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APPLICATION NUMBER:

214324Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA or BLA Number	214324
Link to EDR	\\Cdsesub1\evsprod\NDA214324
Submission Date	04/16/2021
Submission Type	Priority review
Brand Name	Tyvaso DPI®
Generic Name	Treprostinil Inhalation Powder (TreT)
Dosage Form and Strength	Inhalation powder: Single-dose cartridges containing 16 µg, 32 µg, 48 µg, or 64 µg of treprostinil as a dry powder formulation for oral inhalation.
Route of Administration	Inhalation
Proposed Indication	Pulmonary arterial hypertension to improve exercise ability. Pulmonary hypertension associated with interstitial lung disease to improve exercise ability.
Applicant	United Therapeutics Corporation
Associated IND	IND134582
OCP Review Team	Xiaomeng Xu, Manoj Khurana

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1. Executive Summary

The Applicant, United Therapeutics Corporation, has submitted this 505(b)(1) NDA 214324 seeking approval for TreT (Tyvaso DPI®), a treprostinil inhalation powder, intended to treat pulmonary arterial hypertension (PAH) and pulmonary hypertension associated with interstitial lung disease to improve exercise ability. It is a new dosage form for treprostinil being a dry powder for oral inhalation (Tyvaso DPI®) compared to the solution for oral inhalation (Tyvaso®; NDA 022387, US Approval 2002) currently marketed by the same sponsor.

The NDA package for Tyvaso DPI® was received by the Agency on April 16, 2021 under a priority review with the PDUFA date of October 16, 2021.

The applicant submitted three clinical studies, including a single dose-escalation Study MKC-475-001 in healthy subjects, an open-label Study TIP-PH-101 assessing safety and tolerability of TreT in subjects with PAH currently using Tyvaso, as well as a relative bioavailability and bioequivalence (BA/BE) study TIP-PH-102 between TreT and Tyvaso in healthy subjects.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed NDA 214324 submitted on 4/16/2021 and finds it acceptable to support approval.

1.2 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

The clinical pharmacological findings of this application rely on the results from the relative BA/BE study TIP-PH-102 and supported by the open-label study TIP-PH-101. Study MKC-475-001 dose not contribute to the systemic exposure comparison of TreT and Tyvaso, however, was reviewed only for supportive information for the dose proportionality assessment.

- TIP-PH-102: a 6-period crossover study comparing systemic exposure of 3 doses (16, 48, 64 µg) of TreT and 3 doses (18, 54, 72 µg) of Tyvaso in healthy volunteers. The TreT product doses of 16, 48, and 64 µg were claimed to provide similar systemic exposure to Tyvaso 18, 54, and 72 µg, selected to accommodate the design and delivery differences between the two inhalation products.

- TIP-PH-101: an open-label study to evaluate the safety and tolerability of TreT in subjects with PAH currently using Tyvaso. TreT was administered for three consecutive weeks, where the safety, clinical effect, as well as the exposure of TreT at the end of week 3 were evaluated.

The key results from the relative BA/BE study TIP-PH-102 are as followings:

- C_{max} of TreT were consistently higher (24% to 39%) than Tyvaso (geometric mean ratios of TreT / Tyvaso and 90% CI were not within 80 - 125% bounds) across three tested does (low-, mid-, and high-dose levels of 16 µg TreT vs 18 µg Tyvaso, 48 µg TreT vs 54 µg Tyvaso, and 64 µg TreT vs 72 µg Tyvaso, respectively).

- $AUC_{0\text{-}5hr}$ of TreT and Tyvaso was comparable at mid- and high- dose levels. Whereas the $AUC_{0\text{-}5hr}$ ratio for low-dose level (i.e., 16 µg TreT versus 18 µg Tyvaso) was 15% higher.

- The safety data (though limited) from the single and multiple dose studies did not indicate any notable respiratory adverse events (AEs) difference between TreT and Tyvaso.

Given that clinical use of TreT involves titration to therapeutic goal and the observations on respiratory AEs, which were comparable between TreT and Tyvaso across all doses, the higher C_{max} level of TreT in the context of comparable overall AUC (except the modest deviation at the lowest tested dose) do not appear to be clinically relevant.

2. QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of Tyvaso DPI®, treprostinil inhalation powder (TreT)?

The Applicant, United Therapeutics Corporation, submitted this 505(b)(1) application for Tyvaso DPI®, intended for the treatment of PAH and pulmonary hypertension associated with interstitial lung disease to improve exercise ability. The proposed dose regimen: to initiate Tyvaso DPI® from 16 µg per treatment, 4 separate treatment sessions each day, and to increase by additional 16 µg per treatment session at approximately 1- to 2- week intervals, if tolerated.

The main objective of this 505(b)(1) NDA review is to provide evaluations of Study TIP-PH-102, which aimed to compare the systemic exposure of TreT and Tyvaso, as well as study TIP-PH-101, where the efficacy, safety, and tolerability of TreT were assessed. Tyvaso® was originally approved in 2002 under NDA 022387, intended for the treatment of PAH to improve exercise ability, as well as pulmonary hypertension associated interstitial lung disease to improve exercise ability. United Therapeutics Corporation is seeking approval of Tyvaso DPI® for the same indication as Tyvaso®.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What general clinical pharmacology features of treprostinil are relevant to the current submission?

Three studies containing clinical pharmacology information were submitted in the current submission, including a single dose-escalation study MKC-475-001, an open-label study TIP-PH-101, and a relative BA/BE study TIP-PH-102. Food effect study, drug-drug interaction study, as well as special population study were not conducted in the current submission. For details on the general clinical pharmacology of treprostinil, readers are referred to the original NDA 022387 review for Tyvaso®.

2.2.2 Is the systemic exposure of Tyvaso DPI ® (treprostinil inhalation powder, TreT) comparable to that of Tyvaso® (treprostinil inhalation solution, Tyvaso) according to the data from the relative BA/BE study TIP-PH-102?

The data from the relative BA/BE study TIP-PH-102 showed that a higher C_{max} of TreT was observed from all the tested dose levels, where geometric mean ratios of TreT / Tyvaso and 90% CI were not within 80 - 125% bounds (Table 1). Though the $AUC_{0\text{-}5hr}$ of TreT and Tyvaso at mid- and high-dose levels were comparable, the $AUC_{0\text{-}5hr}$ for low-dose level was about 15% higher.

The relative BA/BE study TIP-PH-102 was a 6-period crossover study comparing systemic exposure of 3 doses (16, 48, 64 µg) of TreT and 3 doses (18, 54, 72 µg) of Tyvaso in healthy volunteers. Such dose levels were chosen based on the PK results from study TIP-PH-101, where three dose ranges of Tyvaso were tested, including 36-42 µg (6-7 breaths) Tyvaso vs 32 µg TreT, 54-60 µg (8-10 breaths) Tyvaso vs 48 µg TreT, and 66-72 µg (11-12 breaths) Tyvaso vs 64 µg TreT. Total of 36 healthy male and female subjects aged from 21 to 55 were included. The primary objective was to evaluate the systemic exposure and pharmacokinetics (PK) of treprostinil administered as treprostinil inhalation powder (TreT) and treprostinil inhalation solution (Tyvaso). Subject received a single dose of the study drug per treatment period followed by a washout period of either 24 or 48 hrs (approximately) prior to the next dose. PK samples were collected up to 5 hrs post-dose.

All 36 subjects were included in the PK population. The applicant conducted noncompartmental analysis and reported the corresponding PK parameters including $AUC_{0\text{-}5hr}$, $AUC_{0\text{-}inf}$, C_{max} T_{max}, and $t_{1/2}$ for each tested dose level of TreT and Tyvaso. Bioequivalence procedures were used to compare the exposure of TreT and Tyvaso for each tested dose level by using $AUC_{0\text{-}5hr}$ and C_{max} as the primary PK parameters.

The applicant reported that for $AUC_{0\text{-}5hr}$, the geometric least squares mean (GLSM) ratios for the low-, mid-, and high-dose comparisons were 115% (90% CI: 104.59, 127.42), 101% (90% CI: 91.63, 111.65), and 91.5% (90% CI: 83.16, 100.78), respectively. C_{max} values of treprostinil for TreT were higher than Tyvaso across matched-dose comparisons. The GLSM ratios of C_{max} for the low-, mid-, and high-dose comparisons were 130% (90% CI: 115.55, 145.95), 139% (90% CI: 124.13, 156.73), and 124% (90% CI: 110.56, 139.61), respectively.

The study conduct per the review of study report (clinical and bioanalytical) was reasonable to reliably support the study findings. The study findings for treprostinil were reanalyzed and confirmed by the clinical pharmacology reviewer using SAS® (version 9.4), where $AUC_{0\text{-}inf}$ was also included for comparison (Table 1).

Table 1. Summary of the Systemic Exposure Comparison of Treprostinil from TreT and Tyvaso from Study TIP-PH-102 (Geometric Least Squares Mean Ratio of TreT vs Tyvaso and 90% Confidence Intervals) (n=36)

Dose Level	Parameter	%Ratio TreT/Tyvaso	CI90 Lower	CI90 Upper
TreT 16 µg vs Tyvaso 18 µg	$AUC_{0\text{-}5hr}$	115.44	104.59	127.42
TreT 48 µg vs Tyvaso 54 µg	$AUC_{0\text{-}5hr}$	101.14	91.63	111.65
TreT 64 µg vs Tyvaso 72 µg	$AUC_{0\text{-}5hr}$	91.55	83.16	100.78
TreT 16 µg vs Tyvaso 18 µg	$AUC_{0\text{-}inf}$	117.19	105.38	130.32
TreT 48 µg vs Tyvaso 54 µg	$AUC_{0\text{-}inf}$	103.91	93.45	115.54
TreT 64 µg vs Tyvaso 72 µg	$AUC_{0\text{-}inf}$	94.19	84.71	104.73
TreT 16 µg vs Tyvaso 18 µg	C_{max}	129.87	115.55	145.95
TreT 48 µg vs Tyvaso 54 µg	C_{max}	139.48	124.13	156.73
TreT 64 µg vs Tyvaso 72 µg	C_{max}	124.24	110.56	139.61

The C_{max} of TreT is higher than Tyvaso across the studied dose levels (Figures 1 and 2). The peak concentrations of treprostinil for TreT and Tyvaso were attained with a median T_{max} of 0.17 – 0.25 hr (ranged from 0.08 to 0.52 hr). The $AUC_{0\text{-}inf}$ of TreT and Tyvaso were comparable at mid- and high- dose levels, whereas the $AUC_{0\text{-}inf}$ ratio for the low-dose level was 17% higher.

Figure 1. Plasma Treprostinil Concentration – Time Profiles (Mean and Standard Error) of TreT (Solid Blue Line) and Tyvaso (Dashed Red Line)

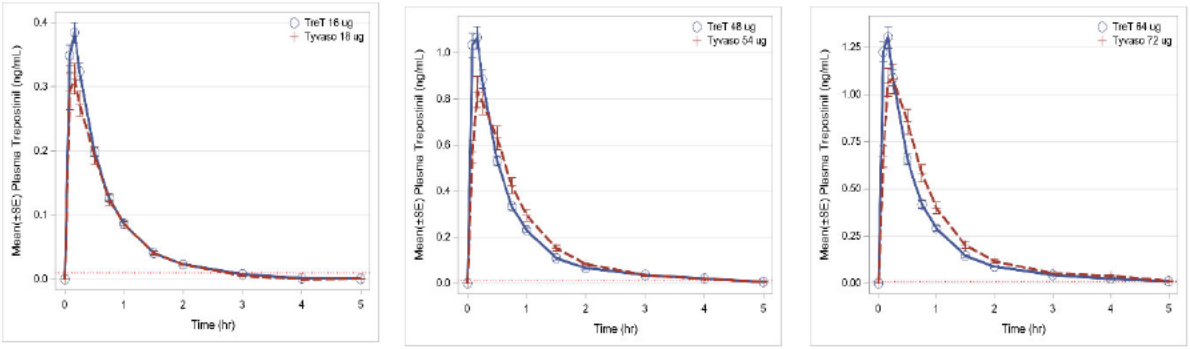
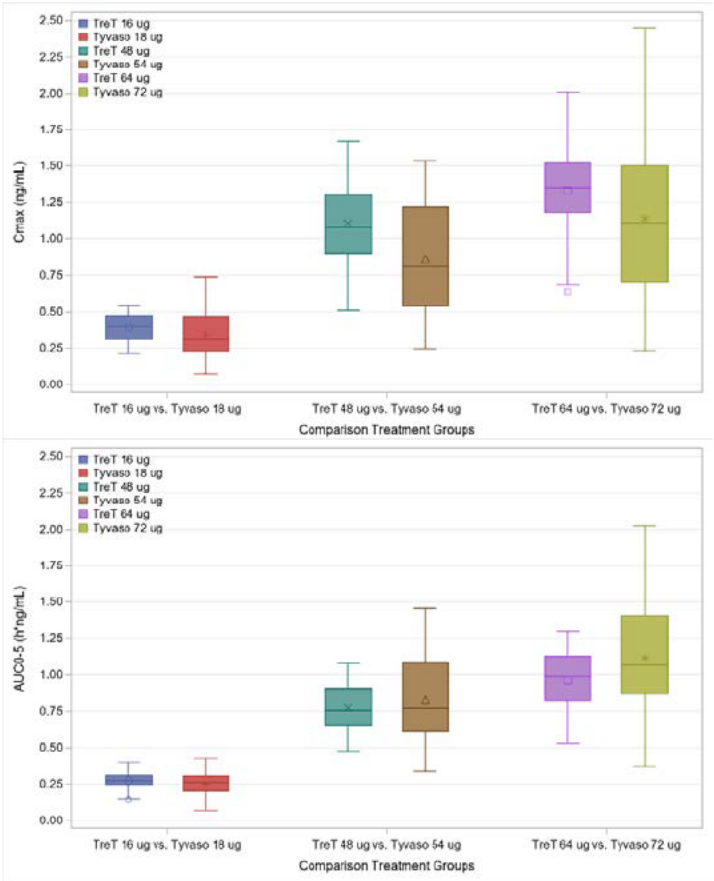


Figure 2. Box-Plot for the PK Parameters (C_{max} and $AUC_{0\text{-}5hr}$) Comparison of TreT and Tyvaso by Dose Levels (16 µg TreT vs 18 µg Tyvaso, 48 µg TreT vs 54 Tyvaso µg, 64 µg TreT vs 72 µg Tyvaso)



In conclusion, data from the relative BA/BE Study TIP-PH-102 indicated a higher C_{max} of treprostinil from TreT than Tyvaso, and a comparable overall AUC (except the modest deviation at the low-dose level).

The conclusions from Study TIP-PH-102 were generally consistent with the data collected from the open label study TIP-PH-101, in which PAH patients who were on stable Tyvaso administration transferred to TreT for three consecutive weeks. PK assessment were conducted at baseline with a dose of Tyvaso administration and at the end of week 3 with a dose of TreT administration. Three dose levels were tested in Study TIP-PH-101, including 32 µg TreT vs 36-42 µg (6-7 breaths) Tyvaso, 48 µg TreT vs 54-60 µg (8-10 breaths) Tyvaso, and 64 µg TreT vs 66-72 µg (11-12 breaths) Tyvaso.

C_{max} was found to be consistently higher following TreT dosing than Tyvaso across the studied dose levels. Geometric mean C_{max} was 38% and 36% higher, respectively, following 48 µg and 64 µg TreT dosing, compared to 54-60 µg (8-10 breaths) and 66-72 µg (11-12 breaths) Tyvaso, respectively (Table 2). Since there were only 2 subjects enrolled into the 32 µg TreT group, exposure comparison of treprostinil could not be made for this dose level.

Table 2. Summary of the Systemic Exposure Comparison of Treprostinil from TreT and Tyvaso from Study TIP-PH-101 (Geometric Least Squares Mean Ratio of TreT vs Tyvaso) (n=51)

Dose Level	Parameter	%Ratio TreT/Tyvaso
TreT 32 µg vs Tyvaso 36 - 42 µg	C_{max}	NA
TreT 48 µg vs Tyvaso 54 - 60 µg	C_{max}	138.32
TreT 64 µg vs Tyvaso 66 - 72 µg	C_{max}	136.05
TreT 32 µg vs Tyvaso 36 - 42 µg	AUC_{0-5hr}	NA
TreT 48 µg vs Tyvaso 54 - 60 µg	AUC_{0-5hr}	104.44
TreT 64 µg vs Tyvaso 66 - 72 µg	AUC_{0-5hr}	128.08

Geometric mean value of AUC_{0-5hr} was 4% higher following 48 µg TreT dosing, compared to 54-60 µg (8-10 breaths) Tyvaso, which is consistent with the findings in Study TIP-PH-102. For the 64 µg TreT treatment group, geometric mean AUC_{0-5hr} was found to be 28% higher than 66-72 µg (11-12 breaths) Tyvaso dosing. However, in Study TIP-PH-102, the AUC_{0-5hr} of treprostinil from 64 µg TreT was 8% lower than 72 µg Tyvaso. This could be due to the difference of the study designs. In study TIP-PH-102, 64 µg TreT was compared with 72 µg Tyvaso, where in Study TIP-PH-101 a dose range of 66 to 72 µg Tyvaso were used.

Dose proportionality:

The applicant assessed the dose-proportionality of TreT single doses of 30 mcg to 180 mcg in Study MCK-574-001, and single doses of 16 mcg, 48 mcg, and 64 mcg in Study TIP-PH-102. A power model was used: $\ln(PK) = \ln(\beta_0) + \beta_1 * \ln(Dose) + \varepsilon$, where $\beta 1$ represents slope and a value of $\beta 1 \approx 1$ indicates dose proportional relationship. Treprostinil was found to be slightly less than proportional increase in both studies (Table 3). These findings for treprostinil were reanalyzed and confirmed by the clinical pharmacology reviewer.

Table 3. Dose Proportionality Assessment of Treprostinil in TreT

Study Number	Dependent Variable	Estimate (β1)	CI 90 Lower	CI 90 Upper
MCK-475-001	ln(Cmax)	0.822	0.698	0.946
	ln($AUC_{0\text{-}8hr}$)	0.865	0.764	0.965
TIP-PH-102	ln(Cmax)	0.900	0.824	0.976
	ln($AUC_{0\text{-}5hr}$)	0.917	0.853	0.982

In addition, the applicant also reported a smaller inter-subject variability of treprostinil exposure from TreT than Tyvaso treatment arms, characterized by geometric coefficient of variance (CV%) of C_{max} and $AUC_{0\text{-}5hr}$. For C_{max}, the inter-subject variability for the TreT arm was ranging from 26.6% to 28.9% compared to the Tyvaso arm ranging from 53.4% to 59.8%. The same trend was found for the inter-subject variability of $AUC_{0\text{-}5hr}$, where the inter-subject variability for the TreT arm $AUC_{0\text{-}5hr}$ was found to be ranging from 21.8% to 24.1%, compared to the Tyvaso arm ranging from 41.9% to 44.1%. This could be due to the difference of the administration devices. TreT is administrated using a single dose cartridge, whereas Tyvaso is administrated using a nebulizer. Regardless, the data indicates relatively more predictable PK behavior for TreT in comparison to Tyvaso.

2.2.3 Are the PK differences noted with TreT compared to Tyvaso clinically relevant?

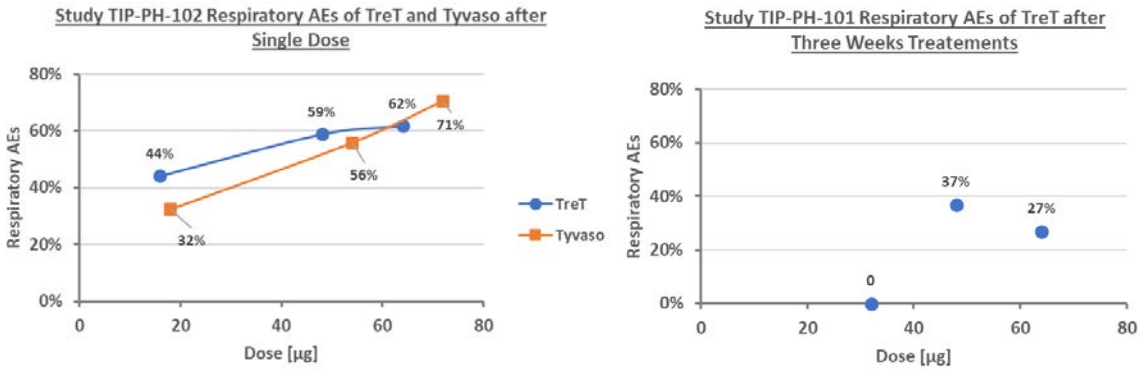
The higher C_{max} level of TreT in the context of comparable overall AUC (except the modest deviation at the lowest tested dose) do not appear to be clinically relevant, given that clinical use of TreT involves titration to therapeutic goal and the observations on clinical effect. Adverse events of interest (respiratory AEs) further support this notion, where no notable respiratory AEs difference were observed between TreT and Tyvaso from Study TIP-PH-102 and TIP-PH-101. Detailed assessment of the respiratory AEs is discussed below.

According to the prescribing information, Tyvaso is recommended to be initiated from 3 breaths (18 µg) per treatment session, and to be increased an additional 3 breaths per treatment session at approximately 1- to 2-week intervals, if tolerated. The target maintenance doses are 9 to 12 breaths (54 to 72 µg) per treatment session, 4 times daily. Similarly, TreT was proposed to be initiated from 16 µg per treatment, 4 separate treatment sessions each day, and to be increased by additional 16 µg per treatment session at approximately 1- to 2- week intervals, if tolerated. Such titration allows patients adjust to proper maintenance dose levels from both clinical efficacy and safety aspects.

The observed respiratory AEs (respiratory, thoracic, and mediastinal disorders) from Study TIP-PH-102 when compared between TreT and Tyvaso, the incidences were comparable between the two treatments at each dose level after single dose administration (Figure 3). Data on respiratory AEs of TreT after three weeks multiple dose treatment from the switching Study TIP-PH-101 was also evaluated (Figure 3). For both studies, no obvious dose-dependent increase of respiratory AEs was observed at the mid- and high-dose levels (Figure 3). In Study TIP-PH-102, there was an approximately 15% increase of respiratory AEs from the low-dose level to mid-dose level. In Study TIP-PH-101, though no respiratory AEs were observed at the dose level of 32 µg TreT, the

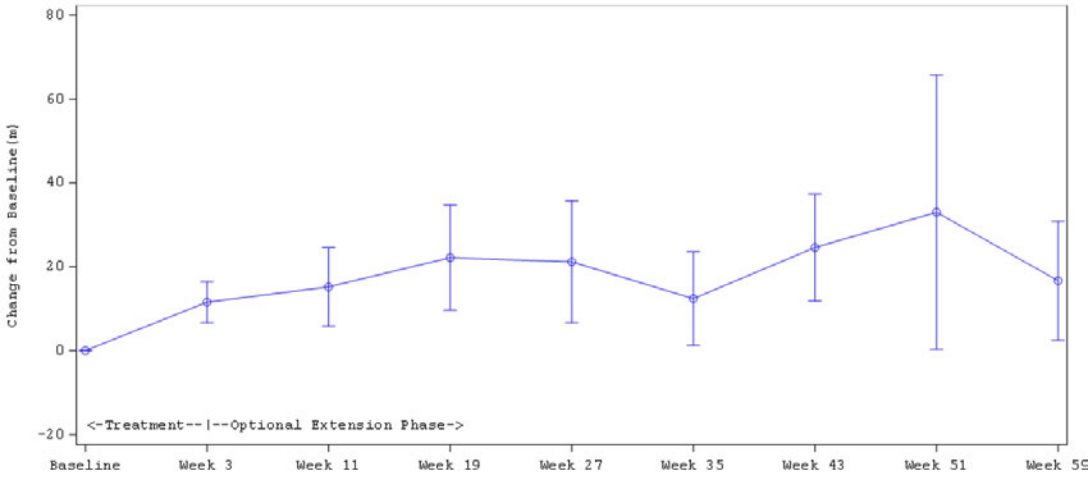
limited sample size (N=2) was not enough to support a statistic conclusion. Regardless, the overall respiratory safety profiles were comparable between TreT and Tyvaso treatments from Study TIP-PH-102 and TIP-PH-101.

Figure 3. Respiratory AEs (Respiratory, Thoracic, and Mediastinal Disorders) of TreT and Tyvaso from Study TIP-PH-102 and TIP-PH-101



Compared to the baseline treatment with Tyvaso, there was a numeric increase from baseline of 6-minute walk distance (6MWD) mean values at the end of week 3 treatment with TreT and during the optional extension phase with TreT (Figure 4). However, in absence of a parallel Tyvaso control group, after accounting for the large variability of 6MWD values, and small number of tested subjects (N=51), the numeric improvement of 6MWD does not support any conclusion of a clinically significant therapeutic effect difference between TreT and Tyvaso.

Figure 4. Mean Change of 6-Minute Walk Distance (6MWD) from Baseline



In summary, in the context of the higher C_{max} of TreT in reference to Tyvaso, the safety data did not show any notable trend in the respiratory AEs. For overall adquacy of the submitted safety databases, as well as the detailed safety assessements, please also refer to the clincial review of this submission.

2.3 ANALYTICAL SECTION

1. Summary of overall performance:

A solid phase extraction followed by HPLC-MS/MS method was used to determine the concentrations of treprostinil in human plasma. Treprostinil-d_4 (Mass 393.2, 335.1) was used as internal standard (IS) for treprostinil (Mass 389.2, 331.3). The analytical method was fully validated, where the validation results met the criteria based on the FDA guidance of bioanalytical method validation (Table 4).

Table 4. Analytical Method Validation Results and Assessment

Parameters	Results	Validation Assessment
Calibration Curve	LLOQ-ULOQ 0.0100 – 5.00 ng/mL (%Bias = -1.6 to 2.2).	8 non-zero calibrators, % Bias±15%
Quality Controls (QCs)	0.0100 ng/mL (%RSD = 17.7, %Bias = 8.0), 0.0300 ng/mL (%RSD = 14.0, %Bias = -3.0), 0.130 ng/mL (%RSD = 1.5, %Bias = 8.5), 0.600 ng/mL (%RSD = 1.2, %Bias = -5.5), 3.75 ng/mL (%RSD = 2.2, %Bias = -6.4%).	%RSD ± 15%, % Bias ±15%, and LLOQ %RSD ± 20%, % Bias ±20%
Selectivity	Six individual normal matrix lots plus one lipemic lot (≥ 300 mg/dL of triglycerides) and one hemolytic blank (2% hemolysis) were analyzed for their potential interferences with the analyte and the internal standard. No significant interference was detected for the analyte and its internal standard.	Blank and zero calibrators is free of interference, spiked samples ± 20% LLOQ, IS response in the blank ≤5% of average IS responses of calibrators and QCs
Sensitivity	LLOQ 0.0100 ng/mL, %RSD = 17.7, %Bias = 8.0%.	%RSD ± 20%, % Bias±20%
Carryover	Two blank matrix samples were analyzed immediately following the highest calibration standard. No evidence of carryover.	≤ 20% LLOQ
Stability	Auto-sampler, bench-top, freeze-thaw, stock solution and long-term stability, performed three replicates at L and HQC concentrations.	%RSD ± 15%, % Bias±15%

2. Method performance information for treprostinil during the analysis of clinical study samples from Study TIP-PH-102 is included below:

   - Calibration standard curve performance in the study was assessed. The precision and mean accuracy values (% Nom.) ranged from 3.5 to 8.0 and from 98.0 to 103.0, respectively.

   - The precision, accuracy, and nominal concentration of low, lower middle, middle, and high QC samples during the study were 7.3% and 98.0% (LQC: 0.0300 ng/mL), 6.9% and 102.3% (LMQC: 0.130 ng/mL), 4.5% and 96.3% (MQC: 0.600 ng/mL), and 5.1% and 97.9% (HQC: 3.75 ng/mL), respectively.

- A total of 2445 samples were analyzed for treprositinil. 2412 samples met the acceptance criteria (98.7%). There were 173 samples reanalyzed to test the reproducibility of the method. It was observed that 98.3% of the ISR results had a relative % difference within ±20%, which is within the acceptance criteria.

- The study sample storage period from first sample collection until the completion of analysis was 250 days at -10 to -30°C. Stability of QC samples after storage in a freezer set to maintain -10 to -30°C for 882 days was established.

- OSIS decided an inspection was not needed for clinical study TIP-PH-102 per their protocol.

In summary, the bioanalytical method was validated and robust in supporting the results and conclusions from the relative BA/BE clinical study TIP-PH-102.

3. Detailed Labeling Recommendations

Recommendations:

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology has the following labeling recommendations for revisions to the Applicant's proposed language based on the information reviewed under the current submission.

[Note: The underlined blue text is the recommended revision and strikethrough text is the deletion]

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/s/

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