CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022387Orig1s017

Trade Name:	TYVASO
Generic or Proper Name:	treprostinil
Sponsor:	United Therapeutics Corp.
Approval Date:	March 31, 2021
Indication:	Tyvaso is a prostacyclin mimetic indicated for the treatment of: • Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies 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 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%).

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 22387/S-017

SUPPLEMENT APPROVAL

United Therapeutics Corp.
Attention: Sarah Gemberling, PhD, RAC
Associate Manager, Regulatory Affairs
55 TW Alexander Drive
PO Box 14186
Research Triangle Park, NC 27709

Dear Dr. Gemberling:

Please refer to your supplemental new drug application (sNDA) dated June 1, 2020, received June 1, 2020, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tyvaso (treprostinil) inhalation solution.

This Prior Approval supplemental new drug application provides for a new indication for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.

APPROVAL & LABELING

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling Prescribing Information, and Instructions for Use, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[6]

If you have any questions, please call Brian Cooney, Regulatory Project Manager, at (301) 796-0886.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Instructions for Use

[6] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

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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/

NORMAN L STOCKBRIDGE
03/31/2021 01:37:04 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TYVASO safely and effectively. See full prescribing information for TYVASO.

TYVASO® (treprostinil) inhalation solution, for oral inhalation use
Initial U.S. Approval: 2002

---------- RECENT MAJOR CHANGES ----------
Indications and Usage (1.2) 03/2021

---------- INDICATIONS AND USAGE ----------
Tyvaso is a prostacyclin mimetic indicated for the treatment of:
- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies 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%). (1.1)
- Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study 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%). (1.2)

---------- DOSAGE AND ADMINISTRATION ----------
- Use only with the Tyvaso Inhalation System. (2.1)
- Administer undiluted, as supplied. A single breath of Tyvaso delivers approximately 6 mcg of treprostinil. (2.1)
- Administer in 4 separate treatment sessions each day approximately 4 hours apart, during waking hours. (2.1)
- Initial dosage: 3 breaths (18 mcg) per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths. (2.1)
- Dosage should be increased by an additional 3 breaths per treatment session at approximately 1- to 2-week intervals, if tolerated. (2.1)
- Titrate to target maintenance doses of 9 to 12 breaths per treatment session, 4 times daily. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg treprostinil (0.6 mg per mL). (3)

---------- CONTRAINDICATIONS ----------
None. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Tyvaso may cause symptomatic hypotension. (5.1)
- Tyvaso inhibits platelet aggregation and increases the risk of bleeding. (5.2)
- Tyvaso dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (5 3, 7.3)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (≥4%) are cough, headache, nausea, dizziness, flushing, throat irritation, pharyngolaryngeal pain, diarrhea, and syncope. (6)

To report SUSPECTED ADVERSE REACTIONS, contact United Therapeutics Corp. at 1-866-458-6479 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

Tyvaso is indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies 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%).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration *[see Clinical Studies (14)]*.

1.2 Pulmonary Hypertension Associated with ILD

Tyvaso is indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study 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%) *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage in Adults

Tyvaso is intended for oral inhalation using the Tyvaso Inhalation System, which consists of an ultrasonic, pulsed delivery device and its accessories.

Tyvaso is dosed in 4 separate, equally spaced treatment sessions per day, during waking hours. Each treatment session will take 2 to 3 minutes. The treatment sessions should be approximately 4 hours apart.

Initial Dosage:

Therapy should begin with 3 breaths of Tyvaso (18 mcg of treprostinil) per treatment session 4 times daily. If 3 breaths are not tolerated, reduce to 1 or 2 breaths and subsequently increase to 3 breaths, as tolerated.

Maintenance Dosage:

Dosage should be increased by an additional 3 breaths per treatment session, 4 times daily at approximately 1- to 2-week intervals. Studies establishing effectiveness in patients with PAH and PH-ILD have used target doses of 9 to 12 breaths per treatment session, 4 times daily. If adverse effects preclude titration to target dose, Tyvaso should be continued at the highest tolerated dose.

If a scheduled treatment session is missed or interrupted, therapy should be resumed as soon as possible at the usual dose.

2.2 Administration

Tyvaso must be used only with the Tyvaso Inhalation System. Patients should follow the instructions for use for operation of the Tyvaso Inhalation System and for daily cleaning of the device components after the last treatment session of the day. To avoid potential interruptions in drug delivery because of equipment malfunction, patients should have access to a back-up Tyvaso Inhalation System device.

Do not mix Tyvaso with other medications in the Tyvaso Inhalation System. Compatibility of Tyvaso with other medications has not been studied.

The Tyvaso Inhalation System should be prepared for use each day according to the instructions for use. One ampule of Tyvaso contains a sufficient volume of medication for all 4 treatment sessions in a single day. Prior to the first treatment session, the patient should twist the top off a single Tyvaso ampule and squeeze the entire contents into the medicine cup. Between each of the 4 daily treatment sessions, the device should be capped and stored upright with the remaining medication inside.

At the end of each day, the medicine cup and any remaining medication must be discarded. The device must be cleaned each day according to the instructions for use.

Avoid skin or eye contact with Tyvaso solution. Do not orally ingest the Tyvaso solution.

3 DOSAGE FORMS AND STRENGTHS

Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg of treprostinil (0.6 mg per mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Symptomatic Hypotension

Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with Tyvaso may produce symptomatic hypotension.

5.2 Risk of Bleeding

Tyvaso inhibits platelet aggregation and increases the risk of bleeding.

5.3 Effect of Other Drugs on Treprostinil

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following potential adverse reactions are described in Warnings and Precautions (5):

- Decrease in systemic blood pressure *[see Warnings and Precautions (5.1)]*.
- Bleeding *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pulmonary Arterial Hypertension

In a 12-week, placebo-controlled study (TRIUMPH I) of 235 patients with PAH (WHO Group 1 and nearly all NYHA Functional Class III), the most commonly reported adverse reactions on Tyvaso included cough and throat irritation, headache, gastrointestinal effects, muscle, jaw or bone pain, dizziness, flushing, and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with Tyvaso than with placebo.

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

The safety of Tyvaso was also studied in a long-term, open-label extension study in which 206 patients were dosed for a mean duration of 2.3 years, with a maximum exposure of 5.4 years. Eighty-nine percent (89%) of patients achieved the target dose of 9 breaths, 4 times daily. Forty-two percent (42%) achieved a dose of 12 breaths, 4 times daily. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week placebo-controlled trial.

In a prospective, observational study comparing patients taking Tyvaso (958 patient-years of exposure) and a control group (treatment with other approved therapies for PAH; 1094 patient-years), Tyvaso was associated with a higher rate of cough (16.2 vs. 10.9 per 100 patient-years), throat irritation (4.5 vs. 1.2 per 100 pt-years), nasal discomfort (2.6 vs. 1.3 per 100 pt-years), and hemoptysis (2.5 vs. 1.3 per 100 pt-years) compared to the control group.

Pulmonary Hypertension Associated with ILD

In a 16-week, placebo-controlled study (INCREASE) of 326 patients with PH-ILD (WHO Group 3), adverse reactions were similar to the experience in studies of PAH.

6.2 Post-Marketing Experience

The adverse reaction of angioedema has been identified during the post-approval use of Tyvaso. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

7.1 Bosentan

In a human pharmacokinetic study conducted with bosentan (250 mg/day) and an oral formulation of treprostinil (treprostinil diolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed.

7.2 Sildenafil

In a human pharmacokinetic study conducted with sildenafil (60 mg/day) and an oral formulation of treprostinil (treprostinil diolamine), no pharmacokinetic interactions between treprostinil and sildenafil were observed.

7.3 Effect of Cytochrome P450 Inhibitors and Inducers

In vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A. Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A.

Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor, gemfibrozil, increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer, rifampin, decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8 *[see Warnings and Precautions (5.3)]*.

7.4 Effect of Other Drugs on Treprostinil

Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively, in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the international normalized ratio (INR) in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited case reports of treprostinil use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. However, there are risks to the mother and the fetus associated with pulmonary arterial hypertension *(see Clinical Considerations)*. In animal studies, no adverse reproductive and developmental effects were seen for treprostinil at ≥9 and ≥145 times the human exposure when based on C_{max} and AUC, respectively, following a single treprostinil dose of 54 mcg.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Pulmonary arterial hypertension is associated with an increased risk of maternal and fetal mortality.

Data

Animal reproduction studies have been conducted with treprostinil via continuous subcutaneous administration and with treprostinil diolamine administered orally. In studies with orally administered treprostinil diolamine, no adverse effect doses for fetal viability/growth, fetal development (teratogenicity), and postnatal development were determined in rats. In pregnant rats, no evidence of harm to the fetus was observed following oral administration of treprostinil diolamine at the highest dose tested (20 mg/kg/day), which represents about 154 and 1479 times the human exposure, when based on C_{max} and AUC, respectively, following a single Tyvaso dose of 54 mcg. In pregnant rabbits, external fetal and soft tissue malformations and fetal skeletal malformation occurred. The dose at which no adverse effects were seen (0.5 mg/kg/day) represents about 9 and 145 times the human exposure, when based on C_{max} and AUC, respectively, following a single Tyvaso dose of 54 mcg. No treprostinil treatment-related effects on labor and delivery were seen in animal studies. Animal reproduction studies are not always predictive of human response.

8.2 Lactation

Risk Summary

There are no data on the presence of treprostinil in human milk, the effects on the breastfed infant, or the effects on milk production.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Tyvaso did not include patients younger than 18 years to determine whether they respond differently from older patients.

8.5 Geriatric Use

Across clinical studies used to establish the effectiveness of Tyvaso in patients with PAH and PH-ILD, 268 (47.8%) patients aged 65 years and over were enrolled. The treatment effects and safety profile observed in geriatric patients were similar to younger patients. In general, dose selection for an elderly

patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

8.6 Patients with Hepatic Insufficiency

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild-to-moderate hepatic insufficiency. Uptitrate slowly when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Impairment

No dose adjustments are required in patients with renal impairment. Treprostinil is not cleared by dialysis *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

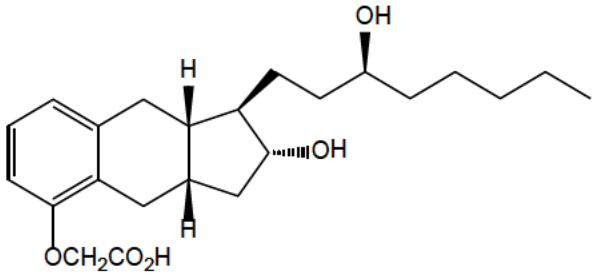
In general, symptoms of overdose with Tyvaso include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

11 DESCRIPTION

Tyvaso is a sterile formulation of treprostinil, a prostacyclin mimetic, intended for administration by oral inhalation using the Tyvaso Inhalation System. Tyvaso is supplied in 2.9 mL low density polyethylene (LDPE) ampules, containing 1.74 mg treprostinil (0.6 mg/mL). Each ampule also contains 18.9 mg sodium chloride, 18.3 mg sodium citrate dihydrate, 0.58 mg sodium hydroxide, 11.7 mg 1 N hydrochloric acid, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinil is (1*R*,2*R*,3a*S*,9a*S*)-[[2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxy]acetic acid. Treprostinil has a molecular weight of 390.52 and a molecular formula of $C_{23}H_{34}O_5$.

The structural formula of treprostinil is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Treprostinil is a prostacyclin analogue. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

12.2 Pharmacodynamics

In a clinical trial of 240 healthy volunteers, single doses of Tyvaso 54 mcg (the target maintenance dose per session) and 84 mcg (supratherapeutic inhalation dose) prolonged the corrected QTc interval by approximately 10 ms. The QTc effect dissipated rapidly as the concentration of treprostinil decreased.

12.3 Pharmacokinetics

Pharmacokinetic information for single doses of inhaled treprostinil was obtained in healthy volunteers in 3 separate studies. Treprostinil systemic exposure (AUC and C_{max}) post-inhalation was shown to be proportional to the doses administered (18 mcg to 90 mcg).

Absorption

In a 3-period crossover study, the bioavailability of 2 single doses of Tyvaso (18 mcg and 36 mcg) was compared with that of intravenous treprostinil in 18 healthy volunteers. Mean estimates of the absolute systemic bioavailability of treprostinil after inhalation were approximately 64% (18 mcg) and 72% (36 mcg).

Treprostinil plasma exposure data were obtained from 2 studies at the target maintenance dose, 54 mcg. The mean C_{max} at the target dose was 0.91 and 1.32 ng/mL with corresponding mean T_{max} of 0.25 and 0.12 hr, respectively. The mean AUC for the 54-mcg dose was 0.81 and 0.97 hr•ng/mL, respectively.

Distribution

Following parenteral infusion, the apparent steady state volume of distribution (V_{ss}) of treprostinil is approximately 14 L/70 kg ideal body weight.

In vitro treprostinil is 91% bound to human plasma proteins over the 330 to 10,000 mcg/L concentration range.

Metabolism and Excretion

Of subcutaneously administered treprostinil, only 4% is excreted unchanged in urine. Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. Metabolites are excreted in urine (79%) and feces (13%) over 10 days. Five apparently inactive metabolites were detected in the urine, each accounting for 10 to 15% of the dose administered. Four of the metabolites are products of oxidation of the 3-hydroxyloctyl side chain and 1 is a glucuroconjugated derivative (treprostinil glucuronide).

The elimination of treprostinil (following subcutaneous administration of treprostinil) is biphasic, with a terminal elimination half-life of approximately 4 hours using a 2-compartment model.

Specific Populations

Hepatic Insufficiency

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects presenting with mild-to-moderate hepatic insufficiency. Treprostinil has not been studied in patients with severe hepatic insufficiency *[see Use in Specific Populations (8.6)]*.

Renal Impairment

In patients with severe renal impairment requiring dialysis (n=8), administration of a single 1 mg dose of orally administered treprostinil pre- and post-dialysis resulted in $AUC_{0\text{-}inf}$ that was not significantly altered compared to healthy subjects *[see Use in Specific Populations (8.7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year rat carcinogenicity study was performed with treprostinil inhalation at target doses of 5.26, 10.6, and 34.1 mcg/kg/day. There was no evidence for carcinogenic potential associated with treprostinil inhalation in rats at systemic exposure levels up to 35 times the clinical exposure at the target maintenance dose of 54 mcg. *In vitro* and *in vivo* genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusions at rates of up to 450 ng treprostinil/kg/min. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

Oral administration of treprostinil diolamine to Tg.rasH2 mice at 0, 5, 10, and 20 mg/kg/day in males and 0, 3, 7.5, and 15 mg/kg/day in females daily for 26 weeks did not significantly increase the incidence of tumors.

Treprostinil diolamine was tested *in vivo* in a rat micronucleus assay and did not induce an increased incidence of micronucleated polychromatic erythrocytes.

13.2 Animal Toxicology and/or Pharmacology

In a 2-year rat study with treprostinil inhalation at target doses of 5.26, 10.6, and 34.1 mcg/kg/day, there were more deaths (11) in the mid- and high-dose treprostinil groups during the first 9 weeks of the study, compared to 1 in control groups. At the high-dose level, males showed a higher incidence of inflammation in teeth and preputial gland, and females showed higher incidences of inflammation and urothelial hyperplasia in the urinary bladder. The exposures in rats at mid- and high-dose levels were about 15 and 35 times, respectively, the clinical exposure at the target maintenance dose of 54 mcg.

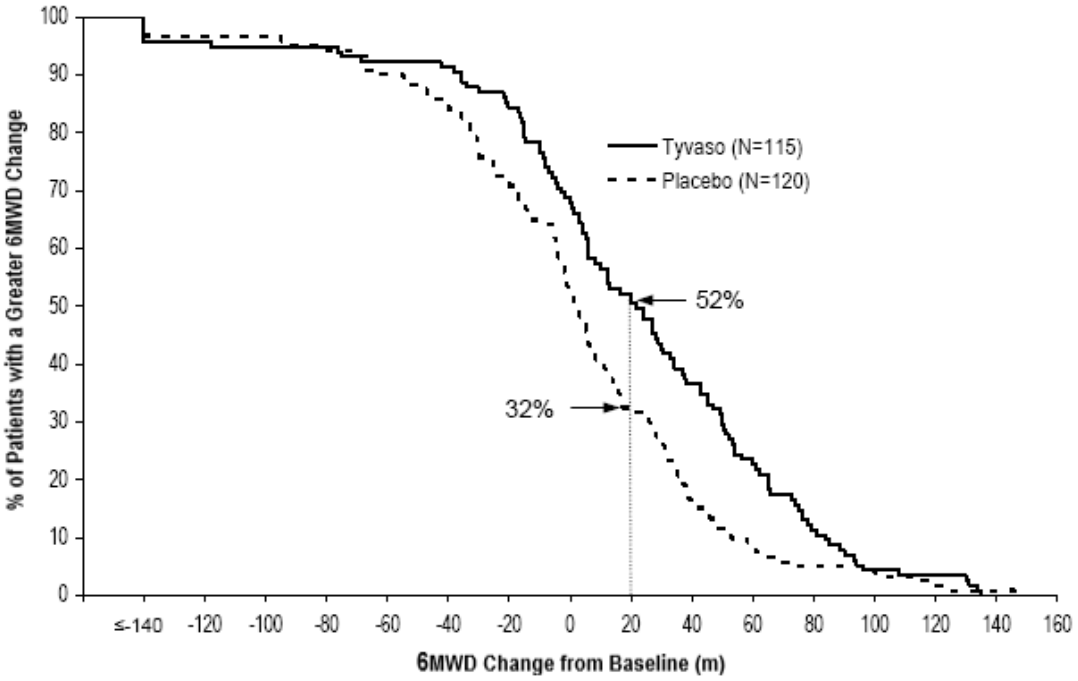
14 CLINICAL STUDIES

14.1 Pulmonary Arterial Hypertension (WHO Group 1)

TRIUMPH I, was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients with PAH. The study population included 235 clinically stable subjects with PAH (WHO Group 1), nearly all with NYHA Class III (98%) symptoms who were receiving either bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase-5 inhibitor) for at least 3 months prior to study initiation. Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Patients were predominately female (82%), had the origin of PAH as idiopathic/heritable (56%), secondary to connective tissue diseases (33%) or secondary to HIV or previous use of anorexigens (12%); bosentan was the concomitant oral medication in 70% of those enrolled, sildenafil in 30%.

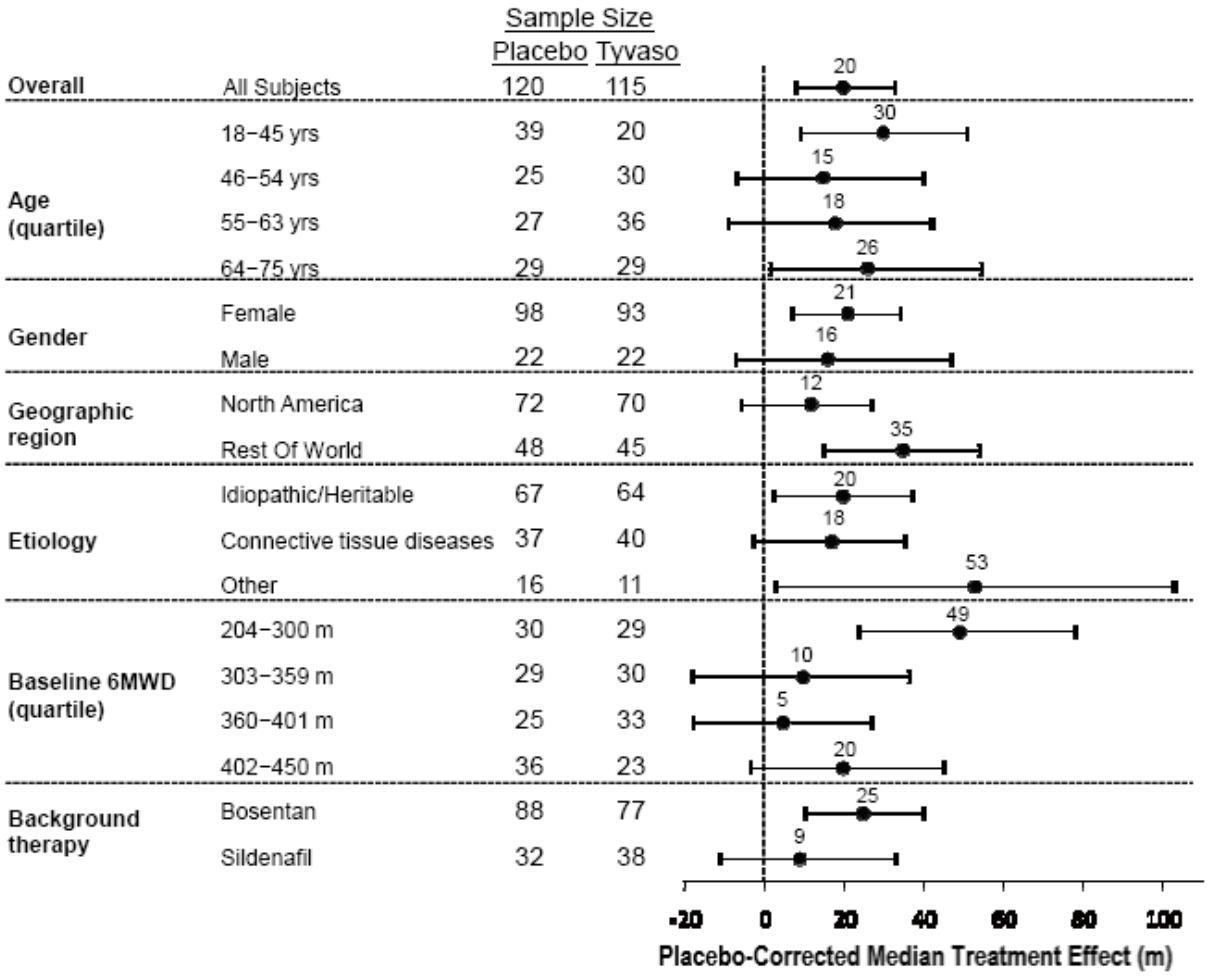
The primary efficacy endpoint of the trial was the change in 6-Minute Walk Distance (6MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3 to 5 hours after bosentan or 0.5 to 2 hours after sildenafil. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 20 meters at Week 12 ($p<0.001$). The distribution of these 6MWD changes from baseline at Week 12 were plotted across the range of observed values (Figure 1). 6MWD measured at trough exposure (defined as measurement of 6MWD at least 4 hours after dosing) improved by 14 meters. There were no placebo-controlled 6MWD assessments made after 12 weeks.

Figure 1: Distributions of 6MWD Changes from Baseline at Week 12 During Peak Plasma Concentration of Tyvaso



The placebo-corrected median treatment effect on 6MWD was estimated (using the Hodges-Lehmann estimator) within various subpopulations defined by age quartile, gender, geographic region of the study site, disease etiology, baseline 6MWD quartile, and type of background therapy (Figure 2).

Figure 2: Placebo-Corrected Median Treatment Effect (Hodges-Lehmann Estimate with 95% CI) on 6MWD Change from Baseline at Week 12 During Peak Plasma Concentration of Tyvaso for Various Subgroups



14.2 Long-term Treatment of PAH

In long-term follow-up of patients who were treated with Tyvaso in the pivotal study and the open-label extension (N=206), Kaplan-Meier estimates of survival at 1, 2, and 3 years were 97%, 91%, and 82%, respectively. These uncontrolled observations do not allow comparison with a control group not given Tyvaso and cannot be used to determine the long-term effect of Tyvaso on mortality.

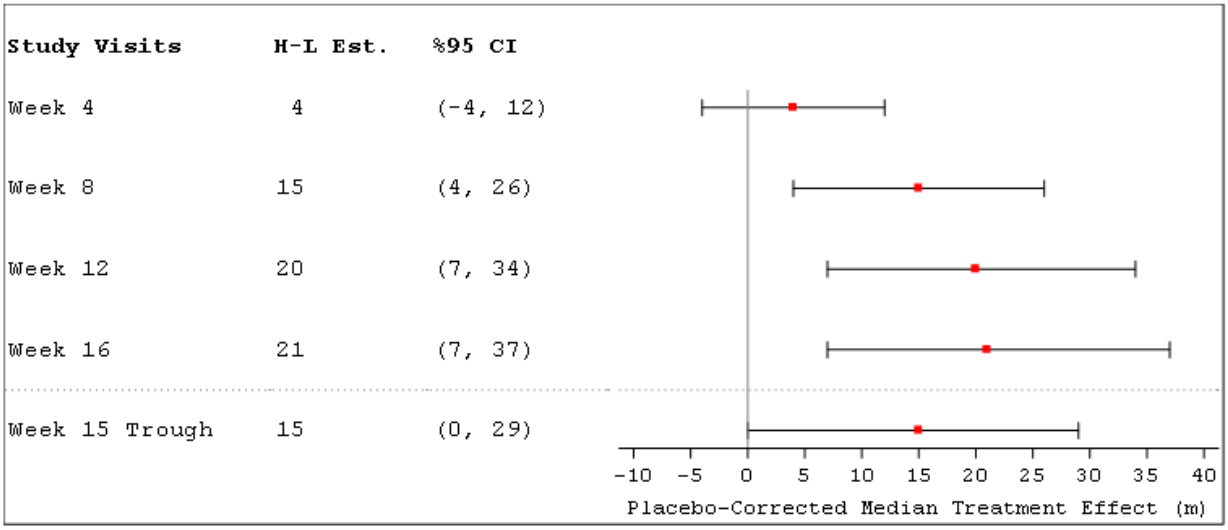
14.3 Pulmonary Hypertension Associated with ILD (WHO Group 3)

INCREASE was a 16-week, randomized, double-blind, placebo-controlled, multicenter study that enrolled 326 patients with PH-ILD. Enrolled study patients predominately had etiologies of idiopathic interstitial pneumonia (45%) inclusive of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema (25%), and WHO Group 3 connective tissue disease (22%). The mean baseline 6MWD was 260 meters.

Patients in the INCREASE study were randomized (1:1) to either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session and a maximum dose of 12 breaths (72 mcg) per session over the course of the 16-week study. Approximately 75% of patients randomized to Tyvaso titrated up to a dose of 9 breaths, 4 times daily or greater, with 48% of patients randomized to Tyvaso reaching a dose of 12 breaths, 4 times daily during the study.

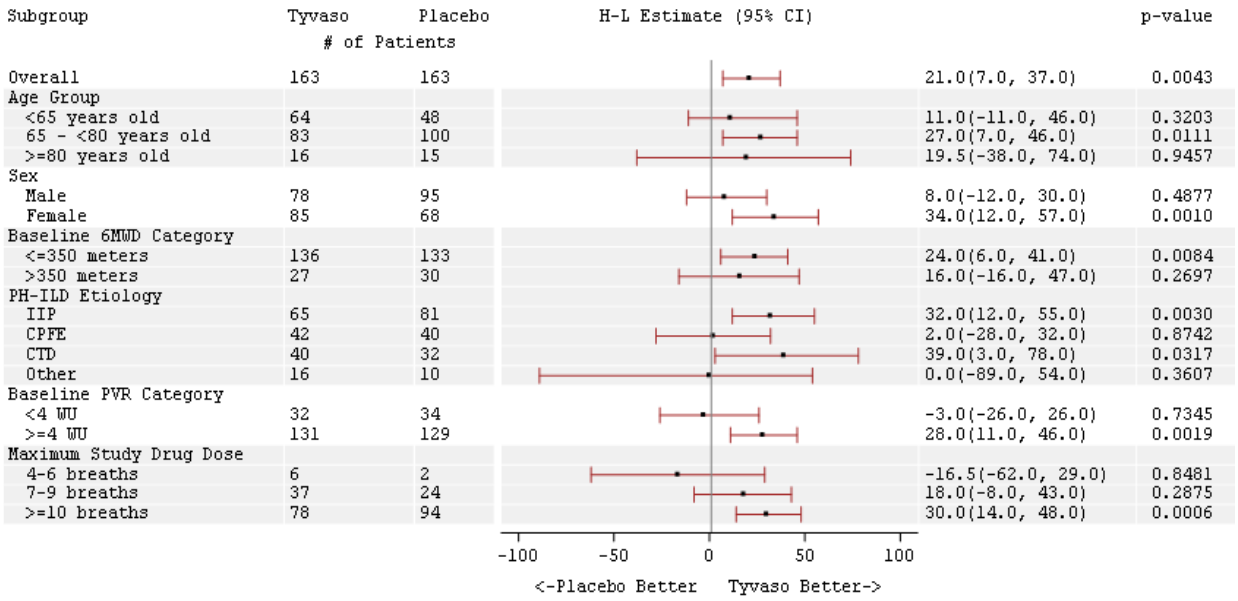
The primary efficacy endpoint was the change in 6MWD measured at peak exposure (between 10 and 60 minutes after dosing) from baseline to Week 16. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 21 meters at Week 16 (p=0.004) using Hodges-Lehmann estimate (Figure 3).

Figure 3: Hodges-Lehmann Estimate of Treatment Effect by Visit for 6MWD at Peak Exposure (PH-ILD)



The treatment effect on 6MWD at Week 16 was consistent for various subgroups, including etiology of PH-ILD, disease severity, age, sex, baseline hemodynamics, and dose (Figure 4).

Figure 4: Forest Plot on Subgroup Analyses of Peak 6MWD (Meter) at Week 16 (PH-ILD)



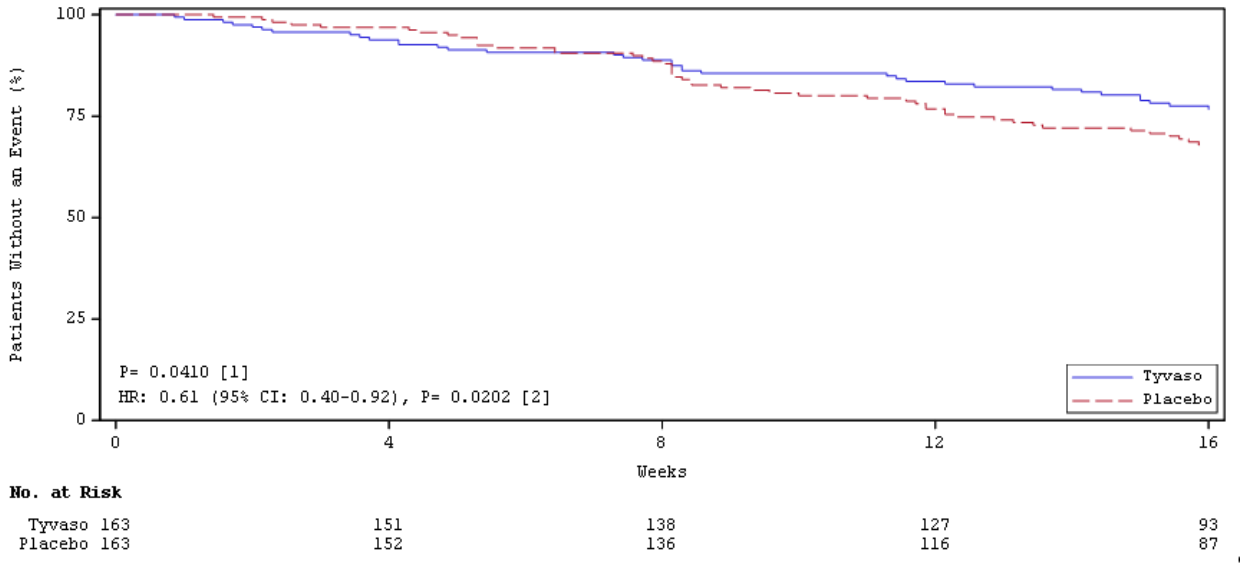
Time to clinical worsening in the INCREASE study was defined as the time of randomization until 1 of the following criteria were met: hospitalization due to a cardiopulmonary indication, decrease in 6MWD >15% from baseline directly related to PH-ILD at 2 consecutive visits and at least 24 hours apart, death (all causes), or lung transplantation. Treatment with Tyvaso in patients with PH-ILD resulted in numerically fewer hospitalizations. The numbers of reported deaths were the same for both treatment groups (Table 2). Overall, treatment with Tyvaso demonstrated a statistically significant increase in the time to first clinical worsening event (log-rank test p=0.041; Figure 5), and a 39% overall reduction in the risk of a clinical worsening event (HR=0.61 [95% CI; 0.40, 0.92]; Figure 5).

Table 2: Clinical Worsening Events (PH-ILD)

		Tyvaso n=163 n (%)	**Placebo n=163 n (%)**	**HR (95% CI)**
Clinical worsening		37 (22.7%)	54 (33.1%)	0.61 (0.40, 0.92)
First contributing event	**Hospitalization due to a cardiopulmonary indication**	18 (11.0%)	24 (14.7%)	
	Decrease in 6MWD >15% from baseline directly related to PH-ILD	13 (8.0%)	26 (16.0%)	
	Death (all causes)	4 (2.5%)	4 (2.5%)	
	Lung transplantation	2 (1.2%)	0	

		Tyvaso n=163 n (%)	Placebo n=163 n (%)	HR (95% CI)
First of each event	**Hospitalization due to a cardiopulmonary indication**	21 (12.9)	30 (18.4%)	
	Decrease in 6MWD >15% from baseline directly related to PH-ILD	16 (9.8%)	31 (19.0%)	
	Death (all causes)	8 (4.9%)	10 (6.1%)	
	Lung transplantation	2 (1.2%)	1 (0.6%)	

Figure 5: Kaplan-Meier Plot of Time to Clinical Worsening Events (PH-ILD)



16 HOW SUPPLIED/STORAGE AND HANDLING

Tyvaso (treprostinil) inhalation solution is supplied in 2.9 mL clear LDPE ampules packaged as 4 ampules in a foil pouch. Tyvaso is a clear colorless to slightly yellow solution containing 1.74 mg treprostinil per ampule at a concentration of 0.6 mg/mL.

Ampules of Tyvaso are stable until the date indicated when stored in the unopened foil pouch at 20-25°C (68-77°F) with excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Once the foil pack is opened, ampules should be used within 7 days. Because Tyvaso is light-sensitive, unopened ampules should be stored in the foil pouch.

One ampule of Tyvaso should be used each day in the Tyvaso Inhalation System. After a Tyvaso ampule is opened and transferred to the medicine cup, the solution should remain in the device for no more than 1 day (24 hours). Any remaining solution should be discarded at the end of the day.

Tyvaso Inhalation System Starter Kit containing a 28-ampule carton of Tyvaso (7 foil pouches each containing four 2.9 mL ampules; each ampule contains 1.74 mg treprostinil [0.6 mg per mL]) and the Tyvaso Inhalation System. (NDC 66302-206-01)

Tyvaso Inhalation System Refill Kit containing a 28-ampule carton of Tyvaso (7 foil pouches each containing four 2.9 mL ampules; each ampule contains 1.74 mg treprostinil [0.6 mg per mL]) and accessories. (NDC 66302-206-02)

Tyvaso 4 Pack Carton with 1 foil pouch containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL). (NDC 66302-206-03)

Tyvaso Inhalation System Institutional Starter Kit containing a 4-ampule carton of Tyvaso (1 foil pouch containing four 2.9 mL ampules; each ampule contains 1.74 mg treprostinil [0.6 mg per mL]) and the Tyvaso Inhalation System. (NDC 66302-206-04)

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

Train patients in the administration process for Tyvaso, including dosing, Tyvaso Inhalation System set up, operation, cleaning, and maintenance, according to the instructions for use *[see Dosage and Administration (2.1, 2.2)]*.

To avoid potential interruptions in drug delivery because of equipment malfunction, patients should have access to a back-up Tyvaso Inhalation System device *[see Dosage and Administration (2.2)]*.

In the event that a scheduled treatment session is missed or interrupted, resume therapy as soon as possible *[see Dosage and Administration (2.1)]*.

If Tyvaso comes in contact with the skin or eyes, instruct patients to rinse immediately with water *[see Dosage and Administration (2.2)]*.

Tyvaso manufactured for:

United Therapeutics Corp.
Research Triangle Park, NC 27709

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022387Orig1s017

SUMMARY REVIEW

DIVISION OF CARDIOLOGY AND NEPHROLOGY

Divisional Memorandum

NDA: 022387 (inhaled treprostinil)

Sponsor: United Therapeutics

Reviewer: N. Stockbridge, M.D., Ph.D.

Inhaled treprostinil has an indication for use in WHO Group 1 PAH. The proposed indication for supplement 017 is pulmonary hypertension associated with WHO Group 3 interstitial lung disease, for which it will be the first approved therapy.

The application was reviewed by Drs. Gordon (clinical) and Bai (statistics). I agree with their findings.

Use in ILD was supported by a single double-blind study INCREASE, conducted in the US, in which 326 subjects were randomized to study drug or placebo with the primary endpoint of 6MW assessed at peak at 16 weeks.

The baseline 6MW was about 260 m, and the double difference from baseline and placebo was about 22 m, according to prespecified rules for imputing missing data, causes for which were similar between groups, so the overall result is not particularly sensitive to imputation rules. See medical-statistical review for details.

There was a reduction in clinical worsening (23% on treprostinil and 33% on placebo), but its late promotion into the analytic hierarchy is troubling, and the effect is mostly on the component related to reduction in 6MW. (b) (4)

At this writing, the labeling negotiations are ongoing.

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/

NORMAN L STOCKBRIDGE
03/13/2021 08:02:16 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022387Orig1s017

MULTI-DISCIPLINE REVIEW

Clinical Review
Statistical Review

COMBINED CLINICAL AND STATISTICAL REVIEW

Application Type	Efficacy supplement
Application Number(s)	022387 SN 187
Priority or Standard	Standard
Submit Date(s)	01 Jun 2020
PDUFA Goal Date	01 Apr 2021
Division/Office	Cardiovascular and Renal Products / Office of New Drugs
Reviewer Name(s)	Maryann Gordon, MD. (clinical) Steve Bai, Ph.D. (statistical)
Review Completion Date	
Established/Proper Name	Inhaled Treprostinil
(Proposed) Trade Name	TYVASO
Applicant	United Therapeutics Corp.
Dosage Form(s)	inhalation solution, for oral inhalation only
Applicant Proposed Dosing Regimen(s)	The recommended starting dose of Tyvaso is: • 3 breaths (18 mcg) per session 4 times daily, approximately 4 hours apart • If 3 breaths are not tolerated, reduce to 1 or 2 breaths and subsequently increase to 3 breaths, as tolerated. Dosage should be increased by an additional 3 breaths per session at approximately 1- to 2-week intervals, if tolerated. Titrate to a target maintenance dose of 9 to 12 breaths per treatment session 4 times daily. If adverse effects preclude titration to target dose, Tyvaso should be continued at the highest tolerated dose.

Applicant Proposed Indication(s)/Population(s)	Tyvaso is indicated for the treatment of pulmonary hypertension (PH) associated with interstitial lung disease (ILD; WHO Group 3) to improve exercise ability (b) (4) (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of PH associated with ILD; WHO Group 3 to improve exercise ability (b) (4).

Table of Contents

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1 EXECUTIVE SUMMARY

Pulmonary hypertension (PH) is an increase in pulmonary arterial pressure and pulmonary vascular resistance. The World Health Organization classifies PH resulting from lung diseases and/or hypoxemia as WHO Group 3 PH. This classification includes PH due to interstitial lung disease (ILD) which consists of an assorted group of parenchymal lung diseases that are defined by significant scarring or fibrosis of the lungs. Deteriorating lung tissue results in worsening oxygenation and free gas exchange. Symptoms can vary and include a wide range of complaints with a range of severity.

There are no approved treatments for patients with PH associated with ILD (PH-ILD).

Treprostinil is a tricyclic analogue of prostacyclin. It is approved for the treatment of pulmonary arterial hypertension and includes a variety of formulations: subcutaneous, intravenous, inhaled and oral.

The indication proposed by this NDA is for the treatment of PH associated with ILD; WHO Group 3 to improve exercise ability (b) (4)

The recommended starting dose of Tyvaso is:
• 3 breaths (18 mcg) per session 4 times daily, approximately 4 hours apart
• If 3 breaths are not tolerated, reduce to 1 or 2 breaths and subsequently increase to 3 breaths, as tolerated.
Dosage should be increased by an additional 3 breaths per session at approximately 1- to 2-week intervals, if tolerated. Titrate to a target maintenance dose of 9 to 12 breaths per treatment session 4 times daily. If adverse effects preclude titration to target dose, Tyvaso should be continued at the highest tolerated dose.

The efficacy of this drug for this proposed indication was supported by one study identified as Study RIN-PH-201. This study was a multicenter, randomized, double-blind, placebo-controlled study of inhaled treprostinil in subjects with PH-ILD. Patients included those with etiologies of idiopathic interstitial pneumonia inclusive of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema, and WHO Group 3 connective tissue disease. The results of this study showed significant improvements in exercise ability (6-minute walk test) at peak concentration compared to placebo. The individual components of clinical worsening events (defined as hospitalization resulting from a cardiopulmonary indication, decrease in 6MWD >15% from baseline directly related to PH-ILD at 2 consecutive visits and at least 24 hours apart, all-cause death, or lung transplantation) were all numerically in favor of inhaled treprostinil group. The treatment with inhaled treprostinil compared to placebo provided a significant overall reduction in the risk of a clinical worsening event during the study.

Regarding safety, the use of inhaled treprostinil by patients with PH associated with interstitial lung disease (WHO Group 3) was well tolerated over the treatment period with most reported events being expected prostanoid-related AEs (e.g., diarrhea, jaw pain, flushing, and edema). No new safety concerns arose during the evaluation of this drug in this new indication.

The positive benefit-risk profile of inhaled treprostinil supports its use in patients diagnosed with PH-ILD (WHO Group 3). Treatment with inhaled treprostinil, therefore, appears to provide sufficient benefit to patients diagnosed with this disease.

2 INTRODUCTION

Pulmonary hypertension (PH) is defined as an elevation in pulmonary arterial pressure and pulmonary vascular resistance. The World Health Organization (WHO) classifies PH due to lung diseases and/or hypoxemia as WHO Group 3 PH. This classification includes PH associated with interstitial lung disease (PH-ILD). Tyvaso (treprostinil) inhalation solution was approved in 2009 in the United States of America for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability, demonstrated by an increase in 6-Minute Walk Distance (6MWD). There are no approved treatments for patients with PH-ILD (WHO Group 3); however, the results from studies of some approved therapies for PAH have suggested that treprostinil therapy in PH-ILD subjects could improve exercise ability and other important clinical outcomes.

2.1 Overview

This supplemental efficacy application provides additional efficacy and safety data of inhaled treprostinil for the treatment of PH-ILD. Study RIN-PH-201 (INCREASE) was a multicenter, randomized, double-blind, placebo-controlled study of inhaled treprostinil in subjects with PH-ILD. The study was designed to evaluate the safety and efficacy of inhaled treprostinil in this subject population. The primary objective was assessed by the change in 6MWD measured at peak exposure from Baseline to Week 16.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: \\CDSESUB1\evsprod\NDA022387\0187\m5.

3 REGULATORY HISTORY

There are no approved treatments for patients with PH associated with ILD (PH-ILD).

Treprostinil is a chemically stable tricyclic analogue of prostacyclin. It is approved for the treatment of pulmonary arterial hypertension (PAH) following either the subcutaneous (SC), intravenous (IV), inhaled (as treprostinil sodium), or oral (as treprostinil diolamine) routes of administration.

The proposed indication is for the treatment of PH associated with ILD; WHO Group 3 to improve exercise ability (b) (4)

In support of the proposed indication and dosing, supplemental efficacy and safety data were provided for a single, pivotal study (Study RIN-PH-201). This study was a multicenter, randomized, double-blind, placebo-controlled study of inhaled treprostinil in subjects with PH-ILD.

There is one ongoing study in subjects with PH-ILD with inhaled dosing: RIN-PH-202 is an open- label extension study enrolling subjects formerly in Study RIN-PH-201. Currently, 243 subjects have been enrolled. The dose is up to 72 µg (12 breaths) 4 times a day.

The benefit-risk safety of inhaled treprostinil builds upon the approved uses of treprostinil (SC, IV, and oral routes) while also providing efficacy and safety data supporting the use of inhaled

treprostinil in patients diagnosed with PH-ILD. The results of Study RIN-PH-201 demonstrated significant improvements in exercise ability as evidenced by changes in the 6MWD test as well as improvements in other clinically meaningful outcomes. The safety profile of inhaled treprostinil in RIN-PH-201 was shown to be similar to that reported in previous studies, with most events that were considered to be attributable to study drug being known and expected prostanoid-related AEs. The results of this study indicated that there were no new safety concerns related to the use of inhaled treprostinil in patients with PH-ILD. Treatment with inhaled treprostinil appeared to provide sufficient benefit to these patients.

Financial Disclosure

Form 3454 check box 1

As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Form 3454 check box 3

As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

Form 3455 check box 3
Any significant payments of other sorts made on or after February 1, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing, consultation, or Honoria are shown below.

ATTACHMENT TO FORM FDA 3455

NDA 022387

Tyvaso® (treprostinil) Inhalation Solution

Investigators with Financial Interests to Disclose

Study RIN-PH-201

Table 1-1 Principal Investigators with Financial Interests to Disclose

Site Number	Investigator	Institution	Significant Payments of Other Sorts During This Study
	(b) (6)		The Significant Payments of Other Sorts made to this investigator were for consulting, speaking fees and honoraria. This was a multi-center study conducted nationwide. The Significant Payments of Other Sorts made to this investigator did not influence the results of this study.
	(b) (6)		The Significant Payments of Other Sorts made to this investigator were for consulting and speaking fees. This was a multi-center study conducted nationwide. The Significant Payments of Other Sorts made to this investigator did not influence the results of this study.

Table 1-2 Sub-Investigators with Financial Interests to Disclose

Site Number	Investigator	Institution	Significant Payments of Other Sorts During This Study
	(b) (6)		The Significant Payments of Other Sorts made to this investigator were for consulting, speaking fees and honoraria. This was a multi-center study conducted nationwide. The Significant Payments of Other Sorts made to this investigator did not influence the results of this study.
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			The Significant Payments of Other Sorts made to this investigator were for consulting and speaking fees. This was a multi-center study conducted nationwide. The Significant Payments of Other Sorts made to this investigator did not influence the results of this study.

4 STUDY DESIGN

Title: A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease.

Study Drug: Inhaled Treprostinil

Indication: Pre-capillary pulmonary hypertension (PH) associated with interstitial lung disease.

Study Number: RIN-PH-201

Investigators and Study Centers: This study was conducted in 119 centers in the United States and Puerto Rico

The primary objective: the change in 6-Minute Walk Distance (6MWD) measured at peak exposure from Baseline to Week 16. Peak exposure is defined as the window that is 10 to 60 minutes after the patient received the most recent study drug dose.

The secondary objectives: evaluate the effects of inhaled treprostinil on the following parameters:

- Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Week 16
- Time to clinical worsening as the time from randomization until one of the following criteria was met:
    - Hospitalization due to a cardiopulmonary indication
    - Decrease in 6MWD >15% from Baseline directly related to disease under study, at two consecutive visits, and at least 24 hours apart
    - Death (all causes)
    - Lung transplantation
- Change in peak 6MWD from Baseline to Week 12
- Change in trough 6MWD from Baseline to Week 15. Trough exposure is defined as the window that is at least four hours after the patient received the most recent study drug dose.

The exploratory objectives: evaluate the effects of inhaled treprostinil on the following parameters:

- Change in peak 6MWD from Baseline to Week 4
- Change in peak 6MWD from Baseline to Week 8
- Change in quality of life (QOL) as measured by the St. George's Respiratory Questionnaire (SGRQ) from Baseline to Week 16
- Change in distance saturation product (DSP) from Baseline to Week 16. DSP is defined as the product of total distance walked and final oxygen saturation (SpO2) during 6MWT.

Methodology: multicenter, randomized, double-blind, placebo-controlled, 16-week, parallel group study designed to investigate the safety and efficacy of inhaled treprostinil in subjects with PH-ILD.

Treatment: inhaled treprostinil or placebo at a dose of 3 breaths (18 mcg) 4 times daily (QID) (during waking hours). Study drug doses were maximized throughout the study.

Dose escalations (additional 1 breath QID) could occur up to every 3 days with a target dosing regimen of 9 breaths (54 mcg) QID and a maximum dose of 12 breaths (72 mcg) QID, as clinically tolerated.

Study visits: once eligible, 5 Treatment Phase visits to the clinic were required at Week 4, Week 8, Week 12, Week 15, and Week 16 (final study visit). An Early Termination (ET) Visit was conducted for subjects who discontinued prior to Week 16; all assessments planned for the final Week 16 Visit were conducted during the ET Visit, if applicable. Subjects were contacted at least weekly by telephone or email to assess tolerance to study drug, AEs, and changes to concomitant medications.

Efficacy assessments: 6MWD, plasma NT-proBNP concentration, and time to clinical worsening. Exploratory endpoints included change in SGRQ, change in DSP, time to exacerbation of underlying lung disease, and PFTs.

Major inclusion criteria

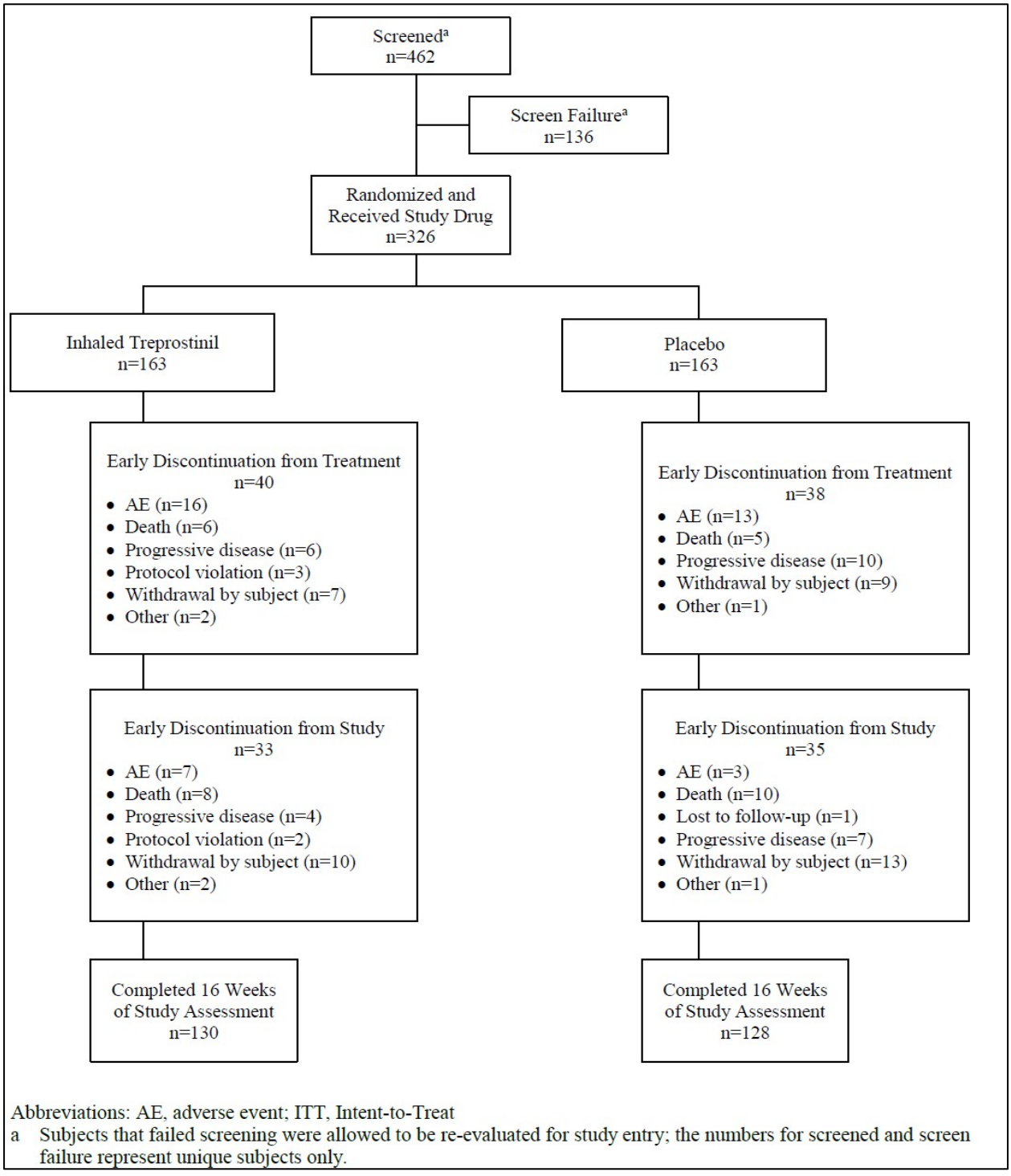
The subject had a confirmed diagnosis of World Health Organization (WHO) Group 3 PH based on computed tomography (CT) imaging which was performed within 6 months prior to randomization and demonstrated evidence of diffuse parenchymal lung disease. Subjects had any form of ILD or combined pulmonary fibrosis and emphysema (CPFE).
Subjects were required to have a right heart catheterization (RHC) within 1 year prior to randomization with the following documented parameters:

a. Pulmonary vascular resistance (PVR) >3 Wood Units (WU), and
b. A pulmonary capillary wedge pressure (PCWP) of $\leqslant$15 mmHg, and
c. A pulmonary artery pressure mean (PAPm) of $\geqslant$25 mmHg
d. Baseline 6MWD $\geqslant$100 m.
e. Subjects on a chronic medication for underlying lung disease (ie, pirfenidone, nintedanib, etc) were on a stable and optimized dose for $\geqslant$30 days prior to randomization.
f. Subjects with connective tissue disease (CTD) had a Baseline FVC of <70%.

5 DISPOSITION OF SUBJECTS

Number and Disposition of Subjects: A total of 326 subjects were enrolled and analyzed. Their disposition, by treatment group, is shown in the figure and table below.

Figure 5.1 Summary of Subject Disposition-ITT population



Abbreviations: AE, adverse event; ITT, Intent-to-Treat

a Subjects that failed screening were allowed to be re-evaluated for study entry; the numbers for screened and screen failure represent unique subjects only.

Table 5.1 Summary of Subject Accountability -ITT Population

	Inhaled Treprostinil n (%)	Placebo n (%)	Overall n (%)
Number of Subjects Randomized and Received Study Drug	**163**	**163**	**326**
Completed 4 weeks of study assessment	154 (94.5)	154 (94.5)	308 (94.5)
Completed 8 weeks of study assessment	138 (84.7)	138 (84.7)	276 (84.7)
Completed 12 weeks of study assessment	133 (81.6)	133 (81.6)	266 (81.6)
Completed 15 weeks of study assessment	125 (76.7)	126 (77.3)	251 (77.0)
Completed 16 weeks of study assessment	130 (79.8)	128 (78.5)	258 (79.1)
Number of Subjects who Discontinued Study Drug Early	**40 (24.5)**	**38 (23.3)**	**78 (23.9)**
Death	6 (3.7)	5 (3.1)	11 (3.4)
Progressive disease	6 (3.7)	10 (6.1)	16 (4.9)
Adverse event	16 (9.8)	13 (8.0)	29 (8.9)
Withdrawal by subject	7 (4.3)	9 (5.5)	16 (4.9)
Protocol violation	3 (1.8)	0	3 (0.9)
Other	2 (1.2)	1 (0.6)	3 (0.9)
Number of Subjects who Discontinued Study Early	**33 (20.2)**	**35 (21.5)**	**68 (20.9)**
Death	8 (4.9)	10 (6.1)	18 (5.5)
Progressive disease	4 (2.5)	7 (4.3)	11 (3.4)
Adverse event	7 (4.3)	3 (1.8)	10 (3.1)
Withdrawal by subject	10 (6.1)	13 (8.0)	23 (7.1)
Protocol violation	2 (1.2)	0	2 (0.6)
Lost to follow-up	0	1 (0.6)	1 (0.3)
Other	2 (1.2)	1 (0.6)	3 (0.9)
Number of Subjects Who Transitioned to Extension Study	**120 (73.6)**	**121 (74.2)**	**241 (73.9)**

Abbreviations: ITT, Intent-to-Treat

There were 462 patients screened and 326 randomized to treatment: 163 to treprostinil as well to placebo. There were 40 treprostinil patients who discontinued treatment early compared to 38 placebo patients. Regarding study discontinuation, 33 treprostinil patients and 35 placebo patients discontinued early. Similar numbers (130 treprostinil and 128 placebo) completed the 16-week study.

Reasons for early drug and/or study discontinuation included death, progressive disease, adverse event, withdrawal by subject, protocol violation, lost to follow up. The number of patients who cited these reasons were similar regardless of treatment group.

Demographics

The demographics and PH-ILD histories at baseline are shown in the table below by treatment group.

Table 5.2 Summary of Demographic Data and PH-ILD History – ITT Population

	Inhaled Treprostinil N=163	Placebo N=163	Overall N=326
Age at Randomization (years)			
n	163	163	326
Mean (SD)	65.6 (12.7)	67.4 (11.2)	66.5 (12.0)
Median	69.0	71.0	70.0
Min, Max	26, 90	36, 85	26, 90
Age Category (years), n (%)			
<65 years	64 (39.3)	48 (29.4)	112 (34.4)
65 to <80 years	83 (50.9)	100 (61.3)	183 (56.1)
≥80 years	16 (9.8)	15 (9.2)	31 (9.5)
Sex, n (%)			
Male	78 (47.9)	95 (58.3)	173 (53.1)
Female	85 (52.1)	68 (41.7)	153 (46.9)
Ethnicity, n (%)			
Hispanic or Latino	11 (6.7)	16 (9.8)	27 (8.3)
Not Hispanic or Latino	152 (93.3)	146 (89.6)	298 (91.4)
Missing	0	1 (0.6)	1 (0.3)
Race, n (%)			
White	112 (68.7)	126 (77.3)	238 (73.0)
Black or African American	41 (25.2)	30 (18.4)	71 (21.8)
American Indian or Alaska Native	2 (1.2)	1 (0.6)	3 (0.9)
Asian	7 (4.3)	5 (3.1)	12 (3.7)
Multiple	0	1 (0.6)	1 (0.3)
Unknown	1 (0.6)	0	1 (0.3)
Time Since PH-ILD Diagnosis (years)			
n	163	163	326
Mean (SD)	0.543 (1.157)	0.539 (1.309)	0.541 (1.233)
Median	0.180	0.230	0.210
Min, Max	0.01, 8.37	0.01, 13.02	0.01, 13.02
Etiology of PH-ILD, n (%)			
Idiopathic interstitial pneumonia	65 (39.9)	81 (49.7)	146 (44.8)
Chronic hypersensitivity pneumonitis	10 (6.1)	9 (5.5)	19 (5.8)
Occupational lung disease	5 (3.1)	1 (0.6)	6 (1.8)
Combined pulmonary fibrosis and emphysema	42 (25.8)	40 (24.5)	82 (25.2)
Connective tissue disease	40 (24.5)	32 (19.6)	72 (22.1)
Other	1 (0.6)	0	1 (0.3)
Idiopathic Interstitial Pneumonia Subcategory, n (%)			
Idiopathic pulmonary fibrosis	37 (22.7)	55 (33.7)	92 (28.2)
Idiopathic nonspecific interstitial pneumonia	21 (12.9)	16 (9.8)	37 (11.3)
Respiratory bronchiolitis-associated with interstitial lung disease	2 (1.2)	0	2 (0.6)
Desquamative interstitial pneumonia	0	1 (0.6)	1 (0.3)
Acute interstitial pneumonia	0	1 (0.6)	1 (0.3)
Unclassified idiopathic interstitial pneumonia	5 (3.1)	8 (4.9)	13 (4.0)

Abbreviations: ILD, interstitial lung disease; ITT, Intent-to-Treat; PH, pulmonary hypertension; SD, standard deviation

The mean age of patients was over 66 years with ages ranging from 26 to 90 years old. There were slightly more males than females in the study and most were white. The treatment groups were well balanced.

Time since PH-ILD diagnosis was about 6 months. The most common etiologies included idiopathic interstitial pneumonia, combined pulmonary fibrosis and emphysema and connective tissue disease (45%, 25%, 22% overall, respectively).

The groups were well balanced.

Table 5.3 Summary of Baseline Characteristics

	Inhaled Treprostinil N=163	Placebo N=163	Overall N=326
Baseline 6MWD (m)			
n	163	163	326
Mean (SD)	254.1 (102.4)	265.1 (93.1)	259.6 (97.9)
Median	256.0	260.0	259.0
Min, Max	100, 538	30, 505	30, 538
Baseline NT-proBNP (pg/mL)			
n	153	158	311
Mean (SD)	223.463 (378.450)	210.886 (370.726)	217.073 (373.994)
Median	67.400	49.655	59.910
Min, Max	2.54, 2589.16	2.71, 1923.05	2.54, 2589.16
Baseline PVR (WU)			
n	163	163	326
Mean (SD)	6.369 (2.863)	6.013 (2.718)	6.191 (2.793)
Median	5.570	5.060	5.275
Min, Max	3.11, 18.05	3.06, 17.62	3.06, 18.05
Baseline PAPm (mmHg)			
n	163	163	326
Mean (SD)	37.2 (8.6)	36.0 (8.4)	36.6 (8.5)
Median	35.0	35.0	35.0
Min, Max	25, 74	25, 61	25, 74
Baseline PCWP (mmHg)			
n	163	163	326
Mean (SD)	10.1 (3.4)	9.6 (3.5)	9.8 (3.5)
Median	10.0	10.0	10.0
Min, Max	2, 20	0, 15	0, 20
Vasodilator Testing During Confirmatory RHC?			
Yes	42 (25.8)	45 (27.6)	87 (26.7)
No	121 (74.2)	118 (72.4)	239 (73.3)
Subjects with Nintedanib and/or Pirfenidone at Baseline	**30 (18.4)**	**44 (27.0)**	**74 (22.7)**
Pirfenidone only	19 (11.7)	25 (15.3)	44 (13.5)
Nintedanib only	11 (6.7)	19 (11.7)	30 (9.2)

Overall, mean baseline 6MWD was 260m. The baseline NT-proBNP and cardiac hemodynamic parameters were similar for the two groups. More than 22% of subjects were receiving either nintedanib or pirfenidone or both at baseline. There were no major differences between the treatment groups for any of these characteristics at baseline.

Protocol deviations

Table 14.1.6.2
Summary of Protocol Deviations
Population: ITT

	Inhaled Treprostinil N=163 n (%)	Placebo N=163 n (%)	Overall N=326 n (%)
Number of Subjects with at least one Protocol Deviation	133 (81.6%)	148 (90.8%)	281 (86.2%)
Type of Deviation			
Assessments/Safety	90 (55.2%)	97 (59.5%)	187 (57.4%)
Assessments/Safety_Primary Endpoint	78 (47.9%)	80 (49.1%)	158 (48.5%)
CTM/IMP/Study Drug	21 (12.9%)	31 (19.0%)	52 (16.0%)
CTM/IMP/Study Drug_Compliance	31 (19.0%)	27 (16.6%)	58 (17.8%)
Facilities and Personnel	0	3 (1.8%)	3 (0.9%)
Inclusion/Exclusion Criteria	7 (4.3%)	7 (4.3%)	14 (4.3%)
Informed Consents	16 (9.8%)	22 (13.5%)	38 (11.7%)
Laboratory/Biological Samples	14 (8.6%)	14 (8.6%)	28 (8.6%)
Mis-randomization/Mis-stratification	3 (1.8%)	7 (4.3%)	10 (3.1%)
Regulatory Issues	0	1 (0.6%)	1 (0.3%)
SAE not reported within protocol timeline	3 (1.8%)	9 (5.5%)	12 (3.7%)
Visit Window	54 (33.1%)	76 (46.6%)	130 (39.9%)

Major violations

Table 14.1.6.2
Summary of Protocol Deviations
Population: ITT

	Inhaled Treprostinil N=163 n (%)	Placebo N=163 n (%)	Overall N=326 n (%)
Number of Subjects with at least one Major Protocol Deviation	26 (16.0%)	42 (25.8%)	68 (20.9%)
Type of Major Deviation			
Assessments/Safety	3 (1.8%)	4 (2.5%)	7 (2.1%)
Assessments/Safety_Primary Endpoint	2 (1.2%)	2 (1.2%)	4 (1.2%)
CTM/IMP/Study Drug	1 (0.6%)	2 (1.2%)	3 (0.9%)
Inclusion/Exclusion Criteria	2 (1.2%)	6 (3.7%)	8 (2.5%)
Informed Consents	14 (8.6%)	15 (9.2%)	29 (8.9%)
Laboratory/Biological Samples	0	2 (1.2%)	2 (0.6%)
Mis-randomization/Mis-stratification	3 (1.8%)	7 (4.3%)	10 (3.1%)
Regulatory Issues	0	1 (0.6%)	1 (0.3%)
SAE not reported within protocol timeline	3 (1.8%)	9 (5.5%)	12 (3.7%)
Visit Window	1 (0.6%)	2 (1.2%)	3 (0.9%)

6 STATISTICAL EVALUATION

6.1 Protocol, Statistical Analysis Plans, and Amendments

The study was initiated 03 Feb 2017 (First visit of first subject) and the completion date was 26 Dec 2019 (Last visit of last subject). The original protocol was drafted on Oct 2015 and finalized with its third amendment on Feb 2017. The original SAP was drafted on Feb 2019 and finalized on Dec 2019 with its one and only amendment. The ordering of secondary and exploratory endpoints was re-ordered in the SAP Amendment 1 and differ from the order specified in RIN- PH-201 Protocol Amendment 3. In the protocol, time to clinical worsening was identified as an exploratory endpoint. However, the time to clinical worsening was analyzed as a secondary

endpoint in the SAP amendment 1, which was finalized about 2 weeks prior to the completion of the study.

This submission is in electronic common technical document (eCTD) format. UTC submitted the datasets and annotated SAS code for all the primary and supportive analyses. Study datasets are provided as SAS XPORT transport files. The submitted data and analysis quality appear adequate. The variables in study datasets are consistently named and used across trials, with clear description in the Define file. The reported analysis results are in good quality. The statistical reviewer was able to reproduce the sponsor's results for the primary and all key secondary endpoints.

6.2 Analysis Populations

The Intent-to-Treat (ITT) Population was defined as all subjects randomized into the study who received at least 1 dose of study drug. All ITT subjects were counted in the group to which they were randomized, regardless of the study drug they were given. All efficacy analyses were performed on this ITT Population, unless otherwise specified.

The Per-protocol (PP) Population included all subjects in the ITT Population, excluding subjects with major protocol deviations that could have impacted the primary efficacy analyses.

6.3 Primary Efficacy Analysis

The primary efficacy endpoint of peak 6MWD assesses if inhaled treprostinil will increase the distance traversed in the peak 6MWT at Week 16 over placebo in subjects with PH-ILD. The effect of inhaled treprostinil versus placebo on change in peak 6MWD at Week 16 will be evaluated via analysis of covariance (ANCOVA). Change from Baseline in peak 6MWD is the dependent variable, and treatment and Baseline 6MWD are covariates in this ANCOVA model. If the ANCOVA assumptions are violated, the primary efficacy analysis will be based on non- parametric analysis of covariance within the framework of the extended Cochran-Mantel- Haenszel test. In addition, the Wilcoxon rank sum test and the Hodges-Lehmann estimate of median difference (as an estimate of location shift between 2 treatment groups for the placebo- controlled treatment effect) will be provided.

To further support the robustness and assess the sensitivity of the primary efficacy analysis of change in peak 6MWD at Week 16. A longitudinal data analysis using mixed model repeated measurement (MMRM) was also performed to estimate the treatment difference in change in peak 6MWD at Week 16. The MMRM includes the change from Baseline in peak 6MWD as the dependent variable; treatment, week, and treatment by week interaction as fixed effects; and Baseline 6MWD as a covariate. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

6.4 Secondary Efficacy Analyses

If the primary efficacy endpoint is statistically significant at alpha level 0.05, the statistical tests for secondary efficacy endpoints will be performed. To control the Type 1 error rate, the secondary efficacy endpoints will be tested using a hierarchical (fixed sequence) testing procedure in the following order.

a. Change in NT-proBNP at Week 16

The difference between treatment groups for the change from Baseline to Week 16 was tested using ANCOVA with change from Baseline in NT-proBNP as the dependent variable, treatment as the fixed effect, and Baseline NT-proBNP as the covariate. NT-proBNP measurements were log-transformed for the analyses.

b. Time to Clinical Worsening

Time to clinical worsening will be summarized by treatment group using product-limit estimates calculated by the Kaplan-Meier method and displayed graphically as Kaplan-Meier curves. The log-rank test, adjusted for Baseline 6MWD category, will be used to calculate the p-value for treatment differences in the ITT population. In addition, the Cox proportional hazards model will be fit to obtain the hazard ratio and its associated 95% confidence interval. The model will include treatment and Baseline 6MWD as explanatory variables.

c. Change in Peak 6MWD at Week 12

The methodology for primary efficacy analysis of change in peak 6MWD at Week 16 will also be carried out for the Week 12 assessment.

d. Change in Trough 6MWD at Week 15

The methodology for primary efficacy analysis of change in peak 6MWD at Week 16 will also be carried out for the Week 15 Trough assessment

6.5 Missing Data Handling of 6MWD

For the analysis of 6MWD, subjects may not have completed the treatment with study drug prior to the Week 16 visit for the following reasons: death, progressive disease, AE, withdrawal of consent by the subject, protocol violation, loss to follow-up, termination of study by the sponsor, or withdrawal for other reasons. In addition, subjects still receiving study drug may be too critically ill to perform the 6MWT, resulting in missing data for that assessment. The following imputation rules will be applied for subjects who's peak 6MWD measures at Week 12 or Week 16 are missing.

Table 6.1 Imputation Rules for Peak 6MWD

Reason for missing 6MWD measure	Imputation
Death (all causes)	Worst score (0 meters)
Clinical worsening event	Worst score (0 meters)
Too ill to perform 6MWT	Worst score (0 meters)
All other reasons	Last (peak) Observation Carried Forward (LOCF)

For subjects whose trough 6MWD measures at Week 15 are missing, the missing values will be imputed as described in the following Table.

Table 6.2 Imputation Rules for Trough 6MWD

Reason for missing 6MWD measure	Imputation
Death (all causes)	Worst score (0 meters)
Clinical worsening	Worst score (0 meters)
Too ill to perform 6MWT	Worst score (0 meters)
All other reasons	Baseline Observation Carried Forward (BOCF)

6.6 Efficacy Results and Conclusions

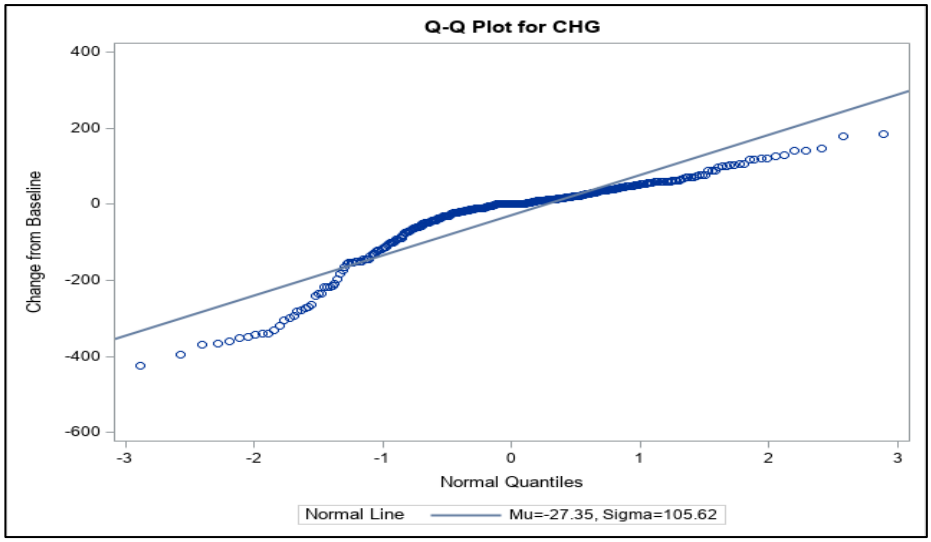
6.6.1 Analysis of Primary Endpoint

As described in the SAP, the normality assumption of change from baseline in peak 6MWD at week 16 should be verified first. However, neither SAP specified which normality tests to perform nor conducted after the conclusion of the study. Hence, this reviewer performed the Shapiro-Wilk test with test statistic W=0.855 (P-value <0.0001). This indicated strong evidence to reject null hypothesis that the variable is normally distributed. Similarly, Kolmogorov- Smirnov, Cramer-von Mises, and Anderson-Darling tests do not reject the null hypothesis, see Table 6.3. Furthermore, the Q-Q plot in Figure 6.1 also shows that data points seriously deviate from the fitted line. Hence, the non-parametric ANCOVA is applied to the primary efficacy endpoint.

Table 6.3 Tests for Normality of Change from Baseline

Test	Statistic		p Value	
Shapiro-Wilk	W	0.855402	Pr < W	<0.0001
Kolmogorov-Smirnov	D	0.190564	Pr > D	<0.0100
Cramer-von Mises	W-Sq	3.124872	Pr > W-Sq	<0.0050
Anderson-Darling	A-Sq	16.70803	Pr > A-Sq	<0.0050

Figure 6.1 Q-Q plot of Change from Baseline



The change from Baseline in peak 6MWD at Week 16 in the inhaled treprostinil group was significantly higher than the placebo group when analyzed using non-parametric ANCOVA (Hodges-Lehmann estimate of location shift: 21.0 m; p=0.0042). Overall, median change from Baseline in peak 6MWD in the inhaled treprostinil group increased by 6.0 m at Week 16 compared with a decrease of 9.0 m in the placebo group, see Table 6.4. The LS mean difference also showed a 21.9 m improvement of inhaled treprostinil group over placebo. However, it failed reached the statistical significance with a p=0.0609. In addition, the treatment difference (inhaled treprostinil – placebo) in peak 6MWD at Week 16 was significant when analyzed using MMRM (31.12 m; p<0.0001; 95% CI: 16.85, 45.39), see Table 6.5.

Table 6.4 Summary and Analysis of Peak 6MWD at Week 16

T-Stat	Visit	Treprostinil N=163	Placebo N=163	p-value
Non-Parametric	Baseline	256.0	260.0	
	Week 16	255.0	240.0	
	Change in Median	6.0	-9.0	
	HL (95% CI)	21.0 (7.0, 37.0)		0.0042
ANCOVA	Baseline	254.1 (102.4)	265.1 (93.1)	
	Week 16	238.2 (137.0)	226.3 (137.9)	
	LS Mean (95% CI)	21.9 (-1.0, 44.8)		0.0609

Table 6.5 Analysis of Peak 6MWD at Week 16 by MMRM

Treatment	LS Mean	Est. Diff	95% CI	P-value
Inhaled Treprostinil	21.08	31.12	16.85,45.39	<0.0001
Placebo	-10.04			

The Impact of Missing 6MWD

Although, the agency's statistical reviewer did not object to the imputation rules proposed in Table 6.1 when the Statistical Analysis Plan was submitted in December 2019. However, there are two issues with the imputation rules:

a. The worst score of 0 meters may be generate the worst change from baseline at Week 16 in the event of missing due to Death, Clinical Worsening and Too ill to perform walk test. For example, a subject had baseline of 50 meters of 6MWD and he subsequently died prior to completing the trial. The change from baseline in 6MWD at Week 16 is only -50 m, which is not worse than the largest observed decline in 6MWD (-269 m).
b. There is also concerns that LOCF may underestimate statistical uncertainty. The Division has reconsidered the use of LOCF following the publication in 2010 of the FDA commissioned report on missing data by the National Academy of Sciences (NAS), "Prevention and Treatment of Missing Data in Clinical Trials." The report specifically recommends (page 110) "Single imputation methods like last observation carried forward and baseline observation carried forward should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified."

Table 6.6 Pattern of Missing Week 16 6MWD measures

6MWD Derivation Reason	Death	Clinical Worsening	Too Critically Ill	Other	Total
Treprostinil	10	15	0	17	42
Placebo	11	12	1	19	43

There is a total of 42 inhaled Treprostinil and 43 placebo subjects' Week 16 6MWD measures were imputed by the proposed rules, see Table 6.6. The pattern of missing due to all the intercurrent events is also balanced crossed both treatment groups. Hence, the statistical reviewer proposed two similar new imputation rules to assess the impact of missing 6MWD.

- Impute missing due to intercurrent events as:
    1. worst observed change from baseline, -269 m, for all events
    2. order the events as Death, Clinical Worsening, and Too ill to walk
- Impute missing due to other reasons by Multiple Imputation method.

This exercise has shown the SAP imputation rules to be robust, and the new imputation rules did not alter the Hodges-Lehmann estimate of location shift significantly, see Table 6.7.

Table 6.7 Comparisons of Imputation Rules on Peak 6MWD at Week 16

Reason for missing 6MWD	SAP Imputation	Imputation #1	Imputation #2
Death	0	Worst Chg (-269)	Worst Chg -30m
Clinical Worsening	0	Worst Chg (-269)	Worst Chg -20m
Too ill	0	Worst Chg (-269)	Worst Chg -10m
Other	LOCF	MI	MI
HL (95% CI) **p-value**	21 (7, 37) 0.0042	19 (4, 35) 0.0044	19 (6, 35) 0.0040

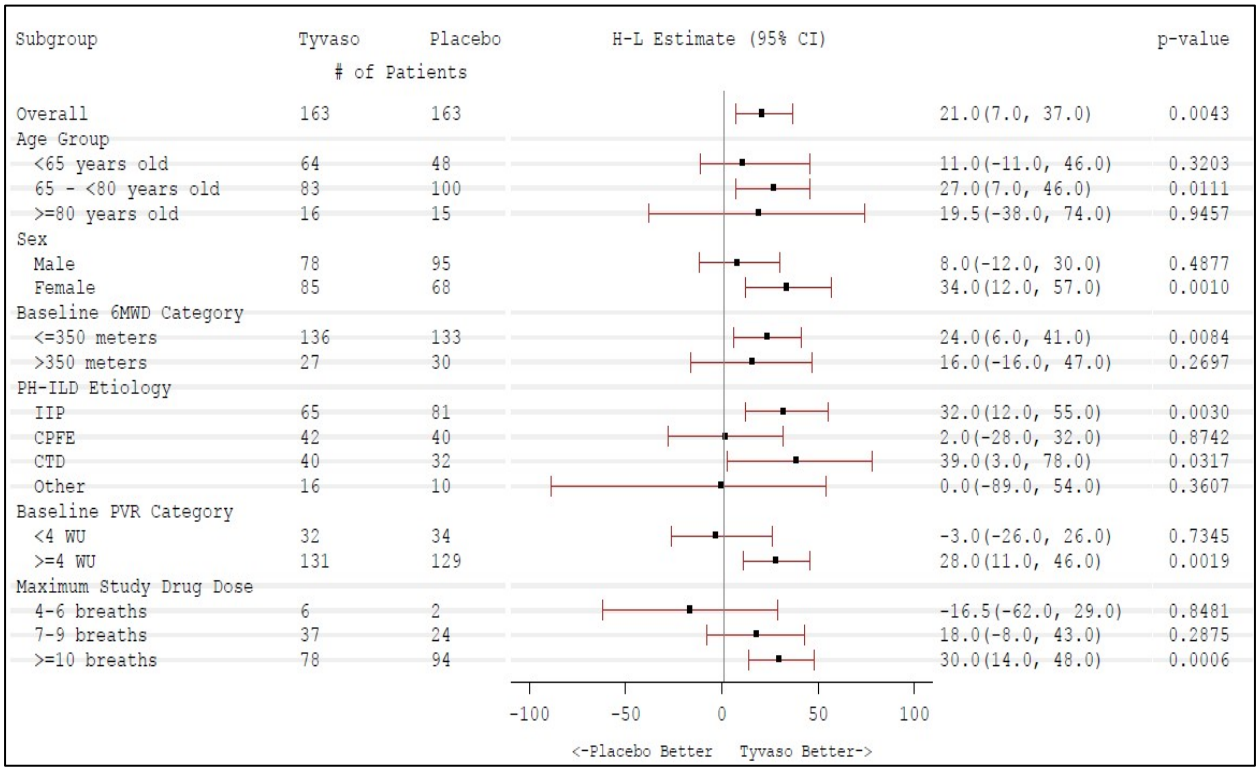
Subgroup Analyses of Peak 6MWD at Week 16

For primary efficacy endpoints of change in 6MWD at Week 16, subgroup analyses were performed. These subgroups included:

- Etiology of ILD (IIP, CHP, occupational, CPFE, CTD, and other)
- Baseline walk categories
- Sex (male versus female)
- PVR (<4 versus ⩾4 WU)
- Age group (<65 years of age, 65 to <80 years of age, and ⩾80 years of age)
- Maximum Study drug dose at Week 16 (4 to 6 breaths, 7 to 9 breaths, and 10 to 12 breaths).

The forest plot on subgroup analyses at week 16 for all randomized patients is shown in Figure 6.2. Most subgroups are numerically in favor of Treprostinil over placebo in term of increased peak 6MWD. Furthermore, the subgroups which showed a statistically significant effect ($p<0.05$) of treprostinil compared to placebo included the 65-80 year age group, female patients, those who walked <= 350m at baseline, those who had IIP or CTD as the etiology of their disease, those with a baseline PVR > 4WU and those who received >10 breathes (higher dose) of study drug.

Figure 6.2 Forest Plot on Subgroups of Peak 6MWD at Week 16



[Source: Sponsor's CSR Figure 11-1, verified by reviewer]

6.6.2 Analyses of Secondary Endpoints

6.6.2.1 Change in Plasma Concentration of NT-proBNP from Baseline to Week 16

Summaries of change from Baseline in NT-proBNP data at Week 16 by ANCOVA and MMRM for the ITT Population are provided in Table 6.8. When analyzed using ANCOVA, the change from Baseline in log-transformed data (or ratio to Baseline) in NT-proBNP at Week 16 was significantly ($p<0.0001$) lower than the placebo group.

The LS mean for ratio to Baseline at Week 16 indicated a 15% reduction in NT-proBNP in the inhaled treprostinil group compared with an increase of 38% in placebo. At Week 16, NT- proBNP in the inhaled treprostinil group was 42% more reduced (MMRM: $p<0.0001$; 95% CI: 0.47, 0.72) than the placebo group.

Table 6.8 Analysis of NT-proBNP (pg/mL) Data

Visit	Treprostinil N=156	Placebo N=163	GM_T/GM_P (95% CI)	p-val
Baseline				
Mean (SD)	1857.5 (3186.6)	1808.9 (3150.5)		
GM (SD)	579.5 (5.2)	544.1 (5.0)		
Week 16				
Mean (SD)	1461.2 (2281.2)	3262.8 (8515.8)		
GM (SD)	492.8 (4.9)	752.5 (5.7)		
Mean Change from Baseline	-396.4 (1904.9)	1454.0 (7296.2)		
LS Mean Ratio from Baseline (GM)	0.85 (1.07)	1.38 (1.07)	0.62 (0.52, 0.74)	<0.0001
MMRM			0.58 (0.47, 0.72)	<0.0001

6.6.2.2 Time to Clinical Worsening

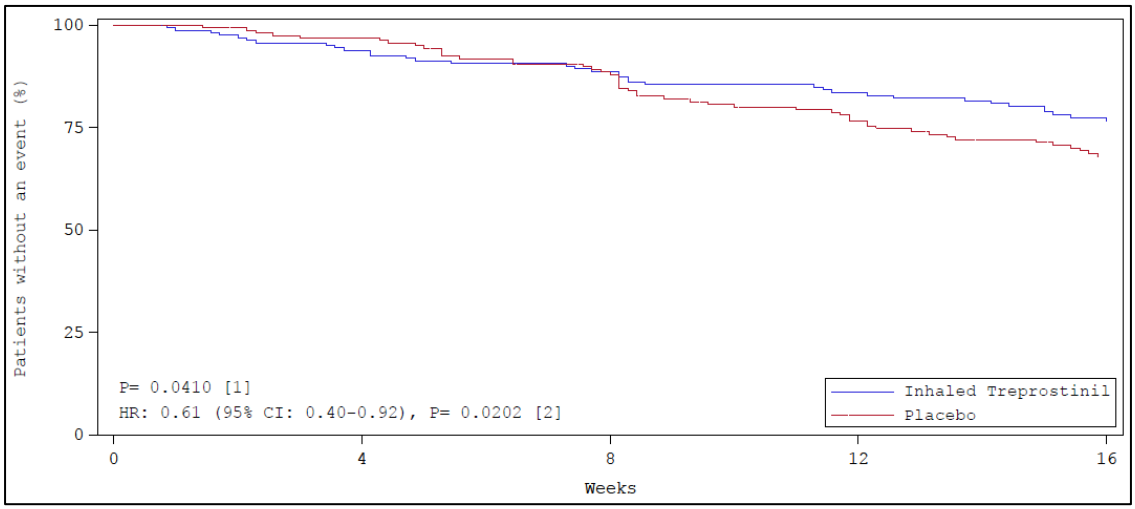
Overall, 37 (22.7%) subjects in the inhaled treprostinil group experienced a clinical worsening event during the study compared with 54 (33.1%) subjects in the placebo group. The individual components of clinical worsening events are all numerically in favor of inhaled treprostinil group, see Table 6.9. The Cox proportional hazards model gave a HR (95% CI) of 0.61 (0.40, 0.92) ($p=0.0202$), demonstrating that treatment with inhaled treprostinil provided a 39% overall reduction in the risk of a clinical worsening event during the study.

Table 6.9 Cox-PH Analysis of Clinical Worsening

	Inhaled Treprostinil	Placebo
Clinical Worsening Events, n(%)	37 (22.7)	54 (33.1)
Hosp due to cardiopulmonary indication	18 (11.0)	24 (14.7)
Decrease in 6MWD>15%	13 (8.0)	26 (16.0)
All Cause Death	4 (2.5)	4 (2.5)
Lung Transplant	2 (1.2)	0
Hazard Ratio (95% CI)	0.61 (0.40, 0.92)	
P-value	0.0202	

The comparison of the Kaplan-Meier estimates of the time to first clinical worsening event between the inhaled treprostinil group and the placebo group was statistically significant (log- rank test: p=0.0410), see Figure 6.3.

Figure 6.3 Kaplan-Meier Plot of Time to Clinical Worsening Events



However, when inspecting the Kaplan-Meyer curves of Figure 6.3, we can clearly see the two curves crossed around week 8 study visit, which indicates that the proportional hazards assumption maybe violated for the Cox Proportional Hazard Model. This would have made the interpretation of Hazard Ratio difficult to interpret. Hence, this statistical reviewer conducted the Restricted Mean Survival Time (RMST) analysis, which is not constricted to proportionality assumption of hazard rates. The RMST method yields a non-significant p-value of 0.318, as compared to the Cox PH HR. The first occurrence of any composite event can be delayed by
0.48 week when compare inhaled Treprostinil with Placebo group over a course of 16 weeks, see Table 6.10.

Table 6.10 Restricted Mean Survival Time Analysis of TCW

Arm	RMST	SE	95% CI	p-value
Treprostinil	14.72	0.34	(14.05, 15.39)	
Placebo	14.24	0.34	(13.58, 14.90)	
Difference	0.48		(-0.46, 1.42)	0.318

The United Therapeutics Corp. is made aware of this issue and conducted their own RMST analyses of time to clinical worsening. They carried out nonparametric analysis, pseudovalue regression, and inverse probability censoring weighting (IPCW) regression. The nonparametric analysis utilized SAS PROC LIFETEST with the RMST option and stratified by baseline 6- minute walk distance as a categorical effect. The regression analyses used SAS PROC RMSTREG with a term for baseline 6-minute walk distance as a continuous effect in the model. To use as much of the survival curves as possible, we set the tau to 17.71 in the nonparametric approach and to 18 in the regression approaches. None of those UTC's RMST analyses generated a statistically significant p-value, see Table 6.11.

Table 6.11 Additional RMST methods of TCW conducted by UTC

Approach	tau	p
Nonparametric	17.71	0.1593
Pseudovalue Regression	18	0.1113
IPCW (Linear)	18	0.0679
IPCW (Log-linear)	18	0.0638

[Source: UTC's Sep 2020 Response to FDA Request for Information]

UTC interpreted the crossing of the Kaplan-Meier curves as a delayed effect after 8 weeks of treatment. Patients in the RIN-PH-201 trial were titrated up to a target Tyvaso dose of 9 breaths and a maximum dose of 12 breaths QID, as clinically tolerated over the 16-week treatment period. Individual patient maximum doses were generally reached around the week 8 study visit (median week 8 doses in the inhaled treprostinil and placebo groups, were 10.0 and 11.0 breaths QID respectively). Once a patient has titrated to a stable treprostinil dose, optimal clinical response would then be realized in individual patient outcomes. Furthermore, the reviewer also examined the Week 4 and Week 8 Peak 6MWD data. They showed an insignificant Hodges- Lehmann estimation of location shift at week 4 (p=0.395), but this estimator became significant at week 8 (p=0.010), see Table 6.12,

Table 6.12 Summary of Peak 6MWD at Week 4 and 8

Visit	Treprostinil N=163	Placebo N=163	p-value
Baseline			
Mean, Median	254.1, 256.0	265.1, 260.0	
Week 4			
Mean, Median	246.3, 245.0	259.7, 244.0	
Week 8			
Mean, Median	243.3, 255.0	237.2 248.0	
Week 4 change from Baseline			
LS Mean	-2.9 (-16.2, 10.5)		73
HL (95% CI)			0. 95
Week 8 change from Baseline	6		
LS Mean (95% CI)	4.0 (-4.0, 12.0)		92
HL (95% CI)			0. 10

In summary, the time to clinical worsening has the following two concerns:

- The assumption of proportional hazards in the data in the context of Cox regression may have been violated.
- It has been promoted from an exploratory endpoint into secondary efficacy endpoint via SAP Amendment just two weeks prior to the completion of the study.

However, this does not invalidate the significant result that was observed in the log-rank test of the time to clinical worsening curves. In particular, the crossing of the survival curves suggests that the treatment effect is not fully realized until therapeutic doses are reached. after up titration during the first 8 weeks while subjects attempt to reach their maximum tolerated dose.

6.6.2.3 Change in Peak 6MWD from Baseline to Week 12

Summaries of change from Baseline in peak 6MWD at Week 12 by parametric and non- parametric ANCOVA for the ITT Population are provided in Table 6.13.

Table 6.13 Summary and Analysis of Week 12 Peak 6MWD

T-Stat	Visit	Treprostinil N=163	Placebo N=163	p-value
Non-Parametric	Baseline (Medians)	256.0	260.0	
	Week 12	245.0	244.0	
	Diff	8.0	-3.0	
	HL (95% CI)	20.0 (7.0, 34.0)		0.0041
ANCOVA	Baseline (Means)	254.1 (102.4)	265.1 (93.1)	
	Week 12	243.2 (133.4)	231.0 (131.1)	
	Diff	-10.9	-34.1	
	LS Mean (95% CI)	22.5 (1.7, 43.4)		0.034

As observed at Week 16, improvement in peak 6MWD was noted in the inhaled treprostinil group at Weeks 12. The changes from Baseline in peak 6MWD in the inhaled treprostinil

group were significantly (by ANCOVA) higher than the placebo group at Week 12 (Hodges- Lehmann estimate of location shift: 20.0 m; p=0.0041). At Week 12, median change from Baseline in peak 6MWD in the inhaled treprostinil group increased by 8.0 m compared with a decrease of 3.0 m in the placebo group.

In addition, the treatment differences (inhaled treprostinil – placebo) in peak 6MWD at Weeks 12 (31.29 m; p<0.0001; 95% CI: 17.37, 45.21) were significant when analyzed using MMRM.

6.6.2.4 Change in Trough 6MWD from Baseline to Week 15

A summary of change from Baseline in trough 6MWD at Week 15 is provided in Table 6.14. The change from Baseline in trough 6MWD at Week 15 in the inhaled treprostinil group was significantly higher than the placebo group when analyzed by ANCOVA (Hodges-Lehmann estimate of location shift: 15.0 m; p=0.0432). Overall, median change from Baseline in trough 6MWD in the inhaled treprostinil group was unchanged (0 m) compared to a decrease of 9.0 m in the placebo group.

Table 6.14 Analysis of Trough 6MWD (m) at Week 15

T-Stat	Visit	Treprostinil N=163	Placebo N=163	p-value
Non-Parametric	Baseline (Median) Week 15 Diff	256.0 238.0 0.0	260.0 240.0 -9.0	
	HL (95% CI)	15.0 (0, 29.0)		0.0432
ANCOVA	Baseline (Mean) Week 15	254.1 (102.4) 225.4 (141.9)	265.1 (93.1) 217.4 (135.8)	
	LS Mean (95% CI)	18.47 (-4.1, 41.1)		0.1089

6.6.3 Efficacy Conclusions

The primary endpoint, Change from Baseline in peak 6MWD at Week 16 in the inhaled treprostinil group was significantly increased compared to the placebo group (Hodges-Lehmann estimate of location shift: 21.0 m; p=0.0043). In addition, similar significant increases in peak 6MWD at Week 12 and Trough 6MWD at Week 15 were observed for the inhaled treprostinil group. Furthermore, the NT-proBNP at Week 16 was 42% more reduced (MMRM: p<0.0001; 95% CI: 0.47, 0.72) than the placebo group. Lastly, there was a significant reduction in the risk of experiencing a clinical worsening event in the inhaled treprostinil group (log-rank p=0.041).

7 EVALUATION OF SAFETY

During the study, vital signs, clinical laboratory parameters, ECG parameters, PFTs, oxygenation, and the development of AEs after treatment were the primary assessments of safety. All hospitalizations were recorded from the time of informed consent until study termination (or the ET Visit for those subjects discontinuing the study prematurely).
Exacerbations of underlying lung disease were recorded from the time of informed consent until study termination.

Adverse Events

AEs were recorded throughout the course of the study from the time that each subject signed the ICF until the time screen failure was documented, or until the subject was either discontinued from the study or all Week 16 study assessments were completed. Each subject was questioned for AEs at each scheduled study visit and during required telephone/email contacts. Subjects were also instructed to spontaneously report all AEs throughout the study.

Exacerbations of Underlying Lung Disease

An exacerbation of underlying lung disease was defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality. The following diagnostic criteria were used to help support a diagnosis of acute exacerbation:

1. Previous or concurrent diagnosis of ILD
2. Acute worsening or development of dyspnea typically of less than 1-month duration
3. CT with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern
4. Deterioration not fully explained by cardiac failure or fluid overload

Events that were clinically considered to meet the definition of acute exacerbation but failed to meet all 4 diagnostic criteria due to missing CT data were still considered an exacerbation for reporting purposes.

Exacerbations of underlying lung disease were recorded throughout the duration of the study from the time of informed consent until study termination. Exacerbations of underlying lung disease were also reported as AEs or SAEs.

EXTENT OF EXPOSURE

All subjects initiated inhaled treprostinil or placebo at a dose of 3 breaths (18 mcg) four times daily (during waking hours). Study drug doses was to be maximized throughout the study, dose escalations (additional one breath four times daily) could occur up to every three days with a target dosing regimen of 9 breaths (54 mcg) four times daily and a maximum dose of up to 12 breaths (72 mcg) four times daily, as clinically tolerated.

A summary of study drug dosing is shown in the table below.

Table 8.1 Summary of Study Drug Dosing and Exposure -Safety Population

	Inhaled Treprostinil N=163	Placebo N=163
Initial Study Drug Dose (breaths/session)		
n	163	163
Mean (SD)	3.0 (0.1)	3.0 (0.1)
Median	3.0	3.0
Min, Max	2, 4	2, 4
Initial Study Drug Dose (breaths/session), n (%)		
n	163	163
0-3	162 (99.4)	162 (99.4)
4-6	1 (0.6)	1 (0.6)
Week 4 Study Drug Dose (breaths/session)		
n	143	153
Mean (SD)	8.1 (2.7)	8.7 (2.8)
Median	8.0	9.0
Min, Max	2, 12	3, 12
Week 4 Study Drug Dose (breaths/session), n (%)		
n	143	153
0-3	3 (2.1)	9 (5.9)
4-6	45 (31.5)	31 (20.3)
7-9	58 (40.6)	53 (34.6)
10-12	37 (25.9)	60 (39.2)
Week 8 Study Drug Dose (breaths/session)		
n	132	137
Mean (SD)	9.5 (2.6)	10.2 (2.3)
Median	10.0	11.0
Min, Max	3, 12	1, 12
Week 8 Study Drug Dose (breaths/session), n (%)		
n	132	137
0-3	5 (3.8)	3 (2.2)
4-6	16 (12.1)	9 (6.6)
7-9	44 (33.3)	39 (28.5)
10-12	67 (50.8)	86 (62.8)
Week 12 Study Drug Dose (breaths/session)		
n	121	129
Mean (SD)	9.9 (2.6)	10.6 (2.0)
Median	11.0	12.0
Min, Max	3, 12	3, 12

	Inhaled Treprostinil N=163	Placebo N=163
Week 12 Study Drug Dose (breaths/session), n (%)		
n	121	129
0-3	5 (4.1)	2 (1.6)
4-6	10 (8.3)	6 (4.7)
7-9	37 (30.6)	29 (22.5)
10-12	69 (57.0)	92 (71.3)
Week 15 Study Drug Dose (breaths/session)		
n	119	123
Mean (SD)	10.0 (2.6)	10.7 (2.1)
Median	12.0	12.0
Min, Max	3, 14	3, 13
Week 15 Study Drug Dose (breaths/session), n (%)		
n	119	123
0-3	5 (4.2)	2 (1.6)
4-6	9 (7.6)	7 (5.7)
7-9	36 (30.3)	27 (22.0)
10-12	68 (57.1)	86 (69.9)
>12	1 (0.8)	1 (0.8)
Week 16 Study Drug Dose (breaths/session)		
n	116	121
Mean (SD)	10.0 (2.6)	10.7 (2.1)
Median	12.0	12.0
Min, Max	3, 12	3, 13
Week 16 Study Drug Dose (breaths/session), n (%)		
n	116	121
0-3	6 (5.2)	2 (1.7)
4-6	8 (6.9)	7 (5.8)
7-9	35 (30.2)	28 (23.1)
10-12	67 (57.8)	83 (68.6)
>12	0	1 (0.8)
Final Study Drug Dose (breaths/session)		
n	163	163
Mean (SD)	9.0 (3.3)	9.7 (3.1)
Median	9.0	12.0
Min, Max	1, 12	2, 13
Final Study Drug Dose (breaths/session), n (%)		
n	163	163
0-3	20 (12.3)	14 (8.6)
4-6	20 (12.3)	16 (9.8)
7-9	46 (28.2)	35 (21.5)
10-12	77 (47.2)	97 (59.5)
>12	0	1 (0.6)

	Inhaled Treprostinil N=163	Placebo N=163
Maximum Study Drug Dose (breaths/session)		
n	163	163
Mean (SD)	9.8 (2.7)	10.4 (2.6)
Median	11.0	12.0
Min, Max	3, 14	3, 15
Maximum Study Drug Dose (breaths/session), n (%)		
n	163	163
0-3	5 (3.1)	8 (4.9)
4-6	18 (11.0)	5 (3.1)
7-9	50 (30.7)	37 (22.7)
10-12	89 (54.6)	111 (68.1)
>12	1 (0.6)	2 (1.2)
Study Drug Exposure (weeks)		
n	163	163
Mean (SD)	13.9 (4.7)	14.1 (4.6)
Median	16.1	16.1
Min, Max	0, 19	0, 22

Abbreviations: SD, standard deviation
Note: If the number of breaths was different across different sessions on the same day, the maximum number of breaths was used.

The mean final study drug dose for the treprostinil group was nine breaths per session. More than 47% of the treprostinil patients were receiving 10-12 breaths per session while 12% were receiving no more than 3 breaths per session. This was roughly the same for the placebo group.

The table below shows the duration of exposure by treatment group.

Table 8.2 Summary of Study Drug Treatment – Safety Population

	Inhaled Treprostinil N=163	Placebo N=163
Number of Days Dosed >0 Breaths		
n	163	163
Mean (SD)	93.45 (35.20)	97.29 (32.47)
Median	112.00	112.00
Min, Max	3.0, 136.0	1.0, 126.0
Percent of Days Dosed >0 Breaths		
n	163	163
Mean (SD)	95.96 (13.65)	98.15 (8.09)
Median	100.00	100.00
Min, Max	16.5, 100.0	16.3, 100.0
Number of Subjects with Maximum Dose ≥9 Breaths/Session, n (%)	122 (74.8)	140 (85.9)
Number of Subjects with Maximum Dose ≥12 Breaths/Session, n (%)	78 (47.9)	100 (61.3)

Abbreviations: SD, standard deviation
Source: Table 14.1.12 and Table 14.1.13

The mean number of days of dosing greater than zero breaths was 93 for treprostinil and 97 for placebo.

A total of 75% of subjects in the inhaled treprostinil group titrated up to a dose of 9 breaths or greater four times daily compared to 86% for the placebo group. Nearly 48% of patients in the inhaled treprostinil group reached a dose of ⩾12 breaths four times daily during the study compared to 61% for the placebo group.

Adverse events

A summary of AEs and exacerbations of underlying lung disease is shown below.

Table 8.3 Overall Summary of AEs and Exacerbations of Underlying Lung Disease - Safety Population

	Inhaled Treprostinil N=163 n (%)	Placebo N=163 n (%)	Overall N=326 n (%)
Total number of AEs	**890**	**793**	**1683**
Number of subjects with at least 1 AE	152 (93.3)	149 (91.4)	301 (92.3)
Total number of SAEs	**53**	**89**	**142**
Number of subjects with at least 1 SAE	38 (23.3)	42 (25.8)	80 (24.5)
Total number of study drug-related AEs	**419**	**288**	**707**
Number of subjects with at least 1 study drug-related AE	125 (76.7)	103 (63.2)	228 (69.9)
Total number of study drug-related SAEs	**16**	**12**	**28**
Number of subjects with at least 1 study drug-related SAE	13 (8.0)	10 (6.1)	23 (7.1)

Most patients in both treatment groups reported at least one AE during the study. About a quarter of patients in each group reported at least one serious AEs.

Table 8.4 Summary of AEs lead to withdrawal and death

	Inhaled Treprostinil N=163 n (%)	Placebo N=163 n (%)	Overall N=326 n (%)
Total number of AEs leading to withdrawal of study drug	**47**	**38**	**85**
Number of subjects with at least 1 AE leading to withdrawal of study drug	28 (17.2)	28 (17.2)	56 (17.2)
Total number of AEs leading to death	**12**	**17**	**29**
Number of subjects with at least 1 AE leading to death	10 (6.1)	11 (6.7)	21 (6.4)
Total number of exacerbations of underlying lung disease	**75**	**124**	**199**
Number of subjects with at least 1 exacerbation of underlying lung disease	43 (26.4)	63 (38.7)	106 (32.5)

Abbreviations: AE, adverse event; SAE, serious adverse event

Reported AEs resulting in discontinuation of study drug occurred in 17% subjects in both the treprostinil and placebo groups.

The number of subjects reporting an AE leading to death was similar between the two groups (10 for the treprostinil subjects and 11 for the placebo subjects.

There were more placebo subjects (63) who reported at least one exacerbation of underlying lung disease compared to the treprostinil group (43).

Adverse events

Table 8.5 Summary of the most frequent adverse events by treatment group

System Organ Class Preferred Term	Inhaled Treprostinil N=163		Placebo N=163	
	n (%)	# of AEs (AE Rate[a])	n (%)	# of AEs (AE Rate[a])
Any Event	**152 (93.3)**	**890 (20.535)**	**149 (91.4)**	**793 (18.010)**
Gastrointestinal disorders	**65 (39.9)**	**88 (2.030)**	**62 (38.0)**	**100 (2.271)**
Nausea	25 (15.3)	26 (0.600)	26 (16.0)	27 (0.613)
Diarrhea	22 (13.5)	24 (0.554)	19 (11.7)	19 (0.432)
General disorders and administration site conditions	**63 (38.7)**	**93 (2.146)**	**50 (30.7)**	**71 (1.613)**
Fatigue	23 (14.1)	24 (0.554)	23 (14.1)	24 (0.545)
Investigations	**33 (20.2)**	**58 (1.338)**	**44 (27.0)**	**68 (1.544)**
N-terminal prohormone brain natriuretic peptide increased	9 (5.5)	9 (0.208)	25 (15.3)	25 (0.568)
Nervous system disorders	**77 (47.2)**	**120 (2.769)**	**61 (37.4)**	**82 (1.862)**
Headache	45 (27.6)	49 (1.131)	32 (19.6)	34 (0.772)
Dizziness	30 (18.4)	31 (0.715)	23 (14.1)	23 (0.522)
Respiratory, thoracic and mediastinal disorders	**123 (75.5)**	**256 (5.907)**	**101 (62.0)**	**204 (4.633)**
Cough	71 (43.6)	76 (1.754)	54 (33.1)	56 (1.272)
Dyspnea	41 (25.2)	46 (1.061)	51 (31.3)	56 (1.272)
Throat irritation	20 (12.3)	20 (0.461)	6 (3.7)	6 (0.136)
Oropharyngeal pain	18 (11.0)	18 (0.415)	4 (2.5)	4 (0.091)

The most frequently reported (>10% of subjects) AEs in the treprostinil group included cough (44%), headache (28%), dyspnea (25%), dizziness (18%), nausea (15%), fatigue (14%), diarrhea (14%), throat irritation (12%), and oropharyngeal pain (11%).

In the placebo group, the most commonly reported (>10% of subjects) AEs included cough (33%), dyspnea (31%), headache (20%), nausea (16%), NT-proBNP increased (15%), dizziness and fatigue (14% each) and diarrhea (12%).

Deaths

Summary of the 22 reported deaths (10 treprostinil and 12 placebo) is shown below.

Table 8.6 Summary of Deaths -Safety Population

	Inhaled Treprostinil N=163 n (%)	Placebo N=163 n (%)
Deaths During the Study	**10 (6.1)**	**12 (7.4)**
Cause of Death		
Progression of disease under study	5 (3.1)	7 (4.3)
Other	5 (3.1)	5 (3.1)

Of the 22 deaths, 12 (five treprostinil and seven placebo) were considered to be the result of PH- ILD progression. The other deaths reported for the treprostinil group were attributed to cardiac arrest, non STEMI, and three unknowns: 67 year old subject (b) (6) missed his study appointment and was found to be deceased in his hotel room; 49 year old subject (b) (6) experienced death due to unknown cause approximately 1 month after the first dose of study drug; 63 year old subject (b) (6) died suddenly approximately 3 months after the first dose of study drug.. There is no indication that use of treprostinil contributed to any of these deaths. The other reported causes of death in the placebo group included cardiac/cardiopulmonary arrest, chronic kidney failure, and influenza B pneumonia.

AEs leading to study drug discontinuation

The table below shows the study drug discontinuations because of an AE, sorted by the most common AEs and by treatment group.

Table 8.7 Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug by Preferred Term – Most Frequent Events (PT >1% of Subjects in Any Group) – Safety Population

	Inhaled Treprostinil N=163		Placebo N=163	
Preferred Term	**n (%)**	**# of AEs (AE Rate[a])**	**n (%)**	**# of AEs (AE Rate[a])**
Any Event Leading to Permanent Discontinuation of Study Drug	**28 (17.2)**	**47 (1.084)**	**28 (17.2)**	**38 (0.863)**
Dyspnea	7 (4.3)	8 (0.185)	4 (2.5)	4 (0.091)
Cough	6 (3.7)	6 (0.138)	1 (0.6)	1 (0.023)
Death	3 (1.8)	3 (0.069)	1 (0.6)	1 (0.023)
Acute respiratory failure	2 (1.2)	2 (0.046)	0	0
Upper respiratory tract infection	2 (1.2)	2 (0.046)	0	0
Cardiac arrest	1 (0.6)	1 (0.023)	2 (1.2)	2 (0.045)
Idiopathic pulmonary fibrosis	1 (0.6)	1 (0.023)	3 (1.8)	3 (0.068)
Respiratory failure	1 (0.6)	1 (0.023)	3 (1.8)	3 (0.068)
Acute kidney injury	0	0	2 (1.2)	2 (0.045)
Pneumonia	0	0	2 (1.2)	2 (0.045)

There were 28 (18%) withdrawals for each of the two groups. The most common AEs resulting in drop out were dyspnea (7 treprostinil and 4 placebo) and cough (6 treprostinil and 1 placebo).

Serious AEs (SAEs)

The table below shows the most frequently reported SAEs by treatment group.

Table 8.8 Summary of the Most Frequent Serious Adverse Events by Preferred Term (PT >1% of Subjects in Any Group) – Safety Population

Preferred Term	Inhaled Treprostinil N=163		Placebo N=163	
	n (%)	# of AEs (AE Rate[a])	n (%)	# of AEs (AE Rate[a])
Any Serious Event	**38 (23.3)**	**53 (1.223)**	**42 (25.8%)**	**89 (2.021)**
Acute respiratory failure	4 (2.5)	4 (0.092)	5 (3.1)	5 (0.114)
Death	3 (1.8)	3 (0.069)	1 (0.6)	1 (0.023)
Dyspnea	3 (1.8)	3 (0.069)	7 (4.3)	7 (0.159)
Interstitial lung disease	3 (1.8)	3 (0.069)	2 (1.2)	2 (0.045)
Bronchitis	2 (1.2)	2 (0.046)	1 (0.6)	1 (0.023)
Chronic obstructive pulmonary disease	2 (1.2)	2 (0.046)	2 (1.2)	2 (0.045)
Chronic respiratory failure	2 (1.2)	2 (0.046)	0	0
Respiratory failure	2 (1.2)	2 (0.046)	5 (3.1)	5 (0.114)
Upper respiratory tract infection	2 (1.2)	2 (0.046)	1 (0.6)	1 (0.023)
Acute myocardial infarction	1 (0.6)	1 (0.023)	2 (1.2)	2 (0.045)
Cardiac arrest	1 (0.6)	1 (0.023)	2 (1.2)	2 (0.045)
Cardiac failure congestive	1 (0.6)	1 (0.023)	2 (1.2)	2 (0.045)
Idiopathic pulmonary fibrosis	1 (0.6)	1 (0.023)	4 (2.5)	4 (0.091)
Pneumonia	1 (0.6)	1 (0.023)	9 (5.5)	9 (0.204)
Right ventricular failure	1 (0.6)	1 (0.023)	2 (1.2)	2 (0.045)
Abdominal pain	0	0	2 (1.2)	2 (0.045)
Cardiac failure	0	0	2 (1.2)	2 (0.045)

The reporting of SAEs was about 24% for both groups and the reported events were similar for both groups.

Laboratory parameters

Laboratory evaluations of clinical chemistry and hematology were collected at the Screening and Baseline Visits and at Week 8 and Week 16 or the ET Visit to assess the effect of study drug on individual laboratory parameters.

Evaluation of the change from Baseline over the study period did not indicate any clinically relevant differences suggestive of treatment-emergent changes in clinical chemistry or hematology for either of the treatment groups.

There were no SAEs related to laboratory assessments considered attributable to study treatment.

Physical findings, vital signs

There were no clinically relevant changes in body weight, heart rate, blood pressure, respiratory rate, temperature, ECG parameters, pulse oximetry or supplemental oxygen requirements for either treatment group.

Pulmonary Function Tests

In a post-hoc analysis, there was an improvement in FVC (% predicted) observed at Week 16 in the inhaled treprostinil group (median improvement of 1.0% compared to a 1.0% reduction in the placebo group).

Table 8.9 Analysis of FVC Data Using Mixed Model Repeated Measurement – ITT Population

Visit	Treatment	N	LS Mean	Contrast	Estimated Difference	95% CI	p-value
FVC (mL)							
Week 8	Inhaled Treprostinil	142	5.49	Inhaled Treprostinil - Placebo	28.47	-30.81, 87.74	0.3453
	Placebo	141	-22.98				
Week 16	Inhaled Treprostinil	130	9.77	Inhaled Treprostinil - Placebo	44.40	-25.25, 114.05	0.2106
	Placebo	126	-34.63				
FVC (% predicted)							
Week 8	Inhaled Treprostinil	142	0.77	Inhaled Treprostinil - Placebo	1.79	0.37, 3.21	0.0139
	Placebo	141	-1.02				
Week 16	Inhaled Treprostinil	130	1.07	Inhaled Treprostinil - Placebo	1.80	0.20, 3.39	0.0277
	Placebo	126	-0.72				

Abbreviations: CI, confidence interval; FVC, forced vital capacity; ITT, Intent-to-Treat; LS, least square; MMRM, mixed model repeated measurement
Note: LS mean, p-values, estimated difference, and associated 95% CIs were from the MMRM with the change from Baseline in FVC/% predicted FVC as the dependent variable; treatment, week, and treatment by week interaction as the fixed effects; Baseline FVC/% predicted FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.
Source: Table 14.2.9.1 and Table 14.2.9.4

SAFETY UPDATE

Title of the Study: Interim Clinical Study Report: An Open-Label Extension Study of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease

Protocol number: RIN-PH-202

Investigators and Study Centers: This study is being conducted in 119 centers in the United States and Puerto Rico.

Data Cut-off for Interim study report: August 13, 2020.

Objectives: The primary objective of this study is to provide or continue to provide inhaled treprostinil for eligible subjects who participated in RIN-PH-201. The secondary objectives of this study are to evaluate the long-term safety and efficacy of inhaled treprostinil in subjects with pulmonary hypertension associated with interstitial lung disease (PH-ILD).

All subjects received inhaled treprostinil during this open label extension trial. When treatment groups are referred to, it means the group to which subjects were randomized during the blinded trial RIN-PH-@01.

Methodology: RIN-PH-202 is a multicenter, open-label study to provide therapy and evaluate longterm safety and efficacy of inhaled treprostinil in subjects who have completed RIN-PH-

201. All subjects initiate inhaled treprostinil at 3 breaths (18 mcg) 4 times daily (QID) regardless of treatment assignment or dose in RIN-PH-201. Doses are maximized throughout the study with dose escalations (additional 1 breath QID) occurring up to every 3 days with a maximum dosing regimen of up to 15 breaths (90 mcg) QID, as clinically tolerated.

Subjects continue in the study until completing Week 108 or until inhaled treprostinil becomes commercially available for subjects with pre-capillary PH-ILD. Subjects return for study visits at Week 4, Week 12, then every 12 weeks for the duration of the study (108 weeks).

Efficacy assessments consist of 6MWD, plasma NT-proBNP concentration, quality of life measured by the St. George's Respiratory Questionnaire (SGRQ) and change in distance saturation product (DSP).

Safety assessments consist of the development of AEs, vital signs, clinical laboratory parameters, hospitalizations due to a cardiopulmonary indication, exacerbations of underlying lung disease, pulmonary function tests (PFTs), and oxygenation.

Number of Subjects (planned and analyzed): This interim study report presents safety data for all subjects that have participated in RIN-PH-202 up to August 13, 2020 (data cut-off date). A total of 242 subjects have received at least 1 dose of study drug in RIN-PH-202: 119 subjects from the inhaled treprostinil group in RIN-PH-201, 121 subjects from the placebo group in RIN- PH-201, and 2 subjects who were not included in RIN-PH-201 analyses. One subject was enrolled in RIN-PH-201 but did not receive study drug.

Diagnosis and Main Criteria for Inclusion: Subjects are eligible for inclusion in this study if they participated in RIN-PH-201, remained on study drug, and completed all scheduled visits; permanently discontinued study drug during RIN-PH-201 due to clinical worsening and completed all remaining required scheduled study visits; or were enrolled in RIN-PH-201 at the time it was discontinued by the Sponsor.

Study drug: Treprostinil 72 mcg to 360 mcg total daily dose inhaled

Duration of Treatment: Subjects continue in the study until completing Week 108 or until inhaled treprostinil becomes commercially available for subjects with pre-capillary PH-ILD.

Subject Disposition

Subject accountability is shown in the table below. Of the 242 subjects included in the study, 52% discontinued the study early. The primary reasons for discontinuing the study include death (17%), withdrawal by the subject (15%), reported adverse event (12%), and progressive disease (5%). As of August 13, 2020, there are 80 active subjects in RIN-PH-202.

Table 8.10 Summary of Subject Accountability – ITT Population

	Received Inhaled Treprostinil in RIN-PH-201 n (%)	Received Placebo in RIN-PH-201 n (%)	Overall n (%)
Number of Subjects Enrolled in RIN-PH-202	120	121	243
Received Study Drug	119 (99.2)	121 (100)	242 (99.6)
Completed 108 Weeks of Study Assessments	18 (15.0)	16 (13.2)	35 (14.4)
Number of Subjects Who Discontinued Study Early	55 (45.8)	71 (58.7)	127 (52.3)
Death	19 (15.8)	21 (17.4)	40 (16.5)
Progressive Disease	4 (3.3)	7 (5.8)	11 (4.5)
Adverse Event	12 (10.0)	17 (14.0)	29 (11.9)
Withdrawal by Subject	15 (12.5)	20 (16.5)	36 (14.8)
Protocol Violation	0	1 (0.8)	1 (0.4)
Lost to Follow-up	1 (0.8)	0	1 (0.4)
Other	4 (3.3)	5 (4.1)	9 (3.7)

Note: The overall column includes 2 subjects who were excluded from RIN-PH-201 due to a labeling issue.

Deaths

A summary of deaths in the safety population is presented in the table below.

Table 8.11 Summary of Deaths – Safety Population

	Received Inhaled Treprostinil in RIN-PH-201 N=119 n (%)	Received Placebo in RIN-PH-201 N=121 n (%)	Overall N=242 n (%)
Deaths During the Study	20 (16.8)	27 (22.3)	47 (19.4)
Cause of Death			
Progression of Disease Under Study	12 (10.1)	14 (11.6)	26 (10.7)
Other	8 (6.7)	13 (10.7)	21 (8.7)

Note: The overall column includes 2 subjects who were excluded from RIN-PH-201 due to a labeling issue.

There have been 47 reported deaths in RIN-PH-202 as of the cut-off date. Of the 47 deaths, more than half (55%) were identified as resulting from progression of disease under study. Other causes of death include cardiac arrest, sepsis, respiratory failure, unwitnessed death, seizure, influenza A, lung cancer (table 14.3.2.1). No death appeared to be unexpected in this patient population.

The median time to death (range) overall was 42 (1 to 117) weeks.

Serious Adverse Events

The table below show the the most frequently reported SAE.

Table 8.12 Summary of the Most Frequent Serious Adverse Events by Preferred Term (PT >1% of Subjects in Any Group) – Safety Population

Preferred Term	Received Inhaled Treprostinil in RIN-PH-201 N=119		Received Placebo in RIN-PH-201 N=121		Overall N=242	
	n (%)	# of AEs (AE Rate[a])	n (%)	# of AEs (AE Rate[a])	n (%)	# of AEs (AE Rate[a])
Any Serious Adverse Event	**53 (44.5%)**	**157 (1.124)**	**62 (51.2%)**	**135 (1.196)**	**117 (48.3%)**	**297 (1.165)**
Acute respiratory failure	9 (7.6%)	13 (0.093)	11 (9.1%)	17 (0.151)	20 (8.3%)	30 (0.118)
Respiratory failure	7 (5.9%)	7 (0.050)	7 (5.8%)	7 (0.062)	14 (5.8%)	14 (0.055)
Dyspnoea	6 (5.0%)	8 (0.057)	2 (1.7%)	2 (0.018)	8 (3.3%)	10 (0.039)
Pneumonia	7 (5.9%)	8 (0.057)	7 (5.8%)	7 (0.062)	15 (6.2%)	16 (0.063)
Acute kidney injury	7 (5.9%)	8 (0.057)	1 (0.8%)	1 (0.009)	8 (3.3%)	9 (0.035)
Right ventricular failure	5 (4.2%)	5 (0.036)	4 (3.3%)	4 (0.035)	9 (3.7%)	9 (0.035)
Fluid overload	5 (4.2%)	7 (0.050)	3 (2.5%)	3 (0.027)	8 (3.3%)	10 (0.039)
Sepsis	4 (3.4%)	4 (0.029)	2 (1.7%)	2 (0.018)	6 (2.5%)	6 (0.024)
Chest pain	3 (2.5%)	3 (0.021)	1 (0.8%)	1 (0.009)	4 (1.7%)	4 (0.016)
Interstitial lung disease	3 (2.5%)	3 (0.021)	3 (2.5%)	4 (0.035)	6 (2.5%)	7 (0.027)
Pulmonary hypertension	4 (3.4%)	4 (0.029)	2 (1.7%)	2 (0.018)	6 (2.5%)	6 (0.024)
Cardiac failure congestive	2 (1.7%)	2 (0.014)	1 (0.8%)	1 (0.009)	3 (1.2%)	3 (0.012)
Chronic obstructive pulmonary disease	2 (1.7%)	3 (0.021)	1 (0.8%)	1 (0.009)	3 (1.2%)	4 (0.016)
Hypoxia	2 (1.7%)	2 (0.014)	3 (2.5%)	3 (0.027)	5 (2.1%)	5 (0.020)
Hypotension	2 (1.7%)	2 (0.014)	2 (1.7%)	3 (0.027)	4 (1.7%)	5 (0.020)
Syncope	2 (1.7%)	2 (0.014)	4 (3.3%)	4 (0.035)	6 (2.5%)	6 (0.024)
Vomiting	2 (1.7%)	2 (0.014)	0	0	2 (0.8%)	2 (0.008)
Cardiac arrest	1 (0.8%)	1 (0.007)	4 (3.3%)	4 (0.035)	6 (2.5%)	6 (0.024)
Influenza	1 (0.8%)	1 (0.007)	2 (1.7%)	2 (0.018)	3 (1.2%)	3 (0.012)
Urinary tract infection	1 (0.8%)	1 (0.007)	3 (2.5%)	3 (0.027)	4 (1.7%)	4 (0.016)

As of the cut-off date, 48% of all subjects (45% inhaled treprostinil and 51% inhaled placebo) reported at least one SAEs. The most commonly reported SAEs were acute respiratory failure, pneumonia, respiratory failure, right ventricular failure, acute kidney injury, dyspnea, fluid overload, cardiac arrest, idiopathic pulmonary fibrosis, interstitial lung disease, pulmonary hypertension, sepsis, syncope, and hypoxia.

There were few differences between the drug groups in the reporting rates for any of these events except for acute kidney failure (6% inhaled treprostinil and 1% inhaled placebo). This is probably inconsequential.

Overall, these events are not unexpected in this patient population.

Adverse Events Resulting in Study Drug Discontinuation

A summary of the most frequent AEs leading to permanent discontinuation of inhaled treprostinil (occurring in >1% of subjects in either group or overall) by preferred term includes are dyspnea (7 subjects), hypoxia (6 subjects), and respiratory failure and right ventricular failure (5 subjects each).

Hospitalizations

There were 61 subjects who reported at least one hospitalization (28 (24%) from the inhaled treprostinil and 32 (26%) from the placebo as randomized in the double blind study). The median time to first hospitalization is 21 weeks for subjects from the inhaled treprostinil and 19 weeks for subjects from placebo groups.

Exacerbations of Underlying Lung Disease

Overall, 51 subjects (30 (25%) from the inhaled treprostinil and 21 (17%) from the placebo group) reported at least one exacerbation of underlying lung disease. The median time to first exacerbation of underlying lung disease is 13 weeks for subjects from the inhaled treprostinil and 10 weeks for subjects from the placebo group.

8 SUMMARY AND CONCLUSIONS

The primary efficacy endpoint of change in peak 6MWD at Week 16 in the inhaled treprostinil group was significantly higher than the placebo group. Overall, median change from Baseline in peak 6MWD in the inhaled treprostinil group increased by 6m at Week 16 compared with a decrease of 9.0 m in the placebo group. Most subgroups examined were numerically higher in the treprostinil compared to placebo for peak 6MWD. The subgroups which showed a statistically significant effect tended to be the older subjects, females, those who walked less at baseline, those who had IIP or CTD as the etiology of their disease, those with a higher baseline PVR > 4WU and those who received a higher dose of study drug.

Regarding the secondary endpoints, there was a significant change from baseline in NT-proBNP (15% reduction in in the inhaled treprostinil group compared with an increase of 38% in placebo) at week 16.

Overall, 37 (22.7%) subjects in the inhaled treprostinil group experienced a clinical worsening Event (defined as one of the following: hospitalization due to a cardiopulmonary indication, decrease in 6MWD >15% from Baseline directly related to disease under study, at two consecutive visits, and at least 24 hours apart, death (all causes) or lung transplantation) during the study compared with 54 (33.1%) subjects in the placebo group. The individual components of clinical worsening events are all numerically in favor of inhaled treprostinil group. The comparison of the Kaplan-Meier estimates of the time to first clinical worsening event between the inhaled treprostinil group and the placebo group was statistically significant.

The changes from Baseline in peak 6MWD and the change from Baseline in trough 6MWD at Week 15 in the inhaled treprostinil group were significantly higher than the placebo group at Week 12.

The change in quality of life (QOL) as measured by the St. George's Respiratory Questionnaire (SGRQ) from Baseline to Week 16 was an exploratory endpoint. The differences between treprostinil and placebo for all of the SGRQ domain scores (symptoms, activity, and impacts) tended to be numerically better for the treprostinil group, but these differences were not statistically significant.

Change in distance saturation product (DSP), an exploratory endpoint, is defined as the product of the final 6-minute walk distance (6MWD) in meters and the lowest oxygen saturation in room air during 6MWT. The mean change from Baseline to Week 16 showed improvement in the inhaled treprostinil group beginning at Week 8 and continuing to Week 16.

An exacerbation of underlying lung disease, also an exploratory endpoint, was defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality. Subjects had to have at least one of the four diagnostic criteria. Overall, there were more placebo subjects (63) who reported at least one exacerbation of underlying lung disease compared to the treprostinil group (43).

Regarding safety, the use of inhaled treprostinil by patients with PH associated with interstitial lung disease (WHO Group 3) was well tolerated over the treatment period. Reported AEs were similar to those reported in inhaled treprostinil studies.

In conclusion, the efficacy results demonstrate that the use inhaled treprostinil in patients with PH associated with ILD (WHO Group 3) prevented a decline in walk distance beginning by week 8 of treatment and lengthened the time to first clinical worsening event. Safety was similar to that reported by patients with pulmonary arterial hypertension (WHO Group 1).

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022387Orig1s017

OTHER REVIEW(S)

LABEL AND LABELING AND HUMAN FACTORS RESULTS REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 13, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 022387/S-17
Product Type:	Drug-device combination product
Product Name and Strength:	Tyvaso (Treprostinil) Inhalation Solution, 1.74 mg/2.9 mL
Device Constituent:	Tyvaso Inhalation System
Rx or OTC:	Rx
Applicant/Sponsor Name:	United Therapeutics Corporation (UTC)
Submission Date:	June 1, 2020
OSE RCM #:	2020-1132 and 2020-1133
DMEPA Primary Reviewer:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD
Associate Director for Human Factors (Acting)	Jason Flint, MBA, PMP
Associate Director for Labeling and Nomenclature:	Tu, Chi-Ming (Alice)

1 REASON FOR REVIEW

This review evaluates the human factors study results, proposed labels and labeling for Tyvaso (treprostinil) inhalation system from a medication error perspective.

1.1 REGULATORY HISTORY

Tyvaso (treprostinil) inhalation solution was approved on July 30, 2009 for use only with the Tyvaso Inhalation System (hereon referred to as device). Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.

Previously in Prior Approval Supplement-15 (NDA 022387/S-15), we reviewed and found acceptable the human factors validation study results for the Third-Generation device on September 6, 2017 and supplement-15 was approved on October 19, 2017.

On April 14, 2020, FDA provided preliminary written responses to address United Therapeutics Corp.'s (UTC) proposal to discuss the adequacy of their planned Efficacy Supplement submission for the new indication: Pulmonary Hypertension (PH) associated with Interstitial Lung Disease (PH-ILD). PH-ILD includes patients with idiopathic interstitial pneumonia (IIP), idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE), and WHO Group 3 connective tissue disease. As part of the preliminary written response, we requested UTC to submit their completed HF Validation study report for review.

On June 1, 2020, UTC submitted the results of their HF validation study to the Efficacy Supplement-17 (NDA 022387/S-17). No changes to the currently marketed Tyvaso product or the Third-Generation device are proposed in S-17. In addition, no change to the Instructions for Use (IFU) was proposed in S-17.

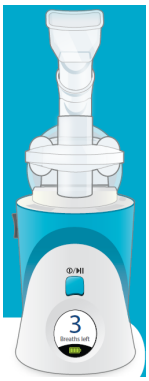
1.2 PRODUCT DESCRIPTION

The Tyvaso (treprostinil) inhalation solution is intended to be administered undiluted using the Tyvaso Inhalation System (see figure 1). Tyvaso (treprostinil) inhalation solution is supplied in 2.9 mL clear LDPE ampules packaged as four ampules in a foil pouch. A single breath of Tyvaso solution delivers approximately 6 mcg of treprostinil. The product is intended to be administered in a home, institutional or hospital setting.

One ampule of Tyvaso contains a sufficient volume of medication for all 4 treatment sessions in a single day. Tyvaso is a clear colorless to slightly yellow solution containing 1.74 mg treprostinil per ampule at a concentration of 0.6 mg/mL. Prior to the first treatment session, the patient should twist the top off a single Tyvaso ampule and squeeze the entire contents into the medicine cup. Between each of the 4 daily treatment sessions, the device should be capped and stored upright with the remaining medication inside.

At the end of each day, the medicine cup and any remaining medication must be discarded. The device must be cleaned each day according to the instructions for use.

Figure 1. Tyvaso Inhalation System: Third-Generation



2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other–CDRH Review	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our assessment of the human factor's validation study (Section 3.1) and the proposed labels and labeling (Section 3.2).

3.1 SUMMARY OF HUMAN FACTORS VALIDATION STUDY DESIGN

The study utilized a simulated-use methodology and evaluated all critical tasks associated with the use of the TYVASO inhalation system. A total of 15 trained adult patients (age 18+) with PH-ILD participated in the study.

In our previous HF protocol review[a], due to the complexity of this drug-device combination product and level of care expected for pulmonary arterial hypertension patients in the usual clinical setting, we accepted that all study participants would be trained. In this HF validation study in PH-ILD patients, we continue to find this approach reasonable.

Each study session lasted up to 6 hours, which consisted of a participant training session with a nurse trainer/product specialist (up to 2 hours), a training decay (~2 hours), and a testing session where participants performed 6 handling (performance-based) scenarios and 2 label comprehension scenarios. To further simulate real-world use of the system, participants were also provided with access to a helpline and instructional materials (e.g., the IFU). According to UTC, all 15 participants (100%) completed all scenarios without committing any safety-critical use problems.

3.2 ANALYSIS OF HUMAN FACTORS STUDY RESULTS

Our review specifically focused on the critical tasks related to the safe and effective use of the product. We note that the Applicant termed the tasks as safety critical and non-safety critical. However, based on the information provided by the Applicant all of the non-safety critical task could still result in patient harm, thus for the purposes of our review of results, we consider all of the use tasks as critical.

The HF validation studies showed use errors (e.g. failures, difficulties, and close calls). We reviewed the available participants' subjective feedback, the Applicant's root cause analysis, and the Applicant's proposed risk mitigation strategy to determine acceptability. Subsequently, our assessment finds the 28 use errors and use difficulties to be minor or as a result of study artifact. For example in Scenario 1 - Prepare new inhalation device for first time use and perform a treatment, users either did not add medicine to medicine cup prior to assembling, had difficulty assembling the filter shells, did not press/hold down blue button due to dexterity issues and inhaled too sharply; however all participants immediately self-corrected without assistance. These errors and failures were similar to those noted in the previous HF study for PAH (WHO group 1) patients. We find that the pattern of use errors has not changed. Thus, our assessment of the aforementioned considerations in totality finds the residual risk is acceptable

[a] Thomas, S. Label and Labeling and Human Factors Results Review for Tyvaso (Treprostinil) Inhalation Solution NDA 22387/S-15. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 6. RCM No.: 2017-61 and 2017-252.

for the use tasks below; thus, we have no further recommendation at this time to address the use errors related to the following use tasks:

Scenario	Success Rate*	Safety-Critical Use Problems	Non-Safety Critical Use Problems & Observations
1. Prepare new inhalation device for first time use and perform a treatment	**100%** (15 of 15)	0	5
1A. Determine time since last treatment	**100%** (15 of 15)	0	1
2. Change device volume and store device (in between uses during day)	**100%** (15 of 15)	0	6
3. Change breath count, pause/resume treatment, end of day storage	**100%** (15 of 15)	0	9
4. Respond to "Add Water" message	**100%** (15 of 15)	0	0
5. Prepare inhalation device for use and perform treatment using IFU	**100%** (15 of 15)	0	3
5A. Label comprehension: IFU Cautions Assessment (knowledge task)	**100%** (15 of 15)	0	1
5B. Label comprehension: symbol interpretation (knowledge task)	**100%** (15 of 15)	0	3
TOTALS		**0**	**28**

**Success rate was calculated as the percentage of participants who completed a given scenario without committing a safety-critical use error.*

3.2 Labeling

Our evaluation of the materials reviewed noted the proposed prescribed information (PI) for Tyvaso includes the newly proposed PH-ILD indication as well as an increase in the recommended maximum maintenance dose from "9 breaths" to "9 to 12 breaths" per treatment session, 4 times daily as needed. We did not identify any recommendation for the proposed PI.

4 CONCLUSION & RECOMMENDATIONS

We found the human factors validation study results acceptable. We conclude that the proposed labels and labeling for Tyvaso (treprostinil) is acceptable from a medication error perspective.

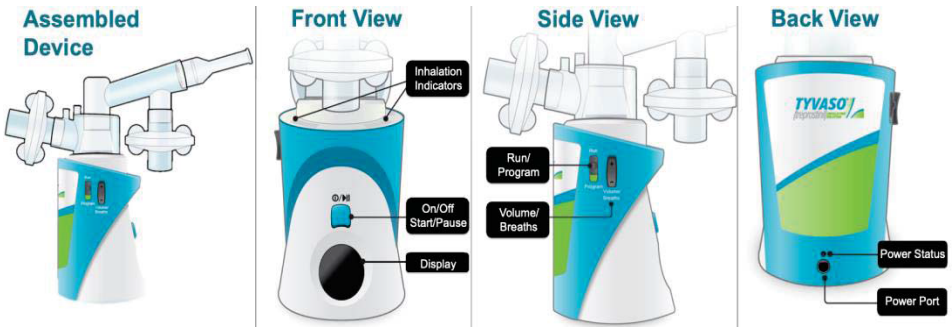
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tyvaso (Treprostinil) NDA 022387 submitted on June 1, 2020.

Table 2. Relevant Product Information for Tyvaso (Treprostinil)	
Initial Approval Date (if applicable)	07/30/2009
Therapeutic Drug Class	Direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation
Active Ingredient	Treprostinil
Indication	Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Proposed: Use by adults (age 18+) to treat: • Pulmonary Hypertension (PH) associated with Interstitial Lung Disease (ILD) (WHO Group 3) to improve exercise ability (b) (6) • Studies 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%).
Route of Administration	Oral inhalation
Dosage Form	Inhalation solution (ampule)
Strength	1.74 mg/2.9 mL ampule (0.6 mg per mL)
Dose and Frequency	-Use only with the Tyvaso Inhalation System: Administer undiluted. A single breath of Tyvaso delivers approximately 6 mcg of treprostinil. Administer in 4 separate treatment sessions each day approximately four hours apart, during waking hours. -Initial dosage: 3 breaths [18 mcg] per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths. -Dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated. Proposed: -Titrate to target maintenance dosage of 9 - 12 breaths per treatment session (b) (4) (b) (4)

How Supplied	-Tyvaso (treprostinil) inhalation solution is supplied in 2.9 mL clear LDPE ampules packaged as four ampules in a foil pouch. Tyvaso is a clear colorless to slightly yellow solution containing 1.74 mg treprostinil per ampule at a concentration of 0.6 mg/mL. - Tyvaso Inhalation System Starter Kit containing a 28 ampule carton of Tyvaso [seven foil pouches each containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL)] and the Tyvaso Inhalation System. (NDC 66302-206-01) -Tyvaso Inhalation System Refill Kit containing a 28 ampule carton of Tyvaso [seven foil pouches each containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL)] and accessories. (NDC 66302-206-02) -Tyvaso 4 Pack Carton with one foil pouch containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL). (NDC 66302-206-03). -Tyvaso Inhalation System Institutional Starter Kit containing a 4 ampule carton of Tyvaso [one foil pouch containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL)] and the Tyvaso Inhalation System. (NDC 66302-206-04).
Storage	-Ampules of Tyvaso are stable until the date indicated when stored in the unopened foil pouch at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Once the foil pack is opened, ampules should be used within 7 days - Tyvaso is light-sensitive, unopened ampules should be stored in the foil pouch. -One ampule of Tyvaso should be used each day in the Tyvaso Inhalation System. After a Tyvaso ampule is opened and transferred to the medicine cup, the solution should remain in the device for no more than one day (24 hours). Any remaining solution should be discarded at the end of the day.

Container Closure/Device Constituent(s)	Treprostinil for Inhalation, 0.6 mg/mL, is filled into a (b) (4) ampoule with an integrated twist-off cap; each ampoule = 2.9 mL of drug product.  Figure 2: *TYVASO inhalation system overview*  *Figure 3: TYVASO inhalation system components – inhalation device, ampules, water level cup*
Intended Users	- adult patients (age 18+) diagnosed with PAH (WHO Group 1) - New proposal: adult patients (age 18+) with PH associated with ILD (WHO Group 3) who can self-administer treatment.
Intended Use Environment(s)	- Home - Institution/ Hospital

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 22, 2020, we searched the L:drive using the terms, "Tyvaso," "Treprostinil," and NDA # "022387," to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 4 previous reviews,[b,c,d,e,f] and we confirmed that our previous recommendations were implemented or considered for this review.

[b] Thomas, S. Label and Labeling and Human Factors Results Review for Tyvaso (Treprostinil) Inhalation Solution NDA 22387/S-15. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 6. RCM No.: 2017-61 and 2017-252.

[c] Park, J. Label and Labeling Review for Tyvaso (Treprostinil Sodium) Inhalation Solution NDA 22387. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 June 12. RCM No.: 2008-1872.

[d] Tobenkin, A. Label and Labeling Review for Tyvaso (Treprostinil) NDA 022387. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 AUG 29. RCM No.: 2011-1763.

[e] Walker, M. Label and Labeling Review for Tyvaso (Treprostinil Sodium) NDA 022387/S-005. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 JULY 18. RCM No.: 2012-751.

[f] Fava, W. Label and Labeling Review for Tyvaso (Treprostinil) NDA 022387/S-011. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 APRIL 29. RCM No.: 2014-267.

APPENDIX C. HUMAN FACTORS STUDY RESULTS SUBMISSION AND INFORMATION REQUEST RESPONSES

- Original June 1, 2020 submission, containing labels and labeling and human factors materials:

  \\cdsesub1\evsprod\nda022387\0187\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ph-ild\5354-other-stud-rep\tyv-ild-hf\hf-validation.pdf
  \\cdsesub1\evsprod\nda022387\0187\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ph-ild\5354-other-stud-rep\tyv-ild-hf\hf-engineering.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] we reviewed the following Tyvaso (Treprostinil) labels and labeling submitted by United Therapeutics Corp.

- Prescribing Information (not shown) submitted June 1, 2020
  - \\cdsesub1\evsprod\nda022387\0187\m1\us\114-labeling\draft\annotated\annotated-draft-labeling.pdf

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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LOLITA G WHITE
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JASON A FLINT
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DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Review

sNDA:	22387/S-017
Drug:	Tyvaso (treprostinil) inhalation solution
Class:	Vasodilator
Applicant:	United Therapeutics Corp.
Supplement description	This supplement provides for changes to labeling based on the results of study #RIN-PH-201, titled "A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease".
Proposed New Indication:	Pulmonary hypertension (PH) associated with interstitial lung disease (ILD, WHO Group 3) to improve exercise ability (b) (4) (b) (4)
Approved Indication:	Pulmonary hypertension (PH) associated with interstitial lung disease (ILD, WHO Group 3) to improve exercise ability.
Date of Submission:	01 June 2020
FDA Received Date:	01 June 2020
Approval date:	31 March 2021
PDUFA date:	01 April 2021

❖ **REVIEW TEAM**

- Office of New Drugs, Office of Cardiology, Hematology, Endocrinology and Nephrology
  - Division of Cardiology and Nephrology (DCN)
    - Norman Stockbridge, MD, PhD (Division Director)
    - Mary Ross Southworth, PharmD (Deputy Director for Safety)
    - Michael Monteleone, MS, RAC (Associate Director for Labeling)
    - Fortunato Senatore, MD, PhD (Cross Discipline Team Leader)
    - Maryann Gordon, MD (Medical Reviewer)
  - Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology, and Nephrology
    - Xuan Chi, PhD (Team Leader)
    - Baichun Yang, PhD (Non-clinical Reviewer)
- Office of Pharmaceutical Quality, Office of Lifecycle Drug Products
  - Ramesh Raghavachari, PhD (Branch Chief)
  - Kris Raman, PhD (CMC Reviewer)
- Office of Regulatory Operations, Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology

- Brian Cooney, MS (Regulatory Project Manager)
- Wayne Amchin, MPA, MIA, RAC (Regulatory Project Manager)

o Office of Biostatistics, Division of Biometrics II
- Jialu Zhang, PhD (Team Leader)
- Steven Bai, PhD (Reviewer)

o Office of Surveillance and Epidemiology, DMEPA
- Hina Mehta (Team Leader)
- Lolita White (Team Leader)
- Mariette Aidoo (Reviewer)

o Office of Medical Policy, Office of Prescription Drug Promotion (OPDP)
- Zarna Patel, PharmD (Regulatory Review Officer)

❖ BACKGROUND

Tyvaso (treprostinil), manufactured by United Therapeutics Corporation (UTC), is a prostacyclin vasodilator. Tyvaso was first approved under NDA 22387 on July 30, 2009 and is currently indicated for the treatment of pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1) to increase exercise ability. Tyvaso is intended for oral inhalation using the Tyvaso Inhalation System, which consists of an ultrasonic, pulsed nebulizer delivery device and its accessories.

Under IND 070362, UTC has developed treprostinil for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD, WHO Group 3) to improve exercise ability. To support this new indication, UTC conducted study #RIN-PH-201, titled "A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease". This study was designed to investigate the safety and efficacy of inhaled treprostinil in 326 patients with PH-ILD. The sponsor randomized 163 subjects into the inhaled treprostinil group and 163 subjects into the placebo group. Each subject received treprostinil or placebo by inhaling 3 breaths (18 mcg) 4 times daily. As clinically tolerated, subjects were permitted to receive a maximum of 12 breaths (72 mcg) 4 times daily.

The primary efficacy endpoint was to evaluate the change in 6-minute Walk Distance (6MWD) measured at peak exposure from Baseline to Week 16. Secondary endpoints included change in plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration, time to clinical worsening, change in peak 6MWD at Week 12, and change in trough 6MWD at Week 15. A pre-sNDA meeting was scheduled for April 20, 2020; the Division's preliminary responses, dated April 14, 2020, were sufficient for the Applicant so the meeting was canceled.

On June 1, 2020, UTC submitted a S-017 to add a new indication based on the results of study #RIN-PH-201; a priority review was requested. The application was filed on July 31, 2020 but was not granted a priority review.

In January 2021, the Regulatory Project Manager (Amchin) retired; Brian Cooney was then assigned to manage this NDA submission.

Please see Discipline Review Section for recommendations.

❖ REGULATORY TIMELINE & SUPPLEMENT DETAILS

o Pre-sNDA Meeting:	14 April 2020 (Preliminary Comments only)
o sNDA Stamp Date:	01 June 2020
o Filing Meeting:	20 July 2020

- 74-day Letter: 14 August 2020
- Mid-cycle Meeting: 02 November 2020
- PeRC Review: 02 February 2021
- Labeling Meeting: 18 February 2021
- PDUFA Date: 01 April 2021
- **Approval Letter Date:** 31 March 2021

User Fee
Per PDUFA VI, there was no user fee associated with this efficacy supplement, Tyvaso also has Orphan designation.

Facilities
N/A

Site Inspections
The review team determined sites inspections were not needed.

Pediatric Review Committee (PeRC)
The Division and the PeRC agreed with the Applicant's request for full waiver of pediatric studies because necessary studies are impossible or highly impracticable.

Advisory Committee
N/A

Review Status
The application was considered a Standard review.

❖ LABELING REVIEW

Labeling negotiations began on March 3, 2021 and concluded on March 22, 2021.

❖ DISCIPLINE REVIEWS

Below are the conclusions reached by the review team members, organized by role and/or discipline.

Divisional Memorandum (13 March 2021 – Stockbridge)
Recommended action**:** Approval

Dr. Stockbridge conveyed his agreement with the review team's recommendation for approval.

Product Quality (14 September 2020 – Raman/Raghavachari)
Recommended action**:** Approval

The CMC reviewer stated that there were no CMC changes proposed in the submission except for the categorical exclusion request for Environmental Assessment. The reviewer stated the categorical exclusion is acceptable.

Clinical/Statistics (2 February 2021 – Bai/Zhang/Gordon/Senatore)
Recommended action**:** Approval

The statistical and clinical reviewers concluded that per 21 CFR 314.126, the applicant conducted an adequate and well controlled trial and that this trial provided substantial evidence of effectiveness to support approval of treprostinil for the following indication: *Pulmonary hypertension (PH) associated with interstitial lung disease (ILD, WHO Group 3) to improve exercise ability.*

When discussing the primary endpoint, the reviewers stated that the "Change from Baseline in peak 6MWD at Week 16 in the inhaled treprostinil group was significantly increased compared to the placebo group (Hodges-Lehmann estimate of location shift: 21.0 m; p=0.0043). In addition, similar significant increases in peak 6MWD at Week 12 and Trough 6MWD at Week 15 were observed for the inhaled treprostinil group. Furthermore, the NTproBNP at Week 16 was 42% more reduced (MMRM: p<0.0001; 95% CI: 0.47, 0.72) than the placebo group. Lastly, there was a significant reduction in the risk of experiencing a clinical worsening event in the inhaled treprostinil group (log-rank p=0.041)."

Regarding safety, the reviewers stated that "the use of inhaled treprostinil by patients with PH associated with interstitial lung disease (WHO Group 3) was well tolerated over the treatment period. Reported AEs were similar to those reported in inhaled treprostinil studies." In addition, the reviewers stated "results of this study indicated that there were no new safety concerns related to the use of inhaled treprostinil in patients with PH-ILD. Treatment with inhaled treprostinil appeared to provide sufficient benefit to these patients."

❖ CONSULT REVIEWS

The following is a list of consult reviews obtained during this review. Refer to DARRTS for complete reviews.

- DMEPA (labeling) – Aidoo, White, Mehta 16 November 2020
- OPDP (labeling) – Patel, 26 February 2021

❖ CONCLUSION

After taking into consideration all primary and consult reviews, the Division issued an approval letter for NDA 22387/S-017 on March 31, 2021. This approval letter was signed by Norman Stockbridge, MD, PhD – Division Director.

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/

BRIAN T COONEY
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: February 26, 2021

To: Brian Cooney, MS, PSM
Regulatory Health Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology/Office of Regulatory Operations

Michael Monteleone, Associate Director for Labeling
Division of Cardiology and Nephrology (DCN)

From: Zarna Patel, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for TYVASO® (treprostinil) inhalation solution, for oral inhalation use

NDA: 22387/Supplement 017

In response to DCN's consult request dated July 20, 2020, OPDP has reviewed the proposed product labeling (PI) for TYVASO® (treprostinil) inhalation solution, for oral inhalation use. This efficacy supplement (S017) provides for the indication for pulmonary hypertension associated with interstitial lung disease (ILD) .

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DCN (Brian Cooney) on February 19, 2021 and are provided below (and inserted into the document on SharePoint).

Thank you for your consult. If you have any questions, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

16 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

ZARNA PATEL
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