CLINICAL PHARMACOLOGY REVIEW

NDAs	NDA 203214 S038 (Xeljanz (Tofacitinib) tablets) (SDN 2744) NDA 208246 S025 (Xeljanz XR (Tofacitinib) extended-release tablets) (SDN 2403) NDA 213082 S010 (Xeljanz (Tofacitinib) oral solution) (SDN 373)
Submission Date	08/23/2024
Brand Name	Xeljanz/Xeljanz XR
Generic Name	Tofacitinib
Sponsor	Pfizer
Formulation; Strength(s)	Xeljanz (Tofacitinib) tablets (5 mg, 10 mg) Xeljanz (Tofacitinib) oral solution (1 mg/mL)
Clinical Pharmacology / Pharmacometrics Reviewer	Lei He, PhD
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OCP Division	Division of Inflammation and Immune Pharmacology
OND Division	Division of Rheumatology and Transplant Medicine
Submission Type; Code	NDA supplements

On August 12, 2015, FDA issued a Pediatric Written Request (PWR) for NDA 203214 tofacitinib for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) and systemic juvenile idiopathic arthritis (sJIA). The PWR was revised with FDA comments issued on July 12, 2016 (Amendment 1), October 3, 2019 (Amendment 2), and February 2, 2024 (Amendment 3).

On August 23, 2024, Pfizer submitted these supplemental applications to submit the required remaining study reports that meet the terms of the PWR – Amendment 3 for the review of Pediatric Exclusivity Determination and to propose updates to the United States Package Insert. The purpose of this memo is to assess whether the clinical pharmacology portion of the written request is fulfilled.

Clinical Pharmacology Findings

The written request is considered to be fulfilled from a clinical pharmacology perspective. See the summary table as below.

	Written Request (clinical pharmacology related)	**Fulfilled (Yes or No)**
Study 1 (A3921103)	*Study 1: A multiple-dose pharmacokinetic (PK) study in juvenile polyarticular idiopathic arthritis (PJIA) patients ages 2 to <18 years. The PK study must be completed before the efficacy trial(s) to inform dosing.*	Yes (Section 6 of NDA 203214 S-026 and NDA 213082 unireview)
	Objectives: PK study in PJIA patients ages 2 to <18 years; The primary objective is to characterize the pharmacokinetics of tofacitinib in PJIA patients. Secondary objectives include the evaluation of safety.	Yes (Section 6 of NDA 203214 S-026 and NDA 213082 unireview)
	Patients: At least 24 males and females with PJIA aged 2 to <18 yrs to be divided into three cohorts: 12 to <18 years, 6 to <12 years, and 2 to <6 years. *The sample size of 24 pediatric patients (8 per age group) will provide 80% probability that the ideal recommended dose resulting from the clearance estimate would achieve a systemic exposure within 66% to 150% of the targeted exposure (5 mg BID).*	Yes (Table 4 of NDA 203214 S-026 and NDA 213082 unireview)
	Representation of Ethnic and Racial Minorities: *The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.*	Yes (Table 60 of NDA 203214 S-026 and NDA 213082 unireview)
	Pharmacokinetic endpoints will include oral clearance (CL/F), area under the curve plasma concentration-time profile of the dosing interval τ at steady state (AUCτ), Cmax, Tmax, PK sampling adequate for non-compartmental analysis. The protocol must specifically state the timepoints for sampling and the protocol must be agreed upon with FDA. *Noncompartmental analysis of plasma concentration time data and non-linear mixed effects analysis of PK data will be performed to determine parameters. The PK parameters from the noncompartmental analysis will be summarized descriptively.*	Yes (Table 5 of NDA 203214 S-026 and NDA 213082 unireview)
Study 2 (A3921104)	*Study 2: Efficacy study in PJIA patients ages 2 to <18 years* *PK parameters will be regarded as secondary endpoints and may include Cmax, Cmin and AUC.*	Yes (Sparse PK samples were collected. Population exposure-response analysis report (PMAR-EQDD-A392l-Other-942) was submitted under

	Sparse PK sampling will be collected for exposure response analysis.	NDA 203214 S-026 and NDA 213082.)
Study 3 (A3921165)	*Study 3: A randomized withdrawal, double blind, placebo-controlled study to evaluate the efficacy, safety and pharmacokinetics of tofacitinib in children 2 to <18 years with active systemic juvenile idiopathic arthritis (SJIA).*	Yes
	Objective of Study 3: Efficacy study in SJIA patients ages 2 to <18 years; To evaluate the efficacy, safety, and pharmacokinetics of tofacitinib to placebo in SJIA patients with active systemic features.	Yes
	PK endpoints will be regarded as secondary endpoints and may include Cmax, Cmin, and AUC. PK endpoints may also be assessed during the open-label, run-in phase. Sparse PK sampling will be collected for exposure-response analysis.	Yes (The primary efficacy objective of Study 3 was not met. Sparse PK samples were collected.)
All studies	*Drug information and Drug formulation:* • *Dosage Form (all studies)* *Tofacitinib oral solution (1 mg/mL)* *Tofacitinib 5 mg film coated tablet.* • *Route of Administration (all studies)* *Oral* • *Regimen* *Studies 1 through 4: Twice daily (BID).* *Study 1: Appropriate dosing to be identified and agreed upon with the Agency.* *Study 2: Appropriate dosing to be identified and agreed upon with the Agency.* *Study 3: Appropriate dosing to be identified and agreed upon with the Agency.* *Study 4: Appropriate dosing to be identified and agreed upon with the Agency.*	Yes
	Use an age-appropriate formulation in the study (ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.	Yes (NDA 203214 S-026 and NDA 213082)
	Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.	Yes (Study A3921354, Section 6 of NDA 203214 S-026 and NDA 213082 unireview)

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/

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