Supplementary Appendix

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Oral Lichen Planus Symptom Severity Measure (OLPSSM) Questions 1 to 7

INSTRUCTIONS: We are interested in finding out about your experience with oral lichen planus.

- Please choose the response that best describes your symptom experience **over the past 24 hours**.
- Choose one answer for each question.

How SORE was your oral lichen planus when you did each of the following activities?

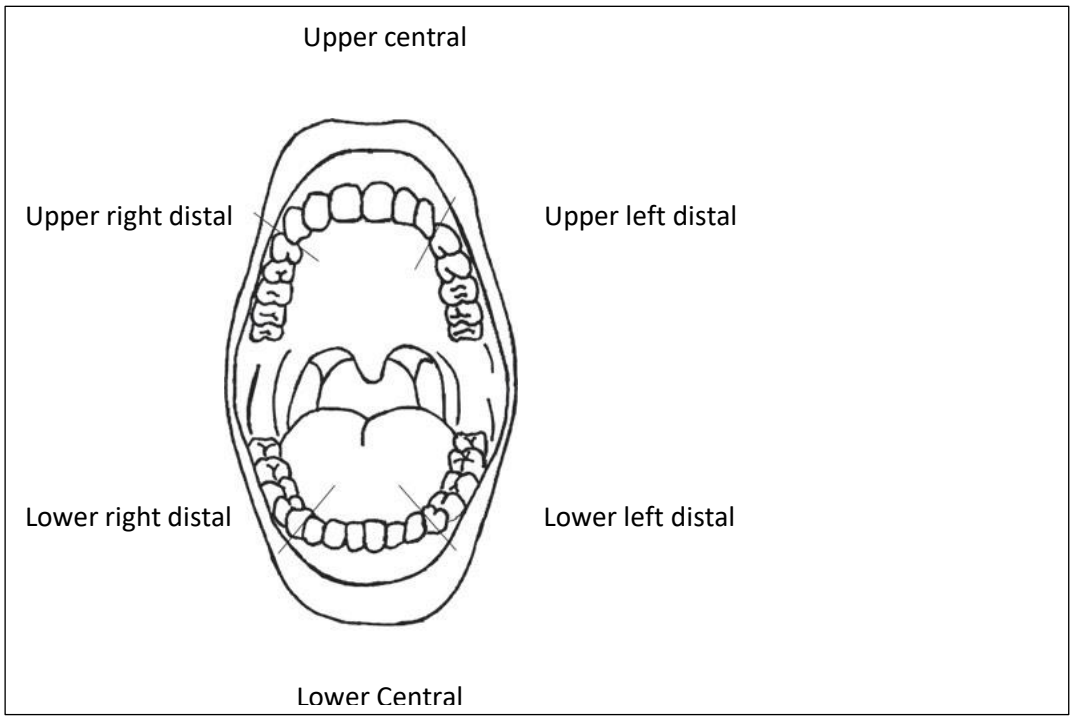
	Not at all sore	Slightly sore	Moderately sore	Severely sore	Too sore to do
1. When you brushed your teeth?	0	1	2	3	4
2. When you ate food?	0	1	2	3	4
3. When you drank liquids?	0	1	2	3	4
4. When you smiled?	0	1	2	3	4
5. When you breathed through your mouth?	0	1	2	3	4
6. When you talked?	0	1	2	3	4
7. When it was touched?	0	1	2	3	4

Oral Lichen Planes Clinician-reported Outcome Measure (OLPClinROM)

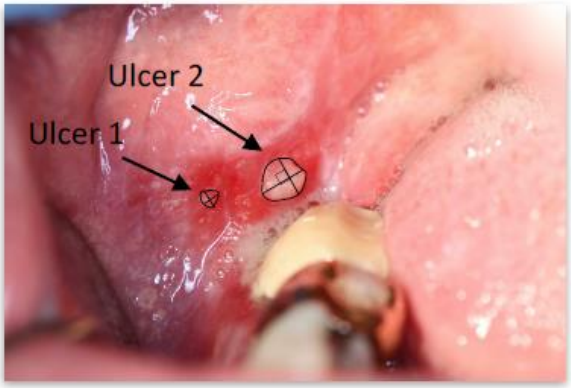
Maximum treated ulcer area of one anatomical site identified at baseline

Individual ulcers are measured by clinicians at clinical visits using a periodontal probe (NCP-15) or a modified Schirmer's strip according to the OLPClinROM training manual by measuring the length and the width of each ulcer. Individual ulcer areas are recorded in the CRF per anatomical area and analyzed as the sum per anatomical site.

The oral cavity is divided into the following anatomical sites: Outer lips, inner lips, left buccal mucosa, right buccal mucosa, lower right gingiva (distal), lower central gingiva, lower left (distal), upper left gingiva (distal), upper central gingiva, upper right gingiva (distal), dorsum of tongue, right lateral tongue, left lateral tongue, floor of mouth, hard palate, soft palate and oropharynx.



The example below includes two ulcers in one anatomical site:



In the rare case that the maximum ulcer area to be treated at baseline is equivalent in two separate areas, the investigator will select the one that the patient states is the most bothersome.

Maximum treated erythema severity score identified at each visit

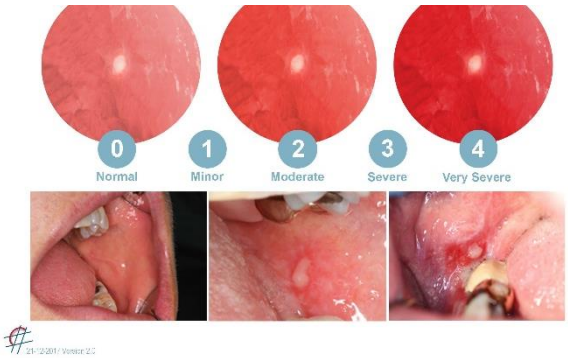
At each visit, the redness from all symptomatic areas will be scored using a 5-point erythema severity score. The highest score at each visit will be monitored. The erythema 5-point severity score is constructed using three intensities of redness and a 0 to 4 score as outline below.

Clinical Global Assessment (CGA) includes the objective component of Guy´s ODSS: Site score (24) + activity score (72)

Site score: 0, no detectable lesion present; 1, evidence of lichen planus seen; 2, > 50% of buccal

mucosa, dorsum of tongue, floor of mouth, hard palate, soft palate or oropharynx affected.

Severity score: 0, keratosis only; 1, keratosis with mild erythema (< 3 mm from gingival margins); 2, marked erythema (e.g. full thickness of gingivae, extensive with atrophy or oedema on non-keratinized mucosa); 3, ulceration present.



Site	Site score (a)	Severity score (b)	Activity score (a·b)
Outer lips	0 or 1	0–3	0–3
Inner lips	0 or 1	0–3	0–3
Left buccal mucosa	0, 1 or 2	0–3	0–6
Right buccal mucosa	0, 1 or 2	0–3	0–6
Gingiva			
Lower right (distal)	0 or 1	0–3	0–3
Lower central	0 or 1	0–3	0–3
Lower left (distal)	0 or 1	0–3	0–3
Upper left (distal)	0 or 1	0–3	0–3
Upper central	0 or 1	0–3	0–3
Upper right (distal)	0 or 1	0–3	0–3
Dorsum of tongue	0, 1 or 2	0–3	0–6
Right lateral tongue	0 or 1	0–3	0–3
Left lateral tongue	0 or 1	0–3	0–3
Floor of mouth	0, 1 or 2	0–3	0–6
Hard palate	0, 1 or 2	0–3	0–6
Soft palate	0, 1 or 2	0–3	0–6
Oropharynx	0, 1 or 2	0–3	0–6
Maximum score	24		72

Laboratory Tests and Vital Signs

In this study, the following laboratory parameters and vital signs and were measured at screening and follow-up:

- Laboratory tests:
    - Hematology: white blood cell count and differential, red blood cell count, hemoglobin, platelet count

- Serum biochemistry: aspartate aminotransferase , alanine aminotransferase, alkaline phosphatase, total bilirubin, creatine kinase, creatinine, albumin, sodium, potassium
- Dipstick urinalysis: protein, hemoglobin, glucose

- Vital signs: blood pressure (systolic and diastolic), pulse, body temperature (by standard method for each participating site), and weight

Supplementary Tables and Figures

Supplemental Table S1: Number of Patches Used and Clobetasol Propionate Dose (Based on Number of Patches Dispensed and Returned)

Study Week		Rivelin®-CLO			Placebo N=31 Median (range)	Total N=138 Median (range)
		20 µg N=33 Median (range)	5 µg N=34 Median (range)	1 µg N=40 Median (range)		
1	Number of patches	32 (10–108)	35 (10–84)	51 (8–95)	42 (12–108)	43 (8–108)
	Daily clobetasol dose (µg)	97 (2–223)	26 (9.3–60)	6.4 (1–13.6)	NA	NA
2	Number of patches	39 (14–77)	40 (11–96)	43 (8–108)	55 (12–108)	43 (8–108)
	Daily clobetasol dose (µg)	91 (34–270)	22 (9.3–64.3)	6.1 (1.8–191)	NA	NA
3	Number of patches	44 (8–78)	42 (9–84)	45 (9–84)	44 (14–108)	44 (8–108)
	Daily clobetasol dose (µg)	109 (23–260)	30 (9–60)	6.4 (1.8–12)	NA	NA
4	Number of patches	43 (9–84)	41 (13–90)	43 (11–84)	41 (14–90)	42 (9–90)
	Daily clobetasol dose (µg)	128 (40–264)	23 (10–60)	6.1 (0.2–12)	NA	NA
NA = not applicable.						

Supplemental Table S2: Change from Baseline to Average of Weeks 3 and 4 for Individual OLPSSM Questions 1 to 7

OLPSSM Question Weekly score[a] (Scale: 0 to 4)	Treatment	Estimate[b]	Comparison to Placebo		
			Difference[c]	95% Confidence Interval	*P* value
1. When you brushed your teeth?	20 µg	-0.895	-0.498	(-0.846, -0.150)	0.0055
	5 µg	-0.594	-0.197	(-0.540, 0.146)	0.2573
	1 µg	-0.489	-0.092	(-0.419, 0.235)	0.5778
	Placebo	-0.397			
2. When you ate food?	20 µg	-1.002	-0.549	(-0.888, -0.211)	0.0017
	5 µg	-0.654	-0.201	(-0.540, 0.137)	0.2415
	1 µg	-0.629	-0.177	(-0.501, 0.147)	0.2815
	Placebo	-0.452			
3. When you drank liquids?	20 µg	-0.702	-0.501	(-0.767, -0.235)	0.0003
	5 µg	-0.491	-0.290	(-0.556, -0.025)	0.0325
	1 µg	-0.421	-0.220	(-0.473, 0.033)	0.0875
	Placebo	-0.201			
4. When you smiled?	20 µg	-0.723	-0.359	(-0.629, -0.089)	0.0095
	5 µg	-0.356	0.007	(-0.260, 0.275)	0.9562
	1 µg	-0.479	-0.115	(-0.370, 0.140)	0.3734
	Placebo	-0.363			
5. When you breathed through your mouth?	20 µg	-0.453	-0.177	(-0.389, 0.035)	0.1015
	5 µg	-0.298	-0.021	(-0.234, 0.192)	0.8438
	1 µg	-0.380	-0.104	(-0.304, 0.097)	0.3091
	Placebo	-0.277			
6. When you talked?	20 µg	-0.630	-0.317	(-0.590, -0.045)	0.0228
	5 µg	-0.244	0.068	(-0.203, 0.338)	0.6199
	1 µg	-0.453	-0.141	(-0.401, 0.118)	0.2839
	Placebo	-0.312			
7. When it was touched?	20 µg	-0.830	-0.606	(-0.977, -0.235)	0.0016
	5 µg	-0.574	-0.350	(-0.720, 0.020)	0.0637
	1 µg	-0.434	-0.210	(-0.564, 0.143)	0.2408
	Placebo	-0.224			

a. 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.

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

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

Supplemental Table S3: All Reported Adverse Events

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 (%)
Any adverse event	15 (45)	16 (47)	17 (43)	15 (48)	63 (46)
Gastrointestinal disorders	7 (21)	9 (26)	6 (15)	8 (26)	30 (22)
Periodontal disease	4 (12)	2 (6)	2 (5)	2 (6)	10 (7)
Salivary hypersecretion	1 (3)	3 (9)	0	1 (3)	5 (4)
Amalgam tattoo	1 (3)	0	0	2 (6)	3 (2)
Diarrhoea	0	0	1 (3)	1 (3)	2 (1)
Gingival bleeding	0	1 (3)	1 (3)	0	2 (1)
Nausea	1 (3)	0	1 (3)	0	2 (1)
Oral pain	0	0	2 (5)	0	2 (1)
Abdominal discomfort	0	0	1 (3)	0	1 (1)
Abdominal pain	0	1 (3)	0 (0)	0	1 (1)
Gingival pain	0	1 (3)	0 (0)	0	1 (1)
Haemorrhoidal haemorrhage	0	0	0	1 (3)	1 (1)
Oral disorder	1 (3)	0	0	0	1 (1)
Oral lichen planus	0	1 (3)	0	0	1 (1)
Oral mucosa haematoma	0	1 (3)	0	0	1 (1)
Saliva altered	0	1 (3)	0	0	1 (1)
Stomatitis	0	0	1 (3)	0	1 (1)
Toothache	0	0	0	1 (3)	1 (1)
Infections and infestations	3 (9)	4 (12)	6 (15)	8 (26)	21 (15)
Nasopharyngitis	0	2 (6)	2 (5)	3 (10)	7 (5)
Application site infection	0	0	2 (5)	2 (6)	4 (3)
Oral candidiasis	0	1 (3)	1 (3)	1 (3)	3 (2)
Urinary tract infection	2 (6)	0	0	1 (3)	3 (2)
Cystitis	1 (3)	0	0	0	1 (1)
Eye infection	0	0	0	1 (3)	1 (1)
Oral fungal infection	0	0	1 (3)	0	1 (1)
Pulpitis dental	0	0	0	0	1 (1)
Varicella zoster virus infection	0	0	0	1 (3)	1 (1)
Viral sinusitis	0	0	1 (3)	0	1 (1)
Vulvovaginal mycotic infection	0	1 (3)	0	0	1 (1)
General disorders and administration site conditions	3 (9)	4 (12)	4 (10)	1 (3)	12 (9)
Application site haemorrhage	2 (6)	1 (3)	1 (3)	0	4 (3)
Application site pain	1 (3)	0	2 (5)	0	3 (2)
Facial pain	1 (3)	0	0	1 (3)	2 (1)
Application site hypersensitivity	0	1 (3)	0	0	1 (1)
Application site injury	0	1 (3)	0	0	1 (1)
Application site plaque	0	0	1 (3)	0	1 (1)
Fatigue	1 (3)	0	0	0	1 (1)
Malaise	1 (3)	0	0	0	1 (1)
Pain	0	1 (3)	0	0	1 (1)

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 (%)
Nervous system disorders	6 (18)	1 (3)	3 (8)	0	10 (7)
Headache	4 (12)	1 (3)	0 (0)	0	5 (4)
Dizziness	3 (9)	0	1 (3)	0	4 (3)
Dysgeusia	0	0	1 (3)	0	1 (1)
Epilepsy	1 (3)	0	0	0	1 (1)
Neuropathy peripheral	0	0	1 (3)	0	1 (1)
Injury, poisoning and procedural complications	1 (3)	4 (12)	1 (3)	2 (6)	8 (6)
Bite	0	1 (3)	0	1 (3)	2 (1)
Contusion	0	1 (3)	0	0	1 (1)
Multiple fractures	0	0	1 (3)	0	1 (1)
Muscle strain	1 (3)	0	0	0	1 (1)
Tooth fracture	0	0	0	1 (3)	1 (1)
Tooth injury	0	1 (3)	0	0	1 (1)
Traumatic ulcer	0	1 (3)	0	0	1 (1)
Respiratory, thoracic and mediastinal disorders	1 (3)	1 (3)	0	2 (6)	4 (3)
Asthma	1 (3)	0 (0)	0	1 (3)	2 (1)
Oropharyngeal pain	0	1 (3)	0	1 (3)	2 (1)
Cough	0	0	0	1 (3)	1 (1)
Vascular disorders	0	2 (6)	0	2 (6)	4 (3)
Hypertension	0	1 (3)	0	2 (6)	3 (2)
Flushing	0	1 (3)	0	0	1 (1)
Psychiatric disorders	0	1 (3)	1 (3)	1 (3)	3 (2)
Insomnia	0	0	1 (3)	0	1 (1)
Restlessness	0	1 (3)	0	0	1 (1)
Sleep disorder	0	0	0	1 (3)	1 (1)
Stress	0	0	1 (3)	0	1 (1)
Ear and labyrinth disorders	1 (3)	0	0	1 (3)	2 (1)
Ear pain	0	0	0	1 (3)	1 (1)
Inner ear disorder	1 (3)	0	0	0	1 (1)
Investigations	0	0	1 (3)	1 (3)	2 (1)
Heart rate increased	0	0	0	1 (3)	1 (1)
Hepatic enzyme increased	0	0	1 (3)	0	1 (1)
Musculoskeletal and connective tissue disorders	1 (3)	0	0	1 (3)	2 (1)
Arthralgia	1 (3)	0	0	0	1 (1)
Back pain	0	0	0	1 (3)	1 (1)
Skin and subcutaneous tissue disorders	0	1 (3)	0	1 (3)	2 (1)
Pruritus	0	1 (3)	0	0	1 (1)
Rash pruritic	0	1 (3)	0	0	1 (1)
Sensitive skin	0	0	0	1 (3)	1 (1)

System Organ Class Preferred Term	Rivelin®-CLO			Placebo N=31 n (%)	Total N=138 n (%)
	20 µg N=33 n (%)	5 µg N=34 n (%)	1 µg N=40 n (%)		
Blood and lymphatic system disorders	0	1 (3)	0	0	1 (1)
Lymphadenopathy	0	1 (3)	0	0	1 (1)
Cardiac disorders	1 (3)	0	0	0	1 (1)
Acute myocardial infarction	1 (3)	0	0	0	1 (1)
Immune system disorders	0	0	0	1 (3)	1 (1)
Allergy to chemicals	0	0	0	1 (3)	1 (1)
Metabolism and nutrition disorders	0	0	1 (3)	0	1 (1)
Type 2 diabetes mellitus	0	0	1 (3)	0	1 (1)

Supplemental Table S4: Patch Adhesion

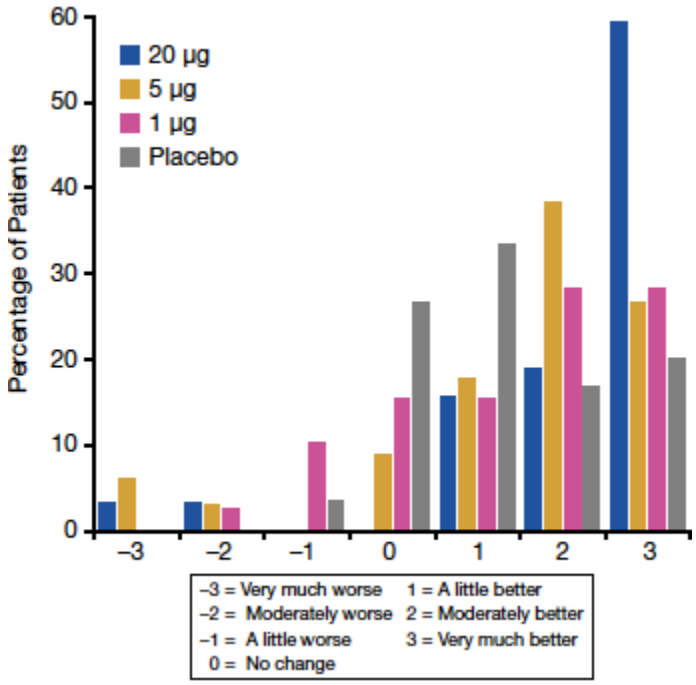
		Statistic	Rivelin®-CLO			Placebo N=31
			20 µg N=33	5 µg N=34	1 µg N=40	
Morning application	Percent of patches adhering at 5 minutes	Mean	96.6	98.1	98.4	96.5
		Median	100.0	100.0	100.0	100.0
		Range	48–100	73–100	80–100	67–100
	Percent of patches adhering at 2 hours[a]	Mean	37.9	40.0	39.2	47.3
		Median	21	26	23	44
		Range	0.0–100	0.0–100	0.0–100	0.0–100
	Adhesion time (minutes)	Mean	85.2	83.0	84.6	90.1
		Median	90	90	93	105
		Range	22–125	0 –122	20–125	20–125
Evening application	Percent of patches adhering at 5 minutes	Mean	93.4	95.4	96.0	97.3
		Median	100.0	100.0	100.0	100.0
		Range	23–100	64–100	0.0–100	77–100
a. Counted as 0 if entry missing at 2 hours						

Supplemental Table S5: Summary of Answers to the Patch Sensation Questionnaire – Frequency of Categories Ordered with Most Favorable Category First and Least Favorable Category Last

Variable	Visit[a]	Rivelin®-CLO 20 µg N=33	Rivelin®-CLO 5 µg N=34	Rivelin®-CLO 1 µg N=40	Placebo N=31
Irritation	Baseline	22/0/7/3/0	23/0/5/4/2	21/0/14/3/1	21/0/3/4/1
	Week 2	17/0/7/6/0	9/0/11/11/2	17/0/6/11/2	9/0/9/6/4
Adhesion	Baseline	11/11/5/1/4	10/9/6/1/8	11/13/6/1/8	6/9/7/1/6
	Week 2	7/4/11/4/4	12/7/8/3/3	6/16/ 8/1/5	5/11/4/5/3
Taste	Baseline	0/13/13/3/3	0/15/15/2/2	1/19/13/4/2	0/17/12/0/0
	Week 2	1/10/13/5/1	1/13/13/6/0	1/16/10/8/1	0/17/11/0/0
Application	Baseline	10/13/9/0/0	14/10/10/00	12/14/12/1/0	9/8/11/1/0
	Week 2	6/13/10/1/0	11/11/11/0/0	10/10/16/0/0	6/13/9/0/0
Speech	Baseline	0/13/15/4/0	0/13/16/4/1	0/10/25/3/1	0/11/16/2/0
	Week 2	0/8/18/2/2	0/7/18/6/2	0/10/14/6/6	0/6/14/4/4
Swallowing	Baseline	0/21/10/1/0	0/24/8/1/1	0/25/12/1/1	0/20/9/0/0
	Week 2	0/18/12/0/0	0/16/13/3/1	0/16/13/5/2	0/14/9/3/2
Saliva production	Baseline	0/20/8/3/1	0/16/17/1/0	0/16/16/6/0	0/13/14/1/1
	Week 2	0/11/15/1/3	0/11/16/6/0	0/11/15/7/3	0/6/13/5/4
Bothersome	Baseline	0/11/19/2/0	0/14/16/3/1	0/8/26/4/0	0/7/14/8/0
	Week 2	0/9/17/3/1	0/6/19/8/0	0/6/21/7/2	0/4/17/5/2
Comfortable	Baseline	4/6/20/2/0	11/8/15/0/0	4/17/16/1/0	5/5/16/3/0
	Week 2	3/13/14/0/0	4/12/16/1/0	1/15/17/3/0	2/9/13/4/0
Removal	Baseline	16/10/6/0/0	24/5/1/2/1	24/9/4/1/0	16/9/3/1/0
	Week 2	15/11/4/0/0	25/6/2/0/0	18/9/7/2/0	15/13/0/0/0
Residue	Baseline	0/12/16/3/1	0/16/12/2/3	0/17/18/2/1	0/14/11/4/0
	Week 2	0/2/21/5/2	0/7/21/2/3	0/8/18/7/3	0/5/18/2/3

a. Baseline = after 1 application; Week 2 = after 2 weeks of treatment.

Supplementary Figure S1: Patient Global Impression of Change at Treatment End



Responses to the following prompt: Please choose the response below that best describes the overall change in your oral lichen planus symptoms since you started this study.