Title: **Ubenimex in Adult Patients with Lymphedema of the Lower Limb: a Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of Efficacy, Safety, and Pharmacokinetics (ULTRA)**

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Protocol:

Objectives

The primary objectives of the study are to evaluate the efficacy and the safety and tolerability of ubenimex in patients with leg lymphedema.

Methodology

This Phase 2, randomized, double-blind, placebo-controlled, proof-of-concept study compared ubenimex 150 mg 3 times daily (TID) with matching placebo in patients with leg lymphedema. Eligible patients had a diagnosis of secondary lymphedema or a diagnosis of primary lymphedema not of congenital onset, based on a positive lymphoscintigraphy (LSG) of the affected leg. In addition, all patients had International Society of Lymphology (ISL) Stage ≥ II lymphedema and swelling of at least 1 leg that was not completely reversed by leg elevation or compression. The number of patients planned for the study is approximately 45.

The study consisted of 3 periods:

- Screening Period: Day –49 to Day 1 (maximum 7 weeks)
- Treatment Period: Day 1 (first day of treatment) through Week 24 (6 months)
- Follow-up Period: Week 25 through Week 28 (1 month)

Patients were randomized equally to receive 1 of the following treatments: ubenimex 150 mg TID or matching placebo TID, which were administered orally for a total of 6 months:

Efficacy assessments included skin thickness (measured by skinfold calipers; primary efficacy measure), PRELYM-Leg results, leg volume, bioimpedance measures, and skin biopsy results. Blood concentrations of ubenimex were measured to characterize the steady-state PK of ubenimex. Blood concentrations of the metabolite (2S, 3R)-3-amino-2-hydroxy-4-phenylbutyric acid [abbreviated as (2S,3R)-AHPA] were also measured. Ex vivo A23187 stimulated plasma LTB4 concentrations were assessed to gauge the degree of peripheral inhibition of LTA4H at selected study sites. Safety measures included AEs, clinical laboratory test results (blood and urine analyte concentrations), vital signs, concomitant medications, electrocardiogram (ECG) findings, and urinary leukotriene E4 (LTE4) concentrations.

Inclusion Criteria

1. Has a diagnosis of secondary leg lymphedema, based on a positive lymphoscintigraphy (LSG) study of the affected leg OR has a diagnosis of primary lymphedema not of congenital onset affecting one or both lower limbs, based on positive LSG.

2. Swelling of at least 1 leg not completely reversed by leg elevation or compression.
3. Stage II or greater lymphedema, based on the International Society of Lymphology (ISL) staging system.
4. Completion of a full course of complete decongestive therapy (CDT).
5. Stable limb volume (within 10% during screening for worse/affected leg) .
6. If patient has had a lymphatic vascularization procedure (lymphovenous bypass or lymph node transfer) or liposuction for lymphedema in the affected limb, then procedure must have been performed at least 1 year (12 months) prior to Screening AND affected limb must be clinically stable over the 3 months prior to Screening AND significant residual disease must be present.
7. Ambulatory status (use of a walking aid is permitted).
8. Agree to use a medically acceptable method of contraception, if the possibility of conception exists.

Exclusion Criteria

- Exclusions Based on Lymphedema:

1. A diagnosis of primary lymphedema with congenital onset. Primary lymphedema is defined as lymphedema with onset prior to or without an inciting event (e.g, surgery, trauma, radiation)
2. Occurrence of significant lymphedema of another body part that is not the lower limb (e.g, upper extremity, trunk, head and neck, genitalia).
3. Lymphedema involving all four limbs
4. Recent initiation of, or intention to initiate CDT or maintenance physiotherapy for lymphedema.

- Exclusions Based on Other Medical Conditions

5. Deep venous thrombosis in either lower limb or systemic anticoagulation within 6 months
6. Other medical condition that could lead to acute or chronic leg edema.
7. Other medical condition that could result in symptoms overlapping those of lymphedema in the affected leg.
8. History of clotting disorder (hypercoagulable state).
9. Chronic (persistent) infection in either lower limb.

10. Cellulitis or other infection in either lower limb or use of antibiotics for cellulitis within 3 months prior to screening.
11. Other unstable or severe medical condition requiring active management and/or likely to decompensate/require active management within the next year
12. Current evidence of malignancy.
13. History of malignancy within the previous 3 years, except for nonmelanoma skin cancer or cervical carcinoma in situ treated with curative intent.
14. Currently receiving chemotherapy or radiation therapy.
15. Life expectancy < 2 years for any reason.
16. Pregnancy or nursing.
17. Substance abuse (such as alcohol or drug abuse) within 6 months prior to screening.

- Exclusions Based on Concurrent Medication Use

18. Regular concurrent use or regular use within 6 months before screening of another leukotriene pathway inhibitor.
19. Concurrent antibiotic use.
20. Concurrent use of any agent active on the sphingosine-1-phosphate (S1P) pathway.
21. Concurrent use of unapproved (including herbal) treatments for lymphedema.

- Exclusions Based on Laboratory Values

22. Significant or chronic renal insufficiency or requires dialytic support.
23. Hepatic dysfunction.
24. Absolute neutrophil count <1500 mm3 at screening.
25. Hemoglobin concentration <9 g/dL at screening

Dose and Mode of Administration

150 mg administered orally three times a day (at 8 ± 2 hr intervals), with or without food.

Duration of Treatment

Duration of treatment was 6 months. Total study participation lasted up to 8.5 months (up to 1.5 months of screening, 6 months of treatment, and 1 month of follow-up).

Criteria for Evaluation

All comparisons were made with placebo. The primary efficacy endpoints are changes from baseline to Week 24 in skin thickness of the calf of the most affected leg, measured by skinfold calipers. The secondary endpoints include change from baseline to Week 24 in lymphedema-specific patient-reported outcome measures (Patient-Reported Evaluation of Lymphedema [Leg]; PRELYM-Leg), change from baseline to Week 24 in leg volume of the most affected leg, change from baseline to Week 24 in bioimpedance measures, and change from baseline to Week 24 in biopsy results.

The safety endpoints include treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), treatment-related AEs, treatment-related SAEs, AEs leading to early discontinuation of study treatment, AEs leading to dose reduction.

Statistical Analysis Plan

Analysis Populations

- Intended to treat (ITT) population: all randomized patients. Patients were analyzed according to the treatment group to which they were randomized with no imputation of missing data.
- Skin thickness (ST-ITT) population: The ST-ITT population comprised the subset of the ITT population with baseline calf thickness (worse leg) $\geqslant$ 10 mm. All primary analyses of skin thickness endpoints were conducted on the ST-ITT population.
- Safety population (Safety Set): all patients who received at least 1 dose of study drug. Patients were analyzed according to treatment received.

Efficacy Analyses

Primary endpoint—The change from Baseline to Week 24 in skin thickness of the calf of the most affected leg was analyzed using the ST-ITT population. The Shapiro-Wilk test was performed to test for normality of the residuals from the analysis of covariance (ANCOVA) model. In the event of departure from normality, the data were log-transformed. If this corrected departures from normality the result was to be the primary analysis. The p-value for difference was calculated using treatment as a factor and the baseline value as a covariate. The treatment effect with its 95% confidence interval and p-value was presented. In addition, the number and percentage of patients with change from baseline $\leqslant$ -10 mm vs. > -10 mm at each visit were presented.

A non-parametric analysis (ANCOVA on ranked change scores with factors for treatment and median-split baseline skin thickness) was conducted. In the event of departure from normality, even after log-transformation, this analysis was to be the primary analysis.

Secondary endpoints—Change in PRELYM-Leg—total score and domain scores analyzed using ANCOVA with treatment as a factor and the baseline value as a

covariate. Patient Global Impression of Lymphedema Symptoms (P-GILS) analyzed using a logistic regression model with treatment and baseline response as independent variables. Change in leg volume of the most affected leg and bioimpedance measures are analyzed using ANCOVA with treatment as a factor and the baseline value as a covariate. Change in biopsy results—listed only.

Pharmacokinetic Analyses

Steady-state PK parameters (Cmax, Cmin, tmax, t1/2, AUC0–8) of ubenimex and the metabolite (2S,3R)-AHPA were determined using plasma concentrations measured from serial blood samples at Week 4.

Safety Analyses

AEs, deaths, concomitant medications, vital signs, electrocardiogram data, and clinical laboratory data for each patient and summarized by treatment group. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA)version 18.1.