Title Page

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

Date: 29-Jun-2020

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

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

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

Final Version 1.0

1 APPROVAL STATEMENT

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

Lars Siim Madsen, PhD

Sponsor's representative

Michael Brennan, DDS

International Coordinating Investigator and Chief Investigator USA

Prof. Thomas Ruzicka, MD

Coordinating Investigator EU and national Chief Investigator GER

Thomas Bengtsson

Biostatistician (statistical analysis)

2 SYNOPSIS

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

Title of study:

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

Study number: DT-001-R-004 **EudraCT number:** 2017-002193-40 **IND number:** 129603

Investigators:

International Coordinating Investigator and Chief Investigator USA:
Prof. Michael Brennan, DDS
Atrium Health, Dept. of Oral Medicine
1000 Blythe Blvd.
Charlotte, NC 28203, USA

Coordinating Investigator EU and national Chief Investigator GER:
Prof. Dr. Dr. Thomas Ruzicka
Klinik und Poliklinik für Dermatologie und Allergologie, Klinikum der Universität München
Frauenlobstraße 9-11, 80337 Munich, Germany

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

Study sites:

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

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

Objectives:

Primary objective:

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

Secondary objectives:

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

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

Exploratory objectives:

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

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

Methodology (design of study):

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

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

Number of patients (planned and analyzed):

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

Diagnosis and main criteria for inclusion:

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

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

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

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

Route of administration: topical, oral patches

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

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

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

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

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

Endpoints:

Primary efficacy endpoint:

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

Secondary efficacy endpoints:

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

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

Exploratory endpoints:

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

Statistical methods:

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

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

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

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

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

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

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

Summary of Efficacy:

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

Summary of Safety:

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

cavity or systemically.

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

Overall conclusions:

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

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

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

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

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

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