CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761180Orig1s000

INTEGRATED REVIEW

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

Review Memorandum: Adbry (Tralokinumab)

BLA 761180, SDN 41	Resubmission (7/2/2021) (Cycle #2) Following FDA Complete Response (4/23/2021) to Cycle #1 review of BLA 761180, SDN 1 initial submission on 4/27/2020
Clinical Reviewer:	Hamid Tabatabai, M.D.
Clinical Team Leader:	David Kettl, M.D.
Project Manager:	Strother Dixon, Senior Regulatory Health Project Manager
Drug Product:	Adbry (Tralokinumab) injection (SC), 150 mg/mL
Indication:	Treatment of moderate to severe Atopic Dermatitis (AD)
Memorandum Date:	December 22, 2021

Executive Summary

This application is a Complete Response resubmission of BLA 761180 for tralokinumab-ldrm for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. BLA 761180 was initially submitted by LEO Pharma A/S under regulatory pathway 351(a) of the Public Health Service Act on 4/27/2020 and received a Complete Response (CR) letter on 4/23/2021 from the Agency.

Tralokinumab is a new molecular entity, first-in-class, fully human immunoglobulin G4 (IgG4) monoclonal antibody. It is an immunomodulator/interleukin (IL) Inhibitor that neutralizes the cytokine IL-13 by inhibiting its interactions with IL-13 receptors α1 and α2. Other than corticosteroids, tralokinumab is the second systemic product (after dupilumab) to be approved for the treatment of moderate-to-severe AD.

The Phase 3 program included two 52-week placebo-controlled monotherapy trials (ECZTRA-1, ECZTRA-2) and a 32-week trial (ECZTRA-3) evaluating the safety and effectiveness of tralokinumab in combination with topical corticosteroids. the results of the three Phase 3 trials showed statistically significant improvement in the primary endpoints (proportion of subjects with an Investigator's Global Assessment [IGA] score of 0 [clear] or 1 [almost clear] [IGA 0/1] at Week 16 and proportion of subjects with at least 75% reduction in Eczema Area and Severity Index (EASI) score from baseline [EASI-75] at Week 16).

Following completion of the Integrated Review of Marketing Application (Cycle #1), the review team concluded that there was substantial evidence to support the effectiveness of tralokinumab and did not identify safety issues that might impact approval of the application. Agreement on draft labeling was achieved with the sponsor as no safety or efficacy issues were identified by the review team, and no nonclinical or clinical pharmacology issues were identified which would preclude approval of the application.

However, the initial BLA 761180 submission received a Complete Response action as recommended by the Center for Devices and Radiological Health (CDRH) review team, because it did not contain sufficient information regarding the needle-safety performance of the device.

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

Since the Complete Response action, the applicant resubmitted BLA 761180 on 7/2/2021, including the following deficiencies outlined in the CR letter of 4/23/2021:

- Final finished combination product needle safety performance (testing results for the accessorized pre-filled syringe (APFS) needle safety performance using final finished product after preconditioning over the proposed shelf-life of (b) (4) month to the appropriate confidence and reliability of 95%/99%.
- Data supporting the combination product's shelf-life at BLA approval (the APFS compressive override force testing using (b) (4) month real-time aged samples, and APFS needle safety activation testing using 24-month real-time aged samples), sequentially preconditioned and tested to ensure 95% confidence /99% reliability to support a shelf-life of (b) (4) months at BLA approval. The applicant plans to extend the shelf-life of tralokinumab to 36 months following further similar needle safety performance testing, and accelerated aging to simulate 36 months of real-time storage.

The CDRH review team (ICC review memorandum of 10/13/2021) recommended that the combination product was approvable and no outstanding unresolved information requests or CR deficiencies remained.

Additionally, the Applicant included safety data update (data cut-off date of 3/31/2021) of their initial 120-day safety data update (data cut-off date of 4/30/2020) for the ISS-AD, which was consistent with the safety profile of tralokinumab from the safety review of the initial BLA submission and identified no new safety concerns.

Pediatrics

Clinical studies were conducted only in adults. Because tralokinumab is a new active ingredient, this BLA is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

On 6/28/2018, the Division agreed to the Agreed initial pediatric study plan (Agreed iPSP) submitted by the sponsor on 6/4/2018, which included the following:

- Partial waiver to conduct studies in pediatric patients less than 6 months of age (studies are impossible or highly impractical)
- Deferral of Phase 3 clinical trials in pediatric patients ages 6 months to < 18 years.

On 2/18/2020, the Agency agreed with the sponsor's submitted revised proposed timelines for the pediatric studies to harmonize with the PIP for EMA/PDCO.

During the first review cycle of this BLA, the Pediatric Review Committee (PeRC) agreed to the pediatric study plan presented at the PeRC meeting on 10/27/2020.

Postmarketing Requirements and Commitment (PMR/PMC)

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

The following 6 PMRs and 1 PMC were agreed to by the FDA and the Applicant, and will be issued with the following milestones:

PMR - 1
Trial LP0162-1334 (ECZTRA 6) Trial: Efficacy and safety (phase 3, randomized, DB, PC, parallel-group, monotherapy) trial in Adolescents (12 to <18 years of age) with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic treatment.

PMR – 1 Schedule Milestones:
Final Protocol Submission: 06/15/2018
Study/Trial Completion: 03/30/2021
Final Report Submission: 03/30/2022

PMR – 2
Trial LP0162-1335: A PK and safety (randomized, single [observer] blinded, parallel-group, monotherapy) dose-ranging trial in pediatric subjects 2 to <12 years of age with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic AD treatment (studied sequentially in 2 cohorts: 6 to <12 years and 2 to <6 years).

PMR – 2 Schedule Milestones:
Final Protocol Submission: 03/31/2022
Study/Trial Completion: 09/30/2025
Final Report Submission: 03/31/2026

PMR – 3
Trial LP0162-1336: An efficacy and safety (phase 3, randomized, double-blind, placebo-controlled, parallel-group) trial with tralokinumab and placebo in combination with topical corticosteroid [TCS] therapy in pediatric subjects 2 to <12 years of age with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic AD treatment (studied simultaneously in 2 cohorts: 6 to <12 years and 2 to <6 years).

PMR – 3 Schedule Milestones:
Draft Protocol Submission: 05/31/2023
Final Protocol Submission: 09/30/2023
Study/Trial Completion: 03/31/2027
Final Report Submission: 09/30/2027

PMR – 4
Study LP0162-1381: An efficacy, safety, and pharmacokinetic (PK) (phase 2, single-arm, open-label, monotherapy) trial in infants and pediatric subjects (6 months to <2 years of age) with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic AD treatment.

PMR – 4 Schedule Milestones:
Draft Protocol Submission: 02/28/2027
Final Protocol Submission: 06/30/2027
Study/Trial Completion: 12/31/2028

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

Final Report Submission: 06/30/2029

PMR – 5
A prospective, pregnancy exposure registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to tralokinumab during pregnancy to an unexposed control population.

PMR – 5 Schedule Milestones:
Draft Protocol Submission: 06/01/2022
Final Protocol Submission: 10/31/2022
Study/Trial Completion: 09/30/2034
Interim/Other: Not applicable
Final Report Submission: 09/30/2035

PMR – 6
An additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to tralokinumab during pregnancy compared to an unexposed control population.

PMR – 6 Schedule Milestones:
Draft Protocol Submission: 06/01/2022
Final Protocol Submission: 10/31/2022
Study/Trial Completion: 06/30/2030
Interim/Other: 06/30/2027
Final Report Submission: 12/30/2030

PMC – 7
The applicant commits to conduct a real-time shipping study of commercial product as a Post Marketing Commitment (PMC).

PMC – 7 Schedule Milestones:
Final Report Submission: 07/2022

Labeling:
Draft labeling has been agreed to by the Applicant, and the final approved labeling will be attached to the action letter.

Hamid Tabatabai, M.D.
Clinical Reviewer
Division of Dermatology and Dentistry (DDD)
Office of Immunology and Inflammation (OII)
OND/CDER

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

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.