Title: **A Phase 2, Randomized, Double-BLInd, Placebo-Controlled Study of UBEnimex in Patients with Pulmonary ARTerial HYpertension (WHO Group 1) (LIBERTY)**

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Protocol:

Objectives

The primary objective for the study is to obtain long-term safety and tolerability data for ubenimex in patients with pulmonary arterial hypertension (PAH).

Methodology

This proof-of-concept study was designed as a Phase 2, multicenter, randomized, double-blind, placebo-controlled study comparing ubenimex (150 mg 3 times daily [TID]) with placebo in patients with PAH who have a WHO/New York Heart Association Functional Classification (WHO/NYHA-FC) of II or III.

Eligible patients must have been on a stable dosage of at least 1 approved PAH-specific therapy before Screening and were willing to remain on the same dosage throughout the study. The treatment period is 24 weks, with 4 weeks follow-up period. Approximately 60 patients were planned to be enrolled in the study. Patients were randomized 2:1 to receive either ubenimex 150 mg TID (total daily dose of 450 mg) or matching placebo TID. Study drug was administered orally for 24 weeks. Eligible patients were stratified by PAH etiology and by number of PAH-specific therapies at baseline (1 versus 2 or more).

The primary endpoint for clinical efficacy was change from baseline to Week 24 in pulmonary vascular resistance (PVR), as assessed by hemodynamic measurements obtained via right heart catheterization (RHC). Secondary efficacy endpoints included 6-minute walk distance (6MWD) and Borg dyspnea score assessments; changes in NT-proBNP, WHO/NYHA-FC status, and disease severity (clinical worsening); and QoL assessments using CAMPHOR.

Steady-state PK characteristics of ubenimex were determined using plasma ubenimex concentrations measured from serial blood samples at Week 4. Safety was evaluated by monitoring adverse events (AEs), clinical laboratory test results, physical examinations, electrocardiograms (ECGs), and vital sign measurements. In addition, an independent data safety monitoring board (DSMB) consisting of 2 expert PAH clinicians and a biostatistician conducted regular safety reviews.

Patients who completed Study EIG-UBX-001 treatment through to Week 24 were eligible to enroll in an open-label extension study, EIG-UBX-002. Eligibility for EIG-UBX-002 was assessed at the Week 24 visit in EIG-UBX-001; if the patient was eligible and enrolled in EIG-UBX-002, treatment with open-label ubenimex was initiated. Patients who did not enter the open-label extension study attended a follow-up visit.

Inclusion Criteria

A patient was included in this study if he or she met all of the following criteria:

1. Male or female, 18-75 years old.

2. Has a diagnosis of WHO Group 1 PAH.
3. Right heart catheterization performed at Screening with results that are:
    a. Mean pulmonary arterial pressure ≥25 mmHg (at rest) and
    b. Pulmonary venous hypertension (measured as pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. If PCWP is not available, then mean left atrial pressure or left ventricular end-diastolic pressure ≤15 mmHg in the absence of left atrial obstruction. and
    c. Pulmonary vascular resistance (PVR) ≥300 dyn•s/cm5 (3.75 Wood units)
4. Has WHO/NYHA-FC of II or III.
5. Be on stable dose of at least one of the following PAH-specific therapies: endothelin receptor antagonist, an agent acting on the nitric oxide pathway (phosphodiesterase type 5 inhibitor or soluble guanylate cyclase stimulator), and/or a prostacyclin or prostacyclin analog.
6. Has a 6-minute walk distance that is ≥150 and ≤500 meters.
7. Have a ventilation-perfusion scan that rules out thromboembolic disease.

Exclusion Criteria

- Exclusions Related to Cardiovascular Disease
    1. History of uncontrolled hypertension
    2. Persistent hypotension at Screening.
    3. Evidence or history of left-sided heart disease and/or clinically significant cardiac disease in which pulmonary hypertension is more likely WHO Group 2.
    4. Acute decompensated heart failure within 1 month of Screening.
    5. Recent initiation (<8 weeks from Screening) or planned initiation of cardiopulmonary rehabilitation exercise program.
- Exclusions Related to Pulmonary Disease
    6. Newly diagnosed with PAH and not on PAH-specific therapy.
    7. Pulmonary hypertension due to:
        a. Uncorrected congenital systemic-to-pulmonary shunt.
        b. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
        c. Persistent pulmonary hypertension of the newborn

d. WHO clinical classification Groups 2-5

8. Evidence of significant airway and/or parenchymal lung disease.
9. Chronic infection related to tuberculosis or fungal or mycobacterial disease.

- Exclusions Based on Other Medical Conditions

10. Chronic infections including, but not limited to tuberculosis (TB), hepatitis B virus (HBV) or hepatitis C virus (HCV).
11. History of portal hypertension or chronic liver disease, including positive serology for infection with HCV and/or HBV.
12. Evidence of active infection requiring intravenous or oral antibiotics within 4 weeks of Screening.
13. Body mass index ≥35.0 at Screening.
14. History of obstructive sleep apnea.
15. History of malignancy within the last 5 years, except nonmelanoma skin cancer and cervical carcinoma in situ treated with curative intent.
16. Neuropsychiatric disorders/symptoms or psychological conditions.
17. Pregnancy or breast-feeding
18. Prior treatment with B cell or lymphocyte-depleting agents (eg, rituximab, Campath)

- Exclusions Based on Concomitant Medication Use

19. Concurrent regular use of another leukotriene pathway inhibitor, including over-the-counter medications or herbal remedies.

- Exclusions Based on Laboratory Values

20. Significant/chronic renal insufficiency.
21. Transaminases (alanine transaminase, aspartate transaminase) levels >3 × upper limit of normal (ULN) and/or bilirubin level >2 × ULN.
22. Absolute neutrophil count <1500 mm3.
23. Hemoglobin concentration <9 g/dL at Screening.
24. Hepatic dysfunction as defined by Child-Pugh Class B or C

Dose and Mode of Administration

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

Duration of Treatment

Duration of treatment was 24 weeks. Total study participation lasted up to 32 weeks (4 weeks for screening, 24 weeks for treatment, and 4 weeks for follow-up).

Criteria for Evaluation

All endpoints were changes from baseline to Week 24, and comparisons were made with placebo. Primary efficacy endpoint is the change in PVR. Secondary efficacy endpoints included 6-minute walk distance (6MWD) and Borg dyspnea score assessments; changes in NT-proBNP, WHO/NYHA-FC status, and disease severity (clinical worsening); and QoL assessments using CAMPHOR.

Safety Endpoints included treatment-emergent (TE) AEs: TEAEs, TE serious adverse events (SAEs), treatment related TEAEs, treatment-related TE SAEs and deaths, TEAEs leading to early discontinuation of study treatment, TEAEs leading to dose reduction, changes in vital signs, clinical laboratory findings, ECGs.

Statistical Methods

Efficacy Analyses

The analyses of the primary and secondary endpoints were performed using the following two stratification factors as covariates: (1) the number of PAH therapies at baseline (1 vs 2 or more) and (2) etiology: PAH associated with connective tissue disease [CTD] vs PAH not associated with CTD. All tests were conducted at the 0.05 level of significance.

Primary endpoint—The change from Baseline to Week 24 in PVR was analyzed using the modified intended to treat population after missing Week 24 values were imputed using multiple imputation. To correct for departures from normality, the data were log-transformed before analysis (and hence the endpoint was the ratio change from baseline). An analysis of covariance (ANCOVA) was used with treatment, the stratification factors, and baseline PVR in the model. The adjusted placebo-adjusted treatment effect with its 95% confidence interval and p-value will be presented.

Secondary endpoints—Change in exercise capacity as determined by the 6MWD—because of departure from normality, analyzed nonparametrically using rank-based ANCOVA. Change in Borg dyspnea score is analyzed using ANCOVA with treatment, the stratification factors, baseline Borg dyspnea score, and baseline PVR in the model. Change in WHO/NYHA Functional Classification—analyzed using logistic regression with treatment, the stratification factors, baseline WHO/NYHA-FC, and baseline PVR in the model. Time to clinical worsening—analyzed by Cox regression. Patients not experiencing clinical worsening were censored on their last day of treatment. The model included treatment, the stratification factors, and baseline PVR. Results for each of the 3 subscales of the CAMPHOR questionnaire were analyzed using ANCOVA with treatment, the stratification factors, the respective scale baseline, and baseline PVR in

the model. Change in disease biomarkers BNP/NT-proBNP is analyzed using ANCOVA with treatment, the stratification factors, baseline BNP/NT-proBNP, and baseline PVR in the model.

Safety Analyses

AEs, deaths, concomitant medications, vital signs, electrocardiogram data, and laboratory data will be listed for each patient and summarized by treatment group. Adverse events were coded using MedDRA version 18.1.