DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22387/S-009

SUPPLEMENT APPROVAL

Attention: Rex Mauthe, MBA
Associate Vice President, Regulatory Affairs
P.O. Box 14185
55 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Mr. Mauthe:

Please refer to your Supplemental New Drug Application (sNDA) dated November 1, 2013, received November 1, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tyvaso (treprostinil) solution for inhalation.

We acknowledge receipt of your amendments dated May 7 and 15, 2014.

This "Prior Approval" supplemental new drug application proposes inclusion of the results of a two-year rat carcinogenicity study in the Nonclinical Toxicology Section, addition of information about long-term treatment of pulmonary arterial hypertension to the Clinical Studies section and provides for edits to the Pregnancy and Nursing Mothers subsections of the Use in Specific Populations section and minor formatting edits. The changes to **USE IN SPECIFIC POPULATIONS, NONCLINICAL TOXICOLOGY AND CLINICAL STUDIES** are noted below (additions are marked as underlined text and deletions are marked as strikethrough text):

In **Full Prescribing Information;**

In **USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well controlled studies with Tyvaso in pregnant women. Animal reproduction studies have not been conducted with treprostinil administered by the inhalation route. However, studies in pregnant rabbits using continuous subcutaneous (sc) infusions of treprostinil sodium at infusion rates higher than the recommended human sc infusion rate resulted in an increased incidence of fetal skeletal variations associated with maternal toxicity *[see ~~Developmental Toxicity~~ Nonclinical Toxicology (13.3)]*. Animal reproduction studies are not always predictive of human response~~; Tyvaso should be used during pregnancy only if clearly needed~~.

8.3 Nursing Mothers

It is not known whether treprostinil is excreted in human milk. ~~Because many drugs are excreted in human milk, caution should be exercised when treprostinil is administered to nursing women.~~

In **NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-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. ~~Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil.~~ 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 (sc) infusions at rates of up to 450 ng treprostinil/kg/min [about 59 times the recommended starting human sc infusion rate (1.25 ng/kg/min) and 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a ng/m^2 basis]. 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.

13.4 Inhalational Toxicity

Rats and dogs that received daily administrations of treprostinil by inhalation for 3 months developed respiratory tract lesions (respiratory epithelial degeneration, goblet cell hyperplasia/hypertrophy, epithelial ulceration, squamous epithelial degeneration and necrosis, and lung hemorrhage). Some of the same lesions seen in animals sacrificed at the end of treatment (larynx, lung and nasal cavity lesions in rats, and lesions of the larynx in dogs) were also observed in animals sacrificed after a 4-week recovery period. Rats also developed cardiac changes (degeneration/fibrosis). A no-effect dose level for these effects was not demonstrated in rats (doses as low as 7 µg/kg/day were administered); whereas 107 µg/kg/day was a no-effect dose level in dogs.

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.

In **CLINICAL STUDIES**

14.1 Pulmonary Arterial Hypertension (WHO Group I)

TRIUMPH I, was a 12-week, randomized, double-blind, placebo-controlled multi-center study of patients with PAH. The study population included 235 clinically stable subjects with pulmonary arterial hypertension (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 three 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 four daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Patients were predominantly 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 six-minute walk distance (6MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3-5 hours after bosentan or 0.5-2 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.

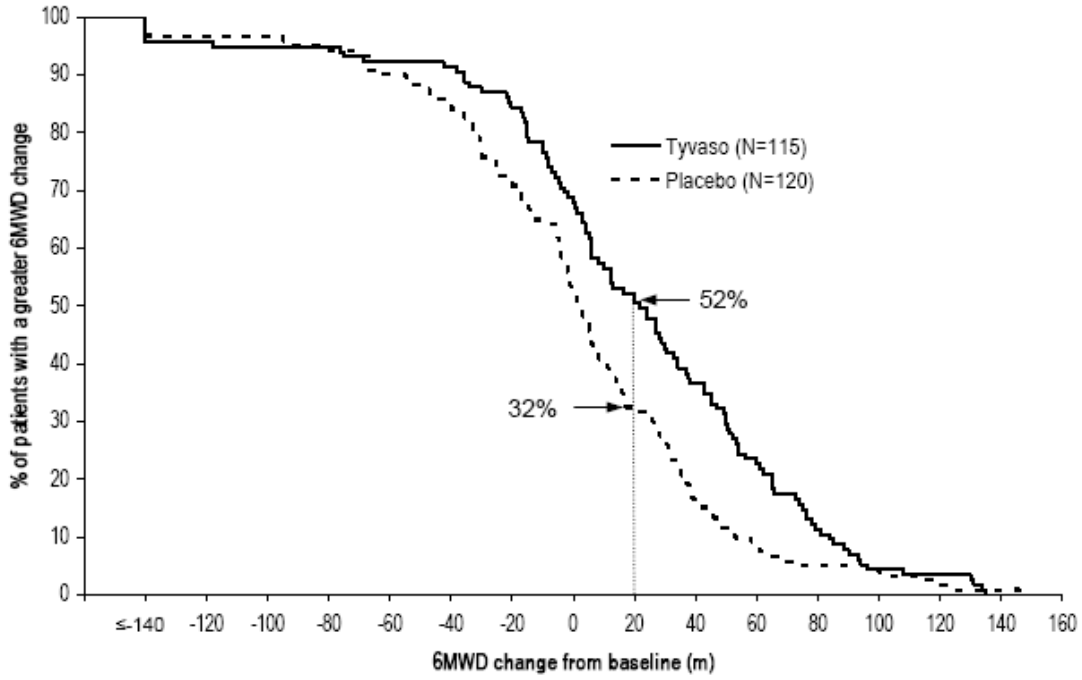

Figure 1: Distributions of 6MWD Changes from Baseline at Week 12 during Peak Plasma Concentration of Tyvaso

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).

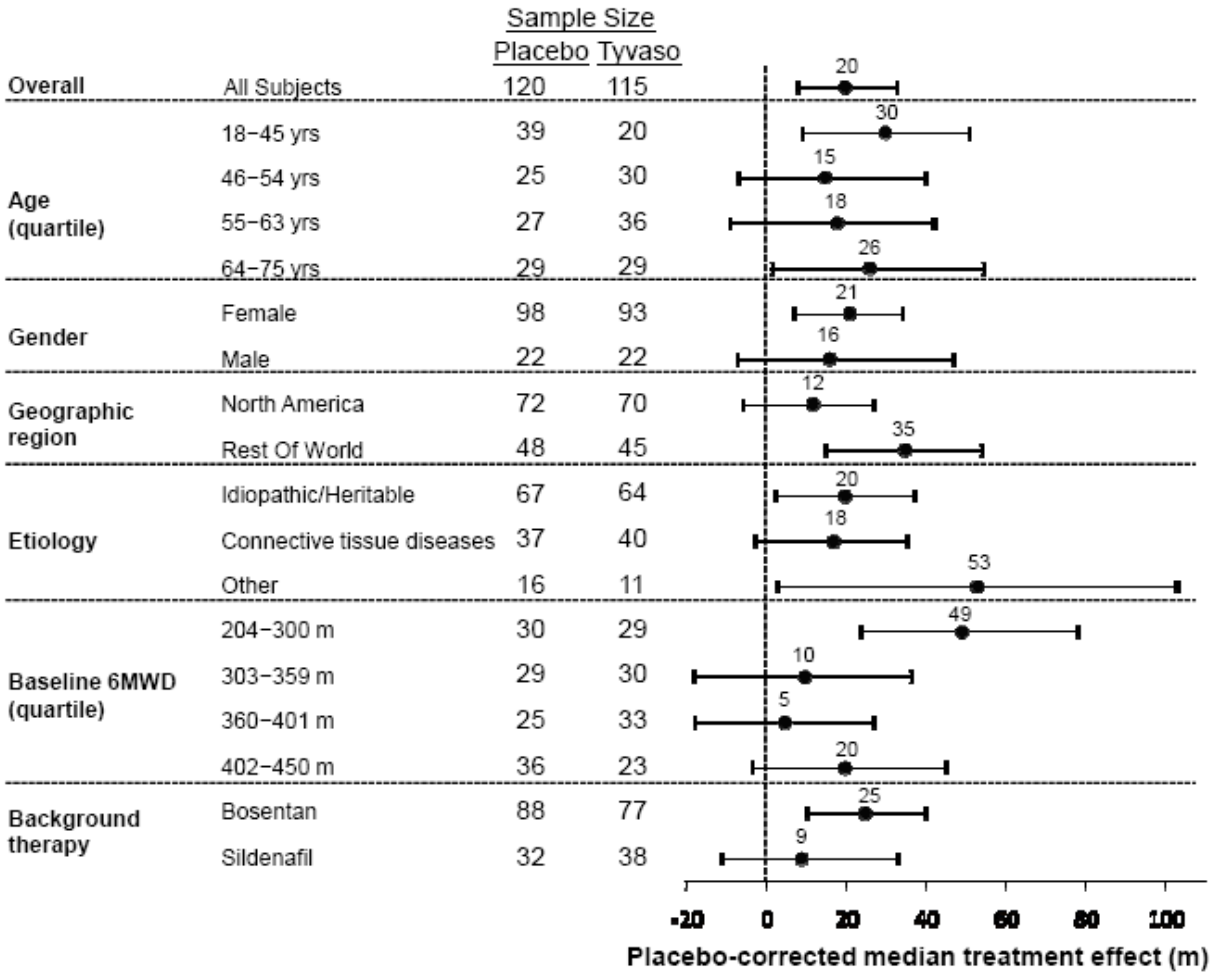

Figure 2. Placebo Corrected Median Treatment Effect (Hodges-Lehmann estimate with 95% CI) on 6MWD Change from Baseline at Week 12 During Peak Plasma Concentration of Tyvaso for Various Subgroups

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.

APPROVAL & LABELING

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

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), 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 titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes 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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), 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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

If you have any questions, call Wayne Amchin, Regulatory Project Manager, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
05/20/2014