CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214324Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 134582

MEETING REQUEST-
WRITTEN RESPONSES

United Therapeutics Corporation
Attention: Sarah Gemberling, PhD, RAC
Associate Manager, Regulatory Affairs
P.O. Box 14186
55 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Dr. Gemberling:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Tyvaso DPI.

We also refer to your submission dated October 2, 2020, containing a meeting request. The purpose of the requested meeting was to discuss your proposal for the filing of a new NDA (Pre-Assigned application number NDA 214324) for Treprostinil Inhalation Powder for the treatment of pulmonary arterial hypertension (PAH) and the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD).

Further reference is made to our Meeting Granted letter dated October 20, 2020, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your October 30, 2020 background package.

If you have any questions, call Wayne Amchin, MPA, MIA, RAC, Regulatory Project Manager at 301-796-0421.

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:

- Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type:	B
Meeting Category:	Pre-NDA
Application Number:	IND 134582
Product Name:	Tyvaso DPI
Indication:	Pulmonary arterial hypertension and pulmonary hypertension due to interstitial lung disease
Sponsor Name:	United Therapeutics Corporation
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

Treprostinil is a prostacyclin vasodilator and has been approved in inhalation(Tyvaso), injection (Remodulin), and oral (Orenitram) formulations. A pre-IND meeting was held with the previous sponsor, and meeting minutes were issued on July 28, 2017. The IND was submitted on January 29, 2018, and a safe-to-proceed letter with non-hold comments was issued on March 1, 2018. A type C guidance meeting was also held on January 11, 2018, following the sponsor's acquisition of this product to discuss the intended product development pathway and to gain agreement on the content of a marketing application.

The proposed product is being developed as a combination drug/device product for oral inhalation consisting of cartridges containing Treprostinil Inhalation Powder for use in a reusable breath-powered dry powder inhaler. The drug/device combination will be used for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. The previous sponsor was developing the proposed product under the 505(b)(2) regulatory pathway, but United Therapeutics is developing it under the 505(b)(1) pathway.

2.0 QUESTIONS AND RESPONSES

2.1. Clinical

Question 1: *Study TIP-PH-101: An Open-label, Clinical Study to Evaluate the Safety and Tolerability of Treprostinil Inhalation Powder (TreT) in Subjects with Pulmonary Arterial Hypertension Currently Using Tyvaso is currently ongoing and open to enrollment. During the pre-IND meeting on 28 June 2017 held with the previous sponsor, it was agreed that a sample size of approximately 45 subjects dosed for 3 weeks (i.e., 2.5 treatment years) would be sufficient to demonstrate safety and tolerability. In response to the ongoing COVID-19 pandemic, UTC re-examined the*

sample size needed to demonstrate safety and tolerability of TreT. Since the TIP-PH-101 study has an Optional Extension Phase, 17.4 treatment years of TreT exposure has already accumulated for all enrolled subjects. The PAH patient population has little margin to tolerate the respiratory compromise caused by COVID-19 pneumonitis, therefore UTC would like to minimize the risk of exposing these patients to SARS-Cov-2 (while in clinic and travelling to clinic) by limiting enrollment to no more than absolutely necessary to meet the study objectives. UTC proposes to decrease the total sample size of TIP-PH-101 to at least 38 subjects and use existing clinical data in support of the NDA. Does the Agency agree?

Note: This question was withdrawn by a November 17, 2020 email from Dr. Sarah Gemberling, PhD, RAC, Associate Manager, Regulatory Affairs, United Therapeutics, informing the Division that enrollment for the study is now complete and it met the protocol specified sample size. Therefore, UTC no longer requires a response for question 1.

Question 2: *Three clinical studies were conducted to support the filing of the NDA. 1) a single ascending dose (SAD) study in healthy volunteers (MKC-475-001), 2) an open-label study to evaluate the short-term safety and tolerability following repeat doses of TreT (TIP-PH-101) in PAH patients currently treated with Tyvaso, and 3) a relative bioavailability study of TreT compared to Tyvaso (TIP-PH-102). Since none of these studies are major, pivotal studies, UTC does not plan to include Bioresearch Monitoring (BIMO) datasets with the NDA submission. Does the Agency agree that BIMO datasets are not required to support this application?*

FDA Response to Question 2: Yes, we agree that BIMO datasets will not be needed.

Question 3: *Study TIP-PH-101: An Open-label, Clinical Study to Evaluate the Safety and Tolerability of Treprostinil Inhalation Powder (TreT) in Subjects with Pulmonary Arterial Hypertension Currently Using Tyvaso, consists of a three-week Treatment Phase followed by an Optional Extension Phase. As described in the Statistical Analysis Plan, after all subjects complete the Treatment Phase, the Treatment Phase database will be locked and analysis of the data from the Treatment Phase will be carried out. Available data from the Optional Extension Phase will also be analyzed at this time. Therefore, the primary TIP-PH-101 Clinical Study Report that will be submitted in the original NDA will contain all data from the Treatment Phase and any available data at the time of data cut from the Optional Extension Phase. Does the Agency agree with this approach?*

FDA Response to Question 3: Yes, we agree.

Question 4: *UTC plans to rely on existing treprostinil evidence of safety and effectiveness from approved treprostinil products, Tyvaso (NDA 022387), Remodulin (NDA 021272), and Orenitram (NDA 203496), in addition to the three agreed clinical studies for Treprostinil Inhalation Powder. Within the Integrated Summaries of Safety*

and Effectiveness, UTC plans to cross reference evidence in the approved NDAs in addition to summaries of the new clinical studies. Sections 2.7.3 and 2.7.4 will be sufficiently detailed to serve as the narrative portion of the ISE and ISS, respectively, while concise enough to meet the suggested size limitations for Module 2. Therefore, UTC proposes to split the ISE and ISS across Module 2 and Module 5, with the narrative portion located in Sections 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in Section 5.3.5.3. Does the Agency agree with this approach?

FDA Response to Question 4: Yes, we agree.

2.2. Format and Administrative Questions

Question 5 (multi-discipline): *Is the planned Table of Contents for the NDA, Section 15.2.2, sufficient for review?*

FDA Response to Question 5: Include the appropriate Regional Information and Appendices in your drug product quality submission, and include the "Summary of Biopharmaceutic studies and associated analytical methods" and "Summary of Clinical Pharmacology Studies" under Module 2.7. From a clinical perspective and pharmacology/toxicology perspective your planned NDA Table of Contents is acceptable.

Question 6 (Clinical): *The clinical development plan, as agreed with the Agency during a pre-IND meeting on 28 June 2017, and subsequent Type C meetings under IND 134,582 (06 January 2019 (preliminary meeting comments accepted as final minutes) and 04 December 2019), included clinical studies to establish safety/tolerability, characterize pharmacokinetics of the drug product, and assess relative bioavailability of treprostinil between Tyvaso and TreT. UTC currently has an efficacy supplement (S-017; NDA 022387) under review for Tyvaso (treprostinil) Inhalation Solution to add the PH-ILD indication. If the data support the approval of the Tyvaso label extension to include treatment of PH-ILD, UTC intends to include the same indication for the Treprostinil Inhalation Powder NDA. Demonstrated relative bioavailability of treprostinil between Tyvaso and TreT should support the use of TreT in all approved Tyvaso indications. Does the Agency agree?*

FDA Response to Question 6: Yes, we agree with your plan.

Question 7 (CMC): *UTC intends to cross reference DMF* (b) (4) *for all information related to the quality of the Treprostinil Inhalation Powder drug product and the dry powder inhaler. All future manufacturing changes will be reflected in the DMF and cross referenced in the Treprostinil Inhalation Powder NDA. Notifications of DMF updates will be submitted to the NDA as annual reports, CBE, or PAS, as appropriate. Does the Agency have any concerns?*

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