An Open-label, Clinical Study to Evaluate the Safety and Tolerance of Treprostinil Inhalation Powder (TreT) in Patients with Pulmonary Arterial Hypertension (BREEZE Study)

INTRODUCTION

United Therapeutics is developing a combination drug-device product consisting of a dry powder formulation of treprostinil (TreT) and a small, portable, dry powder inhaler to treat pulmonary arterial hypertension (PAH). Treprostinil inhalation powder (Tyvaso®), a dry powder inhalation excipient fumaryl diketopiperazine (FDKP), which is an inactive excitant present in Afrezza, an FDA-approved drug product. Treprostinil is a chemically stable tricyclic analogue of PGI2. The pharmacology of treprostinil has been extensively characterized in well-established models, all confirming the suitability of the drug for the treatment of PAH by lowering pulmonary vascular resistance, is a severe hemodynamic abnormality associated with a variety of diseases and disorders.1

- This combination product, TreT, is a change in dosage form for treprostinil from FDA-approved solution for oral inhalation (Tyvaso®), to a dry powder for oral inhalation.2
- In addition to treprostinil, the dry powder contains the inhalation exipient fumaryl diketopiperazine (FDKP), which is an inactive excitant present in Afrezza, an FDA-approved drug product.
- Treprostinil is a chemically stable tricyclic analogue of PGI2. The pharmacology of treprostinil has been extensively characterized in well-established models, all confirming the suitability of the drug for the treatment of PAH by lowering pulmonary vascular resistance, is a severe hemodynamic abnormality associated with a variety of diseases and disorders.1

Clinical Experience with TreT

- An open-label, single ascending dose (SAD) study in healthy normal volunteers (HNVs), MKC-475-001, was conducted to assess the safety and tolerability of TreT.
- A total of 36 HNVs were sequentially assigned to 6 cohorts (6 subjects per cohort) receiving single doses of TreT (30, 60, 120, 150, 180, and 240 mcg).
- The incidence and severity of AEs were assessed and analyzed plasma concentrations of treprostinil.
- Bioanalytical data confirmed that the treprostinil plasma concentrations and exposure for TreT achieved clinically relevant concentrations comparable to those observed in historical ‘Tyvaso®’ single dose clinical studies.
- Treprostinil exposure with TreT increased in a linear manner with increasing dose.

OBJECTIVES

- The primary objective is to evaluate the safety and tolerability of TreT in patients with PAH currently treated with Tyvaso®.
- Secondary Objectives:
  - To evaluate systemic exposure and PK of treprostinil in subjects with PAH when delivered as Tyvaso® and TreT
  - To evaluate 6-Minute Walk Distance (6MWD) at study entry and after 3 weeks of treatment with TreT
  - To evaluate long-term safety and tolerability of TreT in subjects with PAH previously treated with Tyvaso®
  - To evaluate subject satisfaction with and preference for TreT

METHODS

Study Design

- BREEZE (NCT03950739) is a safety and tolerability study in patients with PAH currently treated with Tyvaso®. Subjects with PAH when delivered as Tyvaso® and TreT will undergo PK and safety assessments performed at the Baseline Visit. Subjects will be assigned a corresponding dose of TreT and treated for 3 weeks.

- Patients who complete 3-weeks of treatment with TreT may elect to participate in an Optional Extension Phase (OEP).

Study Entry

- Treatment Phase
  - Tyvaso® dose: 6 to 12 breaths 48 µg 48 µg cartridge
  - TreT dose: 8 to 10 breaths 48 µg 48 µg cartridge
  - Cartridge Strength: 32 µg 32 µg cartridge

Table 1. Dose Assignments

- The 6MWT results will also be summarized using descriptive statistics.
- The number and percent of subjects with AEs for each Treatment Phase will be summarized with descriptive statistics. The AMVT results will also be summarized using descriptive statistics.

- The most frequently reported AEs overall were cough (31%) and headache (22%). There were no severe AEs, serious AE (SAE), or deaths during this study. No clinically significant abnormalities on ophthalmologic examinations, clinical laboratory evaluations, electrocardiograms (ECG), or PFTs (spirometry) were observed.
- Overall, TreT was safe and well-tolerated and produced clinically relevant concentrations of treprostinil when inhaled as a dry powder.

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METHODS (cont’d)

- TreT treatments are assigned based on current stable Tyvaso® dose. Each subject will receive a corresponding dose of TreT for 3 weeks during the Treatment Phase.
- TreT will be administered via a dry powder inhaler in 3 dose levels supplied as cartridges filled to provide 32 µg, 48 µg, and 64 µg of treprostinil.
- Of note: Additional single-dose cartridge strengths (higher and lower strengths) are in development for commercial availability.

- Tyvaso® dose: 6 to 12 breaths 48 µg 48 µg cartridge
- TreT dose: 8 to 10 breaths 48 µg 48 µg cartridge
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SUMMARY

- This study hypothesizes that TreT will achieve similar systemic exposure and tolerability in patients with PAH as Tyvaso®, but delivered in a small, portable dry powder inhaler.
- Enrollment in the BREEZE study is currently ongoing.

REFERENCES


Figure 1. Mean Plasma Treprostinil Concentration-time Profiles after Single-dose Administration of 30 mcg to 180 mcg TreT

Figure 2. TreT Dry Powder Inhaler

Figure 3. Study Flow Chart

Table 1. Dose Assignments

Study Entry

Treatement Phase

Tyvaso® Dose (QID)

6 to 7 breaths
32 µg
32 µg cartridge

8 to 10 breaths
48 µg
48 µg cartridge

11 to 12 breaths
64 µg
2 x 32 µg cartridges

Tyvaso® Dose (QID)

TreT Dose (QID)

Cartridge Strength

32 µg
32 µg cartridge

48 µg
48 µg cartridge

64 µg
2 x 32 µg cartridges

Study Periods

Screening Baseline Week 3 Follow-up Clinic Visits

Day(s)

1-14 Days
3 Weeks

Tyvaso® dose
Serial PK sampling, and
First dose of TreT

Tyvaso® dose and
Serial PK sampling

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