Title: **A PHASE 2, OPEN-LABEL, EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF UBENIMEX IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION (WHO GROUP 1)**

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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 was a Phase 2, open-label, multicenter, extension study to evaluate long-term safety and efficacy of ubenimex (150 mg three times a day) in patients with PAH who completed Study EIG-UBX-001 (a Phase 2, randomized, double-blind, placebo-controlled clinical trial) and met the eligibility criteria for Study EIG-UBX-002.

Patients may have qualified to enter this extension study if they completed study drug treatment and study procedures through Week 24 in Study EIG-UBX-001 and met the entry criteria for Study EIG UBX 002. Data gathered at the Week 24 (End-of-Treatment) Visit formed the baseline data for EIG-UBX-002. Treatment in EIG-UBX-002 continued until the last patient enrolled received at least 24 weeks of open-label treatment with ubenimex and the Sponsor decided to end the study. Clinical assessments were performed on Week 0E, where “E” denotes the extension study EIG-UBX-002 (Week 24 of Study EIG-UBX-001) and on Weeks 4E, 8E, 12E, and 24E, and every 12 weeks thereafter until the end of study. The total duration of treatment for each patient varied depending on when the patient enrolled and the recruitment rate in Study EIG-UBX-001. At the end of the Treatment Period in EIG-UBX-002, patients returned 4 weeks after their last dose of ubenimex for a final Follow-up Visit.

Safety (adverse events [AEs], clinical laboratory tests) was continually monitored throughout the study. An independent data safety monitoring board, consisting of two expert PAH clinicians and a biostatistician, conducted regular safety reviews. Efficacy measures included pulmonary vascular resistance (PVR) and 6 minute walk distance. The steady-state pharmacokinetics of ubenimex and metabolite was to be characterized.

Inclusion Criteria

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

- Patients must have completed Study EIG-UBX-001 through Week 24.
- In the opinion of the Principal Investigator, has been generally compliant with study requirements during Study EIG-UBX-001.
- Agrees to use a medically acceptable method of contraception throughout the entire study period.
- Willing and able to comply with scheduled visits, treatment plans, and laboratory tests and other study procedures.

Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study:

- Is pregnant or lactating.
- Concurrent regular use of another leukotriene pathway inhibitor.
- Any reason that, in the opinion of the investigator, precludes the patient from participating in the study.
    a. Any condition that is unstable or that could jeopardize the safety of the patient and his/her compliance in the study
    b. A serious uncontrolled medical disorder/condition that in the opinion of the investigator would impair the ability of the patient to receive protocol therapy
- An ongoing, drug-related, serious adverse event (SAE).
- Significant/chronic renal insufficiency.
- Transaminases (alanine transaminase, aspartate transaminase) levels >3 × upper limit of normal (ULN) and/or bilirubin level >2 × ULN.
- Absolute neutrophil count <1500 mm3.
- Hemoglobin concentration <9 g/dL at Screening.

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

Treatment Period: minimum of 24 weeks for all patients. Follow-up Period: 4 weeks. The maximum time an individual patient participated varied because treatment continued until the last patient enrolled had received at least 24 weeks of open-label treatment.

Criteria for Evaluation

All endpoints were changes from start of treatment in EIG-UBX-002 to the end of treatment in EIG-UBX-002.

Due to the early termination of the study, only safety information was assessed, and treatment-emergent adverse events and SAEs and deaths were evaluated of the relatedness of the drug treatment.

Statistical Methods

Following the failure to demonstrate efficacy in EIG-UBX-001, the sponsor terminated Study EIG-UBX-002. Only safety data were assessed.

Safety Set (SS) are patients who received at least one dose of study drug in study.

Data collected at Week 24 of Study EIG-UBX-001 were used as baseline values for Study EIG-UBX-002. An event that had onset in Study EIG-UBX-001 was not considered an event in Study EIG-UBX-002 unless it worsened in Study EIG-UBX-002, in which case it became a separate event. Adverse events were coded using MedDRA version 18.1.