Unknown
UV	Ultra Violet
WHO	World Health Organization

Definitions

BfArM	German federal authority for testing, approving and supervising medicinal products and medical devices.
CRC	Name of study site
GCP-V	German law, regulating the compliance to GCP on national level, accompanying Order of Performance to German Drug Law.
LAGeSo	Local authority (Regional office for Health and Social affairs)
LAGeSo-IEC	Department of Ethics Committee for the state of Berlin, responsible IEC for study site.

5. Ethics

5.1 Independent Ethics Committee (IEC)

The clinical study *"The effect of Azelaic acid on symptoms of Acne in female patients aged 20-45 with mild to moderate papulopustular Acne (Acne tarda)"* was reviewed and received a favorable opinion by *Ethikkommission des Landes Berlin* at *Landesamt für Gesundheit und Soziales Berlin (LAGeSo)*, the responsible independent ethics committee for the study center.

- Request for favorable opinion was sent to IEC on the 28th of March 2013.
- Principal investigator/sponsor was invited to a hearing at the IEC on 29nd of April 2013.
- Final favorable opinion was given on the 19th of June 2013[2].

5.2 Ethical Conduct of the Study

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the local law (German Drug Law, GCP-Verordnung), ICH-GCP and the protocol as presented.

5.3 Subject Information and Consent[3]

Recruitment started after approval of the federal authority (BfArM), received 5th of September 2013 and favorable opinion of the IEC (LAGeSo), 17th of September 2013.

First information about the conduct of this clinical trial was given through IEC approved advertisements in the Berlin subway, CRC subject database, CRC homepage, digital Charité intranet notice board, leaflets and addressing patients at the consulting hours for acne of the Department for Dermatology.

Interested persons could contact the Clinical Research Center for Hair and Skin Science (CRC) and were invited to study specific information events.

These information events were organized and conducted by the study team of the CRC. During these events, the potentially eligible subjects were informed about the planned clinical trial and they had the opportunity to ask questions. If they were interested in taking part, they had the chance for individual conversations with the investigators, who pre-screened the potential study participants by examining the acne severity and going through the main in- and exclusion criteria, such as intolerances and concomitant medication. Those who were potentially eligible for participating were given an appointment for the screening visit.

Obtaining informed consent was only carried out by the designated investigators. The information and informed consent process took place prior any study procedures.

Informed consent was obtained during the screening visits. Screening and baseline were carried out separately. Each subject received a copy of the IEC approved subject information and informed consent form and had sufficient time to read it. Prior signing and dating the

[2] List of IEC members and committee chair are provided in appendix 16.1.3
[3] Sample written subject information and informed consent form (German original) are attached in appendix 16.1.3

informed consent form, each volunteer was informed individually and thoroughly about the characteristics, benefits, risks and the rationale of the clinical trial by one of the designated investigators. During this process, room was given for discussion and answering questions.

After individual information, volunteers signed and dated the informed consent form twice, together with the informing investigator. One completely signed copy was given to the subject, together with the subject information and a copy of the subject's insurance. One completely signed copy of each informed consent remained at the study center and was stored in the investigator site file (ISF).

6. Investigators[4] and Study Administrative Structure

This clinical trial was an exploratory, prospective, non-commercial, cohort Investigator Initiated Trial (IIT) and was sponsored by Charité-Universitätsmedizin Berlin, Department of Dermatologyand Allergy, Clinical Research Center for Hair and Skin Science (CRC). Sponsor's representative and coordinating/ principal investigator of this trial was Prof. Dr. med. U. Blume-Peytavi, MD. Deputy principal investigator was Dr. med. K. Hillmann, MD. This sponsorship was supported by the ECARF-Institute GmbH Berlin (Germany).

The study was planned, designed, registered, conducted and evaluated by the CRC. All study relevant procedures, such as writing study documents, statistical calculations, subject's insurance, acquiring an EudraCT number and database listing, study material supply and the order of study medication was organized by CRC. This included sending required study documents (according to GCP-Verordnung §7, paragraphs 2 and 3) and qualification of study site personnel and investigators to responsible IEC (department of ethics committee at LAGeSo) as well as sending the required study documents (according to GCP-Verordnung §7, paragraphs 2 and 4) to the federal authority (Bundesinstitut für Arzneimittel und Medizinprodukte - BfArM). In addition, the local authority (LAGeSo) was informed by CRC about the conduct of the clinical trial according to §67 German Drug Law and §12, paragraphs 1-3 GCP-V.

The CRC study team consisted of the principal investigator, the deputy principal investigator and five co-investigators. Further the investigators were supported by one project manager[5], four study assistants[6] and one documentation/archiving assistant.

To assure independent and ICH-GCP compliant quality assurance (according to ICH-E6, chapter 5.18), periodical monitoring was conducted by an independent monitor to assure data quality (complete, traceable and readable), adherence to the protocol and GCP compliance.

Study statistics were carried out by an independent statistician[7] who calculated the sample size, and determined study analysis parameter and procedures.

For a better overview, the administrative and organizational structure of the study will be displayed in a chart below:

[4] A list of the investigators with their role in the study, their qualifications and affiliations are provided in appendix 16.1.4
[5] The role of the project manager in the study, her qualification and affiliation are provided in appendix 16.1.4
[6] A list of the participating study assistants with their role in the study, their qualifications and affiliations are provided in appendix 16.1.4
[7] A list of the statistician and the authors of the report are provided in appendix 16.1.4

Table 1: Study Administrative Structure

	Person	**Task**
Study Team CRC	Sponsor/ Coordinating Investigator/ Principal Investigator Deputy Principal Investigator	-Sponsor's duties according to ICH-GCP, chapter 5 -Investigator's duties according to ICH-GCP, chapter 4 -Overall responsibility -Training study team -Designing, planning clinical trial, regulatory, financing, delegating study tasks within the study team, supervision of study progress, study management - reporting AEs, SAEs, SUSARs, etc.to competent authorities -GCP compliant study conduct, documentation, monitoring, evaluation, publication, archiving
	Co-Investigators	-Investigator's duties according to ICH-GCP, chapter 4 -training -organizational responsibility for the study -writing study documents -providing study documents according to ICH-GCP, chapter 8 -handing study in to regulatory authorities -managing study team -recruitment -obtaining informed consent -GCP compliant study conduct -documentation of AEs, SAEs -study documentation -assisting monitoring -evaluation -publication
	Project Manager	-organisational responsibility for the study -writing study documents -providing study documents according to ICH-GCP, chapter 8 -handing study in to regulatory authorities -training -recruitment - drug accountability - GCP compliant study conduct -documentation of AEs, SAEs - study documentation -assisting / coordinating monitoring
	Study Assistants	-GCP compliant study conduct -assisting investigators -recruitment -documentation -documentation of AEs, SAEs -drug accountability -dispensing/collecting study medication -time schedule -schedule visits -material supply -study medication supply
	Documentation/ Archiving	-assisting whole study process -preparing data for evaluation -archiving study documents
External Partners	External monitor	Monitoring
	Canfield Scientific	Computerized Visia CR image analysis regarding course of intensity and spreading of pigmentation
	Statistician	Responsible for all statistical matters of the study

7. Introduction

Worldwide acne is one of the most frequent skin diseases (Hay, 2014). Epidemiological studies in western industrialized countries estimated the prevalence of acne in adolescents to be between 50% and 95%. Acne is a disease primarily of adolescence. It is triggered in children by the initiation of androgen production by the adrenal glands and gonads, and it usually subsides after the end of growth. However, to some degree, acne may persist beyond adolescence in a significant proportion of individuals, particularly women, so called acne tarda.

Acne is an androgen-dependent disorder of pilosebaceous follicles. There are four primary pathogenic factors, which interact to produce acne lesions: (1) increased sebum production by the sebaceous gland, (2) alteration in the keratinization process, (3) Propionibacterium acnes follicular colonization, and (4) release of inflammatory mediators (Nast, 2012).

This leads to the development of clinically visible non-inflammatory (microcomedones, open and closed comedones) and inflammatory lesions (papules, pustules and nodules). These are predominantly found in the face but may occur in decreasing frequency on the back and chest, shoulders, neck, and upper arms.

In this study only facial acne was considered. Depending on the severity and visibility of the localization (e.g. face) of the condition, the patients may even suffer from depression because acne is a psychologically burdensome situation (Uhlenhake, 2010).

In a recent guideline for the treatment of acne for mild to moderate papulopustular acne therapies of high and medium strength of recommendation are topical benzoyl peroxide (BPO), azelaic acid and retinoids as well as combinations of adapalene/BPO, clindamycin/BPO and systemic antibiotics/adapalene. Topical BPO acts antimicrobial and just as retinoids comedolytic, sebo-suppressive and anti-inflammatory (Nast A 2012).

Azelaic acid has been shown to reduce the increased keratinocyte production and bacterial colonization. It further possesses a mild anti-inflammatory effect (Fluhr, 2010). As described above azelaic acid is recommended for the treatment of mild to moderate papulopustular acne (Nast 2012) and azelaic gel is officially authorized for the treatment of acne in Germany since 2003 (Zouboulis, 2009).

Clinical observations and patient self-reports suggest an overall improvement of the complexion besides the reduction of papules and pustules after the treatment with azelaic acid.

In consultation especially female patients reported a smoother and softer overall appearance of the skin and an improvement of the complexion. To date there is no evidence for these clinical subjectively reported observations. This raises the question if this reported smoother and softer overall appearance can be measured.

To investigate and quantify this clinical subjective effect of azelaic acid in patients affected by acne after adolescence, an exploratory clinical study on female patients aged 20-45 with mild to moderate forms of the condition was conducted.

8. Study Objectives

The aim of this prospective study was to evaluate, if the treatment with Skinoren® 15% gel leads to a smoother and softer skin besides the improvement of acne symptoms.

8.1 Primary Variable

Skin surface parameter: Smoothness (SEsm) measured by Visioscan® VC98

8.2 Secondary Variables

Skin surface parameters: mean roughness (Rz), scaling (SEsc), measured by Visioscan® VC98

Skin elasticity parameters:, maximum extension (mm), biological elasticity (%) measured by Cutometer® MPA 580.

Pigmentation (brightness- (L*), red- (a*) and yellow chrominance (b*) measured by broadband spectrophotometry

Quality of life scores (Dermatology Life Quality Index (DLQI))

Investigator's Static Global Assessment (ISGA) (0 to 5)

9. Investigational Plan

9.1 Overall Study Design and Plan-Description

An exploratory, prospective cohort clinical trial was conducted. The protocol[8] was established according to ICH-GCP, chapter 6 and in compliance with the Declaration of Helsinki.

Patients complying with the in- and exclusion criteria received the study medication with a patient number, allocated in ascending order in correspondence to the respective study entry date, at the first treatment day (visit 1). All patients received the same therapy for 24 weeks that was a whole face treatment with azelaic acid gel. All study relevant source data was recorded in a trial worksheet first and was then copied into a subject-related case report form.[9]

[8] Study protocol (version 1.2) (date: 11.06.2013), see appendix 16.1.1
[9] Sample Case Report Form, see appendix 16.1.2

work steps	**Screening** (day -28 to 0)	**Visit 1** (Baseline, day 0)	**Visit 2** (end of week 4)	**Telephone call follow up** (week 8)	**Visit 3** (week 12)	**Telephone call follow up** (week 18)	**Visit 4** (week 24)
Information	x						
Check In- and Exclusion criteria	x	x					
Urine pregnancy test (if applicable)	x						x
Physical examination	x						x
Informed Consent	x						
BMI	x						
Vital signs	x	x	x		x		x
Concomitant medication	x	x	x		x		x
Application of study products		←	—	—	—	—	→
Patient Diary		←	—	—	—	—	→
Visioscan® VC98 measurements		x	x		x		x
Cutometer® MPA 580 measurements		x	x		x		x
Investigator's Static Global Assessment (ISGA) direct	x	x	x		x		x
Standardized photography with Visia CR incl. measurement of the Intensity and spreading of the pigmentation		x	x		x		x
Chromametry: Brightness- (L*), red- (a*) and yellow chrominance (b*)		x	x		x		x
DLQI-Index		x			x		x
Telephone call to ensure compliance				x		x	
Local Intolerance		←	—	—	—	—	→
AEs		←	—	—	—	—	→
SAEs		←	—	—	—	—	→

Figure 1: Schedule of Assessments

9.2 Discussion of Study Design, including the choice of Control Group

The overall aim was to evaluate whether the assumed softening and/or smoothening effect does exist. Therefore a cohort study was considered as the best design in order to measure potential changes during the follow up period. A control group was not chosen, because of the explorative nature of this study. In case, skin smoothening and/or softening effects are detected, a subsequent confirmatory approach might be justified.

The chosen skin surface parameters, ISGA score, a standardized photo documentation, skin elasticity (cutometry) and pigmentation (chromametry) are widely used and accepted in dermatological research. In order to take the patients perception into account, the Dermatology Life Quality Index – DLQI was used.

9.3 Selection of Study Population

9.3.1 Inclusion criteria

53 female patients aged 20 - 45 years; with clinical diagnosis of mild to moderate facial papulopustular acne (according to ISGA score) were recruited.

The selection of patients was in accordance with the requirements of the German drug law (Arzneimittelgesetz, AMG) as well as the recommendations of the currently valid revision of the Helsinki Declaration and the ICH efficacy guidelines and “Guidelines for Good Clinical Practice” (GCP) (2002).

Women of childbearing potential had to present one efficient contraception method and a negative pregnancy test at screening.[10]

Subjects had to agree to study schedule, visit appointments, investigation plan and other study related procedures.

The patients were selected according to defined inclusion and exclusion criteria.

[10] See Table 2: Inclusion Criteria

Subjects had to meet the inclusion criteria listed in Table 2:

Table 2: Inclusion Criteria

- Female volunteers
- Age 20 - 45
- Acne papulopustulosa of the face (acne tarda)
- ISGA Score 2 (some non-inflammatory lesions, with few inflammatory lesions) or 3 (non-inflammatory lesions predominate, with multiple inflammatory lesions)
- Good general condition and good state of health
- Written informed consent
- Subjects of childbearing potential must have a reliable negative pregnancy test at baseline and must not be breast-feeding. Women of childbearing potential participating in the trial must use highly effective form[11] of contraception, if use of a hormonal method, the same drug has to be used since at least 6 month.
- Nonsmokers or smokers of maximum 5 cigarettes/day
- BMI between 20 and 28 kg/m²
- Agreement not to use any cosmetics at the days of study visits

[11] Defined as a method that results in a low failure rate (i.e., less than 1% per year (Pearlindex ≤1)) when used consistently and correctly, such as implants, injectables, combined oral contraceptives (no minipill), some IUDs, sexual abstinence, or vasectomized partner.

9.3.2 Exclusion Criteria

Exclusion criteria are listed in Table 3.

Table 3: Exclusion Criteria

- Severe form of Acne (ISGA score 4 or higher)
- Other dermatological disorder: rosacea, atopic dermatitis, perioral dermatitis, psoriasis,
- Previous smoothing or ablative procedures (cryotherapy, fruit acid -/TCA peelings, Fraxel Laser etc.) within 3 month prior Baseline
- Current acne treatment with topical or systemic acne therapeutics or treatment within 4 weeks prior Baseline
- Participation in a clinical trial within the last 30 days prior Baseline
- Planned absences during scheduled visits or planned pregnancy during the course of the study
- Severe acute or chronic diseases
- Known allergy or hypersensitivity to the Investigational product or any of the formulation ingredients
- Intake or use of the following medication:
- Systemic Isotretinoin (within the last 6 month prior Baseline)
- Systemic antibiotics (within the last 4 weeks prior Baseline)
- Systemic corticosteroids (within the last 4 weeks prior Baseline)
- Systemic non-steroidal anti-inflammatory drugs in dosage for the treatment of inflammations (within the last 4 weeks prior Baseline)
- Topical retinoids (extensive application over the body or in the face within the last 2 weeks prior Baseline)
- Topical corticosteroids (extensive application over the body or in the face within the last 2 weeks prior Baseline)
- Topical use of non-steroidal anti-inflammatory drugs for the treatment of inflammations (extensive application over the body or in the face within the last 2 weeks prior Baseline)
- Intensive UV-exposition or regular visits of solariums within the last 4 weeks prior Baseline or during the course of the study
- Persons who are kept in detention.

The following restrictions were applicable during the trial:

A necessary therapy with any of the substances listed under exclusion criteria during the study course led to an exclusion of the patient from the study.

All medications and other treatment options, which are not listed under exclusion criteria, were allowed but needed to be documented in the case report form. All changes regarding concomitant medication during the study course had to be documented in the case report form as well.

9.3.3 Removal of subjects from therapy or assessments

Subjects with a severe form of acne papulopustulosa, other dermatological disorders, a known hypersensitivity to the study- product/ -procedures and an insufficient contraception or existing pregnancy were not included in the trial. Detailed reasons for not including a subject into the study are stated in the exclusion criteria in chapter 9.3.2.

In general, subjects were withdrawn from the study immediately in case of Informed consent withdrawal.

Subjects could be withdrawn from the study by the investigator at any time for security, compliance or scientific reasons.

Security reasons:
If the investigator had the impression that study participation was not reasonable anymore (e.g.):

- Pregnancy (no further administration of IP will be performed).
- Any AE for which treatment continuation would represent an unacceptable risk for the patient, e.g. facial allergic contact dermatitis with erythema and blistering, pseudoallergic reaction with edema. AEs leading to discontinuation of the respective patient should be marked as such in the CRF.
- In case that signs of local irritation (e.g. erythema, stinging/burning, pruritus), dryness, or peeling do not subside after modification of the dosage regime (see 12.1.3) or aggravate the treatment of the individual patient should be discontinued.
- Increase of the ISGA for one or more grades from baseline (this also has to be documented as an AE in the CRF).

Compliance reasons:

- If the patient interrupted use of IMP for more than 14 consecutive days.
- Patient lost to follow-up after 2 emails, 2 telephone calls and one written letter
- Patient refused to cooperate with required study procedures
- Patients who weren't capable to follow all instructions of the study didn't receive the IP and would have been discontinued from the study even if they were willing to participate, fulfilled all inclusion criteria and didn't meet any exclusion criteria.

If the study medication was discontinued temporarily due to irritation, the patient was not necessarily disqualified from the study.

Scientific reasons:
In case of an event which affects the efficacy of study criteria (e.g.):

- Clinical trial protocol deviations or conditions arising from the exclusion criteria, may (but will not necessarily) lead to the patients' discontinuation. All such conditions should be properly documented.
- Any concomitant therapy with noon-authorized medications and treatments.

Any patient who permanently withdrew or has been withdrawn had to return the trial medication and should be asked to complete all procedures for visit 4 (End of Trial). If the patient withdrew consent, no further evaluations should be performed and no attempts should be made to collect additional data. However, the patient will be questioned regarding his reason for withdrawal. All collected information before a patient withdrew her consent were entered into the database and included in the final evaluation. If a patient did not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible.

9.4 Treatments

9.4.1 Treatments administered

For 24 consecutive weeks, the application of the study medication azelaic acid 15% (Skinoren® 15% Gel) was performed twice daily (in the morning and in the evening) by the subject herself on the entire facial skin. The application schedule was in accordance with the product information of the study product.

Subjects were instructed in detail how to perform product application at V1. During the follow-up visits subjects were specially asked whether they applied the product regularly and according the instructions. The daily treatment was documented in the subject's diary.

9.4.2 Identity of investigational products

The study product Skinoren 15% Gel is already approved and on the German market since 2003. The study was conducted with approved medication so no additional labelling was necessary (GCP-V §5 (8) 2004).

The following products were used:

Table 4: Identity of investigational products

Generic name (brand name)	**IMP 1: Skinoren® 15% Gel**	
Formulation	Gel	
Active ingredient	Azelaic acid	
Amount per unit	150 mg/g	
Packaging	Aluminum tube, 50 g	
Storage	No special storage conditions	
Manufacturer	Intendis GmbH Max-Dohrn-Straße 10 10589 Berlin, Germany	Jenapharm GmbH & Co. KG Otto-Schott-Straße 15 07745 Jena, Germany
Batch number	24515C	34618A
Expiry date	10/2015	10/2016

9.4.3 Method of assigning subjects to treatment groups
Not applicable.

9.4.4 Selection of doses in the study
Study medication was used according to product information. It was applied topically on the affected facial areas in a thin layer.

9.4.5 Selection and timing of dose for each patient
Products were applied twice daily in the morning and evening due to application requirements for Skinoren® 15% Gel.[12]

Products were applied in a thin layer on the affected areas of the face.

9.4.6 Blinding
Study medication was neither blinded nor re-labelled.

9.4.7 Prior and concomitant therapy
All kind of medication not listed in the exclusion criteria was allowed prior and during the clinical trial. As study medication were approved products, sufficient safety data on possible drug-drug interactions were investigated in previous clinical trials. According to this safety data, possible medication which might interfere with the study medication was listed as exclusion criteria.

9.4.8 Treatment compliance
The first application of the study medication at baseline visit was explained to the patient and supervised by the study team at the study center. Afterwards the patient applied the medication twice daily in a thin layer on the entire face over a study period of 24 weeks. During the second study visit at the end of week 4 (see Figure 3) the investigator decided whether to continue or to stop the application. Based on the dermatological assessment and in case of treatment success the Skinoren 15% Gel application was continued.

The patients received a written explanation for the product application and a diary which should be updated according to application time points and possible adverse events on a daily basis by the patient at home. During the following study visits patients were asked about their application practice and instructions were repeated. During the two follow-up phone calls compliance was checked additionally.

[12] See attached product information of Skinoren® 15% Gel

9.5 Study Variables

9.5.1 Measurements and Safety Assessments

The following measurements were done:

Table 5: Variables

Variables	Visit	Method	Responsible person(s)
Skin surface parameter: smoothness (Visioscan® VC98)	Baseline (D0) – visit 4	Measuring skin smoothness with Visioscan® VC98 on 4 designated areas on the center and the right side of the face.[13]	Study nurse
Skin surface parameters: roughness, scaling (Visioscan® VC98)	Baseline (D0) – visit 4	Measuring skin surface parameters with Visioscan® VC98 on 4 designated areas on the center and the right side of the face.[14]	Study nurse
ISGA (0-5)	Screening – visit 4	Determintation of acne severity.	Investigator
Skin elasticity: maximum extension (mm), biological elasticity (mm), (Cutometer® MPA 580)	Baseline (D0) – visit 4	Measuring skin elasticity parameters with Cutometer® on 4 designated areas on the center and the right side of the face.[15]	Study Nurse
Pigmentation: (brightness- (L*), red- (a*) and yellow chrominance (b*) measured by broadband spectrophotometry	Baseline (D0) – visit 4	Measuring skin pigmentation with a Chromameter on 4 designated areas on the center and the right side of the face.[16]	Study Nurse
Photo Documentation (VISIA-CR®)	Baseline (D0) – visit 4	Standardized photo documentation of both lateral sides and front view with Visia-CR®	Study Nurse/ Canfield

[13] See figure 3
[14] See figure 3
[15] See figure 3
[16] See figure 3

Quality of Life: Quality of life score (Dermatology Life Quality Index (DLQI))	Baseline (D0), visit 3, visit 4/ end of study	Determining change in quality of life using the DLQI	Patient/ study nurse
Safety measurements			
AE/SAE documentation	Baseline (D0) – visit 4	Documentation in source data and CRF afterwards	Investigator/ Study Nurse
Local intolerances	Baseline (D0) – visit 4	Documentation in source data and CRF afterwards	Investigator/ Study Nurse
Pregnancy Test	Baseline (D0); visit 4/ end of study	Urine pregnancy test	Study Nurse

9.5.1.1 Safety evaluation measurements

Assessing local intolerances[17]

At each onsite visit, the investigator enquired any local intolerance occurrence, by interviewing the patient using an open question taking care not to influence the patient's answer. Symptoms like itching, burning and stinging were investigated by questioning and scaling as well as erythema by clinical examination.

Information regarding AE had to be immediately recorded in the source data via subsequent scale:

[17]Erythema, pruritus, burning, stinging, and scaling assessment in the facial area. Investigators were also asked to rate the severity (none, mild, moderate, or severe)

Table 6: Local tolerability/ safety assessment scale

SCALING		
SCORE	**GRADE**	**DESCRIPTION**
0	None	No scaling
1	Mild	Barely perceptible, fine scales present to limited areas of the face
2	Moderate	Fine scale generalized to all areas of the face
3	Severe	Scaling and peeling of skin over all areas of the face
ERYTHEMA		
SCORE	**GRADE**	**DESCRIPTION**
0	None	No evidence of erythema present
1	Mild	Slight pink discoloration
2	Moderate	Definite redness
3	Severe	Marked erythema, bright red to dusky dark red in color
ITCHING		
SCORE	**GRADE**	**DESCRIPTION**
0	None	No itching
1	Mild	Slight itching, not really bothersome
2	Moderate	Definite itching that is somewhat bothersome
3	Severe	Intense itching that may interrupt daily activities and/or sleep
BURNING		
SCORE	**GRADE**	**DESCRIPTION**
0	None	No burning
1	Mild	Slight burning sensation, not really bothersome
2	Moderate	Definite warm, burning sensation that is somewhat bothersome
3	Severe	Hot burning sensation that causes definite discomfort and may interrupt daily activities and/or sleep
STINGING		
SCORE	**GRADE**	**DESCRIPTION**
0	None	No stinging
1	Mild	Slight stinging sensation, not really bothersome
2	Moderate	Definite stinging sensation that is somewhat bothersome
3	Severe	Stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep

Besides describing the symptoms, patients were asked to localize the area, where they had experienced the local intolerance(s): whole face or area of application.

Date and time of last application prior start of the local intolerance, start and end with date and time as well as intensity (none, mild, moderate, severe) were recorded.

The causal relationship of a local intolerance event to the investigational product was determined by the investigator (none, unlikely, possibly, probably, surely).

In case of severe local intolerance symptoms the investigator could decide to interrupt application.

(Serious) Adverse event documentation and reporting

An adverse event (AE) was defined as any untoward medical occurrence in the clinical investigation subject in the context of the clinical trial, whatever the relationship with the investigational products.

An AE was therefore any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease whether or not considered related to the investigational products.

A serious adverse event (SAE) was any untoward medical occurrence that at any dose:

- Requires hospitalization or prolongation of existing hospitalization
- Is life threatening
- Results in death
- Results in persistent or significant disability / incapacity
- Is a congenital anomaly / birth defect.

At each visit, the investigator enquired any AE occurrence, by interviewing the subject using an open question taking care not to influence the subject's answer and, if appropriate, by questioning and clinical examination.

- Information regarding AE was immediately recorded.
- Each time a concomitant medication was reported during the study, an AE was documented and the reason for the therapy noted.
- Adverse Events intensity was determined, using the following definitions as guideline:

Table 7: Adverse event classification

If required on the adverse event case report forms, the investigator used the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function. Awareness of sign or symptom, but easily tolerated, has not to be treated and is not affecting daily life.
MODERATE	Interferes to some extent with subject's usual function. Discomfort enough to cause interference with daily activity, but with no risk for the subject's health and improvement after slight therapy

SEVERE	Interferes significantly with subject's usual function. Unbearable event, interfering considerably with the subject's daily activity and/or possibly leading to a disability, or a life-threatening situation

The causal relationship of an AE to the investigational product was determined by the investigator, using the definitions given in the CRF as guideline: not related, unlikely, possible, probable, or certain. Classification followed the WHO system for standardized case causality assessment.[18]

- The AE outcome was followed until resolution, steady state or until evidence that the investigational products and/or the subject's participation in the trial are not responsible for the event.

- Each adverse event was to be classified by the investigator as serious or non-serious. This classification determines the reporting procedures to be followed. When a serious adverse event occurred, expedited reporting followed local and international regulations, as appropriate.

- In case of SAE, the sponsor was notified within 24 hours of awareness of the event by the investigator. This timeframe also applied to additional new information (follow-up) on previously forwarded serious adverse event reports.

- In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (e.g., if an outpatient trial subject initially seeks treatment elsewhere), the investigator was obliged to report the event within 24 hours after learning of it and document the time of her first awareness of the adverse event.

9.5.2 Appropriateness of measurements

N.A.

9.5.3 Primary variable

The primary variable was change of the skin surface parameter smoothness (SEsm) measured by Visioscan® VC98[19]. The Visioscan VC 98 (Courage+Kazaka Electronics GmbH, Germany) is an instrument for the analysis of skin micro-topography. The skin is scanned with a high resolution camera for imaging skin the skin surface microtopography. A rectangular area of the skin surface of 6 x 8 mm is irradiated with UV-A light (375nm) and the image captured by a high performance CCD camera. The captured image is converted into an 8 bit digital image. The imaging in 256 bit grey scale produces high-resolution images that are analyzed via image processing.

[18] www.who-umc.org
[19] Please see Appendix 16.4.1

Figure 2: Visioscan® VC98 Device

Measurements were done at baseline, visit 2, 3 and 4 at the pre-defined measurement areas:

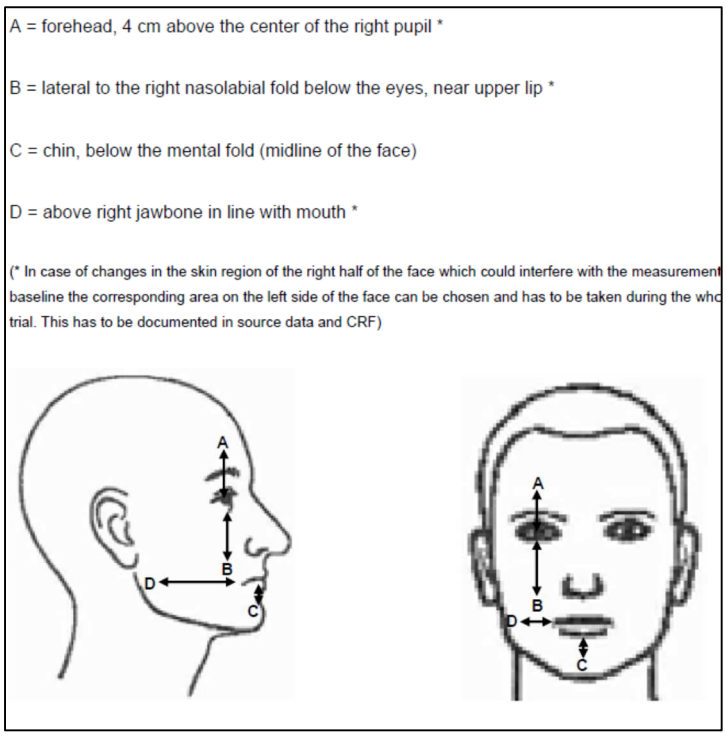

Figure 3: Measurement Areas

In total three replicate images were taken per investigational skin area (A – D) per visit. The replicate measurements were conducted as follows: The camera was positioned exactly on one measurement area (e.g. A, Figure 3). One image was captured. The camera head was removed and positioned again on the same skin area a second time and the second imaged captured. This sequence was repeated a third and last time. This procedure was conducted to increase the reliability of the roughness parameters per skin area.

9.5.3.1 Other variables

At baseline, visit 2, 3 and 4 skin surface parameters: scaling (SEsc), mean roughness (Rz) measured by Visioscan® VC98 at the pre-defined facial areas.[20] Per visit, three pictures were taken per area (A, B, C, D) to increase the reliability of the measurements.

Cutometer®[21]

Skin elasticity parameters: maximum extension (mm), biological elasticity (mm) were measured by Cutometer® MPA 580. The „Cutometer MPA 580“ (Courage&Khazaka, Germany) is connected to the Multiprobe Adapter (MPA, Courage & Khazaka, Germany) and measures the elasticity of the skin layers by means of intake pressure. The Cutometer

[20] See Figure 3
[21] See Appendix 16.4.2

measures the ability of the skin to resist the pressure (“stiffness”) and also its ability to restore its original state (“elasticity”) after discontinuation of the suction pressure.

The Cutometer principle is based on a mechanical intake pressure (suction) measurement procedure. The skin surface is sucked up into a small opening (diameter 2mm) into the probe (size of the opening is optional, depending on the thickness of the skin) by means of a defined intake pressure (vacuum). The optical measurement device in the probe is able to assess the penetration depth of the skin. The incoming light is reduced as soon as the skin is sucked up into the probe. This change of light intensity is then converted into mm. Here measurements were done at baseline, visit 2 – 4. Each facial area[22] was measured twice in order to use the mean values of the two measurements of each area (A – D) for data analysis.

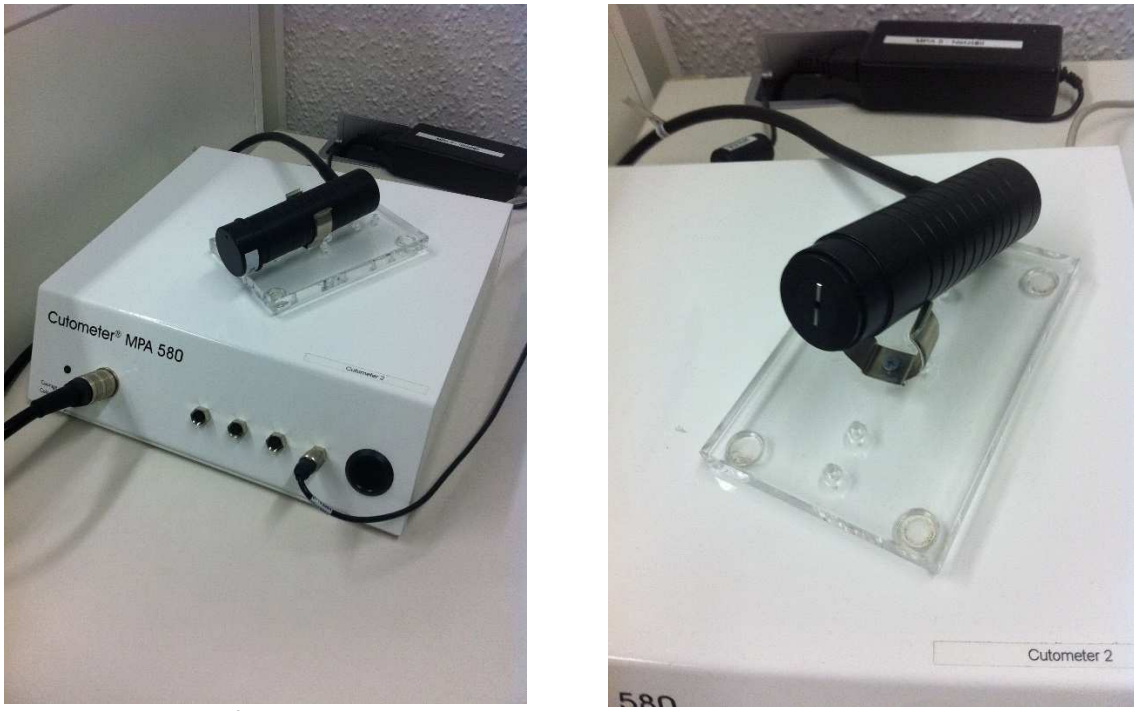

Figure 4: Cutometer® Device

Investigator’s Static Global Assessment (ISGA)[23]
Treatment success was determined by the improvement in ISGA (Zouboulis 2009) (Shalita 2005). At screening, baseline, visits 2 to 4, the investigator assessed the acne severity by using the ISGA 6-point scale (0 to 5). Only patients with an Investigator´s Static Global Assessment Score (ISGA) of 2 to 3 were enrolled.

Patients were discontinued from the trial by the investigator at any time if the ISGA increased for one or more grades from baseline.

[22] See Figure 3.
[23] See references Zouboulis, Shalita

Table 8: Investigator's Static Global Assessment (ISGA)

Score	Definition
Grade 0	**clear**: skin with no evidence of acne vulgaris.
Grade 1	**almost clear**: rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyper pigmented, though not pink-red) requiring no further treatment in the Investigator's opinion.
Grade 2	**mild**: Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodule-cystic lesion).
Grade 3	**moderate**: non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules; there may or may not be 1 small nodule-cystic lesion.
Grade 4	**severe**: inflammatory lesions are more apparent; many comedones and papules/ pustules; there may or may not be a few nodule-cystic lesions.
Grade 5	**very severe**: highly inflammatory lesions predominate: variable number of comedones, many papules/pustules and nodulo-cystic lesions.

Photo documentation (Visia-CR®)[24]

To evaluate the patient´s skin appearance photo documentation (right, left and frontal view) of the patient´s face was performed for the first time at baseline before the trial medication was applied and at visits 2 to 4. The device used was a Visia-CR® photo booth (Canfield Scientific, USA). The photographs were taken under standardized conditions (e.g. distance, illumination, background). Per angle, 7 images with standardized flash sequences were taken. The digital pictures were stored on the CRC server and on CD for documentation. During and after the trial, photographs were sent to Canfield Scientific. Based on computerized algorithms the spread and intensity of pigmentation is planned to be quantified.

Figure 5: Visia-CR® Device

Spectrophotometer CM-700d (Chromametry)[25]

At baseline, visit 2, visit 3 and visit 4 skin colour evaluation of the parameters brightness- (L*), red- (a*) and yellow chrominance (b*) measured by broadband spectrophotometry were conducted. The camera head was placed on the relevant skin area (Appendix 4), an image was taken and the camera head removed. This procedure was repeated 3 times. In total three replicate images were taken per investigational skin area.

[24] Please see appendix 16.4.3
[25] Please see appendix 16.4.4

Figure 6: Chromater Device

Dermatology Life Quality Index (DLQI)[26]:

At baseline, visit 3 and visit 4 the Dermatology Life Quality Index (DLQI) was self-completed by the patient. It consists of 10 standardized questions. The aim of this questionnaire is to measure how much patients' skin problem has affected her life over the last week (AY Finlay 1994). The questions were completed with pre-set answers.[27] The questionnaire was given to the patient and asked to tick the relevant boxes. After completion the research assistant checked the questionnaire for completeness and the form was added to the source data. Formal permission to use this questionnaire was obtained by the copyright holder from the Cardiff University (UK) on February 7th 2013.

9.5.4 Drug concentration measurements

Not applicable

9.6 Data Quality Assurance

Study documents and study documentation strictly followed the ICH-GCP, the Declaration of Helsinki and national applicable laws (AMG, GCP-V and Data Protection Act).

The study team was trained in GCP prior study start by the principal investigator. She also made sure that every member of the team has a thorough knowledge of the study and documentation standards.

Personal data was only recorded in a pseudonymized way. This was realized by using subject identification codes.

Further, quality assurance was realized by monitoring. The external monitor came regularly to the study site and did source data verification, checked quality (accurate, consistent,

[26] See reference (AY Finlay, 1994).
[27] See Appendix 16.4.5

complete and reliable) of the data captured and ICH-GCP compliance. Findings were recorded in monitoring reports.

Analysis of efficacy measurements and safety evaluation took place en bloc after study termination.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and analytical plans

Depending on the level of measurement demographics, primary and secondary outcomes, and AEs were characterized using descriptive statistics including means, standard deviations, ranges and absolute and relative frequencies.

The metric variables smoothness (SE_{sm}), mean roughness (Rz), scaliness (SE_{sc}) maximal extension (mm), biological elasticity (%), brightness- (L*), red- (a*) and yellow chrominance values (b*), DLQI-data were described for each of the visits 1 to 4 with means and standard deviations. All valid data per visit of all patients being included at this visit was used. No imputation methods were conducted and no statistical tests have been conducted at this first step.

In a second step a trend-analysis was performed using a Repeated Measures ANOVA. In this analysis only patients who have been followed-up until the end of the study and for whom all data was valid and available were included. All lost to follow-up patients and patients with missing values (e.g. due to technical or software errors) were excluded. Imputation was not used because the underlying biological phenomena regarding skin surface topography and the other skin characteristics were never investigated before. An alpha-error of 0.05 was applied for this Repeated Measures ANOVA. In case of $p < 0.05$ a trend analysis was conducted to characterize and to quantify the shape of the relationship between the outcome variables smoothness (SEsm), skin scaliness (SEsc), elastic deformation (mm), viscoelastic deformation (mm), maximal extension (mm), elastic resilience (mm), brightness- (L*), red- (a*) and yellow chrominance values (b*), ISGA and DLQI and time. The strength of this relationship was quantified using the eta² statistic. All p-values were considered to be descriptive.

9.7.2 Determination of sample size

The calculation of the sample size was based on the skin smoothness (SE_{sm}) parameter evaluated by Visioscan (K+C, Cologne, Germany). Based on the reported values in the literature a standard deviation of 7 was assumed for SE_{sm} (Kottner et al. 2913). N = 48 women are required to estimate the population value with a desired length of the 95% CI of ± 2. For a follow-up over 6 months a total loss of follow up of 10% (5 women) was estimated. Thus a total of n = 53 women had to be recruited and included in the study to ensure the precision.

9.8 Changes in the Conduct of the Study or Planned Analyses

For report purposes, not all variables have been analyzed. Skin smoothness (SE_{sm}), skin scaliness (SE_{sc}), mean skin roughness (Rz), structural extensibility of skin (mm), relative elastic recovery of skin (mm), brightness- (L*), red- (a*) and yellow chrominance values (b*),

ISGA and DLQI-data have been analysed and are part of the report. Because the most important roughness, elasticity and colour measurements are covered, it is unlikely that similar but different parameters give different results. Demography data and safety data were analyzed as planned.

10 Study Subjects

10.1 Disposition of Subjects

A total of 61 patients were screened and 53 were included into the trial. Twelve patients discontinued the study prematurely. All patients were treated with Skinoren 15% Gel twice daily.

Study Assignment and Design:

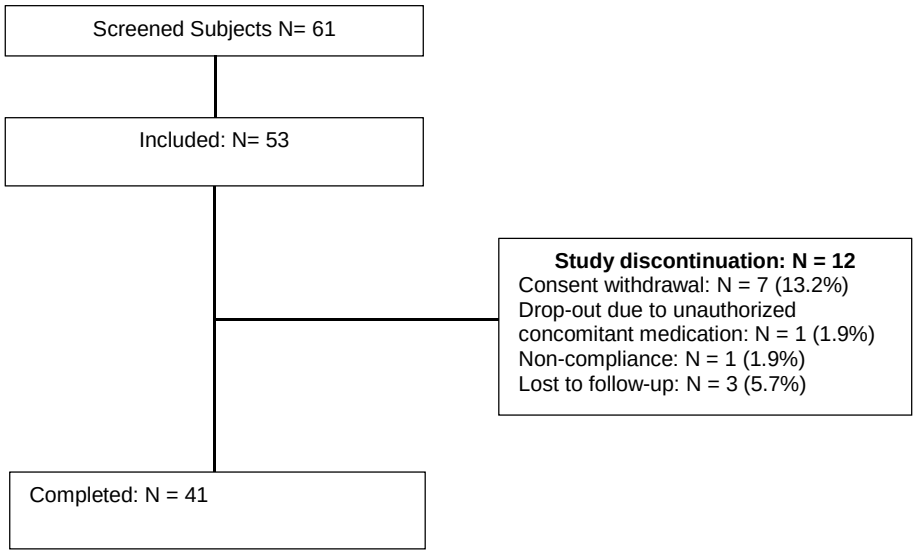

Figure 7: Participant disposition

Study discontinuation after enrollment[28]

In total 12 patients prematurely discontinued the study. Consent was withdrawn by 7 patients, three patients were lost to follow up, one patient had to be excluded due to the prescription of a not allowed concomitant medication and one patient had to be excluded due to non-compliance.

10.2 Protocol Deviations

No protocol deviations occurred.

11 Efficacy Evaluation

11.1 Data Sets Analyzed

The full analysis set (FAS) was used for the descriptive analysis per study visit (n = 53[29]). A per protocol set (PPS) analysis was done for statistical trend testing. Imputation methods were not used.

11.2 Demographic and Other Baseline Characteristics

Table 9: Demographic and baseline characteristics of included participants

		Total (n = 53)
Age (years)	mean (SD)	27.2 (5.0)
	range	20.0 – 45.0
BMI, (kg/m^2)	mean (SD)	22.9 (2.02)
	range	20.0 – 27.4
Phototype, n		
I		2
II		38
III		9
IV		4
ISGA-Score, n		
2		39
3		14
Ethnicity, n		
Caucasian		53

BMI Body mass index; ISGA Investigator´s static global assessment

[28] A summary of the subject that discontinued study after enrollment with patient number, reason for discontinuation is provided in appendix 16.2.1

[29] Due to drop-outs (n = 12) and missing data, analysis couldn't be realized for all patients in all visits.

11.3 Measurements of Treatment Compliance

Patients received a diary at Baseline visit for product application documentation and documentation of AEs. Treatment compliance was controlled according to the records in the diary. To enhance compliance and to follow-up possible AEs, two interim telephone visits (week 8 and week 18) were performed between onsite visit 2 and 3 and visit 3 and 4.

Treatment could be interrupted for up to 14 consecutive days due to severe local intolerances. If local intolerances prolonged, patient would have been excluded from the study.

According the diaries of all patients who (1) completed all visits according the study protocol , (2) completed the diaries, (3) and who returned the diaries (n = 36) the median number of missing applications was 1 ranging from 0 to 19. The mean was 2.9 (SD 5.0). This resembles a strongly skewed distribution indicating that the overall majority of participants applied the products regularly.

11.4 Results and Tabulations for Individual Subject Data

11.4.1 Analysis of Skin Physiology Measurements

Skin surface topography: Skin Smoothness (SE_{SM})

Results of skin topography measurements per skin area (strengths of main effect, eta^2) are displayed in tables 10 to 13 and figures 8 to 11.

Table 10: Skin smoothness forehead per visit of all valid cases (A)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	52	47	45	39
Mean (SD)	55.00 (20.10)	42.09 (11.26)	43.16 (11.00)	49.36 (16.20)
Range	28.82 to 142.17	24.05 to 80.51	26.48 to 73.86	28.36 to 98.19

SD = standard deviation, EoS = end of study

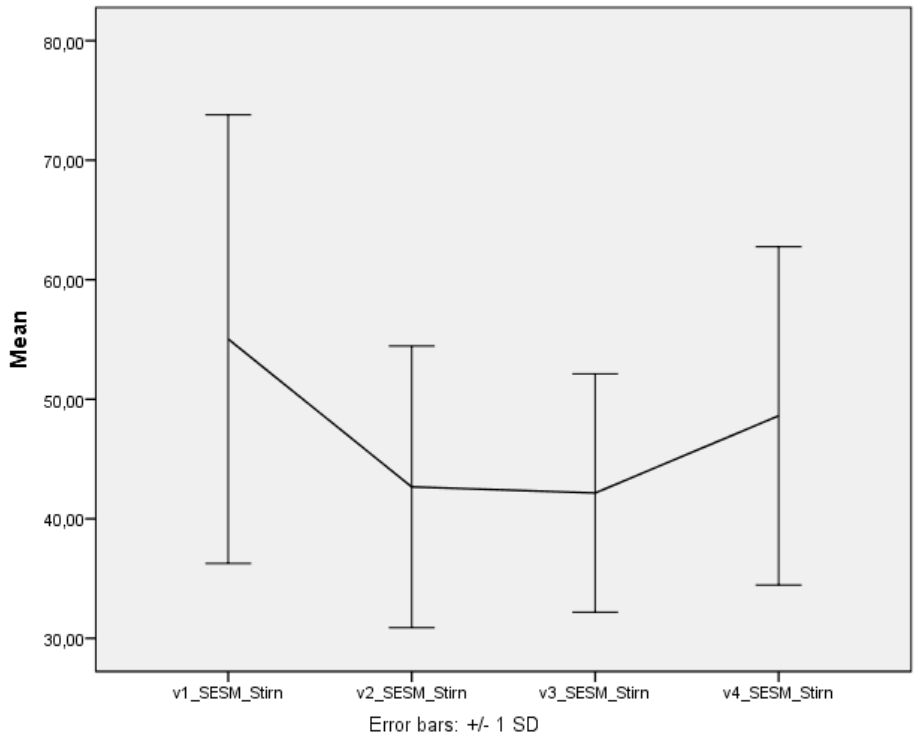

Figure 8: Mean values of smoothness forehead for all subjects who completed all visits with complete measurements (n = 36) (A)

Differences in skin smoothness on forehead between visits were statistically significant (n = 36, F = 8.1, p = 0.001). The shape of the trend can be best described with a quadratic function ($p < 0.001$, $eta^2 = 0.421$).

Table 11: Skin smoothness inner cheek per visit of all valid cases (B)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
N	51	47	46	40
Mean (SD)	48.84 (14.18)	38.90 (7.52)	40.52 (8.90)	46.81 (12.72)
Range	32.41 to 97.67	26.62 to 63.91	25.89 to 75.00	32.25 to 103.03

SD = standard deviation, EoS = end of study

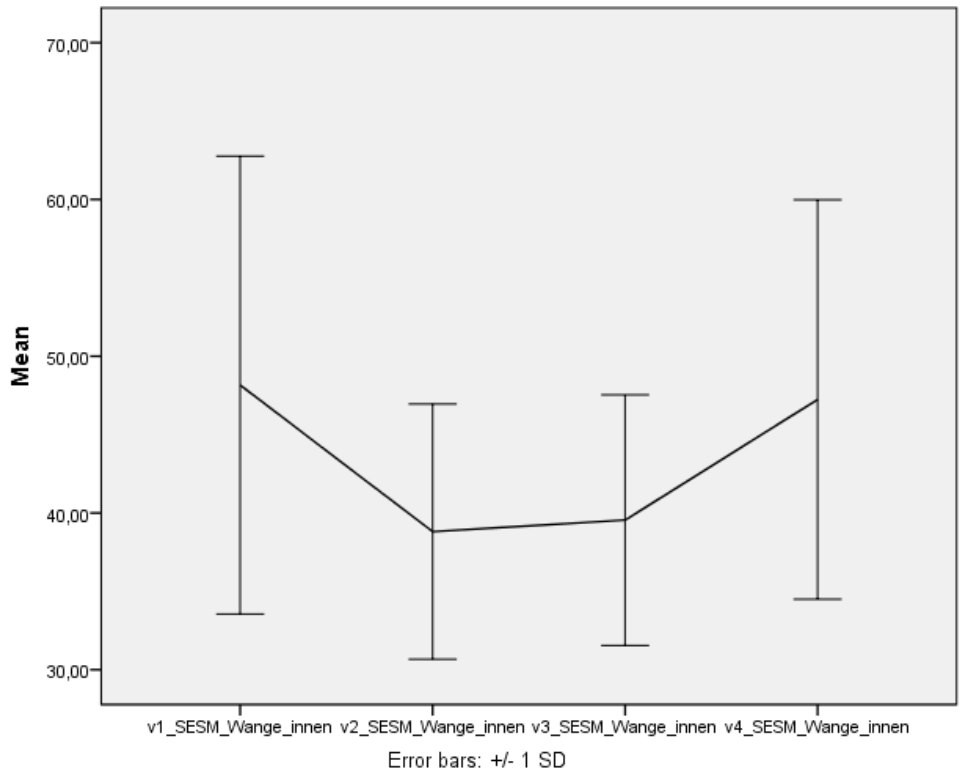

Figure 9: Mean values of smoothness inner cheek for all subjects who completed all visits with complete measurements (n = 37) (B)

Differences in skin smoothness on inner cheek between visits were statistically significant (n = 37, F = 7.9, $p < 0.001$). The shape of the trend can be best described with a quadratic function ($p < 0.001$, $eta^2 = 0.454$).

Table 12: Skin smoothness chin per visit of all valid cases (C)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
N	53	48	47	40
Mean (SD)	51.99 (17.43)	43.09 (15.45)	43.65 (12.78)	48.19 (19.27)
Range	26.43 to 102.49	26.84 to 127.17	25.22 to 81.98	29.36 to 112.70

SD = standard deviation, EoS = end of study

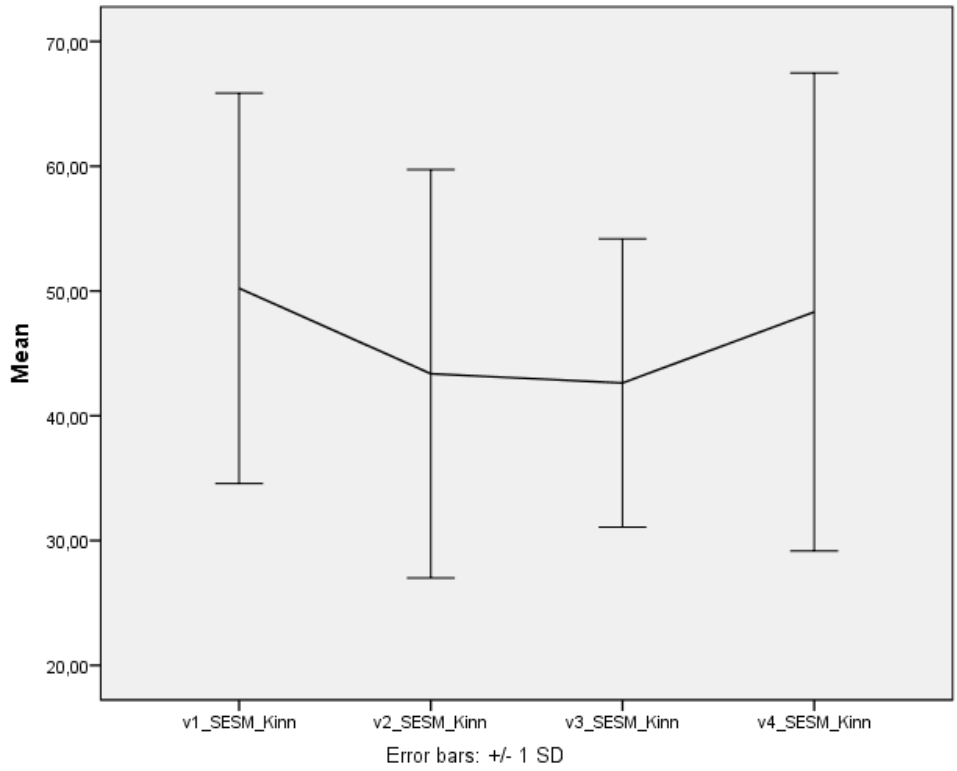

Figure 10: Mean values of smoothness chin of patients who completed all visits with complete measurements (n = 39) (C)

Differences in skin smoothness on chin between visits were not statistically significant (n = 39, F = 2.4, p = 0.089).

Table 13: Skin smoothness jawbone of all valid cases (outer cheek, mandibular) (D)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
N	53	48	47	41
Mean (SD)	50.64 (14.88)	42.87 (9.58)	40.82 (9.43)	48.63 (17.25)
Range	32.03 to 114.80	28.02 to 68.58	27.17 to 69.84	28.88 to 97.42

SD = standard deviation, EoS = end of study

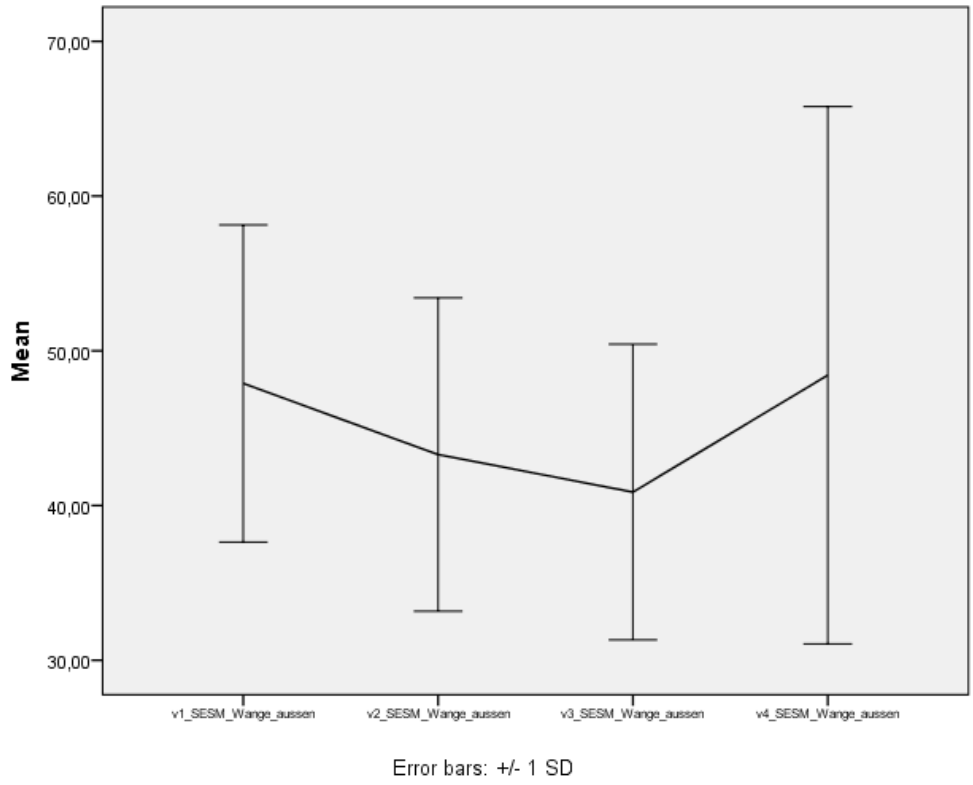

Figure 11: Mean values of smoothness jawbone of patients who completed all visits with complete measurements (n = 40) (outer cheek, mandibular) (D)

Differences in skin smoothness on jawbone (outer cheek, mandibular) between visits were statistically significant (n = 40, F = 4.2, p = 0.021). The shape of the trend can be best described with a quadratic function (p = 0.001, eta² = 0.264).

These results indicate that the skin became slightly smoother at all four investigational facial skin areas during the first 12 weeks of treatment. At week 24 skin smoothness nearly reached baseline again.

Skin surface topography: Skin Scaliness (SE_{SC})

Results of scaliness measurements per skin area (strengths of main effect, eta^2) are displayed in tables 14 to 17 and figures 12 to 15. Measurements were performed at Baseline, visit 2, visit 3 and visit 4.

Table 14: Skin scaliness forehead per visit of all valid cases (A)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	52	47	45	39
Mean (SD)	0.70 (0.22)	0.73 (0.30)	0.68 (0.25)	0.76 (0.29)
Range	0.31 to 1.35	0.26 to 1.48	0.28 to 1.20	0.27 to 1.60

SD = standard deviation, EoS = end of study

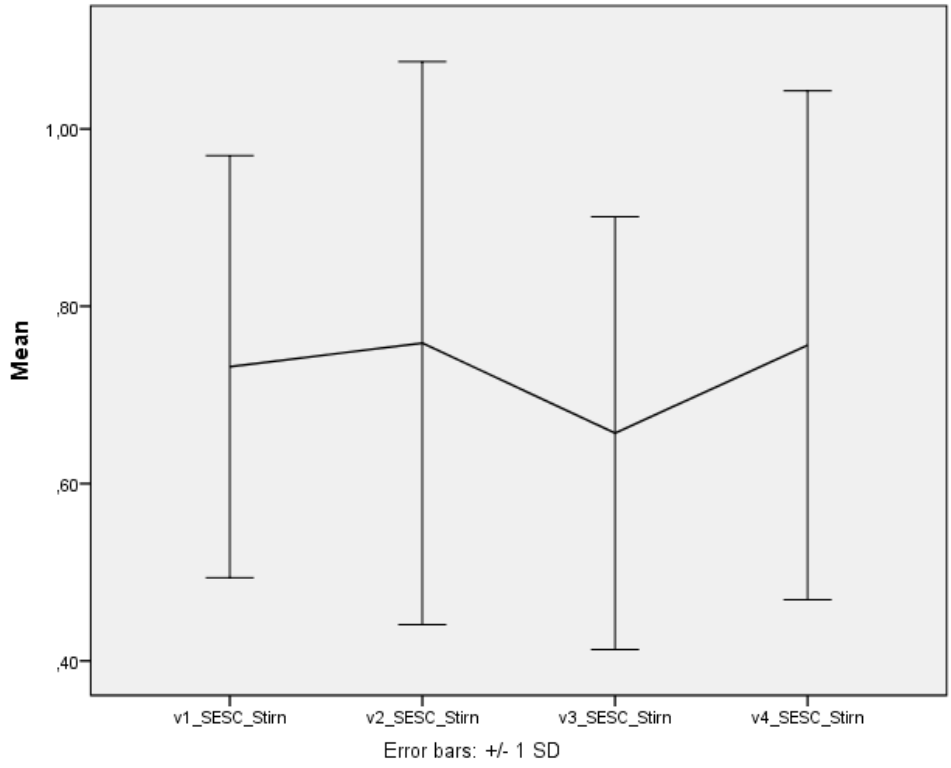

Figure 12: Mean values of scaliness forehead for all subjects who completed all visits with complete measurements (n = 36) (A)

Differences in skin scaliness on forehead between visits were not statistically significant (n = 36, F = 1.79, p = 0.158).

Table 15: Skin scaliness inner cheek per visit of all valid cases (B)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	51	47	46	40
Mean (SD)	0.58 (0.20)	0.62 (0.38)	0.57(0.25)	0.68 (0.30)
Range	0.21 to 1.20	0.13 to 2.43	0.18 to 1.74	0.35 to 2.34

SD = standard deviation, EoS = end of study

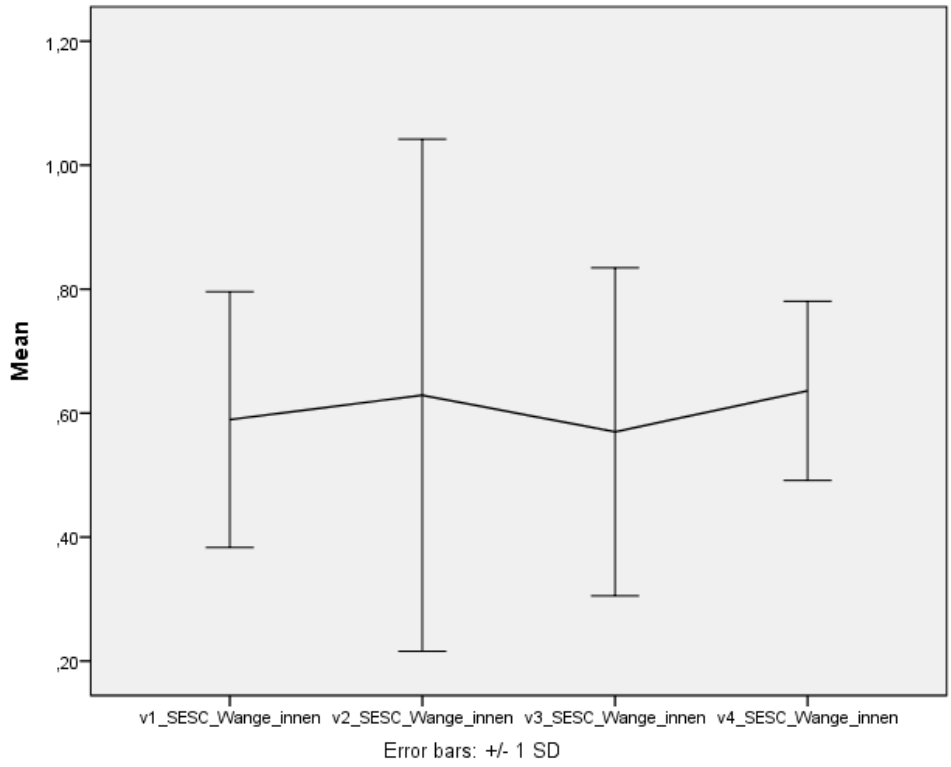

Figure 13: Mean values of scaliness inner cheek for all subjects who completed all visits with complete measurements (n = 37) (B)

Differences in skin scaliness on inner cheek between visits were not statistically significant (n = 37, F = 0.7, p = 0.526).

Table 16: Skin scaliness chin per visit of all valid cases (C)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
N	53	48	47	40
Mean (SD)	0.59 (0.18)	0.50 (0.16)	0.48 (0.21)	0.57 (0.41)
Range	0.19 to 1.04	0.05 to 0.84	0.07 to 0.88	0.23 to 2.88

SD = standard deviation, EoS = end of study

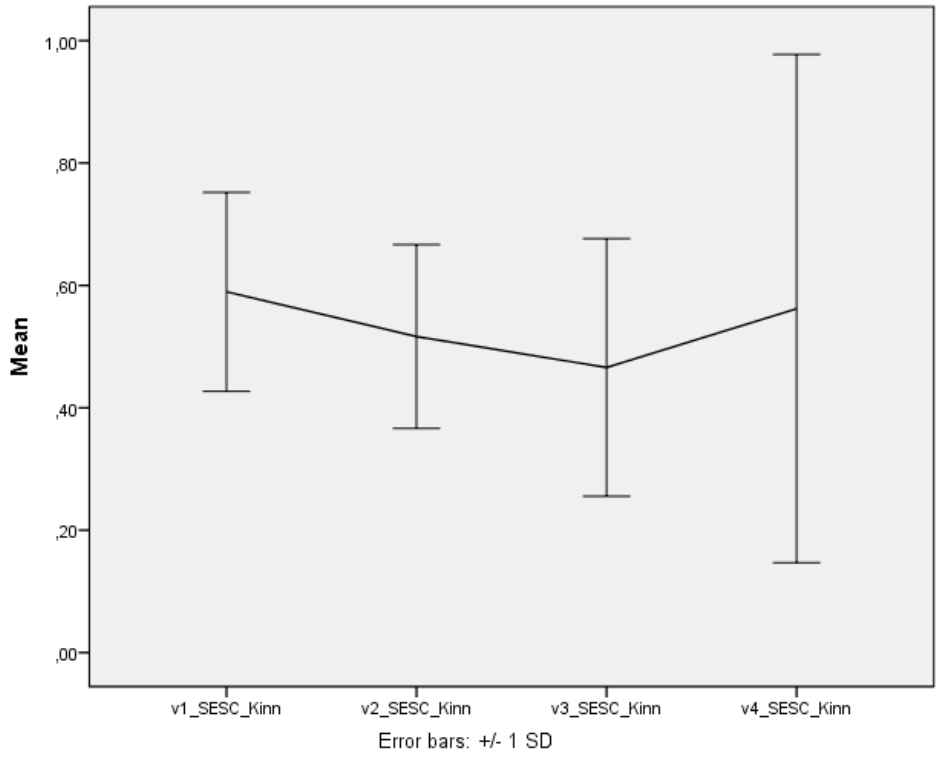

Figure 14: Mean values of scaliness chin for all subjects who completed all visits with complete measurements (n = 39) (C)

Differences in skin scaliness on chin between visits were not statistically significant (n = 39, F = 2.0, p = 0.147).

Table 17: Skin scaliness jawbone per visit of all valid cases (outer cheek, mandibular) (D)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	53	48	47	41
Mean (SD)	0.97 (0.37)	1.10 (0.65)	1.12 (0.59)	1.21 (0.65)
Range	0.43 to 1.85	0.17 to 3.58	0.36 to 2.56	0.36 to 2.99

SD = standard deviation, EoS = end of study

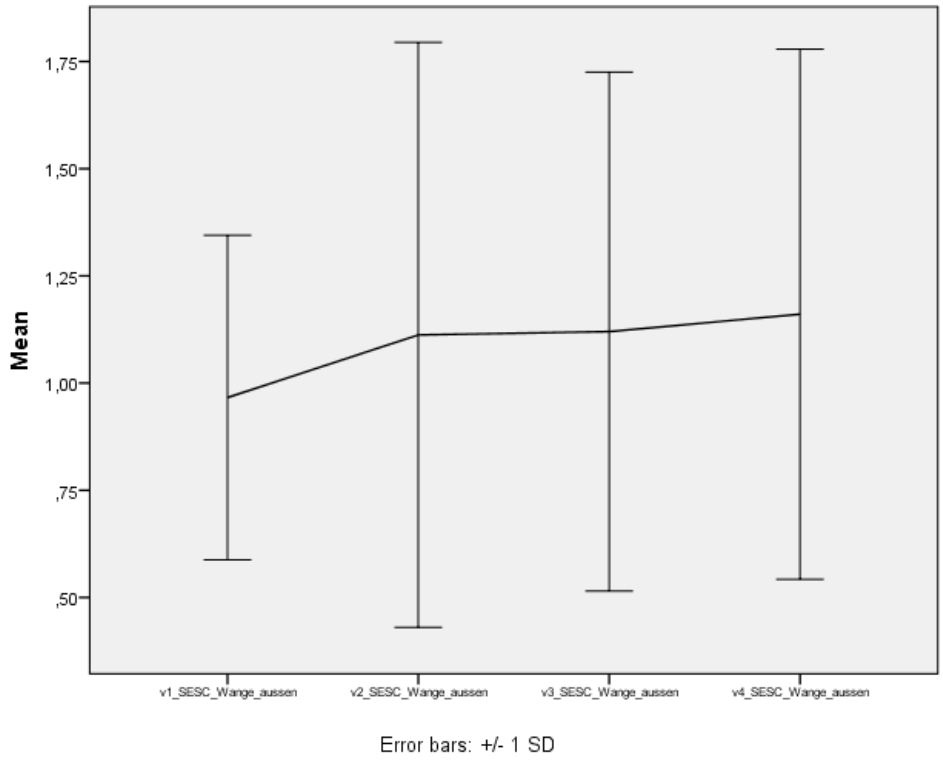

Figure 15: Mean values of scaliness jawbone for all subjects who completed all visits with complete measurements (n = 40) (outer cheek, mandibular) (D)

Differences in skin scaliness between visits were not statistically significant (n = 40, F = 1.7, p = 0.174).

There were no statistically significant changes in skin scaliness during the course of the study at any skin areas.

Skin surface topography: Skin Roughness (Rz)

Results of skin mean roughness measurements per skin area (strengths of main effect, eta^2) are displayed in tables 18 to 21 and figures 16 to 19.

Table 18: Skin roughness (Rz) forehead per visit of all valid cases (A)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	51	46	45	39
Mean (SD)	49.20 (12.57)	43.95 (9.92)	45.10 (10.30)	50.48 (12.21)
Range	22.67 to 82.00	25.67 to 81.33	20.67 to 72.33	31.00 to 83.00

SD = standard deviation, EoS = end of study

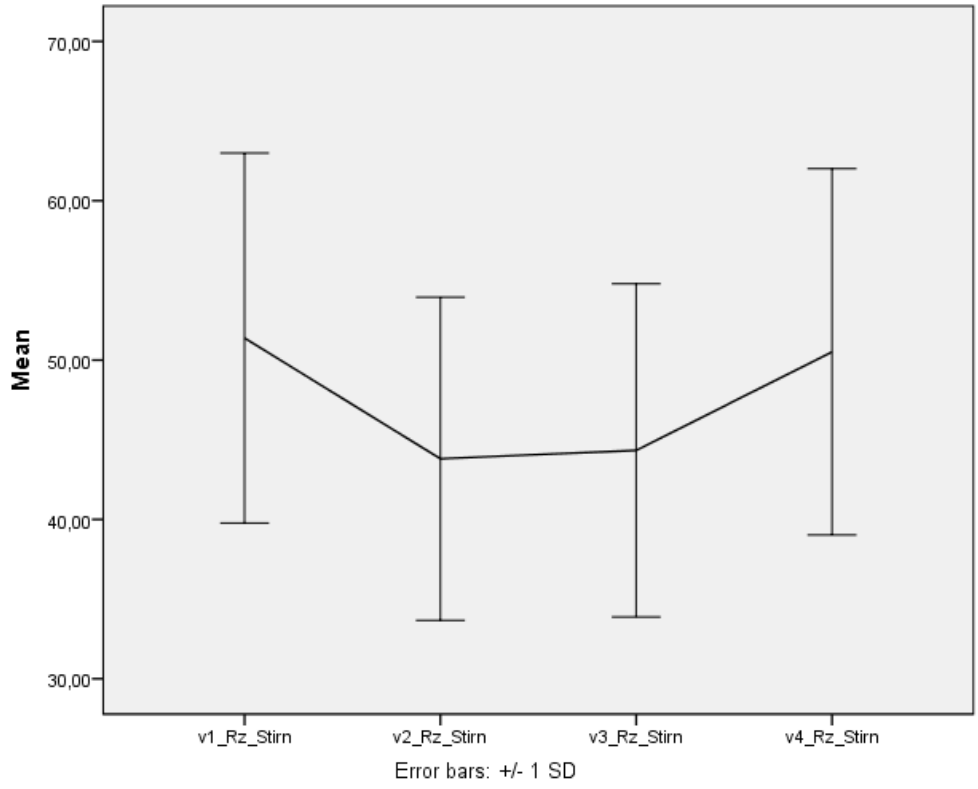

Figure 16: Mean values of roughness forehead for all subjects who completed all visits with complete measurements (n = 34) (A)

Differences in Rz on the forehead between visits were statistically significant (n = 34, F = 6.4, p = 0.002). The shape of the trend can be best described with a quadratic function (p < 0.001, eta² = 0.336).

Table 19: Skin roughness (Rz) inner cheek per visit of all valid cases (B)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
N	51	47	46	40
Mean (SD)	47.80 (10.57)	42.48 (8.10)	44.28 (8.77)	50.33 (8.12)
Range	32.33 to 85.00	29.67 to 67.00	27.00 to 78.00	39.33 to 77.00

SD = standard deviation, EoS = end of study

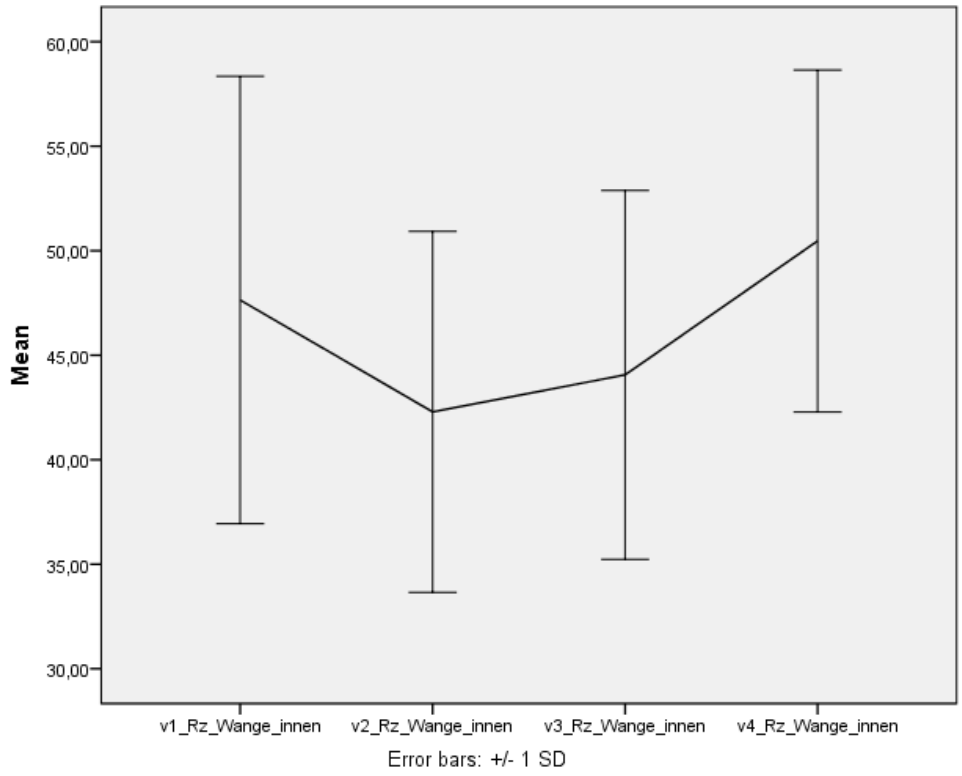

Figure 17: Mean values of roughness inner cheek for all subjects who completed all visits with complete measurements (n = 37) (B)

Differences of Rz on the inner cheek between visits were statistically significant (n = 37, F = 7.9, $p < 0.001$). The shape of the trend can be best described with a quadratic function ($p < 0.001$, $eta^2 = 0.319$).

Table 20: Skin roughness (Rz) chin per visit of all valid cases (C)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	53	48	47	40
Mean (SD)	45.15 (9.68)	41.39 (7.62)	42.28 (10.10)	46.32 (11.64)
Range	26.00 to 85.00	27.00 to 62.00	25.67 to 72.67	30.00 to 81.33

SD = standard deviation, EoS = end of study

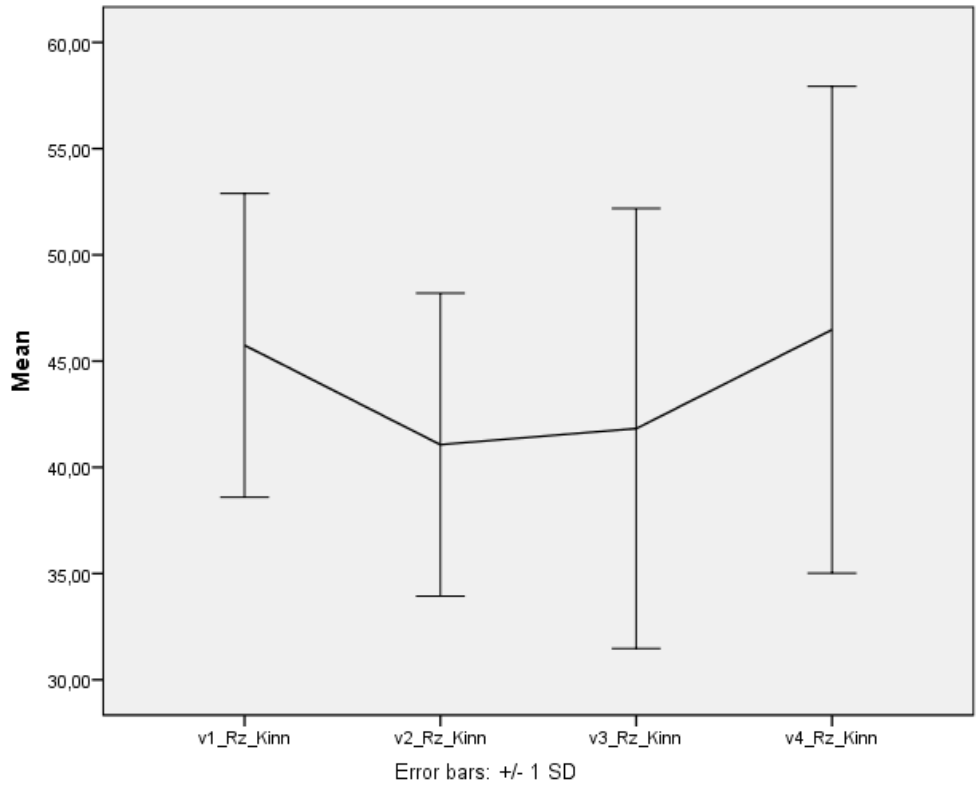

Figure 18: Mean values of roughness chin for all subjects who completed all visits with complete measurements (n = 39) (C)

Differences in Rz on the chin area between visits were statistically significant (n = 39, F = 4.5, p = 0.012). The shape of the trend can be best described with a quadratic function (p = 0.002, eta² = 0.228).

Table 21: Skin roughness (Rz) jawbone per visit of all valid cases (outer cheek, mandibular) (D)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	53	48	47	41
Mean (SD)	49.72 (10.06)	46.97 (9.09)	45.83 (10.88)	51.20 (12.75)
Range	32.33 to 85.00	30.67 to 68.33	24.33 to 86.33	32.33 to 104.33

SD = standard deviation, EoS = end of study

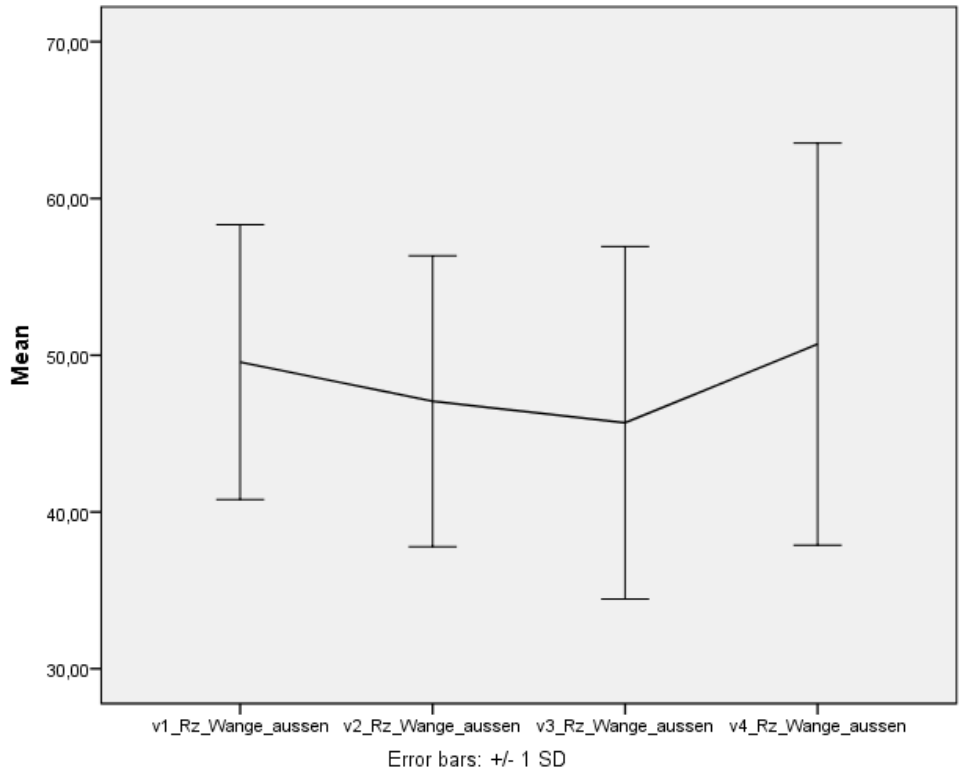

Figure 19: Mean values of roughness jawbone for all subjects who completed all visits with complete measurements (n = 40) (outer cheek, mandibular) (D)

Differences in skin depths of roughness on jawbone (outer cheek, mandibular) between visits were not statistically significant (n = 40, F = 2.5, p = 0.078).

Changes in Rz were statistically significant in the forehead, inner cheek and chin areas. No statistically significant change was observed in the jawbone area. In all four facial areas it could be observed that skin roughness declined during the course of the study and increased again until the end of the study.

Skin elasticity: structural extensibility of skin (R0) and relative elastic recovery of skin (R7)

Results of cutometer skin elasticity measurements per skin area are displayed in tables 22 to 29 and figures 20 to 27.

Table 22: Structural extensibility of skin (R0) forehead per visit of all valid cases (A)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	53	49	47	41
Mean (SD)	0.25 (0.07)	0.22 (0.09)	0.24 (0.08)	0.22 (0.08)
Range	0.14 to 0.43	0.08 to 0.45	0.1 to 0.43	0.08 to 0.44

SD = standard deviation, EoS = end of study

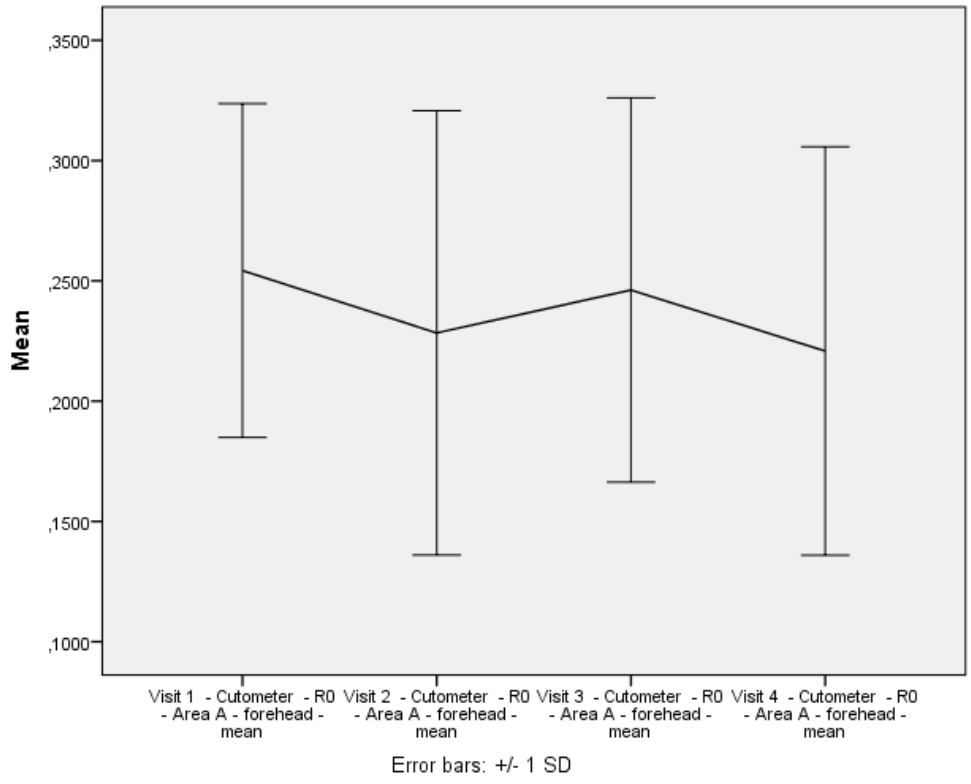

Figure 20: Mean values of structural extensibility of skin (R0) forehead for all subjects who completed all visits with complete measurements (n = 41) (A)

Differences in skin elasticity (R0 = structural extensibility of skin) on forehead between visits were statistically significant (n = 41, F = 3.6, p = 0.020). The shape of the trend can be best described with a cubic function (third order function) (p = 0.003), eta² = 0.198).

Table 23: Relative elastic recovery of skin (R7) forehead per visit of all valid cases (A)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	53	49	47	41
Mean (SD)	0.36 (0.09)	0.36 (0.08)	0.35 (0.10)	0.35 (0.09)
Range	0.21 to 0.57	0.22 to 0.58	0.20 to 0.62	0.21 to 0.53

SD = standard deviation, EoS = end of study

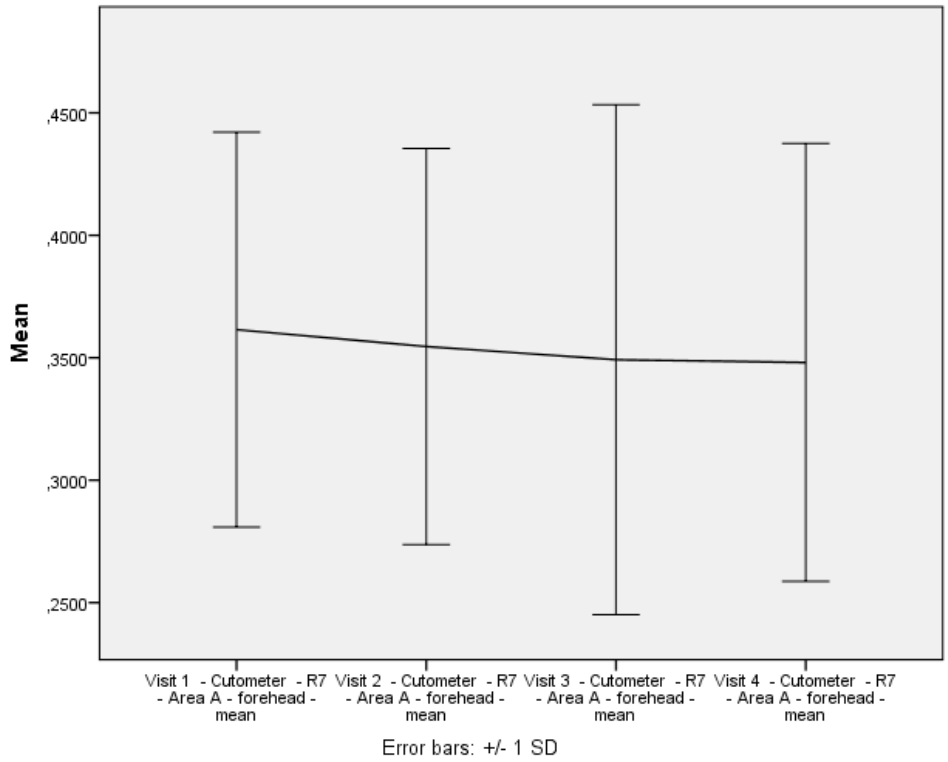

Figure 21: Mean values of relative elastic recovery of skin (R7) forehead for all subjects who completed all visits with complete measurements (n = 41) (A)

Differences in skin elasticity (R7 = relative elastic recovery of skin) on forehead between visits were not statistically significant (n = 41, F = 0.4, p = 0.741).

Table 24: Structural extensibility of skin (R0) inner cheek per visit of all valid cases (B)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
N	53	49	47	41
Mean (SD)	0.35 (0.07)	0.32 (0.09)	0.33 (0.09)	0.27 (0.07)
Range	0.18 to 0.49	0.13 to 0.51	0.15 to 0.62	0.14 to 0.46

SD = standard deviation, EoS = end of study

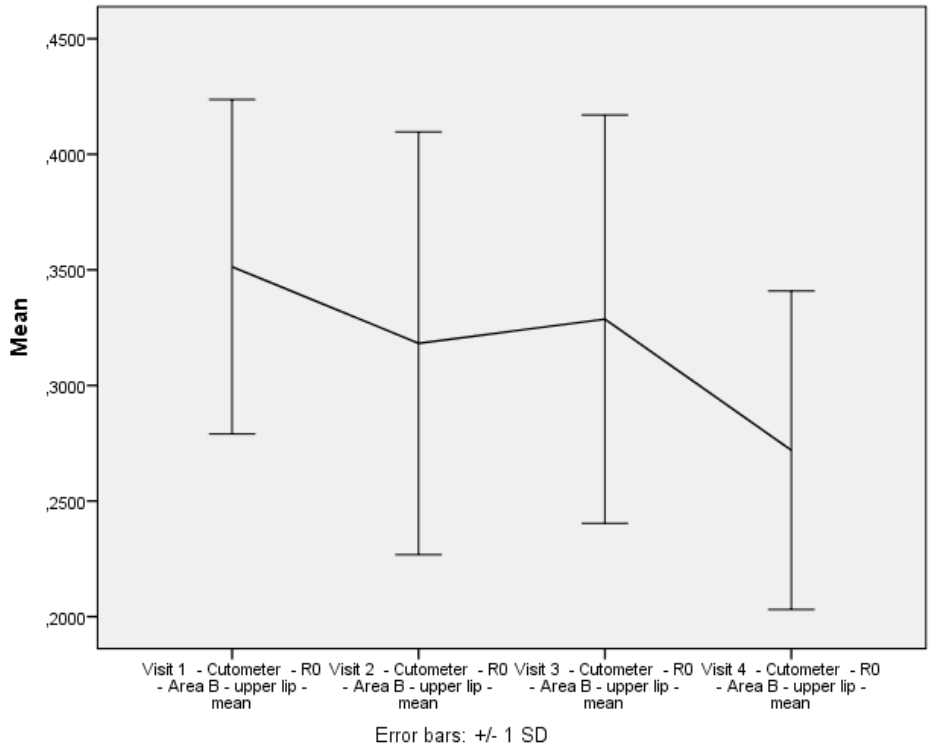

Figure 22: Mean values of structural extensibility of skin (R0) inner cheek for all subjects who completed all visits with complete measurements (n = 41) (B)

Differences in skin elasticity (R0 = structural extensibility of skin) on inner cheek between visits were statistically significant (n = 41, F = 12.5, $p < 0.001$). The shape of the trend can be best described with a linear function ($p < 0.001$, $eta^2 = 0.414$).

Table 25: relative elastic recovery of skin (R7) inner cheek per visit of all valid cases (B)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
N	53	49	47	41
Mean (SD)	0.37 (0.06)	0.36 (0.07)	0.37 (0.08)	0.33 (0.06)
Range	0.22 to 0.47	0.21 to 0.56	0.24 to 0.55	0.24 to 0.51

SD = standard deviation, EoS = end of study

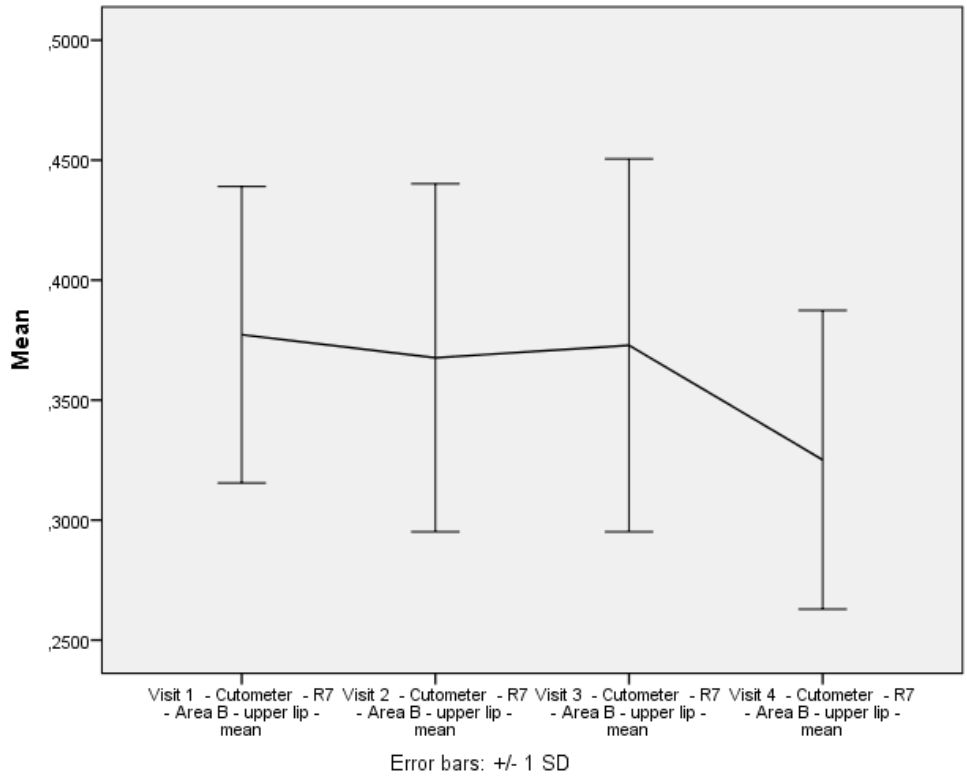

Figure 23: Mean values of relative elastic recovery of skin (R7) inner cheek for all subjects who completed all visits with complete measurements (n = 41) (B)

Differences in skin elasticity (R7 = relative elastic recovery of skin) on inner cheek between visits were statistically significant (n = 41, F = 6.6, $p < 0.001$). The shape of the trend can be best described with a linear function ($p < 0.001$, $eta^2 = 0.328$).

Table 26: Structural extensibility of skin (R0) chin per visit of all valid cases (C)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	53	49	47	41
Mean (SD)	0.22 (0.06)	0.20 (0.06)	0.22 (0.06)	0.19 (0.06)
Range	0.12 to 0.33	0.10 to 0.41	0.12 to 0.34	0.09 to 0.39

SD = standard deviation, EoS = end of study

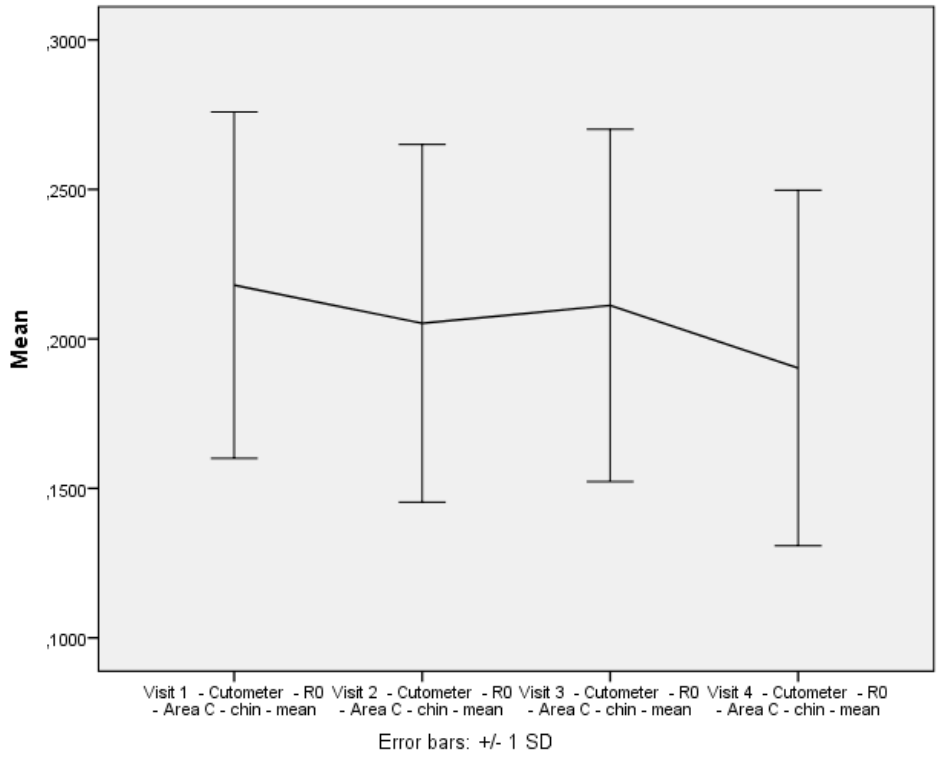

Figure 24: Mean values of structural extensibility of skin (R0) chin for all subjects who completed all visits with complete measurements (n = 41) (C)

Differences in skin elasticity (R0 = structural extensibility of skin) on chin between visits were not statistically significant (n = 41, F = 2.5, p = 0.069).

Table 27: Relative elastic recovery of skin (R7) chin per visit of all valid cases (C)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	53	49	47	41
Mean (SD)	0.32 (0.05)	0.32 (0.06)	0.32 (0.06)	0.31 (0.04)
Range	0.21 to 0.42	0.21 to 0.52	0.22 to 0.50	0.21 to 0.39

SD = standard deviation, EoS = end of study

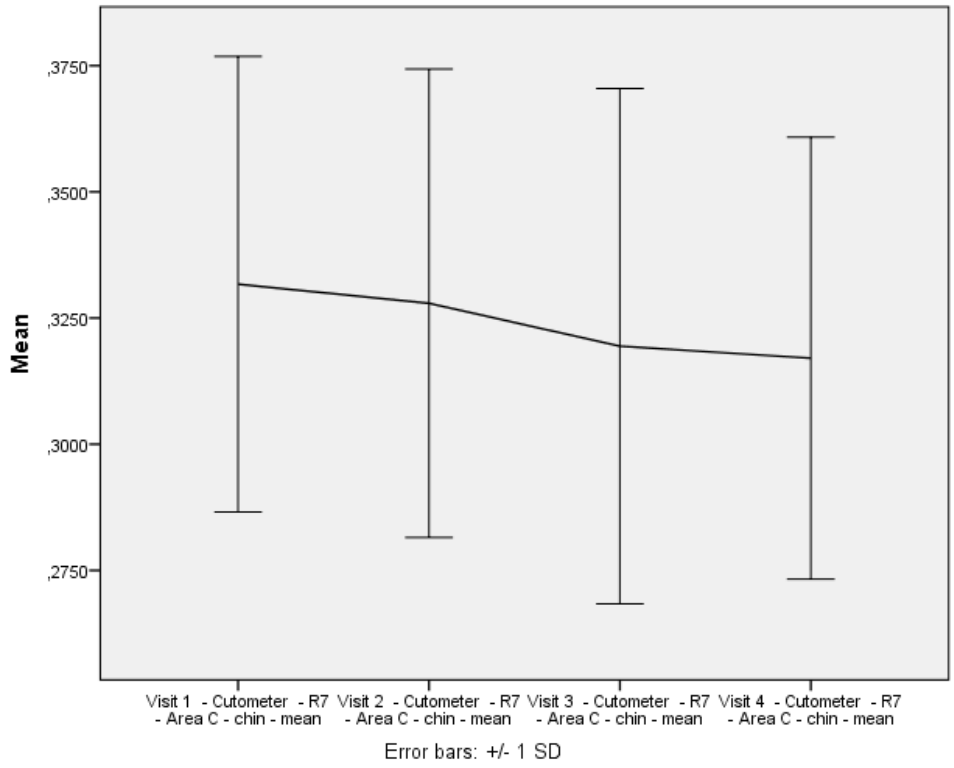

Figure 25: Mean values of relative elastic recovery of skin (R7) chin for all subjects who completed all visits with complete measurements (n = 41) (C)

Differences in skin elasticity (R7 = relative elastic recovery of skin) on chin between visits were not statistically significant (n = 41, F = 1.7, p = 0.170).

Table 28: Structural extensibility of skin (R0) jawbone per visit of all valid cases (outer cheek, mandibular) (D)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	53	49	47	41
Mean (SD)	0.30 (0.07)	0.25 (0.08)	0.27 (0.06)	0.24 (0.06)
Range	0.15 to 0.48	0.10 to 0.46	0.15 to 0.42	0.11 to 0.40

SD = standard deviation, EoS = end of study

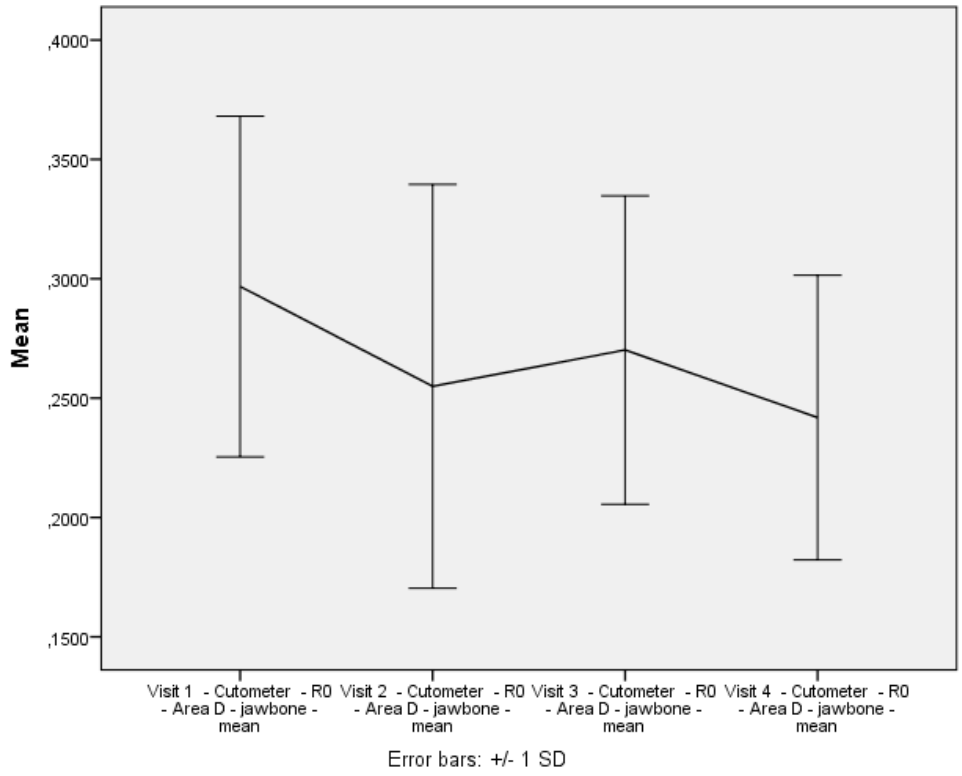

Figure 26: Mean values of structural extensibility of skin (R0) jawbone for all subjects who completed all visits with complete measurements (n = 41) (outer cheek, mandibular) (D)

Differences in skin elasticity (R0 = structural extensibility of skin) on jawbone between visits were statistically significant (n = 41, F = 12.2, $p < 0.001$). The shape of the trend can be best described with a linear function ($p < 0.000$, $eta^2 = 0.323$).

Table 29: Relative elastic recovery of skin (R7) jawbone per visit of all valid cases (outer cheek, mandibular) (D)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	53	49	47	41
Mean (SD)	0.33 (0.08)	0.31 (0.09)	0.30 (0.08)	0.26 (0.09)
Range	0.11 to 0.50	0.16 to 0.53	0.11 to 0.56	0.13 to 0.52

SD = standard deviation, EoS = end of study

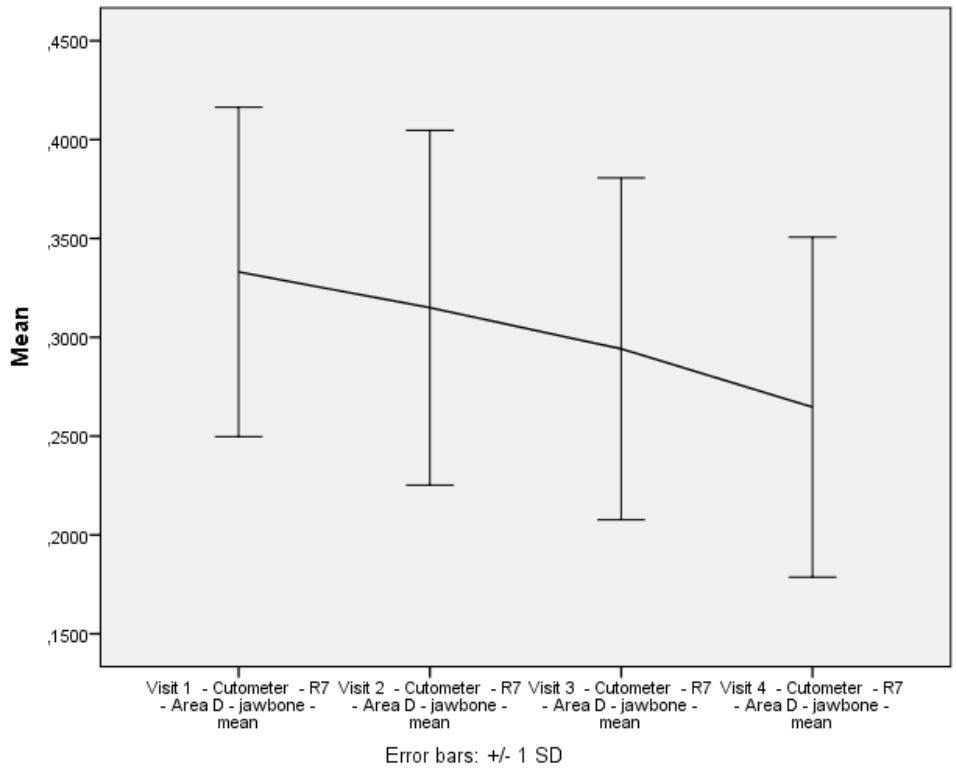

Figure 27: Mean values of relative elastic recovery of skin (R7) jawbone for all subjects who completed all visits with complete measurements (outer cheek, mandibular) (D)

Differences in skin elasticity (R7 = relative elastic recovery of skin) on jawbone between visits were statistically significant (n = 41, F = 11.4, $p < 0.001$). The shape of the trend can be best described with a linear function ($p < 0.001$, $eta^2 = 0.377$).

Results indicate that the skin elasticity did not change at the forehead and chin skin areas. There was a decrease of the overall extensibility at the inner and out cheek areas indicating that skin became firmer during the course of the study. A decrease of the biological elasticity indicates that the ability of the skin to regain its initial position after deformation decreased.

Skin pigmentation/ skin color: brightness (L)

Results of broadband spectrophotometry (chromameter) skin pigmentation/skin color (brightness L) measurements per skin area are displayed in tables 30 to 33 and figures 28 to 31.

Table 30: Chromameter brightness (L) forehead per visit of all valid cases (A)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	53	49	47	41
Mean (SD)	63.80 (3.02)	64.54 (2.39)	64.50 (2.78)	63.98 (3.34)
Range	55.64 to 68.76	57.73 to 69.30	56.30 to 69.47	54.97 to 69.49

SD = standard deviation, EoS = end of study

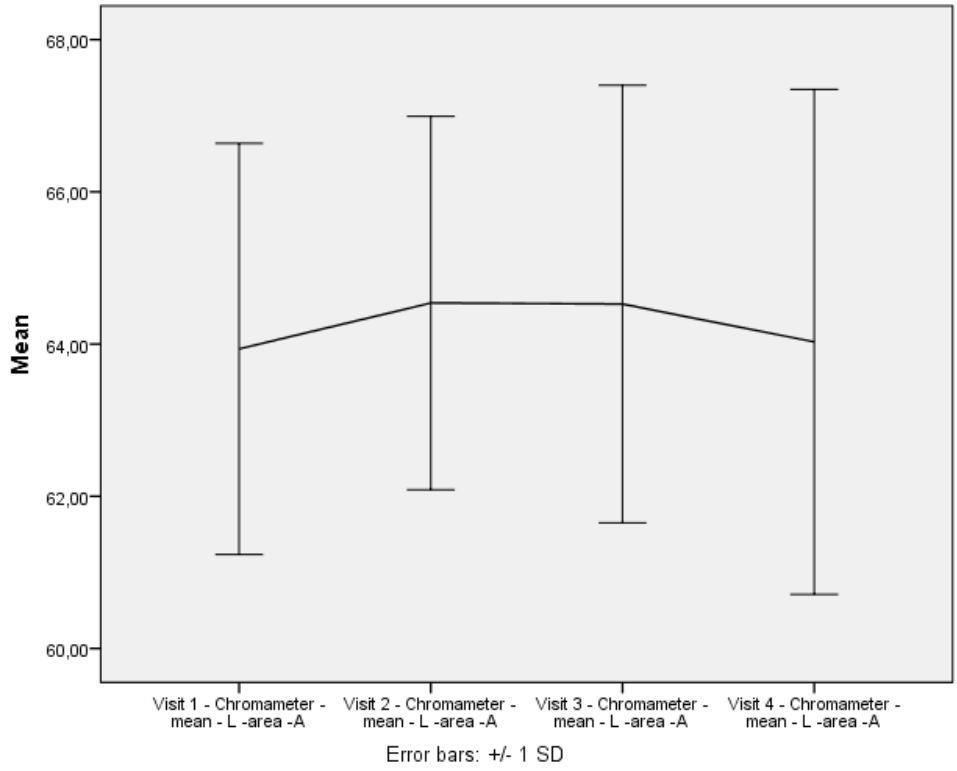

Figure 28: Mean values chromameter brightness (L) forehead for all subjects who completed all visits with complete measurements (n = 41) (A)

Differences in skin brightness (L) on forehead between visits were not statistically significant (n = 41, F = 1.7, p = 0.183).

Table 31: Chromameter brightness (L) inner cheek per visit of all valid cases (B)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
N	53	49	47	41
Mean (SD)	62.86 (2.70)	63.61 (2.41)	62.65 (2.22)	61.91 (2.53)
Range	55.82 to 69.42	58.49 to 68.67	57.64 to 67.83	55.20 to 66.64

SD = standard deviation, EoS = end of study

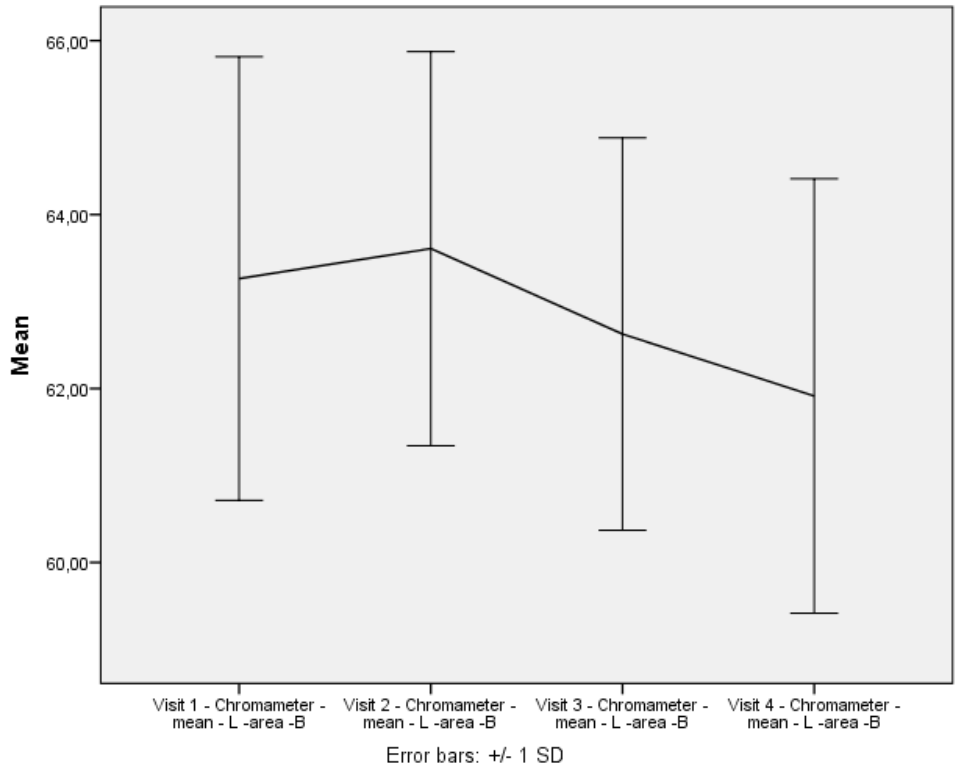

Figure 29: Mean values chromameter brightness (L) inner cheek for all subjects who completed all visits with complete measurements (B)

Differences in mean skin brightness (L) on inner cheek between visits were statistically significant (n = 41, F = 10.9, $p < 0.001$). The shape of the trend can be best described with a linear function ($p < 0.001$, $eta^2 = 0.352$).

Table 32: Chromameter brightness (L) chin per visit of all valid cases (C)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	52	49	47	41
Mean (SD)	62.26 (3.24)	63.31 (2.64)	63.35 (2.75)	62.86 (2.69)
Range	54.59 to 68.40	57.49 to 70.89	55.67 to 69.97	55.02 to 68.39

SD = standard deviation, EoS = end of study

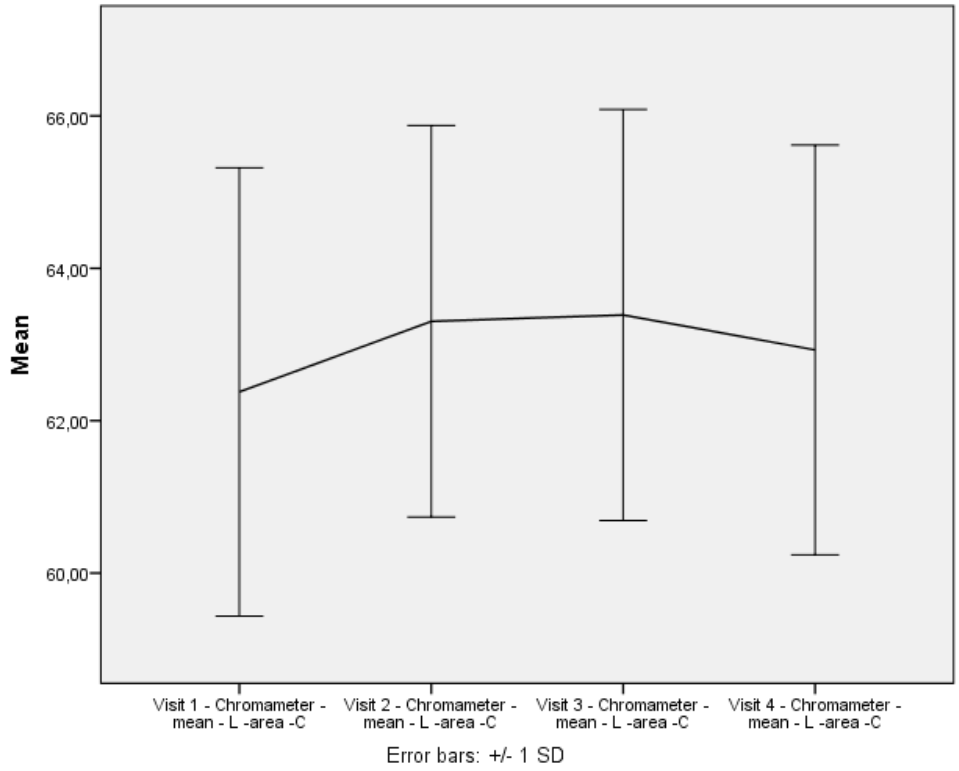

Figure 30: Mean values chromameter brightness (L) chin for all subjects who completed all visits with complete measurements (n = 41) (C)

Differences in skin brightness (L) on chin between visits were statistically significant (n = 41, F = 3.8, p = 0.017). The shape of the trend can be best described with a quadratic function p = 0.002, eta^2 = 0.224.

Table 33: Chromameter brightness (L) jawbone (outer cheek, mandibular) per visit of all valid cases (D)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
N	52	49	47	41
Mean (SD)	65.38 (2.92)	66.10 (4.08)	66.50 (2.58)	66.01 (3.03)
Range	56.15 to 71.21	43.31 to 72.41	56.56 to 71.57	57.48 to 70.95

SD = standard deviation, EoS = end of study

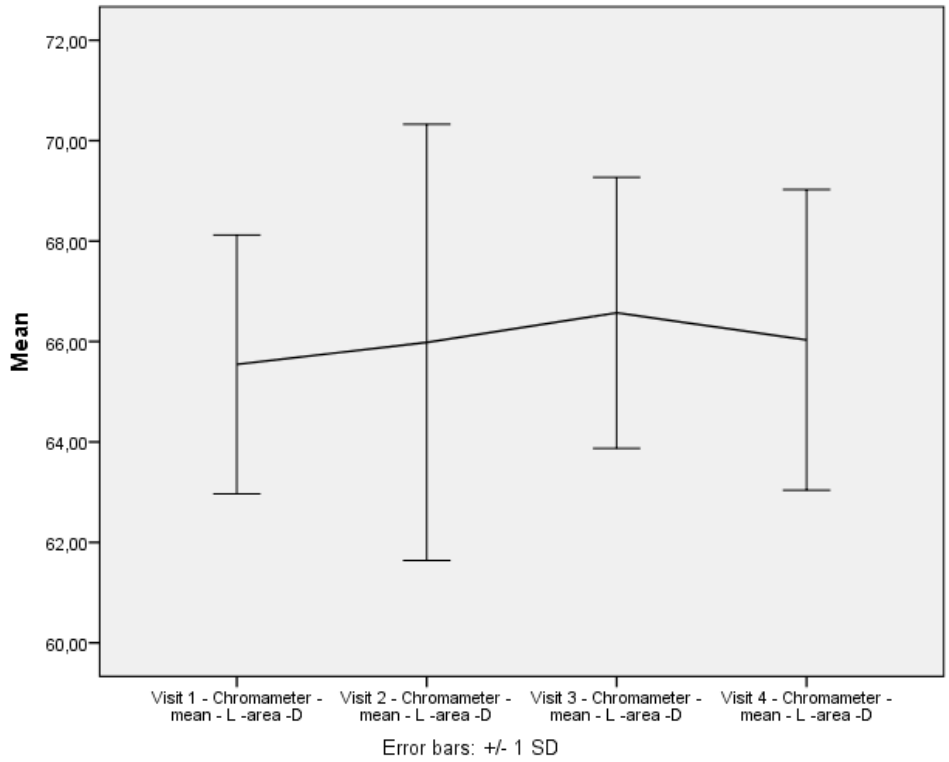

Figure 31: Mean values chromameter brightness (L) jawbone for all subjects who completed all visits with complete measurements (n = 41) (outer cheek, mandibular) (D)

Differences in skin brightness (L) on jawbone between visits were not statistically significant (n = 41, F = 1.3, p = 0.278).

Skin pigmentation/ skin color: red chrominance (a)

Results of broadband spectrophotometry (chromameter) skin pigmentation/skin color (red chrominance a) measurements per skin area are displayed in tables 34 to 37 and figures 32 to 35. Measurements were performed at Baseline, visit 2, visit 3 and visit 4.

Table 34: Chromameter red chrominance (a) forehead per visit of all valid cases (A)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	53	49	47	41
Mean (SD)	11.50 (1.64)	11.14 (1.68)	11.15 (1.73)	11.27 (1.79)
Range	8.54 to 14.73	7.65 to 15.22	6.76 to 15.58	8.68 to 17.35

SD = standard deviation, EoS = end of study

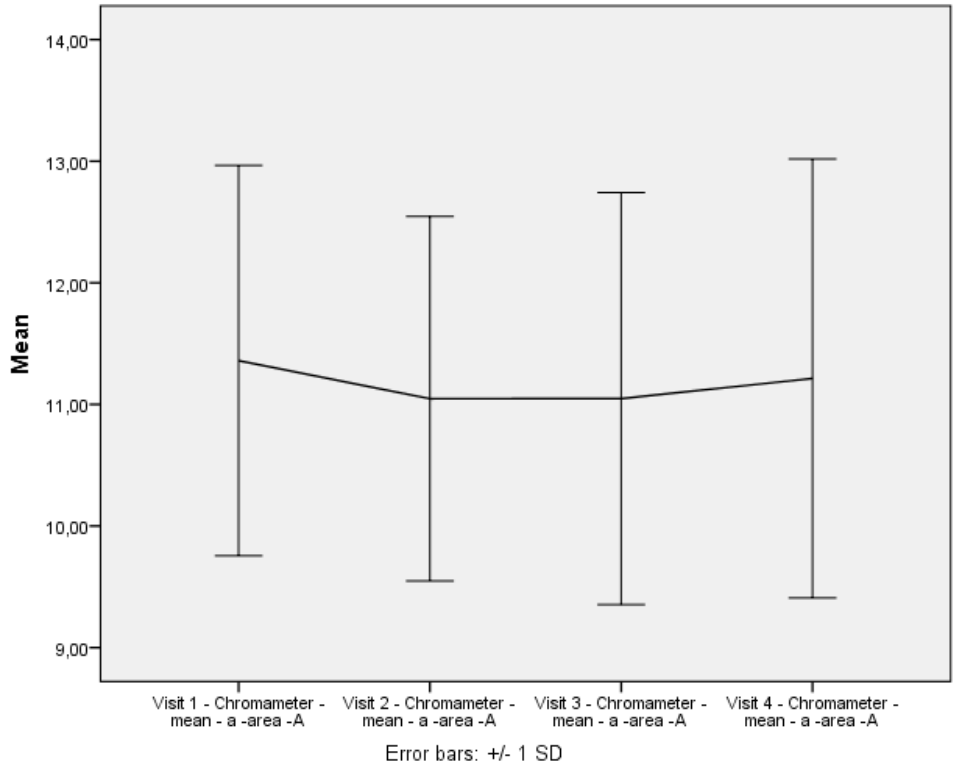

Figure 32: Mean values chromameter red chrominance (a) forehead for all subjects who completed all visits with complete measurements (n = 41) (A)

Differences in skin red chrominance (a) on forehead between visits were not statistically significant (n = 41, F = 0.9, p = 0.409).

Table 35: Chromameter red chrominance (a) inner cheek per visit of all valid cases (B)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
N	53	49	47	41
Mean (SD)	12.89 (1.88)	12.12 (1.71)	12.80 (1.73)	13.31 (2.00)
Range	9.13 to 16.04	8.09 to 15.94	9.02 to 17.20	9.45 to 18.74

SD = standard deviation, EoS = end of study

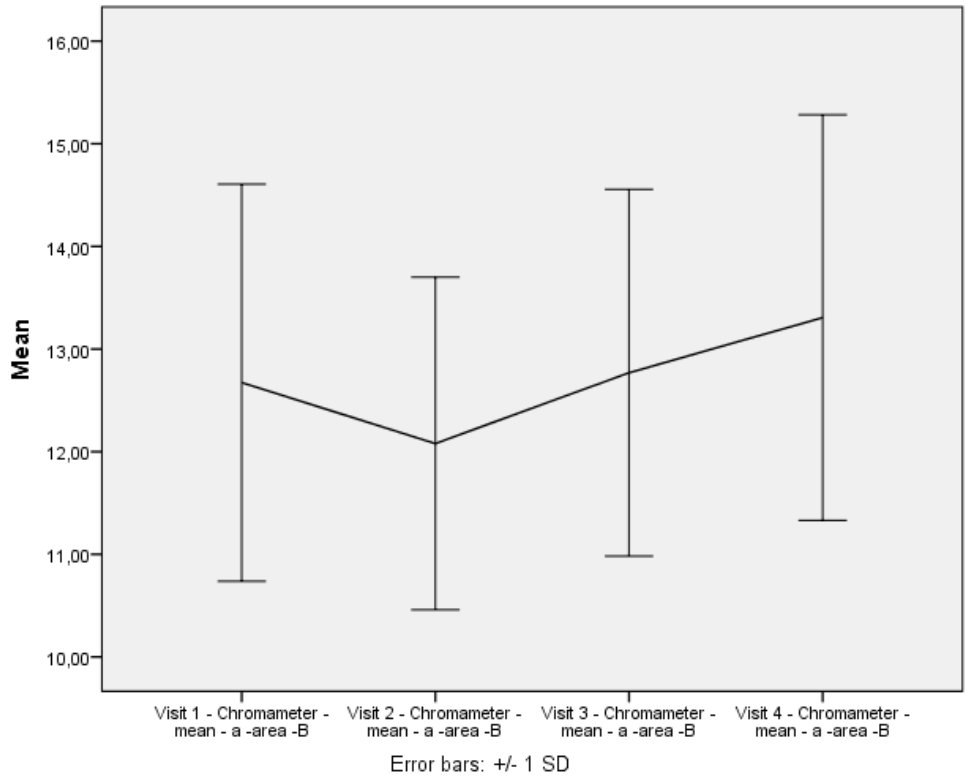

Figure 33: Mean values chromameter red chrominance (a) inner cheek for all subjects who completed all visits with complete measurements (n = 41) (B)

Differences in skin red chrominance (a) on inner cheek between visits were statistically significant (n = 41, F = 7.7, $p < 0.001$). The shape of the trend can be best described with a quadratic function ($p = 0.002$), $eta^2 = 0.222$).

Table 36: Chromameter red chrominance (a) chin per visit of all valid cases (C)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/EoS
n	52	49	47	41
Mean (SD)	14.40 (2.00)	13.96 (2.86)	13.80 (2.07)	13.88 (1.99)
Range	9.75 to 19.68	8.41 to 29.87	8.39 to 18.74	9.21 to 18.35

SD = standard deviation, EoS = end of study

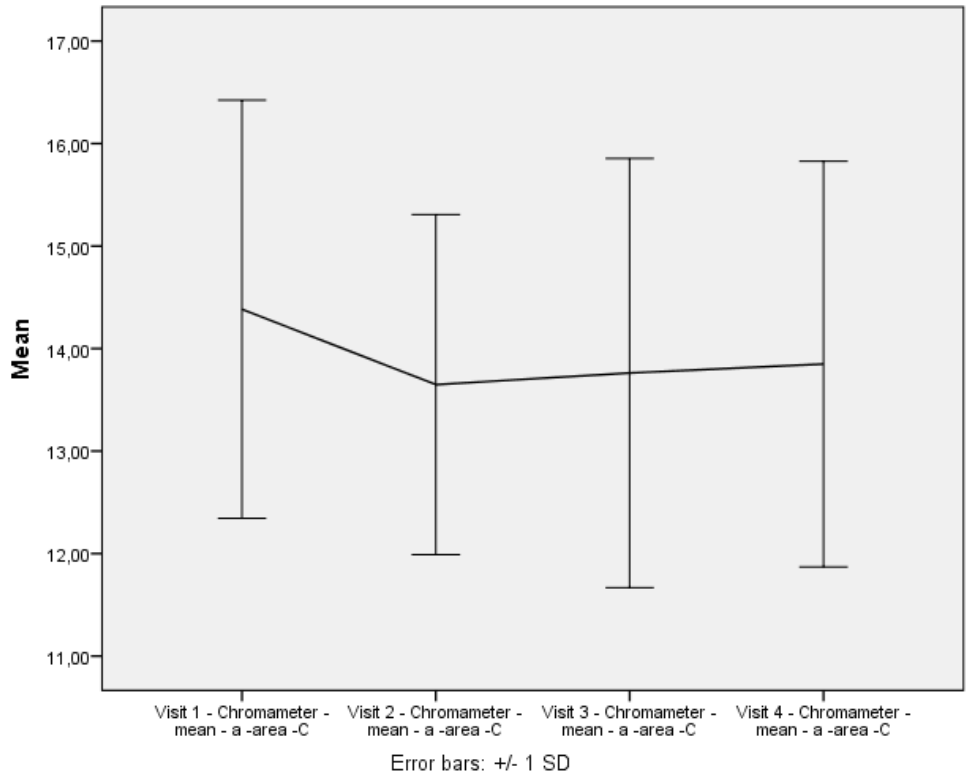

Figure 34: Mean values chromameter red chrominance (a) chin for all subjects who completed all visits with complete measurements (n =41) (C)

Differences in skin red chrominance (a) on chin between visits were statistically significant (n = 41, F = 3.6, p = 0.016). The shape of the trend can be best described with a quadratic function (p = 0.018, eta² = 0.131).

Table 37: Chromameter red chrominance (a) jawbone (outer cheek, mandibular) per visit of all valid cases (D)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	52	49	47	41
Mean (SD)	9.91 (1.97)	9.14 (1.80)	9.14 (1.83)	9.40 (1.65)
Range	5.97 to 15.32	5.02 to 12.85	5.19 to 15.46	6.47 to 13.19

SD = standard deviation, EoS = end of study

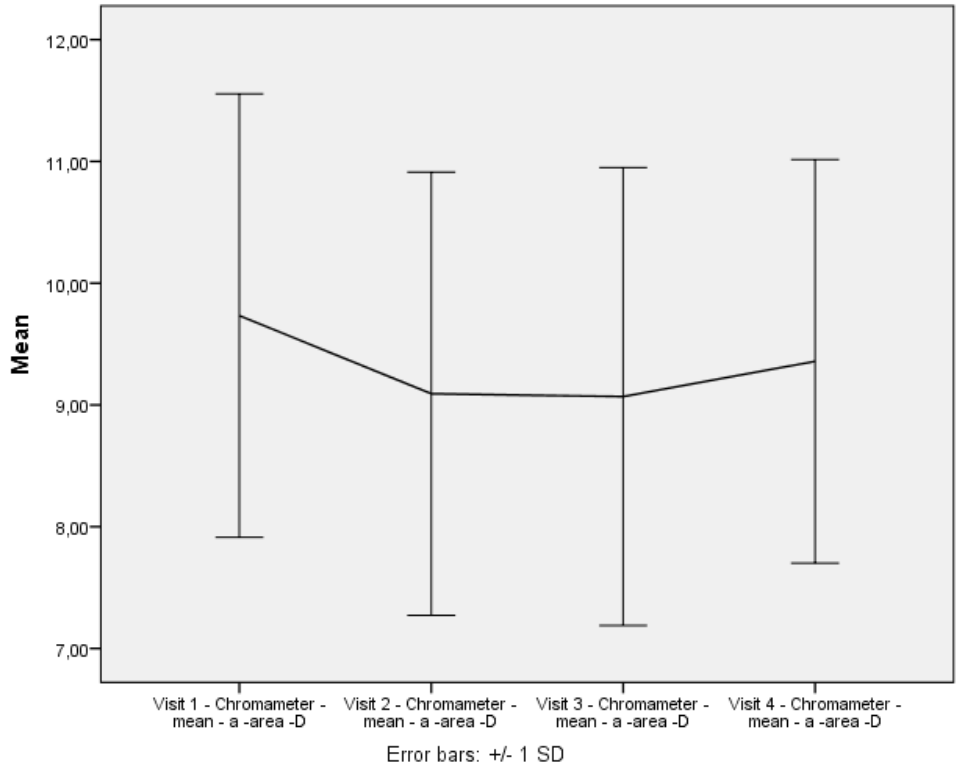

Figure 35: Mean values Chromameter red chrominance (a) jawbone (outer cheek, mandibular) for all subjects who completed all visits with complete measurements (n = 41) (D)

Differences in skin red chrominance (a) on jawbone between visits were statistically significant (n = 41, F = 4.0, p = 0.018). The shape of the trend can be best described with a quadratic function ($p < 0.001$, $eta^2 = 0.330$).

Skin pigmentation/ skin color: yellow chrominance (b)

Results of broadband spectrophotometry (chromameter) skin pigmentation/skin color (yellow chrominance b) measurements per skin area are displayed in tables 38 to 41 and figures 36 to 39. Measurements were performed at Baseline, visit 2, visit 3 and visit 4.

Table 38: Chromameter yellow chrominance (b) forehead per visit of all valid cases (A)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	53	49	47	41
Mean (SD)	16.64 (2.01)	16.91 (2.06)	16.53 (2.15)	16.72 (2.48)
Range	13.49 to 21.65	13.92 to 22.10	13.14 to 21.96	12.50 to 23.22

SD = standard deviation, EoS = end of study

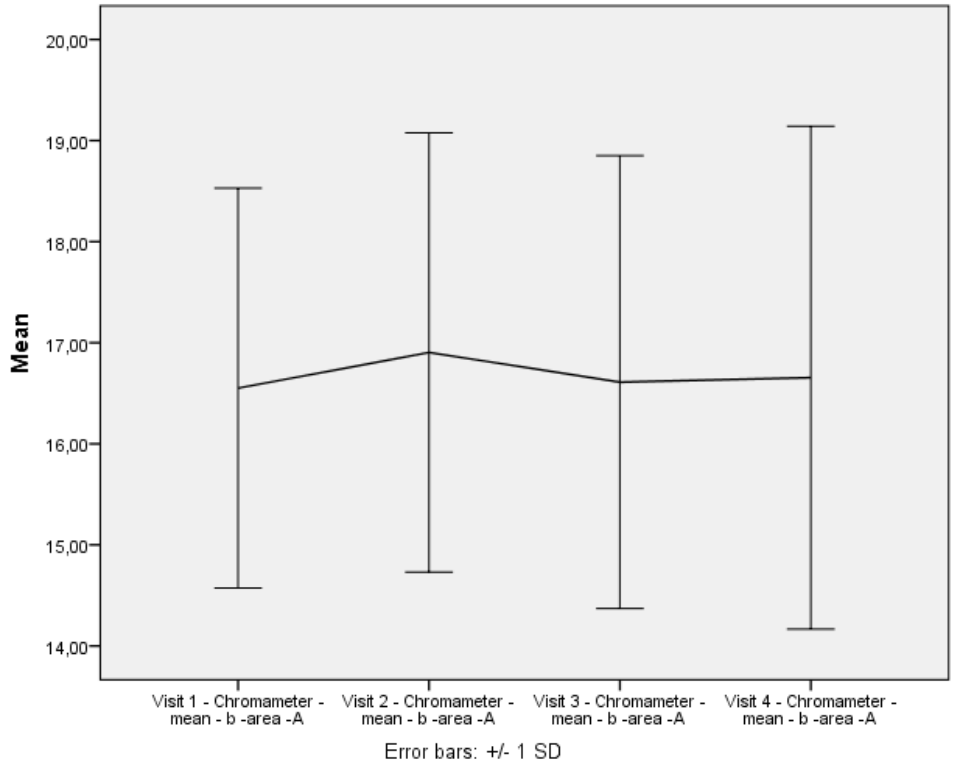

Figure 36: Mean values chromameter yellow chrominance (b) forehead for all subjects who completed all visits with complete measurements (n = 41) (A)

Differences in skin yellow chrominance (b) on forehead between visits were not statistically significant (n = 41, F = 0.9, p = 0.400).

Table 39: Chromameter yellow chrominance (b) inner cheek per visit of all valid cases (B)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
N	53	49	47	41
Mean (SD)	17.39 (2.03)	17.80 (1.95)	17.33 (2.07)	16.83 (2.27)
Range	13.49 to 22.24	14.45 to 21.95	13.36 to 22.60	12.81 to 21.72

SD = standard deviation, EoS = end of study

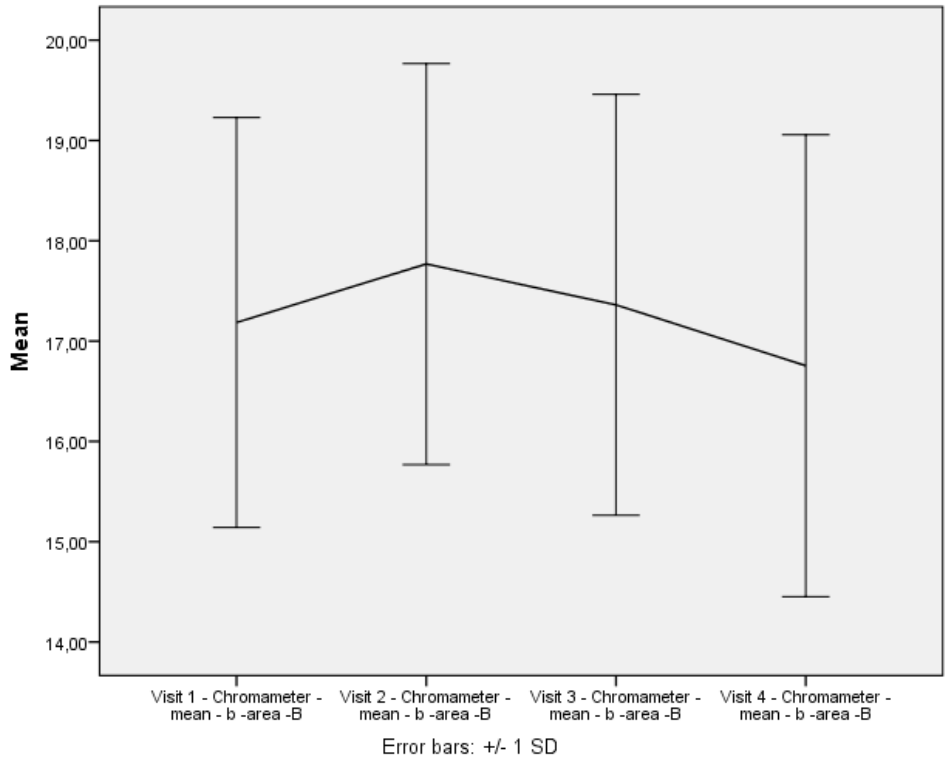

Figure 37: Mean values chromameter yellow chrominance (b) inner cheek for all subjects who completed all visits with complete measurements for all subjects who completed all visits with complete measurements (B)

Differences in skin yellow chrominance (b) on inner cheek between visits were statistically significant (n = 41, F = 4.7, p = 0.007). The shape of the trend can be best described with a quadratic function (p = 0.005, eta² = 0.184).

Table 40: Chromameter yellow chrominance (b) chin of all valid cases per visit (C)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	52	49	47	41
Mean (SD)	15.94 (1.64)	15.88 (1.59)	15.52 (1.96)	15.75 (2.28)
Range	12.92 to 19.94	13.51 to 20.12	12.86 to 21.84	11.49 to 21.66

SD = standard deviation, EoS = end of study

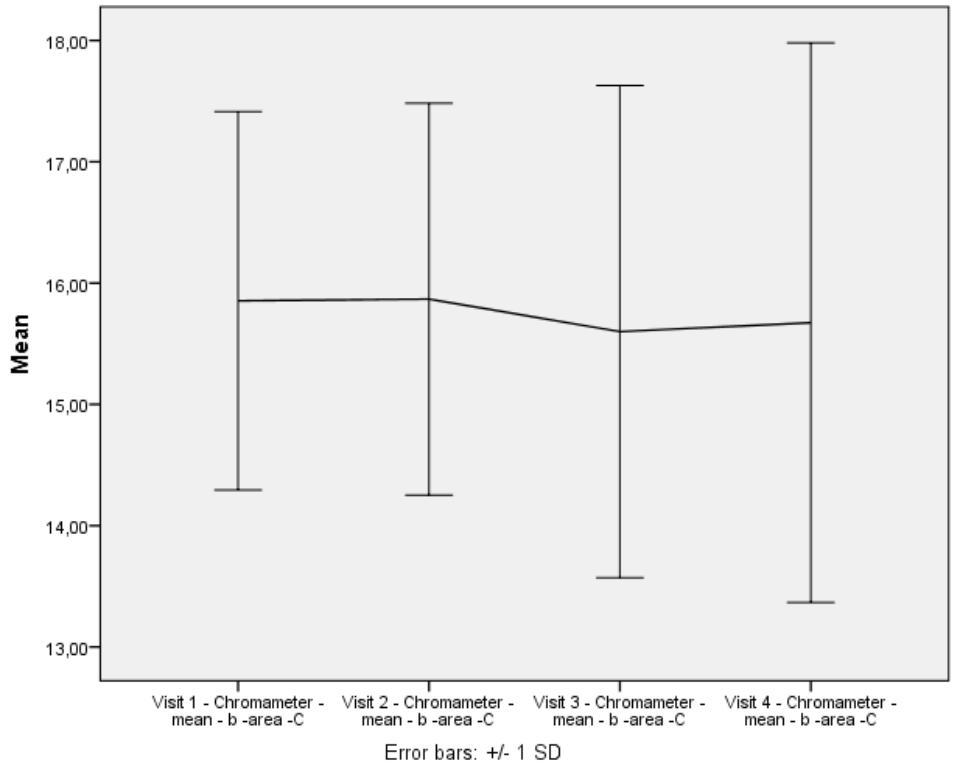

Figure 38: Mean values chromameter yellow chrominance (b) chin for all subjects who completed all visits with complete measurements (C)

Differences in skin yellow chrominance (b) on chin between visits were not statistically significant (n = 41, F = 0.6, p = 0.565).

Table 41: Chromameter yellow chrominance (b) jawbone (outer cheek, mandibular) of all valid cases per visit (D)

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	52	49	47	41
Mean (SD)	16.80 (2.01)	16.89 (1.84)	16.22 (2.01)	16.19 (2.37)
Range	12.77 to 21.78	13.02 to 21.54	12.92 to 21.35	11.37 to 21.36

SD = standard deviation, EoS = end of study

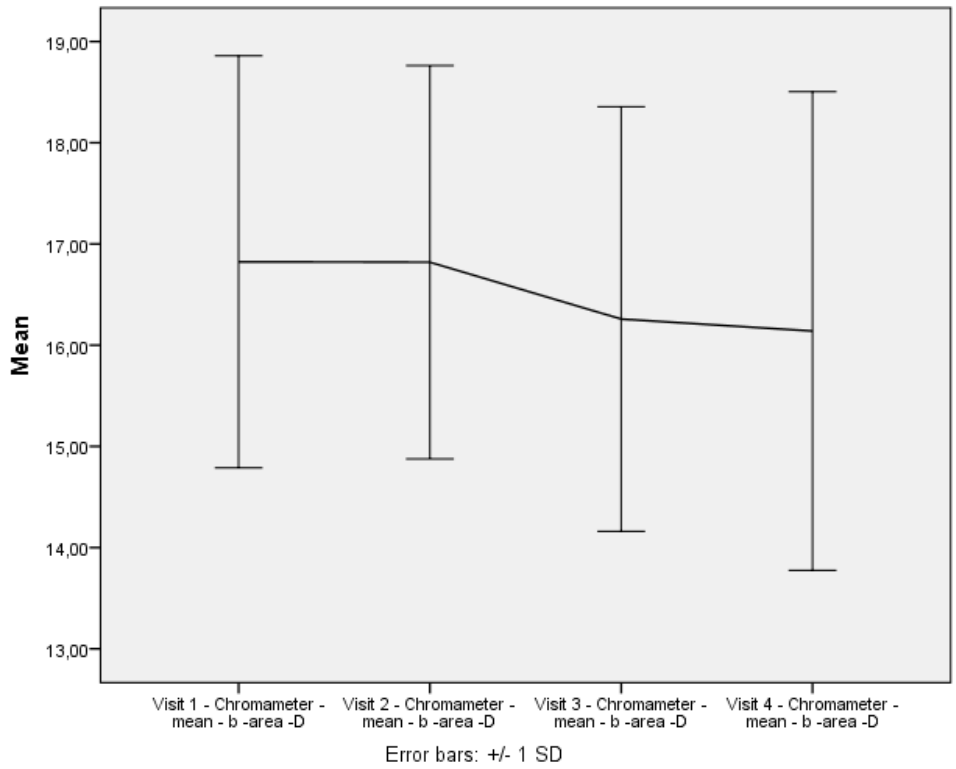

Figure 39: Mean values chromameter yellow chrominance (b) jawbone (outer cheek, mandibular) for all subjects who completed all visits with complete measurements (n = 41) (D)

Differences in skin yellow chrominance (b) on jawbone between visits were statistically significant (n = 41, F = 4.4, p = 0.016). The shape of the trend can be best described with a linear function (p = 0.016, eta² = 0.134).

Results indicate that skin became slightly darker and the red chrominance increased at the inner cheek but did not change at the other skin areas.

Investigator Global Assessment Scores (ISGA)

Results of ISGA scoring are displayed in table 42 and figure 40. Scoring was performed at Baseline, visit 2, visit 3 and visit 4.

Table 42: Investigator Global Assessment Scores (ISGA) of all valid cases per visit

Visit (week)	1 (0)	2 (4)	3 (12)	4 (24)/ EoS
n	53	49	47	41
ISGA categories				
0, n	-	-	-	1
1, n	-	1	12	22
2, n	37	37	32	16
3, n	16	11	3	2
Mean (SD)	2.3 (0.5)	2.2 (0.5)	1.8 (0.5)	1.5 (0.6)
Range	2.0 to 3.0	1.0 to 3.0	1.0 to 3.0	0.0 to 3.0

SD = standard deviation, EoS=end of study

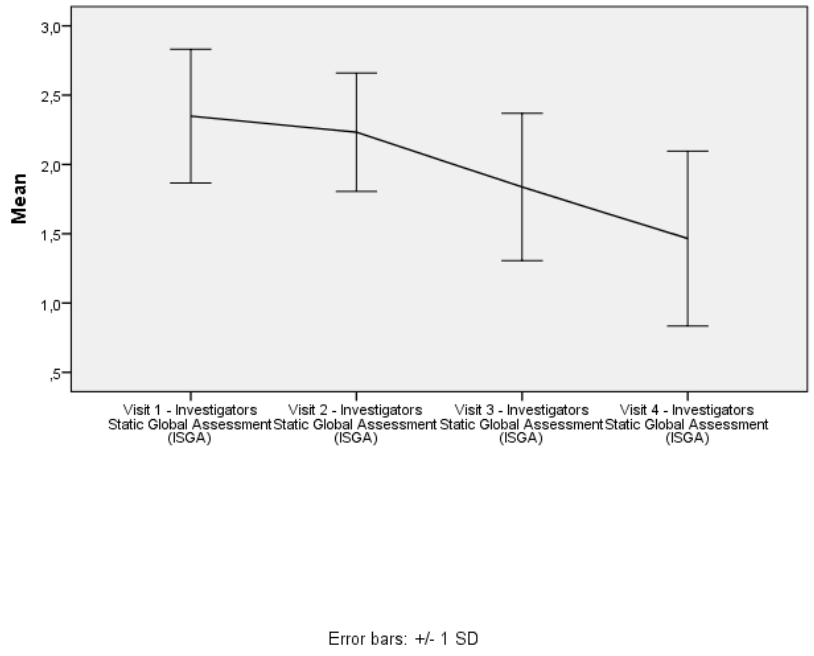

Figure 40: Mean values Investigator Global Assessment Scores (ISGA) per visit of all subjects who completed the whole study, n = 41 (PPS)

Differences of the ISGA scores between visits were statistically significant ($n = 41$, $F = 33.8$, $p < 0.001$). The shape of the trend can be best described with a linear function ($p < 0.001$, $eta^2 = 0.576$).

Acne severity declined statistically significantly during the course of the study, showing that Skinoren 15% gel is an effective topical monotherapy for mild to moderate acne papulopustulosa.

Dermatology Life Quality Index (DLQI)

Results of the DLQI questionnaire are displayed in table 43 and figure 41. Scoring was performed at baseline, visit 3 and visit 4.

Table 43: Dermatology Life Quality Index (DLQI) scores per visit of all valid cases

Visit (week)	1 (0)	3 (12)	4 (24)/ EoS
n	53	47	41
Mean (SD)	5.06 (4.2)	2.81 (3.19)	2.39 (4.00)
Range	0.0 to 18.0	0.0 to 18.0	0.0 to 23.0

SD=standard deviation, EoS=End of study

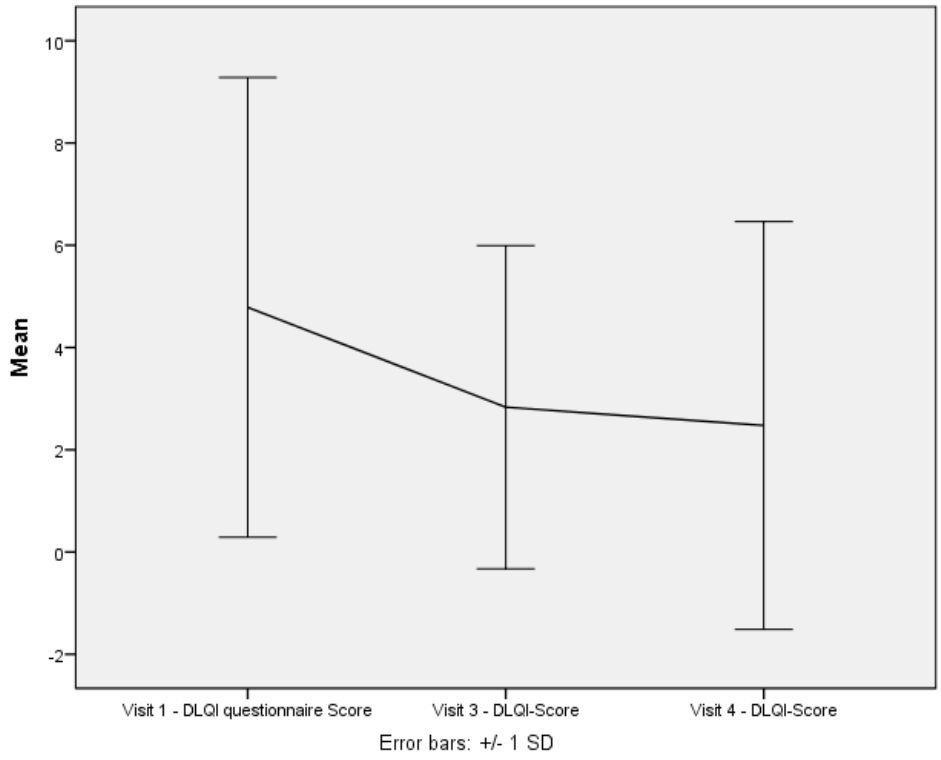

Figure 41: Mean values of DLQI results

Differences in mean quality of life scores between visits were statistically significant (n = 41, F = 7.4, p = 0.002). The shape of the trend can be best described with a linear function (p = 0.004), $eta^2 = 0.191$.

These results underline that the quality of life improved statistically significant during the study.

Photo Documentation

To evaluate the patient´s skin appearance a photo documentation (right, left and frontal view) of the patient´s face was performed for the first time at baseline before Skinoren® 15% gelwas applied and at visits 2, 3 and 4. The device used was a Visia-CR® photo booth (Canfield Scientific, USA). The photographs were taken under standardized conditions (e.g. distance, illumination, background). Per angle, 7 images with standardized flash sequences were taken. Photo documentation illustrated the clinical changes in pigmentation. In table 43 selected image sets of a patient with typical acne tarda manifestation in the facial U-zone are shown, comparing baseline and visit 4.

Table 44: Photo documentation

Visit:	Baseline		
	Right view	Front	Left view
Prior treatment			
Visit:	Visit 4		
	Right view	Front	Left view
Treatment: Skinoren® 15% gel twice daily for 24 weeks			

The Canfield establishment of a software-based pigmentation evaluation system is not part of this study report because results are not available yet. They will be analysed and reported in a subsequent scientific publication.

11.4.2 Statistical/ analytical issues

11.4.2.1 Adjustments of Covariaties
Not applicable.

11.4.2.2 Handling of Dropouts or Missing Data
All included participants were included into data analysis.

11.4.2.3 Interim Analyses and Data Monitoring
Not applicable.

11.4.2.4 Multicentre Studies
Not applicable.

11.4.2.5 Multiple Comparisons/ Multiplicity
Not applicable.

11.4.2.6 Use of an "Efficacy Subset" of Subjects
Not applicable.

11.4.2.7 Active-Control Studies Intended to Show Equivalence
Not applicable.

11.4.2.8 Examination of Subgroups
Not applicable.

11.4.3 Tabulation of individual response data
Not applicable.

11.4.4 Drug dose, drug concentration, and relationship to response
Not applicable.

11.4.5 Drug-drug and drug-disease interactions
Not applicable.

11.4.6 By-patient displays
Not applicable.

11.4.7 Study conclusions
Skinoren® 15% gel reduces acne severity and increases the QoL. It has no effect on skin softness, smoothness, or color.

12 Safety Evaluation

12.1 Extent of Exposure

Patients used Skinoren® 15% gel twice daily on the affected areas for 24 weeks. This regimen followed exactly the product information. Therefore individual exposures weren't assessed. Compliance was controlled by means of a subject diary.

12.2 Adverse Events (AEs)

12.2.1 Brief summary of adverse events

AEs and SAEs were followed throughout the study.

Incidences were differentiated in their correlation to study medication. All AEs that were related as „possibly", „probably" or „certain" regarding their relation to the study medication, received a positive correlation to study medication. The most frequent AEs in both groups were local intolerances (itching, burning, stinging, erythema and scaling) which are associated with product application. Those AEs will be displayed as local intolerances (LIs). Other product related AEs are displayed per treatment group. Unrelated AEs are also displayed in an overview table.

12.2.2 Display of adverse events[30]

In the following an overview of all AEs that occurred during the study is displayed in a chart divided into LIs and AEs related to study medication and unrelated AEs.

During the study all adverse events, which ranged from single symptoms to medical diagnosis were documented in the source data and transferred to the Case report form (CRF) and database.

[30]Summary tables with subject numbers see section 14.3.1

Local Intolerances

Table 45: Number of local intolerances

		Azelaic acid 15% (Skinoren® 15% Gel) N=53
Scaling	**Mild**	**44**
	Moderate	**1**
	Severe	**0**
Erythema	**Mild**	**27**
	Moderate	**3**
	Severe	**0**
Itching	**Mild**	**106**
	Moderate	**44**
	Severe	**9**
Burning	**Mild**	**110**
	Moderate	**38**
	Severe	**2**
Stinging	**Mild**	**83**
	Moderate	**29**
	Severe	**1**
Total (n)		**497**

Adverse Events

Table 46: AEs related to Azelaic acid 15% (Skinoren® 15% Gel) (N = 53)*

Adverse Event related	Intensity			Total number of occurrences
	mild	moderate	severe	
facial dryness	2	2	0	4
erythema nuchal	2	0	0	2
tense feeling of facial skin	3	0	0	3
Total	7	2	0	9

* Number of cases occurred

Table 47: AEs not related to study medication (N = 53)*

Adverse Event unrelated	Intensity			Total number of occurrences
	mild	moderate	severe	
abdominal pain	0	1	0	1
back pain	3	0	1	4
belly ache	1	0	0	1
bursitis shoulder	0	1	0	1
cervical vertebral trauma after car accident	0	1	0	1
common cold	29	10	1	40
common cold sinusitis	1	0	0	1
conjunctivitis	1	0	0	1
cramps in the calf	3	0	0	3
cystitis	1	1	0	2
dandruff head	1	0	0	1
dental inflammation	0	1	0	1
dental operation	0	0	1	1
dizziness	1	0	0	1
dysaesthesia right hand	1	0	0	1
eczema dorsal hand left	1	0	0	1
elevated testosterone level	0	1	0	1
exorication left dorsal hand	1	0	0	1
facial papules increased	0	1	0	1
facial scaling	1	0	0	1
fever	1	0	0	1
gastritis	0	1	0	1
gastroenteritis	1	2	0	3
gastrointestinal infection	1	0	0	1
headache	32	19	1	52
herpes simplex	1	0	0	1
influenza	0	1	0	1
injury head	0	1	0	1
injury knee joint Plica Syndrome	0	1	0	1

irregular pigmentation face	**1**	**0**	**0**	**1**
menstruation pain	**6**	**9**	**0**	**15**
migraine	**0**	**5**	**0**	**5**
nausea	**4**	**0**	**0**	**4**
neck pain	**0**	**1**	**0**	**1**
pain knee right	**2**	**0**	**0**	**2**
pain on left pelvis	**1**	**0**	**0**	**1**
papulous exanthema face and shoulders	**0**	**1**	**0**	**1**
perianal pruritus	**0**	**1**	**0**	**1**
period pains	**0**	**5**	**0**	**5**
plastic surgery breast**	**0**	**0**	**1**	**1**
retrosternal burning	**0**	**0**	**1**	**1**
Rhinitis and sour throat	**1**	**0**	**0**	**1**
silent erythema eyelid	**1**	**0**	**0**	**1**
sinusitis	**2**	**0**	**0**	**2**
slight swelling of left eye	**2**	**0**	**0**	**2**
sour throat	**2**	**0**	**0**	**2**
stomach pain	**1**	**0**	**0**	**1**
sunburn nose	**1**	**0**	**0**	**1**
tick bite left thigh	**1**	**0**	**0**	**1**
tick bite right knee	**1**	**0**	**0**	**1**
tonsillitis	**1**	**2**	**0**	**3**
tooth pain	**1**	**0**	**0**	**1**
torn ligament thumb	**0**	**1**	**0**	**1**
viral infection	**1**	**0**	**0**	**1**
whiplash injury	**1**	**0**	**0**	**1**
Total	**111**	**67**	**6**	**184**

* Number of cases occurred
** due to hospitalization documented as SAE

12.2.3 Analysis of adverse events (AEs)

The most common AEs in this study were related to product application associated local intolerances. The most frequent LI was burning, followed by itching, stinging, scaling and erythema. Other product related AEs were tense feeling on the facial skin and facial skin dryness.

12.2.4 Listing of adverse events by subject

See chapter 14.3

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Listing Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

One serious adverse event occurred, which was neither study nor product related. One subject underwent a breast augmentation.

12.3.1.1 Deaths

Not applicable.

12.3.1.2 Other Serious Adverse Events

Not applicable.

12.3.1.3 Other Significant Adverse Events

Not applicable.

12.3.2 Narratives of deaths, other serious adverse events, and certain other significant adverse events

Not applicable.

12.3.3 Analysis and discussion of deaths, other serious adverse events, and other significant adverse events

Not applicable.

12.4 Clinical Laboratory Evaluation

Not applicable.

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

Not applicable.

12.6 Safety Conclusions

There was an expected rate of AEs related to study products and duration. No other product related events occurred indicating that the study product was safe within the intended use.

13 Discussion and Overall Conclusions

Acne vulgaris is a disorder of the pilosebaceous unit mostly affecting teenagers of both genders but may also persist as so called acne tarda in adults. The pathogenesis of acne is multifactorial. There are four primary pathogenic factors, which interact to produce acne lesions: (1) increased sebum production by the sebaceous glands, (2) alterations in the keratinization process, (3) Propionibacterium acnes follicular colonization, and (4) release of inflammatory mediators. (Nast A 2012) (Youn 2010) (MA Rocha 2014) (Jahns AC 2014).

Hyperkeratinization leads to plugging of the follicular duct, which results in the formation of clinically invisible microcomedones preceding visible acne lesion formation. They might develop into non-inflammatory lesions (closed and open comedones) and to clinically visible inflamed papules, pustules and nodules. Despite this differentiation, the inflammatory potential of acne vulgaris is given throughout the course of the disease; hence acne is an inflammatory disease from its beginning onwards. (MA Rocha 2014) (Harvey A 2014) (Cunliffe WJ 2004) (Jeremy AHT 2003) (Toyoda M 2001) (Farrar MD 2004) (Dessinioti C 2010).

For the treatment of mild to moderate papulopustular acne, topical treatments with benzoyl peroxide (BPO), azelaic acid and retinoids as well as combinations of adapalene/BPO, clindamycin/BPO and systemic antibiotics/adapalene are recommended. (Nast A 2012).

Azelaic acid (AzA) is a saturated, straight-chained, naturally occurring C9 dicarboxylic acid. Its effectiveness was first observerd in hyperpigmentation and later its anti-inflammatory, antimicrobial effect and its antikeratinizing effects in the treatment of acne. Further, no bacterial resistances have been reported for AzA so far (E Vargas-Diez 2014) (MA Sieber 2014).

Acne papulopustulosa is one of the most frequent dermatological disorders worldwide (Hay RJ 2014) and it is typically regarded as an adolescent condition despite its prevalence among adults, particularly adult females (A Thielitz 2014) (E Vargas-Diez 2014) (MA Sieber 2014) (EA Tanghetti 2014).

Due to a high prevalence of persistent acne in adult women and reports of patients in the consultation hour on a smoother and softer overall appearance of the skin and an improvement of the complexion after AzA treatment, we have conducted this exploratory clinical trial.

The main question was, if this subjectively reported observations on a smoother and softer overall appearance of the skin can be verified by skin physiological measurements.

A total of 53 female patients between 20 and 45 years with mild to moderate acne papulopustulosa were included and treated with Skinoren® 15% Gel for 24 weeks. The study was terminated prematurely in 12 patients, of which the majority withdrew informed consent. For skin physiological measurements and to maintain standardization, four pre-defined test areas were selected: forehead (A) – right, inner cheek (upper lip region) (B) - right, chin (C) – central and jawbone (outer cheek, mandibular region) (D) – right. These areas were chosen due to the characteristic acne distribution within the face: T-zone (forehead, inner cheek) and is especially visible at the U-zone (chin and outer cheek/ jawbone). It has been reported that

this type of acne in adults differ from that in teenagers. Acne lesions in adults tend to concentrate in the chin and outer cheek area (CW Choi 2011).

The study results show that Skinoren® 15% gel is a good tolerable and effective topical monotherapy for mild to moderate acne papulopustulosa. ISGA scores constantly declined during the course of the study. Due to its anti-inflammatory, antibacterial effects and negative resistance profile, AzA 15% is highly suitable for the treatment of mild to moderate acne papulopustulosa.

Along with improving acne severity, quality of life increased significantly. This underlines the finding that acne, especially in adult women, has a major impact on self-confidence, self-perception and hence daily life (EA Tanghetti 2014).

The primary outcome variable was changes in skin smoothness (SE_{SM}), measured by the Visioscan® device. What could be observed for all skin areas is, that skin smoothness values declined after starting treatment and start to increase at visit 3 (after 12 weeks). This trend might be explained by the mere keratolytic effect of AzA. Hence, local intolerances such as dryness, pruritus, burning, stinging and scaling often occur at the beginning of topical acne treatment but improve during the course of treatment as skin adapts to the product. Further, patients were allowed to use a facial moisturizer[31] as needed to support their skin condition.

Results indicate that the skin elasticity did not change at the forehead and chin skin area. There was a decrease of the overall extensibility at the inner and out cheek areas indicating that skin became firmer during the course of the study. A decrease of the biological elasticity indicates that the ability of the skin to regain its initial position after deformation decreased.

In sum changes in skin surface condition, elasticity or skin color/ skin pigmentation have been observed after the start the treatment with AzA, but these changes did not remain and reached baseline values after 6 month. Therefore we conclude that AzA treatment has no overall effects on the investigated skin parameters.

This study focused on a subpopulation that has not been studied very well so far. Acne in female adults needs further investigation regarding clinical signs, treatment options and a tailored healthcare regimen for this patient population. Their perception of the disease is different from that in teenagers. Often in adult female acne (AFA) the skin condition also affects the psyche, resulting in lack of self-esteem, self-perception, which also has an impact on social and professional life. Numbers of adult females suffering from persistent acne vulgaris are growing (EA Tanghetti 2014). The subjective reports assuming a clinical softening of skin surface under AzA treatment of acne vulgaris mainly in adult female patients might be possibly be due to reduction of inflammatory acne lesions, leading to significantly improved ISGA score and perceived better skin quality and significantly improved DLQI.

[31] See Appendix 16.4.8

14 Tables, Figures and Graphs referred to but not included in the Text

14.1 Demographic Data

Not applicable.

14.2 Efficacy Data

Not applicable.

14.3 Safety Data

14.3.1 Displays of adverse events

The following tables display the adverse events and local intolerances classified to body system, the AE intensity, its relationship to study product and the randomization numbers of concerned subjects (subject ID).

A) LI/ AE related to Azelaic acid 15% (Skinoren® 15% Gel) (N=53)

Table 48: LI/AE related to Azelaic acid 15% (Skinoren® 15% Gel)

Facial Skin						
LI/ AE	mild		moderate		severe	
	Related	SN* (%)	Related	SN* (%)	Related	SN* (%)
Scaling	N=20	1,2,3,4,6,17,20,22,24,25,27,29, 35,38,42,43,49,50,51,53 (38.0%)	N = 1	4(1.9%)	0	
Erythema	N=19	2,3,8,9,11,13,22,27, 28,32,42,49,51,52 (26.4%)	N=3	40,43 (3.8%)	0	
Itching	N=40	1,2,4,5,6,7,8,9,10,11,12,13,16, 17,18,20,21,22,23,24,26,27, 28,31,32,33,34,35,37,38,41,42, 43,45,46,47,49,50,52,53 (72.5%)	N=19	1,6,7,11,13,16,20,21,24, 27,29,30,35,40,42,43, 44,46,50 (36.0%)	N=5	4,11,48, 49,53 (9.4%)
Burning	N=41	1,2,3,5,6,7,8,9,11,12,13,15, 16,17,18,19,20,21,22,24,25, 26,27,28,29,31,32,33, 34,35,36,37,38,40,41, 42,45,47,50,52,53 (77.4%)	N=15	1,6,7,9,16,17,21,34, 35,42,44,46,47,48,50 (28.3%)	N=1	44(1.9%)
Stinging	N=30	1,3,4,7,8,9,11,13,15,17,21, 22,23,24,26,29,32,33,34, 36,38,43,45,46,47,49,50, 51,52,53 (56.6%)	N=13	1,3,4,11,13,21,29, 30,35,40,43,44,50 (24.5%)	N=1	4(1.9%)
Tense feeling	N=3	6,16,39 (5.7%)	0		0	
Dryness	N=11	2,7,13,15,16,18,20, 26,28,45,48 (20.8%)	N= 2	21, 47(3.8%)	0	

* SN = Subject number (count of subjects)

B) AE not related to study medication (N=53)

Table 49: AE not related to Study Medication

AE	Body System	mild		moderate		severe	
		N	SN (%)	N	SN (%)	N	SN (%)
abdominal pain	Gastrointestinal	0		1	53 (1.9%)	0	
back pain	Musculoskeletal	3	6,9,24 (5.7%)	0		1	44 (1.9%)
belly ache	Gastrointestinal	1	7 (1.9%)	0		0	
bursitis shoulder	Musculoskeletal	0		1	1 (1.9%)	0	
cervical vertebral trauma after car accident	Musculoskeletal	0		1	44 (1.9%)	0	
common cold	Immune System	29	1,2,5,9,12,13,14, 15,16,19,21,22, 25,26,31,32,35, 38,40,43,46,49,51 (43.4%)	10	7,12,15,20, 24,39,40,47 (15.1%)	1	53 (1.9%)
common cold sinusitis	Immune System	1	27 (1.9%)	0		0	
cramps in the calf	Musculoskeletal	3	1(1.9%)	0		0	
cystitis	Urological	1	41(1.9%)	1	12(1.9%)	0	
dandruff head	Skin	1	41(1.9%)	0		0	
dental inflammation	Head-Nose-Throat	0		1	19(1.9%)	0	
dental operation	Head-Nose-Throat	0		0		1	19 (1.9%)
dizziness	Neurological	1	7(1.9%)	0		0	
dysaesthesia right hand	Neurological	1	41(1.9%)	0		0	
eczema dorsal hand left	Skin	1	31(1.9%)	0		0	
elevated testosterone level	Hormone System	0		1	11(1.9%)	0	
exorication left dorsal hand	Skin	1	18(1.9%)	0		0	
facial papules increased	Skin	0		1	33(1.9%)	0	
facial scaling	Skin	1	27(1.9%)	0		0	
fever	Immune System	1	31(1.9%)	0		0	
gastritis	Gastrointestinal	0		1	44(1.9%)	0	

gastroenteritis	Gastrointestinal	1	7(1.9%)	2	2,33 (3.8%)	0	
gastrointestinal infection	Gastrointestinal	1	8(1.9%)	0		0	
headache	Head-Nose-Throat	32	1,2,7,8,9,15,22, 27,28,29,34,45,47 (24.5%)	19	9,12,15,27,28, 33,34,45,47,51 (18.9%)	1	33 (1.9%)
herpes simplex	Immune System	1	39 (1.9%)	0		0	
influenza	Immune System	0		1	13(1.9%)	0	
injury head	Musculoskeletal	0		1	9(1.9%)	0	
injury knee joint Plica Syndrom	Musculoskeletal	0		1	34(1.9%)	0	
irregular pigmentation face	Skin	1	47(1.9%)	0		0	
menstruation pain	Gynecology	6	6,9 (3.8%)	9	9,11 (3.8%)	0	
migraine	Head-Nose-Throat	0		5	4,5,27,39 (7.6%)	0	
nausea	Gastrointestinal	4	7,9,13,46 (7.6%)	0		0	
neck pain	Neurological	0		1	24 (1.9%)	0	
pain knee right	Musculoskeletal	2	34 (1.9%)	0		0	
pain on left pelvis	Musculoskeletal	1	24 (1.9%)	0		0	
papulous exanthema face and shoulders	Skin	0		1	22 (1.9%)	0	
perianal pruritus	Skin	0		1	17 (1.9%)	0	
period pains	Gynecology	0		5	1 (1.9%)	0	
plastic surgery breast	Soft Tissue	0		0		1	22 (1.9%)
retrosternal burning	Skin	0		0		1	44 (1.9%)
Rhinitis and sour throat	Immune system	1	8(1.9%)	0		0	
silent erythema eyelid	Skin	1	16(1.9%)	0		0	
sinusitis	Immune System	2	7(1.9%)	0		0	
slight swelling of left eye	Head-Nose-Throat	2	2(1.9%)	0		0	
sour throat	Head-Nose-Throat	2	31(1.9%)	0		0	
stomach pain	Gastrointestinal	1	9(1.9%)	0		0	
sunburn nose	Skin	1	34(1.9%)	0		0	
tick bite left thigh	Skin	1	34(1.9%)	0		0	

tick bite right knee	Skin	1	31(1.9%)	0		0	
tonsillitis	Immune System	1	47(1.9%)	2	34(1.9%)	0	
tooth pain	Head-Nose-Throat	1	9(1.9%)	0		0	
torn ligament thumb	Musculoskeletal	0		1	1(1.9%)	0	
viral infection	Immune System	1	9(1.9%)	0		0	
whiplash injury	Musculoskeletal	1	39(1.9%)	0		0	

14.3.2 Listings of deaths, other serious and significant adverse events

Serious Adverse Events

Table 50: SAEs unrelated to Azelaic acid 15% (Skinoren® 15% Gel) (N=53)

AE	Body System	mild		moderate		severe	
		N	SN* (%)	N	SN* (%)	N	SN* (%)
plastic surgery breast	Soft Tissue	0		0		1	22 (1.9%)

*SN= subject number

14.3.3 Narratives of deaths, other serious and certain other significant adverse events

N.A.

14.3.4 Abnormal laboratory value listing (each subject)

N.A.

15 Reference List

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16 Appendices

16.1 Study Information

16.1.1 Protocol and protocol amendments

16.1.2 Sample case report form

16.1.3 List of IEC (including the name of the committee chair) – representative written information for patient and sample consent form

16.1.4 List and description of investigators and other important participants in the study including CVs and GCP certificates

16.1.5 Signatures of principal/ coordinating Investigator and sponsor

16.1.6 Listing of patients receiving study medication from specific batches
N.A.

16.1.7 Randomization scheme and codes (subject identification, treatment assigned)
N.A.

16.1.8 Audit certificates (if available)
N.A.

16.1.9 Documentation of statistical methods
N.A.

16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used
N.A.

16.1.11 Publications based on study
N.A.

16.1.12 Important publications referenced in the report
N.A.

16.2 Subject Data Listings

16.2.1 Discontinued subjects

16.2.2 Protocol deviations
N.A.

16.2.3 Patients excluded from efficacy analysis
N.A.

16.2.4 Demographic data
See table 8 in the document.

16.2.5 Compliance and/or Drug Concentration Data (if available)
N.A.

16.2.6 Individual Efficacy Response data
N.A.

16.2.7 Adverse event listings (each subject)
See chapter 12.2 and 14.3

16.3 Case Report Forms

16.3.1 CRFs of SAEs and withdrawals for AE

16.4 Other

16.4.1 VisioScan®

16.4.2 Cutometer®

16.4.3 Visia CR®

16.4.4 Chromameter®

16.4.5 DLQI German
16.4.6 IEC vote

16.4.7 SmPC Skinoren® 15% Gel

16.4.8 Ingredients Unguentum Emulsificans aquosum SR