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RESEARCH**

APPLICATION NUMBER:

217900Orig1s000

OTHER REVIEW(S)

CONSULT REVIEW MEMORANDUM

Consult number: ICCR# 00995643

Application number: NDA 217900

Requestor: Qianyiren Song, Pharmacist,
CDER/OND/ORO/DROI

Consultants: Ashly Huber, Scientific Reviewer,
CDRH/OPEQ/OHT7/DCTD

Through: Keisha Melodi Gussow, Toxicology Team
Lead, CDRH/OPEQ/OHT7/DCTD

Applicant: Sun Pharmaceutical Industries Ltd.

Product name: LEQSELVI™

Date Received: June 14, 2024

Due Date: June 28, 2024

Consult Request

Request for CDRH feedback from CDER:

“Deuruxolitinib is indicated for the treatment of adult patients with severe alopecia areata. In the Phase 3 clinical studies, the 12mg dose had an increased incidence of adverse events, including thrombosis, as compared to the 8mg dose. As the 12mg dose does not have an acceptable risk-benefit profile, CDER plans to contraindicate deuruxolitinib in patients who are CYP2C9 poor metabolizers, due to an approximate 2-fold higher exposure. An authorized test for CYP2C9 variant detection is not currently available. Please provide input on labeling related to CYP2C9 testing and post-marketing commitments to develop a CYP2C9 test.

Will provide the current draft labeling and a copy of the proposed PMC template by email once reviewer assignment received.”

CDER has requested CDRH review the post-marketing commitment (PMC) language and the labeling of deuruxolitinib.

Background

LEQSELVI™ (deuruxolitinib) is currently under review in CDER under NDA 217900.

LEQSELVI is a Janus kinase (JAK) inhibitor indicated for the treatment of adults with severe alopecia areata. Based on drug-drug interaction data collected during Phase 3 of clinical studies, CYP2C9 poor metabolizers (e.g., *2/*3, *3/*3) are expected to have 2-fold higher concentrations of deuruxolitinib, when compared to normal metabolizers and an increased incidence of adverse events, including thrombosis. Although the impact of CYP2C9 genetic variants on the pharmacokinetics of deuruxolitinib has not been directly evaluated, deuruxolitinib (LEQSELVI) will be contraindicated in patients who are CYP2C9 poor metabolizers or using moderate or strong CYP2C9 inhibitors. The drug will be approved with a post-marketing requirement (PMR) to assess the genotypes of patients in the clinical study and determine drug exposure based on genotype.

Currently, an FDA-cleared or -approved test for the detection of CYP2C9 variants to direct the use of LEQSELVI is not available. The drug will be approved with a PMC to develop an in vitro diagnostic (IVD) device for CYP2C9 genotyping which should detect, at a minimum, the presence of the nonfunctional alleles in cytochrome P450 2C9 (CYP2C9) relevant to the US population.

CDRH Comments to CDER

A. PMC commitment

Given the potential for adverse events, CYP2C9 genetic testing would need to be performed prior to prescribing deuruxolitinib. Since the device *“provides information that is essential to the safe and effective use of a corresponding therapeutic product”* (as described in FDA’s guidance document *“In Vitro Companion Diagnostic Devices”* (issued on August 6, 2014)), the IVD device that will be required in the PMC is considered to be a companion diagnostic device (CDx) that would require FDA authorization.

The following draft language for the PMC was provided for CDRH’s review:

“Establish an in-vitro diagnostic device to guide the use of deuruxolitinib in patients with severe alopecia areata. The device should detect, at a minimum, the presence of the nonfunctional alleles in cytochrome P450 2C9 (CYP2C9) relevant to the US population.”

CDRH have reviewed and agree with the PMC language above as well as the boxes in SectionC(5), SectionD(1) and SectionD(2) of the PMC form.

B. Drug label

Use of the CDx should be stipulated in the labeling of the therapeutic product (as well as the labeling of the CDx when it is developed). The relevant sections of the draft labeling for deuruxolitinib were reviewed and the following edits are proposed for CDER’s consideration (proposed edits are listed below in red):

1. Page 1; Warnings and Precautions:

The lead reviewer and team lead briefly discussed the intent of this sentence with Jeffrey Kraft on June 18, 2024, and determined that the statement should be edited to “or”.

Current label: “Increased risk of LEQSELVI-Associated Serious Adverse Reactions in CYP2C9 Poor Metabolizers **and** with Concomitant Use of Moderate or Strong CYP2C9 Inhibitors: (b) (4) who are CYP2C9 poor metabolizers or patients taking a moderate or strong CYP2C9 inhibitor (b) (4) (5.6)”

Suggested edit: “Increased risk of LEQSELVI-Associated Serious Adverse Reactions in CYP2C9 Poor Metabolizers **or** with Concomitant Use of Moderate or Strong CYP2C9 Inhibitors: (b) (4) who are CYP2C9 poor metabolizers or patients taking a moderate or strong CYP2C9 inhibitor (b) (4) (5.6)”

2. Page 1; Drug Interactions:

We believe our suggested language more clearly describes potential drug interactions.

Current label:

- Strong CYP3A4 inducers: Avoid concomitant use. (7.1)
- Moderate or strong CYP2C9 inhibitors: Contraindicated. (7.2)

Suggested edit:

- **CYP3A4 and CYP2C9 Inducers: Decrease in deuruxolitinib exposure; concomitant use of LEQSELVI with moderate CYP2C9 and strong CYP3A4 inducers is not recommended. (7.1)**
- **CYP2C9 Inducers: Increase in deuruxolitinib exposure; LEQSELVI with moderate or strong CYP2C9 inducers is contraindicated. (7.2)**

3. Section 5.6:

- a. See #1 above for comment on this suggest edit.

Current language: “5.6 Increased Risk of LEQSELVI-Associated Serious Adverse Reactions in CYP2C9 Poor Metabolizers **and** with Concomitant Use of Moderate or Strong CYP2C9 Inhibitors”.

Suggested edit: To align with Jeffery Kraft’s statement above in Item #1, the statement should be edited as follows: “...CYP2C9 Poor Metabolizers **or** with Concomitant Use of Moderate or Strong CYP2C9 Inhibitors...”.

- b. We propose the addition of the sentence in red to clarify that the CDx needed for the detection of CYP2C9 variants is not currently available.

Current language: “Prior to LEQSELVI treatment, test patients for CYP2C9 variants to determine if they are poor metabolizers [see Dosage and Administration (2.1)]. LEQSELVI is contraindicated in patients who are CYP2C9 poor metabolizers or patients who are on concomitant moderate or strong CYP2C9 inhibitors [see Contraindications (4)].”

Suggested edit: “Prior to LEQSELVI treatment, test patients for CYP2C9 variants to determine if they are poor metabolizers [see Dosage and Administration (2.1)]. **An FDA-cleared or -approved test for the detection of CYP2C9 variants to direct the use of LEQSELVI is not currently available.** LEQSELVI is contraindicated in patients who are CYP2C9 poor metabolizers or patients who are on concomitant moderate or strong CYP2C9 inhibitors [see Contraindications (4)].”

4. Section 7.1; Strong CYP3A4 and moderate CYP2C9 inducers:

We propose this edit to align with section 7.2 of the deuruxolitinib labeling and add clarity to the statement.

Current language: “Deuruxolitinib is a CYP2C9 and CYP3A4 substrate. Concomitant use with a strong CYP3A4 and moderate CYP2C9 inducer **decreases deuruxolitinib C_{max} and AUC**, which may reduce LEQSELVI efficacy [see Clinical Pharmacology (12.3)].”

Suggested edit: “Deuruxolitinib is a CYP2C9 and CYP3A4 substrate. Concomitant use with a strong CYP3A4 and moderate CYP2C9 inducer **decreases deuruxolitinib exposure (C_{max} and AUC)**, which may reduce LEQSELVI efficacy [see Clinical Pharmacology (12.3)].”

5. Section 8.8; CYP2C9 poor metabolizers:

We suggest including the following statement directly under section 8.8 header to make clear that CYP2C9 genotype should be established prior to treatment and that a CDx is not currently available:

“Before initiation of treatment with LEQSELVI, test patients to determine CYP2C9 genotype. An FDA-cleared or -approved test for the detection of CYP2C9 variants to direct the use of LEQSELVI is not currently available.”

6. Section 12.5; Pharmacogenomics:

We propose the addition of this statement to add additional details and clarity:

Current label: The prevalence of the CYP2C9 poor metabolizer phenotype is approximately 2 to 3% in White populations, 0.5 to 4% in Asian populations, and <1% in Black or African-American populations.

Suggested edit: “The prevalence of the CYP2C9 ***2/*3 and *3/*3 alleles associated with poor metabolizer phenotypes is approximately** 2 to 3% in White populations, 0.5 to 4% in Asian populations, and <1% in Black or African-American populations.”

7. Section 17, Patient counseling information:

See #1 above for comment on this suggest edit.

Current label: “Increased Risk of LEQSELVI-Associated Serious Adverse Reactions in CYP2C9 Poor Metabolizers **and** with Concomitant Use of Moderate or Strong CYP2C9

Inhibitors”.

Suggested edit: To align with Jeffery Kraft’s statement above in Item #1, the statement should be edited as follows: “...CYP2C9 Poor Metabolizers **or** with Concomitant Use of Moderate or Strong CYP2C9 Inhibitors”.

8. We note that Section 7.1 appears to interchangeably use CYP3A4, CYP3, and CYP3A. It is unclear if this is intentional, but if all are meant to refer to the same specific isoenzyme (likely CYP3A4) we recommend using the term consistently.

Additional comments:

Currently, all legally marketed in vitro diagnostic (IVD) devices for CYP2C9 genotyping are intended as an aid in the identification of patients at risk for increased sensitivity to drugs other than deuruxolitinib. The PMC states the sponsor should establish an IVD (CDx) for a new intended use: identification of a subpopulation of patients with CYP2C9 poor metabolizer genotypes who should not receive deuruxolitinib. As stated in [FDA’s Companion Diagnostic Guidance](#), “*If an IVD device is already legally marketed and the IVD device manufacturer intends to market its device for a new use as an IVD companion diagnostic device for a novel therapeutic product, FDA would likely consider the new use of the IVD device with the novel therapeutic product as a new use for the device that would require an additional premarket submission (see 21 CFR 807.81(a)(3)(ii), 814.39(a)).*” Whether the sponsor develops a new device for the new use or identifies an already-legally marketed device that they (the manufacturer of the device) would like to market for a new use, a premarket submission is needed for FDA/CDRH’s review.

We recommend that the drug sponsor, and/or IVD manufacturer identified by the drug sponsor, interact with CDRH as soon as possible via the pre-submission program (<https://www.fda.gov/media/114034/download>) on their proposals for developing this CDx.

Ashly Huber
Scientific Reviewer
CDRH/OPEQ/OHT7/DCTD

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/s/

QIANYIREN SONG
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: June 18, 2024

To: Qianyiren Song
Regulatory Project Manager
Division of Dermatology and Dentistry (DDD)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

David Foss, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): LEQSELVI (deuruxolitinib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 217900

Applicant: Sun Pharmaceutical Industries, Inc.

1 INTRODUCTION

On July 28, 2023, Sun Pharmaceutical Industries, Inc. submitted for the Agency's review an original New Drug Application (NDA) 217900 for LEQSELVI (deuruxolitinib) tablets. The proposed indication is for the treatment of adults with moderate to severe alopecia areata.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) August 10, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for LEQSELVI (deuruxolitinib) tablets.

2 MATERIAL REVIEWED

- Draft LEQSELVI (deuruxolitinib) tablets MG received on July 28, 2023, and received by DMPP and OPDP on June 7, 2024.
- Draft LEQSELVI (deuruxolitinib) tablets Prescribing Information (PI) received on July 28, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 7, 2024.
- Approved OLUMIANT (baricitinib) tablets comparator labeling dated June 13, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: June 18, 2024

To: Qianyiren Song, Regulatory Project Manager,
Division of Dermatology and Dentistry (DDD)

Kapil Verma, Clinical Reviewer, DDD

Matthew White, Associate Director for Labeling, DDD

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for LEQSELVI™ (deuruxolitinib) tablets, for oral use

NDA: 217900

Background:

In response to DDD's consult request dated August 10, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original NDA submission for LEQSELVI.

PI/Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on June 7, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on June 18, 2024.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on June 12, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2023270
NDA#/Referenced IND for NDA:	NDA 217900/IND 131423
Applicant:	SUN pharmaceuticals
Established Name/Trade Name:	deuruxolitinib tablets
Indication:	Treatment of adult patients with moderate to severe alopecia areata ☐ Rare Disease/Orphan Designation ☐ Pediatrics
PDUFA Goal Date:	7/28/2024
Review Division:	Division of Dermatology and Dentistry
Clinical Reviewer:	Kapil (Dev) Verma
Clinical Team Leader (TL)	Melinda McCord
Regulatory Project Manager:	Qianyiren Song
COA Reviewer:	Julia Ju, PharmD, PhD
COA Deputy Director:	Selena Daniels, PharmD, PhD
COA Division Director:	David Reasner, Ph.D.
Instruments reviewed:	1. Satisfaction of Hair PRO (SPRO) ☒ Patient-reported outcome (PRO)

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1. EXECUTIVE SUMMARY

In this submission, the Applicant is seeking approval of deuruxolitinib tablets for the treatment for adult patients with moderate to severe alopecia areata (AA). The Applicant proposes specific targeted clinical outcome assessment (COA)-related labeling claims from two randomized, double-blind, placebo-controlled phase 3 clinical trials (Studies CP543.3001 and CP543.3002). The primary objective of this review is to evaluate from a COA perspective if the submitted information supports the COA-related labeling claims related to satisfaction with hair on scalp¹.

The primary efficacy COA endpoint proposed for labeling is:

- Proportion of subjects who achieved at least 80% scalp hair coverage (Severity of Alopecia Tool (SALT)² score of ≤ 20) at Week 24

The key secondary efficacy COA endpoints proposed for labeling are:

- Percentage of responders (defined as “satisfied” or “very satisfied”) at Week 24 on the SPRO
- Percentage of subjects achieving an absolute SALT score of ≤ 20 at Weeks 20, 16, 12 and 8

The data from Studies CP543.3001 and CP543.3002 demonstrated that deuruxolitinib tablets had statistically significant improvement in the primary efficacy endpoint and selected key secondary efficacy endpoints compared with placebo.

From a COA perspective, the SPRO could potentially support a labeling claim, if supported by the clinical trial study design and statistical analysis. Ultimately, we defer to the Division whether the proposed satisfaction claim is acceptable for product labeling. If the Division were to consider a satisfaction claim, we recommend that the claim specify “satisfaction with hair on scalp”, and consider communicating the full distribution of responses including patients who may have been dissatisfied.

2 REVIEW CONCLUSIONS

The Applicant submitted an evidence dossier³ for the SPRO instrument. The SPRO was reviewed for content validity and other measurement properties, and score interpretability (i.e., meaningful score change).

Review Summary

- The SPRO assesses a relevant and important aspect of AA (i.e., scalp on hair).
- The Applicant, in general, established content validity and the other measurement properties of the SPRO. However, refer to Issue 1 in the Key Issues Identified section.
- There is insufficient evidence to support what represents a meaningful score change in the SPRO score.

¹ (b) (4) this COA review is focused on the review of the Satisfaction of Hair Patient-Reported Outcome (SPRO) per the Divisions’ request.

² The SALT has previously been accepted by the review division for other AA development programs. As such, this instrument was not reviewed.

³ The applicant submitted additional evidence dossiers for other COAs, which are not the focus of this COA review.

Key Issues Identified

1. The qualitative sample is limited in diversity and not sufficiently representative of AA in the US. As such, input from the target population may not be comprehensive and representative of AA. However, the qualitative sample is representative of the clinical trial population.
2. For assessment of test-retest reliability, the intra-class correlation coefficient (ICC) estimates do not fall within an acceptable and reasonable range for the analysis. While the ICC estimates fall below acceptable range for some of the analysis populations and time points, this could be a result of 1) the variability of hair growth and/or (2) the analysis population may not be clinically stable at the specified timeframe.
3. The Applicant's proposed labeling claim (i.e., "satisfied" or "very satisfied") implies a complex, multidimensional concept, which can include multiple components (e.g., efficacy, side effects, convenience, process experience, treatment expectations, willingness to continue etc.). However, the SPRO assesses the "satisfaction with hair on scalp" and not overall satisfaction with treatment.
4. It is unknown what constitutes a meaningful score change in the SPRO in the absence of evidence to support what constitutes a meaningful change on the anchor scales.

3 RECOMMENDATIONS FOR FUTURE STUDIES

For future clinical trials in this indication, we recommend the following:

- For conditions that occur in all race/ethnicities and educational levels, the qualitative sample should be representative of the condition, as well as, clinical trial population and include sufficient numbers of patients in important clinical and demographic subgroups, including subgroups defined by race and ethnicity, age, and education (e.g., literacy) to ensure that the information collected is robust and meaningful information on the aspects of the condition (e.g., symptoms, disease impacts) are important to the target population.
- Applicants should use their phase 2 trials to evaluate measurement properties of COAs and accumulate and document evidence to support a definition of clinically meaningful within-patient change in COA scores prior to initiating phase 3 studies.
- For assessment of test-retest reliability, the selection of time points for this evaluation should not be too distant to ensure reproducible results nor too close together to mitigate any potential carry-over effect (e.g., learning effect).
- For single items that may be directly interpretable in terms of the patient's experience the use of qualitative methods may be more valuable to inform what constitutes a meaningful score change in the measure. In this scenario, meaningful change exercises should be conducted in standalone cognitive interviews or exit interviews to support what constitutes a meaningful change in the measure.

4 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:

There have been several communications regarding the adequacy of the Applicant's COA measurement strategy during the IND stage (IND 131423), which included advice on the following:

- FDA Advice Letter dated September 16, 2020
 - Provided specific advice on the use of external anchor scales.
 - Requested clarification regarding administration of COAs during the COVID-19 pandemic.
- Type B (End of Phase 2) Meeting Minutes dated April 3, 2020
 - Provided considerations for use of COAs in a pediatric population.
 - Concluded that a single satisfaction item is a reasonable option to assess overall satisfaction of the scalp hair in the proposed context of use. However, communicated that the results of the SPRO overall satisfaction item will be expected to be consistent with the results of the Quality of Hair in Patient-Reported Outcome (QPRO) to strengthen the support of a satisfaction claim.
 - Requested evidence of content validity and other measurement properties of the SPRO, as well as a justification of a threshold for a meaningful score change.
 - Expressed concern regarding the interpretability of change from baseline analysis for the SPRO as a mere change in magnitude of satisfaction might not translate to a clinically meaningful benefit.
 - Recommended administering the SPRO and QPRO at intervals throughout the treatment period to see whether there are steady increases in SPRO and QPRO scores over time.
 - Communicated that the Clinical Global Impression of Improvement (CGI-I) and Patient Global Impression of Improvement (PGI-I) scales were viewed as exploratory measures that can be used as anchors to interpret the clinical meaningfulness of the COA endpoints. Noted limitations of the CGI-I and PGI-I as anchors (e.g., susceptibility to recall error).
- FDA Advice Letter dated January 13, 2020
 - Agreed that the item content for the Hair Coverage Satisfaction Scale (renamed to Satisfaction of Hair Patient Reported Outcome (SPRO)) is supported by the qualitative studies.
 - Disagreed that the item content of the Hair Quality Satisfaction Questionnaire (renamed to QPRO) is supported by the qualitative studies as it is missing some important concepts (e.g., satisfaction with amount of hair).
 - Disagreed with the proposed 5-point response scale as the scale was unbalanced ; recommended replacing the “somewhat satisfied” response option with a neutral response option (e.g., “neither satisfied or dissatisfied”) and rewording the “mostly satisfied” response option to “satisfied” to be consistent with the wording of the negative response options (“dissatisfied”).
 - Agreed that the concept of “satisfaction with their hair coverage” is an appropriate measure of the clinical benefit to the patient.
 - Provided specific comments on the Hair Coverage Satisfaction Scale and Hair Quality Satisfaction Questionnaire, including the recommendation to simplify the term hair coverage (e.g., remove the word “coverage”) or include a clear definition of “hair coverage” in the instructions.

- Type B (Pre-IND) Meeting Minutes dated October 19, 2016
 - Concluded that there was limited information to support the use of the Alopecia Areata Symptom Impact Scale (AASIS)
 - Identified several critical issues with content validity of the AASIS.

Previous COA Reviews:

- C2020300_IND 131423_Choudhry dated August 25, 2020 (DARRTS Reference ID: 4661642)
- C2020072_IND 131423_Choudhry dated April 3, 2020 (DARRTS Reference ID: 4585042)
- C2019132_IND 131423_Illoh dated July 17, 2019 (DARRTS Reference ID: 4466345)
- AT 2016-201_IND 131423_Patel dated January 29, 2017 (DARRTS Reference ID: 4009650)

Disease Background:

Alopecia areata (AA) is a non-scarring alopecia characterized by an autoimmune attack on the hair follicle. Hair follicles on the scalp as well as any other parts of the body can be affected. AA is clinically heterogeneous, affecting males and females equally. The most common form is patchy AA, which presents as discrete patches of scalp hair loss. Other forms of AA include alopecia totalis (complete loss of scalp hair), alopecia universalis (complete loss of all body hair), alopecia incognita or diffuse AA (diffuse shedding), ophiasis (symmetric band-like alopecia typically involving the scalp occipital region), and sisaipho (involves the top of the scalp, typically sparing the temporal and occipital areas).

Investigational Product:

Deuruxolitinib is a janus kinase (JAK) inhibitor indicated for the treatment of adults with moderate to severe alopecia areata. JAKs mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression.

Materials reviewed:

- Protocol CP543.3001 (SDN: 1, eCTD: 001, Date: July 28, 2023)
- Protocol CP543.3002 (SDN: 1, eCTD: 001, Date: July 28, 2023)
- Patient-Reported Outcome Evidence Dossier (SPRO/QPRO) (SDN: 1, eCTD: 001, Date: July 28, 2023)
- Development of a Patient-Reported Outcomes (PRO) Measure for Patients with Alopecia Areata (AA) Qualitative Study Report EVA-20786 | December 18, 2018 | Final (SDN: 1, eCTD: 001, Date: July 28, 2023)
- Qualitative Interviews to Develop a PRO for Patients with Alopecia Areata (AA) Round 3 Cognitive Interviews: Study Report EVA-20786-03 | January 21, 2021 | Version 1.0 (SDN: 1, eCTD: 001, Date: July 28, 2023)
- Applicant response to Information Request (IR) dated March 8, 2024. (SDN: 26, eCTD: 0026, Date: July 28, 2023)
- Applicant response to IR dated January 18, 2024 (SDN: 13, eCTD: 0013)

5 CLINICAL OUTCOME ASSESSMENT REVIEW

5.1 Clinical Trial Population

The target population for Studies CP543.3001 and CP543.3002 are adults (18- 65 years) with a definitive diagnosis of AA with a current episode of scalp hair loss lasting at least 6 months and not exceeding 10 years at the time of Screening. Eligible participants must have had at least 50% scalp hair loss, as defined by a SALT score ≥ 50 , at Screening and Baseline.

A complete list of the inclusion and exclusion criteria is summarized in Sections 7.1 and 8.1 of the clinical study protocol for Studies CP543-3001 and CP543-3002, respectively.

Reviewer's comment(s):

For Study CP543.3001, a total of 706 subjects were randomized: 351 subjects to CTP-543 8 mg BID, 215 subjects to CTP-543 12 mg BID, and 140 subjects to placebo. Over half of subjects in each treatment group were female (61.8%, 60.9%, and 63.6% for the CTP-543 8mg BID, CTP-543 12mg BID, and placebo, respectively). The predominant race for all treatment groups was White (68.7%, 67.4%, and 70.0%, respectively), and the predominant ethnicity for all treatment groups was non-Hispanic or Latino (83.2%, 87.4%, and 85.0%, respectively). The median age for the CTP-543 8mg BID, CTP-543 12mg BID, and placebo groups was 37.0, 36.0, and 38.5 years, respectively. The mean baseline SALT scores were 85.5, 85.2, and 88.1 for the CTP-543 8mg BID, CTP-543 12mg BID, and placebo, respectively. Over half of subjects in each group had current eyebrow involvement (69.8%, 70.2%, and 69.3%, respectively) and current eyelash involvement (70.1%, 73.5%, and 65.7%, respectively).

For Study CP543.3002, a total of 517 subjects were randomized: 258 subjects to CTP-543 8 mg BID, 129 subjects to CTP-543 12 mg BID, and 130 subjects to placebo. Over half of subjects in each treatment group were female (68.6%, 65.1%, and 67.7% for the CTP-543 8mg BID, CTP-543 12mg BID, and placebo, respectively). The predominant race for all treatment groups was White (78.7%, 84.5%, and 76.9%, respectively), and the predominant ethnicity for all treatment groups was non-Hispanic or Latino (79.5%, 86.0%, and 83.1%, respectively). The median age for the CTP-543 8mg BID, CTP-543 12mg BID, and placebo groups was 38.0, 38.0, and 41.0 years, respectively. The mean baseline SALT scores were 88.1, 86.7, and 88.9 for the CTP-543 8mg BID, CTP-543 12mg BID, and placebo, respectively. Over half of subjects in each group had current eyebrow involvement (73.6%, 76.0%, and 78.5%, respectively) and current eyelash involvement (69.0%, 66.7%, and 69.2%, respectively).

5.2 Clinical Trial Design

The Applicant conducted two identical multicenter, randomized, double-blinded, placebo-controlled phase 3 clinical trials (Studies CP543.3001 and CP543.3002) to evaluate the efficacy and safety of deuruxolitinib tablets in adult patients with moderate to severe AA.

Studies CP543.3001 and CP543.3002 consisted of a screening and treatment period. The screening period lasted up to 28 days prior to initiation of study drug. The treatment

period was a 24-week, double-blind, placebo-controlled period to define efficacy and safety for deuruxolitinib tablets. Participants were randomized in a 3:5:2 ratio (deuruxolitinib tablets 12mg twice daily [BID]: deuruxolitinib tablets 8mg BID:placebo). Randomization was stratified by scalp hair loss into 1 of the following two categories:

- Partial scalp hair loss (SALT ≥ 50 and < 95)
- Complete or near-complete scalp hair loss (SALT ≥ 95)

Following the 24-week treatment period, participants had the opportunity to continue receiving treatment in an open-label extension (OLE) study. If a participant did not wish to continue into the OLE study, they were to complete treatment at Week 24 and return in 4 weeks for the post-treatment safety follow-up to assess safety following treatment completion.

Refer to Sections 6 and 7 of the clinical study protocol for Studies CP543.3001 and CP543.3002, respectively, for more details on the clinical trial design.

Reviewer's comment(s):

- *Study CP543.3001: A total of 706 patients from the United States (US), Canada, and Europe were randomized.*
- *Study CP543.3002: A total of 517 subjects from the US, Canada, and Europe (Germany, France, Hungary, Spain, and Poland) were randomized.*

5.3 Endpoint Position, Definition, and Assessment Schedule

The placement of the COAs in the endpoint hierarchy, including the endpoint definition and assessment schedule for Studies CP543.3001 and CP543.3002 is summarized below.

Primary efficacy endpoint

- Proportion of patients subjects who achieved at least 80% scalp hair coverage (SALT score of ≤ 20) at Week 24.

Key secondary efficacy COA endpoint(s)

- Percentage of responders (defined as “satisfied” or “very satisfied”) at Week 24 on the SPRO
- Percentage of patients subjects achieving an absolute SALT score of ≤ 20 at Week 20, 16, 12 and 8.

Reviewer's comment(s): *The Applicant administered other COAs as secondary efficacy endpoints, which included the SALT, SPRO, Brigham Eyebrow Tool for Alopecia, Brigham Eyelash Tool for Alopecia, Hair Quality Patient-Reported Outcome (QPRO), Hospital Anxiety and Depression Scale. However, these secondary COA efficacy endpoints are not multiplicity adjusted and therefore viewed as exploratory endpoints.*

5.4 Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

The Applicant has proposed the following specific targeted SPRO-related labeling claims (in *blue italicized text*):

(b) (4)

Reviewer's comment(s):

(b) (4) *satisfaction of the scalp hair in the proposed context of use. Refer to Sections 5.5.4, 5.5.5, and 5.5.6 of this review regarding the evidence to support the fitness-for-purpose of this item.*

This reviewer notes that the results of the SPRO is consistent with the results of the QPRO, which strengthens the support of a satisfaction claim. For Studies CP543.3001 CP543.3002, each item in the QPRO (satisfaction with thickness of hair coverage, satisfaction with evenness of hair coverage, satisfaction with eyebrows, and satisfaction with eyelashes and each time point, treatment group differences favored deuruxolitinib tablets over placebo. Refer to Table 19 in the Clinical Study Report for Studies CP543.3001 CP543.3002.

The SPRO could potentially support a labeling claim, if supported by the clinical trial study design and statistical analysis. This reviewer defers to the Division whether the proposed satisfaction claim is acceptable for product labeling. If the Division were to consider a satisfaction claim, we recommend that the claim specify “satisfaction with hair on scalp”, and consider communicating the full distribution of responses including patients who may have been dissatisfied.

5.5 Clinical Outcome Assessment(s)

5.5.1 Clinical Outcome Assessment Description(s)

5.5.1.1 Satisfaction of Hair Patient Reported Outcome (SPRO)

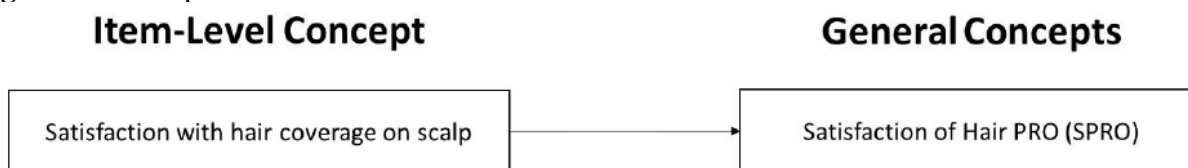
The SPRO is a single item patient-reported outcome (PRO) instrument designed to assess satisfaction with hair on the scalp using a 5-point verbal rating scale (VRS) ranging from 1 (“Very satisfied”) to 5 (“Very dissatisfied”). The recall period is momentary (“today”). The SPRO was administered electronically at on-site study visits on Day 1 (Baseline), and Weeks 12, 16, 20 and 24.

Reviewer’s comment(s): *For the Studies CP543.3001 and CP543.3002, administration and data collection of the SPRO assessments took place on a tablet-based assessment platform (Pathway) via an iPad. The training of the study staff required that the assessment was to be conducted in a quiet room free of distractions and that the administrator was to provide the patient with a handheld mirror (7.4 " x 10.4 " in size) and to instruct the patient to use the mirror in making their assessment. Note that this reviewer does not know whether the instructions were given consistently to participants across sites.*

5.5.2 Conceptual Framework(s)

The conceptual framework for the SPRO is shown in Figure 1 below.

Figure 1. Conceptual framework of SPRO



5.5.3 Scoring Algorithm

The SPRO generates a single item score that ranges from 1 to 5, with lower scores indicating greater satisfaction.

Reviewer’s comment(s): *Note for Studies CP543.3001 and CP543.3002, the SPRO-based endpoint was a responder endpoint. Refer to Section 5.5.6 of this review regarding how the Applicant defined responders.*

5.5.4 Content Validity

The Applicant completed the following instrument development activities to evaluate the content validity of the SPRO:

- Patient input (concept elicitation and cognitive interviews in adults with AA)

A summary of the results for each activity and instrument is described below. Refer to the Applicant's PRO evidence dossier (SDN: 1, received date: July 28, 2023) for full details regarding the methodology and results of each activity.

5.5.4.1 Patient input

Concept elicitation interviews

- Twenty-seven adults with a confirmed diagnosis of AA were interviewed in-person.
- The majority of the participants were White (n= 21/27, 78%) female (n= 16/27; 59%) with a mean age of 39.5 years.
- The mean time since diagnosis was 13.5 years. Most of the participants (n=21; 78%) reported an initial diagnosis of AA patchy. For current diagnosis, participants reported⁴ AA patchy (n=12; 44%), Totalis (n=8; 30%), and Universalis (n=6; 22%).
- Many participants (n=19/27; 70%) reported current hair loss of eyebrows while some (n=10/27; 37%) reported past hair loss of eyebrows. Similarly, many participants (n=17/27; 63%) reported current hair loss of eyelashes, while some reported (n=7/27; 26%) past hair loss of eyelashes (Note: answers not mutually exclusive).
- Approximately half of the participants (n=15/27, 56%) reported that they experienced hair loss all over their body. The remaining participants (n=12, 44%) indicated that their hair loss was limited to certain parts of the body, with all mentioning involvement with the head (n=12/12, 100%); other affected body parts included arms (n=5/12, 42%), eyebrows (n=3/12, 25%), and legs (n=3/12, 25%).
- Many participants (n=17/27, 63%) indicated that they first started to notice hair loss at least 11 years prior (11–15 years: n=4/27, 15%; 16–20 years: n=3/27, 11%; more than 20 years: n=10/27, 37%, including 9 women), while for others it was fairly recent (less than a year: n=3/27, 11%; 1-5 years: n=6/27, 22%; 6-10 years: n=1/27, 4%).
- Regarding past experience with hair loss, participants described the amount of hair they would lose and for many of them it was large amounts such as big handfuls/chunks/clumps of hair (n=12, 44%), large/noticeable quantities (n=5, 19%), or 50-100 “strands” per day (n=2, 7%). Several participants (n=3, 11%) noticed losing small amounts of hair or strands; one participant (4%) had short hair and did not notice.
- Regarding current experience with hair loss (past year), the majority of participants (n=16/22, 73%) indicated that they experienced hair loss on the head, while five (n=5/22, 23%) experienced loss of the eyebrows, three (n=3/22, 14%) experienced loss of the eyelashes, and two (n=2/22, 9%) experienced loss of the beard.
- All participants (n=27/27, 100%) reported that they were currently using treatments for AA or had used treatments in the past (note: responses not mutually exclusive). The treatments

⁴ Note: participant-provided responses are not consistent with the site-completed clinical characteristics for n=9 participants).

most commonly used by participants were injections (n=23/27, 85%), topical lotions, creams, liquids, or foams (n=17/27, 63%), and Rogaine® (n=14/27, 52%).

- Many participants (n=16/23, 69%) reported moderate or severe levels of pain associated with injections. Eight participants each (n=8/27, 30%) reported that they did not experience any hair growth while using topical treatments or Rogaine® or that injections worked at first and then lost effectiveness. Some participants (n=5/23, 22%) mentioned that the topical treatments like creams or foams were not bothersome and were easy to apply.
- Nearly all participants (n=26/27, 96%) reported that the coverage of hair is the most important concept related to their AA.
- The most important aspect of hair coverage had to do with the location of coverage. While seven participants (26%) specifically identified the location of hair regrowth as important, most of the remaining participants also used descriptions of hair loss and re-growth that referenced location. In general, location had to do with being able to use their remaining hair to cover their “spots” and “patches”, or to ensure that the regrowth was symmetrical (even) on their scalp (i.e., hair regrowth wasn’t just on one side of head).
- All participants (n=27/27, 100%) reported that AA currently impacts (n=23/27; 85%) or previously (n=4/27; 15%) impacted their daily life. The most common impact was emotional, which was mentioned by 19 (n=19/27, 70%) participants. Emotional impacts included concern about other people mistaking them for cancer patients (n=9/19, 47%), concerns about self-image (n=5/19, 26%), embarrassment (n=3/19, 16%), loss of confidence (n=3/19, 16%), poor self-esteem (n=2/19, 11%), depression (n=2/19, 11%), or feeling reserved around new people (n=1/19, 5%) (responses are not mutually exclusive). Other important impacts included the impact on work (n=9/27, 33%), difficulty with social interactions (n=7/27, 26%), and difficulty leaving the house (n=5/27, 19%).
- Participants were asked how often they notice change in their hair loss. About one-third of subjects (n=9/27, 33%) notice day-to-day change and many others (n=8/27, 30%) indicated that their hair loss changes on a monthly basis; one of these subjects noted her hair loss changes monthly, biweekly, or weekly. Participants were also asked about how often they notice change in their hair regrowth. These responses were not mutually exclusive and differed slightly from the previous hair loss question, with responses being more varied. The most common responses were monthly change (n=6/27, 22%) weekly change (n=6/27, 22%), or day-to-day change (n=4/27, 15%).

Cognitive interviews

- Twenty-one participants⁵ with a diagnosis of AA were interviewed in one of the two rounds of cognitive interviews. Interviews in Round 1 were conducted in-person, while those conducted in Round 2 were conducted by telephone. A copy of the SPRO version 1.0 cognitively tested is shown in Figure 2 . Note that another round of interviews (Round 3) were conducted to address comments from the Agency (FDA Advice Letter dated January 13, 2020, see Section 4 of this review).

Figure 2. SPRO version 1.0

⁵ Up to 50% of the patients who had participated in the concept elicitation interviews could also participate in the cognitive interviews.

1. How satisfied are you with the hair coverage on your scalp today?

- 0 ☐ Very dissatisfied
 1 ☐ Dissatisfied
 2 ☐ Somewhat satisfied
 3 ☐ Mostly satisfied
 4 ☐ Very satisfied

- For Round 1,
 - A total of 21 cognitive interviews were completed in-person at two sites located in Portland, OR and New Haven, CT. Most participants were White (n= 16/21; 76%), female (n=17/21; 81%) with a mean age of 39.7 years (range: 18-63 years).
 - The mean time since diagnosis was 12.9 years (range: 7 months to 33 years). For current diagnosis, participants reported AA patchy (n=8/21; 38%), Totalis (n=5/21; 24%), and Universalis (n=8/21; 38%).
 - Slightly more than half of the participants were currently participating in a clinical trial for AA (n=12/21, 57%) and slightly more than half had previously participated in the concept elicitation interviews (n=11/21, 52%). Several participants (n=9/21, 43%) mentioned having patchy or areata AA, while four (19%) patients reported having totalis and six (29%) reported having universalis. A majority of participants (n=12/21, 57%) mentioned experiencing hair loss all over their bodies.
 - All participants who were asked (n=20/20, 100%) reported that the item was clear and easy to understand and all (n=20/20, 100%) were able to accurately explain the meaning of “hair coverage.”
 - Most participants (n=17/19, 89%) indicated that there is no other way to describe the amount of hair on their head, while two participants (n=2/19, 11%) suggested “thickness of coverage” or “density”.
 - Many participants (n=13/21, 62%) noted that they were “very dissatisfied” because their hair does not provide adequate coverage or because they are completely bald. Some participants (n=4/21, 19%) indicated that they were “dissatisfied” because they have patchy coverage while others (n=3/21, 14%) were “somewhat satisfied” because their hair provides some coverage, despite the presence of bald spots.
 - The majority of participants (n=18/21, 86%) reported that the response options were easy to understand, self-explanatory, and/or appropriate. The three remaining participants suggested the following: add an additional response option for “completely bald”; consolidate the responses to three options; and all response options should be negative or reflect dissatisfaction.
 - All participants (n=21/21, 100%) noted that it was easy to select a response using the response scale. The majority of participants (n=20/21, 95%) found the response options clear and easy to understand, while one participant (5%) noted that the responses would be easier to interpret if there was a description for each.
 - When asked to describe the response option “very dissatisfied” in their own words, all participants who were asked (n=19/19, 100%)

demonstrated an understanding of the term. Participants reported similar interpretations including no sign of hair, totally bald, no hair coverage or no regrowth (n=15/19, 79%); between 0-20% coverage (n=2/19, 11%); very unhappy with the way things are going (n=2/19, 11%), very active shedding with tiny amounts of regrowth (n=1/19, 5%); and a tiny bit of patchy regrowth (n=1/19, 5%).

- When asked to describe the response option “dissatisfied” in their own words, almost all of the participants who were asked (n=18/19, 95%) demonstrated an understanding of the term; one participant expressed that “very dissatisfied” and “dissatisfied” were the same. Many participants (n= 16/19, 84%) noted that “dissatisfied” means they barely have any hair, they are not completely bald but they need to wear a hat or wig, the hair loss is very noticeable or patchy, they are unhappy with their coverage, or somewhere between 20% and 50% hair coverage.
- When asked to describe the item “Somewhat satisfied” in their own words, all of the participants who were asked (n=20/20, 100%) demonstrated understanding of the option. Participants provided a variety of answers to describe “Somewhat satisfied” including having visible bald spots that can be covered with hair, bald patches that are not noticed by others, a lot of work to cover it but a wig is not necessary (n=9/20, 45%); between 40% and 70% hair coverage (n=6/20, 30%); a good growth pattern or starting to have growth (n=2/20, 10%), above “dissatisfied” but a little bit less than “mostly satisfied” (n=2/20, 10%), and “okay with it” (n=1/20, 5%).
- When asked to describe the response option “mostly satisfied” in their own words, most participants (n=20/21, 95%) demonstrated an understanding of the concept. Most participants (n=20/21, 95%) provided similar responses to describe the concept “mostly satisfied” including good coverage with some bald spots, most of the hair is present, easy to cover patches, able to go out without a wig, able to comb the hair, not 100% satisfied but pretty satisfied with amount of hair, other people cannot tell you have alopecia, hair growing back long and thick, and 70-85% coverage.
- When asked to describe the response option “very satisfied” in their own words, all participants (n=21/21, 100%) demonstrated an understanding of the concept. All participants (n=21/21, 100%) provided similar responses including full regrowth or complete coverage, 90-100% coverage, ability to style the hair, only one or two bald spots, and very satisfied with the amount of hair.
- All participants who were asked (n=18/18, 100%) indicated that this question was a good way to ask about hair coverage on the scalp. Several participants offered suggestions for modifying this item, including adding percentages for each response option (n=6/21, 29%), adding a definition for “coverage” (n=1/21, 5%), and adding definitions next to each response option (n=1/21, 5%). Three participants were not asked the question, but all provided positive feedback about the item.

- For Round 2,
 - A total of 7 cognitive interviews were completed via telephone (participants were recruited from two sites located in Portland, OR and New Haven, CT). Most participants were White (n= 5/7; 71.4%), male (n=4/7; 57.1%) with a mean age of 36.4 years (range: 19-52 years).
 - The mean time since diagnosis was 12.9 years (range: 7 months to 33 years). For current diagnosis, participants reported AA patchy (n=8/21; 38%), Totalis (n=5/21; 24%), and Universalis (n=8/21; 38%).
 - Several participants (n=3/7, 43%) reported having universalis alopecia. One participant (n=1/7, 14%) mentioned not knowing the name of their alopecia and three participants (n=3/7, 43%) commented they had areata alopecia. Six participants (n=6/7, 86%) reported having hair loss all over their body, describing their hair coverage as “patchy” and a percent of the total hair on their body.
 - All participants (n=7/7, 100%) demonstrated an understanding of the item concept and explained that the item was asking about satisfaction with hair growth or overall coverage. All participants (n=7/7, 100%) reported that the item was clear and easy to understand and most (n=6/7, 86%) were able to accurately explain the meaning of “hair coverage.”
 - Most participants (n=6/7, 86%) indicated that there is no other way to describe the amount of hair on their head, while one participant (n=1/7, 14%) suggested asking “how satisfied are you with the regrowth on your scalp.”
 - All participants (n=7/7, 100%) indicated that this question was a good way to ask about hair coverage on the scalp. Several participants offered suggestions for modifying this item, including adding percentages for each response option (n=1/7, 14%) and asking about other body locations (n=1/7, 14%).
 - The majority of participants (n=6/7, 86%) reported that the response options were easy to understand, self-explanatory, and/or appropriate. The remaining participant (n=1/7, 14%) suggested removing “somewhat satisfied.” All participants (n=7/7, 100%) noted that it was easy to select a response using the response scale and found the response options clear and easy to understand.
 - When asked to describe the response option “very dissatisfied” in their own words, all participants (n=7/7, 100%) demonstrated an understanding of the term. Most participants reported similar interpretations including large bald patches, almost bald, unsuccessful treatment, or no hair coverage (n=6/7, 86%).
 - When asked to describe the response option “dissatisfied” in their own words, all of the participants (n=7/7, 100%) demonstrated an understanding of the term. Some participants described this concept as having some hair/growth but not a significant amount (n=3/7, 43%), the presence of some bald patches (n=1/7, 14%), or hair being mostly gone (n=1, 14%).
 - When asked to describe the item “Somewhat satisfied” in their own words, all of the participants (n=7/7, 100%) demonstrated an understanding of the option. Participants provided a variety of answers to describe “Somewhat satisfied” including bigger patches of thinning hair or a bald spot similar to male pattern baldness (n=2/7, 29%), 50-65% coverage (n=2/7, 29%), some

- regrowth (n=1/7, 14%), enough coverage to pass for a full head of hair (n=1/7, 14%) and the presence of eyebrows or a moustache (n=1/7, 14%).
- When asked to describe the response option “mostly satisfied” in their own words, most participants (n=6/7, 86%) demonstrated an understanding of the concept. The participants provided similar responses to describe the concept “mostly satisfied” including full head of hair with some patches or normal hair with some thinning (n=3/7, 43%), 80-90% coverage (n=2/7, 29%), and “looking like your old self” (n=1/7, 14%).
 - When asked to describe the response option “very satisfied” in their own words, all participants (n=7/7, 100%) demonstrated an understanding of the concept. Participants provided similar responses including 90-100% regrowth or full coverage (n=4/7, 57%), what you looked like before alopecia (n=2/7, 29%), and being happy with your hair coverage (n=1/7, 14%).
- For Round 3,
 - The copy of the SPRO cognitively tested is shown in Figure 3.

Figure 3. Final version of SPRO

How satisfied are you with the hair on your scalp today?

- 5 ☐ Very dissatisfied
 4 ☐ Dissatisfied
 3 ☐ Neither satisfied nor dissatisfied
 2 ☐ Satisfied
 1 ☐ Very satisfied

- A total of 10 cognitive interviews were completed via telephone (participants were recruited from two sites located in Palm Springs, CA and Portland, OR. Most participants self-identified as White (n=9/10, 90%), non-Hispanic or Latino (n=9/10, 90%), female (n=7/10, 70%) with a mean age of 37 years. The majority of participants reported some college, college, or post-graduate degree as their highest level of education (n=9/10, 90%).
- The mean time since AA diagnosis reported by participants was 13.1 years (SD=10.9). Most participants (n=8, 80%) reported an initial diagnosis of AA patchy. The other two participants⁶ (n=2/10, 20%) reported an initial diagnosis of Alopecia universalis.
- The majority of participants reported current eyebrow hair loss (n=9/10, 90%) and eyelash hair loss (n=8/10, 80%). Mean (SD) SALT score was 94.8 (6.9), ranging from 82.0-100.0.
- When probed, nine participants (90%) reported that the SPRO question was clear and easy to understand, and one participant (10%) responded that the question was both easy and difficult to understand.

⁶ Participant-provided responses are not consistent with the site-completed clinical characteristics for two participants. Participant (b) (6) and (b) (6) both reported they were initially diagnosed with alopecia universalis, but the sites reported that these participants were initially diagnosed with AA patchy.

- Nine interpretations (90%) included aspects of hair amount or quality, along with an emotional response to the hair. One participant (10%) felt that the question did not pertain to them, as they did not have hair.
- All 10 participants (100%) expressed that the response options to the SPRO item were clear and easy to understand.
 - When asked to describe the response option “very satisfied,” four participants (40%) interpreted the “very satisfied” response option to mean that their hair was “back to normal,” as if they “didn’t have alopecia.” Four other participants (40%) expressed that they would be very satisfied if they had a “full head of hair” and “full coverage of hair.”
 - When asked to describe the response option “satisfied,” four participants (40%) interpreted the “satisfied” response option to mean that most of their hair was back, with few patches and good quality. Three participants (30%) said they would be satisfied if they could style or “work with” the hair growing on their head. Three other participants (30%) thought that “satisfied” meant they were (almost) happy or comfortable with the hair.
 - When asked to describe the response option “neither satisfied nor dissatisfied,” three participants (30%) felt that the “neither satisfied nor dissatisfied” response option meant “indifference,” or that their hair did not “bother” them. Three others (30%) thought that this response option would be used if their hair had some minor issues (i.e., bald patches, thinning, or hair cannot withstand ironing or dying). Two participants (20%) felt that this response option indicated new hair growth.
 - When asked to describe the response option “dissatisfied,” four participants (40%) explained that the “dissatisfied” response option meant that they were discouraged with their hair, that they had minimal hair growth or poor-quality hair, and that they were “not seeing the changes [they wanted] to see” with their hair. Two participants (20%) felt that this response option would indicate they were not happy with their hair, but that they had made peace with the situation. Two participants (20%) explained that being dissatisfied would mean they were uncomfortable in certain social settings because of their hair, and that they could not go out into public without some hair preparation (such as styling it to cover bald patches).
 - When asked to describe the response option “very dissatisfied,” half of the participants (50%) thought “very dissatisfied” meant that they were angry, unhappy, and discontent with their current state of alopecia. One of these five (20%) specified that their unhappiness would be caused by a total lack of hair on their head, and another (20%) explained they would select this response option if they were unhappy with what they saw in the mirror. Another participant (20%) thought that this response option would indicate that their current situation is “unacceptable,” and that corrective action would need to be taken. Three participants (30%) described the meaning of “very dissatisfied” in terms of how they are perceived by others: one participant explained they would select “very dissatisfied” if they were not comfortable enough with their appearance to be in public; another

- participant would select this response if they felt they had to hide their hair; and one participant explained that being bald and female was “not good” and made them very dissatisfied.
- The majority of participants (n=7/10, 70%) thought that no changes were needed to the SPRO item.
 - Of the three participants (30%) that suggested changes, two (67%) suggested changing the word “satisfied” to something else (either to “comfortable” or to something less “passive”), one participant (33%) suggested including “hair/lack of hair” in the question to better represent participants with no head hair, and the same two that suggested changing the word “satisfied” to something else also suggested changing the response options to a numeric rating scale.

Reviewer’s comment(s):

This reviewer notes that the sample for the qualitative interviews is limited in diversity (predominantly White) and not sufficiently representative of AA in the US. According to a 2023 article in JAMA Dermatology⁷, AA is more common in people of nonwhite ethnicity. The educational level was only reported in the sample of Round 3, in which the participants was mostly at the college/university educational level. We generally recommend that for conditions that occur in all race/ethnicities and educational levels, that the qualitative sample be representative of the clinical trial population and include sufficient numbers of patients in important clinical and demographic subgroups, including subgroups defined by race and ethnicity, age, and education (e.g., literacy) to ensure that the information collected is robust and meaningful information on the aspects of the condition (e.g., symptoms, disease impacts) are important to the target population. This reviewer notes that the qualitative sample is representative of the clinical trial population, as the trial population is also predominantly White.

This reviewer concludes that the SPRO is measuring an important aspect of AA (i.e., hair on scalp). Based on the qualitative data, the SPRO appears to be well-understood in the individuals that comprised the study sample (refer to comments above about representativeness, specifically educational level).. The response options also appear to be distinct and non-overlapping. Note that participants were not directly queried as to whether the recall period of “today” was appropriate. Rather, they were asked how often they notice change in their hair loss. This reviewer does not have any concern regarding the use of a momentary recall.

This reviewer notes that the pivotal studies were multinational trials. The Applicant did not provide information as to whether the COAs were translated and culturally adapted. We generally recommend that COAs are fit-for-purpose for all intended study populations for use in multinational trials.

5.5.5 Other Measurement Properties

The Applicant evaluated the psychometric properties of the SPRO using data from the following sources:

⁷ Sy N, Mastacouris N, Strunk A, Garg A. Overall and Racial and Ethnic Subgroup Prevalences of Alopecia Areata, Alopecia Totalis, and Alopecia Universalis. JAMA Dermatol. 2023;159(4):419–423.

- Study CP543.2003, a Phase 2, randomized, double-blind, multi-dose, placebo-controlled study evaluating the efficacy, safety, and tolerability of CTP-543 in treating moderate to severe alopecia in adults.
- Studies CP543.3001 and CP543.3002 (refer to Section 5.2 of this review for a description of the trial design).

The findings from the psychometric analyses conducted in Study CP543.3002 were uninterpretable as the final version of the SPRO⁸ was not used in that study. As such this Section will focus on the psychometric findings from Study CP543.3001.

The analysis population used to evaluate the measurement properties of the scores for the SPRO were approximately two-thirds female (n=420/675; 62.2%), with a mean age of 38.5 years (SD 13.4).

Reviewer's comment(s): *The quantitative summary report did not present data on race/ethnicity of the quantitative sample.*

The quantitative summary report notes the following: “ There was a statistically significant difference by gender for the following scores: SPRO (F:M = 4.6 vs 4.4; $p = 0.0001$), QPRO Item 1 (F:M = 4.6 vs 4.5; $p = 0.0145$) and QPRO Item 2 (F:M = 4.7 vs 4.5; $p = 0.0008$), suggesting greater dissatisfaction with hair for females at baseline, and for QPRO item 4 (F:M = 3.7 vs 4.0; $p = 0.0051$), suggesting greater dissatisfaction with eyelashes for males at baseline. There was also a statistically significant difference by gender for SALT (F:M = 85.0 vs 88.2; $p = 0.0203$), suggesting more hair loss for males at baseline. However, score differences were small and likely not clinically meaningful. Statistically significant differences by gender for the COA change scores from Baseline to Week 24 were only found for SALT (F:M = -32.4 vs -24.9; $p = 0.0060$) and SPRO (F:M = -1.5 vs -1.2; $p = 0.0060$), with females demonstrating greater change in hair loss and satisfaction with hair from baseline to Week 24 compared to males.”

A summary of the psychometric findings from Study CP543.3001 is provided below. For more details on the methodology and results of these analyses, refer to the Sections 3 and 4 of the quantitative summary report (“Validation of Patient-reported Outcomes (PRO) Measures for Alopecia Areata Validation Report EVA-35999 | June 2, 2023 | Version 1.0”) (SDN: 1, received date: July 28, 2023).

5.5.5.1 Item-level Descriptive Statistics

The Applicant provided a description of the SPRO score. Item score distributions were also evaluated in terms of participants' use of the entire response scale and for floor and ceiling effects. Based on the item-level descriptive statistics:

- The mean SPRO item score was 4.5 (SD 0.9), ranging from 1.0-5.0.
- The majority of participants (n= 479/675, 71.0%) endorsed the most severe response category for the SPRO item (i.e., category response corresponding to a “5” [“Very dissatisfied”]) at baseline (Day 1). There were minimal participants (n= 11/675, 1.6%) who

⁸ Note that the response options in SPRO were modified from the phase 2 trial to the phase 3 trials.

endorsed the least severe response category (i.e., category response corresponding to a “1” [“Very satisfied”]) at baseline (Day 1).

- The mean scores for the SPRO item decreased (i.e., improved) throughout the study with similar decreases demonstrated between baseline and each follow-up week. For the SPRO item, there was a mean decrease of 1.3 (SD 1.4) and median decrease of 1.0 to Week 12, 16, and 20. At week 24, the SPRO had a mean decrease of 1.4 (SD 1.6) and median decrease of 1.0.

5.5.5.2 Reliability

5.5.5.2.1 Internal Consistency Reliability

Internal consistency reliability was not evaluated as the SPRO is a single item.

5.5.5.2.2 Test-Retest Reliability

Test-retest reliability analyses⁹ were conducted to assess whether the scores are reasonably consistent over time within clinically stable¹⁰ patients. Based on the test-retest reliability analyses,

- The intra-class correlation coefficient (ICC) estimate for the analysis population defined by the Patient Global Impression of Severity (PGI-S) scores (n= 299) at Baseline and Week 12 was 0.2650.
- The ICC estimate for the analysis population defined by the Patient Global Impression of Improvement (PGI-I) scores (n= 233) at Baseline and Week 12 was 0.1576.
- The ICC estimate for the analysis population defined by the PGI-S scores (n= 361) at Week 12 and Week 16 was 0.7983.
- The ICC estimate for the analysis population defined by the PGI-I scores (n= 193) at Week 12 and Week 16 was 0.5743.

Reviewer’s comment(s):

In the original NDA submission, the Applicant included the test-retest reliability data from their Phase 2 Study CP543.2003 where the test-retest reliability was examined between the Screening (Day -28 to Day -1) and baseline (Day 1) assessments with the ICC value of 0.65 (below the 0.70 which is considered as a threshold of acceptable test-retest reliability). Note that the sample meeting the criteria for test-retest evaluation was very small (n < 10) due to several of the COA measures not being administered at screening for all patients in their Phase 2 Study CP543.2003. Therefore, the Agency requested the Applicant to provide test-retest reliability assessment results using their Phase 3 trial data.

In response to the Agency’s IR, the Applicant performed test-retest reliability analyses using data from Study CP543.3001. The Agency had requested using data from both phase 3 studies, but the Applicant responds that the final validation of the SPRO was based on Study CP543.3001 as it

⁹ The Applicant did not evaluate test-retest reliability in their validation study, as such no results were reported in the quantitative summary report (“Validation of Patient-reported Outcomes (PRO) Measures for Alopecia Areata Validation Report EVA-35999 | June 2, 2023 | Version 1.0”). These analyses were conducted to address the Agency’s information request dated March 8, 2024.

¹⁰ Stability was defined using different approaches: (1) Participants who have the same PGI-S evaluation at both time points and (2) Participants who reported 'No Change' on the PGI-I at the second time point.

was completed several months before Study CP543.3002 was completed and was the larger of the two studies (n=706 for Study CP543.3001 vs. n=517 for Study CP543.3002).

This reviewer notes that in general the ICCs do not fall within an acceptable and reasonable range for the analysis. The Applicant's rationale for this is as follows: "It is of note that in Study CP543.3001, the SPRO assessments were conducted on Day 1 (Baseline), and at Weeks 12, 16, 20 and 24, to reflect the anticipated time to onset of hair re-growth. This resulted in the main assessment of test-retest being between Baseline and Week 12 (Visit 6). As this is a long period of time for an evaluation of test-retest due to the potential for a meaningful amount of hair regrowth, there were significant differences between scores and low ICCs (see Tables 5a and 5b). Given the confounding influence of onset of treatment-related hair regrowth over the first 12 weeks of treatment, additional test-retest analyses were conducted at a more stable period between Weeks 12 and 16 (i.e. a 4-week period between assessments), which might be considered more appropriate for this analysis..."

While the ICC estimates fall below acceptable range for some of the analysis populations and time points, this could be a result of 1) the variability of hair growth and/or (2) the analysis population may not be clinically stable at the specified timeframe. This reviewer agrees with the Applicant that the separation between Baseline and Week 12 may be too far apart which may also have had an impact on the results of the test-retest reliability analyses. This reviewer notes that the ICC estimates fall within acceptable and reasonable range for the analysis population defined by the PGI-S responses at Weeks 12 and 16; however for the same time frame the ICC estimates are not within range when the analysis population is defined by the PGI-I. The general recommendation for selection of time points for test-retest reliability is that they should not be too distant to ensure reproducible results nor too close together to mitigate any potential carry-over effect (e.g., learning effect).

5.5.5.3 Construct Validity

5.5.5.3.1 Convergent and Divergent Validity

Convergent validity and divergent validity were evaluated via correlation analyses to examine the associations between concepts measured by the SPRO score and concepts measured by other instruments and whether these concepts correlate with one another as expected. The reference instruments used included SALT, QPRO, Brigham Eyebrow Tool for Alopecia (BETA), Brigham Eyelash Tool for Alopecia (BELA), PGI-S, PGI-I, Clinical Global Impression- Severity (CGI-S) and Clinician Global Impression- Improvement (CGI-I) were examined.

Based on the correlation analyses,

- At baseline (Day 1) the SPRO was highly correlated with QPRO Item 1 and Item 2 (r= 0.68 and 0.70, respectively) in line with expectations, and both associations were statistically significant (p <0.0001). All other correlations at this time point were very small (close to 0) and were not statistically significant.
- Correlations between the SPRO and the other reference measures were larger overall than at Day 1. The highest correlations were with QPRO Item 1, hair thickness, (r = 0.82), and QPRO item 2, hair evenness (r = 0.79), but the SPRO was also highly correlated with the

PGI-I ($r = 0.69$), CGI-I ($r = 0.58$), PGI-S ($r = 0.57$) and QPRO item 3, eyebrows ($r = 0.53$). In line with expectations, the SPRO was also moderately correlated with the remaining measures, including SALT ($r = 0.46$), CGI-S ($r = 0.48$) and QPRO item 4, eyelashes ($r = 0.42$). All correlations were statistically significant ($p < 0.0001$).

- The SPRO was highly correlated with all COAs at Week 16, with the exception of QPRO item 4, eyelashes, with which it showed a moderate correlation ($r = 0.48$). The large correlations ranged from $r = 0.59$ (QPRO Item 3, eyebrows) to $r = 0.86$ (QPRO Item 1, hair thickness). All correlations were statistically significant at the $p < 0.0001$ level.
- The SPRO was highly correlated with all COAs at Week 20. Correlations ranged from $r = 0.51$ (QPRO Item 4, eyelashes) to $r = 0.92$ (QPRO Item 1, hair thickness). All correlations were statistically significant at the $p < 0.0001$ level.
- The SPRO was also highly correlated with all COAs with which relationships were hypothesized at Week 24. Correlations ranged from $r = 0.53$ (QPRO Item 4, eyelashes) to $r = 0.92$ (QPRO Item 1, hair thickness). All correlations were statistically significant at the $p < 0.0001$ level.
- SPRO demonstrated construct validity as it was highly correlated with the following COAs at Week 24: $r = 0.75$ with CGI-S, $r = 0.77$ with CGI-I, $r = 0.81$ with PGI-S, $r = 0.83$ with PGI-I. All correlations were statistically significant at the $p < 0.0001$ level.

Reviewer's comment(s):

The Applicant also reported results by scatterplots. The Applicant indicates that the observed correlations were expected. At baseline, the Applicant indicated that the small correlations with the SPRO and SALT, BETA, BELA, PGI-S, PGI-I, CGI-S and CGI-I are most likely due to the skewed distribution of SPRO scores at Day 1 (i.e., skewed to "dissatisfaction").

This reviewer notes that the SALT, QPRO, and patient and clinician global rating scales appear to measure similar concepts (convergent validity) of the SPRO score as they are related to aspects of hair on scalp. The concepts measured in the BETA and BELA scores are somewhat dissimilar (divergent validity) to the SPRO as it measures eyelash and eyebrow hair rather than scalp hair.

In general, the SPRO appears to have a relationship to other assessments with similar and dissimilar concepts as expected.

5.5.5.3.2 Known-groups Validity

Known-groups validity was evaluated via empirical comparisons between SPRO and other PRO and clinical measures of disease status:

- PGI-S score categories: normal, no hair loss, borderline hair loss, mild hair loss, moderate hair loss, severe hair loss, among the most extreme hair loss
- Absolute SALT categories: $\leq 20\%$ complete or near complete scalp hair (none/minimal scalp hair loss); > 20 and < 50 (mild scalp hair loss); ≥ 50 and < 90 partial scalp hair loss (moderate); ≥ 95 complete or near complete hair loss (severe)
- CGI-S score categories: normal, no hair loss; borderline hair loss; mild hair loss; moderate hair loss; severe hair loss; among the most extreme hair loss

Based on the known-groups validity analyses, the SPRO mean values increased in all cases in concert with the pre-defined severity grouping at most timepoints.

Reviewer's comment(s):

The Applicant also reported the results by boxplots. The Applicant indicates that the observed comparisons were expected.

This reviewer notes that the SPRO score observed across the patient- and clinician-reported assessments showed better scores (higher satisfaction) on average for patient subgroups as severity of AA decreased. This reviewer notes that it is unclear how the numerical cutoffs were determined from the SALT and whether these cutoffs represent clinically distinct groups.

In general, the SPRO appears to be able to trend in the right direction for the clinically distinct groups. Because the SPRO measures satisfaction, patients may consider various factors when reporting their satisfaction of hair on scalp. As such, this may not always correspond to disease severity.

5.5.5.3.3 Ability to Detect Change/Responsiveness

Responsiveness was evaluated via the effect size (Cohen's d) and correlation analyses.

Based on these analyses,

- The effect size for the SPRO scores monotonically increased from severe to less severe responses (refer to Tables 39-41 in the quantitative summary report ("Validation of Patient-reported Outcomes (PRO) Measures for Alopecia Areata Validation Report EVA-35999 | June 2, 2023 | Version 1.0")).
- The SPRO score change within this timeframe was strongly correlated with the other clinician-and patient-reported assessments (r ranged from 0.69 (CGI-S) to 0.86 (QPRO item 1)), with the exception of QPRO item 3 and item 4, with which the score change was moderately correlated (r= 0.48 and 0.41 respectively). All correlations were statistically significant (all $p < 0.001$). The correlation of change scores in the SPRO score and reference measures are shown in Table 1.

Table 1. Correlations of changes in SPRO scores from Baseline to Week 24

Scale Score Change	N	r^1	p-Value
Absolute SALT	645	0.71824	<0.0001
PGI-S	646	0.74229	<0.0001
PGI-I ²	646	0.76221	<0.0001
CGI-S	644	0.69153	<0.0001
CGI-I ²	645	0.72299	<0.0001
QPRO 1: hair thickness	646	0.85614	<0.0001
QPRO 2: hair evenness	646	0.82429	<0.0001
QPRO 3: eyebrows	646	0.48290	<0.0001
QPRO 4: eyelashes	646	0.40836	<0.0001

Source: Table 39 of the quantitative summary report ("Validation of Patient-reported Outcomes (PRO) Measures for Alopecia Areata Validation Report EVA-35999 | June 2, 2023 | Version 1.0")

- The mean change scores in the SPRO ranged from -3.1 to 0.18 as anchored to the PGI-I scores from 1 (“Very much improved”) to 7 (“Very much worse”), respectively at Week 24.
- The mean change scores in the SPRO ranged from -2.9 to -0.25 as anchored to the PGI-S change scores from <-2 points to No change, respectively at Week 24.
- The mean change scores in the SPRO ranged from -3.01 to -0.17 as anchored to the absolute SALT scores from ≤20 (None/minimal scalp hair loss) to ≥95 (Complete or near complete/severe scalp hair loss), respectively at Week 24.

Reviewer’s comment(s):

Generally, for assessment of responsiveness, sponsors should provide the distribution of change on the target instrument by change on each anchor by providing descriptive statistics for improvement in the target instrument for each level of categorical improvement in the anchors [N (total number), mean, median, standard deviation, range, and confidence intervals]. This Applicant did conduct this analysis; however, it was conducted as part of the anchor-based analyses (refer to Section 5.5.6 of this review). The distribution-based method (i.e., effect size) provides supportive evidence of responsiveness. In general, the SPRO appears to identify differences in scores over time in individuals or groups who have changed with respect to the concept.

5.5.6 Interpretation of Meaningful Within-Patient Changes

The Applicant defined a responder to the SPRO as a response of “very satisfied” or “satisfied” at Week 24. To support this responder definition, the Applicant performed the following analyses using data from:

- Anchor-based analyses
- Distribution of change on the target COAs by change on anchors

5.5.6.1.1 Anchor-based Analyses

The anchors utilized by the Applicant and their corresponding target COA are summarized below. Copies of the anchor scales are in Appendix B.

- **Clinical Global Impression of Improvement (CGI-I)**
The CGI-I¹¹ is a single item clinician-reported outcome (ClinRO) instrument designed to assess clinician perceived change of the patient’s AA using a 7-point VRS ranging from 1 (“Very much improved”) to 7 (“Very Much Worse”). The recall period is a comparison of the current state to an earlier time period. The CGI-I was administered at Weeks 12, 16, 20, and 24.
- **Patient Global Impression of Improvement (PGI-I)**
The PGI-I is a single item PRO instrument designed to assess self-perceived change in AA using a 7-point VRS ranging from 1 (“Very much improved”) to 7 (“Very much worse”). The recall period is a comparison of the current state to an earlier time period. The PGI-I was administered at Weeks 12, 16, 20, and 24

¹¹ To reduce variability, the same rater was to perform the ClinRO assessments for the patient for the duration of the study.

- Clinical Global Impression of Severity (CGI-S)
The CGI-S¹¹ is a single item ClinRO instrument designed to assess AA severity using a 7-point VRS ranging from 1 (“Normal, no hair loss”) to 7 (“Among the most extreme hair loss”). The recall period is current state. CGI-S was administered at baseline and Weeks 12, 16, 20, and 24.
- Patient Global Impression of Severity (PGI-S)
The PGI-S is a single item PRO instrument designed to assess AA severity using a 7-point VRS ranging from 1 (“Normal, no hair loss”) to 7 (“Among the most extreme hair loss”). The recall period is current state. PGI-S was administered at baseline and Weeks 12, 16, 20, and 24.

Table 2 presents the range of responder definitions for the SPRO using an anchor-based analysis, based on change in SPRO from baseline to Week 24, ranging from 0.54 to 3.06.

Table 2. Range of Responder Definitions of the Change in SPRO Based on Anchor-based and Distribution-based Approaches from Baseline to Week 24

Anchor-based Responder Threshold [Mean (SD)]							Distribution-based Responder Definition Estimates			
PGI-I ‘Minimally, or Much, or Very much improved’			PGI-S Improved (Change = -2)		Change in SALT		Absolute SALT Score ≤20% Complete or near complete scalp hair (N=178)			
PGI-I ‘Minimally improved’ (N=151)	PGI-I ‘Much improved’ (N=159)	PGI-I ‘Very much improved’ (N=475)	PGI-S Improved (Change = -2) (N=65)	Mild Reduction (N=91)	Moderate Reduction (N=81)	Strong Reduction (N=157)				
0.54 (1.02)	1.93 (1.10)	1.89 (1.49)	1.75 (1.39)	1.47 (1.17)	2.11 (1.26)	3.06 (1.06)	3.01 (1.04)	0.25	0.65	1.25

Abbreviations: Abbreviations: PGI-I = Patient Global Impression-Improvement; PGI-S = Patient Global Impression-Severity; PRO = Patient-Reported Outcome; SALT = Severity of Alopecia Tool; SD = standard deviation; SEM = standard error of measurement; SPRO = Satisfaction of Hair PRO

1. Distribution-based MID: SEM, (SD of baseline) * SQRT(1-ICC). ICC is derived based on test-retest evaluation.

Source: Table 46 of the quantitative summary report (“Validation of Patient-reported Outcomes (PRO) Measures for Alopecia Areata Validation Report EVA-35999 | June 2, 2023 | Version 1.0”)

Reviewer’s comment(s):

The Applicant also used the SALT and QPRO items 1-4 as external anchors. This reviewer notes that the SALT and ClinRO instruments do not take into account the patient perspective. Further, the concepts measured in the QPRO do not fully align with the concept measured in the SPRO. Regarding the PGI-I and PGI-S, while the concepts measured in these scales are closely related to the concept measured in the SPRO, as previously noted the SPRO measures satisfaction and patients may consider various factors when reporting their satisfaction of hair on scalp. As such, the relationship between satisfaction and disease severity is unknown. This reviewer acknowledges that the Applicant presented results as a range. In the absence of qualitative data, it is difficult to determine what constitutes a meaningful change on the anchor scale.

While the Applicant conducted anchor-based analyses, an anchor-based approach may not be necessary in this scenario as the SPRO is a single item that measures a single distinct concept of interest and the response options appear to correspond to a meaningfully distinct experience based on the qualitative data. In this scenario, the SPRO scores themselves may be directly

interpretable in terms of the patient's experience. It would have been helpful to conduct meaningful change exercises in the cognitive interviews to support what constitutes a meaningful change in this item (i.e., which response option would represent a meaningful experience or change).

5.5.6.1.2 Distribution-based methods

Distribution-based estimates of meaningful-change thresholds for the SPRO were assessed with two evaluations: (1) SD approach; and (2) the standard error of measurement (SEM) approach. The SD and SEM estimates were calculated using the Phase 3 trial data. Three SD definitions were operationalized: (1) 0.25 SD; (2) 0.50 SD; and (3) 0.80 of the baseline and Weeks 24 data. The SEM was based on the test-retest ICC or transtemporal reliability coefficient and pooled (mean) SD from baseline and Week 24 and the change score (Δ) SD between baseline and Week 24.

Table 2 above presents the range of responder definitions for the SPRO using the distribution-based analysis, based on change in SPRO from baseline to Week 24, ranging from 0.32 to 1.25.

Reviewer's comment(s):

Distribution-based methods (e.g., effect sizes, certain proportions of the standard deviation and/or standard error of measurement) are only considered supportive to anchor-based methods.

6 APPENDICES

Appendix A. Satisfaction of Hair Patient-Reported Outcome (SPRO)

Appendix B. Copies of anchor scales

Appendix B1. Clinical Global Impression of Severity (CGI-S)

Appendix B2. Clinical Global Impression of Improvement (CGI-I)

Appendix B3. Patient Global Impression of Severity (PGI-S)

Appendix B4. Patient Global Impression of Improvement (PGI-I)

Appendix A: SPRO

Satisfaction of Hair Patient-Reported Outcome (SPRO)

How satisfied are you with the hair on your scalp today?

- ☐₅ Very dissatisfied
- ☐₄ Dissatisfied
- ☐₃ Neither satisfied nor dissatisfied
- ☐₂ Satisfied
- ☐₁ Very satisfied

Appendix B: Copies of anchor scales

Appendix B1. Clinical Global Impression of Severity (CGI-S)

How would you rate the severity of the patient's alopecia areata at this time:

1. Normal, no hair loss
2. Borderline hair loss
3. Mild hair loss
4. Moderate hair loss
5. Marked hair loss
6. Severe hair loss
7. Among the most extreme hair loss

Appendix B2. Clinical Global Impression of Improvement (CGI-I)

Compared to the patient's alopecia areata prior to treatment at Baseline, the patient's current state of alopecia areata is:

1. Very Much Improved
2. Much Improved
3. Minimally Improved
4. No Change
5. Minimally Worse
6. Much Worse
7. Very Much Worse

Appendix B3. Patient Global Impression of Severity (PGI-S)

How would you rate the severity of your alopecia areata at this time:

1. Normal, no hair loss
2. Borderline hair loss
3. Mild hair loss
4. Moderate hair loss
5. Marked hair loss
6. Severe hair loss
7. Among the most extreme hair loss

Appendix B4. Patient Global Impression of Improvement (PGI-I)

Compared to my alopecia areata prior to treatment at Baseline, my current state of alopecia areata is:

1. Very Much Improved
2. Much Improved
3. Minimally Improved
4. No Change
5. Minimally Worse
6. Much Worse
7. Very Much Worse

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/s/

JING JU
05/22/2024 01:26:20 PM

SELENA R DANIELS
05/24/2024 08:10:21 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 23, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 217900
Product Name, Dosage Form, and Strength:	Leqselvi (deuruxolitinib) tablets, 8 mg
Applicant Name:	Sun Pharmaceutical Industries, Inc
FDA Received Date:	April 16, 2024
TTT ID #:	2023-5772-1
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Sun Pharmaceutical Industries, Inc submitted revised container labels received on April 16, 2024 for Leqselvi. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels for Leqselvi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Sun Pharmaceutical Industries, Inc implemented all of our recommendations and we have no additional recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^a Patel, M. Label and Labeling Review for Leqselvi (NDA 217900). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 FEB 14. TTT ID: 2023-5772.

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/s/

MADHURI R PATEL
05/23/2024 11:13:13 AM

YEVGENIYA M KOGAN
05/23/2024 02:10:02 PM

Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

NDA	217900
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Deuruxolitinib (DRX)
Indication	Moderate to Severe Alopecia Areata
Applicant	Concert Pharmaceuticals
Requesting Division, contact	Division of Dermatology and Dentistry (DDD), Craig Johnson, RPM Verma Kapil, MD – Medical Officer Melinda Mc Cord, MD – Team Lead
Primary Reviewer	Eileen Navarro Almario, MD, DILI Team Lead, OND/DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Other Reviewers	Edwige Chiogo Vouffo, PharmD, PhD Non-clinical analyst, OND/DHN
Reviewer Office of Pharmacoepidemiology	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Joseph Toerner, MD, MPH DHN Division Director
Assessment Date	Apr 14, 2024

Context: Deuruxolitinib (DRX) is an oral, deuterated version of a marketed JAK inhibitor, ruxolitinib. Thus, the two are structurally the same, save the substitution of eight hydrogen atoms (^1H) with eight deuterium atoms (^2H). If approved, DRX would be the third JAK inhibitor for alopecia areata (AA) but the second specifically targeting JAK 1 and 2. Ruxolitinib is not approved for AA. The Division of Dermatology and Dental (DDD) consulted the Division of Hepatology and Nutrition (DHN) Drug Induced Liver Injury (DILI) Team during labeling negotiations because the Sponsor proposed excluding any reference to liver enzyme elevations in the label, citing the lack of a clear dose relationship between the eight and twelve mg twice daily in the phase 2 and 3 trials. DDD specifically asked the DILI team to provide “1. causality assessment based on a review of narrative summaries for subjects with elevated liver enzymes, potential DILI cases, and potential Temple’s Corollary cases and comment on if any cases suggest DILI, 2. comment on whether monitoring for changes in liver enzymes or hepatotoxicity is warranted in labeling for deuruxolitinib.”

Executive Summary: We do not see a DILI risk that would preclude approval, nor do we suggest labeling for DILI other than HBV reactivation risk. Indeed, the increased incidence of aminotransferases (AT) elevation associated with DRX over placebo is likely entirely explained by myopathy with creatine phosphokinase (CPK) elevations that were also seen more frequently with DRX. The imbalance in AT was driven by AST more than ALT which

is consistent with a muscle rather than liver source. AT elevations were relatively modest, also consistent with a muscle origin over significant liver injury, and AT elevations often resolved while still on DRX. Detailed case level assessment in the pivotal phase 3 trials suggest no imbalance in eDISH Temple's Corollary quadrant once myopathy is taken into consideration. There were no Hy's Law cases. Accordingly, labeling does not need language regarding liver enzyme elevations outside the context of a myopathy risk and CPK elevations. However, language regarding hepatitis B reactivation should mirror the label of the closely related ruxolitinib which is associated with such reactivation. The DRX trials excluded subjects with positive hepatitis B surface antigen, so they were unable to assess this risk. Our detailed assessment and recommendations are in **Section 5.0** at the end of this consult.

Consultation Sections:

Section 1.0 – Target Disease and Rationale

Section 2.0 – ADME and DDI pertinent to DILI risk

Section 3.0 - Non-clinical data pertinent to DILI.

Section 4.0 - Clinical data

Section 5.0 – Assessment & Recommendations.

Appendix 1: Mean change in liver analytes and details on two cases of possible DILI

Abbreviations:

ADME: absorption, distribution, metabolism, excretion

AA: alopecia areata

ALP or AP: alkaline phosphatase

ALT: alanine aminotransferase

AP: alkaline phosphatase

AST: aspartate aminotransferase

AT: aminotransferase (ALT and/or AST)

BMI: body mass index

CPK or CK: creatine phosphokinase

CTP-543: deuruxolitinib or DRX

CYP: cytochrome P450

DB: direct bilirubin

DDI: drug-drug interaction

DILI: drug-induced liver injury

DRX: deuruxolitinib (or CTP-543)

GGT: gamma-glutamyl transferase

HBV: hepatitis B virus

HCV: hepatitis C virus

HDS: herbal and dietary supplements

IP: investigational product

JAK: Janus Kinase

MRI: magnetic resonance imaging

NCTR: National Center for Toxicological Research

R-value: $\text{ALT/ULN} \div \text{ALP/ULN}$

STAT: Signal Transducers and Activators of Transcription

TB: total bilirubin

US: ultrasound

ULN: upper limit of normal

1.0 Target Disease and Rationale

1.1 Target Disease: Alopecia areata (AA) is a nonscarring type of alopecia induced by autoimmunity against the hair follicle. Moderate to severe AA which effects about 300,000 individuals in the US, can lead to total scall or full body hair loss and impairs daily function and quality of life, justifying priority review and breakthrough therapy designation. Lifetime risk for AA in the general population is about 2% and the prevalence is 1/1000.¹ There is a significant disruption of the hair growth cycle in AA, but perturbations in hair growth depending on the pattern, severity, and duration of AA are patient specific.² There is still no cure for alopecia, although there are many medications on the markets.³ Prior to the recent approvals of two oral Janus kinase (JAK) inhibitors (baricitinib-approved 2022; ritlecitinib approved 2023) the only approved therapy for AA was intralesional steroids. Oral immunotherapies were used off label.

1.2 Rationale for Drug Use: Deuruxolitinib (DRX) is Janus Kinase (JAK) inhibitor modulating the immune response through intracellular JAK 1 and JAK 2 induction of STAT activation (**Figure 1**). JAKs are tyrosine kinases that initiate the signaling of over 50 cytokines to control innate and adaptive immune response, induce inflammation, and regulate hematopoiesis.⁴ Dysregulation of proinflammatory cytokines via aberrant activation of the JAK/STAT pathway is associated with AA and numerous other chronic inflammatory and autoimmune disorders such as ulcerative colitis, atopic dermatitis, rheumatoid arthritis, and psoriasis.⁵ By inhibition of such pathways, several JAKs (JAK1, JAK2, JAK3, and tyrosine kinase 2) inhibitors have efficacy in treating several of these diseases, and can lead to complete withdrawal or avoidance of glucocorticoids that would otherwise be needed.⁶

¹ Lepe K et al. Alopecia Areata. [Updated 2023 Oct 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. <https://www.ncbi.nlm.nih.gov/books/NBK537000/>

² Abdullah A, et al. Alopecia areata update: Part I. Clinical picture, histopathology, and pathogenesis, *Journal of the American Academy of Dermatology*. 2010 62 (2): 177-188. <https://doi.org/10.1016/j.jaad.2009.10.032>

³Hordinsky MK, et al. Overview of Alopecia Areata, *Journal of Investigative Dermatology Symposium Proceedings*,2013, 16 (1): S13-S15. <https://doi.org/10.1038/jidsymp.2013.4>

⁴[NDA217900 \(217900 - 0031 - \(31\) - 2024-03-26 - TRIAGE-1 /Electronic Submission/Gateway\) - Introduction](#)

⁵ [NDA217900 \(217900 - 0031 - \(31\) - 2024-03-26 - TRIAGE-1 /Electronic Submission/Gateway\) - Pharmacology Written Summary \(#5\)](#)

⁶ Tanaka, Y., et al. Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach. *Nat Rev Rheumatol* **18**, 133–145 (2022).

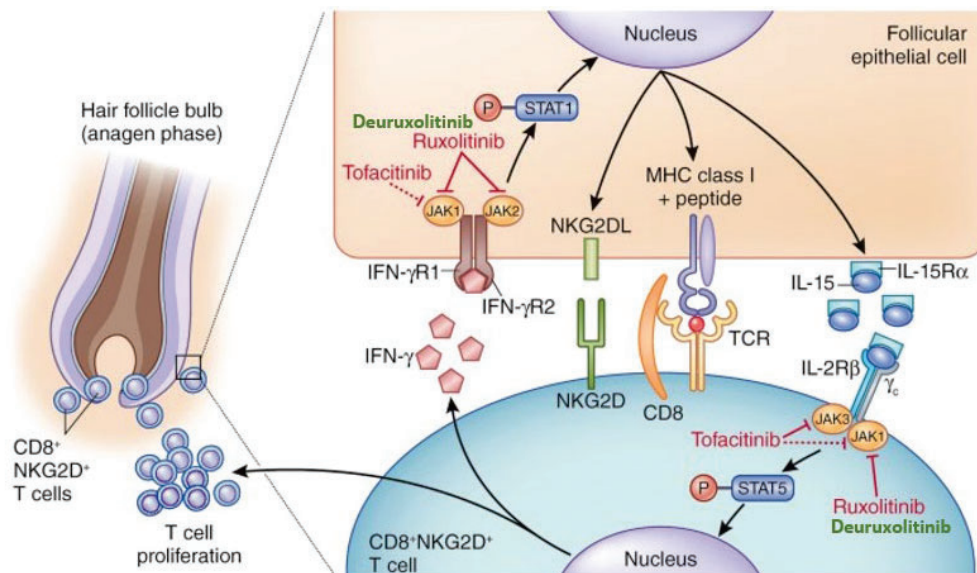
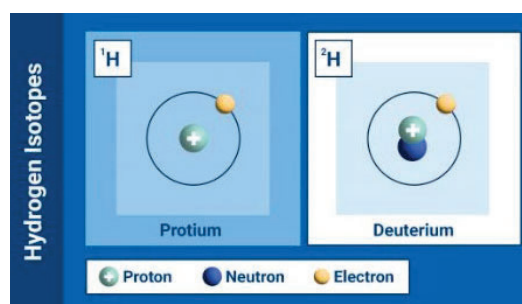


Figure 1: Mechanism of drug action (a) JAK1 and JAK2 receptor-ligand activation with STAT activation leading immune and inflammatory effects. Blocking by inhibitors (DRX, ruxolitinib) is also shown.⁷

2.0 ADME and DDI data pertinent to DILI

2.1 Structure and Structure Activity Alerts: Deuruxolitinib (DRX) has the same chemical formula and basic structure as ruxolitinib, but is deuterated, (i.e., one or more hydrogen atoms are replaced with deuterium atoms which are twice as heavy as hydrogen due to the addition of a neutron.) (**Figure 2**).⁸ Deuterated drugs may affect lipophilicity, in addition to pharmacokinetics and toxicity. A recent review concludes “Deuterium incorporation can modulate drug metabolism; it is not clear how it scientifically differentiates from ruxolitinib or other JAK inhibitors beyond a longer patent life enabling development for this new indication.”⁹

(a)



(b)

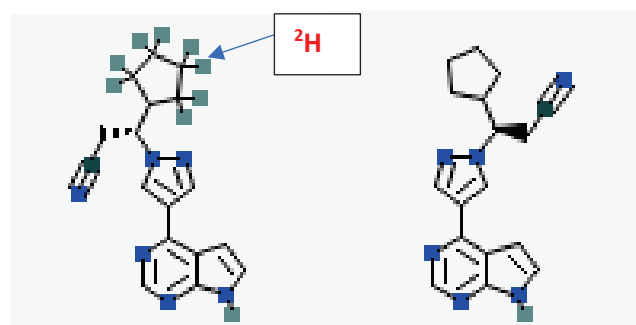


Figure 2. (a) Atomic structure of hydrogen (H) in ^1H and ^2H (deuterium) forms, and (b) Structural formulas of deuruxolitinib (left) and ruxolitinib (right).¹⁰

⁷ Adapted from: Divito, S, et al. Inhibiting Janus kinases to treat alopecia areata. *Nat Med* 2014 **20**: 989–990. <https://doi.org/10.1038/nm.3685>

⁸ <https://www.medchemexpress.com/deuterated-ruxolitinib.html>

⁹ Di Martino RMC, et al. Deuterium in drug discovery: progress, opportunities, and challenges. *Nat Rev Drug Discov* **22**, 562–584 (2023). <https://doi.org/10.1038/s41573-023-00703-8>

¹⁰ <https://www.iaea.org/newscenter/news/what-is-deuterium>

2.2 Absorption: DRZ has a high permeability in Caco-2 and MDCK II cell lines. In dogs, it had 68% bioavailability. Mean T_{max} in mice was 0.5 hour, and peak radioactive concentrations in rats following an oral dosing was 1-2 hours post dose. C_{max} was proportional to dose increase while AUC was proportionately greater than dose increase in a 26-week toxicity experiment in mice. There was no accumulation in mice as exposure was higher on day one than on day 182. Hence, DRX was rapidly absorbed with no evidence of accumulation.

2.3 Distribution: About half of the examined tissue attained their highest concentrations at 10 minutes after administration of the radioactively labeled DRX. DRX has no concentration dependent plasma protein binding, but it is highly plasma protein bound in mice, rats, rabbits, dogs, and human at 89, 71, 82, 81, and 92%, respectively. Thus, DRX is highly protein bound with rapid distribution to tissues.

2.4 Metabolism: DRX is primarily metabolized by CYP 2C9 (76%) and CYP3A4 (21%), and to the lesser extent by CYP1A2 (3.4%), based on both clinical and in vitro data. Following administration of 16 mg in humans, 21 metabolites were identified in plasma and urine. There were no human specific metabolites. Rats and dogs were chosen for toxicology experiments, since they had all significant human metabolites. DRX is a potential CYP3A4 inducer, but not in a time dependent inhibitor manner. It's an inhibitor of BSEP, BCRP, OAT3, and MATE2-K transporters. Thus, DRX was extensively metabolized by the liver with no human unique metabolites identified. It inhibited several transporters including BSEP.

2.5 Excretion: Rapid excretion occurred following oral administration of [^{14}C] DRX to rats, and there was <2% parent drug in urine and feces suggesting that DRX was well absorbed and eliminated as metabolites. Mean overall recovery of radioactivity was 94% of oral administration in rats by 168 hours post dose. Average recovery of radioactivity following a single 20 mg/kg dosing in rats was 42% and 49%, respectively in urine and feces. From cage wash and carcass, the mean recovery was 2.5% and 0.4%, respectively. Following a 26-week dosing of 10, 30, and 100 mg/kg/day in mice, the mean $T_{1/2}$ was 0.78 hour on day 1 and 1.2 hours on day 182. Tissue radioactivity generally declined rapidly, and 24 hours post dosing about three-quarters of the tissues analyzed were at or below the limit of quantification.

2.6 Human PK data: In humans, following a single oral administration of 20 mg, the major route of elimination was urine (~70% recovered), followed by feces (20% recovered). The most abundant metabolites were 21714 and 21717 which are 10-fold less potent than parent drug. Mild to moderate hepatic impairment did not alter DRX protein binding nor C_{max} and AUC, thus no dose adjustment is deemed warranted in such impairment. Population analysis found baseline ALT, BMI, and sex as associated with clearance, but the Sponsor suggests the effects are not clinically relevant. Highlights of ADME data, both animal and human, are in **Table 1**.

Table 1. Summary of ADME data--animal and human.

Item	Finding
Absorption	Rapid with T_{max} : 0.5 hour in mice; 90% oral absorption in human with peak concentration in 1.5 hr and steady state at 1-2 days.

Distribution	High plasma protein binding, 91.5% in humans; wide volume of distribution
Metabolism	Extensive with < 2% as parent drug recovered and several metabolites but none unique to humans.
Elimination	T1/2~1 hour in mice, elimination via feces (49.4%) and urine (42%) in rats; in humans 70% recovered in urine while 20% in feces; Mean half-life in humans was <4 hours.

3.0 Non-clinical data

3.1 In vitro data: No increase in reverse mutations occurred in bacterial reverse mutation assay. There was no deuruxolitinib-induced chromosomal aberration in cultured human lymphocytes with or without rat liver metabolizing system (S9). This may suggest no/low evidence of reactive intermediates during metabolism, as oxidative stress may lead to genotoxicity and mutation.¹¹

3.2 Animal data: NOAEL in rats was 100 mg/kg/day in a 28-day dosing, and 37.5 mg/kg/day (6.1 mg/kg/day in humans) in a 13 and 26-week administration. Doses above these NOAELs were associated with decrease in body weight, death/moribundity, and more severe alterations in hematology parameters and the lymphoid depletion in immune organs. In 13- or 52-week oral dosing in dogs, NOAEL was 3 mg/kg/day (1.7 mg/kg/day in humans). In comparison, DRX's proposed daily dose is 16 mg/day, or 0.18 mg/kg/day and 0.20 mg/kg/day for a US adult male (average weight, 91 kg) and female (average weight, 78 kg), respectively.¹²

Following a 13-week dosing in rats there was an increase in AST and ALP with no correlative microscopic studies. Only minimal increase in ALP occurred in a 26-week experiment in animals receiving ≥ 37.5 mg/kg/day. There was a minimal to moderate hypocellularity in lymphoid tissues at 75 mg/kg/day. Changes in these studies include decrease in white blood cell count, decrease in lymphoid organ weights, and lymphocyte depletion. Those were partially or totally reversible following drug discontinuation.

In a 13-week administration in dogs, transaminase increased, with no evidence of hepatocellular injury. There was DRX related hematology and coagulation findings, including decrease in red blood cells count, hemoglobin, and hematocrit, white blood cells, and reticulocyte count. Microscopic decreased cellularity occurred in sternum and femur bone marrow, cortex of thymus, and lymphoid nodule of spleen, and mesenteric or mandibular lymph nodes at ≥ 1.5 mg/kg/day. There was more severe suppression of hematology parameters and increased severity of microscopic lymphoid depletion in animals receiving ≥ 6 mg/kg/day that led to mortality/moribundity. Mortality secondary to infection was associated with altered immunocompetence. Microscopic findings were reversible in the recovery phase.

Following a 52-week dosing in dogs there was DRX related minimal decreased red blood cell count mass (red blood cell count, hemoglobin, and hematocrit), absolute eosinophil count, and minimal to mild decreased absolute lymphocytes count. The decreased red

¹¹ Donato M and Tolosa L. High-Content Screening for the Detection of Drug-Induced Oxidative Stress in Liver Cells. *Antioxidants* (Basel). 2021 Jan 13;10(1):106. doi: [10.3390/antiox10010106](https://doi.org/10.3390/antiox10010106)

¹² <https://www.cdc.gov/nchs/fastats/body-measurements.htm>

blood cell mass was in correlation with decreased bone marrow cellularity in sternum and decreased lymphocyte count in correlation with decreased lymphocyte cellularity, microscopically identified in different lymphoid tissues at 3 mg/kg/day. These changes were reversible after recovery period.

From the non-clinical prospective, there is minimal evidence for DILI risk from DRX. Minimal liver markers increased with no evidence of microscopic liver findings in animals. However, BSEP being inhibited by deuruxolitinib may lead to some liver injury due to bile acid accumulation. The main target for DRX-induced toxicity were hematopoietic and lymphoid organs. We summarize toxicologic findings pertinent to DILI risk in **Table 2**.

Table 2: Toxicology summary table¹³

Item	Finding
In Vitro Studies	
Major metabolizing CYPs	CYP 2C9
Reactive metabolites (i.e., glutathione [GSH]trapping) which may increase DILI risk	Not assessed
Mitochondria studies/inhibition which may increase DILI risk	Not assessed
Time dependent CYP inhibition which may increase drug exposure and DILI risk	None for CYP2C19, 3A4, 2D6, 2C8, 2C9, 2B6, 1A2
LogP (Measure of drug lipophilicity; values>3 suggest increase DILI risk)	0.5
Covalent binding which may increase DILI risk	Not assessed
BSEP or MRP2 inhibition which may increase DILI risk	BSEP inhibitor with IC50: 33 µg/mL, MRP2 not assessed
Animal Studies	
Elevation in liver analytes (e.g., ALT, AP, TB)	Minimal elevation of liver enzymes in rats and dogs
Liver histopathology findings (animal species)	None seen

3.3 National Center for Toxicological Research (NCTR) summary: Time did not permit a full evaluation by our NCTR colleagues using DILIscore and Rule-of-Two (RO2). However, they did provide an abbreviated assessment shown in **Table 3**. Because reactive metabolite data were not available, two DILIscores are shown. Both drugs were negative on RO2 criteria (low DILI risk) and of moderate risk on DILIscore, if reactive metabolites (RM) were formed. If no RMs are formed, then DILIscores would be in the low-risk category. On this abbreviated evaluation, NCTR thought DRX may have a lower risk of DILI due to the lower dose, lower lipophilicity and less metabolism, but both drugs were of low to moderate risk.

Table 3. DILIscore and Rule of Two (RO2) analyses for Ruxolitinib and Deuruxolitinib¹⁴

	<i>Ruxolitinib</i>	Deuruxolitinib (DRX)
Daily dose (mg/day)	50	24
LogP	2.48	0.5
Reactive metabolite (RM)	NA	NA
RO2 test	negative	negative

¹³ Table made by DILI Team

¹⁴ Table received by email from Minjun Chen, PhD, FDA NCTR, Apr 8, 2024.

DILIscore	5.77 (RM =positive) 2.94 (RM=negative)	4.88 (RM=positive) 2.05 (RM=negative)
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NA = data not available, LogP = measure of lipophilicity (levels >3 associated with greater DILI risk).
RO2 = Rule of Two.

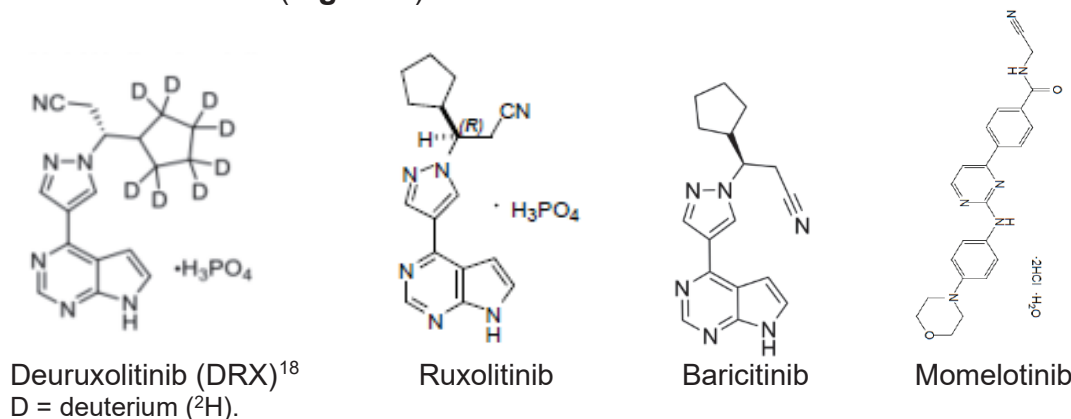
Table notes: When an oral medication is given $\geq 100\text{mg/day}$ and its logP (the measure of lipophilicity) is ≥ 3 , it will be RO2 positive; otherwise, negative. The logP is calculated from the chemical structure of the evaluated drug using AlogP online tool (<http://www.vcclab.org/web/alogs/>). The RO2 positives are associated with a higher risk of DILI in humans. The performance of RO2 is evaluated based on 164 FDA approved drugs: positive predictive value (PPV): 96%; negative predictive value (NPV): 39%; sensitivity: 38%; specificity: 96%; The AUC of receiver operating characteristic (ROC) curve: 0.668; Matthew's correlation coefficient (MCC): 0.342.

DILIscore is another DILI model developed by NCTR to provide a quantitative assessment of risk of clinical DILI by calculating the contribution of daily dose/Cmax, logP, and the formation of reactive metabolites (RM). The formation of reactive metabolites can be determined by the time-dependent inhibition, GSH trapping, or covalent binding. The DILIscore of >6 is defined as high DILI risk and 3-6 as moderate DILI risk and <3 low DILI risk. The performance of DILIscore is evaluated based on 337 FDA approved drugs with AUC of ROC curve of 0.904.^{15, 16}

4.0 Clinical data:

4.1 In-class and near class agents: Of the ten approved JAK inhibitors, three, ruxolitinib, baricitinib, and momelotinib, specifically target JAK 1 and 2, like DRX.¹⁷

Ruxolitinib, being a non-deuterated form of DRX, is most closely related to DRX, though it is marketed for primary myelofibrosis, or myelofibrosis secondary to polycythemia vera or essential thrombocythemia, and not AA. Baricitinib is approved for rheumatoid arthritis and alopecia areata (AA). Momelotinib is not approved for AA and is the most different in chemical structure (**Figure 3**).



¹⁵ Chen M, et al. High Lipophilicity and High Daily Dose of Oral Medications Are Associated with Significant Risk for Drug-Induced Liver Injury. *Hepatology*. 2013; 58:388-396

¹⁶ Chen M, et al. A Model to Predict Severity of Drug-Induced Liver Injury in Humans. *Hepatology*. 2016; 63:931-940

¹⁷ <https://www.drugs.com/medical-answers/jak-inhibitors-approved-3575793/#table>

¹⁸ [NDA217900 \(217900 - 0031 - \(31\) - 2024-03-26 - ORIG-1 /Clinical/Response To Information Request\) - Drug Substance - Dipharma \(#5\)](#)

Figure 3: Chemical Structures of JAK 1 and 2 inhibitors.^{19,20,21}

Labeling data pertinent to DILI risk for approved JAK 1 and 2 inhibitors are shown in **Table 4**. None of the three JAK 1 and 2 inhibitors have Box Warnings for DILI. Liver enzyme monitoring is discussed in Highlighted Warnings and Precautions for baricitinib and momelotinib. All three discuss liver enzyme elevations in Section 5 and/or Section 6. Ruxolitinib has the least discussion of liver enzymes elevations or DILI risk of the three.

Table 4. Summary of DILI Related Labeling and LiverTox® DILI Risk Category for Ruxolitinib, Baricitinib, and Momelotinib. (See references for **Figure 3** for labeling references.)

Drug (Brand), Target Disease(s)	Mechanism of action	Approval year	Labeling concerning DILI Risk in - Box Warning (BW) - Warnings/Precautions, Highlights (W/P, HL) - Adverse Reactions, Highlights (AR, HL) - Sections 5 & 6 (S5 & S6)	LiverTox® category ²²
Ruxolitinib (JAKAFI®) MF, PV, A & C GVHD. AD (topical)	JAK 1 and 2 inhibitor	2011	- BW: No - W/P, HL: No - AR, HL: No - S5: Yes; HBV reactivation - S6: Yes; AT elevations noted	C: probable cause of HBV reactivation
Baricitinib (OLUMIANT), Rheumatoid arthritis, AA	JAK 1 and 2 inhibitor	2018 (RA) 2022 (AA)	- BW: No - W/P, HL: Yes; monitoring of liver enzymes recommended. - AR, HL: Yes, liver enzyme elevations - S5: Yes; liver enzyme elevations - S6: Yes; liver enzyme elevations	E: Unlikely cause of clinically apparent DILI, but potential for HBV reactivation
Momelotinib (OJJAARA), MF, ET	JAK 1 and 2 inhibitor	2023	- BW: No - W/P (HL): Yes; HBV reactivation and hepatotoxicity - AR (HL): No - S5: Yes; hepatotoxicity - S6: references S5	E*: suspected but unproven cause of DILI

AA = alopecia areata; A & C GVHD = acute & chronic graft versus host disease; AD = atopic dermatitis; AR = Adverse Reactions; BW = Box warning; HBV = hepatitis B virus; HL = Highlights of Prescribing Information; MF=myelofibrosis; PV = polycythemia vera; RA = rheumatoid arthritis; W/P = Warnings & Precautions.

We provide label excerpts corresponding to the yellow highlighted sections in **Table 4**.

(a) Ruxolitinib

Section 5.2 Risk of infection

¹⁹ https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202192s023lbl.pdf

²⁰ https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207924s007lbl.pdf

²¹ https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216873s000lbl.pdf

²² LiverTox® <https://www.ncbi.nlm.nih.gov/books/NBK547852/>

Hepatitis B

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

Section 6.1

Additional Data from the Placebo-Controlled Study

- 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations.
- 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was < 1% for Jakafi with no Grade 3 or 4 AST elevations.

Note: Grade 1 ALT elevations are 3x to 5x ULN by CTCAE criteria.

(b) Baricitinib

Highlights

-----WARNINGS AND PRECAUTIONS-----

- Laboratory Abnormalities: Monitor for changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids. (5.8)

Section 5.8

Liver Enzyme Elevations – Treatment with OLUMIANT was associated with increased incidence of liver enzyme elevation compared to placebo. Increases of ALT ≥ 5 times the upper limit of normal (ULN) and increases of AST ≥ 10 times the ULN were observed in patients in OLUMIANT clinical trials. Evaluate at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. If increases in ALT or AST are observed and drug-induced liver injury is suspected, interrupt OLUMIANT until this diagnosis is excluded [see Adverse Reactions (6.1)].

Section 6.1

Liver Enzyme Elevations – Events of increases in liver enzymes ≥ 3 times the ULN were observed in patients treated with OLUMIANT [see Warnings and Precautions (5.8)].

- During the 16-week treatment period, ALT elevations ≥ 3 times the ULN occurred in 1.0% of patients treated with placebo, 1.7% of patients treated with OLUMIANT 2 mg, and 1.4% of patients treated with baricitinib 4 mg.
- During the 16-week treatment period, AST elevations ≥ 3 times the ULN occurred in 0.8% of patients treated with placebo, 1.3% of patients treated with OLUMIANT 2 mg, and 0.8% of patients treated with baricitinib 4 mg.
- In a phase 3 study of DMARD naive patients, during the 24-week treatment period, ALT and AST elevations ≥ 3 times the ULN occurred in 1.9% and 0% of patients treated with methotrexate monotherapy, 1.9% and 1.3% of patients treated with baricitinib 4 mg monotherapy, and 4.7% and 1.9% of patients treated with baricitinib 4 mg plus methotrexate.

(c) Momelotinib

Highlights:

----- **WARNINGS AND PRECAUTIONS** -----

- **Risk of Infections:** Do not initiate OJJAARA in patients with an active infection. Monitor for signs and symptoms of infection, including reactivation of hepatitis B, and initiate appropriate treatment promptly.
- **Hepatotoxicity:** Obtain liver tests before initiation of and periodically throughout treatment with OJJAARA. (5.3)

Section 5.1 Risk of Infections

Hepatitis B Reactivation

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine transaminase (ALT) or aspartate transaminase (AST), have been reported in patients with chronic hepatitis B virus (HBV) infection taking Janus Kinase (JAK) inhibitors, including OJJAARA. The effect of OJJAARA on viral replication in patients with chronic HBV infection is unknown. In patients with HBV infections, check hepatitis B serologies prior to starting OJJAARA. If HBsAg and/or anti-HBc antibody is positive, consider consultation with a hepatologist regarding monitoring for reactivation versus prophylactic hepatitis B therapy. Patients with chronic HBV infection who receive OJJAARA should have their chronic HBV infection treated and monitored according to clinical HBV guidelines.

Section 5.3

5.3 Hepatotoxicity

Two of the 993 patients with MF who received at least one dose of OJJAARA in clinical trials experienced reversible drug-induced liver injury. Overall, new or worsening elevations of ALT and AST (all grades) occurred in 23% and 24%, respectively, of patients treated with OJJAARA; Grade 3 and 4 transaminase elevations occurred in 1% and 0.5% of patients, respectively. New or worsening elevations of total bilirubin occurred in 16% of patients treated with OJJAARA. All total bilirubin elevations were Grades 1-2. The median time to onset of any grade transaminase elevation was 2 months, with 75% of cases occurring within 4 months.

Delay starting therapy in patients presenting with uncontrolled acute and chronic liver disease until apparent causes have been investigated and treated as clinically indicated. When initiating OJJAARA, refer to dosing in patients with hepatic impairment [*see Dosage and Administration (2.3)*].

Monitor liver tests at baseline, every month for 6 months during treatment, then periodically as clinically indicated. If increases in ALT, AST or bilirubin related to treatment are suspected, modify OJJAARA dosage based upon Table 1 [*see Dosage and Administration (2.4)*].

4.1.1 Post-Market Reports: FDA Adverse Event Reporting System (FAERS) and PubMed searches done March 27, 2024.

Ruxolitinib: There were 1436 reports of hepatobiliary events in FAERS through Dec 31, 2023.²³ Of those, 20 were listed as DILI and 44 as hepatotoxicity. Several other descriptors were non-specific from acute hepatic failure to hypertransaminasemia. No details on attribution to ruxolitinib were available to the DILI Team and duplicate reports are likely. According to Metys®, 31,728 patients have been prescribed ruxolitinib (Jakafi) since 2010, excluding the topical product.²⁴ Despite the large number of FAERS reports, there have been no cases of ruxolitinib liver injury published based on a PubMed search using the following syntax: (ruxolitinib) AND ((hepatotoxicity) or (liver injury) or (DILI)).

Baricitinib: FAERS has 197 hepatobiliary reports through Dec 31, 2023. Of those, ten were listed as DILI and eleven as hepatotoxicity. According to Metys®, the number of patients prescribed baricitinib since 2010 is 27,437. Several other report identifiers were non-specific from acute hepatic failure to hypertransaminasemia. No details on attribution to ruxolitinib were available to the DILI Team and duplicate reports are likely. A search of PubMed yielded no case reports of baricitinib hepatotoxicity (search syntax: (baricitinib) AND ((hepatotoxicity) or (liver injury) or (DILI))). However, we did find a real-world disproportionality analysis of FAERS events for baricitinib that suggests a doubling of odds ratio for hepatobiliary disorders reported at the System Organ Class (SOC) level compared to all other medication reports in the FAERS database (**Table 5**).²⁵

Table 5: Relative odds ratio for hepatobiliary reports in FAERS.

System Organ Class (SOC)	Baricitinib Cases Reporting SOC	Relative odds ratio baricitinib/all other cases (95% CI)S	chi-squared with Yates Correction	p-value
Hepatobiliary disorders	84	2.02 (1.62–2.51)	39.73	2.92E-10

The authors suggest that their paper is the “*first...to suggest an increased risk of hepatobiliary disorders other than transaminase elevation with this agent. The relative odds of hepatobiliary disorders may be associated with COVID -19 as has been suggested by the drug label. However, its use in COVID 19 patients is not known and merits additional investigation.*” It is also unclear how many of these were due to hepatitis B reactivation (indirect DILI) versus idiosyncratic direct hepatotoxicity.

Momelotinib:

There was one report of “liver injury” in FAERS and no case reports of DILI in PubMed.

Overall, DILI reports and labeling for the three marketed JAK 1 and 2 inhibitors are mixed, but none are devoid of labeling regarding liver risk. Ruxolitinib, the most closely related to DRX, has the least amount of labeling language regarding liver injury save HBV reactivation. There were no case reports of DILI for any of the three agents on our

²³ <https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/8eef7d83-7945-4091-b349-e5c41ed49f99/state/analysis>

²⁴ <https://metys.symphonyhealth.com/metys/#/home/sob>

²⁵ Ling Peng, et al. A real-world disproportionality analysis of FDA Adverse Event Reporting System (FAERS) events for baricitinib, *Expert Opinion on Drug Safety*. 2020;19:1505-1511, DOI: 10.1080/14740338.2020.1799975

PubMed search. FAERS reporting is a bit more concerning but duplicate reports and lack of detailed attribution to drug confound these data. The disproportionately high number of FAERS hepatobiliary reports for ruxolitinib compared to baricitinib may be in part due to the targeted diseases. For example, graft versus host disease (a ruxolitinib indicated use) often directly effects the liver while rheumatoid arthritis (a baricitinib indicated use) related liver injury is much less common. Ruxolitinib starting dose ranges from five mg twice daily (graft versus host disease) to 20 mg twice daily (myelofibrosis). The Sponsor seeks approval for DRX dosing of 8 mg twice daily for AA.²⁶

4.2 Drug Development Program²⁷:

The development program for DRX includes 23 clinical studies, of which three are ongoing. A total of 1730 subjects received at least 1 dose of DRX. Of these, 497 were enrolled in the phase 2 studies, and 1080 enrolled in the two phase 3 studies (**Figure 4**). Overall, 1475 went into the two long-term extension studies. The placebo-controlled safety pool enrolled 1020 subjects of whom 90% completed 24-weeks of treatment. The long-term extension studies, originally planned for 52 weeks, were extended to beyond 204 weeks. At the time of our analyses, 974 of subjects have been on DRX for over 52 weeks, 104 over 156 weeks and 18 over 204 weeks.

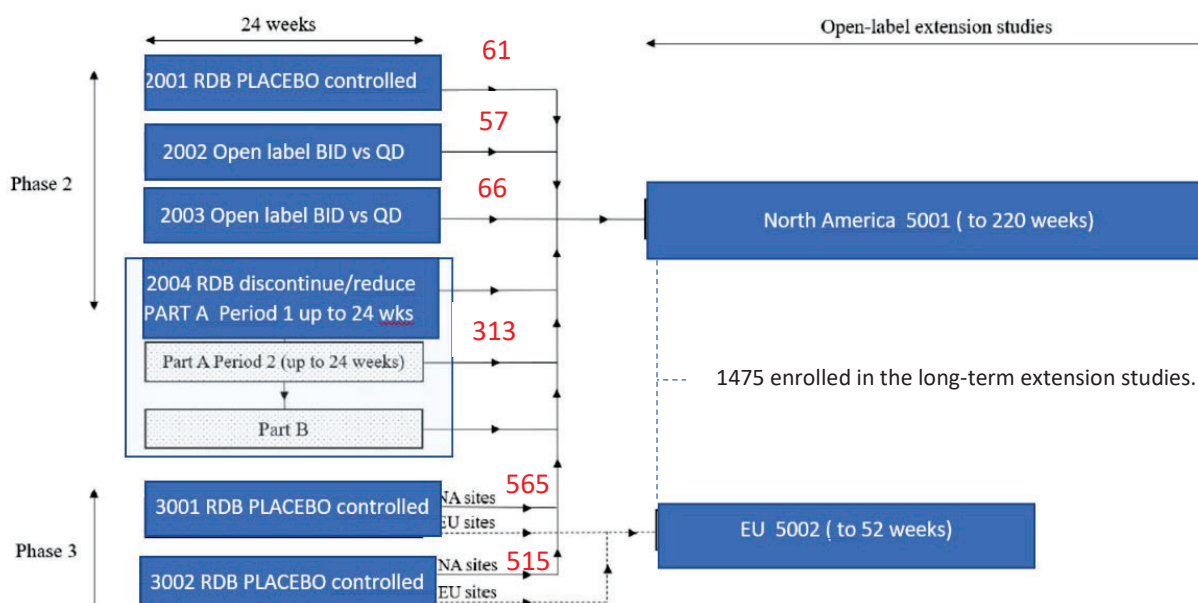


Figure 4: DRX treatment flowchart for Studies 2001, 2002, 2003, 2004, 3001 and 3002.²⁸ Enrollment numbers are in red.

²⁶ [NDA217900 \(217900 - 0033 - \(33\) - 2024-04-04 - ORIG-1 /Patent & Exclusivity/Patent Information\) - Annotated Draft Labeling Text \(#4\)](#)

²⁷ [NDA219195 \(219195 - 0001 - \(1\) - 2023-12-28 - ORIG-1 /Multiple Categories/Subcategories\) - Summary of Clinical Safety](#)

²⁸ Adapted by DILI Team from [NDA217900 \(217900 - 0031 - \(31\) - 2024-03-26 - ORIG-1 /Clinical/Response To Information Request\) - Clinical Safety \(#10\)](#)

Pertinent notes for the phase 2 studies follow.

- Study 2001 Cohorts 1, 2, or 3 compared 4 (n=29) vs 8 (n=38) vs 12 (n=38) DRX vs placebo
- Study 2002 studied DRX 16 mg, given either once daily or in two divided doses.
- Study 2003 studied DRX 24 mg, given either once daily or in two divided doses.
- Study 2004 studied durability of hair regrowth by randomizing patients successfully treated in part A period 1 with DRX 8 or 12 mg BID to dose reduction (4 or 8 mg BID) or placebo (withdrawal) in part A period 2 (both periods lasted 24 weeks). Part B was intended to assess retreatment following dose reduction or discontinuation and is still ongoing.
- Pre-NDA, the Sponsor indicated that only partial data would be submitted for Study 2001, and study 2004 in its entirety is not part of the NDA pooled analyses.

4.3 Study level Assessments for Pivotal Studies 3001 and 3002²⁹

The DHN DILI Team focused our review on the Phase 3 placebo-controlled studies 3001 and 3002 and screened the ISS for serious hepatocellular injury. However, at the subject level we requested and assessed potential DILI cases across all studies.

4.3.1 Study Designs

These two phase 3 studies are of similar design (**Figure 5**).

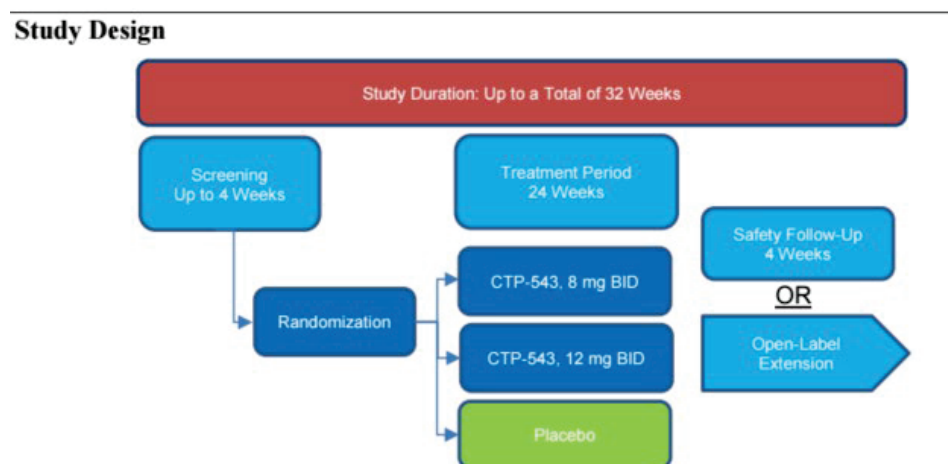


Figure 5: Study Design of Studies 3001 and 3002

Clinical laboratory testing occurred at screening, baseline, and every four weeks from Week 2 to 24, and on safety follow up at week 28. Pertinent exclusion criteria included a liver analyte value $\geq 2 \times$ ULN, a positive tuberculosis test or a positive hepatitis B surface antigen performed at baseline.

4.4 Hepatocellular DILI Screening Plots (eDISH)

²⁹ [NDA217900 \(217900 - 0001 - \(1\) - 2023-07-28 - ORIG-1 /Multiple Categories/Subcategories\) - Study CP543.3002 - Protocol and Amendments \(#7\)](#)

The eDISH plots for the pooled 24-week placebo-controlled study periods and the OLE pool of Study 5001 and 5002 are shown in **Figure 6, Table 6** and **Figure 7, Table 7**, respectively. There were no subjects in the Possible Hy's Law quadrants for either eDISH. The number and rate of Temple's Corollary cases were higher in the DRX arms compared to placebo (**Figure 6, Table 6**).

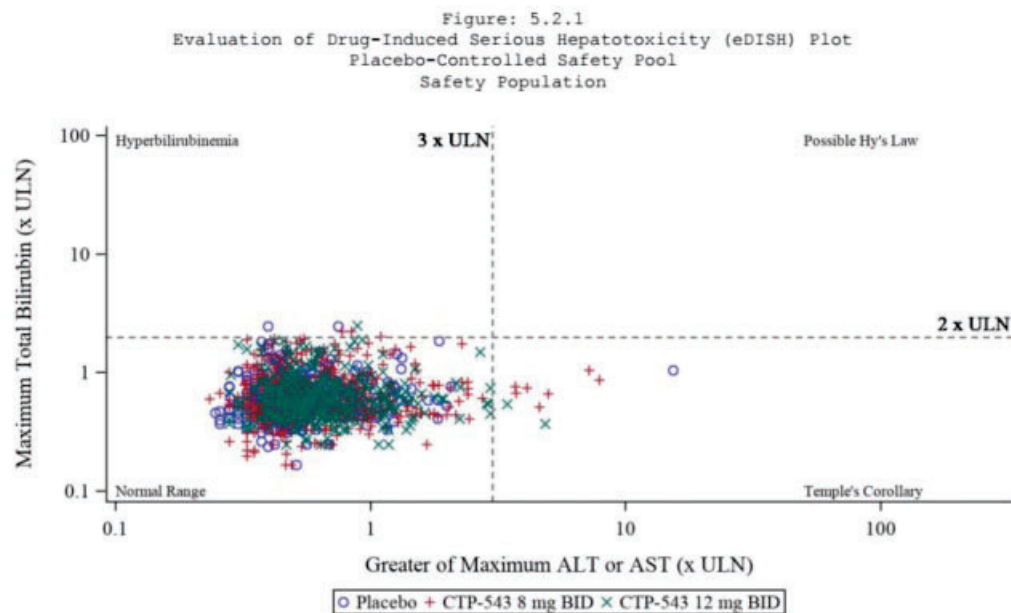


Figure 6: Screening eDISH plot for the placebo-controlled safety pool.

Table 6: Temples Corollary counts and rates for the placebo-controlled safety pool.³⁰

Arm	Number in Temple's	Number Exposed	Rate of Temple's cases
Placebo	1	299	0.3%
8 mg BID	7	640	1.1%
12 mg BID	2	380	0.5%

³⁰ Table made by DILI Team. Number exposed in each arm taken from [NDA217900 \(217900 - 0031 - \(31\) - 2024-03-26 - ORIG-1 /Clinical/Response To Information Request\) - Integrated Summary of Safety - Tables Post-Text \(#5079\)](#)

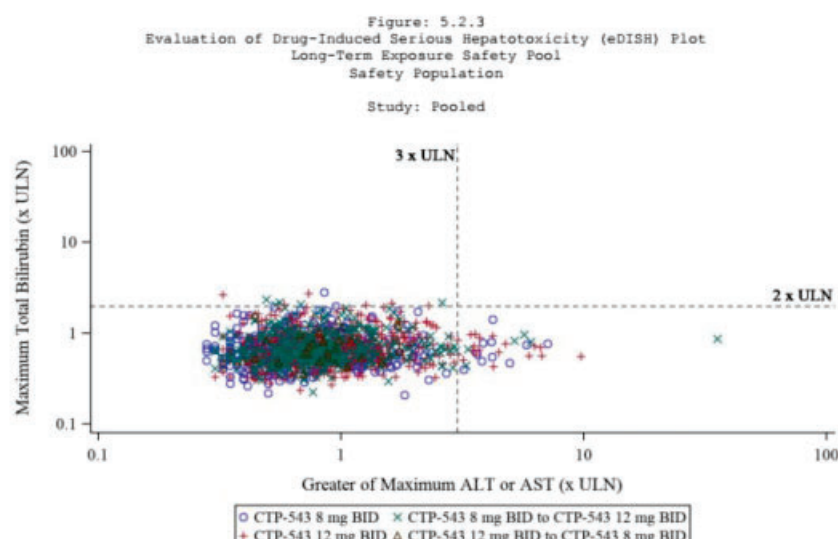


Figure 7: Screening eDISH plot for pooled OLE studies 5001 and 5002.^{31, 32}

Table 7: Temples Corollary counts and rates for the long-term exposure safety pool

Arm	Number in Temple's	Number Exposed	Rate of Temple's cases
8 mg BID	9	296	3.0%
8 mg BID to 12 mg BID	6	238	2.5%
12 mg BID	16	524	3.1%
12 mg BID to 8 mg BID	0	10	0.0%

4.5 Liver Analyte Changes by Shift Tables.

4.5.1 Pooled placebo-controlled safety population including Studies 3001 and 3002:

Shifts in liver analytes by treatment arm are shown in **Tables 8**. Elevations in aminotransaminases (AT; ALT or AST) occurred more in the DRX arms compared to placebo, but the rates were low, typically mild, and not concurrent with any TB elevations (i.e., no potential Hy's Law cases). The differences in ATs elevations compared to placebo were driven by AST elevations. Indeed, the rates of ALT elevations were no different from placebo. There were no ALP elevations over 3x ULN making substantial cholestatic liver injury unlikely. Isolated TB levels without substantial liver enzyme levels are generally not indicative of DILI unless there is underlying cirrhosis or other chronic liver disease, which is unlikely here. These numbers and rates did not change substantially for the Phase 3 Safety Pool.³³

Table 8: Number and percentage of subjects with liver analyte elevations by treatment arm in the placebo-controlled pool.³⁴ CTP-543 = deuruxolitinib.

³¹ [NDA217900 \(217900 - 0007 - \(7\) - 2023-11-22 - ORIG-1 /Clinical/Safety Update\) - 120 Day Safety Update Report - Figures - Post Text \(#40\)](#)

³² [NDA217900 \(217900 - 0001 - \(1\) - 2023-07-28 - ORIG-1 /Multiple Categories/Subcategories\) - Integrated Summary of Safety - Figures Post-Text \(#54\)](#)

³³ [NDA217900 \(217900 - 0031 - \(31\) - 2024-03-26 - ORIG-1 /Clinical/Response To Information Request\) - Integrated Summary of Safety - Tables Post-Text \(#5081\)](#)

³⁴ Adapted by the DILI Team from [NDA217900 \(217900 - 0031 - \(31\) - 2024-03-26 - ORIG-1 /Clinical/Response To Information Request\) - Integrated Summary of Safety - Tables Post-Text \(#5079\)](#)

Parameter(s) Criteria	Placebo (N = 299) n/N (%)	CTP-543 8 mg BID (N = 640) n/N (%)	CTP-543 12 mg BID (N = 380) n/N (%)	Total CTP-543 (N = 1020) n/N (%)
ALT				
≥3 x ULN	1/ 297 (0.3)	1/ 638 (0.2)	0/ 378	1/1016 (<0.1)
≥5 x ULN	0/ 297	0/ 638	0/ 378	0/1016
AST				
≥3 x ULN	1/ 297 (0.3)	6/ 638 (0.9)	2/ 378 (0.5)	8/1016 (0.8)
≥5 x ULN	1/ 297 (0.3)	2/ 638 (0.3)	0/ 378	2/1016 (0.2)
ALT or AST				
≥3 x ULN	1/ 297 (0.3)	7/ 638 (1.1)	2/ 378 (0.5)	9/1016 (0.9)
≥5 x ULN	1/ 297 (0.3)	2/ 638 (0.3)	0/ 378	2/1016 (0.2)
ALP				
≥1.5 x ULN	0/ 297	1/ 638 (0.2)	0/ 378	1/1016 (<0.1)
≥2 x ULN	0/ 297	0/ 638	0/ 378	0/1016
Total Bilirubin				
≥1.5 x ULN	8/ 297 (2.7)	26/ 638 (4.1)	16/ 378 (4.2)	42/1016 (4.1)
≥2 x ULN	2/ 297 (0.7)	3/ 638 (0.5)	1/ 378 (0.3)	4/1016 (0.4)
≥3 x ULN	0/ 297	0/ 638	0/ 378	0/1016
Concurrent ALT and total bilirubin elevation: (ALT ≥3 x ULN) and (total bilirubin ≥2 x ULN)	0/ 297	0/ 638	0/ 378	0/1016
Concurrent ALT/AST and total bilirubin elevation: (ALT or AST ≥3 x ULN) and (total bilirubin ≥2 x ULN)	0/ 297	0/ 638	0/ 378	0/1016
Concurrent ALT/AST and total bilirubin elevation with ALP <2 x ULN: (ALT or AST ≥3 x ULN) and (total bilirubin ≥2 x ULN) and (ALP < 2 x ULN)	0/ 297	0/ 638	0/ 378	0/1016
ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; ULN = upper limit of normal				
NOTE: Baseline is the last observation obtained prior to first dose.				
NOTE: Denominators (N) are the number of subjects with at least one post-baseline value for that parameter (or applicable set of parameters in the case of concurrent elevations).				

We summarize the mean change in liver analytes for the pooled placebo-controlled, 24-week study periods (**Appendix, Table A**). There was consistent dose dependent increase across the DRX arms compared to placebo but the changes in mean were small and of low clinical significance even considering the upper standard deviation values.

4.5.2 Pooled OLE safety population (no placebo comparator)

Shifts in liver analytes by cut-off levels for the OLE pool are shown in **Table 9**. While elevations in bilirubin of >2x ULN occurred, none were associated AT levels >3x ULN. Thus, none had the potential to fulfill Hy's law. The data show higher incidences in ALT, ALP, and bilirubin increases with 12 mg BID compared to 8 mg BID, but the incident increases were small. ALT ≥3x ULN was the only cut-off criterion to reach a change of 1% higher with 12 mg BID. All other differences were less than 0.7%.

Table 9: Liver test elevations in pooled OLE. Yellow highlighted percentages indicate higher rates for 12 mg BID versus 8 mg BID by more than 0.1%.³⁵

³⁵ [NDA217900 \(217900 - 0007 - \(7\) - 2023-11-22 - ORIG-1 /Clinical/Safety Update\) - 120 Day Safety Update Report \(#93\)](#)

Clinically Significant Liver Function Result	Total Deuruxolitinib	12 mg BID Deuruxolitinib	8 mg BID Deuruxolitinib	8 mg BID to 12 mg BID
ALT $\geq 3 \times$ ULN	16 (1.1%)	12 (1.8%)	3 (0.8%)	1 (0.2%)
ALT $\geq 5 \times$ ULN	3 (0.2%)	2 (0.3%)	0	1 (0.2%)
AST $\geq 3 \times$ ULN	24 (1.6%)	11 (1.6%)	7 (1.9%)	6 (1.4%)
AST $\geq 5 \times$ ULN	9 (0.6%)	3 (0.4%)	2 (0.5%)	4 (1.0%)
ALT or AST $\geq 3 \times$ ULN	35 (2.3%)	19 (2.8%)	10 (2.7%)	6 (1.4%)
ALT or AST $\geq 5 \times$ ULN	11 (0.7%)	5 (0.7%)	2 (0.5%)	4 (1.0%)
ALP $\geq 1.5 \times$ ULN	3 (0.2%)	2 (0.3%)	0	1 (0.2%)
ALP $\geq 2 \times$ ULN	1 (<0.1%)	1 (0.1%)	0	0
Bilirubin $\geq 1.5 \times$ ULN ¹	56 (3.8%)	24 (3.6%)	15 (4.0%)	16 (3.8%)
Bilirubin $\geq 2 \times$ ULN	12 (0.8%)	6 (0.9%)	1 (0.3%)	5 (1.2%)

4.6 CPK and Liver Analyte Change in Pooled Analyses and Exposure Adjusted

CPK elevations occurred at rates higher than liver analyte elevations for pooled placebo-controlled and pooled OLE analyses (**Table 10**). Exposure adjusted rates of CPK and liver enzyme elevations do not suggest a dose dependency. CPK elevations suggest myopathies that could cause AT elevations, particularly AST, without liver harm or risk. Indeed, myopathy was the more likely diagnosis in several cases of potential liver injury assessed in Section 4.7 below.

Table 10. Exposure adjusted estimates of liver enzyme elevations in the 24-week, placebo-controlled and open label extension pools.³⁶

	Week 0-24 Placebo Controlled Period						Week 0-52 Long Term Exposure Safety Pool			
	PBO (N = 299, PYE = 132.3)		DEURUX 8 mg BID (N = 640, PYE = 278.9)		DEURUX 12 mg BID (N = 380, PYE = 169.8)		DEURUX 8 mg BID (N = 868, PYE = 665.5)		DEURUX 12 mg BID (N = 991, PYE = 679.8)	
	n (%) [EAIR]	PY	n (%) [EAIR]	PY	n (%) [EAIR]	PY	n (%) [EAIR]	PY	n (%) [EAIR]	PY
CPK increased	3 (0.9) [2.3*]	131.3	22 (3.4) [8.0*]	274.6	21 (5.8) [12.8*]	164.2	34 (3.9) [5.2*]	648.8	36 (3.6) [5.5*]	654.2
Liver enzyme elevations	0	132.3	2 (0.3) [0.7*]	278.2	2 (0.3) [1.2*]	169.1	4 (0.5) [1.4]	663.5	7 (0.7) [1.2]	675.5
Drug-induced liver injury	0	132.3	0	278.9	0	169.8	0	665.5	0	679.8

4.7 Adverse Event Analysis

The statistical analysis plan (SAP) for the Integrated summary of safety lists “*liver enzyme elevations*” based on a customized MedDRA query (that does not differentiate between ALT and AST elevations) and drug-induced liver injury based on the preferred terms “*Drug induced liver injury*” as a treatment emergent adverse event of special interest (TEASI). The exposure adjusted incidence rates for these TEASIs were calculated.

The crude incidence shown in **Table 11** shows a greater rate of liver enzyme elevations with the DRX exposed subjects compared to those on placebo but not clearly different between the 2 doses studied. There were no investigator reported DILI TEASIs.

³⁶ Adapted by DILI Team from [NDA217900 \(217900 - 0030 - \(30\) - 2024-03-22 - ORIG-1 /Clinical/Response To Information Request\) - Response to Clinical Information Request dated 11 March 2024 \(#9\)](#)

Table 11. Incidence of Treatment Emergent Adverse Events of Special Interest (Placebo Controlled Safety Pool)

Category	Placebo (N = 299) n (%)	CTP-543 8 mg BID (N = 640) n (%)	CTP-543 12 mg BID (N = 380) n (%)	Total CTP-543 (N = 1020) n (%)
Liver enzyme elevations	0	3 (0.5)	3 (0.6)	6 (0.6)
Drug-induced liver injury	0	0	0	0

4.8 Case level Assessment for DILI

4.8.1 Sources of Cases: The DILI Team assessed subjects with ATs > 5x ULN, across the phase 2 and 3 trials. There were no cases with TB >2x ULN associated with TAs >3x ULN. Cases were identified via the DILI Team's own eDISH plotting for Studies 3001, 3002 and the ISS (plots not shown), as well as from the following sources:

1. Integrated Summary of Safety Figures "*Ratio to ULN for liver function tests over time for subjects with possible DILI*" for studies 2001, 2002, 2003, 2004 Part A, 3001, 3002, 50001 and 5002 submitted with the original NDA (S000-7/28/2023).
2. 120 Day Safety Update Figures "*Ratio to ULN for liver function tests over time for subjects with possible DILI*" for studies 5001 and 5002 submitted in the Clinical Safety Update (S007-11/22/2023)
3. Response to March 12, 2024, Information request (S31 – 3/26/2024). The data for all these subjects is not complete and a response to an information request made on March 25, 2024, is still outstanding.

Based on the above data sources, we found and assessed fourteen cases of liver injury for potential DILI due to DRX. Of the fourteen, we did not consider any as probable (at least 50% likelihood) of DILI due to DRX. We considered two as possible. The remaining twelve were deemed unlikely, with myopathy being the most common alternative diagnosis (**Table 12**).

Table 12: Case Level Assessments for Fourteen Subjects with TAs >5x ULN from Phase 2 and 3 studies.³⁷ Causality score of 4 means possible DILI (25% to 49% estimated likelihood) while 5 means unlikely DILI (<25% likelihood of DILI).

³⁷ Table made by DILI Team

#	ID	Causality Score*	Alternate diagnosis	Study or Studies	Age (y)	Sex	Race	Hy's Law	Latency from drug start (d)	Latency from drug stop (d)^~	CPK (U/L)**	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)^	Bilirubin peak (mg/dL)	R value peak
1	(b) (6)	4	MASLD	CP543.2004/CP543.5001	26	F	Asian	No	168	[261]	170	192	74	104	0.63	5.6
2		4	Gallstones	CP543.2002	42	M	White	No	83	[83]	214	339	79	104	0.41	10.0
3		5	Myopathy	CP543.3002/CP543.5002	31	M	White	No	313	[9]	21424	73	250	104	0.65	2.1
4		5	Myopathy	CP543.5001	25	M	White	No	364	[6]	40000	357	1203	104	0.55	10.5
5		5	Myopathy	CP543.3001/CP543.5001	18	M	White	No	81	[437]	11615	152	213	104	0.53	4.5
6		5	Myopathy	CP543.2001/CP543.5001	19	F	Asian	No	226	[412]	6180	34	99	104	0.42	1.0
7		5	Myopathy	CP543.2001/CP543.5001	41	F	Asian	No	1261	[175]	40000	158	330	104	0.30	4.6
8		5	Myopathy	CP543.3002	32	M	Asian	No	114	[56]	30008	107	308	104	0.71	3.1
9		5	Myopathy	CP543.3001	24	M	White	No	112	[60]	17622	111	338	105	0.98	3.2
10		5	Myopathy	CP543.2004	24	M	White	No	14	[154]	27742	108	304	104	0.62	3.2
11		5	Myopathy	CP543.5001				No	28	[448]	16709	168	38	104	0.44	4.9
12		5	COVID-19 vaccine	CP543.2004	30	F	White	No	198	[193]	168	442	278	104	0.82	13.0
13		5	Methlyphenidate	CP543_2001	18	M	White	No	28	[140]	101	347	140	111	0.20	9.6
14		5	Unknown	CP543.3001/CP543.5001	34	F	White	No	565	[22]	64	244	151	104	0.46	7.2

MASLD = metabolic dysfunction associated steatotic liver disease

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

** CPK level coincident with peak ALT or AST

^For purposes of R-value calculations, the ULNs were imputed if ALT, AST or AP did rise above the ULN

^^ Subject had two elevations in TAs. Data shown in table are for the first enzyme elevations. Peak ALT on second injury was 271 U/L and AST 112 U/L, ALP 98, TB 0.47

~Bracketed [] day values means the drug continued for that many days after injury onset.

R-value = (ALT/ULN) + (AP/ULN) or (AST/ULN) + (AP/ULN); hepatocellular: R-values ≥ 5; mixed: 2-5; cholestatic: R-value < 5

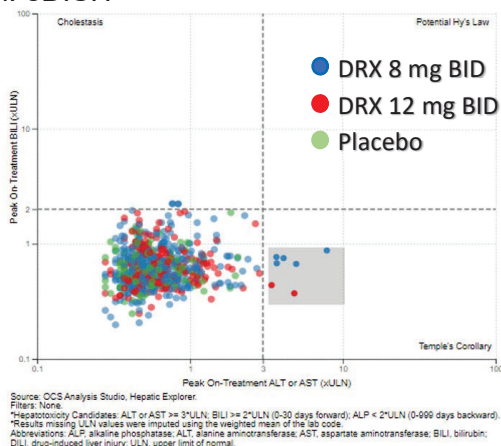
ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL

4.8.2 Case Level Analyses of Temple's Corollary Subjects from Studies 3001 and 3002.

Because myopathy was such a common alternative diagnosis for subjects with ATs >5x ULN, we looked for myopathy amongst the subjects with ATs >3x and <5x ULN that might explain the imbalance in Temple's Corollary quadrants for the two Phase 3 trials. Again, there were no cases plotting to the Potential Hy's Law quadrant in either study. Of the eight Temple's Corollary subjects on DRX with ATs between 3x and 5x ULN, seven were clearly attributable to myopathy with towering CPK levels and modest AST elevation by line graph analyses (**Figure 8**). Only one subject ((b) (6)) did not have concurrent CPK rise, and we assessed this case as indeterminate after review of the narrative. This subject had a modest and temporary rise in ALT early in DRX exposure that was unexplained. DRX was not stopped. Based on these additional case analyses, myopathy explains the imbalance in Temple's Corollary quadrant.

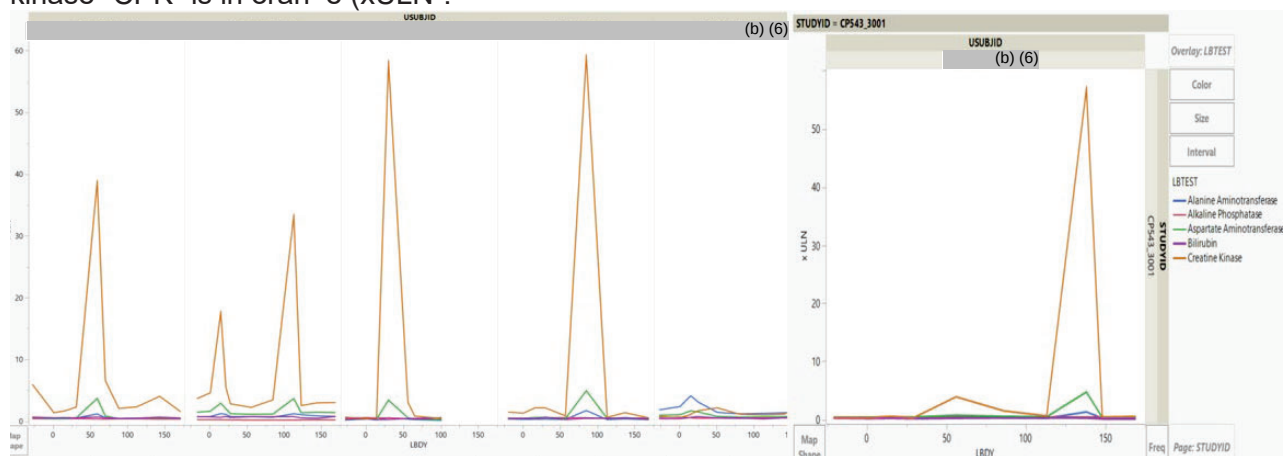
(a) Study 3001

i. eDISH



We already adjudicated Subject (b) (6) with ALT or AST >5x ULN (furthest to the right in Temple's Corollary) as unlikely DILI, and more likely myopathy (see **Table 12**, above). Liver analytes and CPK levels are plotted below (ii) for the remaining six in Temple's Quadrant.

ii. Liver analytes and CPK line graphs for six subjects with ATs between 3x and 5x ULN. Creatine kinase CPK is in orange (xULN).

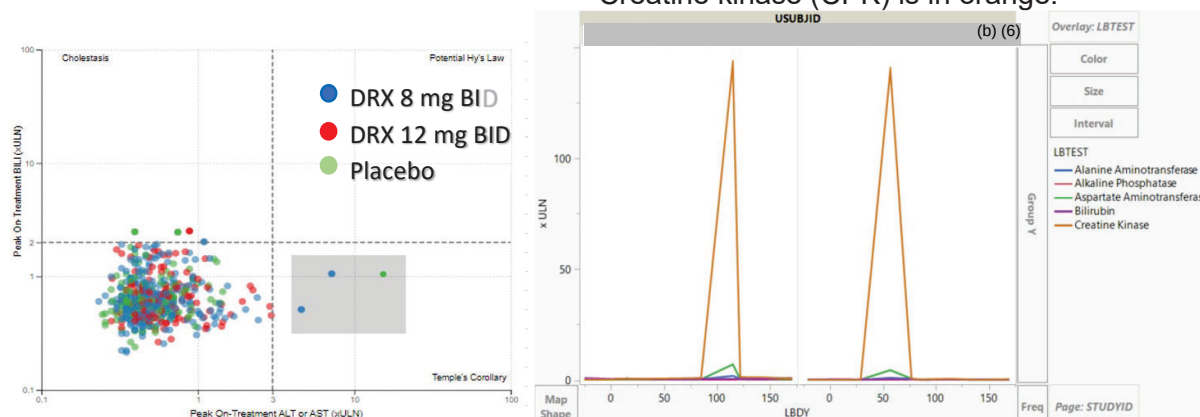


LBDY = lab draw study day

(b) Study 3002

i. eDISH

ii. Liver analytes and CPK line graphs for two subjects on DRX with ATs between 3x and 5x ULN. Creatine kinase (CPK) is in orange.



LBDY = lab draw study day

Figure 8: Hepatocellular DILI Screening Plots (eDISH) and pertinent analyte line graphs for (a) Study 3001 and (b) Study 3002.³⁸

5.0 Assessment & Recommendations

5.1 Assessment: Deuruxolitinib (DRX) is an oral small molecule, JAK 1 and 2 inhibitor. It is structurally the same as the already marketed JAK 1 and 2 inhibitor, ruxolitinib, except for the replacement of eight hydrogen atoms (¹H) with deuterium (²H) (deuteration). This DRX application is for the treatment of alopecia areata (AA). Ruxolitinib is approved for myelofibrosis and graft versus host disease, but not AA. Elevation in aminotransferases (AT) occurred more frequently in the DRX treatment arms compared to placebo, and the

³⁸ Figures made by DILI Team using Analysis Studio <https://analysis-studio.fda.gov/>

Division of Dermatology and Dentistry requested our help with analyzing the potential risk to the liver and labeling.

Non-clinical data do not suggest a significant liver injury risk based on ADME, in vitro, and animal data. Indeed, DRX's LogP, a measure of lipophilicity, is lower at 0.5 compared to ruxolitinib at 2.48 and the DRX dose is also lower. Higher lipophilicity and dose are associated with increased liver injury risk. Clinical data do not support a substantial liver injury risk either. While there were more AT elevations in subjects taking DRX, the elevations were often mild, mainly AST, and often resolved without stopping DRX suggesting either unrelatedness to DRX or DILI adaptation. We found no ATs rising over 450 U/L. There were no cases of jaundice associated with AT elevations and thus no Hy's Law cases. Moreover, case level analyses suggest the AT elevation imbalance was due to concurrent myopathy (high CPK levels with concurrent AT increases), not DILI. We assessed 22 cases, fourteen DRX exposed subjects with AT >5x ULN across the phase 2 and 3 studies, and eight cases with ATs between 3x and 5x ULN in the Phase 3 randomized controlled trials. None of the 22 were considered probable DILI due to DRX, and only two were considered possible. In sixteen of 22, myopathy was clearly the more likely cause of AT elevation with high CPK levels and AST being higher than ALT. Therefore, myopathy completely explains the imbalance seen in the eDISH plots for the phase 3 studies. In the pooled, 24-week placebo-controlled data, there was a higher exposure adjusted incidence of CPK elevation with DRX compared to placebo. Therefore, we do not see a liver injury risk that would preclude approval.

In terms of labeling, the closely related (non-deuterated) ruxolitinib has no highlighted Warnings and Precautions but describes more marked ALT elevations in Section 6 compared to what we see with DRX. Deuteration, while relatively new to drug development, is reported to have favorable changes in pharmacokinetic parameters such as absorption, metabolism, lipophilicity, and albumin binding.³⁹ Such changes are attributed to shortening and strengthening of carbon-hydrogen bonds, which, in turn, may lead to conformational and metabolic pathway changes. The Agency has approved at least one deuterated medication, deutetrabenazine, for Huntington's Chorea. We were unable to do a detailed comparison of PK and metabolites between DRX and ruxolitinib, but as noted above, lipophilicity is less with DRX which could lower the risk of DILI. Also, DRX deuteration may provide more sustained JAK inhibition by avoiding heavy oxidation of the cyclopentyl ring, the location of all eight deuterium atoms, thus implying a lower dose could suffice. The proposed labeling dose for DRX is 8 mg twice daily without mention of dose increase. Ruxolitinib is not approved for AA, but *starting* doses for its target diseases are five mg twice daily to 20 mg twice daily.

Based on the non-clinical, clinical study level and subject level data, we do not think labeling needs to discuss liver enzyme elevations that is out of the context of myopathy which can lead to AT elevations. However, hepatitis B reactivation risk should be addressed in labeling Section 5.0 as it is with ruxolitinib. Subjects positive for hepatitis B surface antigen were excluded from the pivotal DRX trials, so reactivation was not addressed in this NDA. Reactivation can be life-threatening and has been associated with

³⁹ Di Martino, RMC, et al. Deuterium in drug discovery: progress, opportunities and challenges. Nature Reviews Drug Discovery. Deuterium in drug discovery: progress, opportunities, and challenges. Nat Rev Drug Discov 22, 562–584 (2023). <https://doi.org/10.1038/s41573-023-00703-8>

JAK inhibitors, particularly ruxolitinib. Therefore, DRX labeling should discuss hepatitis B reactivation risk similar to ruxolitinib due to their close chemical structure, same mechanism of action, reported risk with ruxolitinib, and lack of data to suggest a lower risk with DRX.

5.2 Recommendations:

1. Do not preclude approval for DILI risk.
2. No need for hepatotoxicity or liver enzyme elevation discussion in sections 5 or 6 outside of the context of myopathy that can increase liver enzymes.
3. Discuss risk of hepatitis B reactivation in Section 5.0 of the label. The label should recommend screening for hepatitis B infection prior to starting DRX and following clinical guidelines or seeking hepatology consultation if hepatitis B infection is discovered.
4. Routine monitoring of liver analytes is not necessary.

**Eileen E. Navarro
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Director, DHN
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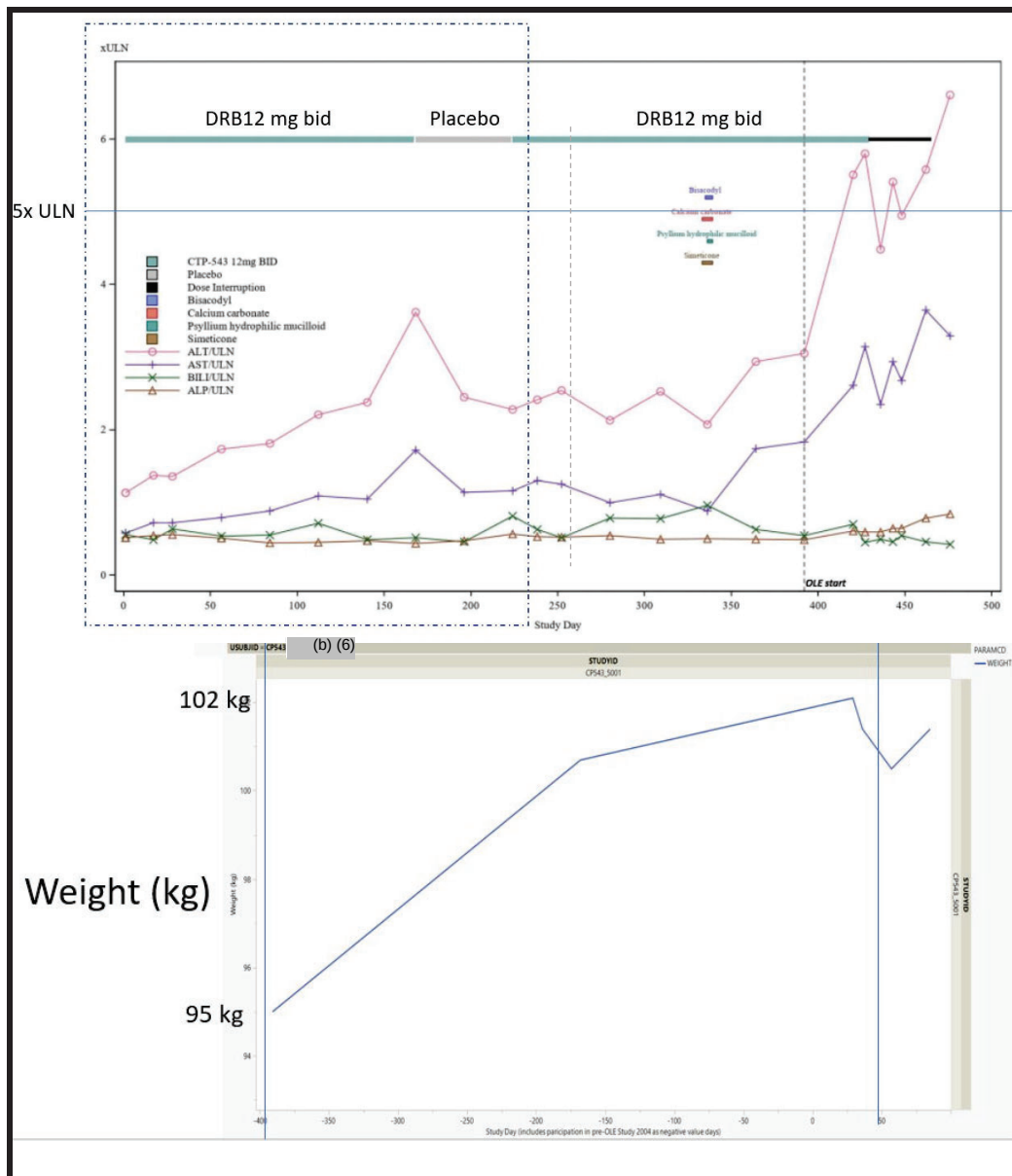
1 **Appendix: Mean Change in liver analytes and two cases of possible DILI due to DRX**

2 **Table A:** Mean (SD) change from Baseline in ALT, AST, and ALP by treatment arm in the Placebo-Controlled Safety Pool.⁴⁰

Week	PLACEBO N=299	8 MG N=640	12 MG N=380	All DRX N=1020
ALT in U/L				
2	0 (11)	0.5 (11.5)	2 (9.3)	1.1 (10.7)
4	-0.1 (8.2)	1.0 (10.4)	2.5 (9.0)	1.6 (9.9)
8	0 (9.1)	1.0 (13.3)	1.8 (9.0)	1.3 (11.9)
12	-0.5 (9.0)	0.8 (13.4)	1.7 (9.1)	1.1 (12.0)
16	-0.2 (8.8)	0.7 (13.0)	1.8 (11.0)	1.2 (12.3)
20	-0.1 (9.0)	0.6 (13.6)	1.7 (10.1)	1.0 (12.4)
24	-0.6 (9.8)	1.3 (14.3)	2.2 (11.6)	1.6 (13.4)
AST in U/L				
2	0.2 (12.9)	1.1 (16.0)	2.8 (5.7)	1.8 (13.4)
4	-0.6 (12.2)	1.1 (15.6)	3.2 (8.8)	1.9 (13.5)
8	-0.6 (12.7)	1.5 (18.1)	2.4 (6.1)	1.8 (14.8)
12	-1.1 (12.5)	1.4 (18.2)	2.6 (6.2)	1.9 (14.8)
16	-0.6 (12.9)	1.3 (16.7)	2.7 (7.1)	1.8 (13.9)
20	-0.4 (12.8)	1.1 (16.9)	3.0 (8.1)	1.8 (14.2)
24	-0.8 (13.0)	1.8 (17.5)	3.3 (7.4)	2.4 (14.6)
ALP in U/L				
2	-0.6 (5.8)	-1.3 (7.2)	-1.6 (6.9)	-1.4 (7.1)
4	-0.5 (6.0)	-2.8 (7.5)	-3.3 (8.4)	-3.0 (7.8)
8	-0.6 (6.9)	-4.1 (8.5)	-6.2 (7.9)	-4.9 (8.3)
12	-0.5 (7.5)	-5.5 (8.7)	-7.9 (8.9)	-6.4 (8.9)
16	-0.1 (7.2)	-6.0 (8.6)	-8.0 (10.1)	-6.8 (9.3)
20	-0.0 (7.8)	-6.3 (9.2)	-8.9 (9.8)	-7.3 (9.5)
24	-1.0 (8.0)	-6.8 (9.0)	-8.8 (10.8)	-7.6 (9.8)

3 Table made by DHN DILI Team, as compiled from sponsor's Tables 5.1.2.1 to 5.1.2.9, ISS, S000

⁴⁰ [NDA217900 \(217900 - 0001 - \(1\) - 2023-07-28 - ORIG-1 /Multiple Categories/Subcategories\) - Integrated Summary of Safety - Tables Post-Text \(#4293\)](#)



Subject (b) (6): Possible DILI due to DRX.

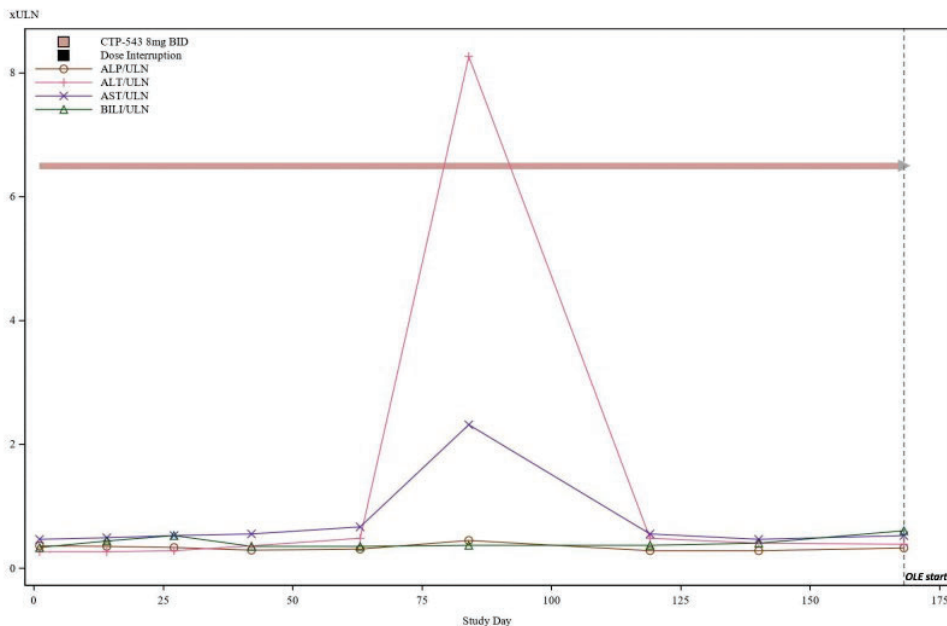
This 25-year-old Asian female enrolled in Study (b) (6) and was randomized to 12 mg BID in Part A. Medical history included obesity, seizure eczema, asthma, dysglycemia and elevated liver enzymes since (b) (6). She was on herbals (not otherwise specified), probiotics, fish oil, fluoxetine, COVID vaccine (b) (6), (b) (6) fexofenadine.

In Part A Period 1 on 12 mg BID from (b) (6) (day 168).

She was on placebo in Period 2 from (b) (6) (Day 224). In part B she resumed 12 mg BID (b) (6) Day 392).

There was no intervening event. She was asymptomatic.

Assessment: We assessed this case as possible DILI due to DRX. While the course of liver enzymes hint at possible positive rechallenge, the subject started with a BMI of 39 kg/m² and gradually increased her weight by 7 kg (15.4 lb.) over the trials. There were no follow-up liver analytes to assess for dechallenge. TB remained normal throughout.



Visit	Creatine Kinase (U/L)	ALT (U/L)	AST (U/L)	ALP (U/L)	Total Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)	Creatinine (mg/dL)
Screening	79 (Normal)	10 (Normal)	15 (Normal)	39 (Normal)	0.7 (Normal)	0.12 (Normal)	1.02 (Normal)
Baseline 8 mg BID	07 (Normal)	11 (Normal)	16 (Normal)	43 (Normal)	0.38 (Normal)	0.06 (Normal)	0.93 (Normal)
Week 2	170 (Normal)	11 (Normal)	17 (Normal)	42 (Normal)	0.49 (Normal)	0.08 (Normal)	1.04 (Normal)
Week 4	154 (Normal)	12 (Normal)	18 (Normal)	40 (Normal)	0.59 (Normal)	0.09 (Normal)	0.98 (Normal)
Week 6	371 (High)	15 (Normal)	19 (Normal)	35 (Low)	0.39 (Normal)	0.06 (Normal)	1.07 (Normal)
Week 8	218 (High)	20 (Normal)	23 (Normal)	37 (Normal)	0.39 (Normal)	0.06 (Normal)	1.06 (Normal)
Week 12	214 (High)	339 (High)	79 (High)	53 (Normal)	0.41 (Normal)	0.07 (Normal)	1.25 (Normal)
Week 16	150 (Normal)	20 (Normal)	19 (Normal)	34 (Low)	0.41 (Normal)	0.07 (Normal)	1.19 (Normal)
Week 20	136 (Normal)	17 (Normal)	16 (Normal)	34 (Low)	0.45 (Normal)	0.07 (Normal)	1.04 (Normal)
Week 24	144 (Normal)	16 (Normal)	18 (Normal)	39 (Normal)	0.67 (Normal)	0.1 (Normal)	1.11 (Normal)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase

Subject (b) (6): Possible DILI due to DRX.

2002 8 mg BID, OLE pending.

This 42-year-old White male enrolled into study (b) (6) and randomized to receive DRX 8 mg BID. Medical history includes hypercholesterolemia, sinus bradycardia. Morphine and oxycodone were received for one day in (b) (6) after the hepatic event. DRX 8 mg BID initiated on (b) (6) (Day 167).

On (b) (6) (Day 82) he developed a TEAESI of ALT (9.97XULN) and AST (2.3XULN) elevation that resolved at the next scheduled visit (34 days) (b) (6).

(b) (6) Evaluation testing was not performed. Drug continued and he entered the OLE.

Assessment: We assessed this case as possible DILI due to DRX. CPK elevation is not concordant nor high enough to explain the ALT of 339 U/L without concurrent AST elevation. If this is DILI, then adaption occurred. Passage of stone could appear this way, but the subject was asymptomatic and there was no imaging done. TB remained normal throughout.

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/s/

PAUL H HAYASHI
04/15/2024 06:37:52 PM

CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA

Consultant Reviewer:	Zimri Yaseen, MD, Senior Physician, ON/DP
Consultation Requestor:	Qianyiren Song
Subject of Request:	NDA 217900; deuruxolitinib for the treatment of moderate to severe alopecia areata
Date of Request:	October 24, 2023
Date Received:	October 25, 2023
Desired Completion Date:	March 21, 2024

I. Background

The Applicant, Sun Pharmaceutical Industries, Inc., has developed deuruxolitinib, a Janus kinase inhibitor (hereafter JAK inhibitor), for treatment of moderate-to-severe alopecia areata (AA), and is seeking marketing approval under NDA 217900.

During the development program one subject died by suicide.

The NDA is supported by two 24-week pivotal trials. During the 24-week pivotal trials, investigators administered the Hospital Anxiety and Depression Scale (HADS), at Baseline and at Week 24 (end of treatment). There were no active assessments for anxiety, depression, or suicidal ideation and behavior during the extension trials. However, subjects were excluded from enrollment in all trials who had “Clinically significant medical condition, psychiatric disease, or social condition.”

The Division of Dermatology and Dentistry (DDD) requested a consult to the Division of Psychiatry (DP) to evaluate the significance of this suicide in the context of the Hospital Anxiety and Depression Scale (HADS) data available from the two the 24-week pivotal trials conducted in support of this NDA, provide recommendations for labeling, and attend milestone meetings.

II. Review of the Fatal Suicide AE

The case of suicide death occurred on Day 58 of the open-label extension (OLE) trial CP543.5001, approximately 2 weeks after the subject discontinued the study product, according to investigator instructions, due to a COVID-19 infection. The decedent was a 34-year-old male subject (subject (b) (6)) with a history of attention-deficit/hyperactivity disorder, hypertension, gastroesophageal reflux disease, and allergic rhinitis who received deuruxolitinib 8 mg BID in Study CP543.3001 and continued treatment in the OLE CP543.5001 for approximately 6 more weeks. Relevant concomitant medications included dextroamphetamine-amphetamine, lisinopril, omeprazole, cyanocobalamin and cholecalciferol, ascorbic acid, ibuprofen, and diphenhydramine. Per the coroner’s report, the cause of death was ascribed to asphyxia due to hanging, and the toxicology report was positive for diphenhydramine (but not dextroamphetamine, amphetamine, or their metabolites). In the investigator’s opinion, the

suicide was not related to the use of study drug, but possibly due to paranoia, relationship issues, and an ongoing lawsuit, as noted in the autopsy report. Neither suicidal ideation nor any psychiatric TEAEs were reported for this subject during his participation in the clinical trials (CP543.3001 and CP543.5001). Review of the coroner's report (SN#0006; <\\CDSESUB1\EVSPROD\nda217900\0006\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5352-stud-rep-uncontr\cp543-5001\narratives\cp543-5001-coroners-report.pdf>) did not provide additional information.

Clinical Reviewer Comment: In the case of the individual suicide, it is noted that this subject reported external stressors and, consistently therewith, had a clinically significant worsening of HADS total score from baseline (total score 9 (borderline)) to Month 6 (total score 16 (abnormal) with higher baseline and Month 6 anxiety scores than depression scores). No depression or anxiety-related AE was reported, however. He was also, at least subjectively, a non-responder to treatment based on his “minimally improved” Month 6 rating of the Patient Global Impression of Improvement in AA (PGI-I) and had a minimal improvement in satisfaction with eyebrows eyelashes and thickness of hair on scalp from “very dissatisfied” at baseline and most intermediate study visits to “dissatisfied” at Week 24. (Source: reviewer examination of adqsoth.xpt, adcpgi.xpt, and adpro.xpt, respectively.) It cannot be determined if disappointment in this lack of meaningful response to treatment was a contributing stressor motivating suicide for this subject, however the above findings suggest there is no evidence for the IP to have played a direct causal role in his mood being worse at Month 6 than at baseline. External stressors and underlying psychiatric diagnoses or diatheses appear to be the most likely causes of the subject's death by suicide.

III. Review of the Pertinent Aspects of the Study Protocols

Study CP543.3001 entitled *Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata* was a phase 3, international, multicenter randomized, double-blind, parallel arm study comparing 24 weeks of treatment with a fixed dose of deuruxolitinib (either 8 mg BID or 12 mg BID) to placebo. Adult male and female subjects 18 to 65 years of age, inclusive, with a definitive diagnosis of AA and at least 50% hair loss, as defined by a SALT score ≥ 50 who met all of the inclusion criteria and none of the exclusion criteria were eligible to participate in the study. The safety population comprised 705 subjects (350 CTP-543 8 mg BID subjects, 215 CTP-543 12 mg BID subjects, and 140 placebo subjects) Study visits occurred every 2 weeks for the first 4 weeks and monthly thereafter. Study CP543.3002 differed minimally in design. Each study was followed by an open label extension study lasting to 212 Weeks with study visits occurring every 8 weeks.

A. Inclusion and Exclusion Criteria Pertinent to Subject Mental Health

The Applicant's exclusion criteria for Studies 3001 and 3002 include the following:

- Abnormal levels of thyroid stimulating hormone at Screening
- History of alcohol, medication, or illicit drug abuse within 1 year before the first dose of study drug.

- Use of strong CYP3A4 inducers (such as, but not limited to barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, ..., St. John's Wort...)
- Clinically significant medical condition, psychiatric disease, or social condition, as determined by the Investigator, that may unfavorably alter the risk-benefit of study participation, adversely affect study compliance, or confound interpretation of study results.

The Applicant's exclusion criteria for open label extension Studies 5001 and 5002 include the following:

- Any medical, psychiatric, or social condition that is likely to unfavorably affect the risk-benefit of continued study participation, interfere with study compliance, or confound safety or efficacy assessments.

B. Psychiatric Safety Monitoring and Stopping Criteria

- There were no psychiatric stopping criteria specified in the study protocols. Psychiatric safety monitoring comprised general AE monitoring at study visits, which occurred every two to four weeks from baseline to Week 24. The HADS was the only psychiatric assessment tool included in the study. As this was administered at baseline and Week 24 only it did not serve a monitoring purpose.

Clinical Reviewer Comment: There is no known safety signal for JAK inhibitors or hypothesis in the current scientific literature to motivate enhanced safety monitoring for psychiatric conditions. Study visit frequency was comparable to or greater than typical outpatient psychiatric management visit frequency and allowed for reasonable opportunity for capture of psychiatric AEs. For these reasons, we consider the Study protocols to be acceptable from a psychiatric perspective and appropriate for a non-psychiatric population.

IV. Review of Study Data (HADS)

The HADS is patient-rated clinical outcome assessment comprised of seven items assessing anxiety (HADS-A) and seven items assessing depressive symptoms (HADS-D). Each item is rated on an anchored 0 to 3 Likert scale, yielding a score range of 0 to 21 for each subscale and 0 to 42 for the total score. There is no specified recall period and items appear to refer to a general current state (e.g., "Worrying thoughts go through my mind"). The HADS has been "found to perform well in assessing the symptom severity and caseness of anxiety disorders and depression in both somatic, psychiatric and primary care patients and in the general population."¹ It is therefore a reasonable safety monitoring instrument for anxiety and depression in a study population such as the that involved in the NDA-supporting studies reviewed here. Estimates of

¹ Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *Journal of psychosomatic research*, 52(2), 69-77.

the Minimal Clinically Important Difference on the HADS range from approximately 0.8 to 5.2 points on the anxiety subscale and 0.5 to 5.6 points on the depression subscale.²

Because the results of the two registration trials were qualitatively similar, the pooled results are discussed below. Likewise, because the subscale score findings were similar within and between trials, for simplicity only the total score results are discussed. These results are shown in Table 1, below. In addition, shifts from scores categorized on the HADS as normal to borderline and/or to abnormal and the incidences of moderate to large (≥ 6 and ≥ 4 point) shifts in HADS scores was examined. In general, no meaningful nor nominally significant differences between active treatment arms and placebo arms in rates of clinically significant worsening from baseline were observed.

² Lemay, Kyle R. BSc; Tulloch, Heather E. PhD; Pipe, Andrew L. MD; Reed, Jennifer L. RKin, PhD. Establishing the Minimal Clinically Important Difference for the Hospital Anxiety and Depression Scale in Patients with Cardiovascular Disease. *Journal of Cardiopulmonary Rehabilitation and Prevention* 39(6):p E6-E11, November 2019. | DOI: 10.1097/HCR.0000000000000379

Table 1. Mean and mean change from baseline in HADS total score, Efficacy Population with observed HADS scores at Baseline and Week 24

Parameter Visit [1]	Pooled				
	Placebo	CTP-543 8 mg BID	CTP-543 12 mg BID	CTP-543 Total	Total
Statistic	(N=267)	(N=600)	(N=342)	(N=942)	(N=1209)
Baseline					
n	246	546	320	866	1112
Mean	9.8	10.2	9.9	10.1	10.0
SD	6.81	6.86	6.61	6.77	6.77
Median	8.0	9.0	9.0	9.0	9.0
Minimum	0	0	0	0	0
Maximum	36	33	35	35	36
Week 24					
n	246	546	320	866	1112
Mean	8.7	8.1	7.7	8.0	8.1
SD	6.45	6.12	6.07	6.10	6.19
Median	7.0	7.0	6.0	7.0	7.0
Minimum	0	0	0	0	0
Maximum	30	35	34	35	35
Change from Baseline					
n	128	318	200	518	646
Mean	-1.0	-1.8	-2.2	-2.0	-1.8
SD	5.00	5.44	5.27	5.37	5.31
Median	-1.0	-1.0	-1.0	-1.0	-1.0
Minimum	-19	-22	-22	-22	-22
Maximum	16	16	12	16	16

BID = twice daily; HADS = Hospital Anxiety and Depression Scale; SD = standard deviation

NOTE: HADS-A and HADS-D total scores are reported as collected. HADS total score is derived as the sum of HADS-A and HADS-D scores. In alignment with study-level analyses, only subjects with a baseline score and a Week 24 score are included. Program: t-hads-tot-ir.sas 2023-12-15T13:30

Source: Applicant provided table with minor formatting changes by Clinical reviewer.

Clinical Reviewer Comment: The review of HADS data from the registration trials did not indicate any negative effect of CTP-543 on mood as assessed by the HADS. Indeed, there is a potential signal for a positive effect on subject mood as assessed by HADS, but this effect could be confounded by its observation in a completers analysis. If the observed signal represents a true treatment effect, that effect could be mediated by neurobiological effects of JAK inhibition³ or by therapeutic effects on severity of alopecia areata, which condition can be expected to be a source of distress and thus potential negative mood symptoms, such that symptomatic improvement in alopecia might result in improved mood for some subjects. Adjudication of these issues is beyond the scope of this consult. In conclusion, regarding the HADS data, there is no indication that the investigational product would increase risk for suicidal ideation or behavior by increasing negative mood symptoms. Although the potential for a positive effect on mood suggests a correlate hypothetical possibility that discontinuation of CTP-543 could worsen mood, there is no evidence of this having been the case for subject (b) (6).

V. Review of Pooled Safety Data

To further evaluate potential adverse mood effects of CTP-543, which, if present, would indicate a potential for this product to increase risk for suicidal ideation or behavior, custom MedDRA queries were used to capture pertinent treatment emergent AEs reported in the placebo-controlled safety and efficacy trials submitted to the NDA. Analysis of these events in placebo-controlled safety and efficacy trials submitted to the NDA is presented in Table 2, below. The results show that treatment-emergent fatigue, and depression and anxiety adverse events were all more common in placebo treated subjects than subjects treated with CTP-543. This finding is consistent across CTP-543 doses and studies, with the exception of depression and anxiety events in the small Phase 2 Study 2001, which were more frequent in CTP-543 treated subjects.

Clinical Reviewer Comment: The results of the grouped TEAE analyses suggest that CTP-543 has no or a modest protective effect with respect to negative mood symptoms in the alopecia areata population.

³ Shariq, A. S., Brietzke, E., Rosenblat, J. D., Pan, Z., Rong, C., Ragguett, R. M., ... & McIntyre, R. S. (2018). Therapeutic potential of JAK/STAT pathway modulation in mood disorders. *Reviews in the Neurosciences*, 30(1), 1-7.

Table 2. NDA217900 ISS: Summary of TEAEs by CMQ for the Placebo-Controlled Safety Pool

Grouped Term Preferred Term	Study 2001				Study 3001				Study 3002				Pooled Analysis			
	CTP-543 8mg BID (N=34)	CTP-543 12mg BID (N=36)	Total CTP- 543 (N=70)	Placebo (N=29)	CTP-543 8mg BID (N=350)	CTP-543 12mg BID (N=215)	Total CTP- 543 (N=565)	Placebo (N=140)	CTP-543 8mg BID (N=256)	CTP-543 12mg BID (N=129)	Total CTP- 543 (N=385)	Placebo (N=130)	CTP-543 8mg BID (N=640)	CTP-543 12mg BID (N=380)	Total CTP- 543 (N=1020)	Placebo (N=299)
Fatigue	2 (5.9)	3 (8.3)	5 (7.1)	1 (3.4)	8 (2.3)	9 (4.2)	17 (3.0)	5 (3.6)	16 (6.2)	8 (6.2)	24 (6.2)	6 (4.6)	26 (4.1)	20 (5.3)	46 (4.5)	12 (4.0)
Fatigue	1 (2.9)	2 (5.6)	3 (4.3)	1 (3.4)	6 (1.7)	7 (3.3)	13 (2.3)	2 (1.4)	9 (3.5)	5 (3.9)	14 (3.6)	3 (2.3)	16 (2.5)	14 (3.7)	30 (2.9)	6 (2.0)
Asthenia	0	1 (2.8)	1 (1.4)	0	1 (0.3)	2 (0.9)	3 (0.5)	1 (0.7)	7 (2.7)	3 (2.3)	10 (2.6)	2 (1.5)	8 (1.2)	6 (1.6)	14 (1.4)	3 (1.0)
Hypersomnia	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0	0	0	0	1 (0.2)	0	1 (0.1)	0
Somnolence	1 (2.9)	0	1 (1.4)	0	0	0	0	1 (0.7)	0	0	0	1 (0.8)	1 (0.2)	0	1 (0.1)	2 (0.7)
Lethargy	0	0	0	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0	1 (0.3)
Depression/Anxiety	1 (2.9)	4 (11.1)	5 (7.1)	0	8 (2.3)	1 (0.5)	9 (1.6)	5 (3.6)	7 (2.7)	3 (2.3)	10 (2.6)	5 (3.8)	16 (2.5)	8 (2.1)	24 (2.4)	10 (3.3)
Anxiety	0	0	0	0	3 (0.9)	0	3 (0.5)	2 (1.4)	2 (0.8)	1 (0.8)	3 (0.8)	0	5 (0.8)	1 (0.3)	6 (0.6)	2 (0.7)
Depression	1 (2.9)	0	1 (1.4)	0	1 (0.3)	1 (0.5)	2 (0.4)	1 (0.7)	3 (1.2)	1 (0.8)	4 (1.0)	2 (1.5)	5 (0.8)	2 (0.5)	7 (0.7)	3 (1.0)
Depressed mood	0	2 (5.6)	2 (2.9)	0	3 (0.9)	0	3 (0.5)	1 (0.7)	1 (0.4)	1 (0.8)	2 (0.5)	0	4 (0.6)	3 (0.8)	7 (0.7)	1 (0.3)
Nervousness	0	0	0	0	0	0	0	0	1 (0.4)	0	1 (0.3)	0	1 (0.2)	0	1 (0.1)	0
Persistent depressive disorder	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0	0	0	0	1 (0.2)	0	1 (0.1)	0
Adjustment disorder	0	0	0	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0	1 (0.3)
Anxiety disorder due to a general medical condition	0	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0	0	0	1 (0.3)
Feeling jittery	0	1 (2.8)	1 (1.4)	0	0	0	0	0	0	0	0	0	0	1 (0.3)	1 (0.1)	0
Grief reaction	0	1 (2.8)	1 (1.4)	0	0	0	0	0	0	0	0	0	0	1 (0.3)	1 (0.1)	0
Intentional self-injury	0	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0	0	0	1 (0.3)
Irritability	0	1 (2.8)	1 (1.4)	0	0	0	0	0	0	0	0	0	0	1 (0.3)	1 (0.1)	0
Panic disorder	0	0	0	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0	1 (0.3)
Stress	0	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0	0	0	1 (0.3)

Source: OCS Analysis Studio, Custom Table Tool.

Columns - Dataset: Demographics; Filter: SAFFL = 'Y', POOL1FL = 'Y'; Column Variable 1: ASTUDYI1 (Analysis Study Integration 1), Column Variable 2: TRTNEW (Treatment Arm New).

Grouped Term Preferred Term - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', APOOL1FL = 'Y', CMQTERM = 'Depression/Anxiety' or 'Fatigue'; Row Variable 1: CMQTERM (CMQ Terms), Row Variable 2: AEDECOD (Dictionary-Derived Term).

Note: Column values of ASTUDYI1 = '2001 Cohort 2' or '2001 Cohort 3' were renamed to 'Study 2001'

VI. Conclusions and Recommendations

The suicide death of subject [REDACTED] (b) (6) does not show evidence of being related to treatment with CTP-543 nor to its discontinuation. There is no evidence in the safety data obtained in the clinical studies submitted to NDA 217900 for CTP-543 to have a meaningful potential to increase risk for suicidal thoughts or behaviors. Standard pharmacovigilance in the post-market setting is appropriate and should be conducted with attention to the potential for the target condition itself, which may be socially embarrassing or stigmatizing, to contribute to background risk.

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/s/

ZIMRI S YASEEN
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03/22/2024 12:10:32 PM

TIFFANY R FARCHIONE
03/22/2024 01:01:34 PM

Clinical Inspection Summary

Date	3/20/2024
From	Stephanie Coquia, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Kapil (Dev) Verma, MD, Clinical Reviewer Melinda McCord, MD, Clinical Team Leader Qianyiren (Cicy) Song, Regulatory Project Manager Division of Dermatology and Dentistry (DDD)
NDA #	217900
Applicant	Sun Pharmaceutical Industries, Inc.
Drug	Deuruxolitinib
NME (Yes/No)	Yes
Therapeutic Classification	Janus kinase (JAK) inhibitor
Proposed Indication	For the treatment of adults with moderate to severe alopecia areata
Consultation Request Date	9/15/2023
Summary Goal Date	4/28/2024
Action Goal Date	7/28/2024
PDUFA Date	7/28/2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Sun Pharmaceutical Industries, Inc., submitted clinical data from Studies CP543_3001 (NCT04518995) and CP543_3002 (NCT04797650) for deuruxolitinib. The proposed indication is for the treatment of adults with moderate to severe alopecia areata (AA).

Four clinical investigators (Drs. Osman, Zirwas, Magnolo, and Tsianakas) and the Sponsor were inspected.

The inspections did not find significant concerns regarding the study conduct, oversight, or management of the clinical trials or Good Clinical Practice (GCP) or regulatory compliance, and based on the results of these inspections, data generated by the inspected clinical investigators and submitted by the Applicant appear acceptable in support of the proposed indication.

II. BACKGROUND

Sun Pharmaceutical Industries, Inc. seeks approval for a new drug application for deuruxolitinib (CTP-543). In support of the NDA, the Applicant submitted clinical data from two phase 3 studies, CP543_3001 and CP543_3002. The following is a summary of the study protocols and key study information relevant to the clinical inspections.

Study Design

Both studies were phase 3, multi-center, randomized, double-blind, placebo-controlled studies of adult subjects with AA and at least 50% hair loss (as defined by a Severity of Alopecia Tool (SALT) score ≥ 50). Subjects were randomized in a 3:5:2 ratio to: CTP-543 12 mg twice a day, CTP-543 8 mg twice a day, or placebo.

The SALT is a measure of hair loss that quantifies the amount of scalp surface without hair. Individual quadrant (right side, top, left side, back) hair-loss scores are multiplied by a quadrant-specific multiplier, reflective of the scalp surface area it contributes, and then added together to obtain the absolute (total) SALT score.

Objectives and Endpoints

The primary objectives of the trials were to assess the efficacy of CTP-543 on regrowth of hair following 24 weeks of treatment and the safety of CTP-543 following 24 weeks of treatment.

The **primary endpoint** was the percentage of subjects achieving an absolute SALT score of ≤ 20 at Week 24.

Key secondary endpoints were:

- The percentage of responders (“satisfied” or “very satisfied”) on the Hair Satisfaction Patient Reported Outcome (SPRO) scale at Week 24
- The percentage of subjects achieving an absolute SALT score of ≤ 20 at Weeks 20, 16, 12, and 8.

Key Eligibility Criteria

- Between 18 and 65 years of age
- Definitive diagnosis of AA with a current episode of scalp hair loss lasting at least 6 months and not exceeding 10 years at the time of Screening. Total disease duration greater than 10 years permitted.
- At least 50% scalp hair loss, as defined by a SALT score ≥ 50 , at Screening and Baseline
- None of the following
 - Hair transplants or use of adhesive wigs during the study
 - Treatment with other medications or agents within 1 month of Baseline or during the study that may affect hair regrowth or immune response
 - Treatment with systemic immunosuppressive medications within 3 months of

Screening or during the study or biologics within 6 months of Screening or during the study

- o Active scalp inflammation, psoriasis, or seborrheic dermatitis, significant trauma to the scalp, or other scalp condition that may interfere with evaluation
- o Moderate to severe androgenic alopecia or female pattern hair loss prior to AA
- o Unable to maintain consistent hair style, products, or treatments or refrain from use of weaves or extensions or shaving scalp
- o History of active tuberculosis (TB) without documentation of successful treatment or a positive TB test at Screening
- o Strong cytochrome P450 3A4 inhibitors and inducers
- o CTP543_3002: Patients with history or family history of major thrombotic events

Study Conduct

For Study CP543_3001, 72 sites randomized at least one subject. The first subject enrolled November 23, 2020. The last subject completed participation on April 19, 2022. A total of 705 subjects received the investigational drug (safety population); 706 subjects were in the efficacy population.

For Study CP543_3002, 63 sites randomized at least one subject. The first subject enrolled June 10, 2021. The last subject completed participation June 29, 2022. A total of 515 subjects received the investigational drug (safety population); 503 subjects were in the efficacy population.

For both studies, an independent Data Monitoring Committee performed regular safety assessments based on review of cumulative safety data.

RESULTS

1. Dr. Lawrence A. Osman (CP543_3001, Site 56)

18546 Roscoe Blvd Ste 306
Northridge, CA 91324-4669

Inspection Dates: December 4 – 7, 2023

This investigator was inspected as a routine PDUFA inspection for Study CP543_3001. This was the first FDA inspection for this investigator.

Subject-related records for the enrolled subjects reviewed included: informed consent forms (ICFs), Investigational Product (IP) accountability records, SALT and SPRO data, and eligibility documentation.

Study-related documents reviewed included: signed investigator agreements, training documentation, the protocol, IRB correspondence, sponsor and monitor correspondence,

financial disclosure forms, IP accountability records, and monitoring reports.

Information in the source documents were consistent with the data submitted in the NDA. There was no under-reporting of adverse events (AEs).

Based on the results of the inspection, data generated at Dr. Osman's site appear acceptable in support of the proposed indication in the NDA.

2. Dr. Matthew J. Zirwas (CP543_3001, Site 57)

2356 E Main Street
Bexley, OH 043209-2422

Inspection Dates: December 4 – 7, 2023

This investigator was inspected as a routine PDUFA inspection for Study CP543_3001. This was the first FDA inspection for this investigator.

There were 28 subjects dosed with the IP. Twenty-four subjects completed all study assessments while four subjects discontinued or withdrew consent. The following subject-related documents were reviewed: SALT and SPRO score reports, subject photographs, AE reports, electronic case report forms (eCRFs), paper worksheets, ECG readings, concomitant medication documentation, laboratory sample shipping documentation, medical records, and progress notes. The source data for all 24 subjects were fully reviewed, except for SPRO where the source data for 10 out of 24 subjects were reviewed.

Study-related documents were also reviewed and included: the protocol, monitoring records, IP accountability records, training logs, signed investigator agreements, and IRB correspondence.

Source documents, including those for the SALT and SPRO assessments, were compared to the data line listings, and there were no discrepancies. No unreported AEs were identified.

Unreported protocol deviations were identified: the same SALT assessor was not used throughout the study for 22 out of 24 subjects. However, for the Week 24 visit, when the primary endpoint was assessed, 23 out of 24 subjects were assessed by the same individual performing their assessment at baseline.

Reviewer comments: Although there was variability in the assessor for each subject throughout the study, at the primary timepoints of interest, Week 24 and baseline, the same assessor was used for all subjects except one, Subject # (b) (6) (assigned to 8 mg arm). Furthermore, the subject consistently showed no response or improvement in SALT score for the entire study period, demonstrating the consistency and validity of the assessments. Both SALT raters at the site were trained and approved by the Sponsor. This specific protocol deviation is unlikely to affect efficacy as there were no responders in the placebo arm (n=5) and there were six responders in the 8 mg arm (n=17) at the site. In response to this observation, the investigator acknowledged responsibility and agreed to make every attempt in the future to have subjects assessed by the same rater.

3. Dr. Nina Magnolo (CP543_3002, Site 155)

Von-Esmarch-Str.58

Muenster, North Rhine-Westphalia, 48149 Germany

Inspection Dates: November 27 – December 1, 2023

This investigator was inspected as a routine PDUFA inspection for Study CP543_3002. This was the first FDA inspection for this investigator.

There were 22 subjects randomized at the site; 21 subjects completed the study (one withdrawal at Week 12). Subject-related records for all subjects were reviewed and included: ICFs, study worksheets, laboratory results, ECG tracings and analysis reports, and documentation related to eligibility, randomization, study completion, efficacy assessments, physical examinations, IP accountability, protocol deviations, and AEs.

Study-related documents reviewed included: the subject screening and enrollment log, IP accountability records, delegation and training logs, monitoring records, financial disclosure forms, and correspondence with the Sponsor, monitors, and the ethics committee.

There were no underreporting of AEs or discrepancies in the efficacy data provided in the NDA.

Subject # (b) (6) (CTP-543 8 mg arm) had unreported protocol deviations related to IP-dosing non-compliance (missed doses or overdoses). This subject had 23 instances of missed IP dosing (1 pill) and approximately 10 instances of over-dosing (1 pill). Only one incident of a missed dose was reported as a protocol deviation. Per the protocol, the contract research organization (CRO) was responsible to record and report any protocol deviations. The study protocol required subject re-training and sponsor notification for any subjects with IP compliance below 80% or over 100%. Because this subject fell outside of this range, she received protocol-specified retraining, and her continued participation was discussed with the Sponsor. The instances of IP non-compliance were recorded elsewhere in the eCRF on the Dosing Exceptions form.

Reviewer comments: Instances of IP dosing non-compliance were to be treated as minor protocol deviations. It was observed that missed doses or overdoses were not always reported as a protocol deviation by the CRO, however, they were recorded elsewhere in the eCRF (Dosing Exceptions). The non-reporting of instances of IP non-compliance as protocol deviations is unlikely to affect study efficacy results for this subject because Subject # (b) (6) (CTP-543 8 mg arm) was not a responder at Week 24 (did not achieve an absolute SALT score of ≤ 20 at Week 24). Therefore, the unreported protocol deviations did not cause bias in favor of the investigational product. Furthermore, the subject was appropriately not excluded from either the Efficacy or the Per Protocol Analysis Populations.

4. Dr. Athanasios Tsianakas (CP543_3002, Site 71)

Am Bade 1

Bad Bentheim, Lower Saxony, 48455 Germany

Inspection Dates: February 12 – 16, 2023

This investigator was inspected as a routine PDUFA inspection for Study CP543_3002. This was the first FDA inspection for this investigator.

There were 52 subjects randomized at the site; 48 subjects completed the study (three discontinued due to AEs and one discontinued for personal reasons). Subject-related records were reviewed for all 52 subjects and included: signed ICFs, photographs, and documentation of eligibility, AEs, primary endpoint data, randomization, IP administration, and other study-related procedures.

Study-related documents reviewed included: financial disclosure forms, IP accountability records, delegation of authority log, screening and enrollment log, monitoring reports, and the monitoring visit log.

There was no underreporting of protocol deviations. No discrepancies were identified in the reported efficacy data.

One unreported AE was identified: a grade 2 cold assessed as possibly related to the study drug in subject (b) (6) (assigned to CTP-543 12 mg). The site was unable to report the AE due to database lock. No other instances of underreporting of AEs were identified.

Reviewer comment: This single unreported AE is unlikely to change the safety review of the drug. The proposed prescribing information includes a warning for increased risk of serious infections; the drug is not recommended for use in combination with other immunomodulators or immunosuppressants.

Based on the results of the inspection, data generated at Dr. Tsianakas's site appear acceptable in support of the proposed indication in the NDA.

5. Sun Pharmaceutical Industries, Inc.

65 Hayden Ave., Suite 3000N

Lexington, MA 02421

Inspection Dates: February 7 – 15, 2023

This sponsor was inspected as a routine PDUFA inspection for Study CP543_3001 and Study CP543_3002. This was the first FDA inspection for this sponsor.

Records reviewed included: IP accountability records, pharmacy manual, eCRFs, financial disclosure forms, master consent forms, monitoring and IRB correspondence, vendor agreements, and documentation related to clinical investigator qualifications, safety reporting

and monitoring, database management, training, vendor oversight, and electronic records and systems.

No significant issues were identified pertaining to the above inspected sites or handling of protocol deviations.

{ See appended electronic signature page }

Stephanie Coquia, M.D.
Primary reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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Review Division/Cross Discipline Team Lead/Melinda McCord
Review Division/Clinical Reviewer/Kapil (Dev) Verma
OSI/Office Director/David Burrow
OSI/GCP Program Analysts/Yolanda Patague

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/s/

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JENN W SELLERS
03/20/2024 02:55:59 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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and Reproductive Medicine
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Division of Pediatrics and Maternal Health Review

Date: 2/9/24 **Date consulted:** 8/9/2023

From: Jane Liedtka, MD, Medical Officer, Maternal Health Team (MHT)
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, MHT, DPMH

Lynne P. Yao, MD, Division Director, DPMH

To: Qianyiren Song, Regulatory Project Manager (RPM)
Division of Dermatology and Dentistry (DDD)

Drug: LEQSELVI (deuruxolitinib)

NDA : 217900

Applicant: Sun Pharmaceutical Industries, Inc

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Review

Proposed

Indication: Treatment of alopecia areata, (b) (4)
[Redacted]

Materials

Reviewed:

- DPMH consult request dated 8/9/23. DARRTS Reference ID 5224789.
- Applicant's application and proposed labeling submitted 7/28/23.
- DPMH labeling review for OLUMIANT (baricitinib), NDA 207924. Jean Limpert, MD. 2/5/21, DARRTS Reference ID 4742935, and Addendum to the DPMH OLUMIANT

(baricitinib) review, Jean Limpert, MD, dated 3/23/21, DARRTS Reference ID 4768173.^{1,2}

- DPMH labeling review for LITFULO (ritlecitinib), NDA 215830. Catherine Roca, MD. 4/27/23, DARRTS Reference ID 5164819.^{3,4}

Consult Question: “Please review the submission and labeling and provide comments regarding the Risk Summary statements for Sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential).”

INTRODUCTION AND BACKGROUND

- On 7/28/23, Sun Pharmaceutical Industries, Inc submitted an original new drug application, NDA 217900 for deuruxolitinib, a selective Janus Kinase (JAK) 1 and JAK 2 inhibitor for the treatment of adults with moderate to severe alopecia areata (AA).
- Analyses of both the deuruxolitinib 8 mg BID and 12 mg BID doses are included in this submission. However, due to the emergence of safety findings in the long-term open label extension (OLE) studies at the 12 mg BID dose, the Applicant is currently seeking approval of only the deuruxolitinib 8 mg BID dose.
- DDD consulted DPMH on 8/9/23, to assist with the Pregnancy and Lactation subsections of labeling and to provide feedback on postmarketing studies.
- Deuruxolitinib was granted Fast Track Designation (FTD) on 12/19/17 and Breakthrough Therapy Designation (BTD) on 7/1/20 initially based on the results of the deuruxolitinib Phase 2 Study CP543.2001.
- In June 2022, the FDA approved the JAK inhibitor Olumiant (baricitinib), NDA 207924, for the treatment of adult patients with severe AA and, in light of this approval, issued an Intent to Rescind – BTD Letter, dated 8/19/22, to the deuruxolitinib sponsor stating that deuruxolitinib no longer met the criteria for BTD. In October 2022, the original sponsor submitted a Response to the Intent to Rescind BTD Letter. This document summarized data from the two completed deuruxolitinib Phase 3 studies (Study CP543.3001 and Study CP543.3002), which they believed showed that deuruxolitinib demonstrated substantial improvement on a clinically significant endpoint over baricitinib. On 2/6/23, the Agency agreed that deuruxolitinib continues to meet the criteria for BTD.
- The Applicant requested a Priority Review but the Agency did not concur.
- Animal data for the class of JAK inhibitors indicates varying degrees of embryofetal toxicity including embryofetal toxicity warnings for some drugs in the class (e.g., upadacitinib).
- See Appendix A for Drug Characteristics for Deuruxolitinib.
- See previous DPMH reviews^{2, 4} for “Alopecia Areata (AA) and Pregnancy”.

¹ The OLUMIANT consult review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

² DPMH labeling review for OLUMIANT (baricitinib), NDA 207924. Jean Limpert, MD. 2/5/21, DARRTS Reference ID 4742935, and Addendum to the DPMH OLUMIANT (baricitinib) review, Jean Limpert, MD, dated 3/23/21, DARRTS Reference ID 4768173.

³ The LITFULO consult review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

⁴ DPMH labeling review for LITFULO (ritlecitinib), NDA 215830. Catherine Roca, MD. 4/27/23, DARRTS Reference ID 5164819.

REVIEW

PREGNANCY

Nonclinical Experience

In animal reproduction studies, oral administration of deuruxolitinib to pregnant rats during the period of organogenesis at a dose 4.8 times the maximum recommended human dose (MRHD) resulted in reduced fetal weight and increased skeletal malformation. Oral administration of deuruxolitinib to pregnant rabbits during the period of organogenesis at a dose 0.3 times the MRHD resulted in maternal toxicity, reduced fetal weight, and increased post-implantation loss. Oral administration of deuruxolitinib to pregnant rats during pregnancy and lactation periods at a dose 5 times the MRHD resulted in maternal toxicity, decreased pup survival, and adverse effects on postnatal development.

Review of Data from the Clinical Trial Program

There were ten cases of maternal exposure during pregnancy in the clinical development program. There was one case of paternal exposure resulting in a healthy full term baby to the unexposed female partner. Of the ten maternal exposures, there were:

- Four elective terminations.
- Three spontaneous abortions (including one pregnancy exposed to placebo).
- One case lost to follow-up.
- One case with an unknown outcome.
- One healthy infant live birth

Details appear in Table 1 below.

Table 1: Table of Potential Deuruxolitinib-Exposed Pregnancies

	Subject ID/ Study #	Study day pregnancy detected	Maternal age	Dose	Outcome
1	(b) (6) CP543.2001	113	21	8 mg BID	Therapeutic abortion (TAB)
2	(b) (6) CP543.2004	84	35	12 mg BID	TAB
3	(b) (6) CP543.3001	106	21	Placebo BID	Spontaneous abortion (SAB)
4	(b) (6) CP543.5001	178	29	12 mg BID	Healthy full-term baby
5	(b) (6) CP543.5001	92	34	8 mg BID	TAB
6	(b) (6) CP543.5001	61	22	12 mg BID	TAB
7	(b) (6) CP543.5001	252	32	8 mg BID	Unknown
8	(b) (6) CP543.5002	207	27	8 mg BID	Lost to follow-up
9	(b) (6) * CP543.5001	365	38	12 mg BID	SAB
10	(b) (6) * CP543.5001	306	27	12 mg BID	SAB

Source: Reviewer's Table

*Pregnancy occurred after cut-off date 11/21/22

Review of Literature

Applicant's Review of the Literature

The Applicant did provide a review of the published literature regarding the safety of the class of "JAK inhibitors" in alopecia areata, hair loss, atopic dermatitis, vitiligo, sarcoidosis, necrobiosis lipoidica, granuloma annulare, psoriasis and systemic lupus erythematosus. Thirty publications were summarized as relevant in the ISS. None of these publications addressed safety in pregnancy so they will not be discussed further in this review. The applicant conducted a literature search on 5/14/23 specifically on the effects of deuruxolitinib on pregnancy and lactation. No publications were identified.

DPMH's Review of the Literature

DPMH performed a search of the published literature on 1/10/24 using the PubMed database using the search terms "deuruxolitinib" AND pregnancy", "safety events", "adverse effects AND pregnancy", "pregnancy outcomes", "adverse pregnancy outcomes", "congenital anomalies", "congenital defects", "pregnant women", "birth defects", "congenital malformations", "stillbirth", "spontaneous abortion", "miscarriage", "prematurity", "low birth weight", "fetal loss", "pregnancy loss", "teratogenicity", "infertility", "reproduction", "lactation", "breast feeding" and "fertility". No published cases or information on deuruxolitinib exposure during pregnancies were located in the literature search.

LACTATION

Nonclinical Experience

Lactating rats were administered a single oral dose of 10 mg/kg [14C] deuruxolitinib on lactation day 14. Total deuruxolitinib concentrations were up to 20 times higher in milk than in plasma.

Review of Data from the Clinical Trial Program

No cases of exposure to deuruxolitinib during lactation were reported in the clinical trial program.

Review of Literature

Applicant's Review of the Literature.

The Applicant did not identify any publications regarding exposure to deuruxolitinib during "breastfeeding" or "lactation" in their literature review.

DPMH's Review of Literature

A search of the published literature was performed using the PubMed, and LactMed⁵ databases and HalesMeds.com⁶ using the terms, "deuruxolitinib" and "lactation," or "breastfeeding." No information related to deuruxolitinib and lactation was found in the published literature.

Reviewer comment:

There are no data on the presence of deuruxolitinib in human milk, the effects on a breastfed infant or effects on milk production. Deuruxolitinib is present in rat milk and total deuruxolitinib

⁵ LactMed: link: <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>

⁶ <https://halesmeds.com>, accessed 4/11/2023

concentrations were up to 20 times higher in milk than in plasma, which could indicate that it accumulates in animal milk. Drug characteristics of deuruxolitinib (a molecular weight below 800 Daltons) increase the likelihood that it passes into breast milk. Given the serious risk for adverse effects seen in adults, such as the increased risk for infections and malignancy, this reviewer recommends against breastfeeding during treatment with deuruxolitinib and for 24 hours (6 half-lives) after the last dose.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Based on the findings in rats, oral administration of deuruxolitinib may impair female reproductive outcome. Fertility was not affected up to 100 mg/kg/day (23 times the MRHD based on exposure comparisons) but there were decreased live implantations/embryos at 30 mg/kg/day (1.5 times the MRHD based on exposure comparisons) [see *Nonclinical Toxicology* (13.1)].

Review of Literature

Applicant's Review of the Literature.

The Applicant did not provide a literature review regarding deuruxolitinib and effects on reproduction.

DPMH's Review of Literature

A search of the published literature was performed using the PubMed database using the terms, "deuruxolitinib" and "fertility," "infertility" and "reproduction". No cases related to effects of deuruxolitinib on fertility were found in the search of the published literature.

Reviewer comment:

Nonclinical data did demonstrate adverse effects on fertility in female animals at multiples of 123-times the MRHD. Fertility studies in human are not available. At these high multiples it is reasonable not to include this in section 8.3 as it is unlikely to be relevant.

DISCUSSION AND CONCLUSIONS

Pregnancy

In animal reproduction studies, oral administration of deuruxolitinib in pregnant rats and rabbits during organogenesis at doses 4.8 or 0.3 times the maximum recommended human dose (MRHD), based on exposure, respectively, resulted in an increase in resorptions, reduced fetal weights and skeletal abnormalities. Human data from the clinical trials program are too limited to determine a risk associated with the use of deuruxolitinib. Labeling will include a Pregnancy Exposure Registry heading (when the registry information is available), Risk Summary, and Data subheadings.

Given the anticipated use of deuruxolitinib in females of reproductive potential who may become pregnant, and the limited data collected in clinical trials, postmarketing safety studies should be considered. DPMH recommends that a pregnancy exposure registry study be conducted along with a complimentary pregnancy study of a different design (such as a retrospective cohort study using claims or electronic medical records data or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, small-for-gestational age, preterm

birth and other adverse maternal and fetal outcomes in women with alopecia areata exposed to deuruxolitinib during pregnancy compared to an unexposed population. For more information, the reader is referred to the May 2019 FDA Draft Guidance for Industry Postapproval Pregnancy Safety Studies.⁷

Lactation

There are no data on the use of deuruxolitinib during lactation. deuruxolitinib is present in rat milk with concentrations up to 20 times higher in milk than in plasma. When a drug is present in animal milk, it is likely to be present in human milk. Based on this and the physical properties of deuruxolitinib (molecular weight < 800 Daltons), deuruxolitinib is likely to be present in breast milk. Given the serious risks seen in adults treated with deuruxolitinib, the proposed labeling recommends against breastfeeding. DPMH agrees with the recommendation not to breastfeed.

Given that deuruxolitinib will be used in females of reproductive potential, DPMH recommends a PMR for a clinical lactation study. Since the current recommendation is that women taking deuruxolitinib should not breastfeed, DPMH recommends a milk-only study that enrolls only healthy volunteers or breastfeeding women prescribed deuruxolitinib who are not planning to breastfeed. This type of study would be useful to evaluate the amount of transfer, if any, into breast milk. If there is no detectable transfer, such a finding could potentially allow for breastfeeding women to take deuruxolitinib. For more information the reader is referred to the FDA draft Guidance for Industry Clinical Lactation Studies: Considerations for Study Design, published May 9, 2019. <https://www.fda.gov/media/124749/download>.⁸

Females and Males of Reproductive Potential

Nonclinical data do show evidence of adverse effects on fertility in females but at multiples unlikely to be relevant. There are no published human data on the effects of deuruxolitinib on fertility. Animal fertility data will be reported in Section 13 of labeling. Contraception is recommended with use of deuruxolitinib in females of reproductive potential so this will be included in subsection 8.3.

POSTMARKETING REQUIREMENTS (PMR) RECOMMENDATIONS:

- Conduct prospective pregnancy exposure registry cohort analyses in the US population that compares the maternal, fetal, and infant outcomes of women with alopecia areata exposed to deuruxolitinib during pregnancy with a control population of women with alopecia areata who have not been exposed to deuruxolitinib before or during pregnancy. The primary outcome of the study will be major congenital malformations (MCMs). Additional outcomes include spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational age infants, and other adverse maternal or fetal outcomes, including infant postnatal growth and development through the first year of life.
- Conduct an additional pregnancy outcomes study that uses a different study design (for example a retrospective cohort study using claims or electronic medical record data or a case-control study) to assess major congenital malformations, spontaneous abortions,

⁷ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safety-studies-guidance-industry>

⁸ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-lactation-studies-considerations-study-design>

stillbirths, elective terminations, preterm births, small-for-gestational age infants in women exposed to deuruxolitinib during pregnancy compared to an unexposed control population.

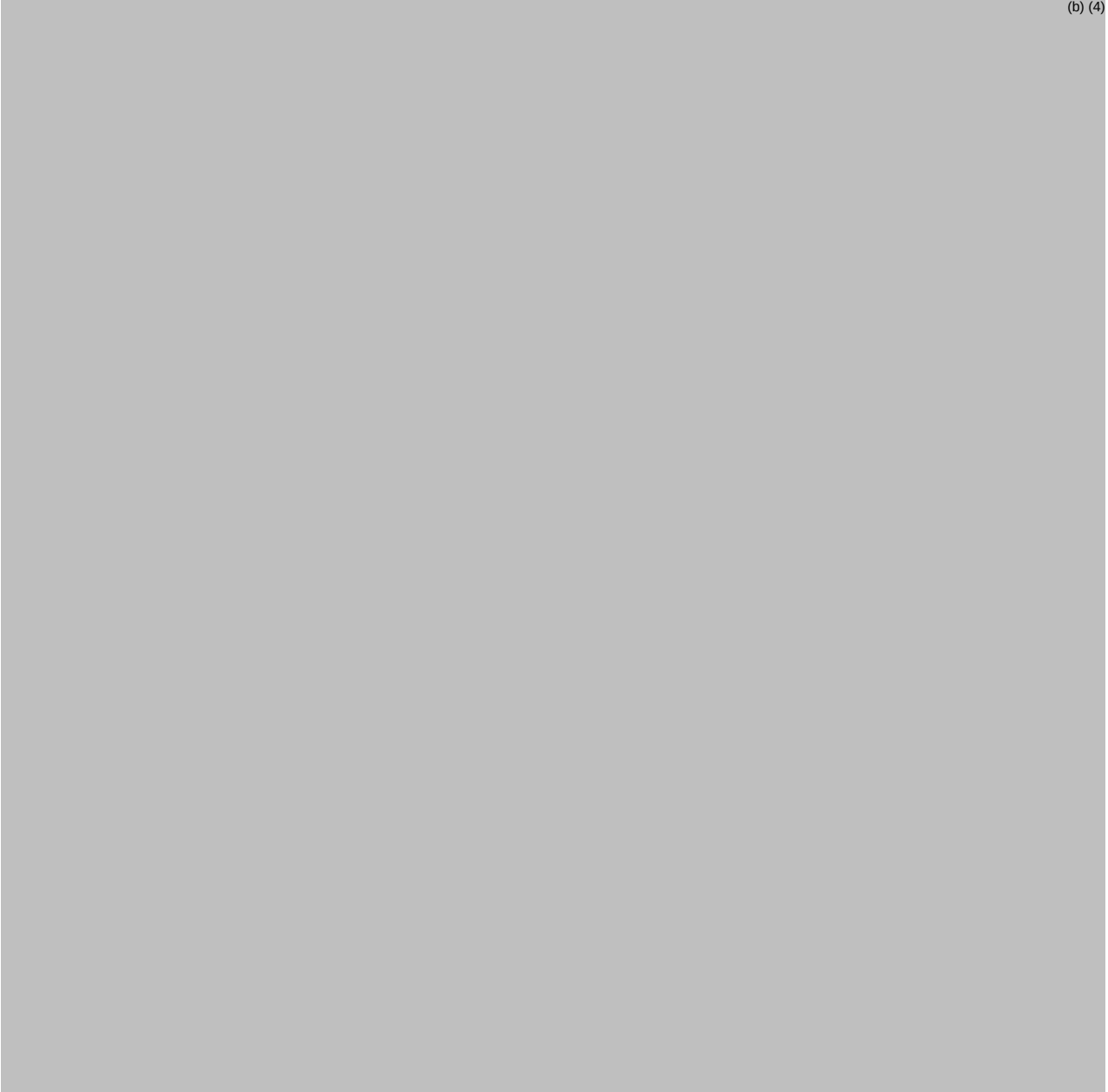
- Perform a lactation study (milk only) in lactating women who have received deuruxolitinib to assess concentrations of deuruxolitinib in breast milk using a validated assay.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, 8.3 and section 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Deuruxolitinib Pregnancy and Lactation Labeling

(b) (4)



Appendix A

Drug Characteristics for Deuruxolitinib⁹

Drug Class	Janus kinase (JAK) inhibitor
Mechanism of action	JAK1/JAK2 inhibitor which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function.
Molecular weight	412.42 g/mol for the Phosphate salt
Half-life	The mean elimination half-life of deuruxolitinib is approximately 4 hrs for BID dosing after multiple dose .
Protein Binding	91.5%
Metabolism	Primarily metabolized by CYP2C9 (76%) and CYP3A4 (21%) and to a lesser extent by CYP1A2 (3%).
Adverse Reactions	Most common adverse reactions (≥1%) are: (b) (4) headache, (b) (4) acne, CPK increased, (b) (4) increased cholesterol, (b) (4) weight increased, anemia, neutropenia, increased platelet count, herpes, folliculitis, (b) (4) asthenia, (b) (4)

⁹ Proposed Labeling, confirmed by the division.

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/s/

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 14, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 217900
Product Name, Dosage Form, and Strength:	Leqselvi (deuruxolitinib) tablets, 8 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sun Pharmaceutical Industries, Inc
FDA Received Date:	July 28, 2023
TTT ID #:	2023-5772
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 REASON FOR REVIEW

As part of the approval process for Leqselvi (deuruxolitinib) tablets, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Leqselvi Prescribing Information (PI), Medication Guide (MG), and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed Prescribing Information (PI), Medication Guide (MG), and container labels may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Sun Pharmaceutical Industries, Inc.

4 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

Table 2. Identified Issues and Recommendations for Division of Dermatology and Dentistry (DDD)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information and Medication Guide – General Issues			

Table 2. Identified Issues and Recommendations for Division of Dermatology and Dentistry (DDD)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	We note the statement “Store in the original bottle in order to protect from moisture” under “Storage and Handling”. We also note the Medication Guide has the following statement “Store LEQSELVI in the original container.” However, this information is not located on the container labels.	Improperly storing this product (i.e., in an inappropriate container) could lead to deteriorated drug medication errors.	We defer to OPQ on the appropriate storage for this product. However, if this product needs to remain in the original container after dispensing, consider adding a similar statement to the container labels.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Use of confusing symbols (e.g., “<” and “≥”)	These symbols may be mistaken as opposite of intended.	Consider replacing the symbols “<” and “≥” with their intended meanings to prevent misinterpretation and confusion.
2.			

(b) (4)

5 RECOMMENDATIONS FOR SUN PHARMACEUTICAL INDUSTRIES, INC

Table 3. Identified Issues and Recommendations for Sun Pharmaceutical Industries, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	As currently presented, the format for the expiration date is not defined on the	We are unable to assess the proposed expiration date format from a medication safety perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the

Table 3. Identified Issues and Recommendations for Sun Pharmaceutical Industries, Inc
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	commercial container label.		expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See <i>Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)</i> .
2.	The placeholder for the expiration date is missing on the professional sample container label.	The label of an official drug product shall bear an expiration date per USP General Chapter <7>.	Add the placeholder for the expiration date in accordance with USP General Chapter <7>. The USP Chapter <7>Labeling requires the expiration date to appear on the immediate container and all other packaging. When all-numeric dates are used, they must be

Table 3. Identified Issues and Recommendations for Sun Pharmaceutical Industries, Inc
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			formatted using the year, the month, and, if applicable, the day, separated by hyphens or forward slashes in one of the following formats: YYYY-MM-DD or YYYY-MM. When alphanumeric dates are used, months must be displayed using at least three letters in one of the following formats: YYYY-MMM-DD or YYYY-MMM. We recommend you ensure that there are no other numbers located in close proximity to the expiration date. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the expiration date format you intend to use.
3.	The placeholder for the lot number is missing on the professional sample container label.	Lot number statement is required on the immediate container per 21 CFR 201.10(i)(1).	Add the placeholder for the lot number in accordance 21 CFR 201.10(i)(1).
4.	As currently presented on the commercial size container label, there are two types of barcodes on the container label located in close proximity to each other.	The drug barcode is often used as an additional verification during the medication use process. The presence of barcodes in close proximity to one another could lead to scan errors.	Ensure there is sufficient blank space surrounding the barcode to allow the barcode to be scanned correctly in accordance with 21 CFR 201.25(c)(i).
5.	The human readable serial number is not defined.	Undefined numeric(s) on product label may lead to misunderstanding and confusion of product identification.	We recommend defining the serial number. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

Table 3. Identified Issues and Recommendations for Sun Pharmaceutical Industries, Inc
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Leqselvi that Sun Pharmaceutical Industries, Inc submitted on July 28, 2023.

Table 4. Relevant Product Information for Leqselvi	
Initial Approval Date	N/A
Active Ingredient	deuruxolitinib
Indication	treatment of adult patients with moderate to severe alopecia areata. <u>Limitations of Use:</u> Not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressants
Route of Administration	oral
Dosage Form	tablets
Strength	8 mg
Dose and Frequency	8 mg orally twice daily, with or without food
How Supplied	debossed, film-coated, immediate-release tablets 60 tablets in a bottle
Storage	20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature] Store in the original bottle in order to protect from moisture. (b) (4)
Container Closure	bottle

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error experiences with similar products, we reviewed the following Leqselvi labels and labeling submitted by Sun Pharmaceutical Industries, Inc.

- Container label received on July 28, 2023
- Professional Sample Container Label received on July 28, 2023
- Medication Guide (Image not shown) received on July 28, 2023, available from <\\CDSESUB1\EVSPROD\nda217900\0001\m1\us\114-label\1141-draft-label\medguide.docx>
- Prescribing Information (Image not shown) received on July 28, 2023, available from <\\CDSESUB1\EVSPROD\nda217900\0001\m1\us\114-label\1141-draft-label\proposed.docx>

F.2 Label and Labeling Images

Container labels

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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