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ORIGINAL RESEARCH

Safety and Efficacy of LP-10 Liposomal Tacrolimus in Oral Lichen Planus: A Multicenter Phase 2 Trial

Michael T. Brennan · Jennifer Frustino · Kamal Al-Eryani · Herve Sroussi · Jennifer L. Parish · Hirak B. Routh · Sunil Dhawan · Gerald L. Klein · Michael B. Chancellor · Alessandro Villa

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ABSTRACT

***Introduction*:** Oral lichen planus (OLP) is a serious chronic inflammatory condition with malignant transformation potential affecting six million Americans which has no US Food and Drug Administration (FDA)-approved therapy. LP-10, a novel liposomal tacrolimus oral rinse, overcomes the poor adherence to oral surfaces and inconsistent drug delivery limitations of existing treatments.

***Methods*:** This phase 2a multicenter dose-ranging study evaluated LP-10 safety and efficacy in symptomatic OLP. Twenty-seven adults (22 female, 5 male) received a 10-mL oral rinse of LP-10 at 0.25 mg, 0.5 mg, or 1.0 mg of tacrolimus, for 3 min twice daily for 4 weeks. Safety assessments included monitoring of adverse events, laboratory studies, and tacrolimus blood levels. Efficacy was measured by investigator global assessment (IGA), reticulation/erythema/ulceration (REU) score, pain/sensitivity numerical rating scale (NRS), OLP symptom severity measure (OLPSSM), and patient global response assessment (GRA).

***Results*:** All participants completed treatment without discontinuation or serious adverse events. Treatment-related treatment-emergent adverse events were mild/moderate (50 mild, 4 moderate). LP-10 demonstrated exceptional pharmacokinetic safety with mean tacrolimus

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M. T. Brennan
Department of Oral Medicine/Oral and Maxillofacial Surgery, Wake Forest University School of Medicine, Atrium Health Carolinas Medical Center, Charlotte, NC, USA

J. Frustino
Erie County Medical Center, Buffalo, NY, USA

K. Al-Eryani
University of California San Francisco, San Francisco, CA, USA

H. Sroussi
Brigham and Women's Hospital, Boston, MA, USA

J. L. Parish · H. B. Routh
Paddington Testing Co, Inc, Philadelphia, PA, USA

S. Dhawan
Center for Dermatology Clinical Research, Inc, Fremont, CA, USA

G. L. Klein
MedSurgPI LLC, Brody School of Medicine, ECU, Franklinton, NC, USA

M. B. Chancellor (✉)
Lipella Pharmaceuticals, Inc., Suite 505, 7800 Susquehanna, Pittsburgh, PA 15208, USA
e-mail: Michael.chancellor@lipella.com

A. Villa
Oral Medicine and Oral Oncology Miami Cancer Institute, Baptist Health South Florida, Miami, FL, USA

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levels remaining < 1.0 ng/mL in 75% of post-baseline measurements; the maximum individual level (4.5 ng/mL) remained well below the toxicity threshold (15 ng/mL) suggesting little absorbance into the blood. All efficacy endpoints showed statistically significant and clinically meaningful improvements at week 4: mean and standard deviation (SD) values for IGA decreased from 3.5 ± 0.51 to 1.8 ± 1.37 ($p < 0.0001$), pain NRS from 6.8 ± 1.90 to 2.3 ± 2.53 ($p < 0.0001$), sensitivity NRS from 7.2 ± 1.71 to 2.9 ± 2.29, REU from 26.5 ± 10.4 to 13.2 ± 8.15 ($p < 0.0001$). Of the 23 participants who responded to the GRA, approximately 78% participants reported that their quality of life was "moderately better" or "very much better" as compared to when they started the study, across all doses. All prior corticosteroid failures (5/5) responded, with benefits sustained through 2-week follow-up.

Conclusions: LP-10 demonstrated excellent safety with minimal systemic absorption and clinically meaningful efficacy, representing substantial improvement over existing therapies for this serious condition with significant unmet medical need. Larger controlled studies are warranted to confirm these promising findings.

Clinical Trial Registration: NCT06233591.

Keywords: Oral lichen planus; Tacrolimus; Liposome; Oral mucosa; Phase 2 clinical trial; Dose-ranging study

Key Summary Points
Oral lichen planus (OLP) is a serious chronic inflammatory condition with debilitating symptoms. Furthermore, OLP represents a serious health risk because of its potential for malignant transformation.
OLP currently affects around six million Americans but has no FDA-approved therapies.
LP-10 is a novel liposomal tacrolimus oral rinse that has potential as an effective treatment for OLP as it overcomes delivery limitations of existing treatments.
This study investigated LP-10 safety and efficacy in 27 patients with symptomatic OLP.
LP-10 demonstrated excellent safety with minimal systemic absorption and clinically meaningful efficacy.
LP-10 oral rinse demonstrated improvements across all efficacy measures in patients with symptomatic OLP, including those who had failed prior corticosteroid therapy. The concordance between investigator-assessed endpoints and patient-reported outcomes provides compelling evidence of LP-10's therapeutic value.
Given that no FDA-approved therapies exist for this potentially malignant disorder, these results support phase 2b controlled studies to confirm these findings and establish LP-10's role as a potential first-in-class approved therapy for OLP.

INTRODUCTION

Oral lichen planus (OLP) is a serious chronic inflammatory condition classified by the World Health Organization (WHO) as an oral potentially malignant disorder, characterized by reticular white lesions often accompanied by atrophic, erosive, or ulcerative areas [1]. Affecting 1–2% of Americans—approximately six million people—OLP causes significant pain, burning, and functional impairment that substantially impact quality of life [2, 3]. Female individuals tend to be affected by OLP more often, at a ratio of 2:1 to male individuals [4].

Beyond its chronic debilitating symptoms, OLP carries serious risks. The malignant transformation rate approximates 1.4% cumulative, increasing to 5.1% in patients with dysplasia [5, 6]. Additionally, OLP increases all-cause mortality, potentially through increased infection risk [7]. Combined with associated psychological distress and depression, effective medical intervention is critically needed [8].

Despite this significant disease burden, OLP has no US Food and Drug Administration (FDA)-approved therapies, representing a serious

unmet medical need. Current therapies provide inadequate symptom control with significant limitations. Topical corticosteroids achieve only a partial response and carry risks of mucosal atrophy, secondary candidiasis, and potential hypothalamic–pituitary–adrenal (HPA) axis suppression with prolonged use [9, 10]. Compounded tacrolimus ointments, while sometimes effective, suffer from poor adherence to moist oral surfaces and inconsistent drug delivery [11–13].

LP-10 addresses these limitations through a novel sphingomyelin-liposomal formulation enabling administration as an oral rinse. This maintains local delivery benefits while improving mucosal contact. Following phase 2a evaluation of an intravesical formulation in hemorrhagic cystitis [14], this study investigated LP-10's safety, tolerability, and efficacy in patients with symptomatic OLP to address the unmet medical need in this serious disease that currently has no FDA approved therapy.

METHODS

This multicenter, dose-ranging study included adult male and female participants (≥18 years old) with symptomatic OLP and was designed to evaluate the safety, tolerability, and efficacy of LP-10 at 0.25 mg, 0.5 mg, and 1.0 mg of tacrolimus. Participants were enrolled at five study sites in the USA: Center for Dermatology Cosmetic and Laser Surgery, Fremont, California; The University of California, San Francisco (UCSF) School of Dentistry, San Francisco, California; Miami Cancer Institute at Baptist Health, Miami, Florida; Erie County Medical Center, Buffalo, New York; Atrium Health Oral Medicine & Maxillofacial Surgery, Charlotte, North Carolina; and Paddington Testing Co, Inc, Philadelphia, Pennsylvania between 10 July 2024 and 02 April 2025. The sample size of up to 24 participants was chosen to enable assessment of the safety and preliminary efficacy of LP-10 in the primary population in whom the therapy is likely to be of benefit. The study comprised a screening, 4-week treatment, and follow-up phase. The treatment phase included 10 mL LP-10 oral rinse for 3 min twice a day for 4 weeks The follow-up phase included one post-treatment visit 2 weeks after the last dose of LP-10 oral rinse.

Ethical Approval

This trial is registered at www.clinicaltrials.gov (NCT06233591) and was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and with 21 Code of Federal Regulations (CFR) 312.32. Ethical approval of this clinical study was obtained from the Advarra institutional review board on 17 November 2023. All participants provided written informed consent before inclusion in the study.

Participants

Participants with moderate OLP were included in the study on the basis of an OLP investigator global assessment (IGA) score of ≥3 [15]; OLP Pain or Sensitivity Numerical Rating Scale (NRS) score of ≥3 [16]; and an oral biopsy performed within the last 10 years before the screening visit demonstrating OLP and/or oral lichenoid mucositis without cancer or dysplasia. This included patients who had previously failed standard corticosteroid therapy.

Participants with a history of oral cavity or oropharyngeal cancers, participants who failed tacrolimus treatment for OLP in the past, participants who were or had previously participated in another oral cavity therapeutic or device study within 3 months of screening and had not returned to baseline, and participants with a known allergy to liposomes and/or egg yolk and/or tacrolimus were excluded.

Participants taking prescription oral steroid or rinse treatment(s) at the time of the screening visit agreed to stop treatment for the duration of the trial and to undergo a 4-week washout period. Participants meeting all eligibility criteria were sequentially assigned to one of three groups: group 1 (LP-10 at 0.25 mg tacrolimus dose), group 2 (LP-10 at 0.5 mg tacrolimus dose), and group 3 (LP-10 at 1.0 mg tacrolimus dose). Eight participants were enrolled in group 1, and once recruitment was completed in that group,

recruitment started in the next group. Following the eighth participant in each group's first dose of LP-10, the sponsor reviewed the safety data for all participants in the current dose group. Upon review of the safety data, the sponsor determined if the next participant could proceed to the next higher dose.

Interventions

The LP-10 drug product was supplied as a sterile, lyophilized, fluffy white powder (dehydrated liposomes containing drug substance) formulated from avian sphingomyelin phospholipids (excipient) and tacrolimus in a 50-mL glass vial. The powder was reconstituted at the time of use with sterile water for injection. The final product was prepared at the clinical site according to protocol instructions to a final dose of 0.25 mg/10 mL, 0.5 mg/10 mL, or 1.0 mg/10 mL. Participants performed a 3-min oral rinse twice daily for a duration of 4 weeks. The dose levels were selected on the basis of results of the phase 2a study of intravesical LP-10 in participants with hemorrhagic cystitis, in which doses of 2, 4, and 8 mg of tacrolimus were dissolved in 40 mL sterile water. Tacrolimus blood levels were consistently below the upper limit of the reference range of 15 ng/mL [14]. These dosages were expected to maintain a significant safety margin because the FDA currently approves doses of tacrolimus for systemic and topical formulations and for both oral and intravenous administration; the FDA has set a maximum daily dose of 14.0 mg.

Assessments

The primary objective of this study was to evaluate the safety of LP-10 for OLP. Safety data was collected by ongoing monitoring of adverse events (AEs) defined as any untoward medical occurrence in a subject participating in the clinical trial and which does not necessarily have a causal relationship with this treatment.

The first LP-10 oral rinse was completed at the investigator's office and the participant remained at the office for at least 30 min. Systemic safety was monitored on the basis of clinical assessment, including vital signs (temperature, blood pressure, heart rate, respiratory rate) before and at 15 and 30 min after the first oral rinse; standard laboratory studies; and whole-blood tacrolimus levels. Local safety was assessed on the basis of oral cavity toxicity of LP-10, such as pain, blood in mouth, or infection. The oral cavity was examined for any local AEs at each visit, and any adverse reactions were recorded and managed.

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 27.0. All treatment-emergent adverse events (TEAEs) were recorded. A treatment-related TEAE was recorded when a causal relationship between the medicinal product and the event was suspected and deemed to be "related" (either "probably related", or "possibly related"). The primary safety endpoint was the incidence and severity of TEAEs over 4 weeks of treatment and 2 weeks of follow-up. Changes in standard laboratory studies and whole-blood tacrolimus levels were assessed. Pharmacokinetic (PK) data regarding LP-10 was also obtained. For whole blood tacrolimus measurements, the samples were analyzed centrally at Mayo Clinic Laboratories using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method. The lower limit of quantification (LLOQ) of this assay is 1.0 ng/mL. The reference range of 5–15 ng/mL represents therapeutic levels for systemic immunosuppression (e.g., in transplant patients). Levels > 15 ng/mL raise concern for systemic toxicity.

Efficacy

The secondary objectives of the study were chosen to evaluate the efficacy of LP-10 oral rinse for OLP: focused oral examination was performed, including intraoral images obtained and reviewed by the investigator; and analyses of the OLP IGA [15]; and the reticulation, erythema, and ulceration (REU) score [17, 18]; pain and sensitivity NRS [16]; modified OLP symptom severity measure (OLPSSM) [19]; and patient global response assessment (GRA) were undertaken. The IGA was measured according to ulceration and erythema on a scale of 0–4 where

0 represents clear and 4 represents severe [15]. The REU scoring system evaluates 10 oral cavity sites, scoring each for reticulation/keratosis (0–1), erythema (0–3), and ulceration (0–3). The total REU score is calculated as total reticular score + (total erythematous score × 1.5) + (total ulcerative score × 2.0), with a possible range of 0–115. Higher scores indicate greater disease severity. Most patients have scores below 45, and a score of 15 is considered to represent significant symptoms [17, 18]. The OLP Pain and Sensitivity NRS measured the pain and sensitivity experienced over the previous 24 h on two separate visual analogue scales of 0–10 where 0 represents "no pain" and 10 represents "pain as bad as you can imagine" [16]. The modified OLPSSM scored self-reported soreness associated with seven different activities within the previous 24 h (items 1–7) [19], symptom severity over the previous waking 24 h (items 8–10) and past week (item 11), and during the study (item 12). The GRA was assessed at the end of the treatment period and involved the following question: As compared to when you started the study, how would you rate your overall quality of life now? The following response options were provided: very much worse; moderately worse; a little worse; no change; a little better; moderately better; very much better.

Statistical Analysis

Participant data are presented as mean ± standard deviation (SD), median (range), mean ± standard error of the mean (SEM), or number (%) as appropriate. Response to therapy was evaluated on a per-subject basis. This study includes a repeated-measures, single-group design and the sample size is based on a power analysis for repeated-measures analysis of variance (ANOVA) with four time points, $\alpha = 0.05$, a medium effect size ($f = 0.25$), and 80% power, accounting for potential loss to follow-up. The significance of change from baseline was analyzed by linear mixed-effects model fit by restricted maximum likelihood, with dose response assessed by Tukey's test using Graphpad Prism version 10.5 (www.graphpad.com).

RESULTS

Demographics

A total of 33 participants were screened, and a total of 27 participants were sequentially enrolled (8 participants each in group 1 and group 2 and 11 participants in group 3) as shown in Fig. 1. The median age of the participants was

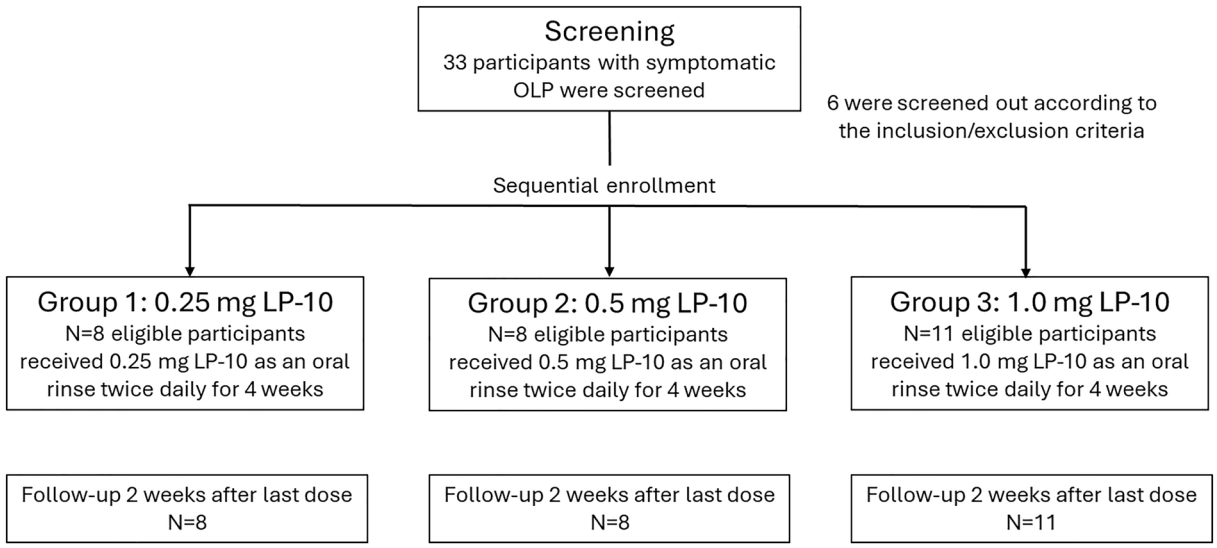

Fig. 1 Flowchart showing the screening and inclusion of participants with oral lichen planus (OLP) in the trial

62.0 years (range 38–83 years) and the majority were female (22/27 [81.5%]). The demographics and baseline symptom scores in each group and of the overall study population can be seen in Table 1. All participants were symptomatic with overall mean ± SD 3.5 ± 0.51 OLP IGA score, 26.46 ± 10.37 REU score, 6.8 ± 1.90 NRS pain score, and 7.2 ± 1.71 NRS sensitivity score.

Table 1 Participant demographics

	Group 1 (0.25 mg) *N* = 8	**Group 2 (0.5 mg)** *N* = 8	**Group 3 (1.0 mg)** *N* = 11	**Overall** *N* = 27
Age [median (range), years]	61.5 (38–72)	61.5 (38–72)	64.0 (38–83)	62.0 (38–83)
Gender [*n*, (%)]				
Female	6 (75.0)	7 (87.5)	9 (81.8)	22 (81.5)
Male	2 (25.0)	1 (12.5)	2 (18.2)	5 (18.5)
Ethnicity [*n* , (%)]				
Hispanic or Latino	0	2 (25.0)	1 (9.1)	3 (11.1)
Not Hispanic or Latino	8 (100.0)	6 (75.0)	10 (90.9)	24 (88.9)
Weight [median (range), kg]	68.65 (52.9–112.0)	73.25 (48.1–113.4)	66.90 (45.1–97.7)	73.00 (45.1–113.4)
Women of childbearing potential [*n* (%)]				
Yes	1 (12.5%)	1 (12.5%)	0	2 (7.4%)
No	5 (62.5%)	6 (75.0%)	9 (81.8%)	20 (74.1%)
OLP characteristics at baseline				
Duration of OLP [median years (range)]	8 (2–20)	9.5 (1–28)	4.3 (5–12)	7 (1–28)
Baseline symptoms efficacy analysis	*N* = 8	*N* = 7	*N* = 10	*N* = 25
IGA score (mean ± SD)	3.5 ± 0.53	3.6 ± 0.53	3.5 ± 0.53	3.5 ± 0.51
REU score (mean ± SD)	27.75 ± 7.68	25.00 ± 9.52	26.45 ± 13.31	26.46 ± 10.37
NRS (mean ± SD)				
Pain score	6.6 ± 2.26	6.1 ± 1.86	7.3 ± 1.64	6.8 ± 1.90
Sensitivity score	7.3 ± 1.83	6.7 ± 1.89	7.6 ± 1.58	7.2 ± 1.71
OLPSSM (mean ± SD)				
Items 1–7	15.4 ± 6.23	12.1 ± 4.30	12.6 ± 4.84	13.4 ± 5.17
Item 8	3.6 ± 0.74	3.1 ± 1.21	3.2 ± 0.92	3.3 ± 0.95
Item 9	3.1 ± 1.13	2.7 ± 0.95	3.4 ± 0.70	3.1 ± 0.93
Item 10	7.0 ± 2.07	6.6 ± 1.90	7.1 ± 1.73	6.9 ± 1.82
Item 11	2.6 ± 0.74	2.4 ± 0.79	3.0 ± 0.82	2.7 ± 0.79

IGA investigator global assessment, *NRS* numerical rating scale, *OLP* oral lichen planus, *OLPSSM OLP* symptom severity measure, *REU* reticulation, erythema, and ulceration, *SD* standard deviation

The OLP duration ranged from 1 to 28 years. Two participants met the inclusion criteria at screening, but at visit 2, the first dosing visit, had an OLP IGA score below the inclusion criteria threshold (a score of < 3). One participant was in group 2 and one in group 3. The participants were therefore excluded from the efficacy analysis, although they completed the study and were included in the safety analysis.

Safety Analysis

Adverse Events

All 27 participants completed the trial and tolerated the full treatment course. No participants discontinued treatment as a result of safety concerns, and no serious adverse events (SAEs) were reported. Table 2 summarizes the AEs recorded during the study and 2-week follow-up. Overall, there were 54 TEAEs that were possibly study treatment related, all of them mild or moderate (50 grade 1 and 4 grade 2). The details of these TEAEs are shown in Supplementary Table 1; the most common TEAE was dry mouth, experienced by 5 (18.5%) participants, with one event each in groups 1 and 2 and three events in group 3, each experienced by a single participant. All of these were grade 1 (mild). The only moderate grade treatment-related TEAEs were one event of oral dysesthesia in group 3, one event of herpes simplex virus infection in group 1, one case of oral fungal infection in group 3, and one case of alanine aminotransferase (ALT) increase in group 1. All these TEAEs resolved spontaneously.

Systemic Pharmacokinetics

Analysis of tacrolimus levels in serum demonstrated a favorable safety profile with minimal systemic exposure. Tacrolimus was below the LLOQ (< 1.0 ng/mL) in 76.4% of all measurements (81/106). Among the 27 participants monitored at multiple timepoints (1 h, 2 h, 1 week, and 4 weeks post-first dose), only 25 observations showed levels ≥ 1.0 ng/mL. Even when detectable, systemic levels remained low: the highest recorded value was 4.5 ng/mL in a single patient receiving the 1.0 mg dose at week 4—well below the established safety threshold of 15 ng/mL [20, 21]. There were 3 instances of detectable levels in the 0.25-mg group (maximum 1.7 ng/mL); in the 0.5-mg group, 9 instances (maximum 2.4 ng/mL); and in the 1.0-mg group, 13 instances (maximum 4.5 ng/mL). Most measurable levels were between 1.0 and 2.0 ng/mL across all dose groups.

Table 2 Summary of adverse events

	Group 1 (0.25 mg) *N* = 8	Group 2 (0.5 mg) *N* = 8	Group 3 (1.0 mg) *N* = 11	Overall *N* = 27
Participants with any AE [*n* (%)]	7 (87.5)	5 (62.5)	11 (100)	23 (85.2)
Participant discontinuation	0	0	0	0
Total number of TEAEs	34	13	38	85
Total number of TEAEs considered treatment related	23	6	24	54
Number of serious AE	0	0	0	0
Number of serious related AE	0	0	0	0
Number of AE leading to treatment withdrawal	0	0	0	0
Number of AE leading to temporary dose interruption	0	0	0	0

AEs adverse events, *TEAEs* treatment-emergent adverse events

Efficacy

As shown in the example participant in Fig. 2, the investigator-conducted oral examinations demonstrated a marked reduction of inflammation and redness, along with clear evidence of healing of ulcerative lesions (Fig. 2a). These findings were supported by significant improvements in OLP IGA and REU. The reductions in OLP IGA (Fig. 2b) and REU score (Fig. 2c) were statistically significant at week 4 ($p < 0.0001$) compared to baseline in all groups including five patients who were using topical corticosteroid oral rinses at the time of screening but remained symptomatic underwent a 4-week washout period before enrolling in our study. All five of these patients reported excellent efficacy responses to LP-10 treatment. Moreover, three of these five patients subsequently requested that their physicians apply to the FDA for compassionate use through the

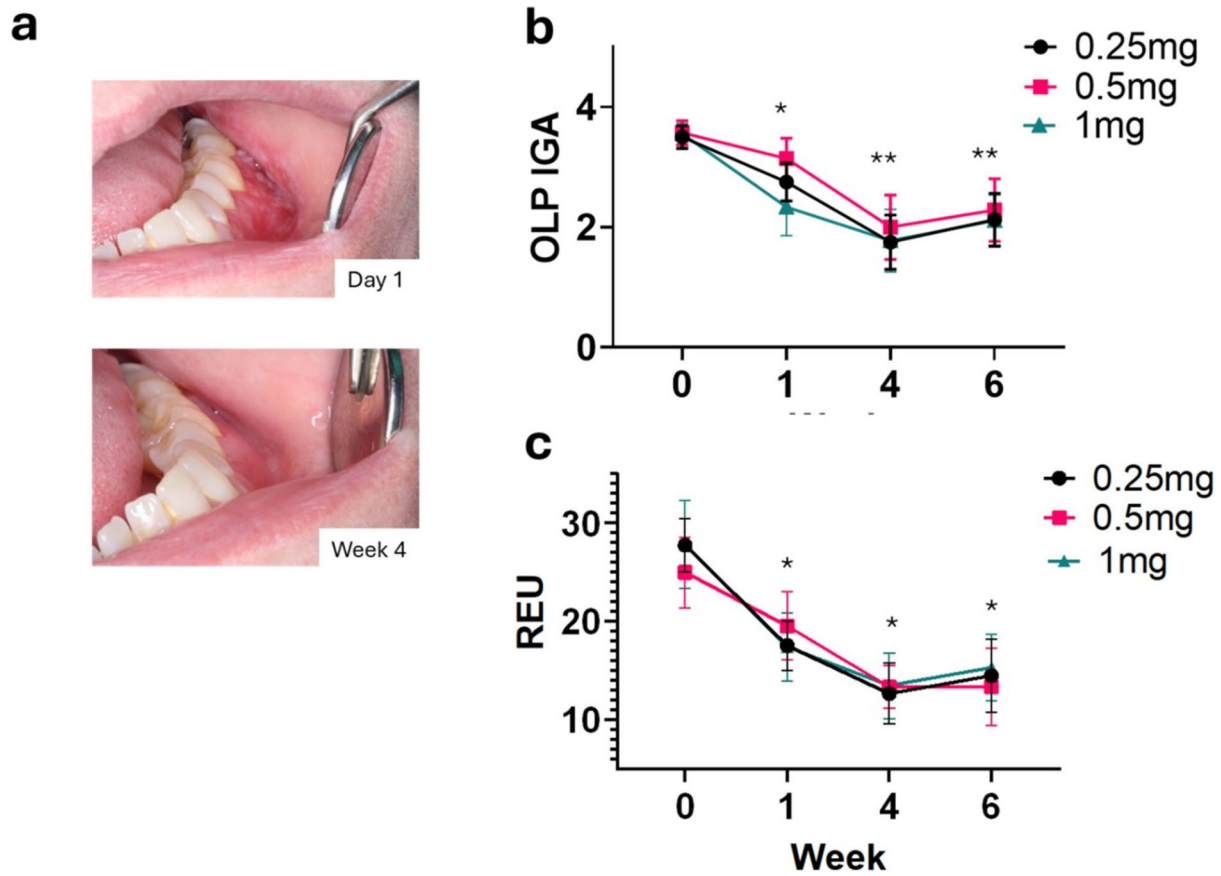

Fig. 2 Investigator measurements of treatment efficacy. **a** An image from a participant with oral lichen planus (OLP) of the left mandibular gingiva. Day 1 is the image taken at the first oral rinse. Week 4 is the image taken at the last oral rinse. The decrease in inflammation, redness, and healing of the white ulcers is remarkable; **b** change in investigator global assessment (IGA) scores from baseline over 4 weeks of treatment and a 2-week follow-up (week 6); **c** change in reticulation, erythema, and ulceration (REU) score from baseline. Group 1 (0.25 mg dose) in black, group 2 (0.5 mg dose) in red, and group 3 (1.0 mg dose) in green. Data are presented as mean ± standard error of the mean (SEM). **b** IGA: $^{*}p < 0.0009$, $^{**}p < 0.0001$, significant decline in IGA score from baseline (week 0). **c** REU: $^{*}p < 0.0001$, significant decline in REU score from baseline (week 0); REU score range up to 40; baseline REU subtracted from REU post-treatment. Significance was evaluated by repeated measures analysis of variance (ANOVA) (mixed-effects model) followed by Tukey's test

Expanded Access (EA) program. EA is granted only for serious diseases where currently available treatments are inadequate. The FDA approved EA for all three cases, further supporting both the unmet medical need and the clinical benefit observed with LP-10 in this corticosteroid-refractory population.

The improvements in symptoms were also evident from the patient-reported evaluations as shown in Fig. 3. A statistically significant reduction in OLP-related pain and sensitivity was measured by the NRS scores (Fig. 3a and b; $p < 0.0001$). There were clear improvements in OLP symptoms assessed by items 1–7 in the OLPSSM, which were significant at week 4 (Fig. 3c; $p < 0.0001$) compared to baseline in all groups. Similar results were found for the other modified OLPSSM items as shown Fig. S1 in the Supplementary Materials. The patient-reported outcomes assessed by GRA are shown in Fig. 3d. Results demonstrate strong therapeutic benefit across all treatment groups. Notably, of the participants who completed the GRA in group 3, 66% reported a quality of life that was "very much better", while more than 70% of those who completed the GRA in groups 1 and 2

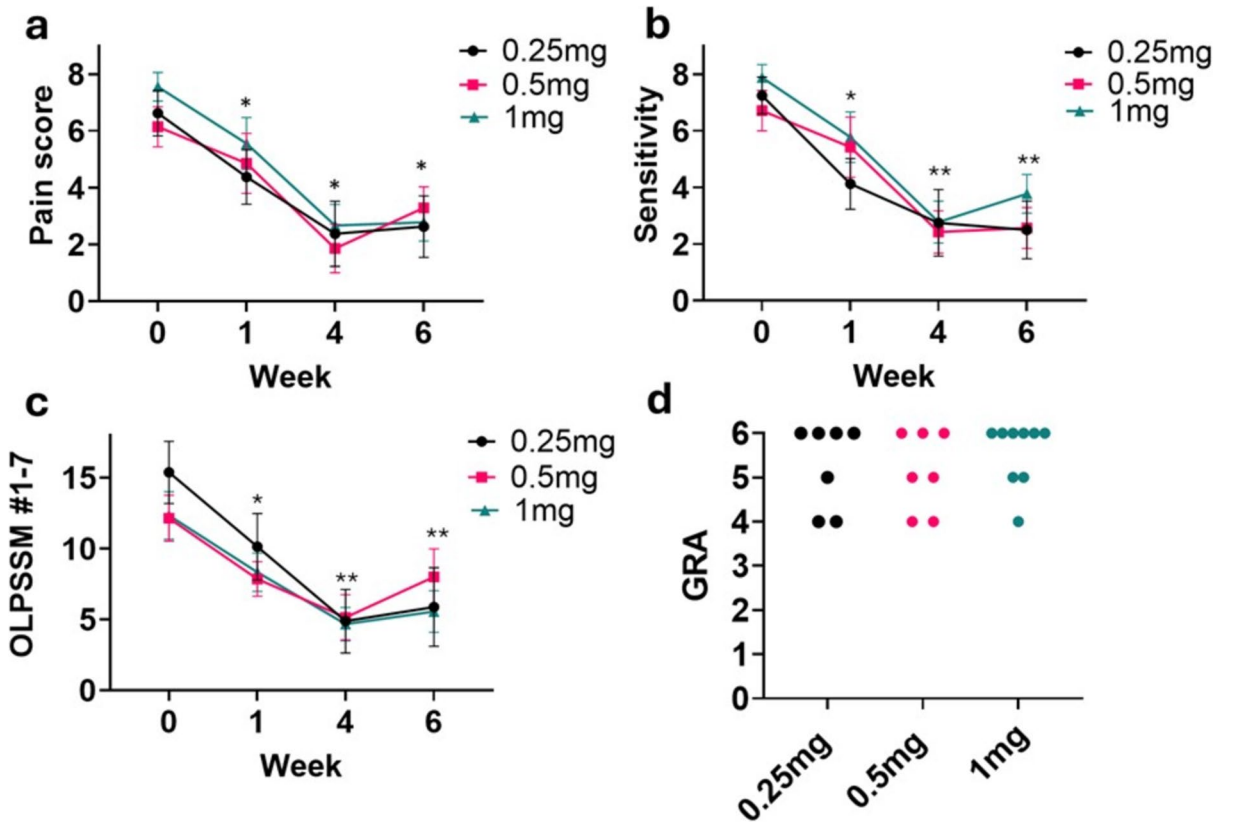

Fig. 3 Patient-reported oral lichen planus (OLP) symptoms over 4 weeks of treatment and a 2-week follow-up (week 6). **a**, **b** Pain and sensitivity numerical rating scale (NRS); **c** OLP symptom severity measure (OLPSSM) for items 1–7. Group 1 (0.25 mg dose) in black, group 2 (0.5 mg dose) in red, and group 3 (1.0 mg dose) in green. Data are presented as mean ± standard error of the mean (SEM). Significance was evaluated by repeated measures analysis of variance (ANOVA) (mixed-effects model) followed by Tukey's test. **a** Pain NRS: $^{*}p < 0.0001$, significant decline in pain score (0–10) from baseline (week 0); **b** $^{*}p < 0.001$, $^{**}p < 0.0001$, significant decline in sensitivity score (0–10) from baseline (week 0); **c** OLPSSM #1–7: $^{*} < p < 0.0003$; $^{**}p < 0.0001$, significant decline in OLPSSM #1–7 from baseline (week 0); **d** Global response assessment (GRA) at week 4. The points indicate the opinions of 23 participants who responded (7 in group 1, 7 in group 2, and 9 in group 3); 0 = very much worse; 1 = moderately worse; 2 = a little worse; 3 = no change; 4 = a little better; 5 = moderately better; 6 = very much better

reported an outcome of "moderately better" or "very much better". All participants across treatment groups experienced improvement on the GRA.

DISCUSSION

No participants in this phase 2a study of LP-10, a novel liposomal tacrolimus oral rinse, experienced a serious adverse event. Furthermore, LP-10 achieved statistically significant improvement across all efficacy endpoints in patients with symptomatic OLP. Importantly, the study included patients who had failed standard corticosteroid therapy, with this refractory subgroup showing 100% response rate. These results address a critical gap in OLP treatment, where no FDA-approved therapies exist despite the disease affecting six million Americans.

The results show that in these 27 participants with OLP, a twice-a-day, 3-min, 10-mL rinse with LP-10 was well tolerated by all participants, with none discontinuing treatment because of safety concerns. No SAE was reported. All treatment-related TEAEs were mild or moderate, and resolved. Tacrolimus levels in serum demonstrated little systemic uptake, with most (75%) measurements below 1.0 ng/mL level, supporting the safety profile previously demonstrated by topical formulations. In terms of efficacy the investigator examinations, IGA, REU, NRS, modified OLPSSM, and GRA all improved over the 4-week treatment period in all dose groups. The combination of excellent safety, minimal systemic absorption, and robust efficacy across multiple endpoints demonstrates substantial improvement over existing therapies for this serious condition with unmet medical need.

The authors believe the oral rinse administration of LP-10 in this study confers similar advantages as the local administration of topical tacrolimus [21]. Topical tacrolimus for local administration was approved by the FDA in 2000 for the noncontinuous treatment of moderate to severe atopic dermatitis and in this situation even long-term use of topical tacrolimus usually causes only local and transient symptoms, such as burning, stinging, soreness, or itching [22]. Topical tacrolimus is expected to minimize the potential for side effects due to local immune response mechanisms, and severe adverse reactions that can occur with systemic administration are rare [23]. Previous topical tacrolimus studies [13, 24] demonstrated few treatment related-TEAEs, potentially as a result of low systemic absorption. This study shows that the tacrolimus in the LP-10 oral rinse was safe and well tolerated in patients with OLP. There were no reports of nephrotoxicity in this study and no reports of fever, headache, and flu-like symptoms, all symptoms that have been seen with topical skin tacrolimus [21]. In our study, only 25 of 106 samples showed levels of tacrolimus in the blood of ≥ 1.0 ng/mL and the maximum serum level reached was 4.5 ng/mL well below the 15 ng/mL safety threshold. These blood levels are lower than the levels found in patients with atopic dermatitis refractory to other topical treatments receiving topical tacrolimus (from undetectable to 20 ng/mL in serum after single or multiple doses of 0.03% and 0.1% tacrolimus ointment) [21].

The investigator- and patient-reported efficacy outcomes in this study all showed that the significant improvements from baseline in OLP symptoms were maintained to some extent during the 2-week follow-up. These evaluations included investigator measurement of oral ulceration score, patient-reported symptom outcome, patient-reported pain and sensitivity, and patient-reported global response assessment. This adds to the available evidence that tacrolimus is an effective treatment for OLP [11–13]. Analysis of patients treated with a magistral oral-rinse tacrolimus formulation after prior treatment with topical steroids found that 97% achieved objective remission at 24 months, with only few and mild long-term side effects, but 4 patients (7%) developed a squamous cell carcinoma [13]. Whether the oral rinse LP-10 treatment results in equivalent or superior efficacy compared to other current treatments requires further study. The next step would be evaluation of LP-10 oral rinse in a multicenter placebo-controlled trial.

The participants in this study were generally typical of the patient population affected by OLP. The prevalence of OLP ranges from 1% to

2% of Americans, with a female to male ratio of 2:1 and an age of onset between 30 and 60 years [4]. Our study population was aged between 38 and 83 years and 81.5% of participants were female.

This study has some limitations, including the small sample size and the absence of a control group. However, the results support the need for conducting larger phase 2b trials.

CONCLUSION

The LP-10 oral rinse demonstrated a favorable safety profile with minimal systemic absorption and statistically significant improvements across all efficacy measures in patients with symptomatic OLP, including in those who had failed prior corticosteroid therapy. The concordance between investigator-assessed endpoints and patient-reported outcomes provides compelling evidence of LP-10's therapeutic value. Given that no FDA-approved therapies exist for this WHO-designated potentially malignant disorder affecting six million Americans, these results support phase 2b controlled studies to confirm these findings and establish LP-10's role as a potential first-in-class approved therapy for OLP.

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Data Availability. This trial is registered at www.clinicaltrials.gov (NCT06233591). The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Michael T. Brennan, Jennifer Frustino, Kamal Al-Eryani, Herve Sroussi, Jennifer L. Parish, Hirak B. Routh, Sunil Dhawan, Gerald L. Klein, Michael B. Chancellor, and Alessandro Villa declare that they have no competing interests.

Ethical Approval. This trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and with 21 Code of Federal Regulations (CFR) 312.32. Ethical approval of this clinical study was obtained from the Advarra institutional review board on 17 November 2023. All participants provided consent for participation in the study.

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