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?*

FDA Response to Question 7: From a CMC perspective, the proposed approach appears reasonable.

Question 8 (multi-discipline): *The draft Treprostinil Inhalation Powder Package Insert was based on the Package Insert for Tyvaso (NDA 022387). Adverse events from the completed TreT clinical studies are summarized in Section 6 Adverse Reactions of the draft Package Insert. Study TIP-PH-102 is further summarized in Section 12 Clinical Pharmacology* (b) (4) *Does the Agency agree with the placement of these studies in the draft Package Insert?*

FDA Response to Question 8: (b) (4) (b) (4) Otherwise your approach seems reasonable.

Question 9 (Clincial, Labeling): *The NDA submission will include Instructions for Use of the combination product. In the Acknowledgement letter dated 13 June 2020 for UTC's Tyvaso (NDA 022387) Supplement 017, the Agency noted that the Patient Package Insert would be removed from the approved labeling because it is duplicative of the Instructions for Use. Does the Agency agree that a separate Patient Package Insert is not required in addition to the Instructions for Use and Package Insert for Treprostinil Inhalation Powder?*

FDA Response to Question 9: We agree this approach is reasonable.

ADDITIONAL COMMENTS:

COMMENTS ABOUT ACCEPTABILITY OF THE DEVICE FOR THE MARKETING APPLICATION:

1. You stated that you have minor changes to the device. However, it is not clear exactly where these changes are made.
    a. To allow the Agency to evaluate whether the proposed changes may affect safety or effectiveness, please provide drawings and description on the changes.

(b) (4)

(b) (4)

3.0 ADDITIONAL IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential:*

[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Labeling for Human Prescription Drug and Biological Products – Content and Format.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[5]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[6] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in

[5] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[6] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[7]

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

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[7] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

[8] https://www.fda.gov/media/84223/download
[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[10]

[10] https://www.fda.gov/media/85061/download

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/

WAYNE S AMCHIN
11/19/2020 10:30:54 AM

NORMAN L STOCKBRIDGE
11/19/2020 11:49:54 AM