CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214324Orig1s000

CLINICAL REVIEW(S)

Clinical/Decisional Memo

Application Type	NDA
Application Number(s)	214324
Priority or Standard	Class 1 resubmission
Submit Date(s)	12/23/22
Received Date(s)	12/23/22
PDUFA Goal Date	5/23/22
Division/Office	Division of Cardiology and Nephrology
Author Name(s)	Mary Ross Southworth through Norman Stockbridge
Review Completion Date	5/23/22
Established/Proper Name	Treprostinil powder
(Proposed) Trade Name	Tyvaso DPI
Applicant	United Therapeutics
Dosage Form(s)	Single-use cartridges containing 16, 32, 48, or 64 mcg
Applicant Proposed Dosing Regimen(s)	Oral inhalation in 4 separate, equally spaced treatment sessions per day
Applicant Proposed Indication(s)/Population(s)	Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies with Tyvaso establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). Pulmonary hypertension associated with interstitial lung disease (PH ILD; WHO Group 3) to improve exercise ability. The study with Tyvaso establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%)
Recommended Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as proposed.

The original application for Tyvaso DPI received a complete response on 10/15/2021 because of deficiencies at a facility involved in producing the drug product. In that review cycle, the clinical review by Mitch Psotka (finalized 9/23/2021) recommended approval based on the submitted data. The sponsor has now resubmitted the application with updated facility information and OPQ advises that the facility deficiencies have been addressed and recommends approval.

No new clinical data were included in the resubmission; however, during the original review cycle DCN became aware of a Citizens Petition (regulations.gov; FDA-2021-P-0714) submitted to the FDA that raised concerns about the pulmonary safety of fumaryl diketopiperazine (FDKP), an excipient included in Tyvaso DPI. An assessment of the Tyvaso DPI drug product in the original clinical review, did not indicate a safety concern.

The excipient FDKP is also found in Afrezza, an FDA-approved form of inhaled insulin powder. The labeling for Afrezza includes warnings[1,2] about the risk of acute bronchospasm in patients with chronic lung disease, a contraindication in patients with asthma or COPD, and instructions to screen patients for these conditions prior to initiation. The Petitioner argued there was a need for additional clinical data and specific statements in product labeling for Tyvaso DPI based on the assertion that FDKP is responsible for the acute bronchospasm observed in Afrezza's clinical trials. In responding to the Citizens Petition, the Division assessed the need for further study and changes to the proposed labeling for the Tyvaso DPI product.

Regarding the concern related to the excipient, the association between FDKP and Afrezza's bronchospasm risk is speculative, and a causal role has not been established. In the view of

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WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE

See full prescribing information for complete boxed warning.

- **Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA. (5.1)**
- **AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD. (4)**
- **Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV_1) to identify potential lung disease in all patients. (2.5), (5.1)**

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5.1 Acute Bronchospasm in Patients with Chronic Lung Disease

Because of the risk of acute bronchospasm, AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD *[see Contraindications (4)]*.

Before initiating therapy with AFREZZA, evaluate all patients with a medical history, physical examination and spirometry (FEV_1) to identify potential underlying lung disease.

Acute bronchospasm has been observed following AFREZZA dosing in patients with asthma and patients with COPD. In a study of patients with asthma, bronchoconstriction and wheezing following AFREZZA dosing was reported in 29% (5 out of 17) and 0% (0 out of 13) of patients with and without a diagnosis of asthma, respectively. In this study, a mean decline in FEV_1 of 400 mL was observed 15 minutes after a single dose in patients with asthma. In a study of patients with COPD (n=8), a mean decline in FEV_1 of 200 mL was observed 18 minutes after a single dose of AFREZZA. The long-term safety and efficacy of AFREZZA in patients with chronic lung disease have not been established.

DCN, there is no need for further study or assessment of the risk given the lack of a clinical safety signal and the labeling for Tyvaso DPI, both described below.

The small clinical trial (BREEZE)[3] of Tyvaso DPI in patients with PAH which included patients with underlying respiratory co-morbidities reported no cases of bronchospasm. These data allow for adequate characterization of the safety profile and supports a positive benefit risk profile consistent with approval. This determination is unchanged from the previous clinical review.

To understand more fully the pulmonary safety of Tyvaso DPI and implications for labeling, FDA's Adverse Event Reporting system (FAERS) was searched for cases of acute bronchospasm associated with marketed Tyvaso inhalation solution (IS-treprostinil solution), which contains the same drug substance as Tyvaso DPI. Several cases of acute bronchospasm shortly after Tyvaso IS use were identified (see postmarketing review of 5/3/2022). Another prostaglandin (Ventavis, NDA 21779) is associated with bronchospasm. Despite the absence of bronchospasm cases with Tyvaso DPI at this time, bronchospasm has been identified as a potential risk for the class of inhaled prostaglandins. Tyvaso DPI will include the following in the Warnings and Precautions section of labeling:

> *5.4* (b) (4) *Bronchospasm*
> *Like other inhaled prostaglandins, Tyvaso DPI may cause acute bronchospasm. Patients with asthma or COPD, or other bronchial hyperreactivity are at increased risk for bronchospasm. Ensure that such patients are treated optimally for reactive airway disease prior to and during treatment with Tyvaso DPI.*

Including this warning in section 5 of labeling adequately informs prescribers about the risk and its mitigation. The indicated population for Tyvaso DPI would be expected to have undergone pulmonary diagnostics. The prescribers of Tyvaso DPI have expertise in managing pulmonary health and are expected to be knowledgeable about co-morbidities.

Completed Reviews

- Integrated Quality Review (1/31/2022)-recommendation approval.
- Proprietary Name Review (2/17/2022)- support approval

[3] BREEZE included 51 patients with PAH (WHO Group 1) who were switched from Tyvaso inhalation solution to Tyvaso DPI and continued use of Tyvaso DPI for 3 weeks. In the study, no cases of bronchospasm were observed. Fourteen patients who participated in BREEZE had a baseline history of chronic lung disease, including asthma, ILD, and COPD. None of these patients, however, experienced bronchospasm or other SAEs. Further, 12 of these 14 patients remained in the open-label extension of BREEZE.

- DMEPA labeling memos (2/18/2022)- support approval

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/s/

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05/23/2022 07:17:38 AM

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CLINICAL REVIEW

Application Type	505(b)(1) NDA
Application Number(s)	214324 / S0002
Priority or Standard	Priority
Submit Date(s)	16 April 2021
Received Date(s)	16 April 2021
PDUFA Goal Date	16 October 2021
Division/Office	Division of Cardiology and Nephrology (DCN) / Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN) / Office of New Drugs (OND)
Reviewer Name(s)	Mitchell Psotka, MD PhD
Review Completion Date	23 September 2021
Established/Proper Name	Treprostinil (powder)
(Proposed) Trade Name	Tyvaso DPI
Applicant	United Therapeutics
Dosage Form(s)	Single-use cartridges containing 16, 32, 48, or 64 mcg
Applicant Proposed Dosing Regimen(s)	Oral inhalation in 4 separate, equally spaced treatment sessions per day, during waking hours
Applicant Proposed Indication(s)/Population(s)	Indicated for the treatment of: • Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies with Tyvaso establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). • Pulmonary hypertension associated with interstitial lung disease (PH ILD; WHO Group 3) to improve exercise ability. The study with Tyvaso establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%).
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the treatment of: • Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies with Tyvaso establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or

	heritable PAH (56%) or PAH associated with connective tissue diseases (33%). • Pulmonary hypertension associated with interstitial lung disease (PH ILD; WHO Group 3) to improve exercise ability. The study with Tyvaso establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%).

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Glossary

6MWD	6-minute walk test distance
AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IQR	interquartile range
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAH	pulmonary arterial hypertension
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PH-ILD	pulmonary hypertension associated with interstitial lung disease
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
WHO	World Health Organization

1. Executive Summary

1.1. Product Introduction

Treprostinil is a prostacyclin mimetic currently indicated for the treatment of WHO group I pulmonary arterial hypertension (PAH) as an intravenous (REMODULIN®), subcutaneous (REMODULIN®), oral (ORENITRAM™), and inhaled liquid formulation (TYVASO®), as well as WHO group III pulmonary hypertension associated with interstitial lung disease (PH-ILD) as an inhaled liquid formulation (TYVASO®), to improve exercise ability. Pharmacologically, treprostinil causes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation, decreasing pulmonary artery pressure.

The current dosing regimen of the Treprostinil inhaled liquid formulation (TYVASO®) is to initiate at 3 breaths of approximately 6 mcg of treprostinil each, or 18 mcg per session, in 4 separate treatment sessions each day approximately 4 hours apart, during waking hours. If 3 breaths are not tolerated the dose can be reduced to 1 or 2 breaths. The dosage should be increased every 1-2 weeks by 3 additional breaths to a target maintenance dose of 9-12 breaths (54-72 mcg) per treatment session, if tolerated. The current liquid formulation is available in 2.9 mL ampules containing 1.74 mg of treprostinil.

Treprostinil inhaled powder formulation (TYVASO DPI™) contains the identical drug substance as the inhaled liquid formulation (TYVASO®) and is submitted with a proposed indication identical to the approved indication for (TYVASO®), specifically for the treatment of WHO group I PAH and WHO group III PH-ILD to improve exercise capacity. TYVASO DPI™ is submitted as a drug-device combination product with the Tyvaso DPI Inhaler, which is comprised of single-use cartridges containing a powder formulation of treprostinil and a hand-held reusable breath-powered inhaler. The single use cartridges contain 16, 32, 48, or 64 mcg of treprostinil powder for inhalation.

The proposed dosing regimen of treprostinil inhaled powder (TYVASO DPI™) is to initiate at one 16 mcg cartridge per treatment session, in 4 separate treatment sessions each day approximately 4 hours apart, during waking hours. The dosage should be increased every 1-2 weeks by an additional 16 mcg cartridge per treatment session. The sponsor did not propose a (b) (4).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for the drug product treprostinil administered by inhalation has been previously concluded based on the liquid formulation in the 12-week, placebo-controlled TRIUMPH I study of 235 patients with WHO group I PAH, and in the 16-

week, placebo-controlled INCREASE study of 326 patients with WHO group III PH-ILD, where treated patients had increased exercise capacity as measured by 6-minute walk test distance compared to placebo.

In the BREEZE study included in this submission, patients on a stable regimen of inhaled liquid treprostinil were transitioned to an approximate corresponding dose of open-label inhaled treprostinil powder (TYVASO-DPI) and followed initially for 3 weeks. The switch from inhaled Treprostinil liquid to the inhaled powder formulation was not associated with a decrement in exercise capacity as measured by the 6-minute walk test distance.

1.3. Benefit-Risk Assessment

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Table 1. Benefit-Risk Integrated Assessment

Benefit-Risk Integrated Assessment
Evidence for the safety and effectiveness of the drug product treprostinil when administered by inhalation comes from the liquid formulation (TYVASO®) used in the 12-week, placebo-controlled TRIUMPH I study of 235 patients with WHO group I PAH, and in the 16-week, placebo-controlled INCREASE study of 326 patients with WHO group III PH-ILD. In these studies, treatment with treprostinil inhaled liquid demonstrated a placebo-corrected median change in peak 6-minute walk test distance (6MWD) of 20 meters after 12 weeks for patients with WHO group I PAH and a placebo-corrected median change in peak 6MWD of 21 meters after 16 weeks for patients with WHO group III PH-ILD. No additional studies evaluating the effectiveness of the treprostinil inhaled powder formulation were submitted for the current review. The safety and tolerability of the treprostinil inhaled powder formulation (TYVASO DPI™) was studied in the 3-week open-label BREEZE study wherein 51 patients with WHO group I PAH treated with stable doses of treprostinil inhaled liquid were transitioned to a similar dose of treprostinil inhaled powder. Pharmacokinetic testing demonstrated similar AUCs for all doses between the treprostinil inhaled liquid formulation and powder formulation, although the Cmax for the inhaled powder formulation was greater than 120% of the liquid formulation for all doses. However, in the BREEZE study there was no clinically significant change in 6-minute walk test distance, patient-reported outcome assessment, or increase in adverse events associated with the transition from treprostinil inhaled liquid to treprostinil inhaled powder. Two patients (3.9%) withdrew from the 3-week study due to treatment-related adverse events of dyspnea and globus pharyngus, and 3 additional patients (4.1%) withdrew in the open-label optional extension phase due to treatment-related adverse events of dyspnea and chest pain. Otherwise, the prevalence of adverse events was similar to those reported in the TRIUMPH I study of the treprostinil inhaled liquid formulation, with the most common being cough and headache. Fumaryl diketopiperazine (FDKP), an excipient of TYVASO DPI™ also contained in the approved human insulin powder (AFREZZA®), was comprehensively evaluated as a potential etiology of acute bronchospasm listed as a black-box warning for patients with chronic lung disease in the AFREZZA® label. However, the labelled black box warning does not specify whether the excipient or drug product may be responsible for concern for increased risk of bronchospasm. Pulmonary function testing did not implicate the excipient as a major cause of pulmonary dysfunction during the evaluation of that product. In addition, no reports of serious bronchospasm were identified during the 3-year assessment for the Risk Evaluation and Mitigation Strategy (REMS) for AFREZZA®.

The exposure to the excipient FDKP by the treprostinil inhaled powder formulation appears acceptable, as the AFREZZA® maximal dose of co-administered FDKP is (b) (4) mg and the co-administered dose of FDKP in the 64 mcg cartridge of treprostinil inhaled powder is (b) (4) mg. The BREEZE clinical trial of treprostinil inhaled powder with the excipient FDKP included patients with asthma, chronic obstructive pulmonary disease, and interstitial lung disease, and there were no bronchospastic adverse events reported during the 3-week randomized follow-up period, nor during the optional extension phase.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pulmonary hypertension manifest as WHO group I (Pulmonary arterial hypertension [PAH]) and WHO group III (pulmonary hypertension associated with interstitial lung disease [PH-ILD]), is a pathologic elevation in pulmonary vascular resistance and pulmonary artery pressures which impair right ventricular function and may cause heart failure and death despite currently available therapies.	WHO group I PAH and WHO group III PH-ILD are serious chronic medical conditions that cause substantial morbidity and mortality.
Current Treatment Options	• Pulmonary vasodilators used in combination are standard of care, including PDE5 inhibitors, Endothelin receptor antagonists, Prostacyclin analogs and mimetics, and a Soluble guanylate cyclase stimulator. These agents reduce pulmonary artery pressure with associated improvements in exercise capacity, and some improve time to clinical worsening, but there is not robust evidence that they improve survival for patients with PAH or PH-ILD. • Treprostinil is a prostacyclin mimetic that causes direct pulmonary vascular and systemic arterial vasodilation as well as inhibits platelet aggregation. Following inhalation of treprostinil in a liquid formulation, pulmonary artery pressure decreases, however	Currently available therapies for WHO group I PAH and WHO group III PH-ILD incompletely reduce risk for serious morbidity and mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients may find this formulation difficult to regularly administer.	
Benefit	• No additional evidence for effectiveness was submitted as part of the application for treprostinil inhaled powder (TYVASO DPI™). The application relies on the evidence from the approved formulations of treprostinil, including those currently indicated for the treatment of WHO group I pulmonary arterial hypertension (PAH) as an intravenous (REMODULIN®), subcutaneous (REMODULIN®), and inhaled liquid formulation (TYVASO®), as well as WHO group III pulmonary hypertension associated with interstitial lung disease (PH-ILD) as an inhaled liquid formulation (TYVASO®), to improve exercise ability. • Evidence for the safety and effectiveness of the drug product treprostinil administered by inhalation comes from the liquid formulation (TYVASO®) used in the 12-week, placebo-controlled TRIUMPH I study of 235 patients with WHO group I PAH, and in the 16-week, placebo-controlled INCREASE study of 326 patients with WHO group III PH-ILD. In these studies, treatment with treprostinil inhaled liquid demonstrated a placebo-corrected median change in peak 6-minute walk test distance (6MWD) of 20 meters after 12 weeks for patients with WHO group I PAH and a placebo-corrected median change in peak 6MWD of 21 meters after 16 weeks for patients with WHO group III PH-ILD. • Evidence for relative bioavailability comes from a 6-treatment, 6-	The applicant seeks approval for a novel formulation of liquid treprostinil based on a demonstration of pharmacokinetic bioequivalence. Relative bioavailability requirements set forth in §21 CFR 320.24 appear to be met by the treprostinil inhaled powder formulation, and no additional evidence of effectiveness was submitted with this application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	period, 6-sequence, crossover study of TYVASO® and TYVASO DPI™ in 36 healthy volunteers. Treprostinil systemic exposure following inhalation of TYVASO DPI™ demonstrated similar AUCs for all doses compared to the treprostinil inhaled liquid (TYVASO®) formulation, although the C_{max} for the inhaled powder formulation was greater than 120% of the liquid formulation for all tested doses.	
Risk and Risk Management	• The current label for treprostinil inhaled liquid (TYVASO®) describes the following adverse reactions: o Warnings and Precautions: Tyvaso may cause symptomatic hypotension. Tyvaso inhibits platelet aggregation and increases the risk of bleeding. Tyvaso dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. o Adverse Reactions: Most common adverse reactions (≥4%) are cough, headache, nausea, dizziness, flushing, throat irritation, pharyngolaryngeal pain, diarrhea, and syncope • The safety of the excipient fumaryl diketopiperazine (FDKP) in TYVASO DPI™ was comprehensively evaluated as part of the approved (AFREZZA®) inhaled human insulin powder application. The AFREZZA® label carries a black-box warning for risk of acute bronchospasm in patients with chronic lung disease. Nevertheless: o Pulmonary function testing did not implicate the excipient as a major cause of pulmonary dysfunction during the evaluation of AFREZZA® o No reports of serious bronchospasm were identified during the 3-year assessment for the Risk Evaluation and Mitigation	No new risks associated with treprostinil formulated as an inhaled powder (TYVASO DPI™) were identified in the BREEZE study. There was no evidence implicating the excipient FDKP as an etiology of adverse events. Despite the limitations of short follow-up and small size of the BREEZE study, labelling is considered sufficient to ensure that the benefits outweigh the risks for treprostinil inhaled powder (TYVASO DPI™) in the target populations.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Strategy (REMS) for AFREZZA® o The exposure to the excipient FDKP by the treprostinil inhaled powder formulation ((b) (4) mg in the highest TYVASO DPI™ cartridge dose of 64 mcg) is (b) (4) than that of the AFREZZA® maximal dose 30-unit cartridge with (b) (4) mg of co-administered FDKP, however TYVASO DPI™ is administered four times daily which would contain a daily maximal FDKP dose of (b) (4) mg and AFREZZA® may be administered at doses up to 300 total units per day, which would contain (b) (4) mg of FDKP. o The 3-week BREEZE clinical study of 51 patients with PAH transitioned from treprostinil inhaled liquid (TYVASO®) to open-label treprostinil inhaled powder (TYVASO DPI™) with the excipient FDKP included patients with asthma, chronic obstructive pulmonary disease, and interstitial lung disease, and there were no bronchospastic adverse events reported during the 3-week randomized follow-up period, nor during the optional extension phase. o The prevalence of adverse events in the BREEZE study of treprostinil inhaled powder (TYVASO DPI™) was similar to those reported in the TRIUMPH I study of the treprostinil inhaled liquid formulation (TYVASO®), with the most common being cough and headache. • In the 3-week open-label BREEZE study wherein 51 patients with were transitioned from the treprostinil inhaled liquid formulation (TYVASO®) to the treprostinil inhaled powder (TYVASO DPI™) there	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	was no clinically meaningful decrease in 6-minute walk test distance or patient-reported outcome assessment, nor any substantial increase in adverse events. For the 49 patients who continued in the optional extension phase the rate of adverse events was similar.	

1.4. Patient Experience Data

Patient-reported outcomes (PROs) were captured with the PAH-SYMPACT tool at baseline and at 3 weeks following the transition to treprostinil inhaled powder in the BREEZE study.

Patient Experience Data Relevant to this Application (check all that apply)
Table 2. Patient Experience Data Relevant to this Application

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		X	Patient reported outcome (PRO)	Section 4.1.2 Study Results
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	X	Patient preference studies (e.g., submitted studies or scientific publications)		Patient Preference Questionnaire
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Regulatory Background

2.1. U.S. Regulatory Actions and Marketing History

The active pharmaceutical ingredient treprostinil is currently indicated for the treatment of WHO group I pulmonary arterial hypertension (PAH) as an intravenous (REMODULIN®, NDA 021272)), subcutaneous (REMODULIN®, NDA 021272), oral extended-release tablet (ORENITRAM™, NDA 203496), and inhaled liquid formulation (TYVASO®, NDA 022387), as well as WHO group III pulmonary hypertension associated with interstitial lung disease (PH-ILD) as an inhaled liquid formulation (TYVASO®, NDA 022387), to improve exercise ability.

3. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

3.1. Nonclinical Pharmacology/Toxicology

The safety of the excipient fumaryl diketopiperazine (FDKP) was previously evaluated as part of the approved (AFREZZA®, BLA 022472) inhaled human insulin powder application. The exposure to the excipient FDKP by administration of the treprostinil inhaled powder formulation appears acceptable, as the AFREZZA® maximal dose of co-administered FDKP is (b) (4) mg and the co-administered dose of FDKP in target maintenance dose 64 mcg cartridge of treprostinil inhaled powder (TYVASO DPI™) is (b) (4) mg.

4. Review of Relevant Individual Trials Used to Support Efficacy

4.1. BREEZE (TIPPH101)

4.1.1. Study Design

Overview and Objective

The primary objective of TIP-PH-101 was to evaluate the safety and tolerability of Treprostinil Inhalation Powder (Tyvaso DPI) in subjects with pulmonary arterial hypertension currently treated with Tyvaso in this multicenter open-label clinical study.

Trial Design

Patients with PAH on a stable regimen of inhaled Tyvaso were transitioned to a corresponding dose of inhaled treprostinil powder (Tyvaso DPI) according to the following table (labelled Table 4-1 by the sponsor).

Table 3. Treprostinil Dose Conversion Assignments

Table 4-1 Treatment Phase Assignments

Study Entry	Treatment Phase	
Tyvaso Dose (QID)	**Tyvaso DPI Dose (QID)**	**Device Requirement**
6 to 7 breaths	32 mcg	32 mcg cartridge
8 to 10 breaths	48 mcg	48 mcg cartridge
11 to 12 breaths	64 mcg	32 mcg + 32 mcg cartridges

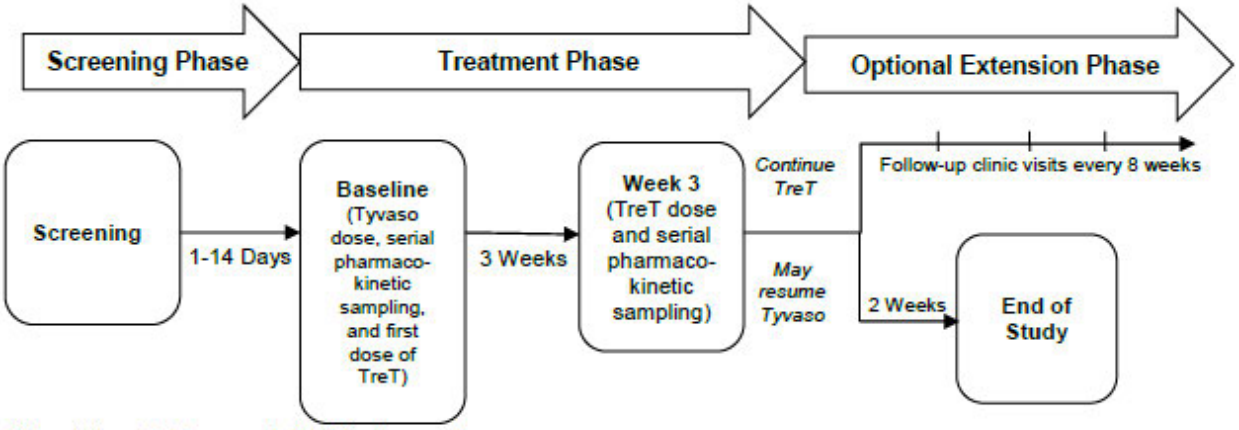
Abbreviations: QID, 4 times daily

TIP-PH-101 is the single study submitted for the regulatory approval of Tyvaso DPI in which patients with PAH were treated with Tyvaso DPI. Patients had WHO group 1 PAH and were on a stable dose of Tyvaso for at least 3 months, with baseline 6-minute walk distance (6MWD) at least 150 meters, and with stable dosing of other pulmonary vasodilator therapies for at least 1 month. Baseline assessments were taken following administration of chronic Tyvaso dosing, then patients were assigned Tyvaso DPI dosing based on their Tyvaso dose. Patients administered Tyvaso DPI at the corresponding dose 4 times daily for 3 weeks, then underwent repeat 6MWD, pharmacokinetic testing, PAH-Symptoms and Impact (PAH-SYMPACT) Questionnaire, and a preference questionnaire specific to the inhaled treprostinil formulations following administration of Tyvaso DPI.

After the 3-week visit patients were offered to continue Tyvaso DPI in an Optional Extension Phase (OEP) or to discontinue the Tyvaso DPI. If Tyvaso DPI was discontinued the patients returned 2 weeks after the 3-week assessment for an End of Study (EOS) visit, if Tyvaso DPI was continued, patients returned every 8 weeks following the 3-week visit. Dosing titration was allowed in the OEP of the study.

Figure 1. Study Design Schematic

Figure 9-1 Study Design Schematic



Abbreviation: TreT, treprostinil inhalation powder

From TIP-PH-101 Clinical Study Report, Version 24

Figure 2. Study Schedule of Events

Table 9-2 Overall Schedule of Times and Events

Study Phase			Treatment Phase		End of Study/Early Termination Visit[b,c]	Optional Extension Phase[d]
Study Visit	Screening[a]	Combined Screening & Baseline[a]	Baseline	Week 3[b]		Week 11 then every 8 weeks[d]
Study Day	-14 to -1	1	1	21		
Informed Consent	X	X				
Inclusion/Exclusion Criteria	X	X	X			
PQ-ITD[e]		X	X	X	X	
PAH-SYMPACT[e]		X	X	X	X	X
Inspiratory Criteria Assessment	X	X	X			
Demographics	X	X				
Medical History	X	X				
Physical Examination	X	X	X	X	X	X
Vital Signs[f]	X	X	X	X	X	X
Urine Pregnancy Test[g]	X	X	X	X	X	X
Clinical Laboratory Assessments		X	X	X	X	X
12-lead ECG[h]		X	X		X	
PK Blood Samples[i]		X	X	X		
Blood Sample for Biomarker Evaluation (Optional)[j]		X	X	X		X
Blood Sample for Whole Genome Sequencing (Optional)[k]		X	X			
6MWT[l]	X	X	X	X	X	X
Dosing Instructions/Dosing Diary/TreT Accountability		X	X	X	X[m]	X
Telephone/Email Contact[n]		X	X	X		X
AEs/SAEs[o]	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X

From TIP-PH-101 Clinical Study Report, Version 24

Study Endpoints

Primary Endpoint:

Safety and Tolerability: Safety assessments included incidence and severity of reported adverse events, as well as changes from screening in vital signs, clinical laboratory tests, electrocardiograms, and physical examinations.

Secondary Endpoints:

1. Pharmacokinetic assessments at 5, 10, 15, 30, 45, 90, 120, 180, 240, and 300 minutes after Tyvaso or Tyvaso DPI administration
2. 6-minute walk test distance at week 3
3. PAH-SYMPACT Questionnaire
4. Preference Questionnaire for Inhaled Treprostinil Devices (PQ-ITD)

Statistical Analysis Plan

The applicant pre-specified pharmacokinetic analyses for plasma concentrations of treprostinil above the lower limit of quantitation to be used to calculate area under the curve from time 0 to 300 minutes (AUC_{0-300}) and maximal drug concentration (Cmax) for each treatment.

No formal statistical analysis plan was formulated for the secondary endpoints, and 6MWD and PAH-SYMPACT Questionnaire scores were summarized with descriptive statistics. Adverse events were tabulated.

Protocol Amendments

The original protocol was dated January 30, 2019, and there were two amendments, one on May 8, 2019, and the second on April 2, 2020. No substantive changes expected to impact the interpretation of the treatment phase data were made by these protocol amendments.

4.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that the studies were conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP).

Financial Disclosure

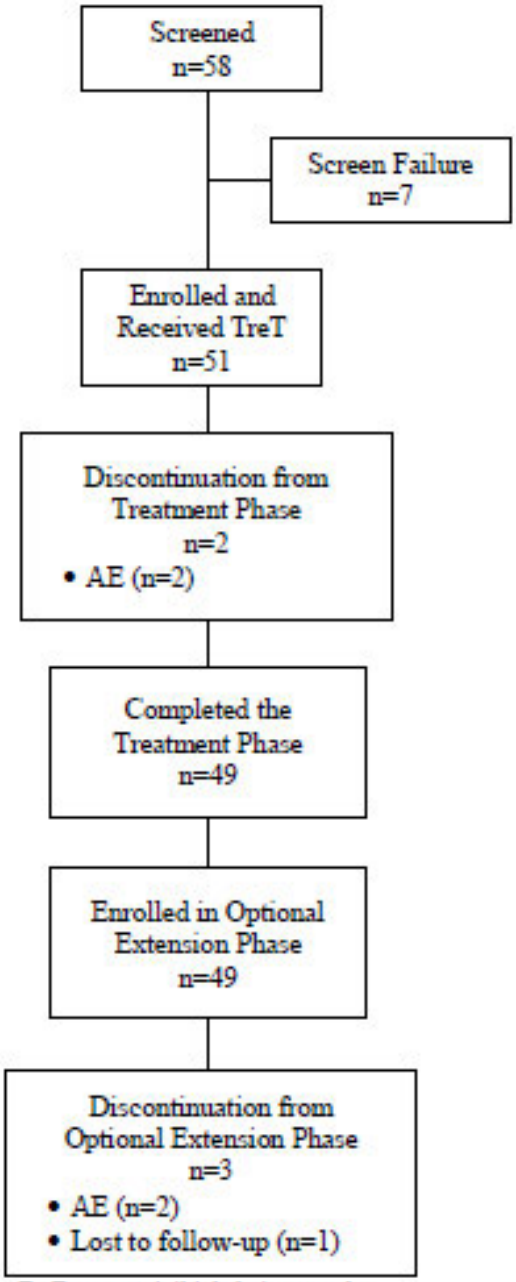
The Applicant has adequately disclosed financial interests and arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators, and there were none to disclose.

Patient Disposition

Appears this way in original

Figure 3. Study Patient Disposition Flow Diagram

Figure 10-1 Summary of Subject Disposition



Abbreviations: AE, adverse event; TreT, treprostinil inhalation powder
Source: Table 14.1.1

Table 4. Patient Disposition

Table 10-1 Summary of Subject Accountability – All Subjects Enrolled

	TreT Dose in Treatment Phase			
	32 mcg N=2 n (%)	48 mcg N=27 n (%)	64 mcg N=22 n (%)	Overall N=51 n (%)
Number of Subjects Enrolled	**2**	**27**	**22**	**51**
Received TreT	2 (100.0)	27 (100.0)	22 (100.0)	51 (100.0)
Completed Treatment Phase	2 (100.0)	26 (96.3)	21 (95.5)	49 (96.1)
Enrolled in Optional Extension Phase	2 (100.0)	26 (96.3)	21 (95.5)	49 (96.1)
Pharmacokinetic Population	2 (100.0)	25 (92.6)	20 (90.9)	47 (92.2)
Number of Subjects Who Discontinued Treatment Phase	**0**	**1 (3.7)**	**1 (4.5)**	**2 (3.9)**
Adverse Event	0	1 (3.7)	1 (4.5)	2 (3.9)
Number of Subjects Who Discontinued Optional Extension Phase	**0**	**3 (11.1)**	**0**	**3 (5.9)**
Adverse Event	0	2 (7.4)	0	2 (3.9)
Lost to Follow-up	0	1 (3.7)	0	1 (2.0)

Abbreviation: TreT, treprostinil inhalation powder
Source: Table 14.1.1

Protocol Violations/Deviations

Two protocol deviations occurred for 1 patient during the study because the patient received the investigational product rather than inhaled Treprostinil liquid at baseline and did not perform the baseline 6MWD or pharmacokinetic measurements. There were no entry criteria violations.

Table of Demographic Characteristics

Table 5. Demographic and Baseline Characteristics for Patients in the BREEZE Study

	TreT Dose in Treatment Phase			
	32 mcg N=2	48 mcg N=27	64 mcg N=22	Overall N=51
Age (years)				
n	2	27	22	51
Mean (SD)	48.0 (28.3)	54.7 (13.1)	58.0 (12.8)	55.9 (13.4)
Median	48.0	55.0	59.5	57.0
Min, Max	28, 68	28, 81	23, 82	23, 82
Age Category (years), n (%)				
<65 years	1 (50.0)	21 (77.8)	16 (72.7)	38 (74.5)
≥65 years	1 (50.0)	6 (22.2)	6 (27.3)	13 (25.5)
Sex, n (%)				
Male	0	5 (18.5)	3 (13.6)	8 (15.7)
Female	2 (100.0)	22 (81.5)	19 (86.4)	43 (84.3)
Ethnicity, n (%)				
Hispanic or Latino	0	1 (3.7)	3 (13.6)	4 (7.8)
Not Hispanic or Latino	2 (100.0)	26 (96.3)	19 (86.4)	47 (92.2)
Race, n (%)				
White	2 (100.0)	23 (85.2)	15 (68.2)	40 (78.4)
Black or African American	0	4 (14.8)	5 (22.7)	9 (17.6)
American Indian or Alaska Native	0	0	1 (4.5)	1 (2.0)
Asian	0	0	1 (4.5)	1 (2.0)
Baseline Weight (kg)				
n	2	27	22	51
Mean (SD)	77.05 (33.73)	75.16 (17.15)	85.66 (18.05)	79.77 (18.43)
Median	77.05	73.30	88.00	78.30
Min, Max	53.2, 100.9	48.4, 109.4	57.5, 122.2	48.4, 122.2
Baseline Height (cm)				
n	2	26	22	50
Mean (SD)	158.5 (6.4)	163.2 (8.7)	163.5 (9.6)	163.2 (8.9)
Median	158.5	164.0	164.0	163.0
Min, Max	154, 163	147, 179	147, 193	147, 193

	TreT Dose in Treatment Phase			
	32 mcg N=2	48 mcg N=27	64 mcg N=22	Overall N=51
Baseline BMI (kg/m²)				
n	2	26	22	50
Mean (SD)	30.20 (11.03)	27.89 (5.94)	32.18 (6.91)	29.87 (6.74)
Median	30.20	26.35	32.35	29.25
Min, Max	22.4, 38.0	18.9, 40.2	20.1, 47.7	18.9, 47.7
Time Since PAH Diagnosis (years)				
n	2	27	22	51
Mean (SD)	5.675 (7.333)	7.973 (7.172)	9.834 (5.634)	8.686 (6.509)
Median	5.675	6.090	9.310	7.820
Min, Max	0.49, 10.86	0.58, 30.88	2.04, 25.22	0.49, 30.88
Current PAH Diagnosis, n (%)				
Idiopathic/Familial	1 (50.0)	17 (63.0)	11 (50.0)	29 (56.9)
Associated with Unrepaired or Repaired Congenital Systemic-to-Pulmonary Shunts	0	2 (7.4)	2 (9.1)	4 (7.8)
Associated with Collagen Vascular Disease	1 (50.0)	6 (22.2)	7 (31.8)	14 (27.5)
Associated with HIV	0	0	1 (4.5)	1 (2.0)
Associated with Appetite Suppressant/Other Drug or Toxin Use	0	2 (7.4)	1 (4.5)	3 (5.9)
WHO Functional Class at Screening, n (%)				
I	1 (50.0)	5 (18.5)	0	6 (11.8)
II	1 (50.0)	18 (66.7)	12 (54.5)	31 (60.8)
III	0	4 (14.8)	10 (45.5)	14 (27.5)
Background PAH Medications, n (%)				
Any Medication	2 (100.0)	27 (100.0)	21 (95.5)	50 (98.0)
ERA	2 (100.0)	22 (81.5)	19 (86.4)	43 (84.3)
Ambrisentan	1 (50.0)	13 (48.1)	10 (45.5)	24 (47.1)
Bosentan	0	2 (7.4)	0	2 (3.9)
Macitentan	1 (50.0)	7 (25.9)	9 (40.9)	17 (33.3)
PDE5-I	1 (50.0)	23 (85.2)	17 (77.3)	41 (80.4)
Sildenafil	1 (50.0)	9 (33.3)	7 (31.8)	17 (33.3)
Tadalafil	0	14 (51.9)	10 (45.5)	24 (47.1)
sGC	0	3 (11.1)	4 (18.2)	7 (13.7)
Riociguat	0	3 (11.1)	4 (18.2)	7 (13.7)

Abbreviations: BMI, body mass index; ERA, endothelin receptor antagonist; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PDE5-I, phosphodiesterase type 5 inhibitor; SD, standard deviation; sGC, soluble guanylate cyclase; TreT, treprostinil inhalation powder; WHO, World Health Organization
Source: Table 14.1.4, Table 14.1.6, and Table 14.1.7.4

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Two patients discontinued treatment with inhaled treprostinil (TreT) powder during the 3-week treatment phase, 1 in the 48 mcg group and 1 in the 64 mcg group. Both treatment discontinuations during the 3 week treatment phase occurred due to adverse events. One patient in the 48 mcg group discontinued due to globus pharyngus and one patient in the 64 mcg group discontinued due to shortness of breath.

Table 6. Treatment Adherence in the Treatment Phase

Visit and Statistics	TreT Dose in Treatment Phase			
	32 mcg N=2	48 mcg N=27	64 mcg N=22	Overall N=51
Initial TreT Dose (mcg)				
n	2	27	22	51
Mean (SD)	32.0 (0.0)	48.0 (0.0)	64.0 (0.0)	54.3 (9.1)
Median	32.0	48.0	64.0	48.0
Min, Max	32, 32	48, 48	64, 64	32, 64
Week 3 TreT Dose (mcg)				
n	2	26	21	49
Mean (SD)	32.0 (0.0)	48.5 (2.4)	64.8 (3.5)	54.8 (9.7)
Median	32.0	48.0	64.0	48.0
Min, Max	32, 32	48, 60	64, 80	32, 80

Abbreviations: NA, not applicable; SD, standard deviation; TreT, treprostinil inhalation powder
Note: If the dose is different across different sessions on the same day, the maximum dose is used.
Source: Table 14.1.8

Results – Primary Endpoint

The median change in 6MWD from baseline to 3-weeks following transition from the treprostinil inhaled liquid formulation to powder was an increase in 8 meters, with an interquartile range of 47.3 meters, and a maximal decrease of 46 meters and maximal increase of 110 meters.

Table 7. 6-Minute Walk Test Distance at Baseline and Week 3 in BREEZE

	Statistics	Baseline	Week 3
6MWD, meters	Median	418	428.5
	IQR	141	140.2
	Mean	418.9	438.9
	Std Dev	109.4	110.5
	Min	192	207

	Max	642	701

Table 8. 6-Minute Walk Test Distance Difference at Week 3 in BREEZE

	Statistics	Week 3
6MWD Change, meters	Median	8
	IQR	47.3
	Mean	11.5
	Std Dev	32.9
	Min	-46
	Max	110

Data Quality and Integrity

No deficiencies in data quality or integrity were identified as part of this review.

Results – Secondary and other relevant endpoints

Table 9. 6-Minute Walk Test Distance by Treprostinil Dose in BREEZE

Visit and Statistics	TreT Dose in Treatment Phase					
	32 mcg N=2		48 mcg N=27		64 mcg N=22	
	Result	Change from Baseline	Result	Change from Baseline	Result	Change from Baseline
Baseline						
n	2	-	27	-	22	-
Mean (SD)	362.0 (79.2)	-	426.8 (116.7)	-	414.4 (104.6)	-
Median	362.0	-	434.0	-	414.0	-
Interquartile	306.0, 418.0	-	341.0, 499.0	-	354.0, 468.0	-
Min, Max	306, 418	-	213, 642	-	192, 622	-
Week 3						
n	2	2	24	24	20	20
Mean (SD)	405.5 (31.8)	43.5 (47.4)	455.9 (114.6)	17.8 (33.8)	422.0 (110.4)	0.8 (28.1)
Median	405.5	43.5	442.5	14.0	428.0	-2.0
Interquartile	383.0, 428.0	10.0, 77.0	369.0, 505.0	-1.5, 33.0	347.5, 485.0	-20.0, 14.5
Min, Max	383, 428	10, 77	260, 701	-46, 110	207, 636	-46, 60

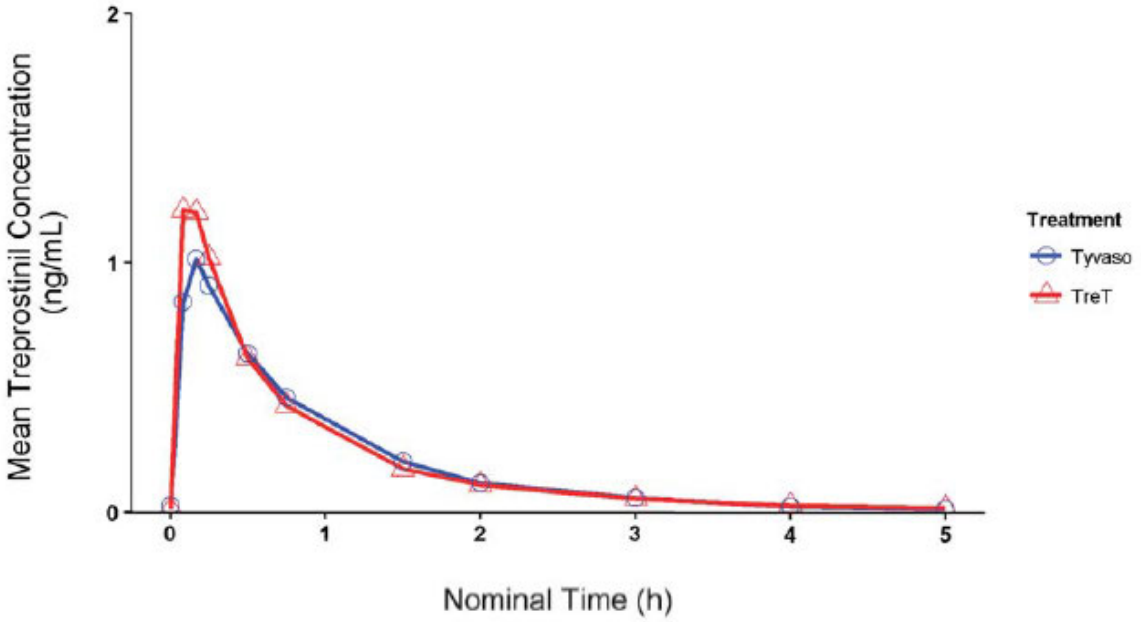
Abbreviations: 6MWD, 6-Minute Walk Distance; SD, standard deviation TreT, treprostinil inhalation powder
a p-value is from a paired t-test to assess change from Baseline in 6MWD for the overall column.
Source: Table 14.2.1.1

Patients in the 32 mcg group had a median increase of 43 meters (IQR 67 meters) in 6MWD. Patients in the 48 mcg group had a median increase of 14 meters (IQR 34.5 meters). Patients in the 64 mcg group had a median decrease of 2 meters (IQR 34.5 meters). Missing data in the optional extension phase limit the utility of that data, but show qualitatively similar results: a combined overall median 2 meter (IQR 62 meters) increase in 6MWD at 35 weeks in 15 patients after the transition from Tyvaso to Tyvaso DPI.

Pharmacokinetic testing demonstrated similar AUCs for all doses between the treprostinil inhaled liquid formulation and powder formulation, although the C_{max} for the inhaled powder formulation was greater than 120% of the liquid formulation for all doses (Figure 4 and Figure 5).

Figure 4. Mean Treprostinil Concentration versus Time (Linear)

Figure 4-2. Mean Treprostinil Concentration vs Time Plots by Treatment with Dose Levels Pooled (linear and semi-log)



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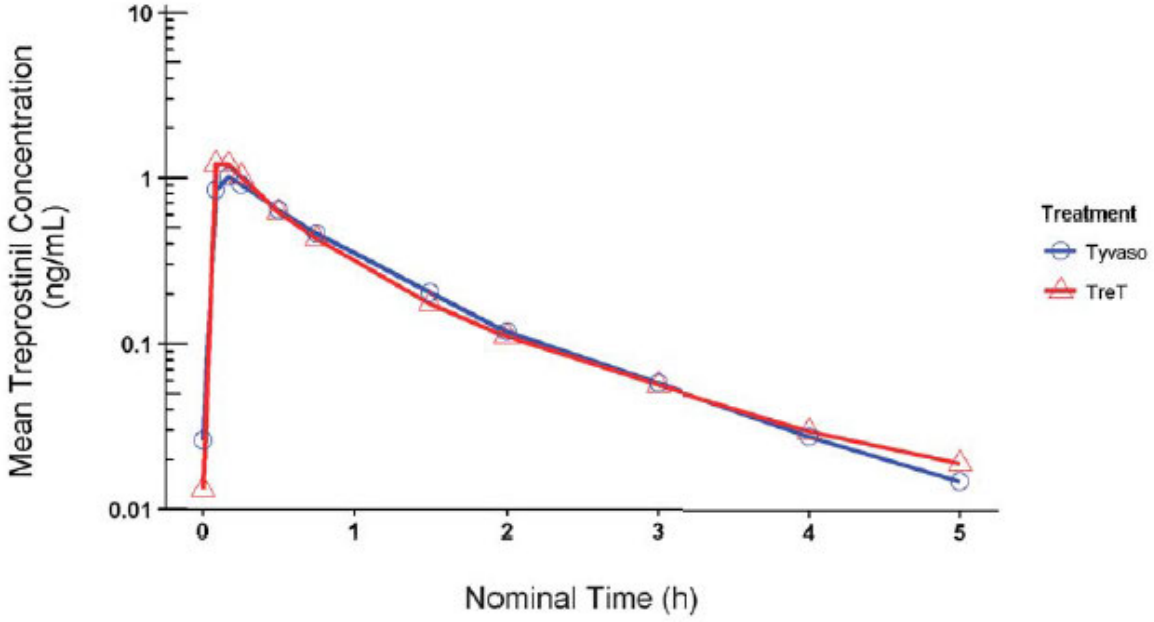
Mean concentrations may be <LLOQ due to imputation of BLQ samples to zero

Each breath of Tyvaso is equivalent to 6 µg of treprostinil

Mean plots include subjects who received Tyvaso 42 µg (n=2), Tyvaso 54 µg (n=22), Tyvaso 60 µg (n=3), Tyvaso 66 µg (n=1), Tyvaso 72 µg (n=18), TreT 32 µg (n=2), TreT 48 µg (n=23), and TreT 64 µg (n=19)

Figure 5. Mean Treprostinil Concentration versus Time (semi-log)



Page 2 of 2

Mean concentrations may be <LLOQ due to imputation of BLQ samples to zero

Each breath of Tyvaso is equivalent to 6 µg of treprostinil

Mean plots include subjects who received Tyvaso 42 µg (n=2), Tyvaso 54 µg (n=22), Tyvaso 60 µg (n=3), Tyvaso 66 µg (n=1), Tyvaso 72 µg (n=18), TreT 32 µg (n=2), TreT 48 µg (n=23), and TreT 64 µg (n=19)

Patient Symptoms as Measured by PAH-SYMPACT:

The PAH-SYMPACT patient reported outcomes measure for PAH can help quantify the symptom burden and health-related quality of life for patients with PAH. Detectable improvements in symptoms on a population level have been associated with a decrease in the cardiopulmonary symptom score of 0.32 points, whereas symptomatic worsening has been associated with an increase in the cardiopulmonary symptom score of 0.08 points. In the BREEZE study, after 3 weeks the median overall population change in the patient-reported outcome measure PAH-SYMPACT was 0 (interquartile range -0.17 to 0.17) (Table 10). Patients in the 32 mcg group had a median cardiopulmonary score increase (consistent with greater symptom burden) of 0.16 (IQR 0.16, 0.17). Patients in the 48 mcg group had a median cardiopulmonary score change of 0 (IQR -0.25, 0.17). Patients in the 64 mcg group had a median cardiopulmonary score decrease (consistent with improvement in symptom burden) of -0.16 (IQR -0.17, 0.17).

Table 10. PAH-SYMPACT Scores at Baseline and Week 3 in BREEZE

Visit and Statistics	TreT Dose in Treatment Phase						Overall N=51	
	32 mcg N=2		48 mcg N=27		64 mcg N=22			
	Score	Change from Baseline	Score	Change from Baseline	Score	Change from Baseline	Score	Change from Baseline
Cardiopulmonary Symptoms Domain Score								
Baseline								
n	2	-	27	-	22	-	51	-
Mean (SD)	0.50 (0.24)	-	0.70 (0.45)	-	0.98 (0.51)	-	0.81 (0.49)	-
Median	0.50	-	0.67	-	1.00	-	0.83	-
Interquartile	0.33, 0.67	-	0.33, 1.17	-	0.50, 1.33	-	0.33, 1.17	-
Min, Max	0.3, 0.7	-	0.0, 1.5	-	0.0, 2.0	-	0.0, 2.0	-
Week 3								
n	2	2	24	24	20	20	46	46
Mean (SD)	0.67 (0.23)	0.16 (0.01)	0.62 (0.42)	-0.06 (0.25)	0.93 (0.45)	-0.05 (0.31)	0.76 (0.45)	-0.05 (0.27)
Median	0.67	0.16	0.50	0.00	0.92	-0.16	0.75	0.00
Interquartile	0.50, 0.83	0.16, 0.17	0.33, 0.83	-0.25, 0.17	0.67, 1.17	-0.17, 0.17	0.50, 1.00	-0.17, 0.17
Min, Max	0.5, 0.8	0.2, 0.2	0.0, 1.5	-0.7, 0.3	0.2, 2.2	-0.7, 0.5	0.0, 2.2	-0.7, 0.5

Reference:
Chin KM, Gomberg-Maitland M, Channick RN, Cuttica MJ, Fischer A, Frantz RP, Hunsche E, Kleinman L, McConnell JW, McLaughlin VV, Miller CE, Zamanian RT, Zastrow MS, Badesch DB. Psychometric Validation of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) Questionnaire: Results of the SYMPHONY Trial. *Chest*. 2018 Oct;154(4):848-861.

Dose/Dose Response

There was no clear evidence of dose response in this small study.

Durability of Response

Durability of response was assessed only in the optional open-label extension in the BREEZE trial. While limited due to small sample size and patient drop out, there was not evidence of waning treatment effect over time.

Persistence of Effect

Effect persistence was not formally evaluated.

Additional Analyses Conducted on the Individual Trial

No additional analyses were performed.

5. Review of Safety

5.1. Safety Results

5.2. Analysis of Submission-Specific Safety Issues

TIP-PH-101 (BREEZE) provides limited safety data, but the results do not show clinical worsening by multiple metrics (6MWD, symptom burden as measured by PAH-SYMPACT) nor a substantial increase in adverse events associated with the transition from Tyvaso to Tyvaso DPI over 3 weeks or longer, noting a higher exposure to the Treprostinil drug product with the DPI formulation. There were no deaths during the 3-week treatment or optional extension phases and the most common adverse events were headache, 8 headaches occurred in 8 patients (17.6%), cough, 13 episodes of cough in 13 patients (25.5%), and shortness of breath, 3 episodes of shortness of breath occurred in 3 patients (5.9%).

Two patients discontinued treatment with inhaled treprostinil powder during the 3-week treatment phase, 1 in the 48 mcg group and 1 in the 64 mcg group. Both treatment discontinuations during the 3 week treatment phase occurred due to adverse events. One patient in the 48 mcg group discontinued due to globus pharyngus and one patient in the 64 mcg group discontinued due to shortness of breath. Three patients in the 48 mcg group had an adverse event leading to study medication withdrawal in the optional extension phase. These were due to shortness of breath and chest pain.

Limited additional safety data can be gleaned from the 3-week 51-patient open-label BREEZE study and the optional open label extension. However, no bronchospastic adverse events were identified during either portion of the study, and the prevalence of adverse events was similar to prior formulations of treprostinil liquid for inhalation. Respiratory comorbidities were present in 10% of the BREEZE study population. Nevertheless, of the 5 subjects who withdrew from the study due to investigational therapy discontinuation during either the 3-week treatment or optional extension phase assessment, none had diagnoses of asthma, chronic obstructive pulmonary disease, nor non-PAH respiratory diseases.

Table 11. Summary of Adverse Events in BREEZE

	TreT Dose in Treatment Phase			
	32 mcg N=2 n (%)	48 mcg N=27 n (%)	64 mcg N=22 n (%)	Overall N=51 n (%)
Treatment Phase				
Total number of AEs	0	37	22	59
Number of subjects with at least 1 AE	0	14 (51.9)	11 (50.0)	25 (49.0)
Total number of SAEs	0	1	1	2
Number of subjects with at least 1 SAE	0	1 (3.7)	1 (4.5)	2 (3.9)
Total number of study drug related AEs	0	30	18	48
Number of subjects with at least 1 study drug related AE	0	14 (51.9)	9 (40.9)	23 (45.1)
Total number of study drug related SAEs	0	0	0	0
Number of subjects with at least 1 study drug related SAE	0	0	0	0
Total number of AEs leading to withdrawal of study drug	0	1	1	2
Number of subjects with at least 1 AE leading to withdrawal of study drug	0	1 (3.7)	1 (4.5)	2 (3.9)

Table 12. Adverse Events >5% by System Organ Class and Treatment Dose

System Organ Class/Preferred Term	TreT Dose in Treatment Phase					
	32 mcg N=2 Total Patient Years=0.12		48 mcg N=27 Total Patient Years=1.54		64 mcg N=22 Total Patient Years=1.29	
	n (%)	# of AEs (AE rate[a])	n (%)	# of AEs (AE rate[a])	n (%)	# of AEs (AE rate[a])
Any event	**0**	**0**	**14 (51.9)**	**37 (23.96)**	**11 (50.0)**	**22 (16.99)**
Nervous system disorders	**0**	**0**	**5 (18.5)**	**5 (3.24)**	**4 (18.2)**	**5 (3.86)**
Headache	0	0	4 (14.8)	4 (2.59)	4 (18.2)	4 (3.09)
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**10 (37.0)**	**15 (9.71)**	**6 (27.3)**	**7 (5.41)**
Cough	0	0	9 (33.3)	9 (5.83)	4 (18.2)	4 (3.09)
Dyspnoea	0	0	2 (7.4)	2 (1.30)	1 (4.5)	1 (0.77)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TreT, treprostinil inhalation powder
a AE rate is calculated as the number of AEs divided by the total patient years of exposure per dose group.
Note: MedDRA version 23.0 was used for coding of AE verbatim terms.
Source: Table 14.3.1.2

Table 13. Adverse Event Profile for Treprostinil Inhaled Liquid Formulation in TRIUMPH I (from the Tyvaso Label)

Table 1: Adverse Events in ≥4% of PAH Patients Receiving Tyvaso and More Frequent[a] than Placebo in TRIUMPH I

Adverse Event	Treatment n (%)	
	Tyvaso n=115	Placebo n=120
Cough	62 (54)	35 (29)
Headache	47 (41)	27 (23)
Throat Irritation / Pharyngolaryngeal Pain	29 (25)	17 (14)
Nausea	22 (19)	13 (11)
Flushing	17 (15)	1 (<1)
Syncope	7 (6)	1 (<1)

[a] More than 3% greater than placebo

6. Labeling Recommendations

6.1. Prescription Drug Labeling

The current label indication for Tyvaso is suggested to be used for Tyvaso DPI, without modification.

Tyvaso DPI is a prostacyclin mimetic indicated for the treatment of:
- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies with Tyvaso establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).
- Pulmonary hypertension associated with interstitial lung disease (PH ILD; WHO Group 3) to improve exercise ability. The study with Tyvaso establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%).

While the current label for Tyvaso targets a maintenance dose of 9-12 breaths per treatment

session, 4 times daily. The Tyvaso DPI label is suggested to target maintenance doses of 64 mcg per treatment session, 4 times daily. Transitions from stable Tyvaso dosing to Tyvaso DPI may be performed using the comparable dose criteria from the TIP-PH-101 clinical study.

Tyvaso DPI Cartridge Strength	Tyvaso Number of Breaths
16 mcg	≤5 (≤30 mcg)
32 mcg	6 to 7 (36 to 42 mcg)
48 mcg	8 to 10 (48 to 60 mcg)
64 mcg	11 to 12 (66 to 72 mcg)

The adverse event rates from the BREEZE (TIP-PH-101) for patients transitioned from Tyvaso to Tyvaso DPI should be reported in the label, and may be reasonably compared to the adverse event rates in the placebo-controlled TRIUMPH I clinical trial performed with Tyvaso.

Adverse Event in BREEZE	Tyvaso DPI n (%)
Cough	(b) (4)
Headache	
Dyspnea	

BREEZE (TIP-PH-101) was not a pre-specified efficacy study and results of the 6MWD and patient-reported outcomes measures do not merit reporting in Section 14 of the label.

7. Appendices

7.1. Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators and no issues arose from the financial disclosures.

Covered Clinical Study (Name and/or Number): BREEZE, TIPPH101

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

		Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Appears this way in original

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MITCHELL A PSOTKA
09/23/2021 12:40:18 AM

FORTUNATO F SENATORE
09/23/2021 07:56:45 AM