CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214324Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader (CDTL) Review

Date	14-October-2021
From	Mohan Sapru, M.S., Ph.D. Branch Chief, New Drug Products Division III, Branch V Office of New Drug Products/OPQ
Subject	CDTL Review
NDA	214324
Type of Application	505(b)(1)
Applicant	United Therapeutics Corp.
Date of Receipt	16-April-2021
PDUFA Goal Date	16-October-2021
Established/Proper Name	Tyvaso DPI (treprostinil) inhalation powder
Dosage forms; Strength	Dry powder for oral inhalation; 16 mcg, 32 mcg, 48 mcg, or 64 mcg per cartridge
Route of Administration	Oral inhalation
Proposed Indication(s)	Treatment of pulmonary arterial hypertension (PAH; WHO Group 1) and pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability
Regulatory Action	***Complete Response***

This CDTL review is based on the primary reviews, memos, and documented review input, as listed below:

Material Reviewed/Consulted	Review Team
Integrated Quality Assessment (DARRTS, dated 30-September-2021)	Daniel Jansen, Alexander Gontcharov, Akm Khairuzzaman, and Mohan Sapru
Device Inter-Center Consult Review ICC2100386 (dated 01-October-2022)	Dongbo Wang (CDRH), and John Bender
Non-Clinical Review (DARRTS, dated 22-June-2021)	Baichun Yang, and Xuan Chi
Clinical Review (DARRTS, dated 23-September-2021)	Mitchell Psotka, and Fortunato Senatore
Clinical Pharmacology Review (DARRTS, dated 23-September-2021)	Xiaomeng Xu, and Manoj Khurana
DMEPA Human Factors Validation Study Review, and Labeling Review (DARRTS, dated 03 September 2021, and 05-October-2021)	Ebony Whaley, and Colleen Little
DNDSI and OSIS Review (DARRTS, dated 24-June-2021)	Folaremi Adeyemo

OPQ: Office of Pharmaceutical Quality; DMEPA: Division of Medication Error Prevention and Analysis; DNDSI: Division of New Drug Study Integrity; OSIS: Office of Study Integrity and Surveillance

I. Background

The Applicant has sought U.S. marketing approval for Tyvaso DPI (treprostinil) inhalation powder in accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. Treprostinil is a prostacyclin analogue, and its major pharmacologic actions are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. The proposed combination product involves a change in dosage form for treprostinil from a solution for oral inhalation (Tyvaso® (treprostinil) inhalation solution (NDA 022387) to a dry powder for oral inhalation. Inhaled treprostinil therapy provides selectivity of the hemodynamic effects to the lung vasculature, thus reducing systemic side effects compared to other routes of administration. The safety and efficacy of treprostinil are supported by a comprehensive set of pharmacology, pharmacokinetic (PK), toxicology, and clinical studies conducted for UTC's Tyvaso (treprostinil) inhalation solution (NDA 022387), Remodulin (treprostinil) Injection (NDA 021272), and Orenitram (treprostinil) extended-release tablets (NDA 203496).

2. Quality Assessment Summary

The proposed Tyvaso (treprostinil) inhalation powder (TYVASO DPI) contains the identical drug substance as the inhaled liquid formulation (TYVASO®). All CMC information regarding the proposed treprostinil inhalation powder formulation (TYVASO DPI) is cross-referenced to DMF # (b) (4) The DMF was reviewed by OPQ review teams and found to be adequate. Specifically, treprostinil drug substance has been well-characterized using state-of-the-art methods with regard to its structure and physicochemical characteristics. It is stable for (b) (4) and its manufacturing process is well-controlled. The critical quality attributes (CQAs) of the drug substance are adequately monitored per release specification.

2.1 Drug Product: The proposed Tyvaso DPI (treprostinil) inhalation powder is a drug-device combination product, comprised of single-use cartridges containing a dry powder formulation of treprostinil inhalation powder at 16, 32, 48, or 64 mcg of treprostinil per cartridge, and a small, portable, reusable, breath-powered, dry powder inhaler. Pharmaceutical development studies adequately support the formulation design, including excipient selection and excipient levels. The proposed formulation involves the use of a non-compendial excipient fumaryl diketopiperazine (FDKP). Selection of FDKP for use in the proposed product is based on its utility as an excipient for pulmonary delivery by oral inhalation because it facilitates the particle matrix formation, crystallizes under acidic conditions and the crystals self-assemble to form particles with the appropriate properties. All CMC information concerning this excipient is provided in DMF-(b) (4) which was previously reviewed and found adequate as a part of the BLA-022472 approval process. The level of FDKP used in the proposed formulation is (b) (4) compared to the level present in the previously approved product (Afrezza; BLA # 022472).

The product manufacturing process is well-controlled and involves: (b) (4) The in-process controls and testing are adequate, and manufacturing process and testing ensure uniformity of the drug substance in the Tyvaso DPI (treprostinil) inhalation powder. The product release specification involves testing of all the product

critical quality attributes (CQAs), including aerodynamic particle size distribution, uniformity of delivered dose, [redacted] and microbial limits. The Applicant has demonstrated: a) suitability of the proposed container closure system for the intended use, and b) product stability for a period of 18 months [redacted] when stored at 5°C in the proposed commercial packaging.

3. Device Evaluation

The inhaler used to deliver treprostinil inhalation powder ("TreT Inhaler") contains [redacted] (FDA approved; reviewed under DMF [redacted]). Briefly, the inhaler is a mechanical device consisting of [redacted]. The TreT inhaler delivers the treprostinil inhalation powder consistently and effectively. [redacted] Extractables testing and toxicological risk assessment of the device component and biocompatibility evaluation of all patient-contacting (via gas pathway) device components of the dry powder inhaler subject device demonstrate that the device is safe for the intended use.

4. Human Factors (HF) Validation Study

The Applicant performed human factors validation study of the proposed combination product, involving the use of dry powder inhaler device. Overall, the results of this study demonstrate that the user interface has been optimized to support the safe and effective use of the proposed combination product. The Applicant's plan to consistently provide routine training to intended user of Tyvaso DPI seems reasonable, and the residual risks are not significant.

5. Non-Clinical

Tyvaso DPI was evaluated by (quantitative) structure-activity relationship ((Q)SAR) using Derek Nexus and Leadscope Model Applier. All 7 impurities ([redacted]) were identified as inactive (non-mutagenic) in DEREK Nexus and negative (non-mutagenic) in the Leadscope Model Applier. [redacted] is identified as an impurity in Tyvaso DPI at a concentration above the qualification threshold of 1% for drug products with a maximum daily dose of the active pharmaceutical ingredient of <10 mg. [redacted] was qualified at a concentration of up to [redacted]% in the final drug product. [redacted] was shown to have reduced pharmacodynamic effects compared to treprostinil, and it is expected to be [redacted] It is unlikely that the presence of [redacted] in Tyvaso DPI would be a safety concern for patients if present at up to [redacted]%. Furthermore, the safety of the excipient fumaryl diketopiperazine (FDKP) is supported by a comprehensive battery of safety pharmacology and toxicology studies conducted for Afrezza (BLA 022472). Based on the results of the nonclinical pharmacology, PK, and toxicology studies conducted to support Tyvaso (NDA 022387), Remodulin (NDA 021272), and Orenitram (NDA 203496), and the assessment of impurities present in Tyvaso DPI, it is considered that Tyvaso DPI has an acceptable safety profile and that there are no findings that preclude long-term inhalation administration in humans. In conclusion, this NDA is considered approvable from Pharmacology/Toxicology perspective.

6. Clinical Pharmacology

The Applicant submitted three clinical studies. These include: i) a single dose-escalation Study MKC-475-001 in healthy subjects, ii) an open-label Study TIP-PH-101, assessing safety and tolerability of proposed treprostinil inhalation powder (TYVASO DPI) in subjects with PAH currently using inhaled liquid formulation (TYVASO®), and iii) a relative bioavailability and bioequivalence (BA/BE) study TIP-PH-102 between TYVASO DPI and TYVASO® in healthy subjects. The safety data (though limited) from the single and multiple dose studies did not indicate any notable difference in respiratory adverse events (AEs) between proposed treprostinil inhalation powder and TYVASO®. Given that the clinical use of proposed treprostinil inhalation powder involves titration to therapeutic goal, the higher Cmax level of treprostinil inhalation powder in the context of comparable overall AUC (except the modest deviation at the lowest tested dose) does not appear to be clinically relevant. In conclusion, the Clinical Pharmacology review team has made approval recommendation for this NDA.

7. Clinical

The proposed indication for treprostinil inhalation powder formulation (TYVASO DPI) is identical to inhaled liquid formulation (TYVASO®), specifically for the treatment of WHO group I PAH and WHO group III PH-ILD to improve exercise capacity. As concluded by the clinical review team, substantial evidence of effectiveness for the proposed treprostinil inhalation powder (TYVASO DPI) has been previously concluded based on the liquid formulation (TYVASO®) in the 12-week, placebo-controlled TRIUMPH I study of 235 patients with WHO group I PAH, and in the 16-week, placebo-controlled INCREASE study of 326 patients with WHO group III PH-ILD, where treated patients had increased exercise capacity as measured by 6-minute walk test distance compared to placebo. In the BREEZE study included in this submission, patients on a stable regimen of inhaled liquid treprostinil were transitioned to an approximate corresponding dose of open-label inhaled treprostinil powder (TYVASO-DPI) and followed initially for 3 weeks. The switch from inhaled Treprostinil liquid to the inhaled powder formulation was not associated with a decrement in exercise capacity as measured by the 6-minute walk test distance.

Fumaryl diketopiperazine (FDKP), an excipient of TYVASO DPI™ also present in the approved human insulin powder (AFREZZA®) formulation, was comprehensively evaluated as a potential etiology of acute bronchospasm listed as a black-box warning for patients with chronic lung disease in the AFREZZA® label. However, the labelled black box warning does not specify whether the excipient or drug product may be responsible for concern for increased risk of bronchospasm. Pulmonary function testing did not implicate the excipient as a major cause of pulmonary dysfunction during the evaluation of that product. In addition, no reports of serious bronchospasm were identified during the 3-year assessment for the Risk Evaluation and Mitigation Strategy (REMS) for AFREZZA®. The exposure to the excipient FDKP via the treprostinil inhaled powder formulation appears acceptable, as the AFREZZA® maximal dose of co-administered FDKP is (b) (4) mg and the co-administered dose of FDKP in the 64 mcg cartridge of proposed treprostinil inhaled powder is (b) (4) mg. The BREEZE clinical trial of treprostinil inhaled powder with the excipient FDKP included patients with asthma, chronic obstructive pulmonary disease, and interstitial lung disease, and there were no bronchospastic adverse events reported during the 3-week randomized follow-up period, nor during the optional extension phase.

8. Assessment of Manufacturing Facilities

The drug substance testing facility, (b) (4) with an Official Action Indicated (OAI) classification is currently out of GMP compliance. The facility is responsible for analytical testing of the drug substance, which includes both physico-chemical and

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.