Medical Officer's Clinical Review Memorandum

Division of Dermatology and Dental Drug Products, HFD-540

NDA #	215985/S-002 (Efficacy Supplement)
SDN:	105
IND:	135681
Stamp date:	12/15/2022
Review date:	9/26/2023
Clinical reviewer:	Hamid Tabatabai, M.D.
Clinical team leader:	David Kettl, M.D.
Project Manager:	Qianyiren (Cicy) Song, PharmD
Sponsor:	Arcutis Biotherapeutics, Inc.
Drug:	Zoryve (Roflumilast, ARQ-151)
Dosage Form:	Cream, 0.3%
Route of Administration:	Topical
Pharmacologic Category:	PDE-4 Inhibitor
Approved Indication:	Topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older

(b) (4)

Summary:

At the time of NDA 215985 approval on 7/29/2022, the following 3 PREA PMRs were issued to the Applicant:

1. PMR 4314-1: An Open Label, 4-Week, Phase 2, Maximal Usage Pharmacokinetics and Safety Study of ARQ-151 Cream 0.3% Administered QD in 20 Pediatric Subjects (ages 6 to 11 years old) with Plaque Psoriasis (Study Protocol ARQ-151-215)

2. PMR 4314-2: An Open Label, 4-Week, Phase 2, Maximal Usage Pharmacokinetics and Safety Study of ARQ-151 Cream 0.3% Administered QD in 10 Pediatric Subjects (ages 2 to 5 years old) with Plaque Psoriasis (Study Protocol ARQ-151-216)

3. PMR 4314-3: A Phase 3, multicenter, open-label extension study of the long-term safety of ARQ-151 cream 0.3% in subjects (≥ 2 years of age) with chronic plaque psoriasis (Study Protocol ARQ-151-306)

Under efficacy supplement S-2, the Applicant submitted the results of the two maximal use studies conducted under PMRs 4314-1/-2, (b) (4) Refer to the clinical pharmacology review of the studies ARQ-151-215/-216 in DARRTS on 9/22/2023 by Dr. Rakesh Gollen for additional details. The recommendation by the clinical pharmacology review team was the following: “From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the Sponsor. Clinical Pharmacology also recommends that the Applicant has fulfilled PMR 4314-1 and PMR 4314-2 and the Applicant be released from these two PMRs”.

Efficacy of roflumilast cream, 0.3% for topical treatment of plaque psoriasis in subjects ≥12 years of age was demonstrated in two multicenter, randomized, double-blind, vehicle-controlled trials (DERMIS-1 [NCT04211363] and DERMIS-2 [NCT04211389]) which enrolled 881 subjects with mild to severe plaque psoriasis between ages 6 to 88 years, including 4 subjects between 6 to <12 years of

age (study results are included in section 14 of the current label).

An Agreed iPSP Agreement letter was conveyed to the Applicant by the FDA on 5/20/2020, which included Applicant's planned extrapolation of effectiveness for treatment of plaque psoriasis from subjects ≥12 years of age [redacted] (b) (4) (Sec. 3 of iPSP). The Applicant's rationale for extrapolation of efficacy included similar disease manifestation and response to treatment across age groups. The Division considered the Applicant's plan for extrapolation of efficacy as consistent with DDD's prior meeting advice; and determined that additional efficacy data for treatment of plaque psoriasis in [redacted] (b) (4) to be unnecessary.

Safety results for Study ARQ-151-215 (PMR 4314-1)
Eight (8) TEAEs were reported for 4/20 subjects., including Candida infection (1), Application site pain (1), Headache (1), Perineal pain (1), Nasal congestion (1), Dermatitis (1) , Perineal erythema (1). All TEAEs were mild; none were SAEs or AELDs, and 2/4 AEs (candida infection [resolved] and application site pain [ongoing]) were related to roflumilast. No AEs in the SOC of Gastrointestinal disorders (potentially related to PDE-4 inhibition) was reported.

Safety results for Study ARQ-151-216 (PMR 4314-2)
One mild TEA (headache [resolved]) was reported for 1/10 subjects. No SAEs, AELDs, or AEs related to roflumilast were reported.

For both studies -215/-216, no clinically significant changes in laboratory (chemistry, hematology) measurements, physical examinations, vital signs, ECGs, changes in body weight, local tolerability (per investigator and per subject), or children's depression inventory (CDI-2 for ages 6 to <12 years) were reported.

Supplement S-2 was presented at the pediatric review committee (PeRC) meeting on 9/19/2023. PeRC agreed with the Division's plan to broaden the population in the "Indications and Usage" section of the label from patients ≥ 12 years of age to ≥6 years of age, and to consider PREA PMRs 4314-1 and 4314-2 as fulfilled.

No subject < 6 years of age was included in the safety population submitted with the initial NDA 215985. The Division considers the available safety database of 10 subjects (between 2 to < 6 years of age) enrolled in study ARQ-151-216 as inadequate [redacted] (b) (4)

Clinical Recommendation and Labeling
The Clinical Review team recommends approval of NDA 215985/S-002 for use of ZORYVE (roflumilast) cream, 0.3% once daily for the topical treatment of plaque psoriasis, including intertriginous areas, in patients 6 years of age and older.

Labeling negotiations with the Applicant are ongoing at the time this clinical review is finalized, and the final label will be attached to the Action letter for this efficacy supplement.

Hamid Tabatabai, MD
Medical Officer
CDER/OND/OII/DDD

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/

HAMID N TABATABAI
09/28/2023 09:56:58 AM

DAVID L KETTL
09/28/2023 10:28:16 AM