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TITLE: Efficacy and Safety of a Novel Mucoadhesive Clobetasol Patch for Treatment of Erosive Oral Lichen Planus

A Phase 2b Randomized Clinical Trial

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CONFLICT OF INTEREST DISCLOSURES

Drs Siim Madsen and Hansen report pending and issued patents broadly relevant to this work. Drs Brennan, Saunders, Napenas, McCreary, Ni Riordain, Lynge Pedersen, Federle, Cook, Abdelsayad, Llopiz, Sankar, Ryan, Culton, Akhlef, Caustillo, Fernandez, Jurge, Kerr, McDuffie, McGaw, Mighell, Sollecito, Schlieve, Carrozzo, Papas, Al-Hashimi, Culshaw, Desai, and Ruzicka report receipt of personal fees or payment to their institutions from Afyx for serving as an investigator in the clinical trial reported. Drs Brennan, Saunders, Ni Riordain, Lynge Pedersen, Federle, Cook, Sankar, Culton, Kerr, Sollecito, Carrozzo, Papas, Desai, Menné, Treister, and Ruzicka, Mr Bengtsson, and Ms Burke report receipt of personal fees from Afyx for service on the advisory board or consultancy in relation to the clinical trial reported. Drs Brennan, Saunders, Ni Riordain, Cook, Sankar, Culton, Kerr, Sollecito, Papas, Al-Hashimi, Treister, and Ruzicka, Mr Bengtsson, and Ms Burke report receipt of funds from Afyx for relevant activities outside the submitted work. Drs Hansen and Thornhill report holding shares/share options in Afyx. Dr Hansen reports receipt of a grant from the Innovation Fund Denmark for this work. Dr Thornhill reports receipt of travel and meeting expenses to attend scientific and other meetings from Afyx. Dr Burkhart and Ms Jensen report no conflicts of interest.

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ROLE OF THE FUNDER/SPONSOR

The sponsor participated in the conception and design of the study, analysis and interpretation of the data, statistical analysis, drafting and critical revision of the report, and gave approval to submit the manuscript for publication.

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ABSTRACT

BACKGROUND Oral lichen planus (OLP) is a chronic inflammatory disorder of the oral mucosa. Currently there is no approved treatment for oral lichen planus (OLP). We report on the efficacy and safety of a novel mucoadhesive clobetasol patch (Rivelin®-CLO) for the treatment of OLP.

METHODS Patients with confirmed OLP and measurable symptomatic ulcer(s) participated in a randomized, double-blind, placebo-controlled, multicenter clinical trial testing a novel mucoadhesive clobetasol patch (Rivelin®-CLO) in OLP across Europe, Canada and USA. Patients were randomized to placebo (non-medicated), 1, 5, 20 µg Clobetasol/patch, twice daily, for 4 weeks. The primary endpoint was change in total ulcer area compared to baseline. Secondary endpoints included improvement from baseline in pain, disease activity, and quality of life.

RESULTS Data were analyzed and expressed as mean [SD]. One hundred thirty-eight (138) patients were included in the study; 99 females and 39 males, mean age was 61.1 [11.6] years. Statistical analyses revealed that treatment with 20-µg Rivelin®-CLO patches demonstrated significant improvement with ulcer area (P=0.047), symptom severity (P=0.001), disease activity (P=0.022), pain (P=0.012), and quality of life (P=0.003) as compared with placebo. Improvement in OLP symptoms from beginning to the end of the study was reported as very much better (best rating) in the 20-µg group (25/32) patients compared to the placebo group (11/30), (P=0.012). Adverse events were mild/moderate. Candidiasis incidence was low (2%).

CONCLUSIONS Rivelin®-CLO patches were superior to placebo demonstrating statistically significant, clinically relevant efficacy in objective and subjective improvement and, with a favorable safety profile.

KEYWORDS: Oral Lichen Planus, Erosive, Treatment, Clobetasol, Mucoadhesive Patch.

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Oral lichen planus (OLP) is a chronic inflammatory oral mucosal disorder, affecting 0.6% to 1.7% of the world's population, generally occurs at 30 to 60 years of age, and is more common in women.[1, 2, 3] Its precise etiopathogenesis remains unknown but is considered a T-cell-mediated process resulting in chronic inflammation and basal keratinocyte apoptosis. OLP manifests as asymptomatic reticular/plaque-type lesions or as symptomatic lesions including erythematous/atrophic-type lesions, erosive, or ulcerative lesions on the buccal, gingival, sublingual, lingual, labial, or palatal mucosae.[4-6] Diagnosis relies on characteristic clinical

findings, often confirmed by biopsy. Chronic symptomatic OLP is often painful, which compromises oral functions, like talking and eating,[7, 8] and quality of life.[9]

Treatment of OLP varies based on the severity of the symptoms, however, there are limited options; and there is no approved treatment. First-line therapy is topical corticosteroids. A variety of formulations, and dose regimens are employed, with no established standard of care.[6, 10-12] This approach presents several challenges, including minimal oral mucosal absorption due to short contact time and poor compliance. To mitigate these challenges, corticosteroids are frequently used in higher and more protracted doses than labeling indicates. The use of corticosteroids is limited by adverse reactions, particularly oral candidiasis and systemic effects related to hypothalamic-pituitary-adrenal axis (HPA) suppression from untargeted, inefficient application of corticosteroids and unintentional swallowing.[13] There is a need for targeted, controlled, sustained-release medication delivery to withstand the challenging oral environment with its moist surfaces and continuous salivary clearance of the medication..

An innovative patch for targeted treatment of erosive OLP lesions incorporating an established glucocorticoid has been developed to address these challenges. Rivelin®-CLO is a bilayer (~300 mm^2) patch combining a mucoadhesive porous layer containing clobetasol propionate and an impermeable, non-adhesive backing layer facing away from the mucosa (Figure 1).[14] The objective of this study was to evaluate the efficacy and safety of this patch (Rivelin®-CLO) for treating erosive OLP.

MATERIALS AND METHODS

A randomized, double-blind, placebo-controlled, Phase 2b trial in symptomatic erosive OLP patients evaluated the efficacy and safety of 3 doses of Rivelin®-CLO alongside ease of application, adhesion time, and comfort in use. Twenty-five outpatient oral medicine, dermatology, otolaryngology and oral and maxillofacial clinics in Canada, Denmark, Germany, Ireland, the UK, and the US participated. This clinical trial was conducted in compliance with Good Clinical Practice, the Declaration of Helsinki's principles and completed according to a written protocol approved by the institutional review board/ethics committee for each center. Informed consent was obtained from each participant. The study sponsor, Afyx Therapeutics A/S, developed the study protocol in cooperation with Drs. Brennan and Ruzicka.

Patients

Inclusion criteria included adult (≥ 18 years) OLP patients with at least one visible and measurable symptomatic ulcerative OLP lesion and symptomatic lesion(s) coverable by ≤6 patches. Exclusion criteria were patients with oral ulcers requiring > 6 patches, oral candidiasis, viral infections, and non-healed mucosal areas (e.g. a recent oral biopsy). Symptomatic OLP was defined on the basis of score on the OLP Symptom Severity Measure (OLPSSM), a questionnaire in which the patient reports how sore OLP is when performing 7 activities that provoke symptoms (brushing teeth, eating, drinking, smiling, breathing through mouth, talking, touching; questions provided in Supplementary Appendix), each on scale from 0 (not at all) to 4 (very severe symptoms).[6] A total OLPSSM score (sum of 7 items) ≥5 on ≥4 days during the week before randomization was required. Biopsy confirmation was added approximately 2 months after enrollment start, following a US Food and Drug Administration recommendation. All patients provided written informed consent to participate in the study.

Intervention

Patients were randomized to 1, 5, 20 μg/patch doses or placebo (identical nonmedicated patch) in a 1:1:1:1 ratio. Up to 6 patches were applied to symptomatic OLP lesions twice-daily (morning and evening) for 4 weeks. Appearance and handling of placebo and active patches was identical. Randomization was stratified by the number of patches needed (1 to 3 or 4 to 6), and block size was 4. A sponsor-supplied computer-generated randomization list was used for assignment of blinded kits by site staff via an internet system.

Assessments

Patients had weekly visits during the 4-week treatment period and a follow-up visit 2 weeks after treatment completion. At each visit, the investigator performed an oral examination including detailed OLP lesion mapping and inspection for pseudomembranous candidiasis. Clinical measurement included ulcer and lesion areas and scored erythema severity on a 5-point scale; these assessments comprise the OLPClinROM (provided in Supplementary Appendix). Measurements also scored clinical global impression (CGI) of each treated anatomical site and the disease activity score (DAS) of the Oral Disease Severity Score (ODSS).[15] All examiners attended

in-person training on objective study assessments and were qualified by agreement of their assessment of 5 calibration cases with predetermined standard assessments.

Patient-reported outcomes were also used to assess disease severity. At each visit, patients rated OLP pain on a numerical rating scale (NRS) and worst symptoms at each treated anatomical site during the last 24 hours (WSAAS). Each patient used a daily diary to complete the OLPSSM and record patch adhesion time. Patients completed a patch sensation questionnaire before and after 2 weeks' treatment and the Chronic Oral Mucosal Disease Questionnaire (COMDQ; a combined symptom assessment and quality of life questionnaire),[16] before and after 2 and 4 weeks' treatment. At treatment completion, the patient also rated overall change in OLP symptoms during the treatment period (patient global impression of change; PGI-C), choosing 1 of 7 answers ranging from "very much better" to "very much worse."

Safety was evaluated by adverse events (AEs) reported throughout the study and vital signs and laboratory parameters (lists in Supplementary Appendix) measured at screening and follow-up. Investigators assessed severity and relationship to clobetasol and to patch application for each AE. The plasma clobetasol concentration was measured at visit 3 (day 8).

Outcomes and Statistical Analysis

The primary endpoint was change in total ulcer area from baseline to average of Week 3 and 4. Data from an unpublished exploratory investigation (MTB) indicated that a standard deviation of approximately 25 mm^2 in ulcer area could be expected for this endpoint evaluated by analysis of covariance (ANCOVA) as described below. A sample size of 45 patients per group would provide 90% power to detect a true difference of 17 mm^2 between any 2 treatments using a 2-sided test at a 5% significance level; an interim analysis was performed to reassess the sample size. The primary endpoint was assessed in the full analysis set (all treated patients with data collected after first dose) according to randomized treatment assignment. Missing data due to withdrawals were imputed (by end-of-study follow-up data in most cases, or, if not available, by last-observation-carried-forward method) and the impact of imputation checked. Treatments were compared using an ANCOVA model with treatment, country, and randomization strata as fixed factors and baseline ulcer area as a covariate. A closed testing procedure was employed to account for

multiplicity of testing each dose group versus placebo (20 µg then 5 µg then 1 µg). *P*-values <0.049 were considered statistically significant to account for the interim analysis, at which testing was made at the 0.001 level.

Secondary endpoints were change from baseline to average of Week 3 and 4 in total lesion area (sum of areas of all OLP-related lesions per patient), erythema severity score, OLPSSM score (weekly means), WSAAS, and CGI. Erythema score, WSAAS, and CGI were averaged over anatomical sites for analysis. Secondary endpoints and the exploratory endpoints of ODSS (DAS and pain NRS), COMDQ score, and PGI-C were analyzed with similar models as for the primary endpoint but without baseline correction for PGI-C. The numbers of patients with positive response (2 most favorable alternatives) in the patch sensation questionnaire and with successful patch application (≥30 minutes on 80% of days) were compared between treatments using a logistic regression model, adjusting for treatment and randomization stratum (planned fixed factor of country not included because of overlap with country giving convergence problems in the algorithm).

Safety analyses were descriptive.

RESULTS

Patients

Enrollment commenced June 28, 2018. Of 204 patients screened, 138 patients were enrolled, and 122 (88.4%) completed the trial. Screen failure and discontinuation reasons are shown in Figure 2. All patients were included in the efficacy and safety analyses. There was a small imbalance in group assignment (Figure 12The Data Safety and Monitoring Board recommended trial termination after a preplanned interim analysis; they raised no safety concerns. The last patient completed the trial on December 20, 2019.

Baseline demographic and OLP characteristics were comparable among the 4 groups except for larger mean ulcer area in the 5-µg group driven by a small number of patients with large ulcers (Table 1). 120 patients had biopsy data, confirming OLP in 119. Number of patches used is summarized in Supplemental Table S1.

Efficacy

The 20-µg group achieved clinically relevant and statistically significant improvement compared to the placebo group for a broad spectrum of clinician-reported outcomes. The 5-µg and 20-µg groups showed statistically significant and clinically relevant change versus placebo in total ulcer area, the study primary endpoint (Table 2). Reductions in ulcer area were seen within the first week and progressed over the 4-week treatment period (Figure 3A). The 20-ug group also demonstrated significant reduction in DAS over the 4-week treatment (Figure3). Among the other clinician-reported outcomes, total lesion area, erythema score, and CGI improved in the 20-µg group although reduction was not statistically significant compared to placebo.

Rivelin®-CLO (20 µg/patch) also produced statistically significant improvements in patient-reported outcomes (Table 2). Reduction in total OLPSSM score was rapid and progressed over the 4-week treatment period (Figure3). In the 20-µg group, all 7 individual OLPSSM trigger items showed improvement from baseline versus placebo except breathing through the mouth (Supplemental Table S2). The pain NRS component of the ODSS (Figure 3D) and the COMDQ score showed clinically and statistically significant improvements in the 20-µg group compared to placebo. WSAAS score decreased but did not achieve statistical significance versus placebo. Finally, the PGI-C assessing patient experience with their OLP at end of dosing also showed clinically meaningful and statistically significant (P=0.012) improvements in the 20-µg group compared to placebo with 25/32 patients (78.1%) in the 20-µg group and 11/30 patients (36.7%) in the placebo group reporting their OLP feeling much better or very much better (Supplementary Figure S1).

Safety

Supplementary Table S3 summarizes all reported AEs. The most common AEs (irrespective of causality) were periodontal disease (10 patients, 7%) and nasopharyngitis (7 patients, 5%) neither of which were considered related to clobetasol or the patch. Two patients (1%) had serious AEs, investigator assessed as unrelated to treatment: multiple fractures (fractured left tibia and right humerus from a fall) and acute myocardial infarction (in a patient with history of ischemic heart disease and type 2 diabetes). AEs in 3 other patients (2%) were severe, all unrelated to treatment: dental trauma, periodontal disease, and hypertension. All other AEs were mild or moderate. AEs in 2 patients (1%) led to discontinuation of treatment: varicella zoster virus infection (in one

patient in the placebo group); and stomatitis (reported term: increased inflammation on left side oral cavity), oral pain (both assessed as related to clobetasol and patch application) and insomnia in one patient in the 1-µg group. The plasma clobetasol concentration was measured at visit 3 (day 8). There were 4 (3%) participants with measurable clobetasol: 2 in 20-µg group; 0 in 5-µg group; 1 in 1-µg group and 1 in placebo group. All remaining levels were below the detectable limit.

Frequencies of AEs considered related to patch use ranged from 6% for 5 µg and 20 µg to 16% for placebo and 18% for 1 µg (Table 3). Most were local events, including fungal infections in the oral cavity. Oral candidiasis occurred in 3 patients (2%), 1 each in the 1-µg, 5-µg, and placebo groups. No oral infections were reported in the 20-µg group. Most AEs considered related to patch application were events also considered related to clobetasol. Frequencies of these AEs were also lowest in the highest dose (20-µg) group.

Ease of Application, Adhesion Time, and Comfort of Patches

The percentage of patches adhering after 5 minutes was 97-98% for morning applications and 93-97% for evening applications. Corresponding values at 2 hours were 38-47% (reported only for morning applications). Median adhesion time was approximately 90 minutes in the clobetasol groups and 105 minutes in the placebo group (Supplementary Table S4). Results from the patch sensation questionnaire showed that patches were easy to apply and remove and well tolerated (Supplementary Table S5).

DISCUSSION

This study is the largest to date for any treatment of OLP, a condition with no currently approved treatment and substantial unmet medical need. The mucoadhesive patch is a novel product designed specifically to meet the challenges of the mucosal environment for delivering clobetasol, an established corticosteroid widely used in OLP, in a targeted, controlled, and sustained and localized manner. The patches were evaluated in a randomized placebo-controlled international multicenter study. The patient population was defined by biopsy-proven, symptomatic, ulcerative OLP, representing the more severe spectrum of OLP manifestations.[17] Rivelin®-CLO (20 µg/patch) showed statistically and clinically significant improvement in a broad spectrum of clinical and patient-reported outcomes important to patients and clinicians. Improvement in

patient-reported outcomes was demonstrated, using an established generic pain measure (pain on a 0-10 NRS) and quality of life measures (COMDQ). Additionally, a new disease-specific instrument (OLPSSM),[8] demonstrated reduction and relief of OLP symptoms while patients performed activities of daily living. Improvements in patient-reported outcomes resulted from successful targeted delivery of clobetasol propionate to the OLP lesions as demonstrated by clinical assessments (ulcer area, lesion size, erythema severity, and the DAS of ODSS).

The 20-µg dose produced superior efficacy results among the 3 doses tested and did so without an adverse effect on safety. Local effects of either the drug or the patch were uncommon, and lowest in the 20-µg group. No oral candidiasis or other oral infections were reported in this group. The rate of oral candidiasis in OLP patients treated with steroid therapy has been estimated as 13.6%.[18] Although the 5-µg group demonstrated ulcer area improvement similar to the 20-µg group, larger mean ulcer area in the 5-µg group likely accounted for the impact on ulcer area change. Only the 20-µg group demonstrated significant improvement in DAS, OLPSSM scores, NRS, COMDQ scores and ODSS scores.

In this Phase 2 study with Rivelin®-CLO, treatment duration was limited to 4 weeks. Several endpoints showed progressive improvement over the 4-weeks treatment period, suggesting that some patients may have benefited further with prolonged treatment. Some patients, however, experienced benefits earlier than 4 weeks. Varying or individualized treatment lengths should be investigated to determine the optimal treatment regimen for the patches.

The comfort, ease of use, and subjective feedback reported by participants in this study was consistent with an earlier Phase 1 study of the nonmedicated patch.[14] The acceptability of the patch combined with the favorable safety and efficacy profile may have promoted the high rates of treatment compliance reported. Rivelin®-CLO provides a new and innovative treatment of OLP. Participating investigators regarded Rivelin®-CLO as a useful tool to manage OLP patient symptoms and lesion manifestations.

In addition to their relevance to the specific product and disease tested, these results suggest the potential of this novel patch for wider applicability. This includes treatment of other mucosal diseases that currently lack a safe and effective treatment, such as recurrent aphthous stomatitis,

pemphigoid, pemphigus, oral manifestations of graft versus host disease, lupus erythematosus, Behçet's disease and inflammatory bowel diseases. The mucoadhesive patch could also be used with other medicines to provide topical treatment with fewer side effects (e.g., immunomodulators, antibiotics, analgesics, neuromodulators). Investigation of these other indications and medicines is warranted.

For this first placebo-controlled study of a patch-based therapy, a measurable, reliable endpoint was needed to establish proof of concept. Change in ulcer size was chosen as the primary endpoint, requiring patients to have a measurable ulcer. While this may have selected for a more severe population, ulcerations are common in symptomatic OLP and are representative of erosive OLP patients who receive treatment.[19] Another limitation of this study was use of the nonmedicated Rivelin® patch as the placebo control. Because no approved standard of care for OLP exists, a placebo comparison was the most appropriate choice. However, while enhancing the robustness of the study through blinding, the nonmedicated patch may not be acting as a true placebo. Results in the placebo group indicate that the patch itself may have some effect in management of OLP, possibly due to acting as a protective physical barrier over the lesions. Thus, the effect of the medicated patches may have been underestimated. The alternative of an unblinded study with a no-treatment arm was not considered feasible because of ethical and patient acceptance concerns, and an open-label design could lead to various types of bias that might impact the estimated effect of the medicated patch.

The efficacy, safety, acceptability, and feasibility results from this study support initiation of additional trials for efficacy and evaluation of long-term safety of Rivelin®-CLO in OLP patients. The 20-µg twice-daily regimen is considered the dose of choice for further development on the basis of its safety and efficacy in this study. In addition, these results suggest the potential of this novel patch for treatment of other oral and nonoral mucosal diseases that currently lack a safe and effective treatment and for use with other medicines to provide topical treatment with fewer side effects of oral diseases and diseases at other accessible mucosal sites.

AUTHOR CONTRIBUTIONS

Drs Brennan and Siim Madsen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Brennan, Siim Madsen, Ni Riordain, Fedele, Cook, Sankar, Culton, Kerr, Sollecito, Papas, Bengtsson, Al-Hashimi, Burke, Burkhart, Hansen, Jensen, Menné, Thornhill, Treister, Ruzicka

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TABLES

Table 1: Baseline Demographic and Oral Lichen Planus Characteristics

Characteristic		Rivelin®-CLO 20 µg N=33	Rivelin®-CLO 5 µg N=34	Rivelin®-CLO 1 µg N=40	Placebo N=31	Total N = 138
Sex, n (%)	Male	9 (27.3)	13 (38.2)	12 (30.0)	5 (16.1)	39 (28.3)
	Female	24 (72.7)	21 (61.8)	28 (70.0)	26 (83.9)	99 (71.7)
Age, years	Mean (SD)	58.6 (11.8)	59.7 (10.5)	62.2 (12.1)	63.9 (11.5)	61.1 (11.6)
	Range	33-77	37-75	19-89	30-81	19-89
Race, n (%)	White	26 (78.8)	32 (94.1)	36 (90.0)	29 (93.5)	123 (89.1)
	Black	1 (3.0)	0	2 (5.0)	1 (3.2)	4 (2.9)
	Asian	4 (12.1)	1 (2.9)	2 (5.0)	1 (3.2)	8 (5.8)
	American Indian/ Alaskan Native	0	1 (2.9)	0	0	1 (0.7)
	Other	2 (6.1)	0	0	0	2 (1.4)
Country, n (%)	Canada	8 (24.2)	7 (20.6)	7 (17.5)	7 (22.6)	29 (21.0)
	Germany	1 (3.0)	1 (2.9)	2 (5.0)	2 (6.5)	6 (4.3)
	Denmark	3 (9.1)	3 (8.8)	5 (12.5)	3 (9.7)	14 (10.1)
	UK	7 (21.2)	7 (20.6)	6 (15.0)	7 (22.6)	27 (19.6)
	Ireland	3 (9.1)	2 (5.9)	3 (7.5)	2 (6.5)	10 (7.2)
	US	11 (33.3)	14 (41.2)	17 (42.5)	10 (32.3)	52 (37.7)
Body mass index, kg/m^2	Mean (SD)	31.2 (6.9)	29.6 (6.0)	29.0 (5.3)	30.0 (7.6)	29.9 (6.4)
	Range	18.7-46.9	18.9-48.2	17.8-42.3	21.2-50.9	17.8-50.9
Time since first diagnosis, years	Mean (SD)	3.9 (4.7)	4.9 (9.3)	4.7 (6.5)	3.7 (6.1)	4.3 (6.8)
	Median (IQR)	2.0 (0.8-4.6)	1.8 (0.2-4.3)	1.5 (0.3-6.1)	1.5 (0.2-4.1)	1.9 (0.2- 4.1)
Biopsy confirmatory of OLP†, n (%)	Yes	26 (78.8)	31 (91.2)	35 (87.5)	27 (87.1)	119 (86.2)
Previous treatment in the last 12 months, n (%)	No	8 (24.2)	11 (32.4)	12 (30.0)	7 (22.6)	38 (27.5)
	Yes	25 (75.8)	23 (67.6)	27 (67.5)	24 (77.4)	99 (71.7)
	Missing	0	0	1 (2.5)	0	1 (0.7)
Extra-oral manifestations of lichen planus	No	27 (81.8)	29 (85.3)	35 (87.5)	24 (77.4)	115 (83.3)
	Yes	6 (18.2)	5 (14.7)	5 (12.5)	7 (22.6)	23 (16.7)
Total ulcer area per patient, mm^2	Mean (SD)	58.5 (84)	147.6 (269)	55.6 (57)	63.0 (129)	

Characteristic		Rivelin®-CLO 20 µg N=33	Rivelin®-CLO 5 µg N=34	Rivelin®-CLO 1 µg N=40	Placebo N=31	Total N = 138
Total lesion area per patient, mm^2	Mean (SD)	647.2 (582)	776.4 (6.82)	684.6 (536)	884.0 (1322)	
Average erythema severity score (Scale: 0 to 4)	Mean (SD)	2.4 (0.80)	2.6 (0.82)	2.7 (0.75)	2.6 (0.81)	
Disease activity score (DAS) (Scale: 0 to 72)	Mean (SD)	9.5 (5.24)	9.7 (4.45)	10.3 (5.27)	9.9 (5.17)	
Clinical global impression (CGI) (Scale: 0 to 4)	Mean (SD)	2.4 (0.83)	2.5 (0.89)	2.7 (0.76)	2.6 (0.74)	
Weekly total Oral Lichen Planus Symptom Severity Measure (OLPSSM) score‡ (Scale: 0 to 28)	Mean (SD)	10.5 (4.55)	11.2 (4.77)	11.3 (4.53)	9.8 (3.50)	
Pain numerical rating scale (NRS) score (Scale: 0 to 10)	Mean (SD)	5.7 (2.44)	5.9 (2.32)	5.8 (2.38)	5.8 (2.22)	
Worst symptom at anatomical site (WSAAS) score (Scale: 0 to 10)	Mean (SD)	5.4 (2.31)	5.6 (2.33)	5.6 (2.37)	5.7 (2.34)	
Chronic Oral Mucosal Disease Questionnaire (COMDQ) score (Scale: 0 to 104)	Mean (SD)	79.3 (12.83)	78.2 (17.66)	77.5 (21.21)	81.8 (15.21)	
Oral Disease Severity Score (ODSS) (Scale: 0 to 106)	Mean (SD)	20.3 (9.05)	20.4 (7.31)	21.2 (7.92)	20.7 (8.34)	

†. The requirement for biopsy confirmation was added approximately 2 months after enrollment start because of a recommendation from the US Food and Drug Administration; 120 patients (87.0%) had biopsy data; OLP confirmed in 119.

‡. Scores for the 7 OLPSSM questions were summed. A weekly mean of the scores was calculated with a week defined as the period between 2 visits. The baseline value was computed over the 7 days prior to the randomization visit. No imputation was performed for missing data, and, if <4 values were available from the week, the weekly OLPSSM total score was set to missing.

Abbreviations: IQR = interquartile range; OLP = oral lichen planus; SD = standard deviation.

Table 2: Efficacy Endpoints

Endpoint (Change from Baseline to Average of Weeks 3 and 4)	Treatment	Estimate†	Comparison to Placebo		
			Difference‡	95% Confidence Interval	*P* value
Total ulcer area per patient, mm^2	20 µg	-43.8	-45.0	(-89.4, -0.7)	0.047
	5 µg	-49.7	-50.9	(-94.5 -7.3)	0.023
	1 µg	-18.1	-19.3	(-60.8, 22.1)	0.358
	Placebo	1.3			
Total lesion area per patient, mm^2	20 µg	-293.1	-168.7	(-348.7, 11.4)	0.066
	5 µg	-183.6	-59.2	(-235.1, 116.6)	0.506
	1 µg	-157.3	-32.9	(-203.1, 137.3)	0.703
	Placebo	-124.4			
Average erythema severity score (Scale: 0 to 4)	20 µg	-1.182	-0.225	(-0.649, 0.200)	0.297
	5 µg	-0.987	-0.029	(-0.446, 0.388)	0.890
	1 µg	-0.829	0.128	(-0.275, 0.532)	0.530
	Placebo	-0.957			
Disease activity score (DAS) (Scale: 0 to 72)	20 µg	-3.450	-2.216	(-4.106, -0.326)	0.022
	5 µg	-1.710	-0.476	(-2.359, 1.407)	0.618
	1 µg	-1.680	0.447	(-4.089, 1.961)	0.627
	Placebo	-1.234			
Clinical global impression (CGI) (Scale: 0 to 4)	20 µg	-0.986	-0.138	(-0.596, 0.321)	0.553
	5 µg	-0.765	0.084	(-0.365, 0.533)	0.713
	1 µg	-0.718	0.130	(-0.303, 0.564)	0.553
	Placebo	-0.848			
Weekly total Oral Lichen Planus Symptom Severity Measure (OLPSSM) score§ (Scale: 0 to 28)	20 µg	-5.170	-2.967	(-4.643, -1.292)	0.001
	5 µg	-3.237	-1.034	(-2.699, 0.630)	0.221
	1 µg	-3.256	-1.054	(-2.645, 0.538)	0.192
	Placebo	-2.203			
Pain numerical rating scale (NRS) score (Scale: 0 to 10)	20 µg	-2.391	-1.261	(-2.241, -0,281)	0.012
	5 µg	-1.556	-0.426	(-1.394, 0.541)	0.385
	1 µg	-1.381	-0.252	(-1.186, 0.683)	0.595
	Placebo	-1.130			
Worst symptoms at anatomical site (WSAAS) score (Scale: 0 to 10)	20 µg	-2.634	-0.887	(-1.841, 0.068)	0.068
	5 µg	-1.950	-0.203	(-1.145, 0.739)	0.671
	1 µg	-1.843	-0.096	(-1.006, 0.814)	0.835
	Placebo	-1.747			
Chronic Oral Mucosal Disease Questionnaire (COMDQ) score¶ (Scale: 0 to 104)	20 µg	-12.062	-9.022	(-14.965, -3.079)	0.003
	5 µg	-6.497	-3.458	(-9.354, 2.438)	0.248
	1 µg	-1.772	1.268	(-4.459, 6.995)	0.662
	Placebo	-3.040			

Endpoint (Change from Baseline to Average of Weeks 3 and 4)	Treatment	Estimate†	Comparison to Placebo		
			Difference‡	95% Confidence Interval	*P* value
Oral Disease Severity Score (ODSS) (Scale: 0 to 106)	20 µg	-6.786	-4.453	(-7.602, -1.303)	0.006
	5 µg	-3.390	-1.057	(-4.195, 2.081)	0.506
	1 µg	-3.397	-1.064	(-4.089, 1.961)	0.488
	Placebo	-2.333			

†. Mean change from baseline for each group from the analysis of covariance model (least squares mean)

‡. Difference between the estimates for active and placebo group in pairwise comparison

§. Scores for the 7 OLPSSM questions were summed. A weekly mean of the scores was calculated with a week defined as the time period between 2 visits. The baseline value was computed over the 7 days prior to the randomization visit. No imputation was performed for missing data, and, if <4 values were available from the week, the weekly OLPSSM total score was set to missing.

¶. Change from baseline to Week 4 (COMDQ not administered at Week 3)

Table 3: Adverse Events Related to Clobetasol or Patch Application

System Organ Class Preferred Term	Rivelin®-CLO 20 µg N=33 n (%)	Rivelin®-CLO 5 µg N=34 n (%)	Rivelin®-CLO 1 µg N=40 n (%)	Placebo N=31 n (%)	Total N=138 n (%)
ADVERSE EVENTS RELATED TO CLOBETASOL					
Any adverse event	2 (6)	2 (6)	7 (18)	5 (16)	16 (12)
Infections and infestations	**0 (0)**	**1 (3)**	**4 (10)**	**3 (10)**	**8 (6)**
Application site infection	0 (0)	0 (0)	2 (5)	2 (6)	4 (3)
Oral candidiasis	0 (0)	1 (3)	1 (3)	1 (3)	3 (2)
Oral fungal infection	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
Gastrointestinal disorders	**1 (3)**	**1 (3)**	**2 (5)**	**1 (3)**	**5 (4)**
Nausea	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
Diarrhoea	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
Gingival bleeding	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
Gingival pain	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
Oral pain	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
Stomatitis	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
General disorders and administration site conditions	**1 (3)**	**1 (3)**	**2 (5)**	**0 (0)**	**4 (3)**
Application site pain	1 (3)	0 (0)	2 (5)	0 (0)	3 (2)
Application site hypersensitivity	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
Facial pain	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
Nervous system disorders	**1 (3)**	**0 (0)**	**1 (3)**	**0 (0)**	**2 (1)**
Dysgeusia	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
Headache	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
Psychiatric disorders	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
Sleep disorder	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
ADVERSE EVENTS RELATED TO PATCH APPLICATION					
Any adverse event	2 (6)	6 (18)	5 (13)	3 (10)	16 (12)
Gastrointestinal disorders	1 (3)	4 (12)	2 (5)	2 (6)	9 (7)
Salivary hypersecretion	0 (0)	2 (6)	0 (0)	1 (3)	3 (2)
Gingival bleeding	0 (0)	1 (3)	1 (3)	0 (0)	2 (1)
Nausea	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
Diarrhoea	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
Gingival pain	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
Oral lichen planus	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)

Oral pain	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
Saliva altered	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
Stomatitis	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
General disorders and administration site conditions	2 (6)	2 (6)	3 (8)	0 (0)	7 (5)
Application site pain	1 (3)	0 (0)	2 (5)	0 (0)	3 (2)
Application site haemorrhage	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
Application site hypersensitivity	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
Application site injury	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
Facial pain	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
Infections and infestations	0 (0)	1 (3)	0 (0)	1 (3)	2 (1)
Application site infection	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
Oral candidiasis	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
Nervous system disorders	1 (3)	0 (0)	1 (3)	0 (0)	2 (1)
Dysgeusia	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)
Headache	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)

FIGURE LEGENDS

Figure 1: Rivelin®-CLO patch containing clobetasol propionate.

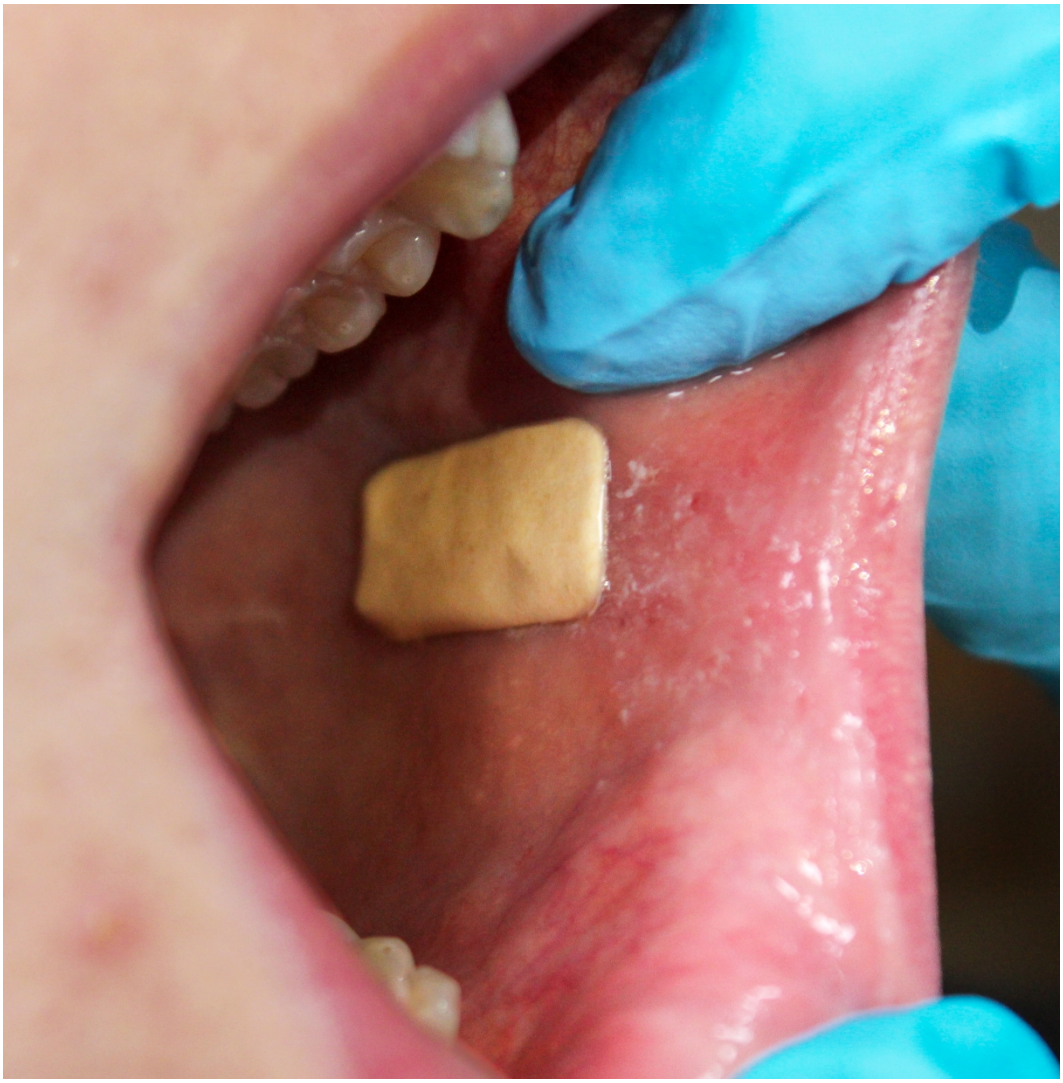
Figure 2: Patient Disposition

Figure 3: Change from Baseline in Efficacy Endpoints Over Time

Panel A: Total ulcer area: Sum of areas of all ulcers for an individual measured at each visit using a periodontal probe (NCP-15) or a modified Schirmer's strip, measuring the 2 longest perpendicular dimensions of each lesion/ulcer.

Panel B: Disease activity score: Clinicians assess disease extent and severity at 17 sites in the oral cavity, using a 2- or 3-point scale for disease extent and a 4-point scale for disease severity. These scores were combined into the disease activity score.

Panel C: Weekly OLPSSM total score: This score is mean of daily total scores, each ranging from 0 to 28 and the total of responses on a scale of 0 to 4 for each of the 7 components of the following question on the Oral Lichen Planus Symptom Severity Measure: How SORE was your oral lichen planus when you did each of the following activities: 1. When you brushed your teeth? 2. When you ate food? 3. When you drank liquids? 4. When you smiled? 5. When you breathed through your mouth? 6. When you talked? 7. When it was touched? Scores for the 7 OLPSSM questions were summed. A weekly mean of the scores was calculated with a week defined as the time period between 2 visits. The baseline value was computed over the 7 days prior to the randomization visit. No imputation was performed for missing data, and, if <4 values were available from the week, the weekly OLPSSM total score was set to missing.
Panel D: Pain numerical rating scale score: Patients were asked at each clinical visit to score pain on a scale from 0 (no pain) to 10 (worst imaginable pain) in response to the following question: How much pain have you had in the last 24 hours from your OLP disease?



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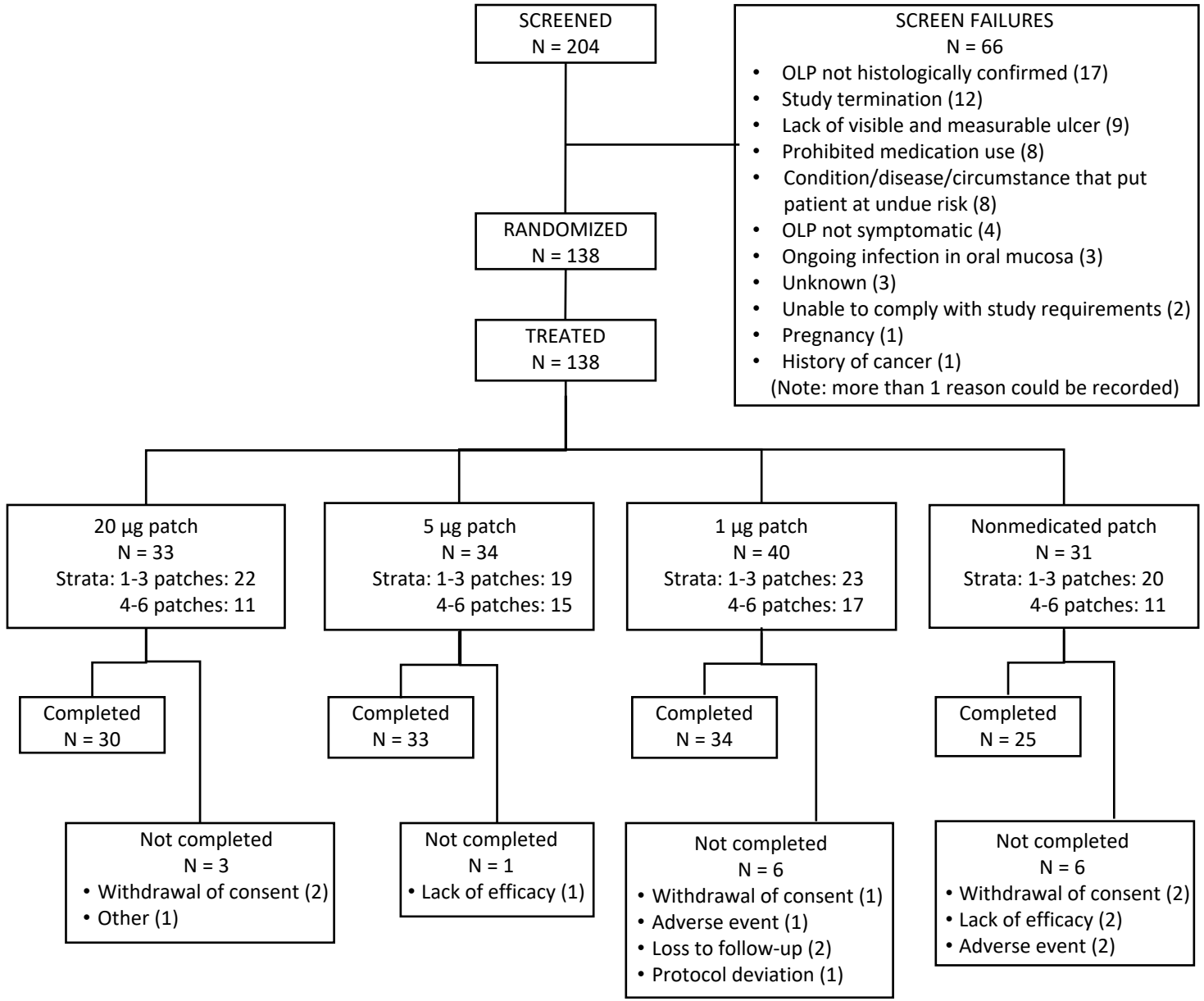
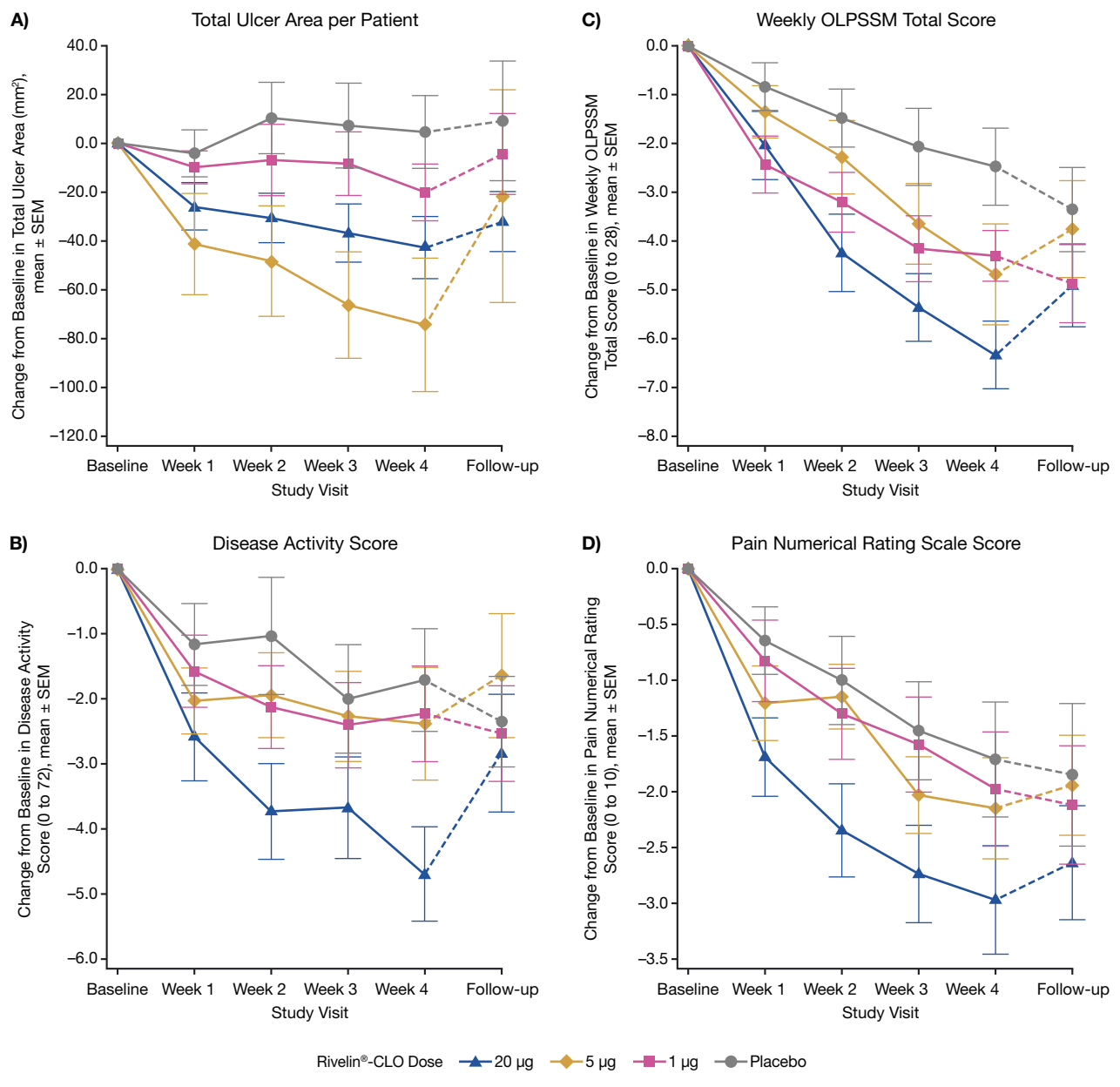

SCREENED
N = 204
SCREEN FAILURES
N = 66
• OLP not histologically confirmed (17)
• Study termination (12)
• Lack of visible and measurable ulcer (9)
• Prohibited medication use (8)
• Condition/disease/circumstance that put patient at undue risk (8)
• OLP not symptomatic (4)
• Ongoing infection in oral mucosa (3)
• Unknown (3)
• Unable to comply with study requirements (2)
• Pregnancy (1)
• History of cancer (1)
(Note: more than 1 reason could be recorded)
RANDOMIZED
N = 138
TREATED
N = 138
20 µg patch
N = 33
Strata: 1-3 patches: 22
4-6 patches: 11
5 µg patch
N = 34
Strata: 1-3 patches: 19
4-6 patches: 15
1 µg patch
N = 40
Strata: 1-3 patches: 23
4-6 patches: 17
Nonmedicated patch
N = 31
Strata: 1-3 patches: 20
4-6 patches: 11
Completed
N = 30
Completed
N = 33
Completed
N = 34
Completed
N = 25
Not completed
N = 3
• Withdrawal of consent (2)
• Other (1)
Not completed
N = 1
• Lack of efficacy (1)
Not completed
N = 6
• Withdrawal of consent (1)
• Adverse event (1)
• Loss to follow-up (2)
• Protocol deviation (1)
Not completed
N = 6
• Withdrawal of consent (2)
• Lack of efficacy (2)
• Adverse event (2)


A)
Total Ulcer Area per Patient
Change from Baseline in Total Ulcer Area (mm²), mean ± SEM
40.0
20.0
0.0
−20.0
−40.0
−60.0
−80.0
−100.0
−120.0
Baseline
Week 1
Week 2
Week 3
Week 4
Follow-up
Study Visit
C)
Weekly OLPSSM Total Score
Change from Baseline in Weekly OLPSSM Total Score (0 to 28), mean ± SEM
0.0
−1.0
−2.0
−3.0
−4.0
−5.0
−6.0
−7.0
−8.0
Baseline
Week 1
Week 2
Week 3
Week 4
Follow-up
Study Visit
B)
Disease Activity Score
Change from Baseline in Disease Activity Score (0 to 72), mean ± SEM
0.0
−1.0
−2.0
−3.0
−4.0
−5.0
−6.0
Baseline
Week 1
Week 2
Week 3
Week 4
Follow-up
Study Visit
D)
Pain Numerical Rating Scale Score
Change from Baseline in Pain Numerical Rating Score (0 to 10), mean ± SEM
0.0
−0.5
−1.0
−1.5
−2.0
−2.5
−3.0
−3.5
Baseline
Week 1
Week 2
Week 3
Week 4
Follow-up
Study Visit
Rivelin®-CLO Dose
20 µg
5 µg
1 µg
Placebo