**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- Tyvaso dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn.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**

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**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

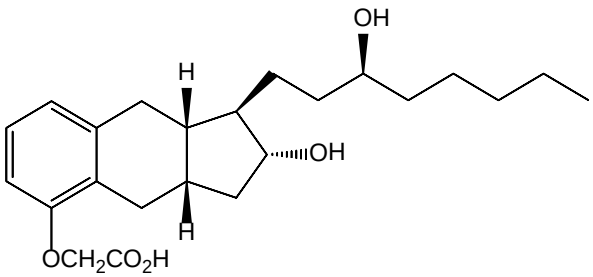
In general, symptoms of overdose with Tyvaso include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

## 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.

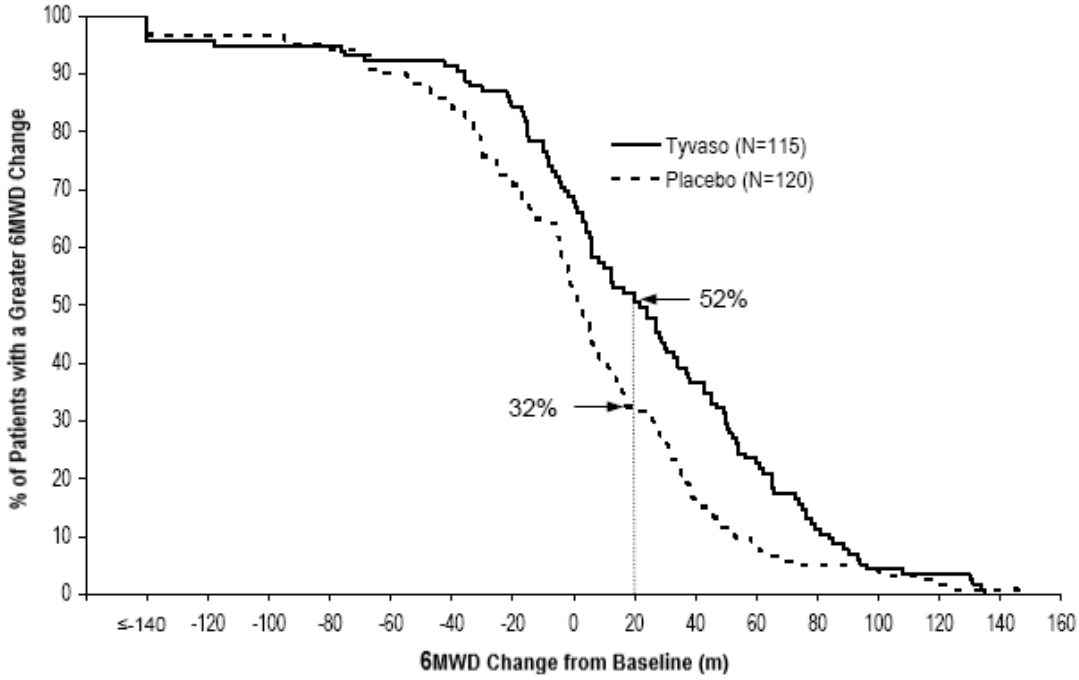
## 14 CLINICAL STUDIES

### 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%.

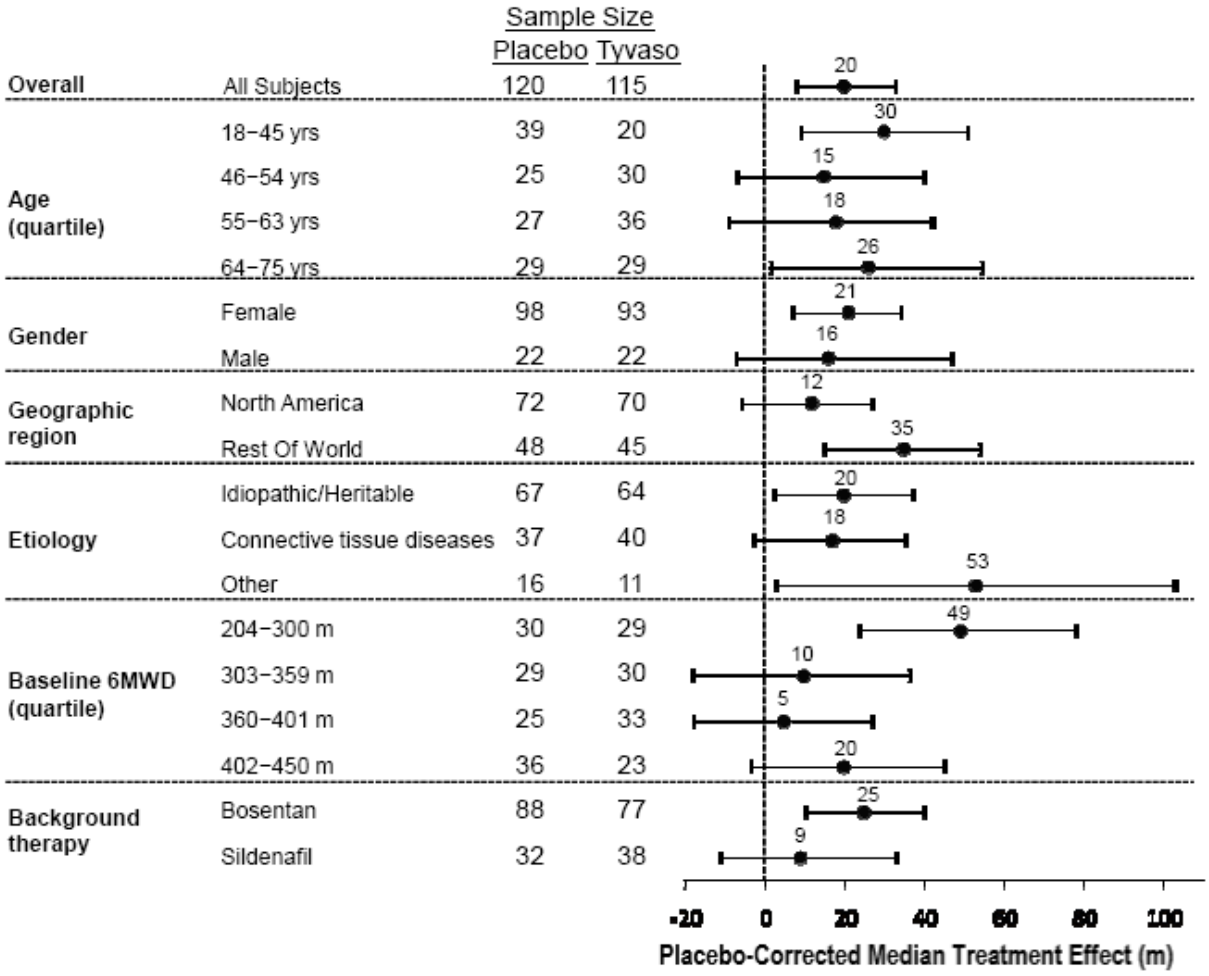
The primary efficacy endpoint of the trial was the change in 6-Minute Walk Distance (6MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3 to 5 hours after bosentan or 0.5 to 2 hours after sildenafil. Patients receiving Tyvaso had a 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.

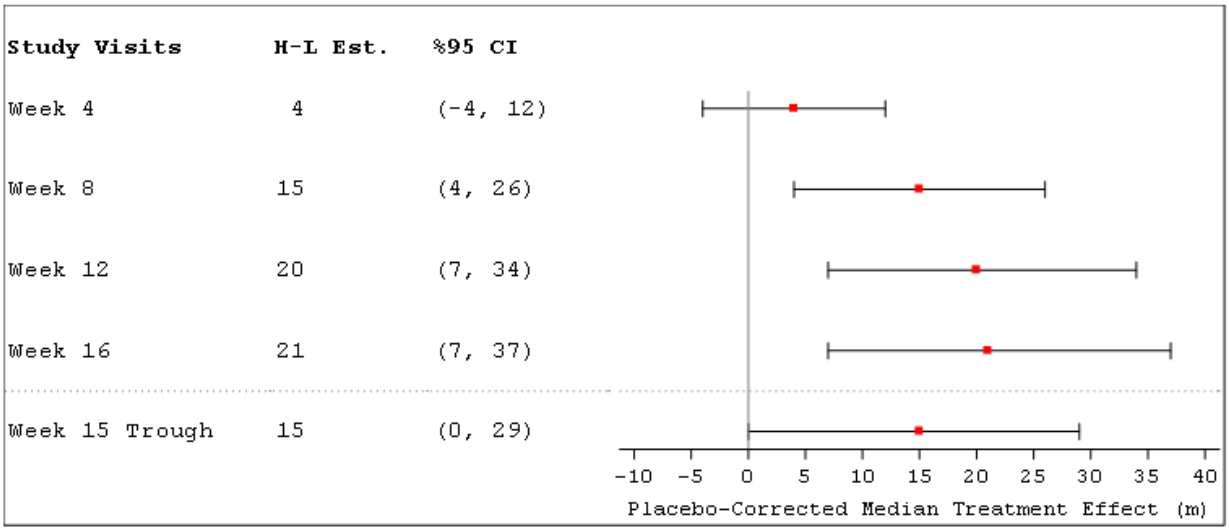
### 14.3 Pulmonary Hypertension Associated with ILD (WHO Group 3)

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)**

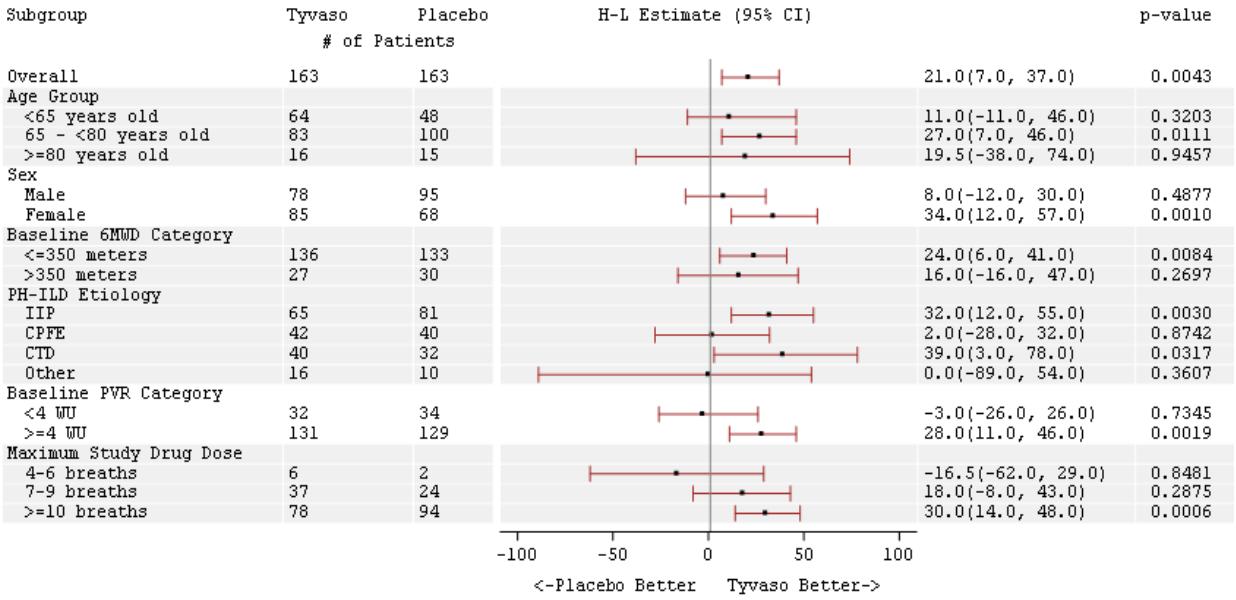
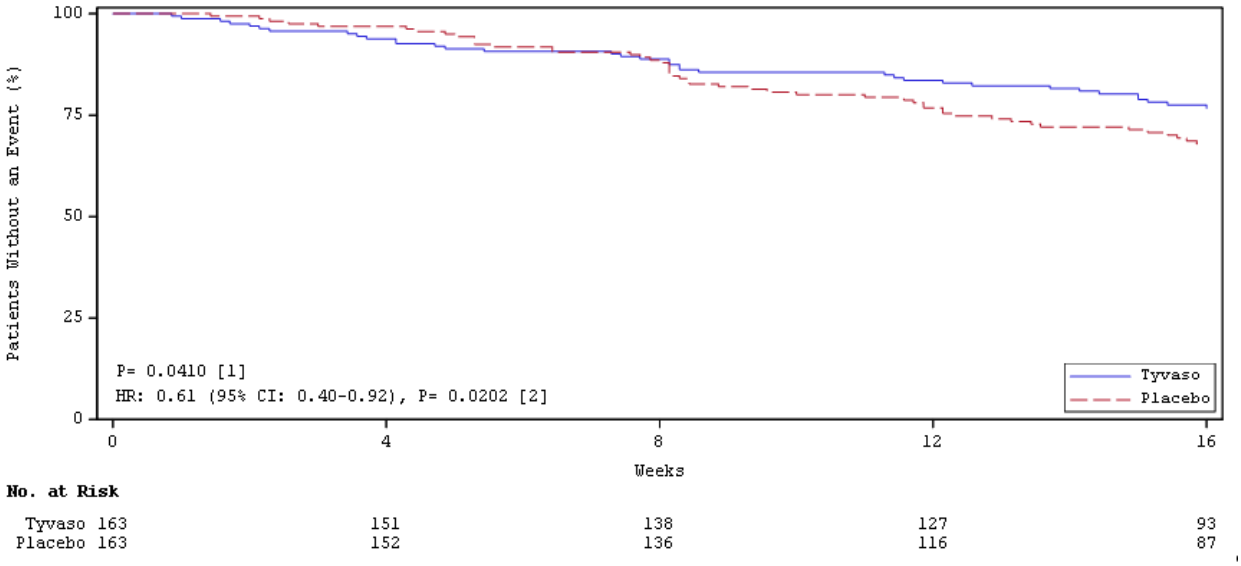

Subgroup
Tyvaso
Placebo
# of Patients
H-L Estimate (95% CI)
p-value
Overall 163 163 21.0(7.0, 37.0) 0.0043
Age Group
<65 years old 64 48 11.0(-11.0, 46.0) 0.3203
65 - <80 years old 83 100 27.0(7.0, 46.0) 0.0111
>=80 years old 16 15 19.5(-38.0, 74.0) 0.9457
Sex
Male 78 95 8.0(-12.0, 30.0) 0.4877
Female 85 68 34.0(12.0, 57.0) 0.0010
Baseline 6MWD Category
<=350 meters 136 133 24.0(6.0, 41.0) 0.0084
>350 meters 27 30 16.0(-16.0, 47.0) 0.2697
PH-ILD Etiology
IIP 65 81 32.0(12.0, 55.0) 0.0030
CPFE 42 40 2.0(-28.0, 32.0) 0.8742
CTD 40 32 39.0(3.0, 78.0) 0.0317
Other 16 10 0.0(-89.0, 54.0) 0.3607
Baseline PVR Category
<4 WU 32 34 -3.0(-26.0, 26.0) 0.7345
>=4 WU 131 129 28.0(11.0, 46.0) 0.0019
Maximum Study Drug Dose
4-6 breaths 6 2 -16.5(-62.0, 29.0) 0.8481
7-9 breaths 37 24 18.0(-8.0, 43.0) 0.2875
>=10 breaths 78 94 30.0(14.0, 48.0) 0.0006
-100
-50
0
50
100
<-Placebo Better
Tyvaso Better->
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