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

Peter M. Smith, PharmD[1]; Catherine B Watkins, PharmD[1]; Jason Scoggin, MA[1]; C.Q. Deng, PhD[1]

[1]United Therapeutics, Research Triangle Park, NC, USA

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).
- PAH, defined as an elevation in pulmonary arterial pressure and pulmonary vascular resistance, is a severe hemodynamic abnormality associated with a variety of diseases and syndromes.[1]
- This combination product, TreT, is a change in dosage form for treprostinil from an 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 excipient fumaryl diketopiperazine (FDKP), which is an inactive excipient present in Afrezza, an FDA-approved drug product.
- Treprostinil is a chemically stable tricyclic analogue of PGI_2. 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 subcutaneous, IV, inhaled (as treprostinil sodium), or oral (as treprostinil diolamine) routes of administration.

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, 90, 120, 150, and 180 µg).
- The incidence and severity of AEs were assessed and pharmacokinetic (PK) parameters were measured by analyzing plasma concentrations of treprostinil.
- Bioanalysis 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.

INTRODUCTION (cont'd)

- The most frequently reported AEs overall were cough (31%) and headache (22%). There were no severe AEs, serious AE (SAEs), or deaths during this study. No clinically significant abnormalities on oropharyngeal examinations, clinical laboratory evaluations, electrocardiograms (ECGs), 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.

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

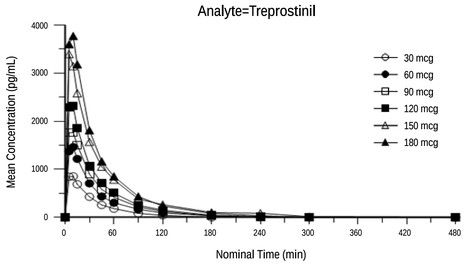
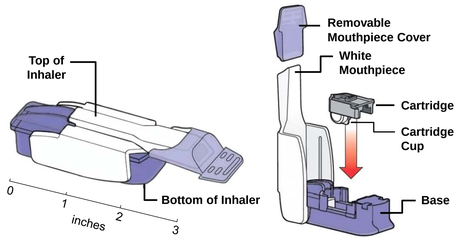


Figure 2. TreT Dry Powder Inhaler



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 which 45 patients on a stable regimen of Tyvaso® will switch to an equivalent dose of TreT.
- At Baseline, patients currently taking stable doses of Tyvaso® (6 to 12 breaths 4 times daily) will undergo PK and safety assessments and complete a 6-Minute Walk Test (6MWT).
- Following these in-clinic assessments and device training, patients will be assigned a corresponding dose of TreT and treated for 3 weeks.
- Patients will return to the clinic and undergo the same assessments performed at the Baseline Visit.
- Patients who complete 3-weeks of treatment with TreT may elect to participate in an Optional Extension Phase (OEP).
- Patient satisfaction and preference for inhaled treprostinil devices will be evaluated with the Preference Questionnaire for Inhaled Treprostinil Devices (PQ-ITD) and patient-reported PAH symptoms and impact will be evaluated with the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) Questionnaire.

METHODS (cont'd)

Figure 3. Study Flow Chart

Study Periods	SCREENING PHASE	TREATMENT PHASE			OPTIONAL EXTENSION PHASE		
	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		• TreT dose and • Serial PK sampling			

Analysis

- PK parameters of treprostinil (Cmax, time of maximal plasma concentration, t½, and AUC from time 0 to 300 minutes) will be obtained from the resulting plasma drug concentration-time data.
- The number and percent of subjects with AEs for each Treatment Phase will be summarized with descriptive statistics. The 6MWT results will also be summarized using descriptive statistics.

- 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.

Table 1. Dose Assignments

Study Entry	Treatment Phase	
Tyvaso® Dose (QID)	TreT Dose (QID)	Cartridge Strength
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

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

1. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* 2013;62(25 Suppl):D34-D41.
2. Tyvaso® Package Insert. Research Triangle Park, NC: United Therapeutics Corporation; 2017.

Presented at PHA's 2019 PH Professional Network (PHPN) Symposium | September 5-7, 2019 | Washington, DC | #1027
Disclosure: This study was sponsored by United Therapeutics Corporation.

United Therapeutics CORPORATION