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APPLICATION NUMBER:

217900Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	217900
Priority or Standard	Standard
Submit Date(s)	July 28, 2023
Received Date(s)	July 28, 2023
PDUFA Goal Date	July 28, 2024
Division/Office	Division of Dermatology and Dentistry /Office of Immunology and Inflammation
Review Completion Date	July 24, 2024
Established/Proper Name	Deuruxolitinib
(Proposed) Trade Name	LEQSELVI
Pharmacologic Class	Janus Kinase inhibitor
Code Name	CTP-543
Applicant	Sun Pharmaceutical Inc.
Dosage Form	Tablet (film coated)
Applicant Proposed Dosing Regimen	One tablet two times a day
Applicant Proposed Indication(s)/Population(s)	Treatment of adults with moderate to severe alopecia areata
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	68225006 | Alopecia areata (disorder) |
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adults with severe alopecia areata
Recommended SNOMED CT Indication Disease Term for Each Indication (if applicable)	68225006 | Alopecia areata (disorder) |
Recommended Dosing Regimen	8-mg tablet two times a day

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Abbreviations: CDRH, Center for Devices and Radiological Health; DCOA, Division of Clinical Outcome Assessment; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis, DMPP, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatric and Maternal Health; DPV, Division of Pharmacovigilance; DTPM; Division of Translational and Precision Medicine; DRISK, Division of Risk Management; DTPM, Division of Translational and Precision Medicine; OCP, Office of Clinical Pharmacology; OPDP, Office of Prescription Drug Promotion; OPEQ, Office of Product Evaluation and Quality; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; OTS, Office of Translational Sciences

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Glossary

AA	alopecia areata
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse events of special interest
AST	aspartate aminotransferase
AR	adverse reaction
AT	aminotransaminases
AUC	area under the concentration-time curve
AUCR	AUC ratio
BPM	beats per minute
BCC	basal cell carcinoma
BELA	Brigham Eyelash Tool for Alopecia
BETA	Brigham Eyebrow Tool for Alopecia
BID	twice daily
BMI	body mass index
BTD	Breakthrough Therapy designation
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CL/F	apparent clearance
COA	clinical outcome assessment
COVID-19	Coronavirus Disease 2019
CPK	creatine phosphokinase
ClinRO	clinician-reported outcome
CMQ	customized MedDRA queries
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DPV	Division of Pharmacovigilance
DVT	deep vein thrombosis
EAIR	exposure-adjusted incidence rate
ECAC	Executive Carcinogenicity Assessment Committee
ECG	electrocardiogram
EE	ethinyl estradiol
FDA	Food and Drug Administration
GCP	good clinical practice
GD	gestation day
GI	gastrointestinal
GMR	geometric mean ratio
HADS	Hospital Anxiety and Depression Scale

HCV	hepatitis C virus
HDL	high-density lipoprotein
IL-6	interleukin-6
IND	investigational new drug
IP	investigational product
JAKi	Janus kinase inhibitors
JTS	juvenile toxicology study
LDL	low-density lipoprotein
LNG	levonorgestrel
MACE	major adverse cardiovascular event
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MG	medication guide
MNAR	missing not at random
MRHD	maximum recommended human dose
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NOAEL	no observed adverse effect level
OATP	organic anion transporting polypeptides
OLE	open-label extension
OSI	Office of Scientific Investigation
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamics
PE	pulmonary embolism
PGI	Patient Global Impression
PGI-I	Patient Global Impression of Improvement
PGI-S	Patient Global Impression of Severity
PI	principal investigator
PK	pharmacokinetics
PM	poor metabolizers
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PT	preferred term
QD	once daily
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SALT	Severity of Alopecia Tool
SMQ	standardized MedDRA queries
SOC	system organ class
SPRO	hair satisfaction patient-reported outcome
STAT	signal transducer and activator of transcription

TB	tuberculosis
TEAE	treatment-emergent adverse event
TRA	total radioactivity
TK	toxicokinetics
ULN	upper limit of normal
U.S.	United States
VTE	venous thromboembolism

1 Executive Summary

1.1. Product Introduction

The Applicant submitted NDA 217900 for LEQSELVI™ (deuruxolitinib) tablets on July 28, 2023, under the 505(b)(1) regulatory pathway. The proposed indication is the treatment of adults with moderate to severe alopecia areata (AA). The proposed dose and dosing regimen are 8 mg orally twice daily, with or without food.

LEQSELVI™ (deuruxolitinib) tablets, hereafter referred to as deuruxolitinib, is a Janus kinase inhibitor (JAKi). JAKi mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression.

In a cell-free, in vitro kinase enzyme activity assay, deuruxolitinib had greater inhibitory potency for JAK1, JAK2 and TYK2 relative to JAK3. The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness or safety is not currently known.

The use of deuruxolitinib is associated with a number of potential toxicities that have been observed with the JAK-inhibitor class of products. Deuruxolitinib labeling will carry a Boxed Warning for increased risk of serious infection, all-cause mortality, including sudden cardiovascular death, malignancies (including lymphoma and lung cancers), major adverse cardiovascular events (MACE),defined as cardiovascular death, myocardial infarction, and stroke) and thrombosis. In addition, the clinical pharmacology team identified a clinically significant difference in the pharmacokinetics (PK) of deuruxolitinib when coadministered with moderate or strong CYP2C9 inhibitors as well as in CYP2C9 poor metabolizers, resulting in increased deuruxolitinib total exposure. Given the potential for dose-dependent adverse events, there is clinical concern that higher plasma concentrations of deuruxolitinib may increase the risk of serious adverse reactions, including thrombosis. The FDA team has determined that these potential risks can be managed through labeling.

The FDA concluded that the proposed proprietary name, LEQSELVI™, was conditionally acceptable from both promotional and safety perspectives (Proprietary Name Review by Division of Medication Error Prevention and Analysis, dated October 24, 2023.)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness from two adequate and well-controlled trials, CP543.3001 and 3002, that evaluated deuruxolitinib (CTP-543) tablets 8 mg and 12 mg twice daily (BID) versus placebo in adult subjects with moderate to severe AA (at least 50% hair loss). Efficacy was evaluated using the Severity of Alopecia Tool (SALT) which assesses the percentage of missing scalp hair (from 0 to 100). Deuruxolitinib 8 mg and 12 mg were superior to placebo ($p<0.001$) in both trials for the primary endpoint of SALT ≤20 response

(i.e., no more than 20% missing hair) at Week 24. The results on the primary efficacy endpoint were consistent across the two trials. Due to the thrombotic events that occurred in the open-label extension trials at the 12-mg BID dose, the Applicant is currently seeking approval of only the deuruxolitinib 8 mg BID dose.

- CP543.3001 SALT ≤20 response: 0.8% (placebo) vs. 29.2% (8 mg) vs. 39.8% (12 mg)
- CP543.3002 SALT ≤20 response: 0.8% (placebo) vs. 32.1% (8 mg) vs. 36.7% (12 mg)

Four key secondary endpoints: hair satisfaction patient-reported outcome (SPRO) responders at Week 24, absolute SALT scores ≤20 at Week 12, Week 16 and Week 20 were statistically significant across both trials. The key secondary endpoint absolute SALT scores ≤20 at Week 8 was significant in Trial CP543.3001 only. The exploratory endpoint SALT scores ≤10 at Week 24, and exploratory endpoints based on the eyebrow (Brigham Eyebrow Tool for Alopecia [BETA]) and eyelash (Brigham Eyelash Tool for Alopecia [BELA]) hair loss measures were nominally significant for 8-mg and 12-mg doses across both trials. Content validity and other measurement properties of the BETA and BELA were not reviewed since they were considered exploratory endpoints. Results from the BETA and BELA scores are not proposed for inclusion in labeling.

Baseline SALT score appears to be related to SALT ≤20 response, that is, SALT ≤20 response rates were higher in all dose groups in subjects with baseline SALT 50 to 94 versus SALT 95 to 100. Thus, while the 12-mg dose had consistently higher response rates than the 8-mg dose for the primary endpoint across the range of baseline SALT scores, a reasonable proportion of subjects with baseline SALT score <95 (approximately 46%) were able to achieve SALT ≤20 response on the 8-mg dose.

According to the literature, clinicians and patients view the loss of 50% or more of the hair on the scalp (SALT ≥50) as "severe" disease, not "moderate to severe" disease (Wyrwich et al. 2020). Therefore, the review team concluded that the Applicant has provided substantial evidence of effectiveness to support the indication of the treatment of "severe alopecia areata."

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Deuruxolitinib (CTP-543), a deuterated form of ruxolitinib, is an orally bioavailable inhibitor of Janus Kinases (JAKs). Janus kinases are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Based on in vitro kinase inhibition assays, CTP-543 demonstrated potency and selectivity for JAK1 and JAK2 and less potency for tyrosine kinase 2 (TYK2) and JAK 3.

Alopecia areata (AA) is a chronic autoimmune, T-cell mediated disease that targets anagen hair follicles and causes nonscarring hair loss. Some authors postulate that hair loss in AA may be mediated by cytotoxic T cell attack of the hair follicle after loss of immune privilege, and that this process may be regulated by upstream JAK signaling (Xing 2014). AA is characterized by the acute onset of oval or round, well-circumscribed, smooth patches on the scalp or other hair bearing areas such as the eyebrows, eyelashes, beard, and extremities. In severe cases, hair loss may involve the entire scalp (alopecia totalis) or all hair-bearing areas (alopecia universalis). Approximately 5% of AA patients develop alopecia totalis and 1% develop alopecia universalis. The risk of progression from limited alopecia areata to alopecia totalis or alopecia universalis is approximately 5% (Strazzulla et al. 2018).

To establish the effectiveness of deuruxolitinib (CTP-543) for the treatment of AA, the Applicant submitted data from two adequate and well-controlled clinical trials of similar design. Trials CP543.3001 (enrolled n=706) and CP543.3002 (enrolled n=517) were randomized, double-blind, placebo-controlled trials that evaluated two doses of deuruxolitinib, 8 mg and 12 mg twice daily (BID). Enrolled subjects were 18 years of age and older with "moderate to severe AA," defined as a Severity of Alopecia Tool (SALT) score of 50 or greater at Baseline, which corresponds to loss of 50% or greater scalp hair. Subjects may also have had loss of eyebrow or eyelash hair. The primary timepoint for efficacy evaluation was Week 24 which was followed by an open-label extension period. In Trials CP543.3001 and CP543.3002, deuruxolitinib 8 mg and 12 mg were statistically superior to placebo on the primary efficacy endpoint of SALT ≤20 response (i.e., no more than 20% missing hair) at Week 24. In Trial CP543.3001, the proportion of subjects who received deuruxolitinib 8 mg, deuruxolitinib 12 mg, and placebo and achieved SALT ≤20 at Week 24 was 29.2%, 39.8% and 0.8%, respectively. In Trial CP543.3002, the proportion of subjects who received deuruxolitinib 8 mg, deuruxolitinib 12 mg, and placebo and achieved SALT ≤20 at Week 24 was 32.1%, 36.7% and 0.8%, respectively.

Other endpoints that supported the efficacy of the 8-mg and 12-mg BID dosage of deuruxolitinib included: the key secondary endpoints of hair satisfaction patient-reported outcome (SPRO) responders at Week 24, SALT scores ≤20 at Week 12, Week 16 and Week 20, and the exploratory endpoints of SALT scores ≤10 at Week 24, the eyebrow (Brigham Eyebrow Tool for Alopecia [BETA]) and eyelash (Brigham Eyelash Tool for

Alopecia [BELA]) hair loss measures. Because the BETA and BELA were not included in the multiplicity hierarchy, these endpoints were considered to be exploratory. As such, the content validity and other measurement properties of the BETA and BELA were not reviewed, and the results are not included in labeling. However, the endpoint of SALT scores ≤10 at Week 24 is included in labeling consistent with current labeling practices for this indication.

SALT ≤20 response rates were higher in both baseline severity groups (subjects with baseline SALT 50 to 94 and SALT 95 to 100) for the 8-mg and 12-mg deuruxolitinib dose groups compared with placebo. Subjects who received the 12-mg dose achieved consistently numerically higher response rates on the primary efficacy endpoint than subjects who received the 8-mg dose. However, because of the risk of thrombosis observed with the higher dose during the Phase 3 trials, the Applicant sought approval of the 8-mg dose only.

The safety profile for deuruxolitinib for the treatment of severe AA was adequately characterized during the development program. The primary safety database consisted of pooled data from subjects from the 24-week placebo-controlled period of Trials CP543.3001, CP543.3002, and CP543.2001. The primary safety database included 640 subjects exposed to deuruxolitinib 8 mg BID and 380 subjects exposed to deuruxolitinib 12 mg BID. Overall exposure, as reported in the 120-day Safety Update Report, included 414 subjects exposed to deuruxolitinib 8 mg BID for ≥52 weeks and 208 subjects exposed for ≥76 weeks. Overall exposure to deuruxolitinib 12 mg BID included 666 subjects exposed for ≥52 weeks and 388 subjects exposed for ≥76 weeks.

The treatment-emergent adverse events (TEAEs) observed in the deuruxolitinib development program were consistent with the known safety profile for other JAK inhibitors used to treat chronic inflammatory conditions. In the placebo- controlled period between Weeks 0 to 24, subjects who received either dose of deuruxolitinib reported higher observed rates of headache, acne, nasopharyngitis, blood creatine phosphokinase (CPK) increased, hyperlipidemia, fatigue, anemia, increased weight, neutropenia, and herpes compared to subjects who received placebo. For some TEAEs, the review team observed a dose- response relationship with greater numbers of adverse events (AEs) in subjects receiving 12 mg versus 8 mg. These TEAEs included: thrombosis, acne, blood CPK increased, hyperlipidemia, pooled fatigue, lymphopenia, leukopenia, anemia, skin and soft tissue infections, folliculitis, pooled neutropenia, herpes, high-density lipoprotein increased and bronchitis. Because of the dose dependent safety signal of thrombosis, the FDA placed the higher 12-mg BID dosage on partial clinical hold on May 17, 2023.

A comprehensive analysis of the deuruxolitinib safety data through Week 52 identified no new safety signals. However, the clinical pharmacology team identified a clinically significant difference in the pharmacokinetics (PK) of deuruxolitinib when coadministered with moderate or strong CYP2C9 inhibitors resulting in increased deuruxolitinib total exposure, and a potential increased risk related to higher estimated total exposure to deuruxolitinib in CYP2C9 poor metabolizers. Specifically, drug-drug interaction studies and physiologically-based

pharmacokinetic (PBPK) simulations showed that deuruxolitinib exposure could be affected by both CYP2C9 induction and strong and moderate CYP2C9 inhibition. In addition, based on the simulations using PBPK modeling, total exposure of deuruxolitinib in CYP2C9 poor metabolizers is estimated to be increased 2-fold when compared to normal metabolizers. Given the potential for dose-dependent adverse events at those exposure levels, there is clinical concern that higher plasma concentrations of deuruxolitinib may increase the risk of serious adverse reactions, including thrombosis. Because the impact of CYP2C9 genetic variants on the pharmacokinetics of deuruxolitinib has not been directly evaluated in the clinical program, there are no data to reliably exclude the possibility of increased serious safety risks in these patient populations. Therefore, the FDA team has determined that these potential risks will be addressed through labeling, including a requirement for CYP2C9 genotype status testing and a contraindication statement for CYP2C9 poor metabolizers. A postmarketing study will be required to assess systemic deuruxolitinib exposure in CYP2C9 poor metabolizers to potentially further inform labeling. The Agency will also request that the Applicant develop an in-vitro diagnostic genotyping assay to determine CYP2C9 genotype status. Of note, there is currently no FDA approved companion diagnostic genotyping assay for CYP2C9 genotype determination. Despite the lack of current availability of an FDA approved companion diagnostic genotyping assay, the team has made the determination that to ensure access to the product, prescribers can utilize other widely commercially available assays to determine genotyping prior to initiating treatment with deuruxolitinib while awaiting development of an assay from the Applicant.

As part of routine pharmacovigilance, the Office of Surveillance and Epidemiology (OSE) Division of Epidemiology-I will use Sentinel Initiative capabilities to monitor the incidence of thrombosis and other safety events of interest that occur during treatment. Postmarketing requirements will be issued to provide additional data to characterize the safety profile of the proposed product in special populations (pregnant females, pediatric population, and those with reduced CYP2C9 activity). Refer to Section 13 of this review for the postmarketing requirements and commitments.

The Applicant developed deuruxolitinib as both an 8-mg and 12-mg tablet for BID administration. However, because the FDA placed the higher 12-mg BID dosage on partial clinical hold for unfavorable benefit-risk, the Applicant is only seeking approval of the lower deuruxolitinib 8-mg dose in this NDA submission. The review team concludes that the benefit-risk of deuruxolitinib 8 mg twice daily is favorable in the population of adult patients with severe alopecia areata with appropriate labeling and recommend approval of this application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• AA is an autoimmune disease which targets the hair follicles, causing hair loss. • In the United States, approximately 500,000 individuals have AA. • AA occurs in three primary patterns: focal, totalis, and universalis. Focal AA consists of one or multiple patches of hair loss on the scalp. Alopecia totalis (AT) consists of total hair loss on the scalp. Alopecia universalis (AU) consists of complete hair loss on all parts of the body. • Patients with AA may experience periods of hair regrowth and hair loss throughout the course of the disease. This autoimmune disease primarily affects hair follicles, but it can also affect fingernails, causing small depressions and roughness. • Most individuals experience onset of alopecia by the age of 40 years, with nearly half experiencing onset before the age of 20 years. For patients with AT and AU, onset is typically before the age of 30 years. In children, the mean age of onset is between 5 and 10 years of age. • Patient input at the Patient-Focused Drug Development meeting (September 11, 2017) emphasized that AA is associated with a significant emotional, psychological, and social burden. Patients reported feelings of depression and anxiety, and described experiencing social isolation, and bullying as a result of their condition.	AA is a chronic disease that has a significant impact on how patients feel and function. Severe AA has considerable detrimental effects on quality of life, emotional wellbeing, social interactions, and ability to live a normal life.
Current Treatment Options	• There is no cure for alopecia areata. • There are two recently approved products for the treatment of patients with extensive AA (≥50% hair loss). On June 13, 2022, OLUMIANT (baricitinib) tablet (JAK ½ inhibitor) was approved for the treatment of adult patients with severe AA. On June 23, 2023, LITFULO (ritlecitinib) capsule (inhibitor of JAK 3 and tyrosine kinase family) was approved for the treatment of severe alopecia areata in adults and adolescents 12 years and	There is a significant unmet medical need for effective treatment for patients with severe AA. Disease of mild severity may remit spontaneously. However, for patients with ≥50% hair loss, spontaneous remission is unlikely and there are a limited number of approved systemic therapies. Existing

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	older. Both products are intended for oral administration with dosing once daily.	approved therapies do not adequately manage the condition for all patients with severe AA. Participants at the Patient-Focused Drug Development meeting emphasized the lack of approved and effective therapies for AA.
Benefit	• Efficacy was evaluated using the SALT which assesses the percentage of missing scalp hair (from 0 to 100). Deuruxolitinib 8 mg and 12 mg were superior to placebo ($p<0.001$) in both trials for the primary endpoint of SALT ≤20 response (i.e., no more than 20% missing hair) at Week 24. The results on the primary efficacy endpoint were consistent across the two trials. ○ CP543.3001 SALT ≤20 response: 0.8% (placebo) vs. 29.2% (8 mg) vs. 39.8% (12 mg) ○ CP543.3002 SALT ≤20 response: 0.8% (placebo) vs. 32.1% (8 mg) vs. 36.7% (12 mg) • Four key secondary endpoints: SPRO responders at Week 24, absolute SALT scores ≤20 at Week 12, Week 16 and Week 20 were statistically significant across both trials. The key secondary endpoint absolute SALT scores ≤20 at Week 8 was significant in Trial CP543.3001 only.	The submitted data has met the evidentiary standard for providing substantial evidence of effectiveness in subjects with severe AA.
Risk and Risk Management	• The key potential risks associated with the use of deuruxolitinib, and the class of JAK inhibitors are communicated in the boxed warning. These potentially serious adverse events which were evaluated by the Applicant as adverse events of special interest (AESI) include: serious infection, all-cause mortality, including sudden cardiovascular death, malignancies (including lymphoma and lung cancers), major adverse cardiovascular events (MACE, defined as cardiovascular death, myocardial infarction, and stroke) and thrombosis.	Based on the safety profile of LEQSELVI, which is consistent with other JAK inhibitors, the proposed labeling (prescribing information and patient labeling via a Medication Guide) and routine pharmacovigilance are considered adequate to manage risks of this product in the treatment of severe AA. However, due to the potential increased risk of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Common adverse reactions (≥1%) that are communicated in labeling include: headache, acne, nasopharyngitis, blood creatine phosphokinase increased, hyperlipidemia, fatigue, weight increased, thrombocytosis, anemia, skin and soft tissue infections, neutropenia, and herpes. • Drug-drug interaction studies and PBPK simulations showed that deuruxolitinib exposure could be affected by both CYP2C9 induction and strong and moderate CYP2C9 inhibition. In addition, based on the simulations using PBPK modeling, total exposure to deuruxolitinib in the CYP2C9 poor metabolizers is predicted to be increased to 2-fold when compared to normal metabolizers. Given the potential for dose-dependent adverse events, there is clinical concern that higher plasma concentrations of deuruxolitinib may increase the risk of serious adverse reactions, including thrombosis. Because the impact of CYP2C9 genetic variants on the pharmacokinetics of deuruxolitinib has not been directly evaluated in a clinical trial, there is some uncertainty about the impact on safety. Therefore, the FDA will address these potential risks through labeling, by requiring a postmarketing study to assess systemic deuruxolitinib exposure in CYP2C9 poor metabolizers, and by directing the Applicant to establish an in-vitro diagnostic genotyping assay to determine CYP2C9 genotype status. Of note, there is currently no FDA approved companion diagnostic genotyping assay for CYP2C9 genotype determination. Despite the lack of current availability of an FDA approved companion diagnostic genotyping assay, prescribers will be able to utilize other commercially available assays to determine genotyping prior to initiating treatment with deuruxolitinib while awaiting development of an assay from the Applicant. • The review identified no additional serious safety concerns that warrant consideration of a risk evaluation and mitigation strategy (REMS).	LEQSELVI-associated serious adverse reactions in CYP2C9 poor metabolizers and with concomitant use of moderate or strong CYP2C9 inhibitors, this risk will be reflected in labeling and the Applicant will be required to perform a postmarketing study to assess systemic deuruxolitinib exposure in CYC2C9 poor metabolizers.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The Prescribing Information and a Medication Guide adequately address the known risks associated with the class of JAK inhibitors and adverse reactions identified during product development.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient-reported outcome (PRO)	Section 8.1
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 8.1
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
X	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	X	Patient-focused drug development or other stakeholder meeting summary reports		Described below
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

On September 11, 2017, FDA held a public meeting to hear perspectives from patients with AA, their caregivers, and other patient representatives regarding the aspects of AA and its treatment that are most important to patients. FDA conducted the meeting as part of the Patient-Focused Drug Development initiative, an FDA commitment under the fifth authorization of the Prescription Drug User Fee Act to gather patient perspectives more systematically on their condition and available therapies to treat their condition. Participants viewed AA as a

chronic disease with both physical and emotional impacts. Participants emphasized the variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of these treatments. Patients and their families urged industry to develop additional therapies especially in the pediatric population to address the unmet medical need. (March 2018).

2 Therapeutic Context

2.1. Analysis of Condition

AA is a chronic autoimmune T-cell mediated disease that targets anagen hair follicles and causes nonscarring hair loss. Some authors postulate that hair loss in AA may be mediated by cytotoxic T cell attack of the hair follicle after loss of immune privilege, and that this process may be regulated by upstream JAK signaling (Xing et al. 2014). Associated factors which may contribute to the development of AA include genetic predisposition, stress, infection, drugs, and vaccinations. Various epidemiologic studies have shown increased risk of AA development in patients with atopy, including atopic dermatitis, asthma, and allergic rhinitis. Multiple autoimmune diseases (including thyroid disease, psoriasis, vitiligo, and inflammatory bowel disease) have been shown to have a high association with AA. Factors that may contribute to prognosis include AA subtype, extent of hair loss, duration of hair loss, age at onset, and family history.

AA is characterized by the acute onset of oval or round, well-circumscribed, smooth patches on the scalp or other hair bearing areas such as the eyebrows, eyelashes, beard, and extremities. AA is a common cause of abrupt onset hair loss but occurs less frequently than androgenic alopecia or telogen effluvium. In severe cases, hair loss may involve the entire scalp (alopecia totalis) or all hair-bearing areas (alopecia universalis) (Messenger 2022). Approximately 5% of AA patients develop alopecia totalis and 1% develop alopecia universalis. The risk of progression from limited alopecia areata to alopecia totalis or alopecia universalis is approximately 5% (Strazzulla et al. 2018). Patchy AA is the most common form of alopecia seen in children. This disease primarily affects hair follicles, but it can also affect fingernails, causing small depressions and roughness.

AA has an estimated prevalence of 1 in 1000, and a lifetime risk of approximately 2%. A large cross-sectional survey study of the prevalence of AA in the United States as of 2020 suggests that the AA prevalence in the United States is approximately 0.21% (700,000 persons) with the current prevalence of “moderate to severe” disease being approximately 0.09% (300,000 persons) (Benigno et al. 2020). Data regarding the prevalence of severe AA in different age groups is limited.

The course of AA is variable with periods of hair loss and spontaneous regrowth. Onset can occur at any age, with a higher incidence at younger age and an equal incidence in males and females. AA affects all ethnic groups (Afford et al. 2021). A review of the worldwide literature indicates that most individuals experience onset of alopecia by the age of 40 years, with nearly half experiencing onset before the age of 20 years. For patients with alopecia totalis and universalis, onset is typically before the age of 30 years. In children, the mean age of onset is between 5 and 10 years of age (Villasante Fricke and Miteva 2015). However, severe AA appears to be less frequent in children younger than 6 years old. This observation is supported

by data from a case series from Kuwait (Nanda et al. 2002). Among children less than 12 years of age (mean 6.7 years), a majority of the children (80.5%) had mild disease and only 13% of children had extensive disease (more than 50% hair loss). Another review of 392 children with AA from a mixed ethnic community in East Asia, reported extensive disease (>50% hair loss – considered severe) in 12% of children aged 11 to 15 years, 5% of children aged 6 to 10 years, and 0% of children aged 1 to 5 years (Tan et al. 2002).

Psychiatric comorbidities occur more frequently in patients with AA. In one review of the worldwide literature, the authors state that patients with AA have an increased prevalence of personality disorders, paranoid disorders, stress, depression, and anxiety disorders, varying from 17-22% (Hon et al. 2020). In another review, nearly 80% of patients with AA reported impaired health related quality of life based on Dermatology Life Quality Index survey results (Toussi et al. 2021). Areas predominantly affected were social interaction and embarrassment, with the severity of the effects being related to percent hair loss and concomitant depression. Patient input at the Patient-Focused Drug Development meeting (September 11, 2017) emphasized that alopecia areata is associated with a significant emotional, psychological, and social burden. Patients reported feelings of depression and anxiety, and described experiencing social isolation, and bullying as a result of their condition (March 2018).

According to Toussi et al., pediatric patients with AA also have a higher psychiatric burden than age-matched controls, with higher prevalence of anxiety, depression, and psychiatry appointments (Toussi et al. 2021). In addition, the same authors report that the Pediatric Quality of Life Inventory, as well as other psychology-oriented questionnaires, revealed that children with AA have higher anxiety, depression, and maladaptive coping habits, which negatively affect their quality of life. The prevalence of major depressive disorder and obsessive-compulsive disorder is as high as 50% and 30%, respectively. Other reported disorders include anxiety, mood, and disruptive behavioral disorders. Healthy children, grades kindergarten through 8, misunderstand the nature of AA and can perceive children with AA as sick or dying (Hankinson et al. 2013).

2.2. Analysis of Current Treatment Options

Until recently, there were no FDA approved products indicated for the treatment of moderate to severe alopecia areata. Key information related to the recently approved products is tabulated below.

Table 1. Summary of Treatment Armamentarium Relevant to Proposed Indication – FDA Approved Products

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
OLUMIANT (baricitinib) tablet	Treatment of adult patients with severe alopecia areata. LOU- Not recommended for use in combination with other JAK inhibitors, biologic immune-modulators, cyclosporine or other potent immune-suppressants.	2022	-The recommended dosage of OLUMIANT is 2 mg once daily orally, with or without food. Increase to 4 mg once daily if the response to treatment is not adequate. For patients with nearly complete or complete scalp hair loss, with or without substantial eyelash or eyebrow hair loss, consider treating with 4 mg once daily, with or without food. Once patients achieve an adequate response to treatment with 4 mg, decrease the dosage to 2 mg once daily. -not rec for use with severe hepatic impairment & dose modifications for renal impairment	**SALT ≤20** **50% to 94% Scalp Hair Loss** Placebo-8% 2 mg-33% 4 mg 48% **95% to 100% Scalp Hair Loss** Placebo-1% 2 mg 10% 4 mg 21%	**Boxed warning** -Serious infections inc TB, invasive fungal infections, and opportunistic infections -All cause mortality -Malignancies inc lymphoma and lung CA -MACE -Thrombosis **W&P** -hypersensitivity -GI perforations -lab abnormal inc neutropenia, lymphopenia, anemia, LFT elev, lipid elev -vaccinations	Carries class labeling for safety (JAKi) Janus kinase (JAK) inhibitor with greater inhibitory potency at JAK1, JAK2 and TYK2

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
LITFULO (ritlecitinib) capsules	Treatment of severe alopecia areata in adults and adolescents 12 years and older. LOU- Not recommended for use in combination with other JAK inhibitors, biologic immune-modulators, cyclosporine, or other potent immune-suppressants	2023	-50 mg orally once daily with or without food -not recommended in patients with severe (Child Pugh C) hepatic impairment	**SALT ≤20** Placebo 1.6 LITFULO 23.0 **SALT ≤10** Placebo 1.5 LITFULO 13.0	**Boxed warning** -Serious infections inc TB, fungal infections, and opportunistic infections -All cause mortality -Malignancies inc lymphoma and lung CA -MACE -Thrombosis **W&P** -hypersensitivity --Lab abnormal inc dec platelets and lymphocytes, LFT elev, CPK elev -vaccinations	Carries class labeling for safety (JAKi) Kinase inhibitor that irreversibly inhibits Janus kinase 3 (JAK3) and tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family

Source: Reviewer's Table
Abbreviations: CA, cancer; CPK, creatine phosphokinase; elev, elevation; inc, including; LOU, limitations of use; MACE, Major Adverse Cardiovascular Events; W&P, Warnings and Precautions

In addition, healthcare providers have used a variety of off-label therapies for the treatment of alopecia areata which include corticosteroids (topical, oral, intralesional injection), immunosuppressants (cyclosporine A, mycophenolate mofetil, and azathioprine), pimecrolimus, minoxidil, anthralin, ultraviolet B and psoralen/ultraviolet A therapy, and contact immunotherapy. Success with these approaches was variable and was limited by the side effect profile, size of the treatment area, concomitant medical conditions, and patient preferences. Although intralesional corticosteroids may be considered to be first line treatment for patchy alopecia, the procedure for administration is painful and impractical for extensive hair loss. Contact immunotherapy may be complicated by chronic contact dermatitis, immunosuppressants may be associated with infection and phototherapy may induce cutaneous malignancy. There is limited data from randomized controlled trials to support the use of these off-label therapies in the treatment of AA (Delamere et al. 2008).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

LEQSELVI™ (deuruxolitinib) tablets are not marketed in the United States. This section is not applicable.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed deuruxolitinib phosphate tablets 8-mg and 12-mg tablets under investigational new drug (IND) application 131423 using the 505(b)(1) regulatory pathway. While the program for the deuterated isotopolog of ruxolitinib was initially conceived as a 505(b)(2) application with JAKAFI as the listed drug, the results of a suboptimal bridging toxicity study caused the Applicant to pursue a 505(b)(1) regulatory pathway and conduct all the required nonclinical studies. The proposed indication is the treatment of adult patients with moderate to severe AA. At the time of initial development, alopecia areata was a novel indication for which there were no FDA approved products. The FDA granted Fast-Track Designation to deuruxolitinib for the treatment adult patients with moderate to severe AA on December 19, 2017, and Breakthrough Therapy designation (BTD) on July 1, 2020.

The Applicant submitted original IND 131423 on October 7, 2016, after receiving advice regarding their development program during a Pre-IND Meeting held October 5, 2016 (Meeting Minutes dated October 19, 2016). In addition to comments related to the submitted protocols, the FDA provided advice during the following key regulatory meetings: an end-of-Phase 2 (EoP2) meeting (Meeting Minutes dated April 3, 2020), a multidisciplinary BTD Meeting (Meeting Minutes dated November 10, 2020), a guidance meeting to discuss the analysis plans for the integrated summary of safety and integrated summary of effectiveness (meeting minutes dated September 10, 2022) and a pre-NDA meeting (meeting minutes dated December 15, 2022).

The Division provided comments regarding the proposed Phase 3 development program in an EoP2 meeting conducted on March 30, 2020. The Division agreed that the proposed primary efficacy endpoint of the percentage of subjects achieving an absolute SALT ≤20 at Week 24 appeared reasonable. In addition, the Division agreed that the proposed secondary endpoint of the percentage of subjects achieving an absolute SALT score of ≤20 at Week 20, 16, 12, 8, and 4 was clinically meaningful and supportive of the primary efficacy endpoint. Other proposed key secondary endpoints included patient reported outcome measures.

Other important recommendations included:

- "You propose to evaluate mean change from baseline in the hair satisfaction patient-reported outcome (SPRO) scale at Week 24 regarding the SPRO:
  - Submit evidence of other measurement properties (reliability, construct validity, ability to detect change), including what constitutes a meaningful within-patient score change (i.e., responder), to further support the adequacy of this instrument. Plan to provide a justification for a threshold of meaningful within-patient score change.
  - Currently, the change from baseline analysis may be difficult to interpret as a mere change in magnitude of satisfaction might not translate to a clinically meaningful benefit. Consider measuring the percentage of subjects achieving "satisfied" or "very satisfied" at prespecified timepoints.
  - The administration of the SPRO at three time points (Baseline, Weeks 12 and 24) may be insufficient and may miss important information on the benefits of the product throughout the trial.
- For the context of this development program, we view the Clinical Global Impression of Improvement (CGI-I) and Patient Global Impression of Improvement (PGI-I) as exploratory measures that can be used as anchors to determine what constitutes a clinically meaningful change in another clinical outcome assessment (COA). Further, the CGI-I and PGI-I have limitations, as they are susceptible to recall error and lacks assessment of change from baseline.
- Based on your qualitative data, eyelash and eyebrow hair loss is important to patients. Consider modifying your secondary endpoint hierarchy to evaluate these outcomes as key secondary endpoints using appropriate scales. Submit exact copies of these instruments, including information regarding its development history, for review and comment.
- Missing Data Handling: We do not agree with your approach towards missing data handling. You have proposed using last observation carried forward as the primary method of handling missing data with sensitivity analyses conducted using observed cases and Worst Observation Carried Forward. We recommend that the sensitivity analyses for the handling of missing data use alternative assumptions from the primary method. We also recommend including a tipping point analysis.
- Your proposed hierarchical approach for analyzing the primary and key secondary endpoints across two doses will not adequately control the type I error rate. One approach that would control the overall type I error rate across your set of primary and key secondary endpoints is to allocate α=0.025 to each set of dose comparison endpoints (12 mg vs. placebo and 8 mg vs. placebo). As the secondary endpoints should be supportive of the primary endpoint, the secondary endpoints for a dose level should only be evaluated if the primary endpoint for that dose level is statistically significant.
- Your sample size calculations are based on an analysis proposal that does not adequately take into account the multiplicity introduced by two doses and multiple key secondary endpoints.
- We agree with your plan to include an Independent Data Monitoring Committee in your Phase 3 trials. Your proposed safety monitoring which includes periodic evaluation of

adverse events, vital signs, physical examinations, concomitant medications, and clinical laboratory parameters appears reasonable. We recommend that you propose acceptable safety monitoring, stopping criteria and follow-up assessments for potential cases of progressive multifocal leukoencephalopathy.

- Given the safety profile of your product and the chronic conditions of use, we need to understand both the short- term and long- term effects of treatment in the target population. To understand the performance of your product, you will need to address how you will determine maintenance dosing (which may differ from the dosing regimen that induced the response), durability of effect, and response after retreatment (e.g., potential for tachyphylaxis).
- An open-label extension trial with a duration of 2 years or less may be insufficient to characterize the potential risk of some rare events that have been observed with Janus Kinase inhibitors (e.g., effects on cardiovascular, immune, and skeletal systems)."

One of the primary topics under discussion in the initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting (October 28, 2020) was the proposed approach to the assessment of durability of effect after drug discontinuation/ dose reduction and response after retreatment (potential for tachyphylaxis). The meeting package included a draft protocol (CP543.2004) to address the FDA requested assessments. While the Division agreed with the overall design and duration of each phase, the Division disagreed with the definition of "responder" and "Loss of Maintenance" and the endpoints selected for each phase. The key comments provided by the Division included:

- Your proposed definition of responder in Part A (Period 1), ≥50% change in SALT score from Baseline at Week 24, is not acceptable. While we acknowledge your rationale, we recommend that treatment success for the evaluation of the durability of effect in Part A (Period 1) be defined using the same the primary efficacy endpoint as you intend to evaluate in the Phase 3 trials, an absolute SALT score of ≤20 at Week 24.
- You propose to define Loss of Maintenance as the greater of either 1) ≥5- point increase in SALT OR 2) ≥30% increase (e.g., worsening) in SALT score compared to the SALT score achieved at the end of Period 1. We recommend that Loss of Maintenance represent loss of treatment success which is defined as an absolute SALT score ≤20.
- Regarding the Primary Efficacy Endpoint for the Treatment phase of Part A, the recommended endpoint is the proportion of subjects who maintain an absolute SALT score of ≤20 at Week 24.
- Regarding the Primary Efficacy Endpoint for the Treatment phase of Part B, the recommended endpoint is the proportion of subjects who achieve an absolute SALT score of ≤20 24 weeks after the re-treatment.

The FDA agreed that the original NDA submission will not include maintenance of response data from Trial CP543.2004, only data from Part A, period 1.

In compliance with the Food and Drug Administration Safety and Innovation Act, the Applicant submitted an Initial Pediatric Study Plan (iPSP). The agreed iPSP dated October 30, 2021,

included a plan to request a product-specific partial waiver of pediatric study requirements for subjects with AA from birth to <6 years old as necessary studies are impossible or highly impractical to conduct because the number of patients with moderate to severe AA in this age group is so small. In accordance with 21 CFR 314.55(b), the Applicant also planned to request a product-specific deferral of pediatric study requirements for subjects until efficacy and safety has been determined in the adult patient population. Refer to Section 8.3.8 of this review regarding *Pediatrics and Assessment of Effects on Growth*.

The Applicant developed deuruxolitinib as both an 8-mg and 12-mg tablet. However, the FDA placed the higher 12-mg BID dosage on partial clinical hold on May 17, 2023, based on a potential dose-dependent safety signal for thrombosis. The FDA received five serious adverse event (SAE) reports of 6 nonfatal thrombotic events that occurred in five subjects receiving the higher deuruxolitinib 12-mg BID dose in ongoing open- label, extension trials. The reports included cases of cerebral venous sinus thrombosis, unilateral pulmonary embolism (PE), bilateral PE (two cases), and bilateral PE with bilateral deep vein thrombosis (DVT) (refer to the Clinical Review dated May 5, 2023 and Section 8.3.4.2 of this review). In this NDA submission of July 28, 2023, the Applicant is only seeking approval of the deuruxolitinib 8-mg BID dosage.

At the time that the FDA granted BTD, there were no FDA-approved products for the treatment of patients with moderate to severe AA. At the time of the submission of this application, there are two approved products for AA. On June 13, 2022, OLUMIANT (baricitinib) tablet (JAK 1/ 2 inhibitor) was approved for the treatment of adult patients with severe AA. On June 23, 2023, LITFULO (ritlecitinib) capsule (inhibitor of JAK 3 and tyrosine kinase family) was approved for the treatment of severe alopecia areata in adults and adolescents 12 years and older. Both products are intended for oral administration once daily. Therefore, the FDA issued an Intent to Rescind Letter-Breakthrough Therapy Designation letter “because the criteria for designation were no longer being met for the following reasons:

- Other drugs, baricitinib and ritlecitinib, gained traditional approvals on June 13, 2022, and June 23, 2023, respectively, for the same proposed indication as CTP-543.
- The available evidence does not indicate that the 8-mg twice daily dose of CTP-543 for which you are seeking approval may demonstrate a substantial improvement over available therapy.” (Intent to Rescind Letter-Breakthrough Therapy Designation dated September 21, 2023, under IND 131423.)

In view of the decision to rescind BTD, the Division planned to review the application on a Standard timeline rather than a Priority timeline as requested by the Applicant. The FDA communicated this determination to the Applicant. (Filing communication dated October 5, 2023; Rescind-Breakthrough Therapy Designation letter dated March 14, 2024).

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate.

Division of Dermatology and Dentistry requested that the Office of Scientific Investigations (OSI) conduct clinical inspections of domestic and foreign sites and the Applicant. The reasons for the inspections of the selected sites were enrollment of large numbers of study subjects and high proportion of treatment responders. Division of Dermatology and Dentistry included foreign sites because the sites enrolling the greatest numbers of subjects were ex-United States (i.e., Germany.)

Table 2. Site Identification

(Name, Address, Phone Number, Email, Fax#)	Site #	Protocol ID	Number of Subjects (SAFPOP)	Study Title	Endpoint
Osman, Lawrence 18546 Roscoe Blvd.,Suite 306 NORTHRIDGE, CA 91324 USA Phone: 818-885-0455 losman@drosman.com Fax:	56	CP543_3001 NCT 04518995	27	A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	Percentage of patients achieving an absolute SALT score <=20 at Week 24
Zirwas, Matthew 2356 East Main St. BEXLEY, OH 43209 USA Phone: 614-725-5010 matt.zirwas@gmail.com Fax:	57	CP543_3001 NCT 04518995	28	A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	Percentage of patients achieving an absolute SALT score <=20 at Week 24
Magnolo, Nina Von-Esmarch-Strase 58 MUENSTER, NORDRHEIN- WESTFALEN, NA 48149 DEU Phone: 49-0251-83-57291 nina.magnolo@ukmuenster.de Fax:	155	CP543_3002 NCT 04797650	22	A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	Percentage of patients achieving an absolute SALT score <=20 at Week 24

(Name, Address, Phone Number, Email, Fax#)	Site #	Protocol ID	Number of Subjects (SAFPOP)	Study Title	Endpoint
Tsianakas, Athanasios Am Bade 1 BAD BENTHEIM, NIEDERSACHSEN, NA 48455 DEU Phone: 49-05922745281 a.tsianakas@fk-bentheim.de Fax:	71	CP543_3002 NCT 04797650	52	A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	Percentage of patients achieving an absolute SALT score <=20 at Week 24

Source: OSI/DCCE CONSULT: CLINICAL INSPECTIONS REQUEST

The OSI team completed inspections of the Applicant and four clinical sites (Drs. Osman, Zirwas, Magnolo, and Tsianakas) that participated in the evaluation of deuruxolitinib for the treatment of adults with moderate to severe AA. The reviewer concluded "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." (Review by Stephanie Coquia dated March 20, 2024.)

4.2. Product Quality

Sun Pharmaceutical Industries, Inc. submitted a new NDA 217900 for LEQSELVI® (deuruxolitinib), Tablet 8 mg via 505 (b)(1) regulatory pathway for the treatment of adults with moderate to severe alopecia areata. The Applicant developed both an 8-mg and 12-mg tablet of deuruxolitinib but proposed only the 8-mg tablet for marketing due to a safety concern.

The drug substance, deuruxolitinib phosphate, is a deuterated version of ruxolitinib phosphate. It is a white to off-white crystalline solid and highly aqueous solubility at low pH and good to poor solubility in a range of common organic solvents. It belongs to Biopharmaceutical Classification System Class I. It is not hygroscopic with a melting point of 196°C. Deuruxolitinib phosphate is packaged (b) (4) The re-test period is (b) (4) months.

Deuruxolitinib phosphate is formulated as a film-coated immediate release tablet. The deuruxolitinib phosphate, (b) (4) (b) (4)

The product has been manufactured at a contract manufacturer, Halo Pharmaceutical, Inc. Six batches for each strength including three primary registration batches have been manufactured for preclinical and clinical use. Their certificate of analysis have been provided. Deuruxolitinib Tablet 8 mg is intended to be packaged in 45 cc white, wide-mouth, square high-density polyethylene bottle, along with one 1-gram silica gel desiccant canister and closed with 24-mm white, child-resistant closures with (b) (4) foil liners.

The Applicant provided 18 months long-term stability data at 25°C/60%RH, 12 months intermediate stability data at 30°C/65%RH and 6 months accelerated data at 40°C/75%RH for three primary registration batches (0000107543, 0000107544 and 0000107545) for 8-mg

strength and three primary registration batches (0000107546, 0000107547 and 0000107548) for 12-mg strength manufactured from (b) (4) drug substance source. The Applicant also provided 3 months long-term and accelerated stability data for one batch (0000133703) for 8-mg strength and one batch (0000133705) for 12-mg strength manufactured from (b) (4) drug substance source. The proposed expiry period for the drug product is 30 months when stored at 20 to 25 °C.

The Applicant's request for categorical exclusion from preparation of environmental assessment has been found adequate and is granted.

The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.

Overall, this application is approvable from a chemistry, manufacturing, and controls perspective.

4.3. Clinical Microbiology

Not Applicable.

4.4. Devices and Companion Diagnostic Issues

Not Applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Deuruxolitinib is a small molecule Janus kinase (JAK) inhibitor. JAKs mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. Deuruxolitinib is a deuterated isotopolog of ruxolitinib, an approved JAK inhibitor. It is structurally similar to ruxolitinib with the only differences of eight deuterium atoms substituting hydrogen. In pharmacology studies, deuruxolitinib exhibited similar pharmacological properties compared with ruxolitinib.

Pivotal repeat-dose oral toxicity studies were conducted in rats and dogs. The major safety signals identified in these studies were consistent with deuruxolitinib's pharmacological activity. The target organs were identified as lymphoid organs in both species, with major study findings including reduced circulating white blood cells and lymphocytes and decreased lymphocytes/cellularity in various lymphoid tissues. Such findings showed reversibility after a treatment-free period.

In genotoxicity studies, deuruxolitinib was negative in the Ames test, an in vitro chromosome aberration assay, and an in vivo rat bone marrow micronucleus assay. It was positive in an in vitro micronucleus assay. The positive response could be due to a potential aneugenic effect. Overall, there is no significant concern for deuruxolitinib's genotoxicity.

Deuruxolitinib was not carcinogenic in a 6-month oral transgenic mouse carcinogenicity study or a 2-year oral rat carcinogenicity study.

In fertility and early embryonic development studies in rats, deuruxolitinib had no adverse effects on male or female fertility at doses up to 100 mg/kg/day. However, adverse effects on early embryonic development were noted, including decreased viable embryos, and increased pre-implantation loss at doses ≥30 mg/kg/day, and increased postimplantation loss and resorption at 100 mg/kg/day.

In an embryo-fetal toxicity study in rats, lower fetal weight and increased skeletal malformations were noted at 60 mg/kg/day, with no significant maternal toxicity observed. In an embryo-fetal toxicity study in rabbits, lower fetal weight and increased postimplantation loss were noted at 60 mg/kg/day. Maternal toxicity (mortality and abortion) was also noted at 60 mg/kg/day.

In a pre- and postnatal developmental study in rats, decreased pup survival, decreased F1 animal body weight, and adverse effects on reproductive outcome in the F1 females were noted at 75 mg/kg/day. Maternal mortality and increased litter loss were noted at 75 mg/kg/day.

Deuruxolitinib did not show phototoxic potential in an in vitro neutral red uptake phototoxicity assay.

This NDA is approvable from a pharmacology/toxicology perspective. There is no recommended nonclinical postmarketing commitment (PMC)/postmarketing requirement (PMR) for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

IND 131423 is the associated IND for this NDA. In nonclinical studies, CTP-543 and C-21543 were used as code names for deuruxolitinib.

5.3. Pharmacology

Primary Pharmacology

Deuruxolitinib is a small molecule JAK inhibitor. 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 to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. In an in vitro kinase activity assay, deuruxolitinib showed greater inhibitory potency for JAK1, JAK2 and TYK2 relative to JAK3 (IC_{50} values were 4.6, 26, 870, and 49nM for JAK1, JAK2, JAK3, and TYK2, respectively).

Deuruxolitinib is a deuterated isotopolog of ruxolitinib. It is structurally similar to ruxolitinib with the only differences of eight deuterium atoms substituting hydrogen. Ruxolitinib has been approved under NDA 202192 (JAKAFI® oral tablets). Deuruxolitinib exhibited similar pharmacology properties compared with ruxolitinib, including the selectivity and potency of JAK inhibition and the inhibition of interleukin-6 (IL-6)-stimulated STAT3 activation. The most abundant deuruxolitinib metabolites in humans, C-21714 and C-21717, showed much weaker inhibition (~10-fold less potent) of JAKs compared with deuruxolitinib, and a similar selectivity profile for JAK1, JAK2, and TYK2.

Secondary Pharmacology

Deuruxolitinib was evaluated in a radioligand binding screen assay using a panel of 55 targets and a kinase activity assay using a panel of 30 targets for its potential off-target effects and compared with ruxolitinib. At 10 µM, deuruxolitinib and ruxolitinib inhibited ligand binding to adenosine A1 77.1% and 76.7%, respectively, and inhibited ligand binding to adenosine A3 64.3% and 65.7%, respectively. In the kinase activity assay, deuruxolitinib and ruxolitinib at 0.2 µM inhibited JAK3 (the only JAK included in this assay) activity 98.6% and 98.8%, respectively, and MARK1 (microtubule affinity-regulating kinase 1) activity 55.7% and 60.2%, respectively. The inhibition of other tested kinases was lower than 50%. No significant differences between deuruxolitinib and ruxolitinib were noted for off-target binding or off-target kinase inhibition.

Safety Pharmacology

In an in vitro hERG assay, deuruxolitinib inhibited the hERG-mediated potassium current at concentrations ≥30 µM, with a calculated IC_{50} of 153 µM. In an in vivo cardiovascular safety pharmacology study in male Beagle dogs, a single oral dose of 10 mg/kg deuruxolitinib induced mild transient decreases in blood pressure, which correlated with mild transient increases in heart rate and decreases in QT interval. These changes resolved after 6 hours postdose.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Assessment of pharmacokinetics following a single or co-dosed oral administration of CTP-543 and ruxolitinib to male and female SD rats / CTP-543 PK-073 Assessment of pharmacokinetics following a single oral and IV administration of CTP-543 and ruxolitinib to male beagle dogs / CTP-543 PK-072	<u>Single oral dose of 30 mg/kg in rats</u> $T_{1/2}$(h) T_{max}(h) C_{max}(ng/ml) $AUC_{0-\infty}$(h·ng/ml) Deuruxolitinib (male): 1.51 0.27 717 1120 Ruxolitinib (male): 1.42 0.19 508 625 Deuruxolitinib (female): 2.56 0.24 2730 5160 Ruxolitinib (female): 2.51 0.19 2510 4730 <u>Single intravenous dose of 2.5 mg/kg in male dogs</u> $T_{1/2}$(h) C_0(ng/ml) $AUC_{0-\infty}$(h·ng/ml) Deuruxolitinib: 0.83 2540 1730 Ruxolitinib: 1.08 2920 2180 <u>Single oral dose of 5.0 mg/kg in male dogs</u> $T_{1/2}$(h) T_{max}(h) C_{max}(ng/ml) $AUC_{0-\infty}$(h·ng/ml) %F Deuruxolitinib: 1.11 0.62 1080 2360 68 Ruxolitinib: 0.84 0.70 1170 2190 50
Distribution	
Protein binding in mouse, rat, dog, rabbit and human plasma / CTP-543 DM-103, 086, 097, and 082 Absorption, distribution, metabolism, and excretion studies following a single oral dose administration to male and female rats / CTP-543 PK-078 Placental transfer and milk secretion studies in the rat following a single oral dose administration / CTP-543 PK-085	The percentage of deuruxolitinib bound to plasma proteins was 89%, 71%, 81%, 82%, and 92% in mouse, rat, dog, rabbit, and human plasma, respectively. Following a single oral dose of 20 mg/kg [^{14}C] deuruxolitinib to SD (albino) rats and Lister Hooded (partially pigmented) rats, a similar pattern of distribution was observed in both rats, with highest radioactive concentrations initially associated with contents of the gastrointestinal tract and urinary bladder. Notable exposure was also observed in liver, kidney, aorta, spinal nerve, and adrenal gland in SD rats and in uveal tract, spinal nerve, aorta, liver, and thyroid gland in Lister Hooded rats. Following a single oral dose of 10 mg/kg [^{14}C] deuruxolitinib administered to pregnant female rats on gestation day 17, radioactivity was measurable at low concentrations (peaked at 1 hr postdose) in fetal blood, brain, liver and muscle, indicating the passage of radiolabeled material across placenta.

Type of Study	Major Findings
	Following a single oral dose of 10 mg/kg [^{14}C] deuruxolitinib administered to lactating female rats at postparturition day 14, the exposure in milk (C_{max} achieved at 2 hr postdose, 14.01 µg/g) was higher than plasma (C_{max} achieved at 1 hr postdose, 1.55 µg/g). Milk/plasma concentration ratios were approximately 7, 13, 19, and 20 at 1 hr, 2 hr, 4 hr, and 8 hr postdose, respectively. The elimination was faster from plasma than milk.
Metabolism	
In vitro metabolite profiling of CTP-543 and ruxolitinib in rat, dog and human hepatocytes / CTP-543 PK-077 In vivo metabolite profiling of CTP-543 and ruxolitinib in dog plasma and urine samples / CTP-543 PK-076 In vivo metabolite profiling of CTP-543 and ruxolitinib in male rat plasma / CTP-543 PK-079	Metabolism is the primary clearance mechanism for deuruxolitinib across species. The metabolites observed both in vitro and in vivo were mostly single, di-oxidations and glucuronidation of oxidative metabolites. A total of 13 metabolites were identified in rat, dog, and human hepatocytes. The two most abundant human metabolites (C-21714 and C-21717) were observed in human and dog hepatocytes. Only one of these two metabolites (C-21717) was observed in rat hepatocytes. C-21717 and C-21714 are present in human plasma at ~5% of total drug related AUC each. No metabolite detected in human plasma exceeded 10% of total drug related AUC. All circulating metabolites >1% of total AUC detected in humans were also detected in rats and dogs. No unique human metabolites were detected.
Excretion	
Absorption, distribution, metabolism, and excretion studies following a single oral dose administration to male and female rats / CTP-543 PK-078 Assessment of the pharmacokinetics and excretion of CTP-543 following oral dose administration to male and female Sprague-Dawley rats / CTP-543 PK-090	Deuruxolitinib is extensively metabolized and is mainly excreted in the urine and feces as metabolites. Following a single oral dose of 20 mg/kg [^{14}C] deuruxolitinib administered to SD rats, the mean overall recovery of radioactivity was 94% of the dose. The recovery in urine was 48% and 36% in males and females, respectively. The recovery in feces was 44% and 55% in males and females, respectively. Following a single oral dose of 20 mg/kg deuruxolitinib administered to bile duct-cannulated SD rats, deuruxolitinib and its 5 metabolites excreted in urine, feces and bile in total were 29%, 1.3%, and 4.3%, respectively (sex combined).
TK data from general toxicology studies 26-Week oral gavage toxicity and toxicokinetic study with CTP-543 in rats with an 8-week recovery phase / CTP-543 TX-116 52-Week oral gavage toxicity and toxicokinetic study of CTP-543 in	<u>Rat (oral daily dosing for 26 weeks)</u> $T_{1/2}$: 0.66-5.29 hours AUC_{0-24h} (ng·hr/ml) at day 182: 18.75 mg/kg/day: 716 (M), 2330 (F) 37.5 mg/kg/day: 1640 (M), 9310 (F) 75 mg/kg/day: 5180 (M), 28400 (F) Accumulation: Slight drug accumulation was noted in females after repeated dosing. Dose proportionality: The AUC increase was higher than dose proportional. <u>Dog (oral daily dosing for 52 weeks)</u> $T_{1/2}$: 0.82-2.04 hours AUC_{0-24h} (ng·hr/ml) at day 364:

Type of Study	Major Findings
Beagle dogs with an 8-week recovery / CTP-543 TX-082	0.5 mg/kg/day: 269 (M), 349 (F) 1 mg/kg/day: 868 (M), 802 (F) 1.5 mg/kg/day: 1330 (M), 1170 (F) 3 mg/kg/day: 4070 (M), 2850 (F) Accumulation: No marked drug accumulation was observed. Dose proportionality: The AUC increase was slightly higher than dose proportional.
TK data from reproductive toxicology studies	
An oral (gavage) study of the effects of CTP-543 on fertility and early embryonic development to implantation in male rats / CTP-543 TX-094	<u>Male rat (oral daily dosing from 28 days prior to mating to conception)</u> $AUC_{0\text{-}24h}$ (ng·hr/ml) at day 28: 10 mg/kg/day: 288 30 mg/kg/day: 761 100 mg/kg/day: 4540
An oral (gavage) study of the effects of CTP-543 on fertility and early embryonic development to implantation in female rats / CTP-543 TX-093	<u>Female rat (oral daily dosing from 2 weeks prior to mating to GD 7)</u> AUC_{Tlast} (ng·hr/ml) at day 14: ($AUC_{0\text{-}24h}$ could not be calculated) 10 mg/kg/day: 492 30 mg/kg/day: 1860 100 mg/kg/day: 27800
An oral study of the effects of CTP-543 on embryo-fetal development in rats / CTP-543 TX-085	<u>Female rat (oral daily dosing from GD 6 to GD 17)</u> AUC_{Tlast} (ng·hr/ml) at GD 17: ($AUC_{0\text{-}24h}$ could not be calculated) 15 mg/kg/day: 750 30 mg/kg/day: 2070 60 mg/kg/day: 9700
An oral study of the effects of CTP-543 on embryo-fetal development in rabbits / CTP-543 TX-087	<u>Female rabbit (oral daily dosing from GD 7 to GD 19)</u> $AUC_{0\text{-}24h}$ (ng·hr/ml) at GD 19: 6 mg/kg/day: 16 30 mg/kg/day: 96 60 mg/kg/day: 638
An oral (gavage) study of the effects of CTP-543 on pre- and postnatal development, including maternal function in rats / CTP-543 TX-122	<u>Female rat (oral daily dosing from GD 6 to LD 20)</u> AUC_{Tlast} (ng·hr/ml) at LD 14: ($AUC_{0\text{-}24h}$ could not be calculated) 15 mg/kg/day: 719 30 mg/kg/day: 1600 75 mg/kg/day: 10000
TK data from Carcinogenicity studies	
104-week oral gavage carcinogenesis study with CTP-543 in rats / CTP-543 TX-107	<u>Rat (oral daily dosing for 2 years)</u> $AUC_{0\text{-}24h}$ (ng·hr/ml) at day 176: 3 mg/kg/day: 61 (M), 164 (F) 10 mg/kg/day: 315 (M), 856 (F) 30 mg/kg/day: 1210 (M), 6050 (F)

5.5. Toxicology

5.5.1. General Toxicology

Pivotal repeat-dose toxicity studies were conducted in rats and dogs. The major safety signals identified in these studies were consistent with deuruxolitinib's pharmacological activity. The target organs were identified as lymphoid organs in both species, with major study findings including reduced circulating white blood cells and lymphocytes and decreased lymphocytes/cellularity in various lymphoid tissues (including spleen, thymus, lymph nodes, and gut-associated lymphoid tissue). Such findings showed reversibility after a treatment-free recovery period.

Study title / number: 26-Week oral gavage toxicity and toxicokinetic study with CTP-543 in rats with an 8-week recovery phase / Study# 8420541, sponsor reference# CTP-543 TX-116

- The noted hematology and histopathology findings in this study were consistent with the pharmacological effects of deuruxolitinib. Reversibility and/or rebound regeneration were noted after the recovery phase.
- The histopathological findings (decreased lymphocytes in lymphoid tissues) at high dose were considered adverse due to severity and with lower body weights. The no observed adverse effect level (NOAEL) was identified as the mid dose, 37.5 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 18.75, 37.5, and 75 mg/kg/day once daily for 26 weeks
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose in reverse osmosis water
Species/Strain:	Rat / Sprague-Dawley
Number/Sex/Group:	18/sex/group
Age:	6-7 weeks old
Satellite groups/ unique design:	Toxicokinetics (TK) animals: 4/sex for vehicle control and 12/sex/group for dose groups
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	Mortality occurred at a low incidence and was not dose related. No significant treatment-related effects were noted.

Parameters	Major findings
Clinical Signs	Dose-related struggling during dosing was noted. It could be assumed that the taste of test article was not well tolerated.
Body Weights	At the end of dosing phase mean body weight was lower in high dose males (-11%) and females (-12%), compared with control. Decreased body weight gain during the dosing phase was also noted in high dose males (-17%) and females (-20%). After the recovery phase, partial recovery was noted in males and full recovery was noted in females.
Ophthalmoscopy	No significant treatment-related findings
Hematology	At the end of dosing phase, dose-related decreases in WBC count (up to -62% in males and -65% in females at high dose) and lymphocyte count (up to -73% in males and -78% in females at high dose) were noted at all doses. Full reversibility was noted at the end of recovery phase.
Clinical Chemistry	At the end of dosing phase, dose-related increases in ALP level were noted in both males (up to +48% at high dose) and females (up to +120% at high dose). Full reversibility was noted at the end of recovery phase.
Urinalysis	No significant treatment-related findings
Gross Pathology	No significant treatment-related findings
Organ Weights	Organ weight data were not collected at terminal necropsy. At recovery necropsy, increased thymus weights were noted in males at all doses (absolute weight: up to +143% at high dose) and in females at mid and high doses (absolute weight: up to +43%). Decreased spleen weights were noted in males at mid dose and high dose (absolute weight: up to -20%) and in high dose females (absolute weight: -15%).
Histopathology Adequate battery: Yes	At terminal necropsy, treatment-related findings were noted in bone marrow and lymphoid tissues including spleen, thymus, lymph nodes, and GALT. Minimally or slightly decreased hematopoietic cells were noted in bone marrow at high dose. Minimally to moderately decreased lymphocytes (dose-related) were noted in various lymphoid tissues at all doses. At recovery necropsy, such findings were no longer noted. Minimally or slightly increased lymphocytes in thymus were noted in males at all doses and females at mid and high doses.

Study title / number: 52-Week oral gavage toxicity and toxicokinetic study of CTP-543 in Beagle dogs with an 8-week recovery / Study# 8354165, sponsor reference# CTP-543 TX-082

- The noted hematology and histopathology findings in this study were consistent with the pharmacological effects of deuruxolitinib. These findings are not considered adverse due to low severity and reversibility.
- The NOAEL was identified as the high dose, 3 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0 (vehicle), 0.5, 1.0, 1.5, 3 mg/kg/day once daily for 52 weeks

Route of administration: Oral gavage

Formulation/Vehicle:	0.5% (w/v) methylcellulose in reverse osmosis water
Species/Strain:	Dog / Beagle
Number/Sex/Group:	4/sex/group
Age:	6-8 months old
Satellite groups/ unique design:	Recovery animals: 3/sex/group
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	No significant treatment-related findings
Physical examination	No significant treatment-related effects on vital signs or blood pressure
Body Weights	No significant treatment-related effects
Ophthalmoscopy	No significant treatment-related findings
ECG	No significant treatment-related findings
Hematology	A decrease in absolute lymphocyte count (-14 to -40%) on Days 176 and 365 of the dosing phase was noted in males treated with doses ≥1.0 mg/kg/day and females treated with doses ≥1.5 mg/kg/day. There was also a decrease in red cell mass (-1.3 to -13%) and absolute eosinophil count (-29 to -64%) on Days 85, 176, and 365 of the dosing phase in high dose animals. These hematology findings exhibited certain reversibility at the end of the recovery phase.
Clinical Chemistry	No significant treatment-related findings
Urinalysis	No significant treatment-related findings
Gross Pathology	No significant treatment-related findings
Organ Weights	No significant treatment-related findings
Histopathology Adequate battery: Yes	Minimal to slight decreased cellularity of the hemolymphopoietic organs [including gut-associated lymphoid tissue (GALT), lymph nodes, and bone marrow] were noted at terminal necropsy in high dose animals. These findings were not observed in recovery animals, indicating full recovery.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: CTP-543 phosphate: bacterial reverse mutation assay / Study# 8329556, sponsor reference # TX-067

Key Study Findings:

- There were no significant increases in revertant colonies at any dose, with or without S9, compared with negative control.
- Deuruxolitinib was not mutagenic, under the study conditions.

GLP compliance: Yes

Test system: Deuruxolitinib was tested up to the maximum dose of 5000 µg/plate in five bacteria strains, including *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2uvrA

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: CTP-543: in vitro human lymphocyte micronucleus assay / Study# 8342119, sponsor reference# TX-073

Key Study Findings:

- There were statistically significant increases in the number of cells with micronuclei compared to the vehicle control in the 3-hr treatment without S9 (at 103 µg/ml), in the 3-hr treatment with S9 (at 103 and 137 µg/ml), and in the 24-hr treatment without S9 (at 32.5 µg/ml). There were also clear dose responses. The cytotoxicity levels were acceptable.
- Deuruxolitinib was positive in this assay.

GLP compliance: Yes

Test system: Deuruxolitinib was tested in human peripheral blood lymphocytes at 7.72, 24.4 and 103 µg/ml for 3 hr treatment without S9, 77.1, 103, and 137 µg/ml for 3 hr treatment with S9, and 7.72, 18.3 and 32.5 µg/ml for 24 hr treatment without S9. The high dose was selected based on cytotoxicity.

Study is valid: Yes

Study title/ number: CTP-543: in vitro human lymphocyte chromosome aberration assay / Study# 8360759, sponsor reference# TX-081

Key Study Findings:

- Deuruxolitinib did not induce a biologically significant increase in the number of cells with either chromosome aberration or numerical chromosome abnormalities.
- Deuruxolitinib was not clastogenic, under the study conditions.

GLP compliance: Yes

Test system: Deuruxolitinib was tested in human peripheral blood lymphocytes at 20.0, 30.0, and 43.1 µg/ml for 3 hr treatment without S9, 10.0, 40.0, and 51.3 µg/ml for 3 hr treatment with S9, and 8.22, 11.4 and 18.5 µg/ml for 24 hr treatment without S9. The high dose was selected based on cytotoxicity.

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: CTP-543: in vivo rat bone marrow micronucleus assay / Study# 8348335, sponsor reference# TX-074

Key Study Findings:

- Deuruxolitinib did not induce significant increases in micronucleated polychromatic erythrocytes at any dose. In addition, bone marrow toxicity was not noted (no significant decrease in the % polychromatic erythrocytes). The plasma concentrations of deuruxolitinib at 30 min postdose were in the range of 1030-2650 ng/ml in high dose animals.
- Deuruxolitinib was not clastogenic, under the study conditions.

GLP compliance: Yes

Test system: Deuruxolitinib was tested at single oral doses of 0 (vehicle: 1% Tween 80 and 1% methylcellulose in reverse osmosis water), 75, 150, and 300 mg/kg in male Sprague Dawley rats. The high dose was selected from a dose-ranging study, and it was considered the maximum tolerated dose.

Study is valid: Yes

5.5.3. Carcinogenicity

The carcinogenicity of deuruxolitinib was evaluated in two studies, including a 6-month oral carcinogenicity study in Tg.rasH2 mice and a 2-year oral carcinogenicity study in Sprague Dawley rats. The detailed review of these two studies is in Section 16.3.1.

In a 2-year oral carcinogenicity study, oral (gavage) doses of 0 (water), 0 (vehicle), 3, 10, and 30 mg/kg/day deuruxolitinib were administered once daily to Sprague Dawley rats (65/sex/group). All surviving animals from all groups were terminated early due to declining survival (males were sacrificed during Week 91 and females during Week 92). However, there was no test article-related effect on mortality. A decrease in body weight gain was noted in high dose males at Week 90. For histopathology examination, a complete tissue list was examined for all main study animals. There were no biologically significant test article-related neoplastic findings in this study.

In a 6-month oral carcinogenicity study, oral (gavage) doses of 0 (vehicle), 10, 30, and 100 mg/kg/day deuruxolitinib were administered once daily to Tg.rasH2 mice (25/sex/group). A positive control group (10/sex) was also included [receiving a single intraperitoneal dose of 75 mg/kg/day (b) (4) on Day 1]. There was no deuruxolitinib-related effect on mortality. For histopathology examination, a complete tissue list was examined for all main study animals. There were no significant deuruxolitinib-related neoplastic findings in this study. In the positive control group, all animals developed neoplasms, demonstrating validity of this study.

Deuruxolitinib was not carcinogenic when administered orally to Sprague Dawley rats once daily for 2 years or to Tg.rasH2 mice once daily for 6 months.

5.5.4. Recommendations

From a Clinical Pharmacology standpoint, this NDA 217900 is acceptable to support the approval of deuruxolitinib 8 mg twice daily with or without food for the treatment of adults with severe AA.

5.5.5. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: An oral (gavage) study of the effects of CTP-543 on fertility and early embryonic development to implantation in male rats / Study# 1513-115, sponsor reference# CTP-543 TX-094

Key Study Findings

- The NOAEL for paternal toxicity was identified as 30 mg/kg/day, based on body weight decrease noted at 100 mg/kg/day.
- The NOAEL for male fertility was identified as the high dose, 100 mg/kg/day.

Conducting laboratory and location	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 10, 30, and 100 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	1% methylcellulose and 0.1% Tween® 80 in deionized water
Species/Strain:	Rat / Sprague-Dawley
Number/Sex/Group:	24 males/group
Satellite groups:	TK animals: three males for control, and six males/group for the three dose groups
Study design:	The male rats were dosed from 28 days prior to mating to conception, for a total of at least 56 days. Female rats used for pairing were not dosed.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	No treatment-related effects
Body Weights	Mean body weight at high dose was lower on Days 15 through 57 (-4.6% to -14.3%), compared with concurrent control.
Necropsy findings	No adverse effects were observed on reproductive and fertility indices (mating, fertility, and fecundity indices and copulatory interval), male reproductive organ weights, or sperm parameters (motility, cauda epidydimal sperm total count and concentration, and morphology) at any dose. In addition, no test article-related effects were observed on ovarian and uterine parameters of untreated females at any dose.

Study title/ number: An oral (gavage) study of the effects of CTP-543 on fertility and early embryonic development to implantation in female rats / Study# 1513-116, sponsor reference# CTP-543 TX-093

Key Study Findings

- The NOAEL for maternal toxicity was identified as 30 mg/kg/day, based on body weight decrease noted at 100 mg/kg/day.
- The NOAEL for female fertility was identified as the high dose, 100 mg/kg/day.
- The NOAEL for early embryonic development was identified as the low dose, 10 mg/kg/day, based on decreased viable embryos and increased pre-implantation loss noted at 30 mg/kg/day.

Conducting laboratory and location	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 10, 30, and 100 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	1% methylcellulose and 0.1% Tween® 80 in deionized water
Species/Strain:	Rat / Sprague-Dawley
Number/Sex/Group:	24 females/group
Satellite groups:	TK animals: three females for control, and six females/group for the three dose groups
Study design:	The female rats were dosed from 2 weeks prior to mating, through conception and implantation to gestation day (GD) 7. Male rats used for pairing were not dosed.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	No treatment-related effects
Body Weights	Mean body weight at high dose was lower on GD 13 (-5.6%), compared with control. A decrease in body weight gain during gestation (GD 0-13) was also noted at high dose (-28.9%), compared with control.
Necropsy findings	No adverse effects were observed in estrous cyclicity, mating and fertility indices (mating, fertility, and fecundity indices and copulatory interval), numbers of ovarian corpora lutea, or ovary weights at any dose. Decreases in number of implantation sites (10.4 and 9.8 vs. 13.8 in control) and viable embryos (9.8 and 2.8 vs. 12.9 in control) and increases in pre-implantation loss (36.4% and 30.4% vs. 18.5% in control) were noted at mid dose and high dose, respectively. Also, at high dose, postimplantation loss (71.4% vs. 9.6% in control) and number of resorptions (7.0 vs. 0.9 in controls) were much higher, and 7 of 21 pregnant females had total litter resorption.

Embryo-Fetal Development

Study title/ number: An oral study of the effects of CTP-543 on embryo-fetal development in rats / Study# 1513-110, sponsor reference# CTP-543 TX-085

Key Study Findings

- The NOAEL for maternal toxicity was identified as the high dose, 60 mg/kg/day.
- The NOAEL for embryo-fetal toxicity was identified as the mid dose, 30 mg/kg/day, based on lower fetal weight and increased skeletal malformation noted at 60 mg/kg/day.

Conducting laboratory and location	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 15, 30, and 60 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	1% methylcellulose and 0.1% Tween® 80 in deionized water
Species/Strain:	Rat / Sprague-Dawley
Number/Sex/Group:	23 females/group
Satellite groups:	TK animals: three females for control, and eight females/group for the three dose groups
Study design:	Pregnant female rats were dosed from GD 6 to GD 17.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	No treatment-related effects
Body Weights	No treatment-related effects
Necropsy findings (Cesarean section data)	No test article-related effects were observed in ovarian and uterine parameters (number of corpora lutea, implantation sites, viable fetuses, litter size, resorptions, and pre- and postimplantation loss) at any dose.
Necropsy findings (offspring)	There were no treatment-related findings in fetal sex ratio, fetal external examination, or visceral examination. Decreased fetal weight (up to -5%) was noted at high dose, compared with control. A significant increase in the incidence of fetal skeletal malformation was noted at high dose (18% in all fetuses and 44% in litter incidence, vs. 0% in control), including bent bones (femur, humerus, scapula, radius, and ulna) and ossification variations (bent ribs, irregular superior border of the scapula, and additional ossification center of the neural arches of the cervical vertebrae).

Study title/ number: An oral study of the effects of CTP-543 on embryo-fetal development in rabbits / Study# 1513-112, sponsor reference# CTP-543 TX-087

Key Study Findings

- The NOAEL for maternal toxicity was identified as the mid dose, 30 mg/kg/day, based on mortality and abortion noted at 60 mg/kg/day.
- The NOAEL for embryo-fetal toxicity was identified as the mid dose, 30 mg/kg/day, based on lower fetal weight and increased postimplantation loss noted at 60 mg/kg/day.

Conducting laboratory and location	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 6, 30, and 60 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	1% methylcellulose and 0.1% Tween® 80 in deionized water
Species/Strain:	Rabbit / New Zealand White
Number/Sex/Group:	20 females/group
Satellite groups:	TK animals: three females for control, and four females/group for the three dose groups
Study design:	Pregnant female rabbits were dosed from GD 7 to GD 19.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	One high dose main study animal aborted on GD 26 and one high dose TK animal was found dead on GD 17. The mortality and abortion noted at high dose was considered treatment related. One mid dose animal was found dead on GD 13, likely due to gavage-related trauma (not considered test article-related).
Clinical Signs	No significant test article-related findings
Body Weights	No treatment-related effects
Necropsy findings (Cesarean section data)	No test article-related effects were observed in ovarian and uterine parameters (number of corpora lutea, implantation sites, viable fetuses, litter size, resorptions, and pre- and postimplantation loss) at low dose or mid dose. At high dose, increased postimplantation loss (13.6% vs. 2.7% in control) was noted.
Necropsy findings (offspring)	There were no treatment-related findings in fetal sex ratio, fetal external examination, visceral examination, or skeletal examination. Decreased fetal weight (up to -8%) was noted at high dose, compared with control.

Prenatal and Postnatal Development

Study title/ number: An oral (gavage) study of the effects of CTP-543 on pre- and postnatal development, including maternal function in rats/ Study# 1513-123, sponsor reference# CTP-543 TX-122

Key Study Findings

- The NOAEL for maternal toxicity and parturition was identified as the mid dose, 30 mg/kg/day, based on mortality noted at 75 mg/kg/day.
- The NOAEL for pre- and postnatal development toxicity was identified as the mid dose, 30 mg/kg/day, based on decreased pup survival, decreased F1 animal body weight, and adverse effects on reproductive outcome in the F1 females noted at 75 mg/kg/day.

Conducting laboratory and location	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 15, 30, and 75 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	1% methylcellulose and 0.1% Tween® 80 in deionized water
Species/Strain:	Rat / Sprague-Dawley
Number/Sex/Group:	F0: 22 females/group; Selected F1: 14-21/sex/group
Satellite groups:	TK F0 animals: four females for control and 8 for dose groups
Study design:	Pregnant female rats were dosed from GD 6 to lactation day (LD) 20. The F1 offspring were potentially exposed to the

	test article in utero and as neonates during the lactation period but were not dosed directly.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Generation	Major Findings
F0 Dams	One main study high dose animal was found dead on LD 3 with no significant clinical signs or macroscopic findings. One TK high dose animal was euthanized in moribund condition on LD 0. The moribundity was likely related to complications during delivery. There were no significant test article-related findings in clinical signs, body weight, or gross pathology. Slightly longer gestation length (22.7 days vs. 22.2 days in control), decreased numbers of liveborn pups (9.9 vs. 11.5 in control) and increased total litter loss (6 main study dams within 2 days after birth) were noted at high dose.
F1 Generation	No adverse effects were observed on F1 sex ratios, physical development (pinna detachment and eye opening), neurobehavioral evaluations (motor activity, auditory startle and habituation, and Morris water maze), estrous cyclicity, reproductive performance (mating, fertility, and pregnancy indices and pre-coital interval), or macroscopic findings at any dose. Adverse effects on F1 animals were noted at high dose, including decreased pup survival (mean viability 62% vs. 100% in control), clinical findings of decreased activity, and lower body weight [up to -39% during postnatal day (PND) 1 to 28]. Lower body weight was also noted in selected F1 animals at high dose (up to -31% in males and -25% in females during PND 28 to 112). Following mating of the F1 generation, lower numbers of corpora lutea (16.5 vs. 18.0 in control), implantations (13.2 vs. 15.9 in control) and live embryos (11.6 vs. 14.8 in control), and increased resorptions (1.5 vs. 1.0 in control) and postimplantation loss (15.2 vs. 6.6 in control) were observed in pregnant F1 females at high dose.

5.5.6. Other Toxicology Studies

Phototoxicity

The phototoxic potential of deuruxolitinib was assessed in an in vitro neutral red uptake phototoxicity assay (Study# 45999 TIP, sponsor reference# CTP-543 TX-088, GLP). The phototoxic potential was assessed using reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to the test article and UV radiation compared to the viability of cells exposed to the test article in the absence of UV radiation. Concentrations of deuruxolitinib tested were in the range of 6.7 to 100 µg/ml, based on a solubility test and a preliminary test. Cells were exposed to ultraviolet A radiation at 5 J/cm^2. Deuruxolitinib did not show phototoxic potential in this assay.

Potential Impurity Evaluation

The mutagenic potential of impurities in deuruxolitinib was evaluated in accordance with the International Conference on Harmonisation M7 Guidance. The daily threshold of toxicological concern of 1.5 µg/day will be used to control an individual mutagenic impurity.

In total 31 potential process impurities were evaluated with two (Q)SAR methodologies (expert rule-based and statistical) using the Leadscope® Model Applier (version 2022.0.0-31 or 2022.0.2-3). Most compounds were predicted to be negative. One potential mutagenic impurity, (b) (4), was reported positive and will be controlled at an acceptable level. Drug substance batches tested for (b) (4) were all found to be (b) (4) ppm, which is far below the threshold of toxicological concern. Another impurity, (b) (4), was predicted positive. However, it was tested in the Ames test and the results were negative. Two other potential impurities, (b) (4), were also tested in the Ames test and the results were all negative. One impurity, (b) (4), was predicted negative in the (Q)SAR Genetox Expert Alerts and indeterminate in the (Q)SAR Genetox Statistical prediction. Subsequently it was assessed using the DEREK Nexus® software (version 6.2.0) and in this complementary assessment, (b) (4) was not expected to be mutagenic in bacteria.

The Applicant proposed control strategy for the potential impurities appear acceptable from a pharmacology/toxicology perspective. Overall, there is no significant safety concern for the potential impurities at proposed specification levels.

6 Clinical Pharmacology

6.1. Executive Summary

Deuruxolitinib (CTP-543) is a deuterated selective Janus kinase (JAK) inhibitor that modulates an immune response through intracellular JAK1 and JAK2 signaling. Deuruxolitinib is being developed as a potential oral treatment for adults with moderate to severe AA. Janus kinases bind to the intracellular domains of cytokine receptor subunits that dimerize or oligomerize upon cytokine binding. Juxtaposition of JAKs results in their phosphorylation, which activates the kinases and triggers phosphorylation of STAT proteins (signaling pathway referred to as JAK/STAT). The proposed dosing regimen is 8 mg BID with or without food.

The Applicant evaluated the PK of deuruxolitinib in eleven separate Phase 1 trials, and three trials in the target patient population with AA incusing one Phase 2 and two Phase 3 trials. Additional trials conducted to obtain clinical information include a thorough QT study, a dose-ranging trial, a mass-balance study, a renal impairment study, a hepatic impairment study, five clinical drug-drug interaction studies, two Food effect and two relative bioavailability studies. Population PK (PopPK) analyses and the exposure-response (E-R) analyses were also performed to support the application.

The key review findings with specific recommendations and comments are summarized below in Table 3.

Table 3. Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Efficacy of the proposed dosing regimen is established in two Phase 3 trials (CP543.3001 and CP543.3002). The exposure-response (E-R) analyses for efficacy (SALT of ≤20) from a Phase 2 trial and two Phase 3 trials provide supportive evidence of efficacy. See Section 16.4.2 for details.
Pharmacokinetics (PK)	The PK of deuruxolitinib at the proposed dosing regimen of 8 mg twice daily was characterized using PopPK modeling which used sparse data from one Phase 2 (CP543.2001) and two Phase 3 trials (CP543.3001 and CP543.3002) in subjects with AA.

Review Issues	Recommendations and Comments
Pharmacodynamics (PD)	Deuruxolitinib showed inhibition of the interleukin 6 (IL-6)-mediated pSTAT3 signaling pathway after ex vivo stimulation of whole blood on Day 1 and Day 7. For the timepoints tested (2, 8, and 24 hours postdose), maximum inhibition generally occurred at the 2 hours postdose timepoint. Inhibition of IL-6-mediated pSTAT3 was moderate across the dosing cohorts and ranged from 31% to 67% at 2 hours postdose.
General dosing instruction	The food effect study (CP543.1003) conducted using high-fat high-calorie meal supports the dosing instruction without regards to meal.
Dosing in specific populations (intrinsic and extrinsic factors)	Deuruxolitinib is not recommended in patients with severe hepatic impairment (Child-Pugh C), severe renal impairment, strong and moderate CYP2C9 inhibitors, strong CYP3A4 and moderate CYP2C9 inducers and CYP2C9 poor metabolizers.
Bridge between the to-be-marketed and clinical trial formulations	Three oral formulations were used to support the clinical development program [oral solution, powder in capsule (PIC), and film-coated tablet]. Two studies (IM011002 and IM011031) were conducted to evaluate the relative bioavailability of the capsule compared to solution and the tablet to capsule, respectively. The Phase 3 tablet formulation is similar to the proposed to-be-marketed formulation except the coating and printing, and these differences are supported by dissolution data per the Biopharmaceutics review team.
QTc prolongation potential	A thorough QT study (Study CP543.1010) was conducted. At a dose 6 times the proposed dose of the 8 mg twice daily, deuruxolitinib does not prolong the QTc interval to any clinically relevant extent.

Abbreviations: IRT, interdisciplinary review team; TQT, thorough QT/QTc

6.1.1. Postmarketing Requirement

A Pediatric Research Equity Act (PREA)-PMR will be issued to evaluate safety, efficacy, and PK of deuruxolitinib in pediatric subjects 6 years to less than 17 years of age.

Another PMR will be issued to conduct a PK study in subjects who are CYP2C9 normal metabolizers, intermediate metabolizers, and poor metabolizers (PM) in order to characterize the systemic exposure of deuruxolitinib in these subgroups. See Section 13 for details.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

Deuruxolitinib (CTP-543) is a deuterated selective Janus kinase (JAK) inhibitor that modulates an immune response through intracellular JAK1 and JAK2 signaling. The exact mechanism of action of deucravacitinib for the treatment of AA is unknown.

Pharmacokinetics

Deuruxolitinib showed a rapid and close to complete absorption (oral absorption is 90%) and systemic exposure parameters were proportional to dose between 4 mg BID and 12-mg BID regimens in healthy subjects using uncoated tablet formulation. The mean terminal half-life of deuruxolitinib following once daily and BID dosing of tablet formulation in healthy subject was 2.9 and 4.2 hr. There was minimal accumulation of deuruxolitinib, which is consistent with short terminal half-life of 4 hours following twice daily dosing. The PK of deuruxolitinib was comparable between healthy subjects and subjects with AA. The population pharmacokinetics (PopPK) model predicted geometric mean steady state AUC_{0-12} following 12 mg BID was 1300 ng*h/mL compared to 869 ng*h/mL for 8-mg BID regimens, representing an approximately 1.47-fold increase in area under the concentration-time curve (AUC) with a 1.50-fold increase in dose. Similarly, AUC increased by approximately 2-fold between 4 mg BID and 8 mg BID. While geometric mean C_{max} increased slightly less than proportional between 4 mg and 8 mg (1.83-fold for a 2-fold increase in dose), geometric mean C_{max} increased by 1.48-fold from 8 mg to 12 mg BID for the same 1.50-fold increase in dose. Median (range) T_{max} occurred at 1.02 (0.366-2.37) hours for the 4-mg BID regimen and 1.07 (0.266-3.37) hours for both the 8-mg and 12-mg doses. The estimated terminal elimination half-life was independent of dose with a mean between 3.97 and 4.46 hours for 4 to 12-mg BID regimens. Overall, apparent clearance (CL/F) and apparent volume of distribution (V2/F) were consistent across studies where subjects with moderate to severe AA were treated and included in the E-R analysis (Studies CP543.2001, CP543.2004, and CP543.3002). Mean (coefficient of variation percentage) CL/F and V2/F for subjects with AA included in the E-R population was 10.3 (55.1%) L/h and 53.8 (29.9%) L, respectively.

Deuruxolitinib was metabolized by three primary biotransformation pathways, including oxidation, di-oxidation, and glucuronidation. The 2 most abundant human metabolites, C-21714 and C-21717, accounted for approximately 5.39% and 4.96% of total drug-related AUC, respectively. Both the metabolites are pharmacologically inactive.

Following oral administration, deuruxolitinib was eliminated via renal and fecal elimination predominantly as metabolites. After a single dose of radiolabeled deuruxolitinib, approximately 70% and 20% of the dose was recovered in urine and feces. Unchanged deuruxolitinib represented less than 2% of the radioactivity in excreta. No single metabolite in feces

represented more than 10% of the administered radioactive dose, and no single metabolite represented more than 25% of the administered radioactive dose in urine.

Pharmacodynamics

Deuruxolitinib (CTP-543) is a deuterated selective Janus kinase (JAK) inhibitor that modulates an immune response through intracellular JAK1 and JAK2 signaling. Deuruxolitinib showed inhibition of the IL-6-mediated pSTAT3 signaling pathway after ex vivo stimulation of whole blood on Day 1 and Day 7. For the timepoints tested (2, 8, and 24 hours postdose), maximum inhibition generally occurred at the 2 hours postdose timepoint. Inhibition of IL-6-mediated pSTAT3 was moderate across the dosing cohorts and ranged from 31% to 67% at 2 hours postdose.

Clinical Drug Interaction Studies

Article I. A clinically significant difference in the PK of deuruxolitinib were observed when coadministered with multiple doses of rifampin (a strong CYP3A4 and moderate CYP2C9 inducer), resulting in decreased deuruxolitinib total exposure by 78% and peak exposure by 41% relative to a single 12-mg deuruxolitinib dose given alone. Given the reduced exposure and potential for loss of efficacy, it is recommended to avoid the concomitant use of strong CYP3A4 and moderate CYP2C9 inducers with deuruxolitinib.

Article II. No clinically significant difference in the PK of deuruxolitinib were observed when coadministered with multiple doses of efavirenz (a moderate CYP3A4 inducer), resulting in decreased deuruxolitinib total exposure by 33% and peak exposure by 10% relative to deuruxolitinib dose given alone. No adjustment of deuruxolitinib dosing is recommended for patients requiring the concomitant use of a moderate CYP3A4 inducer.

Article III. No clinically significant difference in the PK of deuruxolitinib were observed when coadministered with multiple doses of itraconazole (a strong CYP3A4 inhibitor), resulting in increased deuruxolitinib total exposure by 27% and peak exposure by 13% relative to deuruxolitinib dose given alone. No adjustment of deuruxolitinib dosing is recommended for patients requiring the concomitant use of a strong CYP3A4 inhibitor.

Article IV. A clinically significant difference in the PK of deuruxolitinib were observed when coadministered with multiple doses of fluconazole (a dual CYP3A4 and CYP2C9 inhibitor), resulting in increased deuruxolitinib total exposure by 140% and peak exposure by 21% relative to deuruxolitinib dose given alone. Given the significant increase in exposure and potential concern for safety associated with higher exposure of deuruxolitinib, the concomitant use of moderate CYP2C9 inhibitors with deuruxolitinib is contraindicated as CYP2C9 is the major metabolizing enzyme.

Article V. A clinically significant difference in the PK of deuruxolitinib were predicted when coadministered with multiple doses of sulphaphenazole (a strong CYP2C9 inhibitor), resulting in increased deuruxolitinib total exposure by greater than 200% and peak exposure by 25%

relative to deuruxolitinib dose given alone. Given the significant increase in exposure and potential concern for safety associated with higher exposure of deuruxolitinib, the concomitant use of strong CYP2C9 inhibitors with deuruxolitinib is contraindicated as CYP2C9 is the major metabolizing enzyme.

Article VI. Deuruxolitinib is not anticipated to induce the metabolism of CYP3A4 substrates to a clinically meaningful extent, and dose adjustment of the CYP3A4 substrate is not needed, when coadministered with deuruxolitinib in clinic.

Food Effect

The effect of a high fat/high-calorie meal (approximately 50% fat and 800-1000 calories) on the PK of 8 mg deuruxolitinib was evaluated in healthy subjects. Under fed conditions, C_{max} of deuruxolitinib decreased by 30-40% and no corresponding decrease in plasma deuruxolitinib AUC respectively. Deuruxolitinib is recommended to be taken without regards to meals.

QT Prolongation

At a dose of 48 mg which is 6 times the recommended dose of 8 mg, deuruxolitinib did not show significant QTcF prolongation effect. The estimated mean values of the ΔQTcF at the geometric mean deuruxolitinib C_{max} resulted in a CI upper bound of 2.0 msec for the 48-mg dose (supratherapeutic). Also, the corresponding safety margin for free deuruxolitinib based on the in vitro hERG assay deuruxolitinib IC_{50} result of 153 µM, is at least 3900 times higher than the systemic exposure of 8-mg BID dose.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

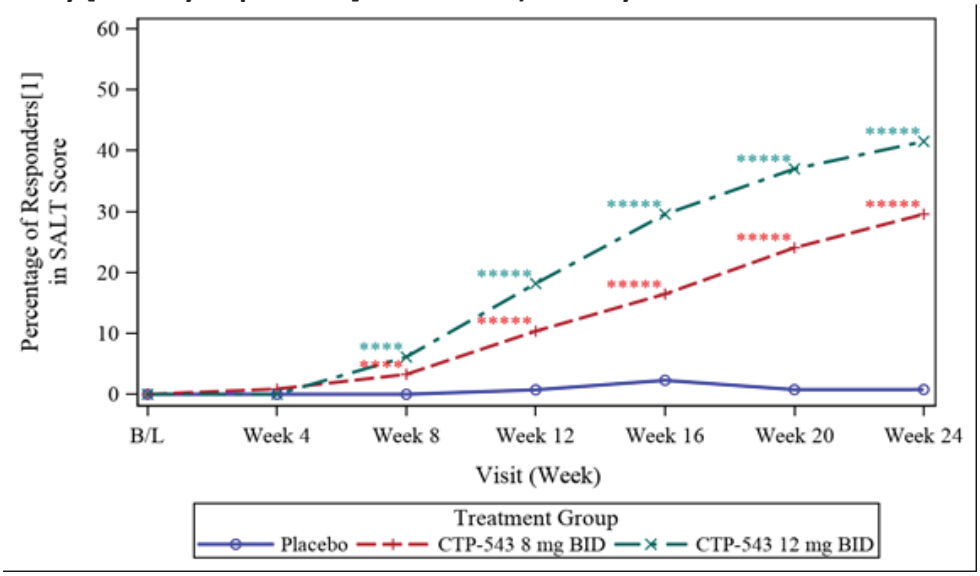
The proposed dosing regimen is 8 mg deuruxolitinib tablet administered orally BID, with or without food. This dosing regimen is supported by the efficacy and safety data from one Phase 2 dose-ranging trial (CP543.2001) and efficacy and safety data from two separate Phase 3 trials (CP543.3001 and CP543.3002).

The food effect studies (Study CP543.1003 and Study CP543.1011) supports dosing instruction without regards to meal.

The 8-mg BID dose was selected based on the findings from two pivotal Phase 3 trials (Study CP543.3001 and Study CP543.3002), which had the same overall design except for the randomization ratio. Both studies were multicenter, randomized, double-blind, placebo-controlled trials to evaluate the safety and efficacy of deuruxolitinib 12 mg BID or 8 mg BID following 24 weeks of dosing in adults with moderate to severe AA. The results from both trials showed dose-response as shown in Figure 1 from Study # CP543.3001 and Figure 2 from Study # CP543.3002 respectively. Although 12 mg BID show better efficacy, but is not proposed as the final dose, due to emerging long-term safety concerns of thrombosis and hence only 8-mg BID

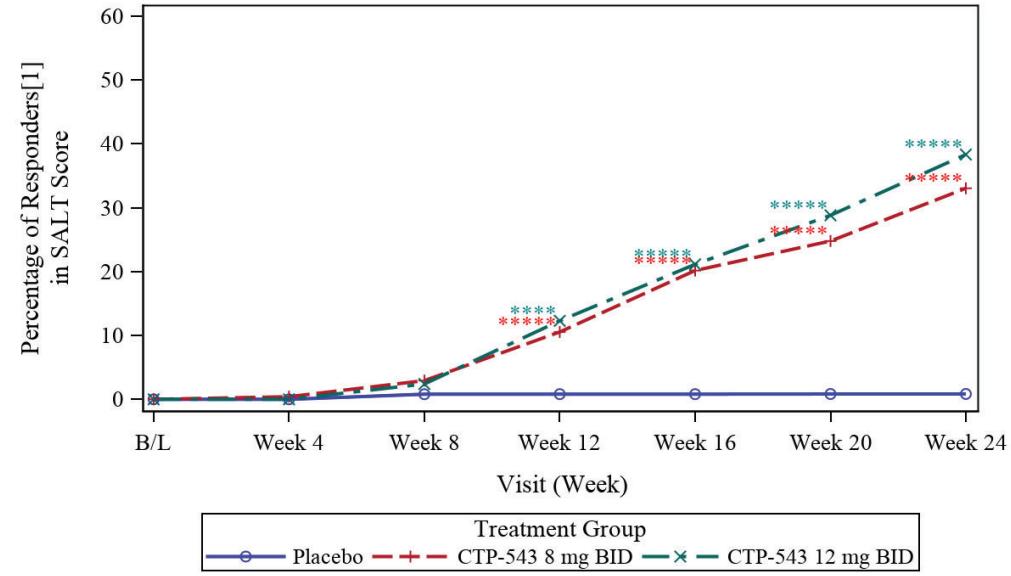
dose was selected for final dose selection in adults' population. See Section 8 for additional details of safety.

Figure 1. Primary Efficacy Analysis (Subjects With SALT Scores of ≤20 by Treatment, Visit, and Study [Efficacy Population] at Week 24) – Study# CP543.3001



Source: CP543.3001 Post-text Figure 14.2.1.2
Abbreviations: BID, twice daily; CTP-543, deuruxolitinib; MAR, missing at random; MI, multiple imputation; SALT, Severity of Alopecia Tool

Figure 2. Primary Efficacy Analysis (Subjects With SALT Scores of ≤20 by Treatment, Visit, and Study [Efficacy Population] at Week 24) – Study# CP543.3002



Source: CP543.3002 Figure 14.2.1.2
Abbreviations: BID, twice daily; CTP-543, deuruxolitinib; MAR, missing at random; MI, multiple imputation; SALT, Severity of Alopecia Tool

Therapeutic Individualization

No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Deuruxolitinib is not recommended in patients with severe hepatic impairment (Child Pugh C) as the PK of deuruxolitinib have not been studied in severe hepatic impairment.

Also, no adjustment of deuruxolitinib dosing is recommended in patients with mild or moderate renal impairment. Deuruxolitinib is not recommended in patients with severe renal impairment or end-stage renal disease as the PK of deuruxolitinib has not been studied in severe renal impairment or end-stage renal disease.

Deuruxolitinib is primarily metabolized by CYP2C9. CYP2C9 activity is reduced in patients with genetic variants in CYP2C9, such as the CYP2C9*2 and CYP2C9*3 alleles. The impact of CYP2C9 genetic variants on the pharmacokinetics of deuruxolitinib has not been directly evaluated. Based on the physiologically based pharmacokinetic (PBPK) modeling and simulations, the total exposure (AUC_{0-t}) is estimated to increase 2-fold in CYP2C9 poor metabolizers (CYP2C9*3/*3 genotype), compared to normal metabolizers (CYP2C9*1/*1 genotype) and thus deuruxolitinib is not recommended in CYP2C9 poor metabolizers patients. Since the impact of CYP2C9 genetic variants on the pharmacokinetics of deuruxolitinib has not been directly evaluated in the clinical program, there are no data to reliably exclude the possibility of increased serious safety risks in these patient populations. Therefore, we recommend including a requirement for CYP2C9 genotype status testing and a contraindication statement for CYP2C9 poor metabolizers. A postmarketing study will be required to assess systemic exposure of deuruxolitinib in CYP2C9 poor metabolizers to further inform the dosing is these patients.

Outstanding Issues

There are no outstanding issues from the Clinical Pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Mechanism of Action

Deuruxolitinib (CTP-543) is a deuterated selective JAK inhibitor that modulates an immune response through intracellular JAK1 and JAK2 signaling. JAKs bind to the intracellular domains of cytokine receptor subunits that dimerize or oligomerize upon cytokine binding. Juxtaposition of JAKs results in their phosphorylation, which activates the kinases and triggers phosphorylation of STAT proteins (signaling pathway referred to as JAK/STAT). Based on in vitro studies, deuruxolitinib inhibits cytokine-stimulated, and JAK-mediated, phosphorylation of STAT proteins in human cells, suggesting that suppression of JAK/STAT signaling is the primary mechanism of action for deuruxolitinib.

Pharmacokinetics

PK after single ascending dose/multiple ascending dose (Study CP543.1001):

Study CP543.1001 is a 2-part (Part A and Part B) trial designed to assess the safety, tolerability, PK, and pharmacodynamics (PD) profile of single and multiple doses of deuruxolitinib in healthy subjects under fasted conditions. The PK parameters after single ascending dose and multiple ascending dose obtained from this trial are summarized in Table 4 and Table 5, respectively. The descriptive steady-state PK parameters of deuruxolitinib for each dose using PopPK modeling are presented in Table 6.

Table 4. Mean PK Parameters of Deuruxolitinib Following a Single Oral Dose in Healthy Subjects From Study# CP543.1001

	Oral Deuruxolitinib (Mean (CV%))							
Treatment (n)	**$AUC_{(0-24)}$ (ng.h/mL)**	**AUC(INF) (ng.h/mL)**	**C_{max} (ng/mL)**	**T_{max}[a] (h)**	**$t_{1/2}$ (h)**	**C24 (ng/mL)**	**CL/F (mL/h)**	**Vz/F (mL)**
Deuruxolitinib 8 mg (n=6)	584 (31.3)	589 (31.6)	118 (28.4)	1.23 (0.5-1.5)	3.14 (28.4)	1.02 (94.9)	14.92 (34.9)	64.1 (27.8)
Deuruxolitinib 16 mg (n=6)	1329 (34.7)	1347 (35.2)	260 (39.2)	1.5 (0.5-3.2)	3.32 (25.9)	2.77 (78.4)	13.87 (52.4)	61.0 (28.0)
Deuruxolitinib 32 mg (n=6)	2424 (25.2)	2462 (26.3)	535 (29.0)	1.25 (0.5-2.00)	3.52 (15.9)	5.6 (104.5)	13.88 (30.2)	68.4 (21.3)
Deuruxolitinib 48 mg (n=5)	4098 (34.2)	4159 (35.1)	853 (25.7)	1.5 (0.5-2.00)	3.61 (21.4)	9.26 (80.1)	12.75 (34.1)	63.2 (25.6)

Source: Study CP543.1001 CSR, Table 12
For T_{max}, the median, min and max are presented

Table 5. Mean PK Parameters of Deuruxolitinib Following a Multiple Oral Dose in Healthy Subjects From Study# CP543.1001

		Oral Deuruxolitinib (Mean (CV%))				
Treatment (n)	**Study Day**	**AUC_{tau}/ AUC_{0-last} (ng.h/mL)**	**C_{max} (ng/mL)**	**T_{max}[a] (h)**	**$t_{1/2}$ (h)**	**C_{trough} (ng/mL)**
Deuruxolitinib 8 mg QD (n=7)	Day 1	704 (26.4)	156 (31.2)	1.0 (0.5-2.00)	3.23 (9.6)	0.86 (45.3)
	Day 7	668 (27.8)	151 (34.1)	1.0 (0.25-1.5)	3.51 (20.9)	1.01 (75.0)
Deuruxolitinib 24 mg QD (n=8)	Day 1	1672 (25.7)	384 (22.2)	0.5 (0.25-2.00)	3.14 (28.8)	2.48 (134)
	Day 7	1534 (25.2)	310 (22.9)	1.0 (0.5-2.0)	3.5 (25.2)	3.39 (160)
Deuruxolitinib 32 mg QD (n=8)	Day 1	2219 (36.2)	509 (32.8)	0.75 (0.5-2.00)	2.86 (32.1)	2.95 (141)
	Day 7	2104 (27.8)	492 (18.0)	0.75 (0.5-2.00)	3.45 (37.1)	5.12 (153)
Deuruxolitinib 8 mg BID (n=4)	Day 1	703 (24.5)	160 (17.5)	1.0 (0.5-1.5)	3.77 (23.4)	13.7 (55.9)
	Day 7	844 (39.8)	183 (25.7)	1.5 (0.25-2.0)	4.2 (32.3)	13.2 (59.6)

		Oral Deuruxolitinib (Mean (CV%))				
Treatment (n)	Study Day	AUC_{tau}/ $AUC_{0\text{-last}}$ (ng.h/mL)	C_{max} (ng/mL)	T_{max}[a] (h)	$t_{1/2}$ (h)	C_{trough} (ng/mL)
Deuruxolitinib 16 mg BID (n=8)	Day 1	1062 (22.5)	290 (19.7)	1.0 (0.5-2.00)	2.89 (31.4)	15.3 (53.9)
	Day 7	1127 (26.6)	288 (36.3)	0.75 (0.5-2.00)	3.53 (19.3)	16.5 (71.6)

Source: Study CP543.1001 CSR, Table 13, Table 14
[a] For T_{max}, the median, min and max are presented

Table 6. Descriptive Steady-State PK Parameters of Deuruxolitinib Following Dose Using PopPK Modeling

	4 mg (N = 30)	8 mg (N = 322)	12 mg (N = 232)	16 mg[a] (N = 54)	24 mg (N = 8)	32 mg (N = 14)	48 mg (N = 5)	Total (N = 665)
$AUC_{0\text{-}12}$ (ng•h/mL)								
Mean (CV%)	498 (49.1%)	1010 (64.4%)	1550 (77.3%)	1360 (31.5%)	1420 (25.9%)	2040 (28.4%)	3650 (32.3%)	1250 (75.1%)
Median [min, max]	446 [145, 1270]	881 [184, 6040]	1260 [362, 8560]	1280 [529, 2500]	1330 [1030, 2160]	2110 [1160, 3040]	3510 [2380, 4890]	1050 [145, 8560]
Geo. mean (Geo. CV%)	446 (51.0%)	869 (57.2%)	1300 (60.9%)	1290 (32.9%)	1380 (24.6%)	1960 (30.7%)	3490 (34.2%)	1040 (65.5%)
C_{max} (ng/mL)								
Mean (CV%)	85.1 (42.1%)	157 (48.2%)	237 (54.9%)	270 (37.1%)	317 (22.0%)	424 (19.1%)	681 (25.9%)	202 (60.9%)
Median [min, max]	83.2 [21.9, 203]	145 [24.9, 689]	222 [48.6, 954]	255 [104, 508]	320 [228, 451]	430 [276, 563]	682 [399, 837]	179 [21.9, 954]
Geo. mean (Geo. CV%)	78.1 (46.0%)	141 (50.5%)	209 (54.3%)	251 (41.0%)	311 (21.8%)	416 (20.3%)	660 (30.7%)	173 (62.3%)
C_{min} (ng/mL)								
Mean (CV%)	15.5 (103.0%)	36.2 (116.5%)	59.0 (140.8%)	29.7 (65.0%)	24.3 (82.7%)	36.3 (73.6%)	72.7 (56.9%)	42.8 (138.1%)
Median [min, max]	8.44 [1.59, 69.8]	23.6 [0.825, 371]	34.2 [3.50, 538]	25.7 [4.29, 76.3]	19.3 [7.98, 71.8]	36.2 [5.52, 89.6]	60.8 [23.7, 117]	26.5 [0.825, 538]
Geo. mean (Geo. CV%)	9.94 (124.0%)	23.4 (117.4%)	35.8 (117.9%)	23.7 (80.8%)	19.7 (72.5%)	26.4 (111.8%)	62.1 (74.6%)	26.3 (122.4%)
C_{avg} (ng/mL)								
Mean (CV%)	41.5 (49.1%)	84.1 (64.4%)	129 (77.3%)	113 (31.5%)	118 (25.9%)	170 (28.4%)	304 (32.3%)	104 (75.1%)
Median [min, max]	37.2 [12.1, 106]	73.4 [15.3, 503]	105 [30.2, 714]	107 [44.0, 208]	111 [86.0, 180]	176 [97.0, 254]	293 [198, 408]	87.4 [12.1, 714]
Geo. mean (Geo. CV%)	37.1 (51.0%)	72.4 (57.2%)	108 (60.9%)	108 (32.9%)	115 (24.6%)	163 (30.7%)	291 (34.2%)	86.3 (65.5%)

	4 mg (N = 30)	8 mg (N = 322)	12 mg (N = 232)	16 mg[a] (N = 54)	24 mg (N = 8)	32 mg (N = 14)	48 mg (N = 5)	Total (N = 665)
T_{max} (h)								
Mean (CV%)	1.15 (42.5%)	1.18 (50.3%)	1.18 (53.7%)	1.28 (69.1%)	0.791 (17.6%)	1.11 (28.2%)	1.35 (21.9%)	1.18 (52.7%)
Median [min, max]	1.02 [0.366, 2.37]	1.07 [0.266, 3.37]	1.07 [0.266, 3.07]	0.866 [0.266, 3.37]	0.766 [0.566, 1.07]	1.22 [0.566, 1.57]	1.27 [0.966, 1.77]	1.07 [0.266, 3.37]
Geo. mean (Geo. CV%)	1.04 (48.0%)	1.05 (52.7%)	1.03 (57.5%)	1.04 (71.1%)	0.780 (17.6%)	1.06 (33.0%)	1.32 (22.5%)	1.04 (55.0%)
T1/2 (h)								
Mean (CV%)	4.41 (53.2%)	4.86 (52.6%)	5.04 (63.8%)	3.35 (23.3%)	3.07 (26.2%)	3.06 (27.3%)	3.19 (16.1%)	4.71 (57.7%)
Median [min, max]	3.64 [2.11, 11.3]	4.04 [1.88, 16.5]	4.16 [2.15, 28.6]	3.10 [2.17, 5.52]	2.93 [2.35, 4.93]	3.03 [2.11, 5.03]	3.07 [2.46, 3.72]	3.95 [1.88, 28.6]
Geo. mean (Geo. CV%)	3.97 (46.2%)	4.38 (45.3%)	4.46 (47.5%)	3.27 (22.7%)	3.00 (23.0%)	2.96 (26.4%)	3.15 (16.9%)	4.22 (45.4%)

Source: Concert-PopPK_Covariate Model Run21014-Simulated Exposures_v3.Rmd
Abbreviations: $AUC_{0\text{-}12}$, area under the plasma concentration-time curve over the dosing interval; C_{avg}, average plasma concentration; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CV%, percentage of the coefficient of variation; Geo., geometric; max, maximum; min, minimum; N, number of subjects with available information; PK, pharmacokinetic; $T_{1/2}$, half-life; T_{max}, time to C_{max}

Mass Balance (Study CP543.1004)

An open-label study in healthy male subjects (N=6) was conducted to assess the absorption, metabolism, route(s) of elimination and mass balance of deuruxolitinib following a single oral dose of [14C]-deuruxolitinib, quantitating total radioactivity (TRA) concentration equivalents in plasma following a single oral dose of [14C]-deuruxolitinib. In addition, collected plasma, urine, and fecal samples were used to evaluate biotransformation profiles. Following administration of a single oral dose of radiolabeled deuruxolitinib, an average of 90% of administered radioactivity was recovered with 70% recovered in urine and 20% recovered in feces indicating urinary excretion as the major elimination pathway for drug-related material in humans. The mean deuruxolitinib plasma C_{max} and AUC_t were approximately 72% and 62% those of TRA in plasma, respectively, indicating that the parent drug accounted for the majority of radioactivity in systemic circulation over the first 12 hours postdose compared to metabolites. The mean t½ was around 3.5 hours for plasma deuruxolitinib compared to 5.8 and 5.5 hours for TRA in plasma and whole blood, respectively, indicating that some metabolites are eliminated at slightly slower rates than the parent drug. Mean C_{max} were 8.984 and 8.424 ng/mL for the metabolites C-21714 and C-21717, respectively, which is approximately 50 times lower than the mean C_{max} of deuruxolitinib (434.1 ng/mL). The mean CL/F and Vz/F values for deuruxolitinib in plasma were 9.044 L/h and 43.57 L, respectively. Considering total exposure (AUC_∞), C-21714 and C-21717 constituted about 6% and 5% of the parent drug, respectively. Unchanged deuruxolitinib was the major component detected in plasma, no other components were observed at >10% of the circulating radioactivity in plasma; however, it was not observed as a radioactive component in either urine or feces. No single component contributed more than 25% of the radiolabeled dose in either urine or feces. All metabolites >1% of total AUC detected in humans were also detected in rats and dogs (although sometimes at <1% of total AUC).The PK parameters for deuruxolitinib and TRA are summarized in Table 7.

Table 7. Summary of PK Parameters for Plasma Deuruxolitinib, C-21714 and C-21717, and Total Radioactivity in Plasma and Whole Blood From a Mass Balance From Study# CP543.1004

PK Parameter (Mean (CV%))	Deuruxolitinib (N=6)	C-21714 (N=6)	C-21717 (N=6)	TRA in Plasma (N=6)	TRA Blood (N=6)
C_{max} (ng/mL)	434.1 (27.1	8.98 (75.2)	8.42 (61.2)	606.2 (21.5)	641.9 (13.8)
T_{max} (hr)a	0.76 (0.5-1.5)	3.0 (2.0-4.0)	0.78 (0.5-4.0)	0.78 (0.51-2.01)	0.53 (0.52-1.09)
AUC_{0-12} (hr*ng/mL)	2056 (23.6)	NC	NC	3312 (16.1)	NC
AUC_{inf} (hr*ng/mL)	2254 (27.1)	134.2 (64.8)	108.1)52.9)	3885 (19.9)	4584 (12.7)
$T_{1/2}$ (hr)	3.49 (±0.83)	9.724 (±2.44)	6.342 (±1.28	5.79 (±2.08)	5.500 (±0.64)
CL/F (L/hr)	9.044 (±2.653)	NC	NC	NC	NC
Vz/F (L)	43.57 (±7.573)	NC	NC	NC	NC

Source: Study CP543.1004 CSR, Table 11-3

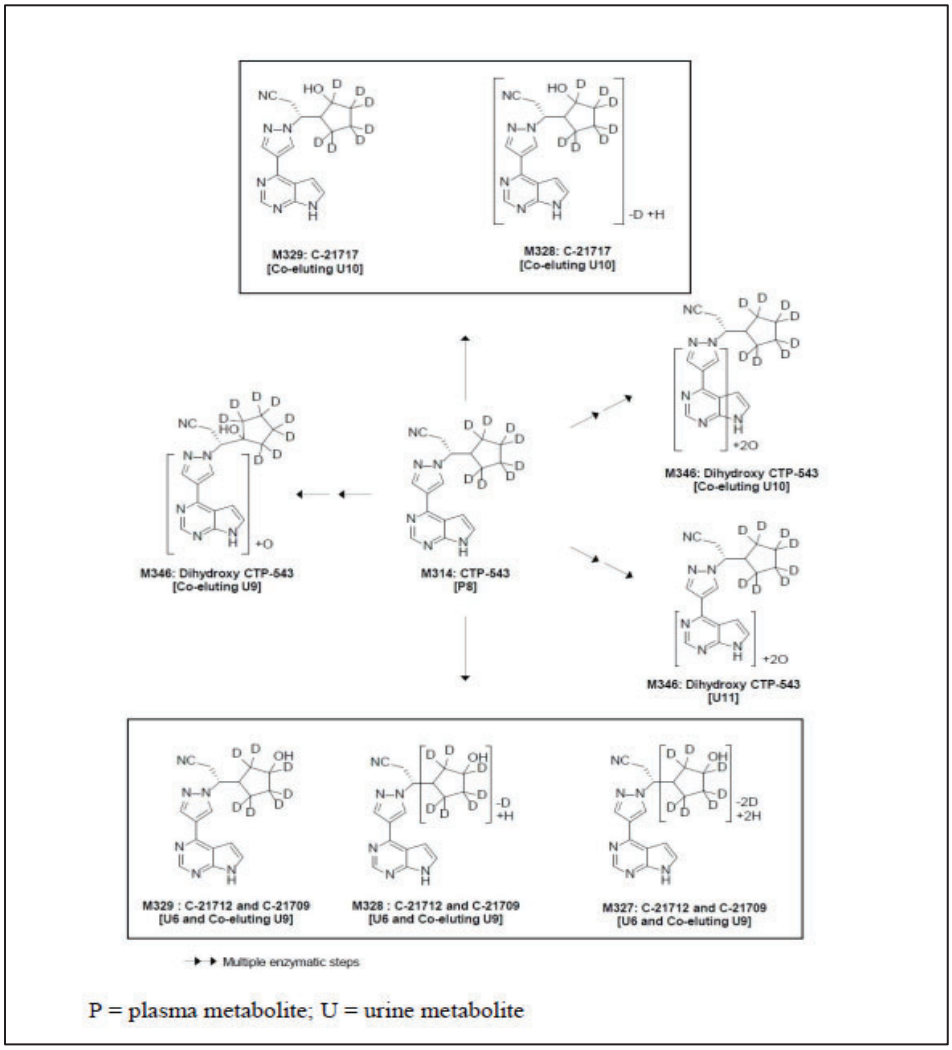
Metabolite profiling in feces identified a mean of 57.7% of metabolites in feces are the result of oxidation, which is equivalent to 11.6% of the administered radioactivity, leaving only 8.47% of the dose unassigned in the feces. From this study, it was observed that 69.93% of the dose was excreted in urine; of these components, 90.3% have been identified, equivalent to 63.1% of the

administered radioactive dose. These data further support deuruxolitinib is extensively absorbed and subsequently excreted, largely as metabolites.

Following a single 20 mg (75 µCi) orally administered dose of [14C]-deuruxolitinib to healthy adult male subjects (N=6), unchanged deuruxolitinib was the major component detected in plasma, no other components were observed at >10% of the circulating radioactivity in plasma; however, it was not observed as a radioactive component in either urine or feces. No single component contributed more than 25% of the radiolabeled dose in either urine or feces. All metabolites >1% of total AUC detected in humans were also detected in rats and dogs (although sometimes at <1% of total AUC).

The proposed biotransformation pathways of [^{14}C] Deuruxolitinib in human for components greater than 10% sample radioactivity (plasma) or greater than 10% dose in the excreta is shown in Figure 3.

Figure 3. Proposed Biotransformation Pathway for Components >10% Sample Radioactivity (Plasma) or >10% Dose (Excreta) in Humans



Source: Study CP543.1004

Hepatic Impairment (Study CP543.1013)

An open-label, single-dose, single-period, parallel-group designed study with the primary objective of determining the effect of mild and moderate hepatic impairment on the PK of deuruxolitinib following administration of a single 12-mg oral dose of deuruxolitinib. The summary of plasma deuruxolitinib PK parameters between mild and moderate hepatic impairment and normal hepatic function groups are shown in Table 8.

Table 8. Summary of Plasma Deuruxolitinib PK Parameters Among Subjects With Mild and Moderate Hepatic Impairment and Subjects With Normal Hepatic Function Following Administration of 12-mg Deuruxolitinib Tablet

PK Parameter (Mean (CV%))	Normal Hepatic Function (Reference) n=8	Mild Hepatic Impairment (Test) n=6	Moderate Hepatic Impairment (Test) n=7
C_{max} (ng/mL)	192 (35.2)	173 (31.5)	180 (46.6)
T_{max} (hr)a	0.75 (0.5-1.5)	0.5 (0.5-1.5)	1.00 (1.5-4.0)
$AUC_{0\text{-}last}$ (hr*ng/mL)	1000 (35.2)	938 (43.1)	1140 (30.0)
AUC_{inf} (hr*ng/mL)	1010 (35.2)	942 (42.9)	1150 (29.7)
$T_{1/2}$ (hr)	4.55 (±1.13)	4.46 (±0.99)	5.27 (±1.51)
CL/F (L/hr)	12.5 (±4.40)	13.7 (±5.89)	10.9 (±3.41)
Vz/F (L)	43.57 (±7.5714)	83.0 (±22.5)	79.4 (±22.3)

Source: Study CP543.1013 Pharmacokinetic Report, 5.3.1.
AUC and C_{max} values are presented as geometric mean (CV%). T_{max} values are presented as median (minimum, maximum). Other parameters are presented as arithmetic mean (±SD).

The results of this study show no adjustment of deuruxolitinib dosing is warranted in mild or moderate hepatic impairment. The PK of deuruxolitinib have not been studied in severe hepatic impairment. Hence it will not be recommended to be administered in severe hepatic impaired patients.

Renal Impairment: Study CP543.1014

An open-label, single-dose, sequentially designed, single-period study with the primary objective of determining the effect of moderate renal impairment on the PK of deuruxolitinib following administration of a single 12-mg oral dose of deuruxolitinib. The summary of plasma deuruxolitinib PK parameters between subjects with moderate renal impairment (eGFR ≥30 to <60) and normal renal function (eGFR ≥90) with the outlier excluded is shown in Table 9.

Table 9. Deuruxolitinib PK Parameters Summary Statistics

PK Parameter	Normal Renal Function (Reference) n=8	Moderate Renal Impairment (Test) n=7
C_{max} (ng/mL)	199 (21.4)	207 (38.4)
T_{max} (hr)a	0.71 (0.25-1.0)	0.5 (0.25-3.0)
$AUC_{0\text{-}last}$ (hr*ng/mL)	836 (20.9)	1040 (41.6)
AUC_{inf} (hr*ng/mL)	843 (20.6)	1050 (41.6)
$T_{1/2}$ (hr)	4.36 (±1.44)	4.54 (±1.36)
CL/F (L/hr)	14.5 (±2.76)	12.3 (±5.15)
Vz/F (L)	88.9 (±29.5)	74.5 (±18.5)

Source: Study CP543.1014 Pharmacokinetic Report, Table 8.4.1.1 and Table 8.4.2.2
AUC and C_{max} values are presented as geometric mean (CV%). t_{max} values are presented as median (minimum, maximum). Other parameters are presented as arithmetic mean (±SD).

No adjustment of deuruxolitinib dosing is warranted in patients with mild or moderate renal impairment. The PK of deuruxolitinib has not been studied in severe renal impairment or end-stage renal disease. Hence it is not recommended in patients with severe renal impairment or end-stage renal disease.

Thorough QT: Study CP543.1010

A single-center, 4-arm, randomized, crossover design, placebo, and active-controlled study. The primary objective was to evaluate the effect of maximum therapeutic and supratherapeutic doses of deuruxolitinib on QTcF in healthy subjects.

The primary endpoint of the ΔΔQTcF showed the largest mean increase for deuruxolitinib in the QTcF was 1.4±7.27 msec (mean ± SD) for deuruxolitinib at 24 hours postdose, with an upper bound of 3.2 msec for the 1-sided 95% CI. Placebo-adjusted least-squares mean values for the ΔQTcF were all ≤10 msec at all timepoints, with the largest least-squares mean seen in the 48-mg dosing group at 8 hours postdose (4.8 msec, 95% upper bound 8.2 msec). Assay sensitivity was demonstrated using 400 mg moxifloxacin. Estimated mean values of ΔQTcF at the geometric mean C_{max} levels for the 48-mg supratherapeutic dose of deuruxolitinib had an upper bound of 2.0 msec and at the C_{max} of deuruxolitinib evaluated (2080.0 ng/mL), the estimated ΔQTcF was 0.8 msec with a 1-sided 95% CI upper bound of 3.4. The model was found without significant influence of hysteresis, HR effects, or effects due to QTcF correction. All mean QTcF increases were <5 msec.

Steady State PK of Deuruxolitinib at the Proposed Dosing Regimen

Based on the population PK (PopPK) model developed using data from Phase 1, 2, and 3 trials, the systemic exposures of deuruxolitinib in patients with AA were predicted at 4- and 8-mg BID dosing regimen. The details of the PopPK model can be found in Section 16.4.1. The summaries of deuruxolitinib exposures (C_{max}, C_{avg}, C_{min}, and AUC) at steady state are listed in Table 10.

Table 10. PopPK Model Predicted Deuruxolitinib Exposures at Steady-State at 4 mg and 8 mg QD

Deuruxolitinib	4 mg (N=30)	8 mg (N=322)
C_{max} (ng/mL) Median [min, max]	83.2 [21.9, 203]	145 [24.9, 689]
Geo. mean (geo. CV%)	78.1 (46.0%)	141 (50.5%)
C_{min} (ng/mL) Median [min, max]	8.44 [1.59, 69.8]	23.6 [0.825, 371]
Geo. mean (geo. CV%)	9.94 (124.0%)	23.4 (117.4%)

Deuruxolitinib	4 mg (N=30)	8 mg (N=322)
C_{avg} (ng/mL) Median [min, max]	37.2 [12.1, 106]	73.4 [15.3, 503]
Geo. mean (geo. CV%)	37.1 (51.0%)	72.4 (57.2%)
AUC_{0-12} (ng*h/mL Median [min, max]	446 [145, 1270]	881 [184, 6040]
Geo. mean (geo. CV%)	446 (51.0%)	869 (57.2%)

Source: Report CONC-PMX-CTP543-3280, Table 14

Formulation Bridge

In total, 3 oral formulations (powder-in-capsule, immediate-release tablet, and film-coated tablet) were utilized in the clinical development program of deuruxolitinib.

Study CP543.1009 was conducted to evaluate the relative bioequivalence of the final proposed commercial tablet formulation with the clinical coated tablet formulation used in Phase 3 trials (CP543.3001 and CP543.3002) as well as in the pivotal food-effect study (CP543.1011) and open-label extension (OLE) trial (CP543.5001, U.S. sites only). This study was an open-label, single-dose, randomized, 2-treatment, 2-period crossover study under fasted conditions in eligible healthy male or female adult subjects where a 12-mg tablet of the proposed commercial formulation was compared to the clinical formulation. Office of Study Integrity and Surveillance inspection of the clinical portion of the Study CP543.1009 conducted at Clinical Pharmacology of Miami, Hialeah, Florida, concluded that neither any objectionable conditions were observed and nor form FDA 483 was issued at the inspection close out.

The geometric mean C_{max} (coefficient of variation percentage) for the deuruxolitinib proposed commercial formulation was comparable to the clinical formulation, 275 (40.9%) and 299 (35.3%) ng/mL, respectively. The results are shown in Table 11.

Based on the results of this relative bioavailability study using 12-mg dose of Phase 3 formulation and comparative dissolution results, the Applicant requested a biowaiver for 8-mg strength of Phase 3 formulation. The biowaiver request was reviewed by Biopharmaceutics review team and was deemed acceptable.

Table 11. Relative Bioavailability Between Capsule and Solution Formulations of Deuruxolitinib

Formulation	Geometric LS Mean Ratio % (90% CI)		
	C_{max}	AUC_{last}	AUC_{inf}
Commercial tablet formulation vs. clinical coated tablet formulation (fasted)	92.01 (82.12, 103.10)	95.27 (90.36, 100.45)	95.35 (90.44, 100.53)

Source: Study CP543.1009 CSR; Appendix 16.2.10, PK Report Table 5-2, Table 5-3

The systemic exposures of proposed commercial formulation were slightly lower than those of clinical tablet formulation, but the relative bioavailability results assessing the 90% confidence

intervals (CIs) on the ratio of the geometric mean for C_{max} and AUCs were within the no effect boundary of 80% and 125%. It was also noted that the to-be-marketed tablet formulation is similar to the tablet formulation used in the Phase 3 trials, but with different coating and printing. Per the Applicant, the changes in coating and printing are considered minimal, and their comparability are supported by dissolution data. Also, based on the high aqueous solubility and in vitro permeability of the active pharmaceutical ingredient, rapid in vitro dissolution in 0.1 N HCl media, the rapid absorption, and the dose proportionality between 12-mg and 8-mg strengths support low risk from a biopharmaceutics perspective and the bridging using the 12-mg strength Phase 3 formulation can be extrapolated to support the bridging to 8-mg Phase 3 formulation. Based on the data from the pivotal relative BA study (CP543.1009), there are no concerns with utilizing clinical pharmacology information obtained from different formulations to support the deuruxolitinib development program.

Pharmacodynamics

Change in the SALT score at Week 24 was selected for the exposure-efficacy analysis employing all subjects with valid exposure values, baseline SALT scores, and a Week 24 SALT score. In the exposure-efficacy analysis population, of the 662 subjects in Studies CP543.2001, CP543.2004, and CP543.3002 combined, 162 subjects were randomized to placebo, 28 subjects for the dose of 4 mg, 276 subjects for the dose of 8 mg, and 196 subjects for the dose of 12 mg (Table 12). The steady-state exposures of C_{avg}, C_{max}, and C_{min} were used to model SALT score at Week 24 by using the following endpoints:

- Binary endpoint: Whether the subject had a SALT score ≤20 at Week 24
- Continuous endpoint: percent change from baseline SALT score

Table 12. Summary of SALT Scores ≤20 at Week 24 by Dose

SALT ≤20	Placebo (N=162)	4 mg (N=28)	8 mg (N=276)	12 mg (N=196)
No	158 (97.5%)	24 (85.7%)	202 (73.2%)	116 (59.2%)
Yes	4 (2.5%)	4 (14.3%)	74 (26.8%)	80 (40.8%)

Source: Report CONC-PMX-CTP543-3280, Table 17
Abbreviations: N, number of subjects with available information; SALT, Severity of Alopecia Tool

In the exposure-efficacy analysis population, of the 662 subjects, SALT score ≤20 at Week 24 was achieved in 4 subjects (2.5%) for the placebo group, 4 subjects (14.3%) for the 4-mg group, 74 subjects (26.8%) for the 8 mg group and 80 subjects (40.8%) for the 12-mg group.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The efficacy of deuruxolitinib for the treatment of moderate to severe AA was demonstrated in the two Phase 3 trials (CP543.3001 and CP543.3002). The clinical pharmacology data such as dose/exposure-response relationships for efficacy which is

described in Section 16.4.2 and results of pharmacodynamic in Section 6.3.1 provide supportive evidence of effectiveness. See Section 8 for additional details on efficacy.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen, 8 mg twice daily, is appropriate for the general patient population for the treatment of severe AA in adults (18 to 65 years old). The dosing regimen is supported by clinical safety and efficacy and the exposure-response analyses findings in one Phase 2 (CP543.2001) and two Phase 3 trials (CP543.3001 and CP543.3002) in subjects with AA which are described in Section 16.4.2. In addition, population PK (PopPK) model which indicated no clinically meaningful differences on deuruxolitinib exposures based on various intrinsic/extrinsic factors. A total of eleven continuous covariates and 5 categorical covariates were tested in the PopPK analysis. Which includes age, body weight, Height, body mass index (BMI), Ideal Body weight, Serum creatinine, creatinine clearance (CLcr), eGFR, ALT, aspartate aminotransferase (AST), Albumin, bilirubin, alkaline phosphatase (U/L), supports the proposed dosing regimen for the general patient population of 18 to 65 years old (Section 16.4.1). It is recommended that coadministration of deuruxolitinib with strong CYP2C9 inhibitors, dual moderate CYP2C9 and CYP3A4, and with strong CYP3A4 inducers be avoided. No adjustment is recommended when deuruxolitinib is coadministered with ethinyl estradiol (EE) and levonorgestrel (LNG) containing oral contraceptive preparations.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Use of deuruxolitinib is not recommended in patients with severe hepatic impairment (Child Pugh C), and severe renal impairment as no data is available in patients with severe hepatic and renal impairment. See Section 6.3.1 for details.

The Applicant conducted dedicated renal impairment (with moderate impairment (eGFR ≥30 to <60), compared with healthy matched control group) and hepatic impairment (with mild and moderate hepatic impairment according to the Child-Pugh Assessment criteria) studies in order to evaluate the effect of renal and hepatic functions on the PK of deuruxolitinib. The changes in the exposures of deuruxolitinib were not significant to warrant dose modifications in mild and moderate renal and hepatic impairment based on the PK study results. The summary of these studies is described below.

Renal Impairment Study (CP543.1014)

A dedicated, open-label, single-dose (12 mg), single-period, renal impairment study was conducted to evaluate the effect of moderate renal impairment, on PK of deuruxolitinib. No subjects with severe renal impairment, and end-stage renal disease subjects requiring hemodialysis (end-stage renal disease) are included in the study. The renal function groups and the number of subjects who completed the study in each group were outlined in Table 13 and

the summaries of the effect of renal impairment on exposures of deuruxolitinib is shown in Table 14.

Table 13. Number of Subjects in Renal Function Groups A and B in Study# CP543.1014

Group	Population	eGFR (mL/min/1.73 m^2)	Number of Subjects
A	Normal renal function[a]	≥90	8
B	Moderate renal function impairment	≥30 to <60	8

Source: Study report CP543.1014
[a] Control group

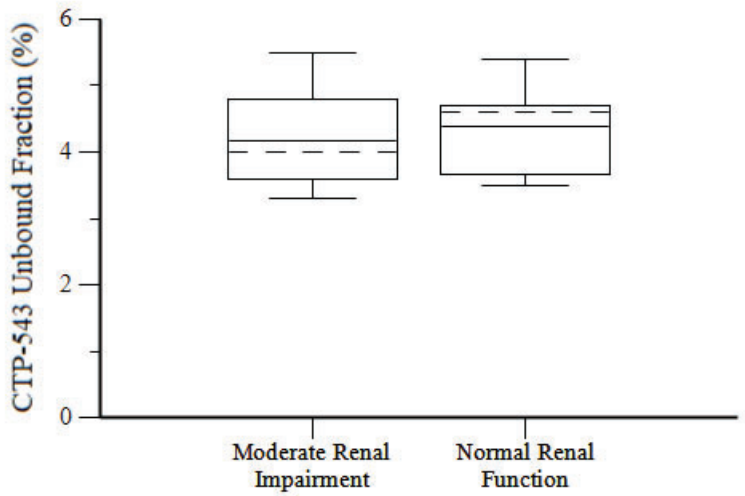
Table 14. Effect of Renal Impairment on PK of Deuruxolitinib

Comparison (Test/Reference)	PK Parameter Deuruxolitinib	Test n	Test Geo LS Mean	Reference n	Reference Geo LS Mean	Geo LS Mean % Ratio (Test/Reference) Estimate	90% CI
Moderate vs. normal renal function	C_{max} (ng/mL)	7	207.18	8	199.28	103.96	79.28, 136.34
	AUC_{tlast} (h•ng/mL)	7	1041.6	8	836.19	124.57	93.68, 165.64
	AUC_{INF} (h•ng/mL)	7	1047.96	8	843.03	124.31	93.58, 165.13

Source: Study CP543.1014 Pharmacokinetic Report Table 10.1.2.1
Note: Subject (b) (6) was excluded from Moderate Renal Impairment Cohort based on outlier test. Geometric LSMs are calculated by exponentiating the LSMs from the ANOVA. GMR =100*(test/reference).
Abbreviations: ANOVA, analysis of covariance; AUC, area under the plasma concentration versus time curve; AUC_{tlast}, area under the plasma concentration versus time curve from time 0 to the last observable time; AUC_{inf}, area under the plasma concentration versus time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum measured plasma concentration; CV, coefficient of variation; GMR, geometric mean ratio; LSM, least-squares means; n, number of subjects in the subgroup; PK, pharmacokinetic

The protein binding of deuruxolitinib (unbound fraction (%)) was comparable and does not appear to significantly alter between subjects with moderate renal impairment and normal renal function is shown in Figure 4. Moderate renal impairment (eGFR ≥30 to <60) did not appear to significantly alter the PK in patients with moderate renal impairment when compared to subjects with normal renal functions.

Figure 4. Box and Whisker Plots of Deuruxolitinib Unbound Fraction (%) by Cohort (Normal Renal Function vs. Moderate Renal Function Impairment)



Source: Study CP543.1014 Pharmacokinetic Report, Figure 9.1.2.5
Note: Subject (b) (6) was excluded from the moderate renal impairment cohort based on outlier test.
In the box plot, the dashed line is the median; the solid line is the arithmetic mean. The ends of the "box" are the 25th and 75th percentiles. These are also referred to as the first and third quartiles. The whiskers show the lowest data value still within 1.5 IQR of the lower quartile, and the highest value still within 1.5 IQR of the upper quartile, where IQR is the interquartile range (the difference between the third and first quartiles, the middle 50%). N=8 for Normal Renal Function Cohort. N=7 for Moderate Renal Impairment Cohort.
Abbreviations: IQR, interquartile range; PK, pharmacokinetic

There were no clinically meaningful differences in the PK of deuruxolitinib in moderate renal impairment (eGFR ≥30 to <60) when compared to subjects with normal renal functions (eGFR ≥90). The maximal changes on the PK of deuruxolitinib were 4% and 39% increase in in C_{max} and AUC_{inf} respectively. No subjects with severe renal impairment, and end-stage renal disease subjects requiring hemodialysis (end-stage renal disease) are included in the study. Based on the results from this study, in addition to the PopPK analyses which included renal function as a covariate, no dose adjustment is recommended in mild and moderate renal impairment. Deuruxolitinib should be avoided in subjects with severe renal impairment and ESRD requiring hemodialysis due to lack of the data in this sub-population.

Hepatic Impairment Study (CP543.1013)

A dedicated, open-label, single-dose (12 mg), single-period, parallel-group designed hepatic impairment study was conducted to evaluate the effect of mild and moderate hepatic impairment on PK of deuruxolitinib and its 2 most abundant human metabolites (C-21714 and C-21717). A total of 22 subjects completed the study, six (6) subjects in Child Pugh class A (mild), and eight (8) subjects in Child Pugh class B (moderate) and normal hepatic function. The summaries of the effect of hepatic impairment on exposures of deuruxolitinib are shown in Table 15.

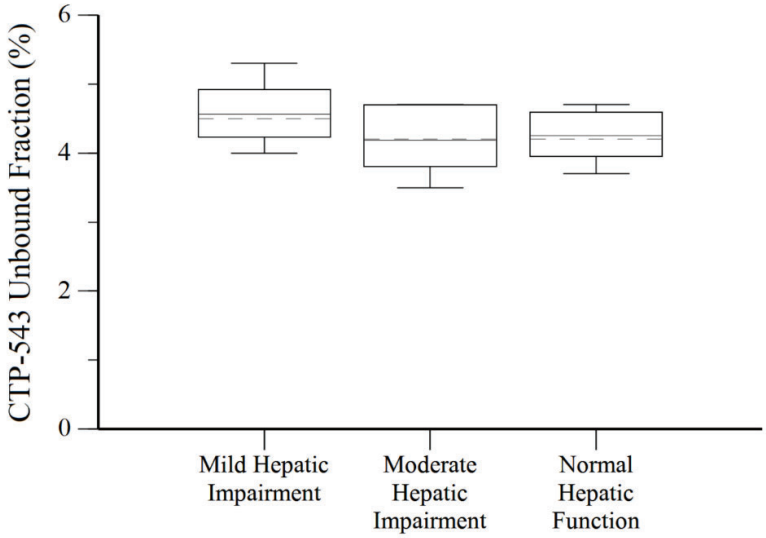
Table 15. Effect of Hepatic Impairment on PK of Deuruxolitinib

	Geometric LS Mean % Ratio (90% CI)		
Comparison (Test/Reference)	**C_{max}**	**AUC_{Tlast}**	**AUC_{inf}**
Mild HI (n=6)/ normal (n=8)	90.11 (65.71, 123.58)	93.46 (65.25, 133.87)	93.41 (65.29, 133.65)
Moderate HI (n=8)/ normal (n=8)	93.86 (65.55, 134.40)	113.64 (84.72, 152.43)	113.82 (84.95, 152.50)

Source: Data extracted from Study CP543.1013 Pharmacokinetic Report, Table 10.1.1

The summary of unbound fraction (%) of deuruxolitinib between subjects with mild and moderate hepatic impairment and normal hepatic function is shown in Figure 5. Hepatic impairment did not appear to significantly alter the protein binding of deuruxolitinib.

Figure 5. Box and Whisker Plots of Deuruxolitinib Unbound Fraction (%) by Cohort (Mild and Moderate Impaired Hepatic Function vs. Normal Hepatic Function)



Source: Study CP543.1013 Pharmacokinetic Report, Figure 9.1.5
Note: In the box plot, the dashed line is the median; the solid line is the arithmetic mean. The ends of the "box" are the 25th and 75th percentiles. These are also referred to as the first and third quartiles. The whiskers show the lowest data value still within 1.5 IQR of the lower quartile, and the highest value still within 1.5 IQR of the upper quartile, where IQR is the interquartile range (the difference between the third and first quartiles, the middle 50%).
Abbreviation: IQR, interquartile range

Both mild and moderate degrees of hepatic functions decrease C_{max} of deuruxolitinib. The AUC_{tlast} and AUC_{inf} of deuruxolitinib increased by 13% in subjects with moderate hepatic impairment and decreases 7% in subjects with mild hepatic impairment, respectively, compared to those with normal hepatic function. The PK of deuruxolitinib have not been studied in severe hepatic impairment. Based on the results from this study, no dose adjustment

is recommended in mild and moderate hepatic impairment. Deuruxolitinib should be avoided in subjects with severe hepatic impairment due to lack of the data in this sub-population.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Deuruxolitinib is recommended to be taken without regards to meal, as the effect of high-fat/high-calorie meal on the PK of deuruxolitinib was not clinically significant. The effect of food on the PK is evaluated in 2 separate studies (Study # CP543.1003 and CP543.1011), which indicate that the presence of high-fat, high-calorie meal (approximately 50% fat and 800-1000 calories), under fed conditions significantly decreases the peak exposure (C_{max} of deuruxolitinib decreased by 30-40%) but does not significantly affect the total exposure of deuruxolitinib. The decrease in peak concentration with food is not considerably clinically significant based on the cumulative efficacy data in the Phase 2 and Phase 3 studies that permitted deuruxolitinib dosing without regard to food. Additionally, a PopPK analysis followed by E-R for efficacy does not suggest C_{max} as an important predictor of clinical response. As such, deuruxolitinib can be taken with or without food. The summary of effect of food on PK parameters of deuruxolitinib from Study # CP543.1003 and CP543.1011 respectively are shown in Table 16.

Table 16. PK Parameters Under Fasted and Fed Conditions After Single Dose of Deuruxolitinib

Study #	Formulation	n	Strength	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	CL/F (L/hr)	Vz/F (L)	t½
1003	Tablet	14	16 mg	0.63 (0.25, 2.00)	342.6 (27.1%)	1568 (33.4%)	10.72 (32.7%)	56.75 (24.3%)	3.87 (25.7%)
1003[a]	Tablet	14	16 mg	3.00 (0.50, 4.01)	205.4 (36.1%)	1373 (32.3%)	12.18 (29.8%)	70.43 (33.1%)	4.19 (34.7%)
1011	Tablet (to-be-marketed formulation)	16	12 mg	0.75 (0.5-1.5)	344.07 (21.67%)	1392.12 (22.1%)	8.81 (21.6%)	45.09 (21.3%)	3.62 (21.9%)
1011[a]	Tablet (to-be-marketed formulation)	16	12 mg	1.5 (0.75-4.00)	245.55 (24.80%)	1287.18 (27.2%)	9.64 (26.9%)	49.68 (20.4%)	3.68 (20.5%)

Source: CP543.1003 CSR, Table 11-2; CP543.1011 CSR, Table 9
Note: t_{max} is presented as median (minimum, maximum); AUCs and C_{max} values are presented as geometric mean (CV%), with CL/F, V/F, and t½ presented as arithmetic mean (CV%).
[a] Fed status.
Abbreviations: AUC_{∞}, area under the plasma concentration versus time curve from time 0 (before dosing) to infinity; CL/F, apparent clearance; C_{max}, maximum measured plasma concentration; CV, coefficient of variation; t½, apparent first-order terminal elimination half-life; t_{max}, time of the maximum measured plasma concentration; Vz/F, apparent volume of distribution

A modest decrease in systemic exposures of deuruxolitinib was observed when deuruxolitinib was taken under fed conditions with a high-fat/high-calorie meal (approximately 50% fat and 800-1000 calories), compared to when taken under fasted conditions. C_{max} was decreased by 30% - 40% for deuruxolitinib. AUC_{inf} was comparable for deuruxolitinib under fasted condition when compared to fed conditions, respectively. The magnitudes of these reductions are not considered clinically meaningful and thus the study results support the dosing instruction for deuruxolitinib to be taken without regards to meal.

In addition, drug-drug interactions (DDIs) with deuruxolitinib have been evaluated in seven DDI clinical studies as well as PBPK modeling and simulations. Deuruxolitinib is not anticipated to have clinically meaningful induction of CYP3A4 substrates, or impact exposure of the oral

contraceptive levonorgestrel/ethinyl estradiol. Drug-drug interaction studies and PBPK simulations showed that deuruxolitinib exposure could be affected by both cytochrome P450 (CYP) induction and strong and moderate CYP inhibition as described below.

Effect of Other Drugs on Deuruxolitinib

1. A clinically significant difference in the PK of deuruxolitinib were observed when coadministered with multiple doses of rifampin (a strong CYP3A4 inducer), resulting in decreased deuruxolitinib total exposure by 78% and peak exposure by 41% relative to a single 12-mg deuruxolitinib dose given alone (Clinical Study CP543.1008). Given the reduced exposure and potential for loss of efficacy, it is recommended to avoid the concomitant use of strong CYP3A4 inducers with deuruxolitinib.
2. No clinically significant difference in the PK of deuruxolitinib were observed when coadministered with multiple doses of efavirenz (a moderate CYP3A4 inducer), resulting in decreased deuruxolitinib total exposure by 33% and peak exposure by 10% relative to deuruxolitinib dose given alone (PBPK modeling report). No adjustment of deuruxolitinib dosing is recommended for patients requiring the concomitant use of a moderate CYP3A4 inducer.
3. No clinically significant difference in the PK of deuruxolitinib were observed when coadministered with multiple doses of itraconazole (a strong CYP3A4 inhibitor), resulting in increased deuruxolitinib total exposure by 27% and peak exposure by 13% relative to deuruxolitinib dose given alone (Clinical Study CP543.1007). No adjustment of deuruxolitinib dosing is recommended for patients requiring the concomitant use of a strong CYP3A4 inhibitor.
4. A clinically significant difference in the PK of deuruxolitinib were observed when coadministered with multiple doses of fluconazole (a dual CYP3A4 and CYP2C9 inhibitor), resulting in increased deuruxolitinib total exposure by 140% and peak exposure by 21% relative to deuruxolitinib dose given alone (Clinical Study CP543.1015). Given the significant increase in exposure and potential concern for safety associated with higher exposure of deuruxolitinib, the concomitant use of moderate CYP2C9 inhibitors with deuruxolitinib is contraindicated in patients as CYP2C9 is the major metabolizing enzyme.
5. A clinically significant difference in the PK of deuruxolitinib were predicted when coadministered with multiple doses of sulphaphenazole (a strong CYP2C9 inhibitor), resulting in increased deuruxolitinib total exposure by greater than 200% and peak exposure by 25% relative to deuruxolitinib dose given alone (PBPK modeling report). Given the significant increase in exposure and potential concern for safety associated with higher exposure of deuruxolitinib, the concomitant use of strong CYP2C9 inhibitors with deuruxolitinib is contraindicated in patients.
6. Effect of acid-reducing agents: While deuruxolitinib exhibits pH dependency in terms of solubility, the solubility of deuruxolitinib is at least 0.12 mg/mL across the relevant physiological pH range (pH 1.0 to 6.8), which is greater than the proposed therapeutic dose (8 mg, divided by 250 mL =0.03 mg/mL). Since the to-be-marketed tablet dissolves by greater than 80% within 15 minutes across the relevant physiologic pH range, similarity factor cannot be reliably estimated, thus deuruxolitinib is unlikely to have in vivo drug

interactions with acid-reducing agents and consequently, a clinical study was not conducted.

Effect of Deuruxolitinib on Other Drugs

1. Deuruxolitinib is not anticipated to induce the metabolism of CYP3A4 substrates to a clinically meaningful extent, and dose adjustment of the CYP3A4 substrate is not needed, when coadministered with deuruxolitinib in clinic (Clinical Study CP543.1012).
2. Following multiple administration of 12-mg deuruxolitinib BID with a single dose of combination oral contraceptive (0.03 mg EE/0.15 mg LNG), mean plasma EE concentrations were similar in the presence or absence of deuruxolitinib; however, the mean plasma LNG concentrations were higher in the presence of deuruxolitinib compared to absence of deuruxolitinib. The increase in LNG levels is considered as minimal and therefore it is concluded that deuruxolitinib may be coadministered with OCs containing EE or LNG without dose adjustment (Clinical Study CP543.1005).
3. Deuruxolitinib is not an inducer of CYP1A2 or CYP2B6 at all concentrations tested. Deuruxolitinib was found to be a CYP3A4 inducer in cultured hepatocytes at the highest concentration 10 M, but showed no induction at 1 M and 5 M.

Based on clinical studies and PBPK modeling along with the metabolism and excretion data and the biotransformation pathways of deuruxolitinib, it is recommended to avoid concomitant use of deuruxolitinib with strong CYP3A4 and moderate CYP2C9 inducers like rifampin. Strong CYP2C9 inhibitors and moderate dual CYP2C9 and CYP3A4 inhibitors increases deuruxolitinib C_{max} and AUC and may increase the risk of adverse reactions and thus should not be administered with deuruxolitinib. Following multiple administration of 12-mg deuruxolitinib BID with a single dose of combination oral contraceptive, there was a negligible effect on the total and peak exposures of EE (geometric mean ratio [GMR] values of approximately 103% and 105%, respectively) and a minor effect on the total and peak exposures of LNG (GMR values of approximately 117% and 116%, respectively) and thus no dose adjustment is recommended when deuruxolitinib is coadministered with OCs containing EE or LNG. The to-be-marketed tablet dissolves by greater than 80% within 15 minutes across the relevant physiologic pH range and due to this extremely rapid dissolution of deuruxolitinib, it unlikely to have in vivo drug interactions with acid-reducing agents, which is in line with FDA draft Guidance for Industry, Evaluation of Gastric pH-Dependent Drug Interactions with Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications.

Effect of CYP2C9 Pharmacogenomics

Since CYP2C9 is major metabolizing enzyme ($f_{mCYP2C9}$=0.76), CYP2C9 activity is expected to be decreased in individuals with genetic variants such as CYP2C9*2 and CYP2C9*3 alleles. The Applicant has used the proportion of CYP2C9 poor metabolizers (PMs) as 1 and the CYP2C9*3/*3 mean (25.2 pmol/mg) and coefficient of variation (79%) abundance values used for the population as input in the PBPK model, which is acceptable. Using the PBPK simulations, the simulated mean total exposure (AUC_{0-t}) values following a single oral dose of deuruxolitinib in normal metabolizer subjects and CYP2C9*3/*3 genotyped (poor metabolizer) subjects is

estimated to be increased to 2-fold in CYP2C9 poor metabolizer (CYP2C9*3/*3 genotyped) subjects, when compared to normal metabolizer subjects.

Given the potential for dose-dependent adverse events at 2-fold higher exposure levels in CYP2C9 poor metabolizers which may result in the increased risk of serious adverse reactions, including thrombosis, the concomitant use of deuruxolitinib in patients who are known CYP2C9 poor metabolizers is contraindicated. Since the impact of CYP2C9 genetic variants on the pharmacokinetics of deuruxolitinib has not been directly evaluated in clinical studies, we further recommend the Applicant to consider conducting a clinical postmarketing study with CYP2C9 IMs & PMs, (including *2/*3 and *3/*3), to verify the model predictions and inform the impact of intermediate metabolizers and poor metabolizers on the exposure and safety of deuruxolitinib and further update labeling as appropriate, pending review of this information in the future.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Trials

In the clinical development program for deuruxolitinib for the treatment of adults with moderate to severe AA, the Applicant conducted 23 trials. Among these trials, 20 are completed and 3 are ongoing (CP543.2004, CP543.5001 and CP543.5002). The Applicant conducted 14 trials to characterize the clinical pharmacology of deuruxolitinib.

To support the safety and efficacy of the proposed product, the Applicant submitted data from two Phase 3 trials (CP543.3001, CP543.3002), two extension trials (CP543.5001 and CP543.5002) and one Phase 2 trial (CP543.2001). Two open-label, randomized, parallel-group, trials (CP543.2002 and CP543.2003) provided additional safety data and explored the optimal dosing interval (twice daily compared with once daily dosing during 24 weeks of treatment.) Ongoing Trial CP543.2004 is evaluating the durability of response and increased and decreased doses based on treatment response.

Both Phase 3 trials were similar in design: double-blind, placebo-controlled, parallel-group, 2-arm, 24-week trials in adult subjects with moderate to severe AA (≥50% hair loss.) Subjects who completed the 24-week treatment period were eligible to enroll in CP543.5001 [United States/Canada; dosing up to 276 weeks] or CP543.5002 [EU; dosing up to 108 weeks]).

Because of the known safety profile of JAKi, dose ranging Trial CP543.2001 evaluated 3 doses of deuruxolitinib (4 mg, 8 mg, and 12 mg) compared with placebo sequentially in a randomized, double-blind, 24- week trial with a 28 week, open- label extension.

The two tables below provide a summary of the trials in the development program for deuruxolitinib for the treatment of moderate to severe AA in adults. The first table summarizes the key features of the trials that were intended to support the efficacy and safety of the drug product and the second table provides a listing of clinical pharmacology trials that inform the efficacy and safety of deuruxolitinib.

Table 17. Phase 3 and Phase 2 Clinical Trials Relevant to NDA 217900

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
CP543.3001	04518995	Multicenter, randomized, double-blind, placebo-controlled Phase 3 trial	8 mg, 12 mg, placebo oral tablets BID Randomized 3:5:2 ratio	Primary: Percentage of subjects achieving an absolute SALT score ≤20 at Week 24 Key Secondary: Percentage of responders (defined as "satisfied" or "very satisfied") on the SPRO scale at Week 24 Percentage of subjects achieving an absolute SALT score of ≤20 at Week 20 Percentage of subjects achieving an absolute SALT score of ≤20 at Week 16	24 weeks treatment roll over into OLE CP543.5001/ CP543.5002	706 Safety population: 705	18-65 years of age with AA lasting at least 6 months and not exceeding 10 years, at least 50% scalp hair loss defined by SALT ≥50.	73 North America (United States and Canada) and the EU

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
				Percentage of subjects achieving an absolute SALT score of ≤20 at Week 12 Percentage of subjects achieving an absolute SALT score of ≤20 at Week 8 Safety: AEs, labs, VSs, PEs, ECGs, con meds				
CP543.3002	04797650	Multicenter, randomized, double-blind, placebo-controlled Phase 3 trial	8 mg, 12 mg, placebo oral tablets BID Randomized 1:2:1 ratio	Primary: Percentage of subjects achieving an absolute SALT score ≤20 at Week 24 Key Secondary: Replicate to trial CP543.3001 Safety: AEs, labs, VSs, PEs, ECGs, con meds	24 weeks treatment roll over into OLE CP543.5001/ CP543.5002	517 Safety population: 515	18-65 years of age with AA lasting at least 6 months and not exceeding 10 years, at least 50% scalp hair loss defined by SALT ≥50.	63 North America (United States and Canada) and the EU

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
CP543.2001		Multicenter, randomized, double-blind, placebo-controlled Phase 2 dose-ranging trial	4 mg, 8 mg, 12 mg, placebo oral tablets BID	Primary: Percentage of subjects achieving at least a 50% relative reduction in SALT score at Week 24 PK Safety: AEs, labs, VSs, PEs, ECGs, con meds	24 weeks roll over into OLE CP543.5001 or 4 weeks of safety follow-up	147 Safety population: 147	18-65 years of age with AA lasting at least 6 months and not exceeding 10 years, at least 50% scalp hair loss defined by SALT ≥50.	13 sites in the United States

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
		Studies to Support Safety						
CP543.2004	04518995	Multicenter, double-blind, randomized, Phase 2 trial to evaluate the regrowth of hair and subsequent durability of that regrowth following dose reduction or drug discontinuation (Part B re-treatment phase for subjects with LOM is ongoing)	4 mg, 8 mg, 12 mg, placebo oral tablets BID	Co-primary efficacy endpoints: the percentage of subjects who maintained an absolute SALT score ≤20 compared to the percentage who achieved loss of maintenance (LOM) at Week 24 following either dose reduction or drug discontinuation	Part A Period 1 treatment phase (double blind randomized treatment): 24 weeks treatment Part A Period 2 dose modification phase (EOT responders only, double-blind randomized dose reduction/interruption: up to 24 weeks	Part A Period 1- 8 mg BID: 180 12 mg BID: 137 Part A Period 2- 8 mg BID to 4 mg BID: 18 12 mg BID to 8 mg BID: 25 8 mg BID to placebo: 18 12 mg BID to placebo: 25	To enter the trial: 18-65 years of age with AA lasting at least 6 months and not exceeding 10 years, at least 50% scalp hair loss defined by SALT ≥50. To enter Part A Period 2: subject had to have an absolute SALT score ≤20 at Week 24 of Part A Period 1 (responder).	United States (39 sites)

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
CP543.5001		OLE (ongoing) Long-term safety Maintenance of treatment effect	8 mg, 12 mg oral tablets BID		276 weeks	Safety population: 1068	Males or females with AA who previously completed CP543.2001 (Cohort 3), CP543.2002, CP543.2003, CP543.2004, CP543.3001, or CP543.3002	North America (75 center United States, 21 centers Canada)
CP543.5002		OLE (ongoing) Long-term safety Maintenance of treatment effect	8 mg, 12 mg oral tablets BID		108 weeks	Safety population: 407	Males or females with AA who previously completed CP543.3001 or CP543.3002	Europe: France (8 centers), Germany (7 centers), Hungary (3 centers), Poland (14 centers), Spain (7 centers)

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
CP543.2002		Randomized, multicenter Phase 2 trial	8 mg BID, 16 mg QD oral tablets	Relative change in SALT score from baseline at Week 24	24 weeks	57 adults 8 mg: 29 16 mg: 28	Adult males or females with moderate to severe AA	United States
CP543.2003		Randomized, multicenter Phase 2 trial	12 mg BID, 24 mg QD oral tablets	Relative change in SALT score from baseline at Week 24	24 weeks	66 adults 12 mg: 34 24 mg: 32	Adult males or females with moderate to severe AA	North America

Table 18. Clinical Pharmacology Trials Pertinent to This NDA

Study Number	Study Description
	Safety/Pharmacokinetics/Pharmacodynamics
CP543.1001	Single ascending dose and multiple ascending dose study which first examined the safety and PK profile of single ascending doses (8 mg, 16 mg, 32 mg, and 48 mg) and multiple ascending doses (8 mg QD, 8 mg BID, 24 mg QD, 32 mg QD, and 16 mg BID) of deuruxolitinib in healthy subjects.
CP543.1002	Comparative bioavailability study examining the PK of a single 16 mg dose of deuruxolitinib compared to a single 15 mg dose of non-deuterated ruxolitinib (Jakafi) in healthy subjects.
	Pharmacokinetics and Metabolism of [14C]-Deuruxolitinib
CP543.1004	Mass-balance study that assessed the absorption, metabolism, excretion, and elimination of a single oral 20 mg dose of [14C]-deuruxolitinib in healthy adult male subjects.
	Drug-Drug Interactions (Deuruxolitinib as a Perpetrator)
CP543.1005	Drug-drug interaction (DDI) study that assessed the effect of multiple 12 mg BID doses of deuruxolitinib on the PK of the components of a single dose of the combination oral contraceptive (OC) ethinyl estradiol/levonorgestrel in healthy subjects (deuruxolitinib as a perpetrator).
CP543.1012	DDI study to assess the effect of multiple 12 mg BID doses of deuruxolitinib on the PK of a single dose of midazolam (a CYP3A4 substrate) in healthy adult subjects (deuruxolitinib as a perpetrator).
	Drug-Drug Interactions (Deuruxolitinib as a Victim)
CP543.1007	DDI study to assess the effect of a strong CYP3A4 inhibitor (itraconazole) on the single dose PK profile of 12-mg deuruxolitinib in healthy adult subjects (deuruxolitinib as a victim).
CP543.1015	DDI study to assess the effect of multiple doses of fluconazole, a CYP3A4 and CYP2C9 inhibitor, on the single dose PK profile of 12-mg deuruxolitinib in healthy adult subjects (deuruxolitinib as a victim).
CP543.1008	

Study Number	Study Description
	DDI study to assess the effect of a strong CYP3A4 inducer (rifampin) on the single dose PK profile of 12-mg deuruxolitinib in healthy adult subjects (deuruxolitinib as a victim).
	Biopharmaceutics Study
CP543.1006	Relative bioavailability (rBA) that assessed the PK profile of deuruxolitinib after a 12-mg single dose of an immediate release (IR) formulation and 2 exploratory delayed release formulations; only data from the IR formulation is presented in this NDA (n-45).
CP543.1009	Bioequivalence (BE) study in healthy volunteers to compare a single 12-mg dose of the proposed commercial formulation of deuruxolitinib to the clinical formulation (n=20).
CP543.1011	Relative bioavailability study that compared a single 12-mg dose of the proposed commercial formulation of deuruxolitinib formulation in a fed state versus a fasted state (n=16).
CP543.1003	Relative bioavailability study that compared a single 16 mg dose of deuruxolitinib in a fed state versus a fasted state (n=14).
	TQT Study
CP543.1010	To evaluate the effect of a single therapeutic (12 mg) or supratherapeutic (48 mg) dose of deuruxolitinib on the QT intervals in healthy adult subjects using a positive control (moxifloxacin 400 mg) to establish assay sensitivity.
	Special Population
CP543.1013	To assess the effect of mild and moderate hepatic impairment on the PK of a single 12-mg dose of deuruxolitinib.
CP543.1014	To assess the effect of moderate renal impairment (eGFR ≥30 to <60) on the PK of a single 12-mg dose of deuruxolitinib.

7.2. Review Strategy

The sources of data used for the evaluation of the efficacy and safety of deuruxolitinib for the proposed indication to treat moderate to severe alopecia areata included final trial reports submitted by the Applicant, datasets [Study Data Tabulation Model and Analysis Data Model (ADaM)]. This application was submitted in electronic common technical document format and entirely electronic. The electronic submission included protocols, statistical analysis plans, clinical trial reports, Statistical Analysis Software transport datasets in Study Data Tabulation

Model, and Analysis Data Model (ADaM) format. The datasets were in the following network path:

Original submission: \\CDSESUB1\evsprod\NDA217900\0001\m5

The Applicant submitted the required certification and disclosure information for participating investigators (Form 3454). Refer to Section 16.2. Financial Disclosure of this review for additional information.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. CP543.3001/3002

Trial Design

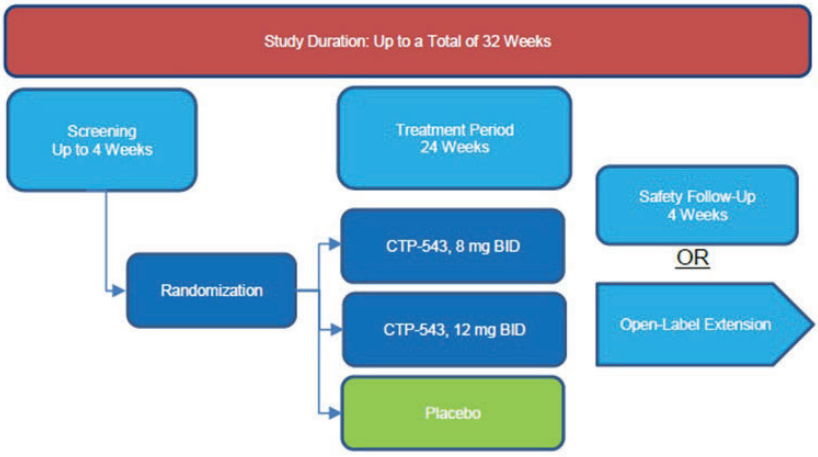
The Applicant conducted two identically designed, double-blind, randomized, placebo-controlled multicenter, Phase 3 trials (CP543.3001/3002) to evaluate the safety and efficacy of deuruxolitinib (CTP-543) tablets 8 mg in adult subjects with moderate to severe AA. Approximately 700 adult male and female subjects 18 to 65 years of age, inclusive, with moderate to severe AA were planned to participate in the study CP543.3001. And approximately 440 adult male and female subjects were planned to participate in the study CP543.3002. Subjects 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 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 CTP-543. In trial CP543.3001, subjects were randomized in a 3:5:2 ratio (CTP-543 12 mg BID: CTP-543 8 mg BID: placebo). In trial CP543.3002, subjects were randomized in a 1:2:1 ratio (CTP-543 12 mg BID: CTP-543 8 mg BID: placebo). Randomization was stratified by scalp hair loss into one of the following two categories: 1) Partial scalp hair loss (SALT ≥50 and <95); 2) Complete or near-complete scalp hair loss (SALT ≥95).

Enrolled subjects took the first dose of study drug in the clinic on Day 1 and were instructed to take study drug daily approximately every 12 hours without regard to food, for the duration of the Treatment Period (24 weeks). Subjects were to take study drug in the clinic on all study visit days after clinical laboratory blood draws were completed. Following the 24-week Treatment Period, subjects had the opportunity to continue receiving treatment in an OLE study. If a subject 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. See Figure 6.

Efficacy of CTP-543 was assessed by analyzing SALT, CGI-I, Clinical Global Impression of Severity (CGI-S), PGI-I, Patient Global Impression of Severity (PGI-S), BETA, BELA, SPRO, Hair Quality Patient Reported Outcome, and Hospital Anxiety and Depression Scale (HADS) scores. Safety of CTP-543 was assessed by analyzing adverse events, vital signs, concomitant medications, and clinical laboratory results, as well as physical examinations.

Figure 6. Study Design



Source: pg7 of CP543-3001 protocol (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3001\cp543-3001-e3-16-1-01-protocol-amendments.pdf)

Study Endpoints

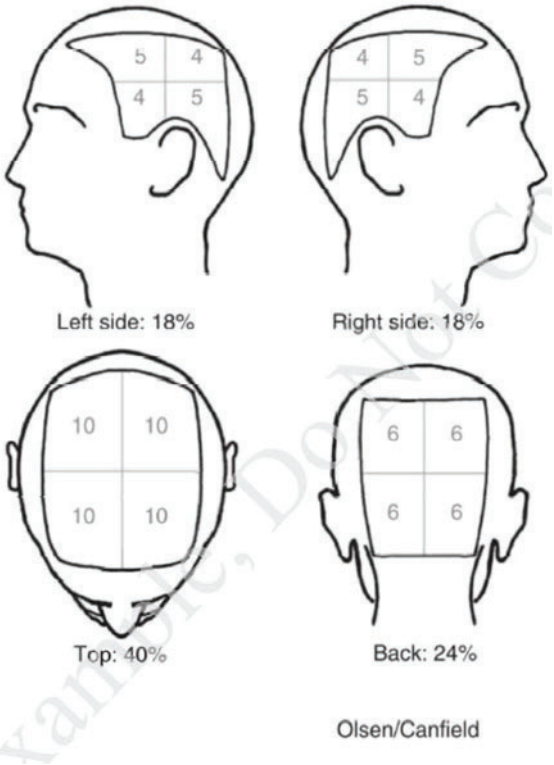
Severity of Alopecia Tool

The SALT is a single item clinician-reported outcome (ClinRO) instrument designed to assess the extent of scalp hair loss in AA based on the percentage of scalp surface area involvement on the top, back, and each side of the scalp. The SALT assessment occurred via live examination of the patient by the investigator during clinic visits at Screening, Baseline, and Weeks 4, 8, 12, 16, 20, and 24.

The SALT generates a total score, which ranges from 0 (absence of hair loss) to 100 (complete hair loss). To calculate the total score, the scalp is divided visually by the clinician into 4 quadrants (right, left, back, and front) and a percentage of hair loss is rated for that quadrant (0%-100%). The SALT uses a visual aid (Figure 7) showing the division of scalp hair into 4 areas with the left side and right side of scalp accounting each for 18% of the total surface, top constituting 40%, and the posterior/back constituting 24%. The percentage of hair loss in each area is determined and is multiplied by the percentage of scalp covered by that area. The total sum of the 4 products of each area will give the SALT score.

The SALT is an accepted instrument to evaluate the severity of hair loss in subjects with AA. An evaluation of the measurement properties is not included in this review.

Figure 7. Illustration of SALT Score



Source: pg 71 of CP543-3001 protocol (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3001\cp543-3001-e3-16-1-01-protocol-amendments.pdf)

Satisfaction of Hair Patient-Reported Outcome

The SPRO is a single item patient-reported outcome instrument designed to assess satisfaction with hair on the scalp using a 5-point verbal rating scale 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.

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

Brigham Eyebrow Tool for Alopecia

The BETA is a ClinRO instrument designed to assess the total eyebrow hair present. The scale assesses the density and surface area of each individual eyebrow. The left and right eyebrow scores are summed for a total eyebrow score with a range of 0 (no eyebrows) to 6 (full eyebrows). An independent certified rater performed central readings based on photographs of the eyebrows and provided a total score for each patient with eyebrow involvement following each visit where an assessment of eyebrow hair presence was assessed. The BETA was performed at baseline, Week 12, and Week 24. If a subject was unable to attend an in-person clinic visit due to Coronavirus Disease 2019 (COVID-19), the BETA was not performed due to the inability to take photographs of the eyebrows.

Brigham Eyelash Tool for Alopecia

The BELA is a ClinRO instrument designed to assess the total eyelash hair present. The scale assesses the distribution and grade (0 = no eyelash density; 1 = minimal eyelash density; 2 = moderate eyelash density; 3 = complete eyelash density) of the right and left eyelashes individually. The total eyelash score is the sum of each eye with a range of 0 (no eyelash hair) to 6 (full eyelash hair). An independent certified rater performed central readings based on photographs of the eyelashes and provided a total score for each patient with eyelash involvement following each visit where an assessment of eyelash hair presence was assessed. The BELA was performed at baseline, Week 12, and Week 24. If a subject was unable to attend an in-person clinic visit due to COVID-19, the BELA was not performed due to the inability to take photographs of the eyelashes.

The protocol-specified primary efficacy endpoint is the percentage of subjects achieving an absolute SALT score of ≤20 at Week 24.

The first key secondary endpoint is the percentage of responders per the SPRO (defined as "satisfied" or "very satisfied") at Week 24.

The next key secondary endpoints are the percentage of patients achieving an absolute SALT score of ≤20 (i.e., the binary endpoint denoting a SALT score ≤20) at Weeks 20, 16, 12, and 8.

Additional secondary efficacy endpoints included the following:

- Relative change in SALT scores from baseline at Weeks 4, 8, 12, 16, 20, and 24.
- Percentage of responders (defined as "much improved" or "very much improved") using the CGI-I at Weeks 12, 16, 20, and 24.
- Percentage of responders (defined as "much improved" or "very much improved") using the PGI-I at Weeks 12, 16, 20, and 24.
- Change from baseline in the CGI-S at Weeks 12, 16, 20, and 24.
- Change from baseline in the PGI-S at Weeks 12, 16, 20, and 24.
- Percentage of subjects achieving at least a 75% relative reduction in SALT score from baseline at Weeks 12 and 24.
- Percentage of subjects achieving at least a 90% relative reduction in SALT score from baseline at Weeks 12 and 24.
- Change from baseline on the BETA score at Weeks 12 and 24.
- Change from baseline on the BELA score at Weeks 12 and 24.
- Percentage of responders (defined as "satisfied" or "very satisfied") on the SPRO scale at Weeks 12, 16, and 20.
- Change from baseline in the SPRO scale at Weeks 12, 16, 20, and 24.
- Percentage of subjects achieving a ≥-point change from baseline in the SPRO scale at Weeks 12, 16, 20, and 24.
- Change from baseline on the individual items of the Hair Quality Patient Reported Outcome scale at Weeks 12, 16, 20, and 24.

- Change from baseline in the depression scale of the HADS at Week 24.
- Change from baseline in the anxiety scale of the HADS at Week 24.
- Percentage of subjects achieving an absolute SALT score of ≤20 at Week 24.
- Percentage of subjects achieving an absolute SALT score of ≤10 at Week 24.

Statistical Analysis Plan

The primary analysis population is the Efficacy Population defined as all patients who are randomized in the trial and dispensed study drug during the Treatment Period. Pairwise treatment group differences from placebo will be assessed with the Mantel-Haenszel test (common risk difference) using baseline scalp hair loss (partial vs. complete/near-complete) as the stratification factor, for each active treatment group versus placebo.

The protocols did not use the estimand framework, and no intercurrent events were explicitly defined for the primary analysis. However, the statistical analysis plan notes that subjects "who have discontinued treatment but remain on study will not have their SALT scores censored" implying a treatment policy strategy for subjects who discontinued treatment.

In addition, prior to database lock, the missing data pattern for missing SALT scores will be classified as either missing at random (MAR) or potentially missing not at random (MNAR). Subjects with missing data due to COVID-19 will have data reviewed to determine the specific reason for the missingness. For example, missing at random will be considered plausible for COVID-19 related reasons such as site closures and travel limitations. In general, however, if a MAR assumption is not considered plausible, MNAR will be assumed. Patterns of missing values across visits will be listed and summarized with numbers and percentages by treatment and visit.

Otherwise, multiple imputation will be used to handle missing data using the Fully Conditional Specification regression method. Under this method, missing SALT scores will be imputed in a sequential manner using regression models with baseline SALT score and the observed or imputed values of previous visits as covariates. For each imputed dataset, treatment differences will be assessed using the Mantel-Haenszel estimate of a common risk difference, with the variance estimator. The resulting 100 estimates of the treatment differences and standard errors will then be combined using SAS PROC MIANALYZE. The observed number and percentage of patients with an absolute SALT score ≤20 among non-imputed data will be reported by treatment group along with the appropriate p-value, the combined treatment differences, combined standard errors, and 95% CI. This analysis will be completed for the Efficacy Population and the Per Protocol Population. The Per Protocol Population includes all subjects in the Efficacy Population who were dosed according to protocol and had no major protocol deviations. Inclusion in the Per Protocol Population was determined prior to breaking the study blind. The analysis utilizing the Per Protocol Population is considered supportive.

Two sensitivity analyses of the primary efficacy endpoint will be conducted to evaluate the robustness of study results under different assumptions and imputation algorithms. For the

primary endpoint, the following sensitivity analyses will be performed for the Efficacy Population only.

Sensitivity 1: Multiple Imputation; Missing Not at Random

Patients who discontinued the study early due to a treatment-emergent adverse event (including COVID-19) or due to lack of efficacy will be considered MNAR, and the SALT scores missing after discontinuation will be imputed using the control arm. This assumes that patients, regardless of treatment, who discontinue the study early for those reasons would have similar SALT scores to placebo patients with complete data.

For patients who discontinued the study due to reasons other than treatment-emergent adverse event or lack of efficacy, missing SALT scores after subjects discontinue the study early will be multiply imputed from subjects within the same treatment group who have complete data at that time. Terms will include baseline values and the weekly data through the time point being imputed. The proportion of patients who have a SALT score ≤20 will be calculated for each imputed dataset. The primary analysis will be repeated for the Efficacy Population using the multiple imputation with MNAR assumption datasets.

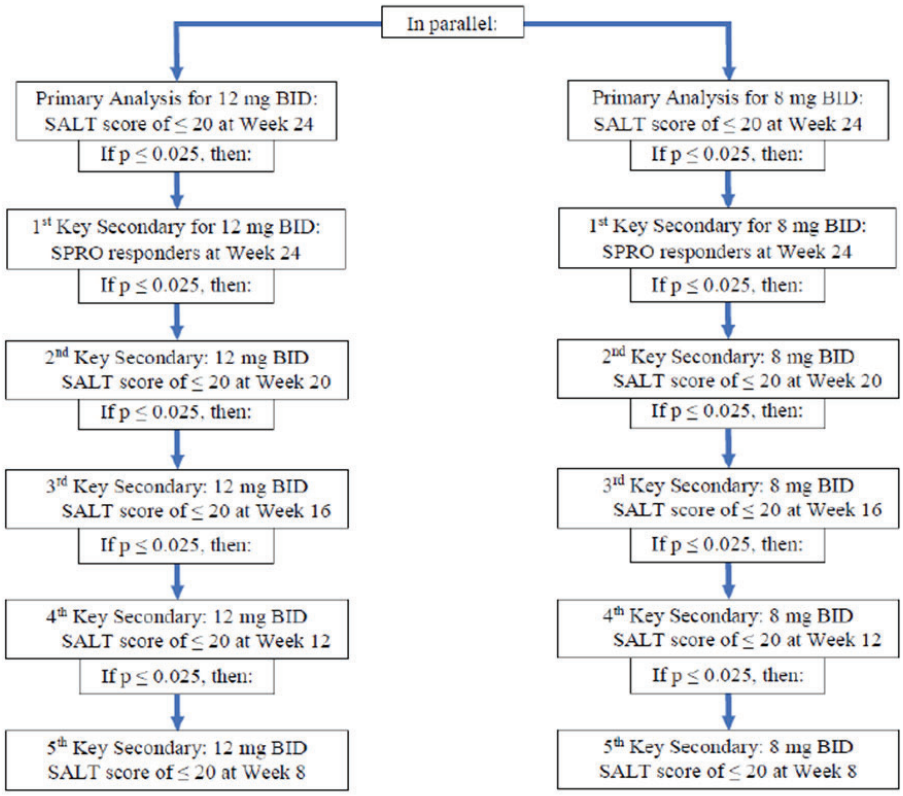
Sensitivity 2: Tipping Point

Additionally, a tipping point sensitivity analysis will be conducted for each dose compared to placebo at Week 24 if the result of the multiple imputation analysis is statistically significant at the alpha ≤0.025 level, in favor of treatment, for the given dose. The tipping point analysis will use the primary MAR assumption datasets, where all imputed values are adjusted.

The tipping point analysis will apply delta adjustments for both treated and placebo. For the tipping point analyses, δT values (adjustments for treated patients) will represent a percentage difference between the imputed value and baseline and can vary from 0% to 100% of the difference for subjects with an imputed SALT score less than baseline, or zero otherwise. For the placebo arm, δP values will represent a percentage difference between the imputed value and 0 hair loss. Accordingly, the maximum delta value of 100% provides for an adjusted imputed value equal to either baseline (for treated subjects, representing non-response) or zero hair loss for placebo, representing response. Tipping points will therefore be provided for combinations of δT and δP to provide a range of assumptions about hypothetical improvements on placebo missing data values and reduction in efficacy for treated imputed values such that there is no longer evidence of efficacy.

Multiplicity was controlled using graphical procedures for Trial CP543.3001 and Trial CP543.3002. See Figure 8.

Figure 8. Hierarchical Testing



Source: pg 72 of CP543-3001 clinical study report (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3001\cp543-3001-body.pdf)

Protocol Amendments

Protocol CP543.3001 was amended five times in North America and four times in the European Union. The first subject was enrolled on November 23, 2020. The key changes to the North American version of Protocol CP543.3001 impacting the design and analysis were as follows:

North America

Amendment 1 (8/26/2020) – Clarified Exclusion Criteria. Added preliminary summary results from oral contraceptive study CP543.1005.

Amendment 2 (10/15/2020) – Added Week 8 to Key Secondary Endpoints for SALT score assessment. Added Week 16 and 20 to key secondary endpoints for CGI/PGI. Removed stratification restriction to enable the study to cover the overall eligible patient population. Adjustment to randomization ratio due to reevaluation of power calculations.

Amendment 3 (2/18/2021) – Completed study information updated. No endpoint or analysis changes were proposed.

Amendment 4 (2/23/2021) – Clarification of study procedures. No endpoint or analysis changes were proposed.

Amendment 5 (4/28/2021) – Criteria modified for consistency with European protocol for CP543.3001. No endpoint or analysis changes were proposed.

Protocol CP543.3002 has one amendment in North America and one amendment in European Union. The first subject was enrolled on June 10, 2021. No endpoint or analysis changes were proposed.

8.1.2. Study Results

Compliance With Good Clinical Practices

The following GCP statement by the Applicant is included in the protocol: "The procedures set out in the study protocol, pertaining to the conduct, evaluation, and documentation of the study, were designed to ensure that the sponsor and the investigator abided by Good Clinical Practice, including but not limited to Title 21 CFR Parts 50, 56, and 312, and the International Conference on Harmonisation guidelines and directives. Compliance with these regulations also constituted compliance with the ethical principles described in the current revision of the Declaration of Helsinki and applicable local regulatory requirements and law."

Financial Disclosure

Refer to Section 16.2. Financial Disclosure of this review for additional information.

Patient Disposition

Trial CP543.3001 randomized 706 subjects. Study drug was received by 705 subjects. One subject (20-309) in the CTP-543 8-mg BID group withdrew consent after randomization before receiving any study drug. Among the subjects who discontinued the study, the general reasons for study discontinuation were withdrawal of consent and lost to follow-up. Trial 3002 randomized 517 subjects. Two subjects were randomized but were not dispensed study drug. Of the 517 subjects randomized, 468 subjects (90.5%) completed treatment. Among the subjects who discontinued the study, the general reasons for study discontinuation were withdrawal of consent and lost to follow-up. See Table 19.

Table 19. Summary of Subject Disposition and Reasons for Discontinuation (All Screened Subjects)

	Trial 3001			Trial 3002		
Parameter	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=130)	CTP-543 8 mg BID (N=258)	CTP-543 12 mg BID (N=129)
Treatment status, N%						
Completed	129 (92.1)	316 (90)	197 (91.6)	119 (91.5)	232 (89.9)	117 (90.7)
Complete (follow-up visit)	2 (1.4)	4 (1.1)	3 (1.4)	4 (3.1)	10 (3.9)	2 (1.6)
Complete-entering open label	127 (90.7)	312 (88.9)	194 (90.2)	115 (88.5)	222 (86)	115 (89.1)
Discontinued	11 (7.9)	35 (10)	18 (8.4)	11 (8.5)	26 (10.1)	12 (9.3)
Reason for treatment discontinuation, N(%)						
Adverse event	2 (1.4)	9 (2.6)	6 (2.8)	2 (1.5)	9 (3.5)	3 (2.3)
Failure to meet continuation criteria	2 (1.4)	2 (0.6)	0 (0)	0	0	0
Lost to follow-up	1 (0.7)	7 (2)	6 (2.8)	4 (3.1)	6 (2.3)	1 (0.8)
Other	0 (0)	2 (0.6)	0 (0)	0 (0)	1 (0.4)	3 (2.3)
Pregnancy	0 (0)	0 (0)	1 (0.5)	0	0	0
Protocol violation	0 (0)	2 (0.6)	2 (0.9)	0	0	0
Physician decision	0	0	0	2 (1.5)	6 (2.3)	1 (0.8)
Withdrawal of consent	6 (4.3)	13 (3.7)	3 (1.4)	3 (2.3)	4 (1.6)	4 (3.1)

Source: pg 60-62 of cp543-3001 study report (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3001\cp543-3001-body.pdf) and pg 58-60 of cp543-3002 study report (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3002\cp543-3002-body.pdf) and reviewer analysis

Due to suspected noncompliance concerns, U.S. site 102 in Trial CP543.3002 (Principal Investigator [PI]: Dr. Alexander Beyzer) was placed on an enrollment hold on October 1, 2021. During the course of an expanded investigation, the site showed continued resistance to accommodate an onsite audit leading to questions about a potential lack of PI oversight. The nature of the issues warranted early termination of all 17 active subjects. The Applicant notified the site of the decision to terminate the clinical trial agreement on November 4, 2021, via an email copy of a certified letter (via certified mail on November 5, 2021). Confirmation of early termination of all active subjects was completed on November 16, 2021. The Applicant notified the Institutional Review Board of the site discontinuation due to suspected noncompliance by the PI of his obligations under 21 CFR 312.60 at the same time as the site (November 4, 2021, or November 5, 2021) and notified the FDA on November 9, 2021 (IND 131423 Serial Number 0147). The site was formally closed on March 1, 2022. There was no known impact on subject safety or wellbeing. The data for subjects treated at site 102 were excluded from the Efficacy Population, and the Per Protocol Population in Trial CP543.3002. The decision to exclude efficacy data for subjects treated at site 102 was made prior to study unblinding. The Modified Efficacy Population and the Safety Population includes subjects from site 102.

Analysis Population

The Efficacy Population included all subjects who were randomized in the study and dispensed study drug during the Treatment Period, excluding those at Site 102 in Trial CP543.3002. It was determined by the Applicant during the course of the study that Site 102 would be terminated early due to suspected noncompliance. The decision to exclude efficacy data for subjects treated at Site 102 was made prior to study unblinding.

The Modified Efficacy Population included all subjects who were randomized in the study and dispensed study drug during the Treatment Period. This population included subjects from site 102 and was used for sensitivity analyses of the primary and key secondary endpoints.

The Safety Population included all subjects who received study drug during the Treatment Period. The Safety Population included subjects from site 102.

The Per Protocol Population included all subjects in the Efficacy Population who were dosed according to protocol and had no major protocol deviations.

Protocol Violations/Deviations

For Trial CP543.3001, the most common categories of major protocol deviations were investigational product/device, informed consent/assent, eligibility criteria, and study procedure related. For Trial 3002, the most common categories of major protocol deviations were investigational product/device, COVID-19 deviation, study procedure related, and concomitant/rescue medication. See Table 20. The rates of major protocol deviations were generally consistent across treatment arms.

Table 20. Summary of Protocol Deviations (All Randomized Subjects)

	Trial 3001			Trial 3002		
Classification Category	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=130)	CTP-543 8 mg BID (N=258)	CTP-543 12 mg BID (N=129)
Major						
AE/SAE reporting	0	0	1 (0.5)	0	0	0
Concomitant/rescue medication	1 (0.7)	0	1 (0.5)	1 (0.8)	3 (1.2)	3 (2.3)
COVID-19 deviation	1 (0.7)	2 (0.6)	1 (0.5)	4 (3.1)	5 (1.9)	1 (0.8)
Eligibility criteria	4 (2.9)	8 (2.3)	6 (2.8)	1 (0.8)	3 (1.2)	0
Informed consent/assent	7 (5)	10 (2.8)	6 (2.8)	1 (0.8)	3 (1.2)	0
Investigational product/device	4 (2.9)	17 (4.8)	5 (2.3)	18 (13.8)	21 (8.1)	11 (8.5)
Study procedure related	1 (0.7)	12 (3.4)	5 (2.3)	3 (2.3)	5 (1.9)	1 (0.8)
Study visit related	1 (0.7)	1 (0.3)	0	1 (0.8)	0	2 (1.6)

Source: pg 62-63 of cp543-3001 study report ((\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3001\cp543-3001-body.pdf) and pg 60-62 of cp543-3002 study report (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3002\cp543-3002-body.pdf) and reviewer analysis

Table of Demographic Characteristics

The baseline demographics were generally balanced across the treatment groups in the two trials. See Table 21. The majority of subjects were female, white, and not Hispanic or Latino. The mean age was 38-39 years. The median BMI was 26-27.

Table 21. Summary of Demographics (All Randomized Subjects)

	Trial 3001			Trial 3002		
Parameter	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=130)	CTP-543 8 mg BID (N=258)	CTP-543 12 mg BID (N=129)
Age (years)						
N	140	351	215	130	258	129
Mean	38.73	38.87	38.21	39.71	38.38	39.71
SD	13.81	13.32	12.8	12.49	12.3	12.9
Median	38.5	37	36	41	38	38
Minimum	18	18	18	18	18	18
Maximum	65	65	65	65	65	65
Sex, N (%)						
F	89 (63.6)	217 (61.8)	131 (60.9)	88 (67.7)	177 (68.6)	84 (65.1)
M	51 (36.4)	134 (38.2)	84 (39.1)	42 (32.3)	81 (31.4)	45 (34.9)
BMI (kg/m^2)						
N	140	349	215	130	258	129
Mean	26.56	27.07	26.62	26.92	26.27	26.52
SD	5.98	5.68	5.95	6.27	6.13	5.85
Median	25.35	25.9	25.8	25.4	24.95	25.1
Minimum	18.1	16.3	17.2	16.3	17.6	18.5
Maximum	51.2	54.4	53.5	52.1	53.6	50.1
Ethnicity, N (%)						
Hispanic or Latino	11 (7.9)	30 (8.5)	13 (6)	11 (8.5)	23 (8.9)	9 (7)
Non-Hispanic or Latino	119 (85)	292 (83.2)	188 (87.4)	108 (83.1)	205 (79.5)	111 (86)
Unknown	10 (7.1)	29 (8.3)	14 (6.5)	11 (8.5)	30 (11.6)	9 (7)
Race, N (%)						
American Indian or Alaska Native	0	2 (0.6)	1 (0.5)	1 (0.8)	5 (1.9)	0 (0)
Asian	10 (7.1)	22 (6.3)	21 (9.8)	7 (5.4)	4 (1.6)	4 (3.1)
Black or African American	16 (11.4)	40 (11.4)	27 (12.6)	10 (7.7)	17 (6.6)	7 (5.4)
Native Hawaiian or other Pacific Islander	1 (0.7)	3 (0.9)	1 (0.5)	0	0	0
Not applicable	10 (7.1)	26 (7.4)	14 (6.5)	11 (8.5)	28 (10.9)	9 (7)
Other	5 (3.6)	17 (4.8)	6 (2.8)	1 (0.8)	1 (0.4)	0 (0)
White	98 (70)	241 (68.7)	145 (67.4)	100 (76.9)	203 (78.7)	109 (84.5)

Source: pg 62-63 of cp543-3001 study report (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3001\cp543-3001-body.pdf) and pg 60-62 of cp543-3002 study report (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3002\cp543-3002-body.pdf) and reviewer analysis

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Baseline characteristics were balanced across the treatment groups. For Trial CP543.3001, the mean baseline SALT scores of placebo group are slightly higher than the CTP-543 8-mg BID, CTP-543 12-mg BID groups. Just over half of subjects in each group had an AA classification of

complete or near-complete scalp loss. The median duration of the current episode for each treatment group was 3.3, 2.9 and 2.5 years in the placebo, CTP-543 8-mg and CTP-543 12-mg groups, respectively. Over half of subjects in each group did not have current nail involvement. More than half of subjects in each group had current eyebrow involvement and current eyelash involvement.

For Trial CP543.3002, the mean baseline SALT scores of CTP-543 12-mg BID group is slightly lower than the CTP-543 8-mg BID and placebo groups. Over half of subjects in each group did not have current nail involvement. The median duration of the current episode for each treatment group was 2.8, 2.9 and 3.5 years in the placebo, CTP-543 8-mg and CTP-543 12-mg groups, respectively. More than half of subjects in each group had current eyebrow involvement and current eyelash involvement. See Table 22.

Table 22. Summary of Baseline Characteristics (All Randomized Subjects)

	Trial 3001			Trial 3002		
Characteristic	**Placebo (N=140)**	**CTP-543 8 mg BID (N=351)**	**CTP-543 12 mg BID (N=215)**	**Placebo (N=130)**	**CTP-543 8 mg BID (N=258)**	**CTP-543 12 mg BID (N=129)**
Baseline total SALT score						
N	140	351	215	130	258	129
Mean	88.09	85.51	85.17	88.86	88.06	86.69
SD	15.1	18.35	18.41	16.2	17.4	18.18
Median	97.5	98.02	97.22	99.49	100	98.64
Minimum	50	50	50	50	50	50
Maximum	100	100	100	100	100	100
Alopecia areata classification (randomization strata), N (%)						
Complete or near-complete scalp hair loss (95 and over) SALT score	78 (55.7)	196 (55.8)	120 (55.8)	79 (60.8)	159 (61.6)	79 (61.2)
Partial scalp hair loss (50 to <95) SALT score	62 (44.3)	155 (44.2)	95 (44.2)	51 (39.2)	99 (38.4)	50 (38.8)
Duration of current episode (years)						
N	140	351	215	130	258	129
Mean	3.9	3.58	3.62	3.82	3.77	4.02
SD	2.88	2.63	2.86	3.1	2.76	2.93
Median	3.26	2.85	2.52	2.75	2.93	3.5
Minimum	1	1	0	0	0	0
Maximum	10	11	11	18	10	11
Current nail involvement, N (%)						
N	87 (62.1)	235 (67)	140 (65.1)	79 (60.8)	134 (51.9)	73 (56.6)
Y	53 (37.9)	116 (33)	74 (34.4)	50 (38.5)	119 (46.1)	54 (41.9)
Missing	0 (0)	0 (0)	1 (0.5)	1 (0.8)	5 (1.9)	2 (1.6)

	Trial 3001			Trial 3002		
Characteristic	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=130)	CTP-543 8 mg BID (N=258)	CTP-543 12 mg BID (N=129)
Current nasal hair involvement, N (%)						
N	53 (37.9)	170 (48.4)	91 (42.3)	86 (66.2)	143 (55.4)	66 (51.2)
Y	87 (62.1)	180 (51.3)	124 (57.7)	44 (33.8)	113 (43.8)	63 (48.8)
Missing	0 (0)	1 (0.3)	0 (0)	0 (0)	2 (0.8)	0 (0)
Current eyebrow involvement, N (%)						
N	31 (22.1)	75 (21.4)	47 (21.9)	24 (18.5)	53 (20.5)	25 (19.4)
Y	97 (69.3)	245 (69.8)	151 (70.2)	102 (78.5)	190 (73.6)	98 (76)
Missing	12 (8.6)	31 (8.8)	17 (7.9)	4 (3.1)	15 (5.8)	6 (4.7)
Current eyelash involvement, N (%)						
N	47 (33.6)	102 (29.1)	57 (26.5)	35 (26.9)	67 (26)	40 (31)
Y	92 (65.7)	246 (70.1)	158 (73.5)	90 (69.2)	178 (69)	86 (66.7)
Missing	1 (0.7)	3 (0.9)	0 (0)	5 (3.8)	13 (5)	3 (2.3)
Any past or concomitant diseases, conditions, exposures to serious infections such as HIV, or past surgeries?, N (%)						
N	12 (8.6)	38 (10.8)	30 (14)	31 (23.8)	52 (20.2)	20 (15.5)
Y	128 (91.4)	313 (89.2)	185 (86)	99 (76.2)	206 (79.8)	109 (84.5)

Source: pg 62-63 of cp543-3001 study report (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3001\cp543-3001-body.pdf) andd pg 60-62 of cp543-3002 study report (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3002\cp543-3002-body.pdf) and reviewer analysis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Treatment compliance was summarized as percent of planned dose received for each dosing regimen. Percent of planned dose received was calculated for the entire treatment period as follows:

100*(Tablets Dispensed - Tablets Returned) / (Tablets Expected)

Tablets Expected was defined as the time on treatment multiplied by the expected number of pills taken daily (×2 for the CTP-543 12-mg BID group; ×2 for the CTP-543 8-mg BID group; ×2 for the placebo group), where time on treatment was defined as treatment end date – treatment start date +1. Dose interruptions were ignored in this calculation. Derived subject compliance, compliance per the eCRF (80% or higher versus less than 80%), and dosing exceptions were listed in by-subject data listings.

Table 23. Summary of Compliance by Treatment Group (Safety Population)

	Trial 3001			Trial 3002		
Statistic	Placebo (N=140)	CTP-543 8 mg BID (N=350)	CTP-543 12 mg BID (N=215)	Placebo (N=130)	CTP-543 8 mg BID (N=256)	CTP-543 12 mg BID (N=129)
Percent of planned dose received (%)						
Mean	95.38	95.23	95.79	95.55	94.61	97.27
SD	9.94	14.32	11.89	11.41	12.92	9.2
Median	97.02	97.87	97.67	97.05	97.95	97.89
Minimum	0	0	0	0	0	59.7
Maximum	125	203.6	137.7	129.3	145.9	158.9

Source: pg 100-101 of cp543-3001 study report (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3001\cp543-3001-body.pdf) and pg 99-100 of cp543-3002 study report (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3002\cp543-3002-body.pdf) and reviewer analysis

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the percentage of subjects achieving an absolute SALT score of ≤20 at Week 24. The primary endpoint for both the 8 mg versus placebo and the 12 mg versus placebo comparisons were statistically significant. The primary endpoint for each dose comparison was compared with 0.025 to control for multiplicity due to the two doses. The results of the common risk difference with multiple imputation analysis of the primary efficacy endpoint are summarized in Table 24 for the Efficacy Population. Both CTP-543 dose groups had a statistically significant larger proportion of subjects with a SALT score ≤20 at Week 24 compared with placebo. The common risk difference was numerically superior for the CTP-543 12-mg BID group versus placebo compared with the CTP-543 8-mg BID dose group versus placebo.

Table 24. Primary Endpoint: Mantel-Haenszel Common Risk Difference Analysis of Subjects With Absolute SALT Scores ≤20 at Week 24 (MI With MAR Assumption) (Efficacy Population)

	Trial 3001			Trial 3002		
Visit Endpoint Statistic	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=127)	CTP-543 8 mg BID (N=249)	CTP-543 12 mg BID (N=127)
Week 24						
SALT score ≤20						
Y[1]	1 (0.8)	94 (29.6)	83 (41.5)	1 (0.8)	77 (33.0)	46 (38.3)
N[1]	127 (99.2)	224 (70.4)	117 (58.5)	118 (99.2)	156 (67.0)	74 (61.7)
Missing	12	33	15	8	16	7
Estimated proportion[2]	0.8	29.2	39.8	0.8	32.1	36.7

Visit Endpoint Statistic	Trial 3001 Placebo (N=140)	 CTP-543 8 mg BID (N=351)	 CTP-543 12 mg BID (N=215)	Trial 3002 Placebo (N=127)	 CTP-543 8 mg BID (N=249)	 CTP-543 12 mg BID (N=127)
Treatment difference [3]						
Common risk difference		0.28	0.39		0.31	0.36
SE		0.026	0.034		0.031	0.044
95% CI		(0.23, 0.33)	(0.32, 0.46)		(0.25, 0.37)	(0.27, 0.45)
p value		<0.0001	<0.0001		<0.0001	<0.0001

Source: pg 21 of ISE tables (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5353-rep-analys-data-more-one-stud\ise\ise-tables.pdf) and reviewer analysis.
[1] Counts and percentages based on non-missing data.
[2] Percentages based on multiple imputed data.
[3] The common risk difference, SE, 95% Cis, and P value were based on the Mantel-Haenszel estimate stratified by baseline scalp hair loss (partial vs. complete/near-complete) for each treatment group compared to placebo. Missing values were imputed using MI under MAR assumptions.

For the primary efficacy analysis described above, missing SALT scores were imputed under a MAR assumption. Data from subjects who have discontinued treatment but remain on study will have their observed data included in the analysis.

Sensitivity Analysis 1: Multiple Imputation; Missing Not at Random

For the sensitivity analysis, subjects who discontinued the study early due to a treatment-emergent adverse event (including COVID-19) or due to lack of efficacy will be considered MNAR, and the SALT scores missing after discontinuation will be imputed using the control arm. This assumes that patients, regardless of treatment, who discontinue the study early for those reasons would have similar SALT scores to placebo patients with complete data. For patients who discontinued the study due to reasons other than treatment-emergent adverse event or lack of efficacy, missing SALT scores after subjects discontinue the study early will be multiply imputed from subjects within the same treatment group who have complete data at that time.

Results from the sensitivity analysis assuming data were MNAR for the Efficacy Population are very similar to the primary analysis, as the analysis differs only in the handling of subjects who discontinued the study early due to a treatment-emergent adverse event or due to lack of efficacy (see Table 25).

Table 25. Primary Endpoint: Mantel-Haenszel Common Risk Difference Analysis of Subjects With Absolute SALT Scores ≤20 at Week 24 (MI With MNAR Assumption) (Efficacy Population)

	Trial 3001			Trial 3002		
Visit Endpoint Statistic	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=127)	CTP-543 8 mg BID (N=249)	CTP-543 12 mg BID (N=127)
Week 24						
SALT score ≤20						
Y[2]	1 (0.8)	94 (29.6)	83 (41.5)	1(0.8)	77 (33.0)	46 (38.3)
N[2]	127 (99.2)	224 (70.4)	117 (58.5)	118 (99.2)	156 (67.0)	74 (61.7)
Missing	12	33	15	8	16	7
Estimated proportion[2]	0.8	28.3	39.8	0.8	31.6	36.6
Treatment difference [2]						
Common risk difference		0.28	0.39		0.31	0.36
SE		0.026	0.035		0.03	0.043
95% CI		(0.22, 0.33)	(0.32, 0.46)		(0.25, 0.37)	(0.27, 0.44)
p value		<0.0001	<0.0001		<0.0001	<0.0001

Source: pg 70 of CTP543.3001 study report (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3001\cp543-3001-body.pdf), pg 69 of CTP543.3002 study report (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3002\cp543-3002-body.pdf), and reviewer analysis.
[1] Counts and percentages based on non-missing data.
[2] Percentages based on multiple imputed data.
[3] The common risk difference, SE, 95% Cis, and P value were based on the Mantel-Haenszel estimate stratified by baseline scalp hair loss (partial vs. complete/near-complete) for each treatment group compared to placebo. Missing values were imputed using MI under MNAR assumptions.

Sensitivity Analysis 2: Tipping Point

The Applicant conducted a tipping point analysis to assess the impact of missing data on the primary endpoint results. The imputed records for treated subjects were shifted towards nonresponse; the imputed records for placebo subjects were shifted towards response. The minimum delta of 0% represents no shift. The maximum delta of 100% represents a shift to complete nonresponse for treated subjects and complete response for placebo subjects. Delta shifts were applied in increments of 5% to the placebo arm only, each active arm only, and then the placebo and active arms simultaneously. For both trials, when only the placebo group was made more effective, the common risk difference for both CTP-543 groups maintained evidence of efficacy through shifts of 0% to 100%.

For Trial CP543.3001, when only the CTP-543 groups were penalized, the common risk difference for both CTP-543 groups maintained evidence of efficacy through shifts of 0% to 100%. With both the placebo group being made more effective and the treatment groups being penalized simultaneously, the common risk difference for both CTP-543 groups maintained evidence of efficacy through shifts of 0% to 100% for the active groups, and 0% to 80% for the placebo group. The placebo group could only be shifted to a maximum delta of 80%, where the P value for the difference between each treatment group was no longer estimable. Therefore, the tipping point was never reached.

For Trial CP543.3002, when only the placebo group was made more effective, the common risk difference for both CTP-543 groups maintained evidence of efficacy through shifts of 0% to 100%. When only the CTP-543 groups were penalized, the common risk difference for both

CTP-543 groups maintained evidence of efficacy through shifts of 0% to 30% for CTP-543 8 mg BID and 35% for CTP-543 12 mg BID; common risk differences were not estimable past this point. With both the placebo group being made more effective and the treatment groups being penalized simultaneously, the common risk difference for both CTP-543 groups either maintained evidence of efficacy or were not estimable. When the placebo arm was shifted from 0% to 55% and from 80% to 100%, the difference for the active arms remained estimable from shifts of 0 to 30% (CTP-543 8 mg BID)/35% (CTP-543 12 mg BID) and maintained evidence of efficacy. When the placebo arm was shifted from 60% to 75%, the active arms remained estimable from shifts of 0 to 100%.

Table 26. Tipping Point Analysis of Subjects With Absolute SALT Scores ≤20 at Week 24 in Trial 3001 (MI With MAR Assumption) (Efficacy Population)

		CTP-543 8 mg BID (N=351)		CTP-543 12 mg BID (N=215)	
Placebo Shift Parameter[1]	Active Shift Parameter[1]	Common Risk Difference (SE)[2]	p-Value[2]	Common Risk Difference (SE)[2]	p-Value[2]
0	0	0.28(0.026)	<0.0001	0.39(0.034)	<0.0001
50	0	0.28(0.027)	<0.0001	0.38(0.035)	<0.0001
100	0	0.20(0.035)	<0.0001	0.31(0.041)	<0.0001
0	50	0.26(0.025)	<0.0001	0.38(0.034)	<0.0001
50	50	0.25(0.026)	<0.0001	0.37(0.034)	<0.0001
75	50	0.22(0.030)	<0.0001	0.34(0.038)	<0.0001
0	100	0.26(0.025)	<0.0001	0.38(0.034)	<0.0001
50	100	0.25(0.026)	<0.0001	0.37(0.034)	<0.0001
75	100	0.22(0.030)	<0.0001	0.34(0.038)	<0.0001

Source: pg 160-189 of CTP543.3001 study report (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3001\cp543-3001-14-tables.pdf), and reviewer analysis.
[1]Imputed records for treated patients are shifted towards non-response. Imputed records for placebo patients are shifted toward response.
[2]The common risk difference, SE, and P value were based on the Mantel-Haenszel estimate stratified by baseline scalp hair loss (partial vs. complete/near-complete) for each treatment group compared to Placebo. Missing values were imputed using MI under MAR assumptions. Estimates displayed are the combined statistics from PROC MIANALYZE after imputations. P value that is not estimable is due to lack of variation across imputations when the imputed values can no longer be shifted.

Table 27. Tipping Point Analysis of Subjects With Absolute SALT Scores ≤20 at Week 24 in Trial 3002 (MI With MAR Assumption) (Efficacy Population)

		CTP-543 8 mg BID (N=351)		CTP-543 12 mg BID (N=215)	
Placebo Shift Parameter[1]	Active Shift Parameter[1]	Common Risk Difference (SE) [2]	p-Value[2]	Common Risk Difference (SE)[2]	p-Value[2]
0	0	0.31(0.031)	<0.0001	0.36(0.044)	<0.0001
50	0	0.31(0.031)	<0.0001	0.36(0.044)	<0.0001
100	0	0.25(0.037)	<0.0001	0.30(0.049)	<0.0001
0	50	0.30(0.030)	<0.0001	0.35(0.043)	<0.0001

		CTP-543 8 mg BID (N=351)		CTP-543 12 mg BID (N=215)	
Placebo Shift Parameter[1]	**Active Shift Parameter[1]**	**Common Risk Difference (SE) [2]**	**p-Value[2]**	**Common Risk Difference (SE)[2]**	**p-Value[2]**
50	50	0.30(0.030)	<0.0001	0.35(0.043)	<0.0001
75	50	0.29(0.031)	<0.0001	0.34(0.044)	<0.0001
0	100	0.30(0.030)	NA	0.35(0.043)	NA
60	100	0.30(0.030)	<0.0001	0.35(0.043)	<0.0001
75	100	0.29(0.031)	<0.0001	0.34(0.044)	<0.0001

Source: pg 109-134 of CTP543.3002 study report (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3002\cp543-3002-14-tables.pdf), and reviewer analysis.
[1]Imputed records for treated patients are shifted towards non-response. Imputed records for placebo patients are shifted toward response.
[2]The common risk difference, SE, and P value were based on the Mantel-Haenszel estimate stratified by baseline scalp hair loss (partial vs. complete/near-complete) for each treatment group compared to Placebo. Missing values were imputed using MI under MAR assumptions. Estimates displayed are the combined statistics from PROC MIANALYZE after imputations. P value that is not estimable is due to lack of variation across imputations when the imputed values can no longer be shifted. NA = not applicable/estimable.

Sensitivity Analysis 3: Modified Efficacy Population

A third sensitivity analysis was performed using the Modified Efficacy Population in Trial 3002 (including data from 17 subjects from site 102). The primary analysis was repeated on this population. The results of this analysis are similar to the results on the primary Efficacy Population. See Table 28.

Table 28. Primary Endpoint: Mantel-Haenszel Common Risk Difference Analysis of Subjects With Absolute SALT Scores ≤20 at Week 24 (MI With MAR Assumption) (Modified Efficacy Population)

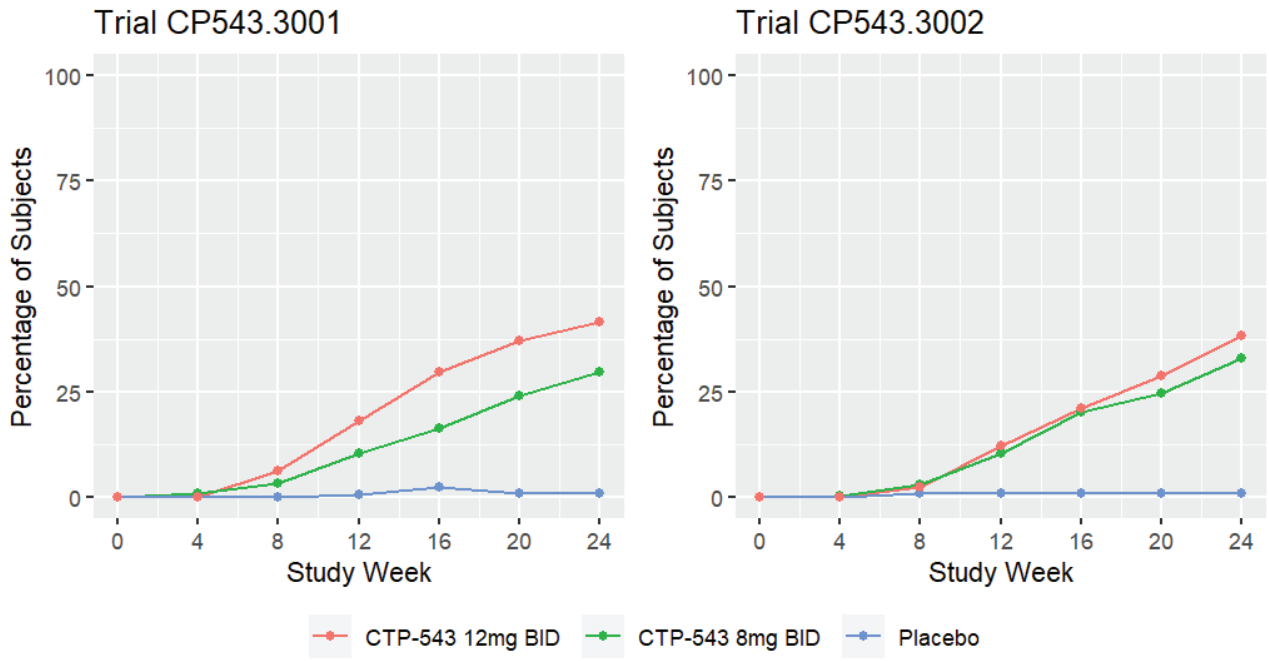
	Trial 3002		
Visit Endpoint Statistic	**Placebo (N=130)**	**CTP-543 8 mg BID (N=256)**	**CTP-543 12 mg BID (N=129)**
Week 24			
SALT score ≤20			
Y[1]	1 (0.8)	77 (33.0)	46 (38.3)
N[1]	118 (99.2)	156 (67.0)	74 (61.7)
Missing	11	23	9
Estimated proportion[2]	0.8	32.1	36.6
Treatment difference[3]			
Common risk difference		0.31	0.36
SE		0.031	0.043
95% CI		(0.25, 0.37)	(0.27, 0.44)
p value		<0.0001	<0.0001

Source: pg 21 of ISE tables (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5353-rep-analys-data-more one-stud\ise\ise-tables.pdf) and reviewer analysis.
[1] Counts and percentages based on non-missing data.
[2] Percentages based on multiple imputed data.
[3] The common risk difference, SE, 95% Cis, and P value were based on the Mantel-Haenszel estimate stratified by baseline scalp hair loss (partial vs. complete/near-complete) for each treatment group compared to placebo. Missing values were imputed using MI under MAR assumptions.

Efficacy Over Time

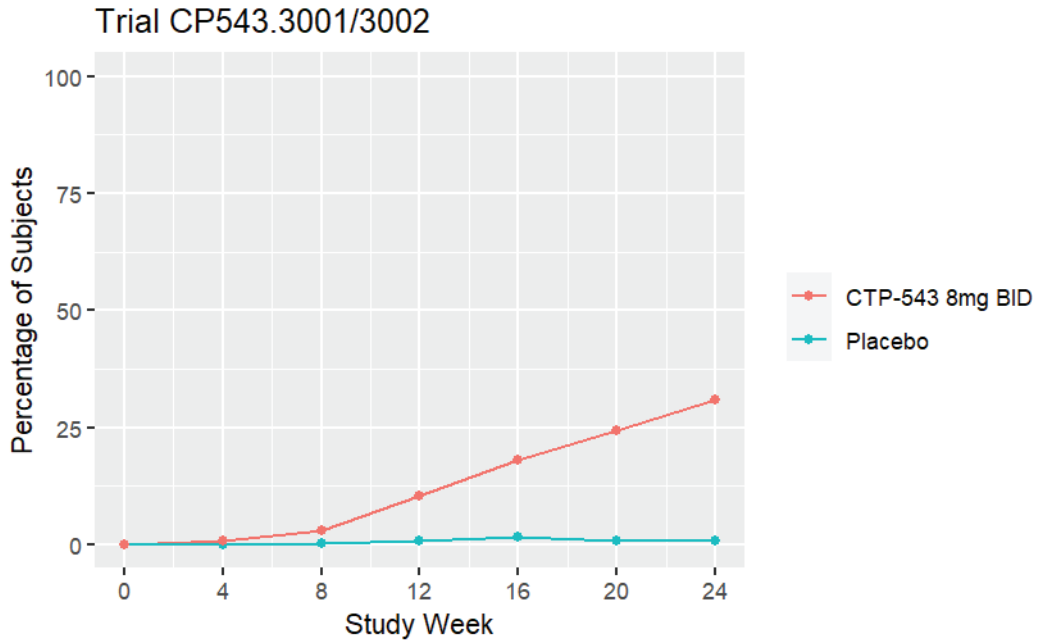
The SALT ≤20 response rates by visit for the evaluated dosing regimens are presented in Figure 9 and Figure 10. For Trial CP543.3001, the proportion of responders among subjects who received the 12-mg dose was generally higher than the proportion of responders among subjects who received the 8-mg dose throughout the trial; however, the proportion of responders for both the 8- and 12-mg dose arms were much more similar throughout the trial in Trial CP543.3002, with only a small difference between the arms in the later part of the trial.

Figure 9. SALT Scores ≤20 by Visit, CTP-543 12 mg BID and CTP-543 8 mg BID (Efficacy Population)



Source: Reviewer analysis using dataset adsalt.xpt.

Figure 10. SALT Scores ≤20 by Visit, CTP-543 8 mg BID (Efficacy Population)

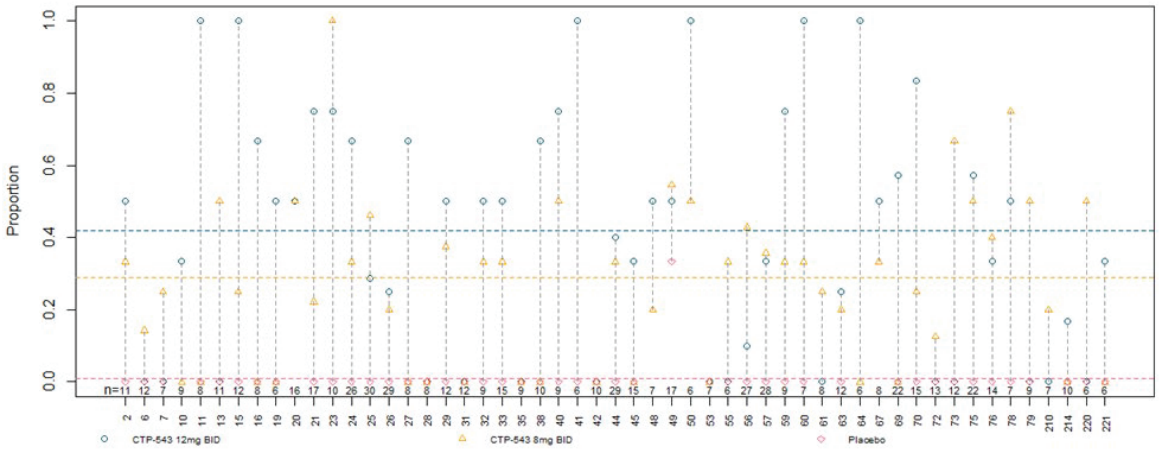


Source: Reviewer analysis using dataset adsalt.xpt.

Efficacy by Center

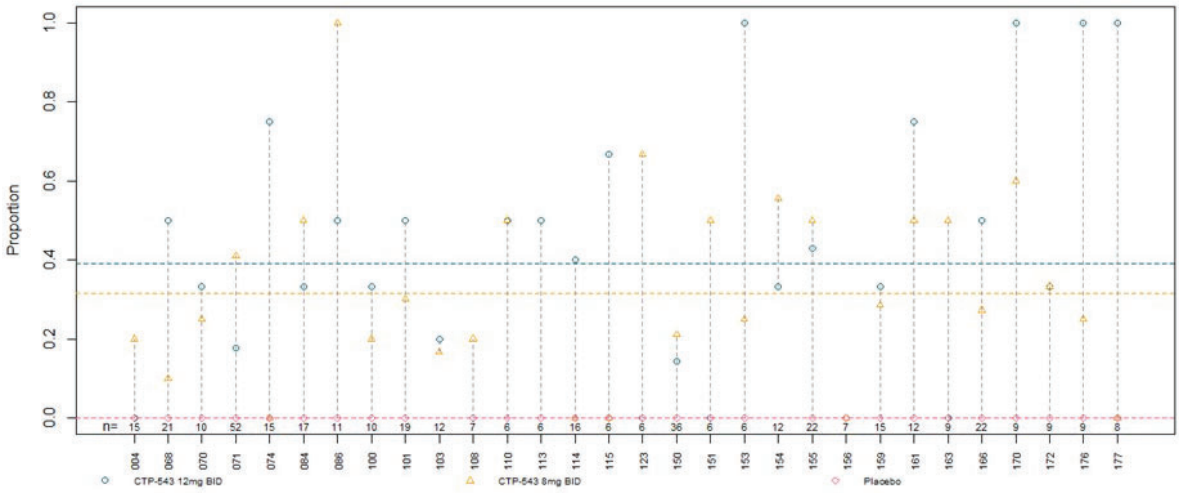
Trial CP543.3001 enrolled 706 subjects at 72 sites in 5 countries (United States, Canada, France, Spain, and Poland), including 61 sites in the U.S. Trial CP543.3002 enrolled 503 subjects at 63 sites in 7 countries (United States, Canada, France, Spain, and Poland), including 61 sites in the United States. Because many of the sites in the two trials enrolled relatively few subjects, Figure 11 and Figure 12 present the primary endpoint results by sites that enrolled at least eight subjects for Trial CP543.3001 and at least five subjects for Trial CP543.3002, respectively. Although there is some variability due to relatively small centers, the results were generally consistent across centers in the two trials.

Figure 11. SALT Scores ≤20 at Week 24 by Site in Trial 3001 (Efficacy Population)



Source: Reviewer analysis using dataset adsalt.xpt.

Figure 12. SALT Scores ≤20 at Week 24 by Site in Trial 3002 (Efficacy Population)



Source: Reviewer analysis using dataset adsalt.xpt.

Findings in Subgroup Populations

Treatment effects for the primary endpoint were generally consistent across age, gender, race, and ethnicity subgroups. Within each dose group, treatment effects were larger in subjects with age <50 years old than in subjects with age ≥50 years, and treatment effects were larger in female subjects than in male subjects. See Table 29 and Table 30.

Table 29. Response at Week 24 by Demographic Subgroups With SALT Scores ≤20 (Efficacy Population)

	Trial 3001			Trial 3002		
Demographic/ Subgroup	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=127)	CTP-543 8 mg BID (N=249)	CTP-543 12 mg BID (N=127)
Age (years)						
<50 years	0/91 (0.1%)	77/239 (31.7%)	68/150 (43.5%)	1/90 (0.1%)	60/181 (31.7%)	41/91 (43.5%)
≥50 years	1/37 (2.6%)	17/79 (21.6%)	15/50 (28.7%)	0/29 (2.6%)	17/52 (21.6%)	5/29 (28.7%)
Gender						
Female	0/81 (0.2%)	67/196 (33.2%)	55/122 (42.9%)	1/80 (0.2%)	63/161 (33.2%)	34/77 (42.9%)
Male	1/47 (2%)	27/122 (22.7%)	28/78 (34.9%)	0/39 (2%)	14/72 (22.7%)	12/43 (34.9%)
Race						
American Indian or Alaska Native	0	1/2 (50%)	1/1 (100%)	0/1 (0%)	0/2 (0%)	0
Asian	0/9 (0%)	8/22 (36.4%)	10/21 (47.6%)	0/7 (0%)	2/3 (66.7%)	1/4 (25%)
Black or African American	0/14 (0%)	3/30 (10%)	2/23 (8.7%)	0/6 (0%)	0/10 (0%)	1/4 (25%)
Native Hawaiian or other Pacific Islander	0/1 (0%)	0/3 (0%)	1/1 (100%)	0	0	0
White	1/91 (1%)	73/221 (32.1%)	62/135 (43.2%)	1/93 (1%)	68/190 (32.1%)	42/103 (43.2%)
Other	0/4 (0%)	6/15 (41.1%)	2/6 (33.3%)	0/1 (0%)	0/1 (0%)	0
Ethnicity						
Hispanic or Latino	0/10 (0%)	9/26 (37.4%)	2/10 (19.1%)	1/9 (0%)	5/22 (37.4%)	4/9 (19.1%)
Non-Hispanic or Latino	1/109 (1%)	81/264 (29.7%)	76/177 (41.1%)	0/99 (1%)	65/184 (29.7%)	40/102 (41.1%)

Source: Reviewer analysis using dataset adsalt.xpt, adsaltmi.xptand adsl.xpt.
Counts are based on non-missing data and percentages are based on the MI data.

Table 30. Response at Week 24 by Demographic Subgroups With SALT Scores ≤20 (Pooled Trials 3001 and 3002) (Efficacy Population)

	Pooled		
Demographic/Subgroup	Placebo (N=267)	CTP-543 8 mg BID (N=600)	CTP-543 12 mg BID (N=342)
Age (years)			
<50 years	1/181 (0.1%)	137/420 (31.7%)	109/241 (43.5%)
≥50 years	1/66 (2.6%)	34/131 (21.6%)	20/79 (28.7%)
Gender			
Female	1/161 (0.2%)	130/357 (33.2%)	89/199 (42.9%)
Male	1/86 (2%)	41/194 (22.7%)	40/121 (34.9%)

	Pooled		
Demographic/Subgroup	Placebo (N=267)	CTP-543 8 mg BID (N=600)	CTP-543 12 mg BID (N=342)
Race			
American Indian or Alaska Native	0/1 (100%)	1/4 (50%)	1/1 (100%)
Asian	0/16 (0%)	10/25 (36.4%)	11/25 (47.6%)
Black or African American	0/20 (0.9%)	3/40 (14.2%)	3/27 (11.3%)
Native Hawaiian or other Pacific Islander	0/1 (0%)	0/3 (0%)	1/1 (100%)
White	2/184 (1%)	141/411 (32.1%)	104/238 (43.2%)
Other	0/5 (0%)	6/16 (41.1%)	2/6 (33.3%)
Ethnicity			
Hispanic or Latino	1/19 (0%)	14/48 (37.4%)	6/19 (19.1%)
Non-Hispanic or Latino	1/208 (1%)	146/448 (29.7%)	116/279 (41.1%)

Source: Reviewer analysis using dataset adsalt.xpt and adsl.xpt.
Counts are based on non-missing data and percentages are based on the MI data. Source: Reviewer analysis using dataset adsalt.xpt and adsl.xpt. Counts and percentages based on non-missing data.

Both the 8-mg and 12-mg doses of deuruxolitinib demonstrated efficacy relative to placebo on the primary efficacy endpoint (SALT ≤20 at Week 24). Response on the 12-mg dose was higher than the 8-mg dose across demographic and baseline disease severity subgroups. Baseline SALT score appears to be related to SALT ≤20 response, that is, SALT ≤20 response rates were higher in all dose groups in patients with baseline SALT 50 to 94 versus SALT 95 to 100. Thus, while the 12-mg dose had consistently higher response rates than the 8-mg dose for the primary endpoint across the range of baseline SALT scores, a reasonable proportion of subjects with baseline SALT score <95 (approximately 47%) were able to achieve SALT ≤20 response on the 8-mg dose. Table 32 summarizes the efficacy results by baseline SALT score for the two studies pooled together.

Table 31. SALT Scores ≤20 at Week 24 by Baseline SALT Category (Efficacy Population)

	Trial 3001			Trial 3002		
SALT	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=127)	CTP-543 8 mg BID (N=249)	CTP-543 12 mg BID (N=127)
50% to 94% scalp hair loss	1/62 (1.8%)	57/155 (41.7%)	50/95 (55.0%)	1/48 (2.1%)	46/93 (52.2%)	27/48 (56.8%)
95% to 100% scalp hair loss	0/78 (0%)	37/196 (19.3%)	33/120 (27.7%)	0/79 (0%)	31/156 (20.2%)	19/79 (24.5%)

Source: Reviewer analysis using dataset adsalt.xpt, adsaltmi.xpt and adsl.xpt.
Counts based on non-missing data, proportions based on the MI dataset.

Table 32. SALT Scores ≤20 at Week 24 by Baseline SALT Category (Pooled Trials) (Efficacy Population)

SALT	Placebo (N=267)	CTP-543 8 mg BID (N=600)	CTP-543 12 mg BID (N=342)
50% to 94% scalp hair loss	2/110 (1.9%)	103/248 (45.6%)	77/143 (55.6%)
95% to 100% scalp hair loss	0/157 (0%)	68/352 (20.0%)	52/199 (26.5%)

Source: Reviewer analysis using dataset adsalt.xpt, adsaltmi.xpt and adsl.xpt.
Counts based on non-missing data, proportions based on the MI dataset.

Data Quality and Integrity

No issues with data quality and integrity were identified in these trials, except for issues at one site in Trial CP543.3002 identified by the Applicant while the trial was ongoing. The OSI conducted inspections of four clinical investigators (Site 56 [Osman] and Site 57 [Zirwas] in Trial CP543.3001 and Site 071 [Tsianakas] and Site 155 [Magnolo] in Trial CP543.3002) and the Applicant. The inspections did not find significant concerns regarding the study conduct, oversight, or management of the clinical trials or 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. Refer to Section 4.1 of this review.

The Applicant identified issues with one site in Trial CP543.3002 while the trial was ongoing. U.S. Site 102, PI Dr. Alexander Beyzer, showed continued resistance to accommodate an onsite audit by the Applicant leading to questions about a potential lack of PI oversight during the course of an expanded investigation. The site was formally closed on March 1, 2022, and any ongoing subjects were discontinued. The data for subjects treated at Site 102 were excluded from the Efficacy Population, and thus, the Per Protocol Population. The inclusion or exclusion of the data from site 102 did not impact the conclusions.

Efficacy Results – Secondary and Other Relevant Endpoints

For the primary efficacy analysis and the key secondary efficacy analysis, $\alpha \leq 0.025$ (two-sided) alpha-level was allocated to each dose for comparison with placebo to adjust for multiplicity of testing associated with 2 doses. Once $p>0.025$ was observed for a treatment group comparison, inference for additional endpoints was no longer alpha-level protected for that dose group; however, nominal p-values were still reported. Four key secondary endpoints: SPRO responders at Week 24, absolute SALT scores ≤20 at Week 12, Week 16 and Week 20 were statistically significant across both trials. The risk differences of key secondary endpoint absolute SALT scores ≤20 at Week 8 was significant in Trial CP543.3001 only. And the exploratory endpoint SALT scores ≤10 at Week 24 was also nominally significant across both trials. See Table 33, Table 34 and Table 35.

Table 33. Key Secondary Endpoint: Mantel-Haenszel Common Risk Difference Analysis of Hair Satisfaction, Patient-Reported Outcome Responders at Week 24 (MI With MAR Assumption) (Efficacy Population)

	Trial 3001			Trial 3002		
Visit Endpoint Statistic	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=127)	CTP-543 8 mg BID (N=249)	CTP-543 12 mg BID (N=127)
Week 24						
SPRO responses[2], n (%)						
1 = Very satisfied	2 (1.6%)	58 (18.2%)	52 (26%)	0 (0%)	40 (17.5%)	24 (20%)
2 = Satisfied	4 (3.1%)	76 (23.9%)	54 (27%)	2 (1.7%)	66 (28.9%)	38 (31.7%)
3 = Neither satisfied nor dissatisfied	19 (14.8%)	62 (19.5%)	38 (19%)	16 (13.6%)	34 (14.9%)	23 (19.2%)
4 = Dissatisfied	31 (24.2%)	58 (18.2%)	30 (15%)	20 (16.9%)	34 (14.9%)	18 (15%)
5 = Very dissatisfied	72 (56.2%)	64 (20.1%)	26 (13%)	80 (67.8%)	54 (23.7%)	17 (14.2%)
Missing	12	33	15	9	21	7
SPRO responders[3]						
Y[1]	6 (4.7%)	134 (42.1%)	106 (53%)	2 (1.7%)	106 (46.5%)	62 (51.7%)
N[1]	122 (95.3%)	184 (57.9%)	94 (47%)	116 (98.3%)	122 (53.5%)	58 (48.3%)
Missing	12	33	15	9	21	7
Estimated proportion[2]	4.8	42.4	51.8	1.6	46.3	50.3
Treatment difference[4]						
Common risk difference		0.38	0.47		0.45	0.49
SE		0.033	0.039		0.035	0.047
95% CI		(0.31, 0.44)	(0.39, 0.55)		(0.38, 0.52)	(0.4, 0.58)
p value		<0.0001	<0.0001		<0.0001	<0.0001

Source: pg 31-32 of ISE tables (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5353-rep-analys-data-more-one-stud\ise\ise-tables.pdf) and reviewer analysis.
[1] Counts and percentages based on non-missing data.
[2] Percentages based on multiple imputed data.
[3] SPRO responders were subjects with responses of "Very satisfied" or "Satisfied."
[4] The common risk difference, SE, 95% Cis, and P value were based on the Mantel-Haenszel estimate stratified by baseline scalp hair loss (partial vs. complete/near-complete) for each treatment group compared to placebo. Missing values were imputed using MI under MAR assumptions.

Table 34. Key Secondary Endpoint: Mantel-Haenszel Common Risk Difference Analysis of Subjects With Absolute SALT Scores ≤20 at Week 8, Week 12, Week 16, and Week 20 (MI With MAR Assumption) (Efficacy Population)

	Trial 3001			Trial 3002		
Endpoint	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=127)	CTP-543 8 mg BID (N=249)	CTP-543 12 mg BID (N=127)
SALT ≤20 (Wk 20)[1]	1/131 (0.7%)	76/316 (24.0%)	74/200 (35.4%)	1/120 (0.8%)	58/234 (24.0%)	34/118 (27.8%)
Difference (95% CI)[2]		23% (19, 28)	35% (28, 41)		23% (18, 29)	27% (19, 35)
p value		<0.0001	<0.0001		<0.0001	<0.0001
SALT ≤20 (Wk 16)[1]	3/131 (2.1%)	53/322 (16.5%)	60/203 (28.7%)	1/124 (0.8%)	48/238 (19.9%)	26/123 (20.6%)
Difference (95% CI)[2]		14% (10, 19)	27% (20, 33)		19% (14, 24)	20% (13, 27)
p value		<0.0001	<0.0001		<0.0001	<0.0001
SALT ≤20 (Wk 12)[1]	1/136 (0.7%)	34/328 (10.7%)	38/209 (17.9%)	1/123 (0.8%)	25/237 (10.4%)	15/122 (12.3%)
Difference (95% CI)[2]		10% (6, 14)	17% (12, 22)		10% (6, 14)	12% (6, 17)
p value		<0.0001	<0.0001		<0.0001	0.0001

	Trial 3001			Trial 3002		
Endpoint	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=127)	CTP-543 8 mg BID (N=249)	CTP-543 12 mg BID (N=127)
SALT ≤20 (Wk 8)[1]	0/138 (0%)	11/336 (3.5%)	13/212 (6.1%)	1/125 (0.8%)	7/239 (2.9%)	3/125 (2.4%)
Difference (95% CI)[2]		3% (1, 5)	6% (3, 9)		2% (0, 5)	2% (-1, 5)
p value		0.0005	0.0002		0.102	0.3103

Source: pg 23-29 of ISE tables (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5353-rep-analys-data-more-one-stud\ise\ise-tables.pdf) and reviewer analysis.
[1] Counts are based on non-missing data, and percentages are based on multiple imputed data.
[2] The common risk difference, SE, 95% Cis, and P value were based on the Mantel-Haenszel estimate stratified by baseline scalp hair loss (partial vs. complete/near-complete) for each treatment group compared to placebo. Missing values were imputed using MI under MAR assumptions.

Table 35. Mantel-Haenszel Common Risk Difference Analysis of Subjects With Absolute SALT Scores ≤10 at Week 24 (MI With MAR Assumption) (Efficacy Population)

	Trial 3001			Trial 3002		
Visit Endpoint Statistic	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=127)	CTP-543 8 mg BID (N=249)	CTP-543 12 mg BID (N=127)
Week 24						
SALT score ≤20						
Y[1]	0 (0%)	66 (20.8%)	69 (34.5%)	0 (0%)	58 (24.9%)	32 (26.7%)
N[1]	128 (100%)	252 (79.2%)	131 (65.5%)	119 (100%)	175 (75.1%)	88 (73.3%)
Missing	12	33	15	8	16	7
Estimated proportion[2]	0	20.5	32.8	0	24.1	25.5
Treatment difference[3]						
Common risk difference		0.21	0.33		0.24	0.25
SE		0.022	0.032		0.027	0.039
95% CI		(0.16, 0.25)	(0.27, 0.39)		(0.19, 0.3)	(0.18, 0.33)
p value		<0.0001	<0.0001		<0.0001	<0.0001

Source: pg 115 of ISE tables (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5353-rep-analys-data-more-one-stud\ise\ise-tables.pdf) and reviewer analysis.
[1] Counts and percentages based on non-missing data.
[2] Percentages based on multiple imputed data.
[3] The common risk difference, SE, 95% Cis, and P value were based on the Mantel-Haenszel estimate stratified by baseline scalp hair loss (partial vs. complete/near-complete) for each treatment group compared to placebo. Missing values were imputed using MI under MNAR assumptions.

Additional Efficacy Considerations

Review of COA for Evaluation of Clinical Benefit

The FDA reviewed the Applicant's COA evidence dossier for the SPRO. This COA was reviewed for content validity and other measurement properties (reliability, construct validity, responsiveness), as well as score interpretability.

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)

The review team evaluated the data generated from these instrument development activities.

Patient input confirmed that the content of the SPRO assesses an important aspect of AA. An issue that was identified was that the qualitative sample was limited in diversity and not sufficiently representative of AA in the U.S. As such, input from the target population may not be comprehensive and fully representative of AA. However, the qualitative sample appears to be representative of the clinical trial population (i.e., predominantly White).

Refer to the full COA review by Julia Ju, PharmD, PhD, dated May 24, 2024, the Division of Clinical Outcome Assessment for detailed results of the content validity of these COAs.

Other Measurement Properties (Reliability, Construct Validity, Responsiveness)

The Applicant evaluated other measurement properties of the SPRO using data from Study CP543.3001.

For the assessment of the other measurement properties of the SPRO, the results were generally within acceptable and within reasonable range. For assessment of test-retest reliability, the intra-class correlation coefficient estimates do not fall within an acceptable and reasonable range for the analysis. While the intra-class correlation coefficient 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.

Refer to the full review by Julia Ju, PharmD, PhD, Division of Clinical Outcome Assessment, for detailed discussion of the other measurement properties of these COAs.

Score Interpretability

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

Regarding the clinical meaningfulness of the SPRO-based endpoint, the Applicant utilized multiple anchor scales. some of which were not ideal as they did not account for the patient perspective (e.g., ClinRO assessments). However, there were patient-reported anchor scales that closely aligned with the SPRO-based endpoint. The results from the anchor-based analyses were difficult to interpret in the absence of qualitative data, as it is unknown what constitutes a meaningful change on the anchor scales. 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.

Refer to the full COA review by Julia Ju, PharmD, PhD, Division of Clinical Outcome Assessment for detailed results of the score interpretability of these COAs.

Conclusion

The SPRO could potentially support a labeling claim, if supported by the clinical trial study design and statistical analysis. The full distribution of SPRO responses including patients who may have been dissatisfied should communicated in labeling.

Dose/Dose Response

Both the 8-mg and 12-mg doses of deuruxolitinib demonstrated efficacy relative to placebo on the primary efficacy endpoint (SALT ≤20 at Week 24) and the key secondary endpoints (SPRO, SALT ≤20 at Week 12, Week 16, and Week 20). Response on the 12-mg dose was higher than the 8-mg dose across demographic and baseline disease severity subgroups. For the primary endpoint, the risk difference between 12-mg dose and placebo is 11% higher than the risk difference between 8-mg dose and placebo in Trial CP543.3001, and the risk difference between 12-mg dose and placebo is 5% higher than the risk difference between 8-mg dose and placebo in Trial CP543.3002. See Table 36.

Due to the thrombotic events that occurred in the open-label extension trials at the 12-mg BID dose, the Applicant is currently seeking approval of only the deuruxolitinib 8-mg BID dose.

Table 36. Primary Endpoint: Mantel-Haenszel Common Risk Difference Analysis of Subjects With Absolute SALT Scores ≤20 at Week 24 (MI With MAR Assumption) (Efficacy Population)

	Trial 3001			Trial 3002		
Visit Endpoint Statistic	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=127)	CTP-543 8 mg BID (N=249)	CTP-543 12 mg BID (N=127)
Week 24						
SALT score ≤20						
Estimated proportion[1]	0.8	29.2	39.8	0.8	32.1	36.7
Treatment difference [2]						
Common risk difference		0.28	0.39		0.31	0.36
SE		0.026	0.034		0.031	0.044
95% CI		(0.23, 0.33)	(0.32, 0.46)		(0.25, 0.37)	(0.27, 0.45)
p value		<0.0001	<0.0001		<0.0001	<0.0001

Source: pg 21 of ISE tables (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5353-rep-analys-data-more-one-stud\ise\ise-tables.pdf) and reviewer analysis.
[1] Percentages based on multiple imputed data.
[2] The common risk difference, SE, 95% Cis, and P value were based on the Mantel-Haenszel estimate stratified by baseline scalp hair loss (partial vs. complete/near-complete) for each treatment group compared to placebo. Missing values were imputed using MI under MAR assumptions.

Durability of Response

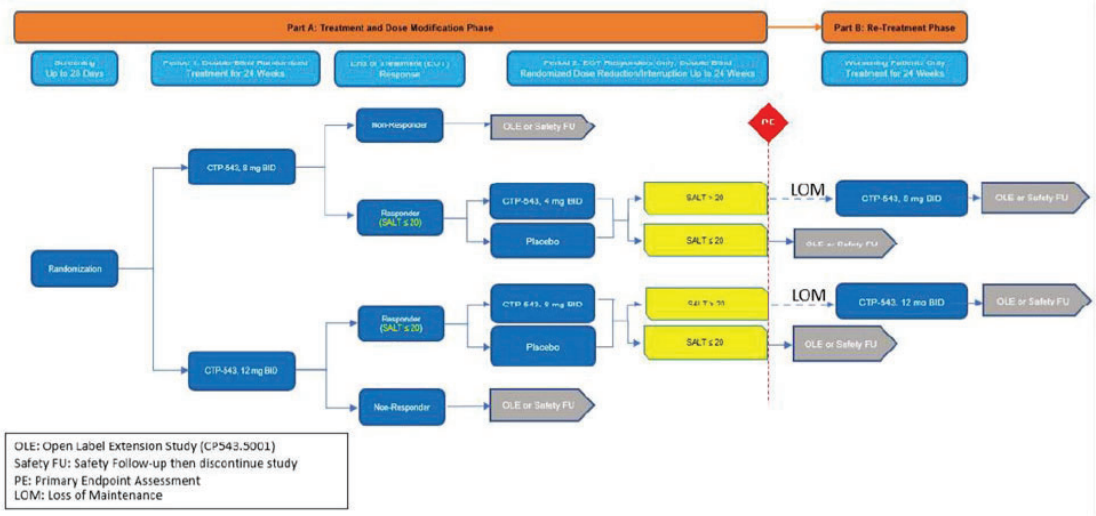
The Applicant evaluated durability of response to treatment with deuruxolitinib in Trial CP543.2004. Trial CP543.2004 was a 2-part, double-blind, randomized, multicenter trial to evaluate the regrowth of hair with one of two doses of deuruxolitinib (CTP-543) and subsequent durability of that regrowth following dose reduction or drug discontinuation in adult subjects with moderate to severe alopecia areata. Part A included a Treatment Phase

(Period 1) followed by a Dose Modification Phase (Period 2), and Part B included a Retreatment Phase (Figure 13).

Part A Period 1 was a double-blind treatment phase in which subjects were randomized to receive either CTP-543 8 mg BID (approximately 170 subjects) or CTP-543 12 mg BID (approximately 130 subjects) for 24 weeks. Part A Period 2 was a double-blind design, in which responders (SALT ≤20) were re-randomized in a 1:1 ratio to receive either a lower dose of CTP-543 or placebo. Subjects who previously received CTP-543 12 mg BID in Part A Period 1 received either CTP-543 8-mg BID or placebo tablets BID for up to 24 weeks in Part A Period 2. Subjects who previously received CTP-543 8 mg BID in Part A Period 1 received either CTP-543 4 mg BID or placebo tablets BID for up to 24 weeks in Part A Period 2 (Figure 13).

Subjects who discontinued study drug at any time for any reason but did not withdraw consent were to continue to be followed for all protocol-planned study visits through the completion of the 24-week treatment period and have all endpoints (including efficacy) collected accordingly. The last observed non-missing SALT value for the end of Part A Period 2 for the co-primary endpoint was used. Otherwise, missing data were not imputed.

Figure 13. Trial CP543.2004 Trial Design



Abbreviations in addition to those above: BID = twice daily; EOT = end of treatment; SALT = Severity of Alopecia Tool
Note: This interim report describes the efficacy and safety data from Part A Period 1 and Part A Period 2. Results for both Part A and Part B of the study will be described in a final clinical study report.

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Source: pg14 of CP543-2004 protocol (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-2004\cp543-2004-e3-16-1-01.pdf)

At the end of Part A period 1, 36 subjects with 8-mg dose and 50 subjects with 12-mg achieved treatment success (SALT ≤20). In Part A period 2, responders were randomized in a 1:1 ratio to either a lower dose of CTP-543 or placebo. For dose reduction groups, 13 of 18 subjects (72.2%) in the 8-mg to 4-mg group and 17 of 25 subjects (68%) in the 12-mg to 8-mg group remained responders at the end of Period 2. For drug discontinuation groups, 3 of 18 subjects (16.7%) in the 8-mg to placebo group and 3 of 25 subjects (20%) in the 12-mg to placebo group remained responders at the end of Period 2. See Table 37.

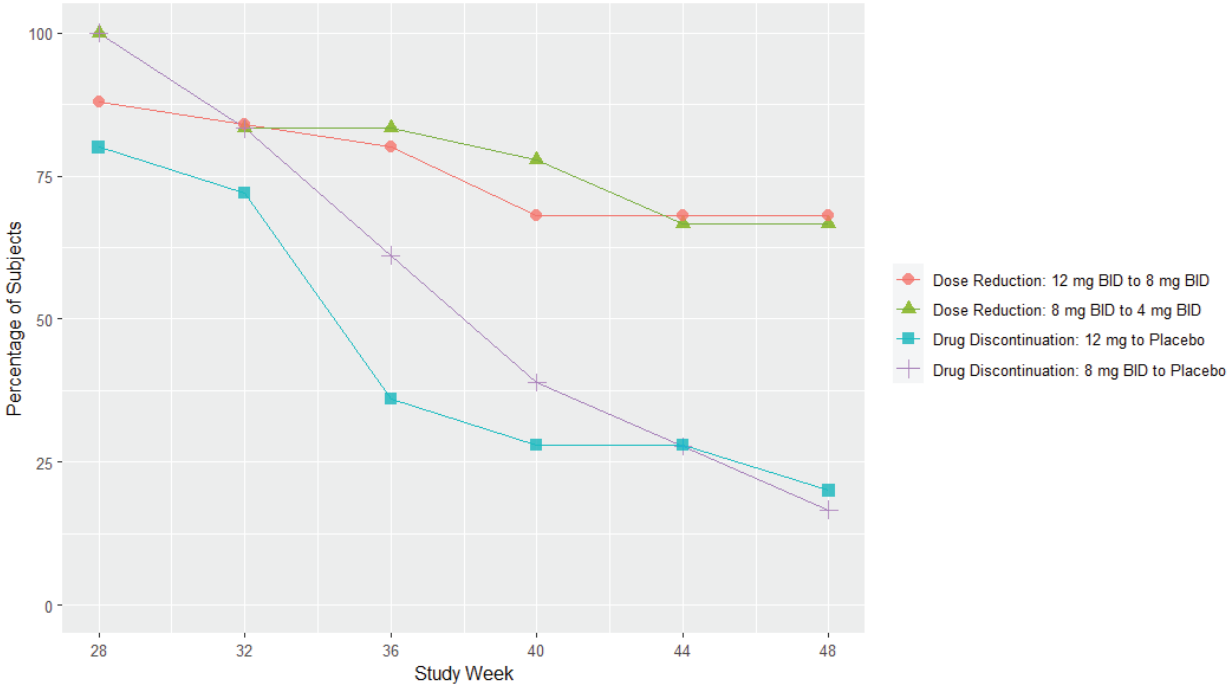
Table 37. Trial CP543-2004 Part A, Period 2 Responders (SALT Score ≤20) (Efficacy Population)

	Dose Reduction		Drug Discontinuation	
Visit Endpoint/Statistic	CTP-543 8 mg BID to 4 mg BID (N=18)	CTP-543 12 mg BID to 8 mg BID (N=25)	CTP-543 8 mg BID to Placebo (N=18)	CTP-543 12 mg BID to Placebo (N=25)
End of Part A Period 2[1]				
Responder (SALT score ≤20), n (%) [2]	13 (72.2)	17 (68.0)	3 (16.7)	5 (20.0)
95% CI for percentage [3]	(51.5, 92.9)	(49.7, 86.3)	(0.0, 33.9)	(4.3, 35.7)

[1] The Part A Period 2 population consists of responders from Part A Period 1.
[2] Percentages are out of the number of patients in each treatment group.
[3] Confidence intervals use the binomial approximation with a Wald continuity correction.

The efficacy data suggest that following the successful regrowth of hair in Part A Period 1 (SALT ≤20 at Week 24), discontinuation of CTP-543 results in the most severe loss of response, with over 80% of subjects losing response over a 24-week period. Reduction of CTP-543 dose to 4 mg or 8 mg results in approximately 30% of subjects losing response over the 24-week study period. See Figure 14.

Figure 14. Trial CP543-2004 Part A, Period 2 Responders (SALT Score ≤20) (Efficacy Population)



[1] Source: reviewer analysis using dataset adsl.xpt in trial CP543-2004. Percentages are out of the number of patients in each treatment group.

Efficacy Results – Secondary or Exploratory COA (Patient-Reported Outcome) Endpoints

The secondary endpoints for eyebrow and eyelash assessments were: Change from Baseline on the BETA score at Weeks 12 and 24, and Change from Baseline on the BELA score at Weeks 12

and 24. The risk differences of both endpoints were nominally significant for 8-mg and 12-mg doses across both trials (See Table 38 and Table 39). These endpoints were not included in the multiplicity hierarchy. Content validity and other measurement properties of the BETA and BELA were not reviewed since they were considered exploratory endpoints. Results from the BETA and BELA scores are not proposed for inclusion in labeling.

Table 38. Mixed Model for Repeated Measures Analysis of Change From Baseline in Brigham Eyebrow Tool for Alopecia at Week 24 (Efficacy Population)

	Trial 3001			Trial 3002		
Parameter	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=127)	CTP-543 8 mg BID (N=249)	CTP-543 12 mg BID (N=127)
Observed values						
N	72	192	118	86	156	83
Mean (SD)	1.35 (2)	2.87 (2.1)	3.24 (2.02)	0.62 (1.26)	1.97 (2.06)	2.43 (2.02)
Median	0.09	3	3.65	0	1.4	2.2
Change from baseline						
Mean (SD)	-0.24 (1.68)	1.62 (1.96)	1.77 (2.17)	-0.32 (1.1)	1.2 (1.76)	1.21 (1.81)
Median	0	1.55	1.6	0	0.32	0.9
(Min, max)	(-6, 3.1)	(-3.2, 6)	(-2.5, 6)	(-4.15, 3.25)	(-1.76, 6)	(-3.4, 5.85)
LS mean	-0.19	1.53	1.72	-0.35	1.1	1.38
SE	0.21	0.13	0.16	0.16	0.12	0.17
95% CI	(-0.6, 0.21)	(1.28, 1.78)	(1.41, 2.04)	(-0.67, -0.03)	(0.86, 1.34)	(1.05, 1.7)
Treatment difference						
LS Mean		1.72	1.91		1.45	1.73
SE		0.24	0.26		0.2	0.23
95% CI		(1.24, 2.2)	(1.4, 2.43)		(1.06, 1.85)	(1.27, 2.19)
p value		<0.0001	<0.0001		<0.0001	<0.0001

Source: pg 272-274 in cp543-3001-14-tables (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3001\cp543-3001-14-tables.pdf), pg 209-211 in in cp543-3002-14-tables (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3002\cp543-3002-14-tables.pdf) and reviewer analysis using dataset adqsoth.xpt.
Note: LS means, SEs, CIs, and P values are based on a mixed model repeated measures analysis with effects for treatment, visit, treatment-by-visit interaction, baseline value, and baseline SALT score. The model is fit using an unstructured covariance structure. Missing data were not multiply imputed.

Table 39. Mixed Model for Repeated Measures Analysis of Change From Baseline in Brigham Eyelash Tool for Alopecia at Week 24 (Efficacy Population)

	Trial 3001			Trial 3002		
Parameter	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=127)	CTP-543 8 mg BID (N=249)	CTP-543 12 mg BID (N=127)
Observed values						
N	78	209	138	78	153	69
Mean (SD)	1.61 (2.24)	3.06 (2.4)	3.77 (2.26)	0.62 (1.37)	2.22 (2.19)	2.61 (2.42)
Median	0	3.6	4	0	1.75	2
Change from baseline						
Mean (SD)	0.25 (1.3)	1.68 (1.99)	1.98 (2.28)	-0.02 (0.93)	1.39 (2.09)	1.31 (1.97)
Median	0	0.9	1.5	0	0.8	0.82
(Min, max)	(-5.7, 4)	(-4, 6)	(-2.95, 6)	(-3.25, 3)	(-4.5, 6)	(-4.05, 6)
LS mean	0.15	1.63	2.07	-0.07	1.41	1.47
SE	0.21	0.13	0.16	0.2	0.14	0.21
95% CI	(-0.26, 0.56)	(1.38, 1.89)	(1.76, 2.38)	(-0.46, 0.32)	(1.13, 1.69)	(1.06, 1.88)

	Trial 3001			Trial 3002		
Parameter	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=127)	CTP-543 8 mg BID (N=249)	CTP-543 12 mg BID (N=127)
Treatment Difference						
LS Mean		1.48	1.92		1.48	1.54
SE		0.24	0.26		0.24	0.29
95% CI		(1.00, 1.74)	(1.41, 2.43)		(1.00, 1.96)	(0.98, 2.10)
p value		<0.0001	<0.0001		<0.0001	<0.0001

Source: pg 265-267 in cp543-3001-14-tables (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3001\cp543-3001-14-tables.pdf), pg 203-205 in in cp543-3002-14-tables (\\CDSESUB1\EVSPROD\nda217900\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\cp543-3002\cp543-3002-14-tables.pdf) and reviewer analysis using dataset adqsoth.xpt.
NOTE: LS means, SEs, CIs, and P values are based on a mixed model repeated measures analysis with effects for treatment, visit, treatment-by-visit interaction, baseline value, and baseline SALT score. The model is fit using an unstructured covariance structure. Missing data were not multiply imputed.

8.1.3. Assessment of Efficacy Across Trials

Efficacy was demonstrated in Trial CP543.3001 and 3002 for the primary endpoint of SALT ≤20 response and four key secondary endpoints (SPRO responders at Week 24, SALT scores ≤20 response at Week 12, Week 16 and Week 20) for both the 8-mg and 12-mg twice daily dosage of deuruxolitinib. The risk differences of key secondary endpoint absolute SALT scores ≤20 at Week 8 was significant in Trial CP543.3001 only. The efficacy of the 8-mg and 12-mg twice daily dosage was additionally supported by secondary endpoints change from baseline in BETA, change from baseline in BELA, and SALT ≤10 response. However, due to insufficient evidence to support the content validity and reliability of the BETA and BELA endpoints, in conjunction with the fact that these endpoints were not included in the multiplicity hierarchy, presenting the results based on these endpoints may not be appropriate for labeling. The secondary endpoints Change from Baseline in BETA and BELA, and SALT scores ≤10 at Week 24 were nominally significant for 8-mg and 12-mg doses across both trials.

Table 40. Efficacy Across Trials – CP543.3001 and 3002

	Trial 3001			Trial 3002		
Parameter	Placebo (N=140)	CTP-543 8 mg BID (N=351)	CTP-543 12 mg BID (N=215)	Placebo (N=127)	CTP-543 8 mg BID (N=249)	CTP-543 12 mg BID (N=127)
SALT ≤20 (%)	0.8	29.2	39.8	0.8	32.1	36.7
Difference (95% CI)		28 (23, 33)	39 (32, 46)		31 (25, 37)	36 (27, 45)
p-value		<0.0001	<0.0001		<0.0001	<0.0001

8.2. Review of Safety

8.3. Safety Review Approach

The primary review of safety for deuruxolitinib tablets, 8 mg and 12 mg, for the treatment of AA focused on placebo-controlled data from Phase 2 Trial CP543.2001, Phase 3 Trial CP543.3001 and Phase 3 Trial CP543.3002. The clinical trials were conducted in adult subjects with at least 50% scalp hair loss (Severity of Alopecia Tool [SALT] score ≥50).

The primary analysis dataset for the review of safety included pooled data from the placebo-controlled Phase 2 trial CP543.2001 (excluding subjects from Cohort 1 dosed with deuruxolitinib 4 mg) and Phase 3 trials CP543.3001 and CP543.3002 for subjects treated from Week 0-24. The dataset included 640 subjects treated with deuruxolitinib 8 mg BID, 380 subjects treated with deuruxolitinib 12 mg BID and 299 subjects treated with placebo. The safety review focused on subjects who received ≥1 dose of deuruxolitinib up to Week 52.

Supportive safety data included pooled data from the first 52 weeks of the open- label, long-term extension Trials CP543.5001 and CP543.5002. These trials enrolled subjects who completed 24 weeks of treatment in the Phase 2 and Phase 3 trials. Both OLE trials enrolled subjects from the Phase 3 Trials CP543.3001 and CP543.3002. Trial CP543.5001 also enrolled subjects from Phase 2 trials CP543.2001, CP543.2002 and CP543.2003, and CP543.2004. (Refer to the Table of Clinical Trials). The safety population from the pooled OLE trials included 868 subjects who received deuruxolitinib 8 mg BID, and 991 subjects who received deuruxolitinib 12 mg BID for 52 weeks. At the discretion of the investigator, dose changes (8 mg BID to 12 mg BID or 12 mg BID to 8 mg BID) were only permitted in these OLE trials. Adverse events (AEs) were considered treatment-emergent with respect to the most recent dose taken prior the start of the AE.

The review team analyzed the following types of pooled data: exposure, demographics and baseline characteristics, treatment-emergent adverse events (TEAEs), SAEs, AEs leading to discontinuation and adverse events of special interest (AESI). The Applicant specified AESI based on the known class effects of JAK inhibitors which include infections, malignancies, hypersensitivity reactions, MACE, thrombosis, gastrointestinal perforation, blood creatine phosphokinase increased, thrombocytopenia, thrombocytosis, cytopenias (lymphopenia, neutropenia and anemia), lipid elevations, and liver enzyme elevations including drug-induced liver injury (DILI). In addition, because patients with alopecia areata are at higher risk of anxiety and depression (Okhovat et al. 2023), the review team analyzed findings from the HADS that was administered during Phase 3 Trials CP543.3001 and CP543.3002.

8.3.1. Review of the Safety Database

Overall Exposure

The primary analysis dataset for the review of safety for deuruxolitinib for the treatment of moderate to severe AA included pooled data from the placebo-controlled Phase 2 trial CP543.2001 (excluding subjects from Cohort 1 who received deuruxolitinib 4 mg) and Phase 3 Trials CP543.3001 and CP543.3002 from Week 0-24. The safety population includes all randomized subjects who received at least one dose of the study medication during the double-blind, 24-week treatment period in the three trials listed above. Safety data from this population were analyzed according to the treatment that subjects actually received. The safety population by trial and dose is presented below in Table 41.

Table 41. Safety Population by Trial and Dose

Treatment	CP543.2001	CP543.3001	CP543.3002	Total
Placebo	29	140	130	299
Deuruxolitinib 8 mg BID	34	350	256	640
Deuruxolitinib 12 mg BID	36	215	129	380

Source: Reviewer's table, data from Applicant's Summary of Clinical Safety

The 120-day Safety Update Report (data cut of May 5, 2022) provided the most recent information regarding exposure to deuruxolitinib in the AA program. The median duration of continuous exposure was 79.14 weeks for the total pooled subjects treated with deuruxolitinib (59.43 weeks for 24 mg total daily dose and 36.79 weeks for 16 mg total daily dose). A total of 1295 subjects had ≥52 weeks of continuous exposure to any dose of deuruxolitinib. The number of subjects by dose and duration of cumulative exposure in the pooled long-term exposure safety pool population (from subjects in the open label long-term extension trials CP543.5001 and CP543.5002) is summarized below in Table 42.

Table 42. Cumulative Exposure to Deuruxolitinib by Dose

Treatment	Deuruxolitinib 16 mg TDD	Deuruxolitinib 24 mg TDD
≥24 weeks	814	1015
≥52 weeks	414	666
≥76 weeks	208	388
≥156 weeks	8	89
≥204 weeks	4	18
≥220 weeks	1	13

Source: Reviewer's table, adapted from Applicant's 120-day Safety Update Report, Table 4
Abbreviations: N, number of subjects; TDD, total daily dose

The overall cumulative exposure reported in the 120-day Safety Update was 973.3 patient-years for deuruxolitinib 8 mg BID and 1515.4 patient-years for deuruxolitinib 12 mg BID.

Relevant Characteristics of the Safety Population

The demographics of the safety population were similar to the intent-to-treat population. The majority of subjects were white (73.6%) and female (64.3%). The mean age was 37 years, 24.1% were 50 years of age or older and a total of six subjects were 65 years of age or older. There were a low number of subjects over 65 since the inclusion criterion for the placebo-controlled trials was "between 18 and 65 years of age inclusive at the time of informed consent," and these six subjects were aged 65 at the time of informed consent. The demographic characteristics were comparable across treatment groups. Refer to Table 21 for a summary of the baseline characteristics of the intent-to-treat population.

Adequacy of the Safety Database

The total subject exposure to deuruxolitinib tablets, 8 mg and 12 mg twice daily for the treatment of moderate to severe AA provides adequate data for the evaluation of safety. The

demographics of the study population are sufficiently representative of the target population. The total exposures for 24 weeks and 52 weeks are sufficient to characterize the safety of the product over longer treatment periods.

8.3.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The review team evaluated data quality and fitness in conjunction with the Office of Computational Science clinical services team. The review team identified no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

The Applicant defined an adverse event as "any untoward medical occurrence that may appear or worsen in a patient during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the patient's health, including laboratory test values, regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an adverse event." The Applicant defined a TEAE as a TEAE "if the onset is after the first dose of study drug." If a subject changed dose during a trial (8 mg BID to 12 mg BID or 12 mg BID to 8 mg BID, only permitted in the OLE trials CP543.5001 and CP543.5002 at the discretion of the investigator), AEs were considered treatment-emergent with respect to the most recent dose taken prior to the start of the AE and were tabulated under that treatment column.

For the analyses of pooled safety data, AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) Coding Dictionary, Version 23.1.

Investigators conducted assessment for TEAEs at trial visits and recorded them in the electronic case report form (eCRF). The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) (v5.0) was used to grade the severity/intensity of all events. If a NCI-CTCAE criterion did not exist, the Investigator graded the severity according to the following criteria:

1. "Grade 1 (mild): does not interfere with the patient's usual function
2. Grade 2 (moderate): interferes to some extent with patient's usual function
3. Grade 3 (severe): interferes significantly with patient's usual function
4. Grade 4 (life-threatening): results in a threat to life or in an incapacitating disability
5. Grade 5 (death): results in death."

An SAE was defined as any AE that fulfilling the following criteria:

Article I. Is fatal (results in death).
Article II. Is life-threatening.

Article III. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay).
Article IV. Results in persistent or significant disability/incapacity (a substantial disruption of the patient's ability to conduct normal life functions).
Article V. Is a congenital anomaly/birth defect.
Article VI. Constitutes an important medical event that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed above.

The Investigator was required to notify the Applicant and the Applicant's designation Drug Safety Unit within 24 hours after becoming aware of the occurrence of an SAE. Although pregnancy was not considered an AE or SAE, the Applicant was to be informed within 24 hours of learning a subject or partner had become pregnant and subject pregnancies were followed until termination of pregnancy or birth of the child.

The Applicant also designated AESIs based on the mechanism of action of deuruxolitinib and the known safety concerns for Janus kinase inhibitors. AESIs are discussed in more detail in Section 8.3.4 of this review.

Relationship to Study Drug:

Relationship was assessed and provided for every adverse event/serious adverse event based on currently available information. Adverse events were classified by the Investigator as follows:

Related for Regulatory Reporting Assessment

- Definitely related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The event resolves or improves upon withdrawal of drug (de-challenge). The event would be considered as definitely related to the study drug upon results of a positive re-challenge procedure.
- Probably related: There is evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors that may have contributed to the event (e.g., the patient's clinical condition, other concurrent disease, concomitant medications or events) is unlikely, and the event follows a clinically reasonable response upon withdrawal of drug (de-challenge).
- Possibly related: There is evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concurrent disease, concomitant medications or events).

Unrelated for Regulatory Reporting Assessment

- Unlikely related: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial

medication) and in which other drugs or concurrent or underlying disease provide plausible explanations (e.g., the patient's clinical condition, other concomitant treatments).
- Not related: The adverse event is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician."

Routine Clinical Tests

The trial safety assessments included clinical evaluation of AEs, SAEs, vital signs, physical examinations, and clinical laboratory evaluation (chemistry, hematology, lipids, and urinalysis). Electrocardiograms (ECGs) were performed at Screening, Week 12 and at the end of the trials. Safety assessments also included pregnancy testing at Screening and periodically throughout the trials. Investigators assessed subjects for the onset or worsening of anxiety and depression using the HADS in the Phase 3 trials CP543.3001 and CP543.3002. Subjects received a pre-treatment evaluation for tuberculosis (TB), and subjects were actively assessed for exposure to TB during the trials. An independent data monitoring committee performed regular safety assessments based on a review of cumulative safety data. The schedules of safety assessments were similar among the trials.

8.3.3. Safety Results

Deaths

There was one death (a completed suicide) reported in the development program in a 34-year-old male receiving deuruxolitinib 8 mg BID. A brief narrative is below:

A 34-year-old male ([redacted] (b) (6)) with a history of deficit hyperactivity disorder, hypertension, gastroesophageal reflux disease, and allergic rhinitis died of suicide on Day 58 of the OLE trial after discontinuing deuruxolitinib 8 mg. The subject received 8 mg deuruxolitinib BID in Trial CP543.3001 for 24 weeks, followed by the same dose for approximately 44 days in OLE Trial CP543.5001. Per protocol, the subject had discontinued the study product approximately 2 weeks earlier due to a COVID-19 infection. Relevant concomitant medications included dextroamphetamine, 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. In the investigator's opinion, the suicide was considered 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.

An analysis of this case was performed by the Division of Psychiatry (refer to review by Dr. Zimri Yaseen dated March 31, 2024). Consistent with the onset of reported external stressors, the subject had a clinically significant worsening of HADS total score from baseline (total score 9 [borderline] to Week 24 (total score 16 [abnormal]). The subject had higher anxiety scores at baseline and Week 24 than depression scores. According to the (PGI-I) in AA, BETA and BELA

instruments (described in Section 8.1.1), the subject assessed his status as "minimally improved" and he was "dissatisfied" with his response at Week 24. However, the subject reported no depression or anxiety-related AE. The Psychiatry review concluded that "there is no evidence for the IP [investigational product] 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." Refer to Section 8.3.4.7 for a description of the HADS.

Serious Adverse Events

During the 24-week placebo-controlled period, SAEs were reported at a comparable rate in subjects who received deuruxolitinib compared to placebo. SAEs were reported in 7/640 (1.1%) of subjects who received deuruxolitinib 8 mg BID, 4/380 (0.9%) of subjects treated with deuruxolitinib 12 mg BID, and 4/299 (1.5%) of subjects who received placebo. Most SAE preferred terms (PTs) were reported by single subjects in any treatment group. Most SAEs were in the Infections and infestations system organ class (SOC) across both deuruxolitinib 8-mg BID and 12-mg BID treatment groups. Refer to Section 8.3.4.5 of this review for further details regarding serious infections.

Four subjects (three subjects who received deuruxolitinib [one subject in the 12-mg group and two subjects in the 8-mg group] and one subject who received placebo) developed 4 treatment-emergent SAEs leading to treatment discontinuation (appendicitis [12 mg]; influenza pneumonia, chest pain, and dyspnea [8 mg]; and abortion spontaneous [placebo]). SAEs reported during the placebo-controlled period are presented below in Table 43.

Table 43. SAEs by SOC and PT, 24-Week Placebo-Controlled Period

System Organ Class	Preferred Term	PBO n (Adj%) (N=299)	DEURUX 8 mg BID n (Adj%) (N=640)	DEURUX 12 mg BID n (Adj%) (N=380)
Total SAEs		4	9	5
Number of subjects with any SAE		4 (1.5)	7 (1.1)	4 (0.9)
Infections and infestations	Appendicitis	1 (0.4)	2 (0.3)	1 (0.3)
	COVID-19	0	1 (0.2)	0
	Cellulitis	0	0	1 (0.3)
	Meningitis	0	1 (0.2)	0
	Pneumonia influenzal	0	1 (0.2)	0
General disorders and administration site conditions	Chest pain	0	1 (0.2)	0
	Pyrexia	0	1 (0.2)	0
Gastrointestinal disorders	Ileus	0	0	1 (0.2)
Injury, poisoning and procedural complications	Radius fracture	0	0	1 (0.3)

System Organ Class	Preferred Term	PBO n (Adj%) (N=299)	DEURUX 8 mg BID n (Adj%) (N=640)	DEURUX 12 mg BID n (Adj%) (N=380)
Musculoskeletal and connective tissue disorders	Osteoarthritis	0	0	1 (0.3)
Nervous system disorders	Migraine with aura	0	1 (0.2)	0
	Epilepsy	1 (0.4)	0	0
Respiratory, thoracic, and mediastinal disorders	Dyspnoea	0	1 (0.2)	0
Pregnancy, puerperium, and perinatal conditions	Abortion spontaneous	1 (0.4)	0	0
Psychiatric disorders	Adjustment disorder	1 (0.4)	0	0

Source: Reviewer's table adapted from Integrated Summary of Safety Table 21
NOTE: Percentages are adjusted for study size.
Abbreviations: DEURUX, deuruxolitinib; n, number of subjects with event; PBO, placebo

The narrative for the subject who developed meningitis on deuruxolitinib 8 mg is presented in Section 8.3.4.5 of this review.

For subjects who remained on deuruxolitinib from Weeks 0-52 in the OLE trials (Trials CP543.5001 and CP543.5002), SAEs were reported at a similar frequency for subjects who received 8 mg BID compared to subjects who received 12 mg BID. During this period, a total of 41 treatment-emergent SAEs were reported by 33 (2.2%) subjects: 18 subjects [1.8%] who received deuruxolitinib 12 mg BID and 16 subjects [1.8%] who received deuruxolitinib 8 mg BID. Most SAEs were in the following SOCs: Infections and infestations; Neoplasms benign, malignant, and unspecified; and Musculoskeletal and connective tissue disorders across both deuruxolitinib treatment groups (8 mg BID and 12 mg BID). SAEs reported during the Week 0-52 open- label, long- term safety period are presented below in Table 44.

Table 44. SAEs by SOC and PT, Weeks 0 to 52

System Organ Class	Preferred Term	DEURUX 8 mg BID n (%) [EAIR] (N=868)	DEURUX 12 mg BID n (%) [EAIR] (N=991)
Total SAEs		17	24
Number of subjects with any TESAE		16 (1.8)	18 (1.8)
Infections and infestations	Appendicitis	1 (0.1) [0.2]	2 (0.2) [0.3]
	COVID-19	2 (0.2) [0.3]	0
	Cellulitis	0	1 (0.1) [0.1]
	Peritonsillar abscess	0	1 (0.1) [0.2]
	Postoperative wound infection	1 (0.2) [0.2]	0
	Pyomyositis	1 (0.1) [0.2]	0
	Malignant melanoma in situ	1 (0.1) [0.2]	1 (0.1) [0.1]

System Organ Class	Preferred Term	DEURUX 8 mg BID n (%) [EAIR] (N=868)	DEURUX 12 mg BID n (%) [EAIR] (N=991)
Neoplasms benign, malignant, and unspecified	Clear cell renal cell carcinoma	1 (0.1) [0.2]	0
	Colon cancer	0	1 (0.1) [0.1]
	Signet-ring cell carcinoma	1 (0.1) [0.2]	0
	Testis cancer	0	1 (0.1) [0.1]
Injury, poisoning and procedural complications	Ankle fracture	1 (0.1) [0.2]	1 (0.1) [0.1]
	Humerus fracture	0	1 (0.1) [0.1]
	Radius fracture	0	1 (0.1) [0.1]
Musculoskeletal and connective tissue disorders	Arthralgia	1 (0.1) [0.2]	0
	Back pain	1 (0.1) [0.2]	0
	Intervertebral disc protrusion	0	1 (0.1) [0.1]
	Osteoarthritis	1 (0.1) [0.2]	1 (0.1) [0.1]
	Osteolysis	1 (0.1)	0
	Spinal stenosis	0	1 (0.1) [0.1]
Nervous system disorders	Encephalopathy	0	1 (0.1) [0.1]
	Migraine with aura	1 (0.1) [0.2]	0
	Presyncope	0	1 (0.1) [0.1]
	Syncope	0	1 (0.1) [0.1]
Psychiatric disorders	Completed suicide	1 (0.1) [0.2]	0
	Emotional distress	0	1 (0.1) [0.1]
	Psychotic disorder	0	1 (0.1) [0.1]
Cardiac disorders	Atrial fibrillation	0	2 (0.2) [0.3]
	Supraventricular tachycardia	0	1 (0.1) [0.1]
Gastrointestinal disorders	Abdominal pain	1 (0.1) [0.2]	1 (0.1) [0.1]
Immune system disorders	Anaphylactic reaction	1 (0.1) [0.2]	0
Investigations	Electrocardiogram T wave inversion	0	1 (0.1) [0.1]
Respiratory, thoracic, and mediastinal disorders	Pulmonary embolism	0	1 (0.1) [0.1]

Source: Reviewer's table adapted from Integrated Summary of Safety Table 4.2.2.4 and Applicant's response to Information Request SDN 22 (2/21/24)
NOTE: During the open-label long term trials, dose changes were permitted at the discretion of the Investigator (i.e., 8 mg BID to 12 mg BID or 12 mg BID to 8 mg BID). Adverse events are considered treatment-emergent with respect to the most recent dose taken prior the start of the adverse event and are tabulated as such. Subjects may be counted in more than one column.
NOTE: Overall and within each system organ class and preferred term, multiple occurrences of the same event in a single subject are counted multiple times in the total number of events, but the subject is counted only once per treatment group, as applicable, in the number of subjects experiencing at least one event.
Abbreviations: DEURUX, deuruxolitinib, EAIR, exposure-adjusted incidence rate which equals 100* incidence / (sum of the individual risk-times in years)

The narrative for the subject who died by suicide is presented above in "Deaths," select narratives for subjects with malignancies are presented in Section 8.3.4.3 of this review, and narratives for subjects with thromboses (including beyond Week 52) are presented in Section 8.3.4.2 of this review.

Dropouts and/or Discontinuations Due to Adverse Effects

During the 24-week placebo-controlled period, AEs leading to permanent discontinuation of study drug were reported more commonly in subjects who received deuruxolitinib than subjects who received placebo. During this period, permanent discontinuations of treatment because of an AE were reported in 19/640 (2.8%) of subjects who received deuruxolitinib 8 mg BID, 9/380 (2.4%) of subjects who received deuruxolitinib 12 mg BID, and 5/299 (1.5%) of subjects who received placebo. The most frequent reason for treatment discontinuation related to AEs in any arm was headache (reported in five subjects, 0.8%, who received 8 mg). For subjects who received deuruxolitinib 8 mg, the majority of AEs leading to discontinuation were in the following SOCs: Nervous system disorders; Blood and lymphatic system disorders; and Infections and infestations. The PTs reported by >1 subject included the following:

- Headache: 5 (0.5%) for deuruxolitinib (8-mg BID group only; 0.8%), compared with 0 for placebo.
- Anemia: 4 (0.4%) for deuruxolitinib (2 [0.3%] for 8 mg BID and 2 [0.6%] for 12 mg BID), compared with 0 for placebo.
- Neutropenia: 3 (0.3%) for deuruxolitinib (1 [0.2%] for 8 mg BID and 2 [0.6%] for 12 mg BID), compared with 1 (0.2%) for placebo.
- Platelet count increased: 3 (0.3%) for deuruxolitinib (8-mg BID group only, 0.5%), compared with 0 for placebo.
- Vertigo: 2 (0.2%) for deuruxolitinib (8-mg BID group only, 0.3%), compared with 0 for placebo.

AEs leading to discontinuation of treatment during the 24-week placebo-controlled period are presented below in Table 45.

Table 45. Adverse Events Leading to Discontinuation, 24-Week Placebo-Controlled Period

System Organ Class	Preferred Term	PBO n (Adj%) (N=299)	DEURUX 8 mg BID n (Adj%) (N=640)	DEURUX 12 mg BID n (Adj%) (N=380)
Total TEAE		5	29	9
Number of subjects with any TEAE		5 (1.5)	19 (2.8)	9 (2.4)
Blood and lymphatic system disorders	Anaemia	0	2 (0.3)	2 (0.6)
	Neutropenia	1 (0.2)	1 (0.2)	2 (0.6)
Nervous system disorders	Headache	0	5 (0.8)	0
	Disturbance in attention	0	1 (0.2)	0
	Dizziness	0	0	1 (0.2)
	Memory impairment	0	1 (0.2)	0
	Migraine	0	1 (0.2)	0
	Appendicitis	0	0	1 (0.2)

System Organ Class	Preferred Term	PBO n (Adj%) (N=299)	DEURUX 8 mg BID n (Adj%) (N=640)	DEURUX 12 mg BID n (Adj%) (N=380)
Infections and infestations	Conjunctivitis	0	1 (0.2)	0
	Nasopharyngitis	0	0	1 (0.2)
	Pneumonia	0	0	1 (0.2)
	Pneumonia influenzal	0	1 (0.2)	0
	Folliculitis	1 (0.4)	0	0
Investigations	Platelet count increased	0	3 (0.5)	0
	Lipase increased	0	1 (0.2)	0
General disorders and administration site conditions	Asthenia	0	1 (0.2)	0
	Chest pain	0	1 (0.2)	0
	Fatigue	0	1 (0.2)	0
Ear and labyrinth disorders	Vertigo	0	2 (0.3)	0
Respiratory, thoracic and mediastinal disorders	Asthma	0	1 (0.1)	0
	Dyspnoea	0	1 (0.2)	0
Vascular disorders	Flushing	0	1 (0.2)	0
	Hypertension	0	1 (0.2)	0
Cardiac disorders	Bundle branch block left	0	0	1 (0.2)
Gastrointestinal disorders	Abdominal pain	0	1 (0.2)	0
	Irritable bowel syndrome	1 (0.2)	0	0
Hepatobiliary disorders	Hyperbilirubinaemia	0	1 (0.2)	0
Skin and subcutaneous tissue disorders	Acne	0	1 (0.2)	0
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	1 (0.4)	0	0
Psychiatric disorders	Intentional self-injury	1 (0.3)	0	0

Source: Reviewer's table adapted from Integrated Summary of Safety Table 4.2.7.1
NOTE: Percentages are adjusted for study size.
NOTE: Overall and within each system organ class and preferred term, multiple occurrences of the same event in a single subject are counted multiple times in the total number of events, but the subject is counted only once in the number of subjects experiencing at least one event.
Abbreviation: DEURUX, deuruxolitinib

For subjects who remained on deuruxolitinib from Weeks 0-52 in the OLE trials, permanent discontinuations of treatment because of an AE were reported in 6/868 (0.7%) of subjects treated with deuruxolitinib 8 mg BID, and in 11/991 (1.1%) of subjects treated with deuruxolitinib 12 mg BID. During this period, the distribution of AEs leading to discontinuation included more discontinuations in the SOC of Neoplasms benign, malignant, and unspecified compared to the 24-week placebo-controlled period. Key narratives for subjects with malignancies are presented in Section 8.3.4.3 of this review. AEs leading to discontinuation of treatment from Weeks 0-52 are presented below in Table 46.

Table 46. Adverse Events Leading to Discontinuation, Weeks 0 to 52

System Organ Class	Preferred Term	DEURUX 8 mg BID n (%) (N=868)	DEURUX 12 mg BID n (%) (N=991)
Total TEAE		7	13
Number of subjects with any TEAE		6 (0.7)	11 (1.1)
Blood and lymphatic system disorders	Leukopenia	1 (0.1)	1 (0.1)
	Neutropenia	0	2 (0.2)
	Anaemia	1 (0.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Clear cell renal cell carcinoma	1 (0.1)	0
	Colon cancer	0	1 (0.1)
	Signet-ring cell carcinoma	1 (0.1)	0
	Testis cancer	0	1 (0.1)
	Vulvovaginal warts	0	1 (0.1)
Infections and infestations	Herpes zoster	0	1 (0.1)
	Urinary tract infection	0	1 (0.1)
Skin and subcutaneous tissue disorders	Alopecia	1 (0.1)	0
	Drug eruption	0	1 (0.1)
Cardiac disorders	Atrial fibrillation	0	1 (0.1)
Musculoskeletal and connective tissue disorders	Back pain	1 (0.1)	0
	Osteolysis	1 (0.1)	0
Nervous system disorders	Presyncope	0	1 (0.1)
Reproductive system and breast disorders	Uterine cervical metaplasia	0	1 (0.1)
Respiratory, thoracic, and mediastinal disorders	Pulmonary embolism	0	1 (0.1)

Source: Reviewer's table adapted from Integrated Summary of Safety Table 4.2.7.4
NOTE: Adverse events are considered treatment-emergent with respect to the most recent dose taken prior the start of the adverse event and are tabulated as such. Subjects may be counted in more than one column.
NOTE: Overall and within each system organ class and preferred term, multiple occurrences of the same event in a single subject are counted multiple times in the total number of events, but the subject is counted only once in the number of subjects experiencing at least one event.
Abbreviation: DEURUX, deuruxolitinib

Significant Adverse Events

Significant AEs included AESIs and AEs for which a significant imbalance between the active treatment arms and the placebo arm was observed. Refer to Section 8.3.4 of this review for an analysis of AESIs which were reported by subjects in the development program.

Treatment Emergent Adverse Events and Adverse Reactions

During the 24-week placebo-controlled period, TEAEs were reported more commonly in subjects who received either dose of deuruxolitinib compared to placebo. During this period at least one TEAE was reported in 190 subjects (62.2%) who received placebo, 463 (69.8%) of subjects who received 8 mg BID, and in 272 (68.6%) of subjects who received 12 mg BID. The

majority of TEAEs were considered mild or moderate in severity for both the placebo group and deuruxolitinib groups. Severity of TEAEs was comparable between the treatment arms.

- Mild TEAEs: 121 (39.8%) subjects on placebo, 286 (43.2%) subjects on 8 mg BID, 160 (39.4%) subjects on 12 mg BID
- Moderate TEAEs: 63 (20.1%) subjects on placebo, 162 (24.3%) subjects on 8 mg BID, and 99 (25.7%) subjects on 12 mg BID
- Severe TEAEs: 6 (2.2%) subjects on placebo, 15 (2.3%) subjects on 8 mg BID, and 13 (3.5%) subjects on 12 mg BID

The analysis of TEAEs includes pooled preferred terms (PTs) for clinically similar AEs to provide a more accurate assessment of the overall frequency. The PTs included in the AE pooling are presented in table footnotes. TEAEs reported in 1% or more subjects in either deuruxolitinib group and more frequently than in the placebo group are presented below in Table 47. Incidence rates were adjusted for trial size.

Table 47. Treatment-Emergent Adverse Events Reported (≥1%) in Any Deuruxolitinib Group, and More Frequently Than Placebo, 24-Week Placebo-Controlled Period

Preferred Term/Pooled Term	Placebo n (Adj%) [EAIR] (N=299)	DEURUX 8 mg BID n (Adj%) [EAIR] (N=640)	DEURUX 12 mg BID n (Adj%) [EAIR] (N=380)
Headache	30 (9.4) [31.2]	83 (12.4) [44.1]	44 (10.5) [39.3]
Pooled acne	13 (4.3) [11.7]	66 (10.0) [29.7]	52 (12.6) [38.6]
COVID-19	30 (9.7) [23.7*]	79 (12.1) [30.2*]	39 (11.0) [24.1*]
Nasopharyngitis	21 (6.7) [17.8]	54 (8.1) [24.2]	33 (7.7) [21.6]
Blood creatine phosphokinase increased	7 (2.2) [4.0]	35 (5.3) [9.5]	27 (7.4) [13.3]
Pooled hyperlipidemia	10 (3.1) [7.7*]	30 (4.4) [11.0*]	19 (5.2) [11.5*]
Pooled fatigue	12 (3.9) [10.3]	26 (3.9) [11.2]	20 (4.9) [14.5]
Lymphopenia	2 (0.6) (1.5*)	2 (0.3) (0.7*)	7 (2.0) (4.2*)
Leukopenia	0	1 (0.2) (0.4*)	4 (1.1) (2.4*)
Pooled anemia	3 (1.0) [3.5]	18 (2.6) [11.9]	16 (3.4) [17.6]
Nausea	9 (2.5) [7.7]	24 (3.5) [10.5]	10 (2.5) [9.0]
Weight increased	4 (1.4) [2.8]	19 (2.9) [6.5]	10 (2.5) [5.8]
Pooled skin and soft tissue infections	2 (0.8) [1.4]	11 (1.6) [3.8]	15 (4.0) [9.5]
Folliculitis	2 (0.8) [1.5]	8 (1.2) [3.1]	10 (2.7) [7.2]
Pooled abdominal pain	6 (1.7) [5.8]	15 (2.3) [7.4]	9 (2.4) [7.1]
Pooled thrombocytosis	0	18 (2.7) [6.6*]	6 (1.6) [3.6*]
Pooled urinary tract infection	5 (1.7) [3.8*]	14 (2.1) [5.1*]	8 (2.0) [4.8*]
Pooled neutropenia	3 (0.7) [2.3*]	10 (1.4) [3.6*]	10 (2.8) [6.0*]
Pyrexia	5 (1.7) [3.8*]	12 (1.8) [4.4*]	3 (0.9) [1.8*]
Pooled herpes	2 (0.6) [1.5*]	8 (1.2) [2.9*]	6 (1.6) [3.6*]

Preferred Term/Pooled Term	Placebo n (Adj%) [EAIR] (N=299)	DEURUX 8 mg BID n (Adj%) [EAIR] (N=640)	DEURUX 12 mg BID n (Adj%) [EAIR] (N=380)
Rhinitis	2 (0.8) [1.5*]	9 (1.4) [3.3*]	5 (1.4) [3.0*]
Hypertension	2 (0.7) [1.5*]	8 (1.2) [2.9*]	4 (1.1) [2.4*]
C-reactive protein increased	2 (0.7) [1.5*]	7 (1.1) [2.5*]	4 (1.1) [2.4*]
Contusion	2 (0.8) [1.5*]	9 (1.3) [3.3*]	2 (0.6) [1.2*]
Vomiting	4 (1.2) [3.0*]	8 (1.2) [2.9*]	3 (0.6) [1.8*]
Lipase increased	0	6 (0.9) [2.2*]	4 (1.0) [2.4*]
Vaccination complication	1 (0.4) [0.8*]	5 (0.8) [1.8*]	5 (1.2) [3.0*]
High density lipoprotein increased	2 (0.8) [1.5*]	4 (0.6) [1.4*]	5 (1.2) [3.0*]
Increased appetite	0	5 (0.8) [1.8*]	4 (1.0) [2.4*]
Bronchitis	3 (0.9) [2.3*]	2 (0.3) [0.7*]	5 (1.4) [3.0*]
Herpes zoster	0	3 (0.5) [1.1*]	3 (0.9) [1.8*]

Source: Reviewer's table adapted from Applicant response to Information Requests submitted February 12, 2024 (SDN 18) and February 26, 2024 (SDN 23).
NOTE: Subjects are counted only once for each pooled term or preferred term.
NOTE: Percentages and EAIRs [100 * incidence / (sum of the individual risk-times in years)] are adjusted for study size. Adjusted EAIRs come from a Poisson regression model with study and treatment as explanatory variables. Unadjusted EAIRs are marked with an asterisk (*) and are reported if the model fails to converge or provide meaningful results.
Pooled acne includes: Acne, Dermatitis acneiform, and Acne pustular.
Pooled hyperlipidemia includes: Blood cholesterol increased, Low density lipoprotein increased, Blood triglycerides increased, Hypercholesterolaemia, Hyperlipidaemia, Hypertriglyceridaemia, and Dyslipidaemia.
Pooled fatigue includes: Fatigue, Asthenia, Hypersomnia, Somnolence, and Lethargy.
Pooled anemia includes: Anaemia, Haematocrit decreased, Haemoglobin decreased, and Red blood cell count decreased.
Pooled skin and soft tissue infections includes: Folliculitis, Impetigo, Skin infection, Subcutaneous abscess, Furuncle, Paronychia, and Pustule.
Pooled abdominal pain includes: Abdominal pain, Abdominal discomfort, Abdominal pain upper, and Abdominal pain lower.
Pooled thrombocytosis includes: Thrombocytosis and Platelet count increased.
Pooled urinary tract infection includes: Urinary tract infection, and Cystitis.
Pooled neutropenia includes: Neutropenia and Neutrophil count decreased.
Pooled herpes includes: Oral herpes, Herpes simplex, Genital herpes simplex, and Nasal herpes.

The TEAEs observed are consistent with the known safety profile for other JAK inhibitors used to treat chronic inflammatory conditions. Compared to subjects who received placebo, subjects who received either dose of deuruxolitinib reported higher observed rates of headache, acne, nasopharyngitis, blood creatine phosphokinase (CPK) increased, hyperlipidemia, fatigue, anemia, increased weight, neutropenia, and herpes. There is a dose-response relationship with a greater number of adverse events reported for subjects receiving 12 mg BID versus 8 mg BID for the following TEAEs: acne, blood CPK increased, hyperlipidemia, pooled fatigue, lymphopenia, leukopenia, anemia, skin and soft tissue infections, folliculitis, neutropenia, herpes, high-density lipoprotein (HDL) increased and bronchitis. Analysis of adverse events through Week 52 did not reveal any new safety signals.

TEAEs reported in 1% or more subjects in either deuruxolitinib group and more frequently than in the placebo group and considered related to study drug by the Investigator are presented below in Table 48.

Table 48. Treatment-Emergent Adverse Events Reported (≥1%) in Any Deuruxolitinib Group, and More Frequently Than Placebo, Considered Treatment-Related by Investigator, 24-Week Placebo-Controlled Period

Preferred Term/Pooled Term	Placebo n (Adj%) [EAIR] (N=299)	DEURUX 8 mg BID n (Adj%) [EAIR] (N=640)	DEURUX 12 mg BID n (Adj%) [EAIR] (N=380)
Pooled acne	9 (2.9) [6.3]	61 (9.3) [21.3]	42 (10.4) [23.2]
Headache	18 (5.5) [16.0]	48 (7.2) [20.9]	25 (6.1) [18.5]
Blood creatine phosphokinase increased	3 (0.9) [2.3*]	22 (3.4) [8.0*]	21 (5.8) [12.8*]
Pooled hyperlipidemia	7 (2.3) [5.4*]	22 (3.3) [8.0*]	16 (4.4) [9.6*]
Pooled fatigue	5 (1.7) [3.7]	15 (2.3) [5.7]	13 (3.2) [8.2]
Lymphopenia	1 (0.3) [0.8*]	2 (0.3) [0.7*]	4 (1.2) [2.4*]
Leukopenia	0	1 (0.2) [0.4*]	4 (1.1) [2.4*]
Pooled Anemia	2 (0.7) [2.4]	14 (2.0) [9.6]	14 (2.9) [15.9]
Nasopharyngitis	7 (2.2) [4.6]	18 (2.7) [5.9]	8 (2.2) [4.5]
Weight increased	3 (1.1) [2.3]	16 (2.4) [6.3]	7 (1.7) [4.5]
Nausea	6 (1.6) [4.6*]	11 (1.6) [4.0*]	7 (2.0) [4.2*]
Pooled skin and soft tissue infections	2 (0.8) [1.5*]	7 (1.1) [2.5*]	11 (2.9) [6.6*]
Folliculitis	2 (0.8) [1.5*]	6 (0.9) [2.2*]	9 (2.4) [5.4*]
Pooled thrombocytosis	0	14 (2.1) [5.1*]	3 (0.8) [1.8*]
Pooled neutropenia	2 (0.4) [1.5*]	6 (0.8) [2.2*]	8 (2.3) [4.8*]
Pooled abdominal pain	4 (1.1) [5.0]	8 (1.2) [5.5]	4 (0.9) [3.5]
Diarrhoea	3 (1.0) [2.3*]	7 (1.1) [2.5*]	5 (1.2) [3.0*]
High density lipoprotein increased	2 (0.8) [1.5*]	4 (0.6) [1.4*]	5 (1.2) [3.0*]

Source: Reviewer's table adapted from Applicant response to Information Requests submitted February 12, 2024 (SDN 18), February 26, 2024 (SDN 23), and March 18, 2024 (SDN 29).
NOTE: TEAEs Considered Related by Investigator
NOTE: Subjects are counted only once for each pooled term or preferred term.
NOTE: Percentages and EAIRs [100 * incidence / (sum of the individual risk-times in years)] are adjusted for study size. Adjusted EAIRs come from a Poisson regression model with study and treatment as explanatory variables. Unadjusted EAIRs are marked with an asterisk (*) and are reported if the model fails to converge or provide meaningful results.
Pooled acne includes: Acne, Dermatitis acneiform, and Acne pustular.
Pooled hyperlipidemia includes: Blood cholesterol increased, Low density lipoprotein increased, Blood triglycerides increased, Hypercholesterolaemia, Hyperlipidaemia, Hypertriglyceridaemia, and Dyslipidaemia.
Pooled fatigue includes: Fatigue, Asthenia, Hypersomnia, Somnolence, and Lethargy.
Pooled anemia includes: Anaemia, Haematocrit decreased, Haemoglobin decreased, Iron deficiency anemia, and Red blood cell count decreased.
Pooled skin and soft tissue infections includes: Folliculitis, Impetigo, Skin infection, Subcutaneous abscess, Furuncle, Paronychia, and Pustule.
Pooled thrombocytosis includes: Thrombocytosis and Platelet count increased.
Pooled neutropenia includes: Neutropenia and Neutrophil count decreased.
Pooled abdominal pain includes: Abdominal pain, Abdominal discomfort, Abdominal pain upper, and Abdominal pain lower.

Adverse Reactions Reported in <1% of Subjects Treated With Deuruxolitinib

During the 24-week placebo-controlled period, adverse reactions (ARs) reported in fewer than 1% of subjects treated with deuruxolitinib and more frequently than placebo included urinary tract infection, depression/anxiety, lipase increased, and tachycardia.

- Urinary tract infection was reported in 6/640 (0.9%) of subjects who received deuruxolitinib 8 mg BID, 2/380 (0.3%) of subjects who received 12 mg BID, and zero subjects treated with placebo.
- Depression/anxiety was reported in 4/640 (0.6%) of subjects who received deuruxolitinib 8 mg BID, 2/380 (0.4%) of subjects who received 12 mg BID, and zero subjects who received placebo. Refer to 8.2.5.7 for discussion of the review team's analysis of the mean and mean change in HADS total score for all subjects in the placebo-controlled trials from Weeks 0 to 24, which did not indicate any negative effect of deuruxolitinib on mood as assessed by the HADS.
- Lipase increased was reported in 5/640 (0.7%) of subjects who received deuruxolitinib 8 mg BID, zero subjects who received 12 mg BID, and zero subjects who received placebo.
- Tachycardia was reported in 3/640 (0.5%) of subjects who received deuruxolitinib 8 mg BID, 1/380 (0.3%) of subjects who received 12 mg BID, and zero subjects who received placebo.

Additional ARs reported in <1% of subjects who received any dose of deuruxolitinib (each in one subject) included vulvovaginal candidiasis (8 mg BID), oral candidiasis (12 mg BID), and herpes zoster in 3/640 (0.5%) of subjects who received 8 mg BID and in 3/380 (0.9%) of subjects who received 12 mg BID.

ARs reported in <1% of subjects of subjects who received any dose of deuruxolitinib between Week 0-52 in the OLE trials included pulmonary embolism (one subject on 12 mg BID), testis cancer (one subject on 12 mg BID), and signet-ring cell carcinoma (one subject on 8 mg BID). The AEs of pulmonary embolism (thrombosis) and malignancy were also AESI and are discussed further in Sections 8.3.4.2 and 8.3.4.3 respectively of this review. There were no unique safety signals identified after 52 weeks.

Although the Applicant is only seeking approval of the 8-mg BID dose (due to dose-dependent concerns with thromboses observed with the 12-mg BID dose summarized in Section 3.2 and 8.3.4.2 of this review), there are potential dose-response relationships for multiple adverse reactions (including acne, blood CPK increased, hyperlipidemia, skin and soft tissue infections, anemia, neutropenia, and lymphopenia). Therefore, the review team considered it important to include safety information for both doses in labeling by clearly differentiating the 8-mg BID approved dose (using its brand name, "LEQSELVI") from the non-approved 12-mg BID dose (using "deuruxolitinib"). An additional statement, "Deuruxolitinib 12 mg is not approved," will be added to Section 6.1 Clinical Trials Experience for clarity. The review team proposes the following adverse reactions to be added to Section 6.1 of product labeling.

Table 49. Adverse Reactions That Occurred in ≥1% of Patients Treated With Deuruxolitinib 8 mg BID or Deuruxolitinib 12 mg BID, and More Frequently Than Placebo (For Inclusion in Labeling)

Adverse Reaction	Placebo (N=299) n (%)[a]	LEQSELVI 8 mg twice daily (N=640) n (%)[a]	Deuruxolitinib 12 mg twice daily (N=380) n (%)[a]
Acne[b]	13 (4.3)	66 (10.0)	52 (12.6)
Headache	30 (9.4)	83 (12.4)	44 (10.5)
Nasopharyngitis	21 (6.7)	54 (8.1)	33 (7.7)
Blood creatine phosphokinase increased	7 (2.2)	35 (5.3)	27 (7.4)
Hyperlipidemia[c]	10 (3.1)	30 (4.4)	19 (5.2)
Fatigue[d]	12 (3.9)	26 (3.9)	20 (4.9)
Skin and soft tissue infections[e]	2 (0.8)	11 (1.6)	15 (4.0)
Anemia[f]	3 (1.0)	18 (2.6)	16 (3.4)
Weight increased	4 (1.4)	19 (2.9)	10 (2.5)
Neutropenia[g]	3 (0.7)	10 (1.4)	10 (2.8)
Thrombocytosis[h]	0	18 (2.7)	6 (1.6)
Lymphopenia	2 (0.6)	2 (0.3)	7 (2.0)
Herpes[i]	2 (0.6)	8 (1.2)	6 (1.6)

a. %-study size adjusted percentages.
b. Acne includes: acne, dermatitis acneiform, and acne pustular.
c. Hyperlipidemia includes: blood cholesterol increased, low density lipoprotein increased, blood triglycerides increased hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, and dyslipidaemia.
d. Fatigue includes: fatigue, asthenia, hypersomnia, somnolence, and lethargy.
e. Skin and soft issue infections includes: folliculitis, impetigo, skin infection, subcutaneous abscess, furuncle, paronychia, and pustule.
f. Anemia includes: anaemia, haematocrit decreased, haemoglobin decreased, iron deficiency anemia, and red blood cell count decreased.
g. Neutropenia includes: neutropenia and neutrophil count decreased.
h. Thrombocytosis includes: thrombocytosis and platelet count increased.
i. Herpes includes: oral herpes, herpes simplex, genital herpes simplex, and nasal herpes.

Laboratory Findings

ARs related to laboratory findings included blood CPK increased, hyperlipidemia, thrombocytosis, anemia, and leukopenia. The ARs related to laboratory parameters are AESIs and are discussed in more detail in Section 8.3.4 of this review.

Vital Signs

During the clinical trials, investigators documented systolic and diastolic blood pressure, pulse and weight. The review team conducted analyses of the placebo-controlled safety pool (Week 0-24) and the long-term exposure safety pool (all subjects who received deuruxolitinib [8 mg BID or 12 mg BID] in the OLE trials). This review included mean changes from baseline, analyses of individual shift tables for baseline to worst postbaseline NCI-CTCAE grade in systolic and diastolic blood pressure and weight, and evaluation of outliers.

For the placebo-controlled safety pool, there were similar percentages of subjects with a heart rate of >100 beats per minute (BPM) with a ≥20 BPM increase from baseline, or a heart rate of

<60 BPM with a ≥15 BPM decrease from baseline across the pooled deuruxolitinib and pooled placebo groups. For the long-term exposure safety pool, there was no imbalance in these parameters between subjects who received 8 mg BID versus those who received 12 mg BID.

For the placebo-controlled safety pool, there were no group trends or imbalances between subjects who received placebo versus deuruxolitinib in vital sign measurements except weight increased (discussed below). For the Week 0-52 long-term safety period, similar to the Week 0-24 placebo-controlled Safety Pool, there were no group trends in vital sign measurements except weight.

Weight

Weight was measured throughout the placebo-controlled Phase 3 and long-term safety trials. The review team analyzed the proportion of subjects with a change in weight (an increase or decrease) from Baseline.

In the placebo-controlled period from Week 0 to 24, treatment-emergent increases in weight were reported in 4/299 (1.4%) of subjects who received placebo, 19/640 (2.9%) of subjects who received deuruxolitinib 8 mg BID, and 10/380 (2.5%) of subjects who received with deuruxolitinib 12 mg BID. The mean change in weight from baseline at Week 24 as +1.41 kg [3.1 lbs] for subjects who received 8 mg BID and +2.06 kg [4.54 lbs] for subjects who received 12 mg BID, compared with +0.15 kg (0.33 lbs) in the placebo group. NCI-CTCAE Grade 3 in body weight gain (≥20% increase in body weight from baseline) was reported in 1/636 (0.2%) of subjects who received 8 mg BID, and in no subjects who received wither 12 mg BID or placebo.

In the long-term safety pool, the mean change in weight from Baseline at Week 52 was +2.09 kg [4.61 lbs] for subjects who received 8 mg BID, +2.99 kg [6.6 lbs] for subjects who received 12 mg BID, and +2.75 kg [6.1 lbs] for subjects who received 8 mg BID to 12 mg BID. NCI-CTCAE Grade 3 in body weight gain (≥20% increase in body weight from baseline) was reported in 3/499 (0.7%) of subjects who received 8 mg BID, 17/660 (2.6%) of subjects who received 12 mg BID, and 5/325 (1.5%) of subjects who received 8 mg BID to 12 mg BID.

Increased weight is reported as an adverse reaction in labeling for other JAK inhibitors. There is mechanistic plausibility for this finding. Based on pre-clinical studies on adipocyte-specific knockout of JAK2, pharmacological inhibition of JAK2 is anticipated to impair lipolysis, normally mediated by growth hormone and leptin signaling, leading to weight gain (Dodington et al. 2018). As discussed in Section 8.3.3 of this review, proposed labeling will include “weight increased” in Section 6.1 (Adverse Reactions) of labeling.

ECGs

In Phase 3 Trials CP543.3001 and CP543.3002, twelve-lead ECGs were performed at Screening, Week 12, and Week 24. In the OLE Trial CP543.5001, twelve-lead ECGs were performed at Weeks 52, 108, and 164. In the OLE trial CP543.5002, twelve-lead ECGs were performed at Weeks 52 and 108**.** A central reading center was used to evaluate all ECGs and determine

QT/QTc intervals. Although there were small imbalances in QTcF findings among treatment groups in both the placebo-controlled trials and OLE trials, no subjects developed a postbaseline QTcF interval ≥500 msec. See QT section below regarding the relevant nonclinical findings and results of the thorough QT study.

As discussed in Section 8.3.4.1 of this review, based on the customized MedDRA queries (CMQ) used for MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), no subjects experienced MACE in the deuruxolitinib development program.

Narrative summaries for subjects who received deuruxolitinib and experienced TEAEs of "supraventricular extrasystoles," "arrhythmia," "supraventricular tachycardia" and "electrocardiogram T wave inversion" are discussed in Section 8.3.4.1 of this review.

QT

As previously described in Section 6, the Applicant conducted a thorough QT study (CP543.1010) to evaluate the effect of therapeutic and supratherapeutic doses of deuruxolitinib (CTP-543) on the QTc intervals in healthy volunteers. The Interdisciplinary Review Team for Cardiac Safety Studies reviewed both the protocol and the final study report for CP543.1010. The data indicated that deuruxolitinib is not associated with significant prolongation of QTc. This conclusion is supported by the lack of QTc prolongation in nonclinical studies and exposure-response analysis (See Review by Tengfei Li dated May 19, 2023).

Immunogenicity

Deuruxolitinib is a small molecule that is not expected to be associated with immunogenicity. Therefore, the Applicant did not assess the potential for antibody formation.

8.3.4. Analysis of Submission-Specific Safety Issues

Adverse Events of Special Interest

The pre-specified AESIs for closer monitoring included the following based on the mechanism of action of deuruxolitinib (as a JAK inhibitor with greater inhibitory potency for JAK1, JAK2 and TYK2 relative to JAK3) and the established risk profile for the class of Janus Kinase Inhibitors:

- All infections (SOC of "Infections and infestations")
- Serious infections (SOC of "Infections and infestations" and serious adverse event)
- Opportunistic infections (standardized MedDRA queries [SMQ] of "Opportunistic infections")
- Opportunistic infections excluding Herpes Zoster and TB (SMQ of "Opportunistic infections" excluding herpes zoster CMQ and TB CMQ)
- Herpes Zoster (CMQ)
- Herpes Simplex (CMQ)
- TB (CMQ)

- All malignancies (SMQ of “Malignancies”)
- Malignancies excluding non-melanoma skin cancer (SMQ of “Malignancies” excluding CMQ for non-melanoma skin cancer)
- Non-melanoma skin cancer (CMQ)
- MACE (CMQ)
- Thrombosis (preferred term [PT] of “Pulmonary embolism,” “Deep vein thrombosis,” or “arterial thrombosis”)
- Gastrointestinal perforation (SMQ: “Gastrointestinal perforation”
- Blood CPK increased (PT of "Blood creatine phosphokinase increased")
- Thrombocytopenia (PT of “Thrombocytopenia” or “Platelet count decreased”)
- Thrombocytosis (PT of “Thrombocytosis”, “Secondary thrombocytosis”, “Essential thrombocythaemia” or “Platelet count increased”)
- Lymphopenia (PT of “Lymphopenia” or “Lymphocyte count decreased”)
- Neutropenia (PT of “Neutropenia” and “Neutrophil count decreased)
- Lipid elevations (CMQ)
- Hypersensitivity reactions (Adjusted SMQ of "Hypersensitivity")
- Anaphylaxis (SMQ of "Anaphylactic Reaction")
- Angioedema (SMQ of "Angioedema")
- Anemia (CMQ)
- Liver enzyme elevations (CMQ)
- DILI (PT of “Drug-induced liver injury”)
- Retinal detachment (CMQ)

No subjects developed AESI of MACE, DILI, or retinal detachment in either the Week 0-24 placebo-controlled trials or the Week 0-52 long term exposure safety trials.

Narratives for subjects with thromboses are presented in Section 8.3.4.2 of this review, narratives for subjects with malignancies are presented in Section 8.3.4.3, narratives for subjects with opportunistic infections are presented in Section 8.3.4.5, and narratives for subjects with gastrointestinal perforation are presented ion Section 8.3.4.6.

The review team analyzed AESIs reported during the pooled 24-week placebo-controlled trials and the pooled Week 0-52 OLE trials in subjects who received deuruxolitinib continuously from initial randomization through Week 52. The review team also evaluated events documented in the 120-day safety update report. In addition to raw incidence rates, the analysis included exposure-adjusted incidence rates (EAIRs) in order to characterize whether the risk of AESIs increased with a longer duration of exposure. The analysis of selected AESIs is presented below.

Table 50. Adverse Events of Special Interest, Weeks 0 to 24 and Weeks 0 to 52

	Week 0-24 Placebo-Controlled Pool			Week 0-52 Long Term Exposure Safety Pool	
Adverse Events of Special Interest	PBO (N=299) PYE =132 n (Adj %) [EAIR]	DEURUX 8 mg BID (N=640) PYE =279 n (Adj %) [EAIR]	DEURUX 12 mg BID (N=380) PYE =170 n (Adj %) [EAIR]	DEURUX 8 mg BID (N=868) PYE =666 n (%) [EAIR]	DEURUX 12 mg BID (N=991) PYE =680 n (%) [EAIR]
All infections	97 (31.8) [88]	222 (33.7) [101.5]	153 (38.7) [117]	435 (50.1) [95.5]	408 (41.2) [74.1]
Serious infections	1 (0.4) [0.8]	5 (0.8) [1.8]	2 (0.3) [1.2]	5 (0.6) [0.7]	4 (0.4) [0.5]
Opportunistic infections	1 (0.4) [0.8]	0	0	1 (0.1) [0.1]	2 (0.2) [0.3]
Herpes zoster	0	3 (0.5) [1.1]	3 (0.9) [1.8]	10 (1.2) [1.5]	15 (1.5) [1.9]
Herpes simplex	3 (1.0) [2.3]	8 (1.2) [2.9]	6 (1.6) [3.6]	16 (1.8) [2.4]	14 (1.4) [1.8]
Tuberculosis	0	0	0	0	0
Malignancies excluding NMSC	1 (0.4) [0.8]	0	0	3 (0.3) [0.4]	4 (0.4) [0.5]
NMSC	1 (0.3) [0.8]	0	0	1 (0.1) [0.1]	0
MACE	0	0	0	0	0
Thrombosis	1 (0.4) [0.8]	0	0	0	1 (0.1) [0.1]
Gastrointestinal perforation	0	1 (0.2) [0.4]	0	1 (0.1) [0.1]	0
CPK increased	7 (2.2) [5.4]	35 (5.3) [12.9]	27 (7.4) [16.6]	49 (5.6) [7.6]	46 (4.6) [6.1]
Thrombocytopenia	0	0	1 (0.3) [0.6]	0	2 (0.2) [0.3]
Thrombocytosis	0	18 (2.7) [6.6]	6 (1.6) [3.6]	20 (2.3) [3.0]	26 (2.6) [3.4]
Lymphopenia	2 (0.6) [1.5]	2 (0.3) [0.7]	7 (2.0) [4.2]	4 (0.5) [0.6]	10 (1.0) [1.3]
Neutropenia	3 (0.7) [2.3]	10 (1.4) [3.6]	10 (2.8) [6.0]	11 (1.3) [1.6]	15 (1.5) [1.9]
Lipid elevation	10 (3.1) [7.7]	30 (4.4) [11.0]	18 (4.9) [10.9]	47 (5.4) [7.2]	66 (6.7) [8.7]
Hypersensitivity reactions	7 (2.1) [5.4]	6 (0.9) [2.2]	4 (0.7) [2.4]	13 (1.5) [2.0]	11 (1.1) [1.4]
Anaphylaxis	0	0	0	1 (0.1) [0.1]	1 (0.1) [0.1]
Angioedema	2 (0.7) [1.5]	5 (0.8) [1.8]	2 (0.6) [1.2]	8 (0.9) [1.2]	2 (0.2) [0.3]
Anemia	3 (1.0) [2.3]	19 (2.7) [6.9]	16 (3.4) [9.6]	17 (2.0) [2.6]	38 (3.8) [5.0]
Liver enzyme elevations	0	3 (0.5) [1.1]	3 (0.6) [1.8]	8 (0.9) [1.2]	9 (0.9) [1.2]
Drug-induced liver injury	0	0	0	0	0
Retinal detachment	0	0	0	0	0

Source: Reviewer's table adapted from Integrated Summary of Safety Table 26, 4.5.1, 4.3.4, 4.5.4, and confirmed with OCS Analysis Studio, Safety Explorer
NOTE: Percentages are adjusted for study size for the 0-24 Week Placebo period. Percentages are not adjusted for study size for the 0-52 week long term safety pool since no comparison is made against placebo, subjects changed doses within the OLE trials and subjects can be counted under more than 1 treatment group in the analyses, and the pool incudes data from subject participation in more than one trial.
NOTE: EAIR is 100 times the number of subjects with at least one event (n) divided by the total PY. PY is the sum across all subjects in the treatment group of the individual subject risk-times divided by 365.25, where risk-time is the number of days in which an event could be deemed treatment-emergent for the given treatment, except any period after the treatment end date in a given study, or after a subject's first TEAE in the category, is excluded.
NOTE: unadjusted EAIR is displayed for all preferred terms, because due to small number of subjects adjusted EAIR were not estimable for all preferred terms
NOTE: Subjects who experienced multiple adverse events in the same TEAESI category are only counted once for that category (and treatment group, as applicable).
Opportunistic infections defined using narrow scope Standard MedDRA Query from MedDRA version 23.1.
Abbreviations: BID, twice daily; CPK, creatine phosphokinase, DEURUX, deuruxolitinib; EAIR, exposure-adjusted incidence rate, MACE, major adverse cardiac events, MSC, non-melanoma skin cancer, PBO, placebo PY, person-years, PYE, person-years of exposure

AESIs considered related to the study drug by the investigator is presented below.

Table 51. Adverse Events of Special Interest Considered Related by Investigator, Weeks 0 to 24 and Weeks 0 to 52

	Week 0-24 Placebo Controlled Pool			Week 0-52 Long Term Exposure Safety Pool	
Adverse Events of Special Interest	PBO (N=299) PYE =132 n (Adj %) [EAIR]	DEURUX 8 mg BID (N=640) PYE =279 n (Adj %) [EAIR]	DEURUX 12 mg BID (N=380) PYE =170 n (%) [EAIR]	DEURUX 8 mg BID (N=868) PYE =666 n (%) [EAIR]	DEURUX 12 mg BID (N=991) PYE =680 n (%) [EAIR]
All infections	25 (8.3) [23.0]	59 (8.9) [28.8]	40 (9.7) [28.1]	100 (11.5) [22.4]	123 (12.4) [25.2]
Serious infections	0	2 (0.3) [0.7*]	1 (<0.1) [0.6*]	0	1 (0.1) [0.1*]
Opportunistic infections	0	0	0	1 (0.1) [0.2*]	2 (0.2) [0.3*]
Herpes zoster	0	2 (0.3) [0.7*]	1 (0.3) [0.6*]	7 (0.8) [1.1*]	9 (0.9) [1.3*]
Herpes simplex	1 (0.3) [0.8*]	4 (0.6) [1.4*]	3 (0.8) [1.8*]	8 (0.9) [1.2*]	8 (0.8) [1.2*]
Tuberculosis	0	0	0	0	0
Malignancies excluding NMSC	0	0	0	1 (0.1) [0.2*]	1 (0.1) [0.1*]
NMSC	0	0	0	1 (0.1) [0.2*]	0
MACE	0	0	0	0	0
Thrombosis	0	0	0	0	0
Gastrointestinal perforation	0	0	0	0	0
CPK increased	3 (0.9) [2.3*]	22 (3.4) [8.0*]	21 (5.8)	34 (3.9) [5.2*]	36 (3.6) [5.5*]
Thrombocytopenia	0	0	1 (0.3) [0.6*]	0	2 (0.2) [0.3*]
Thrombocytosis	0	14 (2.1) [5.1*]	3 (0.8) [1.8*]	17 (2.0) [2.0]	21 (2.1) [2.7]
Lymphopenia	1 (0.3) [0.8*]	2 (0.3) [0.7*]	4 (1.2) [2.4*]	4 (0.5) [0.6*]	5 (0.5) [0.7*]
Neutropenia	2 (0.4) [1.5*]	6 (0.8) [2.2*]	8 (2.3) [4.8*]	5 (0.6) [0.8*]	14 (1.4) [2.1*]
Lipid elevation	7 (2.3) [5.4*]	22 (3.3) [8.0*]	16 (4.4) [9.6*]	36 (4.1) [4.1]	55 (5.5) [6.9]
Hypersensitivity reactions	2 (0.7) [1.5*]	0	0	1 (0.1) [0.2*]	1 (0.1) [0.1*]
Anaphylaxis	0	0	0	0	0
Angioedema	0	0	0	1 (0.1) [0.2*]	0
Anemia	2 (0.7) [2.4]	14 (2.0) [9.6]	14 (2.9) [15.5]	9 (1.0) [1.4*]	28 (2.8) [4.2*]
Liver enzyme elevations	0	2 (0.3) [0.7*]	2 (0.3) [1.2*]	4 (0.5) [1.4]	7 (0.7) [1.2]
Drug-induced liver injury	0	0	0	0	0
Retinal detachment	0	0	0	0	0

Further discussion of select AESIs is presented below.

8.3.4.1. MACE

Labeling for JAK inhibitors that treat certain chronic inflammatory conditions carry a boxed warning for MACE, defined as cardiovascular death, myocardial infarction, and stroke.

In the general population, risk factors associated with atherosclerosis and poor cardiovascular outcome include obesity, sedentary lifestyle, smoking, and an abnormal lipid profile. Due to the documented impact of JAK inhibitors on lipid levels, the Applicant designated MACE as an AESI. MACE was defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke. An independent data monitoring committee performed periodic reviews of cumulative safety data to identify cases of MACE among other cardiovascular AEs.

There is limited data regarding the risk of developing cardiovascular disease in patients with AA. A retrospective cohort study which evaluated 1377 patients with AA concluded that patients with AA had diminished risk for developing stroke, and a trend toward decreased risk for myocardial infarction (Huang et al. 2016). While reports of an association of cardiovascular comorbidities and AA are rare, some studies have shown an elevated level of troponin I, a

biomarker for myocardial ischemia and inflammation, in patients with AA. (Wang et al. 2018; El-Sayed Mahmoud Marie et al. 2021).

During the Phase 3 trials to evaluate deuruxolitinib, the protocol specified the documentation of many risk factors for the development of MACE. However, data regarding smoking status was not systematically collected during conduct of the clinical trials. Overall, the risk factors for MACE in this study population with AA were well-balanced among the treatment groups. The baseline risk factors for MACE in the safety population are summarized below.

Table 52. Risk Factors for MACE in Subjects in the Placebo-Controlled Safety Pool

Risk Factor	PBO (N=299) n (%)	DEURUX 8 mg BID (N=640) n (%)	DEURUX 12 mg BID (N=380) n (%)
Any MACE risk factor	192 (64.2)	446 (69.7)	247 (65.0)
Age ≥50 years	78 (26.1)	153 (23.9)	93 (24.5)
Male	100 (33.4)	226 (35.3)	138 (36.3)
BMI (kg/m²) >30	62 (20.7)	160 (25.0)	84 (22.1)
Baseline HDL <40	29 (9.7)	74 (11.6)	33 (8.7)
Medical history of:			
DM	10 (3.3)	16 (2.5)	4 (1.1)
Hypertension	34 (11.4)	67 (10.5)	34 (8.9)
CAD	1 (0.3)	3 (0.5)	0
MI	1 (0.3)	0	0
Stroke	0	2 (0.3)	0
Thrombosis	0	1 (0.2)	0

Source: Reviewer's table adapted from Integrated Summary of Safety Table 9
Abbreviations: BMI, body mass index, DEURUX, deuruxolitinib; DM, diabetes mellitus, CAD, coronary artery disease, MI, myocardial infarction; PBO, placebo

In the placebo-controlled safety pool, a total of 67.9% of subjects who received deuruxolitinib (69.7% for 8 mg BID and 65.0% for 12 mg BID) and 64.2% of subjects who received placebo had associated MACE risk factors (≥50 years of age, male, BMI >30 kg/m^2, HDL <40 mg/mL, diabetes mellitus, hypertension, coronary artery disease, myocardial infarction, stroke, thrombosis). The most common risk factors for MACE in this study population were male sex and age ≥50 years. A total of 35.7% (35.3% and 36.3%) subjects who received deuruxolitinib and 33.4% of subjects who received placebo, respectively, were male; and a total of 24.1% (23.9% and 24.5%) subjects who received deuruxolitinib and 26.1% who received placebo were ≥50 years old. Other than sex and age, the majority of subjects who had MACE risk factors were those with high BMI (>30 kg/m^2; 23.9% [25% and 22.1%] and 20.7%, respectively).

In the long-term exposure safety pool, the proportion of subjects with risk factors for MACE at baseline was similar to the Placebo-Controlled Safety Pool. Overall, the risk factors for MACE in the study population with AA were also well-balanced among the treatment groups. A total of 67.7% of subjects who received deuruxolitinib (68.4% for 8 mg BID and 66.9% for 12 mg BID)

had associated MACE risk factors (≥50 years of age, male, BMI >30 kg/m^2, HDL <40 mg/mL, diabetes mellitus, hypertension, coronary artery disease, myocardial infarction, stroke, thrombosis). The most common risk factors for MACE in this study population were male sex and age ≥50 years. A total of 35.5% (33.8% for 8 mg BID and 37.6% for 12 mg BID) were male; and a total of 25.6% (25.2% for 8 mg BID and 26.0% for 12 mg BID) were ≥50 years old. Other than sex and age, the majority of subjects who had MACE risk factors were those with high BMI (>30 kg/m^2; 22.9% [22.6% for 8 mg BID and 23.3% for 12 mg BID]).

In an analysis of MACE based on the CMQ (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), no subjects experienced MACE in the deuruxolitinib development program. There were no reported MACE events in the development program up to the last safety data cut-off of May 5, 2023 (confirmed with Applicant in response to information request dated February 28, 2024 [SDN 24]). This may be due to the demographic characteristics of the study population which included relatively younger age (the mean age in the Phase 3 trials across all treatment groups was 38.9 years) and a majority of female subjects (there was a mean of 64.6% female subjects in the Phase 3 trials).

Other Cardiovascular Events

Among the cardiovascular adverse events that were observed in some subjects in both treatment groups were "supraventricular extrasystoles." There was no imbalance between treatment groups for supraventricular extrasytoles. Narrative summaries for representative subjects who received deuruxolitinib and developed TEAEs of "supraventricular extrasystoles" are below. The clinical reviewer agreed with the investigator's causality assessments.

- A 32-year-old female ([(b) (6)]) with a history of seasonal allergy, hyperlipidemia, vitamin D deficiency, depression, atopic dermatitis, and autoimmune thyroiditis, received 8-mg BID deuruxolitinib in trial CP543.3002. Baseline ECG was normal. On Day 85 during the Week 12 visit ECG showed supraventricular extrasystoles as a result of premature atrial complexes with an interpretation of abnormal. The 12-lead ECG was repeated approximately 45 minutes later, and the same finding of supraventricular arrhythmias as a result of premature atrial complexes were interpreted as normal. The event of supraventricular extrasystoles was considered possibly related to study drug by the investigator. Study drug was discontinued. The subject discontinued from the trial due to the TEAE on Day 115. Repeat ECG on Day 115 was normal.
- A 42-year-old female ([(b) (6)]) with a history of exercise induced asthma was enrolled in trial CP543.3002 and received 12-mg BID deuruxolitinib. Baseline visit ECG was normal. On Day 88 she experienced supraventricular extrasystoles. Two subsequent ECGs revealed ectopic atrial rhythm. The events were considered by the investigator to be possibly related. No action was taken with the study drug, and all events resolved. The subject also experienced lipid elevation on Day 113 considered possibly related by the investigator (The subject's cholesterol level was normal [198 mg/dL] at baseline, was high at the Week 4 [210 mg/dL] and Week 8 [210 mg/dL], was normal at Week 12 [192 mg/dL], and again high

at Week 16 [233 mg/dL] and remained elevated for the duration of the trial. Low-density lipoprotein (LDL) remained normal throughout the trial).

Despite the absence of MACE reported in the deuruxolitinib development program, MACE will be included in the Boxed Warning, and Section 5 of labeling as a known class effect of JAK inhibitors.

8.3.4.2. Thrombosis

Labeling for JAK inhibitors that treat certain chronic inflammatory conditions carry a Boxed Warning for thrombosis, including increased incidence of pulmonary embolism, venous and arterial thrombosis. The Applicant evaluated thrombosis as an AESI.

No cases of thrombosis were reported among subjects who received either dose of deuruxolitinib during Weeks 0 to 24, the placebo- controlled period. During Week 0 to 52 period, one subject who received deuruxolitinib 12 mg BID developed non-fatal bilateral pulmonary embolism at Week 41.

Between Week 52 to Week 98 in the OLE Trials CP543.5002 and CP543.5001, four subjects (0.3% overall) developed 7 non-fatal thrombotic events (0.2 per 100 patient years), including deep vein thrombosis, bilateral pulmonary embolism, pulmonary embolism, and cerebral venous thrombosis. All subjects were receiving deuruxolitinib 12 mg BID at the time of the thrombotic events. There was no clear relationship observed between platelet count elevations and thrombotic events.

In response to reports of thromboses that occurred among subjects who were receiving deuruxolitinib 12 mg, the FDA placed the Phase 3 trials on partial clinical hold (May 17, 2023, Week 98). This regulatory action prohibited further administration of the 12-mg dose to any subject (Refer to Section 3.2 of this review for details). The partial clinical hold resulted in the Applicant only seeking approval of the lower deuruxolitinib 8-mg dose in this NDA submission.

The review team consulted with the Division of Pharmacovigilance (DPV), for assistance in characterizing the strength of the safety signal of thrombosis for deuruxolitinib through a systematic review of the literature and FDA Adverse Event Reporting System reports (review under IND 131423 dated April 24, 2023). The FDA Adverse Event Reporting System search did not retrieve additional reports of thrombotic events associated with ruxolitinib (structurally similar to deuruxolitinib) and used off-label for the treatment alopecia areata. According to their causality assessment, DPV concluded that three cases were possibly related to exposure to deuruxolitinib. All subjects reporting events of thrombosis had multiple underlying risk factors (including obesity [BMI >30], comorbid inflammatory conditions, or use of oral contraceptives or hormone replacement therapy) and the number of identified events was low. However, in view of the established relationship of JAK inhibitors as a class with thrombosis and despite the presence of additional risk factors, the review team could not exclude a role for deuruxolitinib use in potentiating the development of serious thrombotic events.

Narrative summaries of the cases of thromboses in the deuruxolitinib development program with causality assessments are below. All subjects who reported thrombosis had received deuruxolitinib 12 mg orally BID for AA.

Weeks 0 to 52

- Bilateral pulmonary embolism: A 60-year-old male ([(b) (6)]) with BMI 30.6 kg/m^2 and a history of hypertension, and concomitant medications of candesartan, omeprazole, ibuprofen developed bilateral pulmonary emboli after receiving deuruxolitinib 12 mg BID for approximately 41 weeks. At day 90 of the OLE trial, the subject sustained a humerus fracture requiring surgical intervention with implant. One month later, the subject required surgical repair due to implant failure. The subject developed septic shock with hypoxemic respiratory failure requiring intensive care unit admission. Three days later, the subject was diagnosed with bilateral PE (approximately 41 weeks after initiation of deuruxolitinib 12 mg BID). The last platelet count preceding the event was 255 x10^9/L and platelet counts ranged from 235-255 x10^9/L during Trial CP543.5002. This SAE was assessed by the investigator and Applicant as unlikely related to the IP. Study drug was discontinued, and the subject withdrew from the trial. Per DPV review, based on the presence of multiple moderate risk factors for venous thromboembolism (VTE) (e.g., instrumentation in the intensive care unit for febrile sepsis and respiratory failure, such as central venous line placement) and other risk factors for VTE (e.g., age, male sex, BMI, immobility, humerus fracture, and history of multiple surgical repairs), the causality assessment was “unlikely.” However, since it is unclear if deuruxolitinib contributed to potentiating thrombosis in the setting of background increased subject risk factors, the clinical reviewer considers the thrombosis to be possibly related to deuruxolitinib.

Weeks 52 to 98

- Cerebral venous sinus thrombosis: A 46-year-old female ([(b) (6)]) with a BMI of 32.6 kg/m^2, irritable bowel syndrome, hypothyroidism, and concomitant medications of oral contraceptive pills and levothyroxine developed cerebral venous sinus thrombosis after receiving deuruxolitinib 12 mg BID for 1 year and 24 days. At approximately 56 weeks the subject presented with progressive headaches with “imbalance”, nausea, and double vision, and was admitted to the hospital. Nine days prior to admission, the subject developed waxing and waning headaches, which progressed in severity and persistence over the following week. CT scan showed cerebral venous sinus thrombosis and possible aneurysm of the left carotid. The subject’s last platelet count preceding the event was 412 x10^9/L. During Trial CP543.5001, platelet counts ranged from 226-412 x10^9/L. Protein C and S levels were normal. Study drug was withdrawn due to the adverse event. The event was considered resolved on Day 598. This SAE was assessed by the investigator as possibly related to investigational product. Per Division of Pharmacovigilance review dated April 24, 2023, based on the temporal relationship between deuruxolitinib use and the event, and the subject’s risk factors for VTE (e.g., age, BMI, and oral contraceptive pills use), this was assessed as possibly related causality.
- Bilateral PE: A 46-year-old female ([(b) (6)]) with BMI 47.2 kg/m^2 and a history of sinusitis, asthma, depression, previous smoking (12 years prior), and concomitant

medications of progesterone, estradiol, budesonide/formoterol fumarate, fluticasone, omega-3 supplement, clindamycin, and escitalopram developed bilateral pulmonary emboli after receiving deuruxolitinib 12 mg BID. Approximately 45 weeks after receiving 12 mg BID (and 65 weeks on active), the subject experienced tachycardia, shortness of breath, left calf tenderness, and upper back pain between shoulders, and was found to have bilateral PE. One month prior to the SAE, the subject had traveled internationally. The last recorded platelet count preceding the event was 439 $x10^9$/L; the platelet counts ranged from 273-439 $x10^9$/L during trial CP543.5001. This SAE was assessed by the investigator and Applicant as possibly related to investigational product. Per DPV review (dated April 24, 2023), based on the temporal relationship between deuruxolitinib use and the event, the SAE of PE was assessed as possibly related. Though the subject had background risk factors for thrombosis (receiving hormone replacement therapy, high BMI, recent prolonged immobility), the clinical reviewer also considered the event of thrombosis to be possibly related to deuruxolitinib.

- Bilateral PE and bilateral DVT: 38-year-old female ([(b) (6)]) with of BMI 32.3 kg/m^2 and a history of hypothyroidism, obesity, lupus and rheumatoid arthritis, developed bilateral PE and DVT after a total of approximately 60 weeks of deuruxolitinib 8 mg followed by approximately 38 weeks of deuruxolitinib 12 mg. Concomitant medications included levothyroxine, Mirena intrauterine device (levonorgestrel), and ergocalciferol. Approximately 38 weeks after receiving 12 mg, the subject experienced left leg DVT. Four days later, the subject developed left PE. The following day she developed right leg DVT and left PE. The last platelet count prior to the SAE was 512 $x10^9$/L and platelet counts ranged from 421-527 $x10^9$/L during Trial CP543.5001. The events were considered by the investigator and clinical reviewer as possibly related (possible contributing factors were hypothyroidism, obesity, and a history of other underlying autoimmune disease of lupus and rheumatoid arthritis).
- Unilateral pulmonary embolism: 61-year-old female ([(b) (6)]) with BMI 32.6 kg/m^2 and history of hypothyroidism, hyperlipidemia, left hip bursitis, and concomitant medications of vitamin D, celecoxib, acetaminophen, and levothyroxine, developed PE approximately 76 weeks after initiating deuruxolitinib 12 mg. The subject presented with shortness of breath and was diagnosed with unilateral left PE on thoracic imaging. The event was non-fatal. The platelet counts ranged from 461-562 $x10^9$/L during Trial CP543.5001. This SAE was assessed by the investigator and Applicant as possibly related to the IP. Per DPV review the causality assessment was possibly related. The subject's other background risk factors for VTE included age, BMI, celecoxib use, hypothyroidism, and hyperlipidemia.

Of the five subjects described in the narratives above who developed thrombotic events between Week 0 to 98, one subject ([(b) (6)], with cerebral venous thrombosis diagnosed at Week 56) had received a single dose of a moderate CYP2C9 inhibitor, fluconazole, for a suspected yeast infection during the same week that the cerebral venous thrombosis was diagnosed. Nine days prior to receiving the fluconazole dose, the subject had already developed waxing and waning headaches, which progressed in severity and persistence over the following

week prior to fluconazole administration. This subject did not have any PK samples to determine the plasma concentration of deuruxolitinib at the time of the thrombosis event. Therefore, it is unclear if the moderate CYP2C9 inhibitor was contributory to the thrombotic event.

Refer to Section 8.3.4.13 of this review for discussion of the increased risk of serious adverse events resulting from higher deuruxolitinib plasma concentrations in patients on concomitant moderate or strong CYP2C9 inhibitors.

New thrombotic events not reported in the integrated summary of safety at the time of the NDA submission.

In the 120-day safety update report, the Applicant provided the following narratives of additional subjects who reported thrombotic events not reported in the initial NDA.

- Thrombophlebitis: A 59-year-old female ([(b) (6)]) with a history of asthma, osteopenia, sleep apnea, and substance abuse (marijuana) - on concomitant medications of ibuprofen, cetirizine hydrochloride, estradiol, calcium/cholecalciferol, hydrocortisone, venlafaxine, topical ivermectin, melatonin -received placebo in trial CP543.3001 and then received deuruxolitinib 12 mg BID in Trial CP543.5001. On Day 347, the subject developed thrombophlebitis. Risk factors included a concomitant medication of estradiol and a BMI of 25.2 kg/m^2. The last platelet count preceding the event was 294 $x10^9$/L (range 204-338 $x10^9$/L during Trial CP543.5001). The event was considered by the investigator and clinical reviewer to be possibly related. The study drug was withdrawn due to the event.
- Transient ischemic attack: A 54-year-old female ([(b) (6)]) with a history of hypothyroidism on – concomitant medications of levothyroxine, phenazopyridine hydrochloride, ibuprofen, naproxen, and gabapentin - received deuruxolitinib 12 mg BID in Trial CP543.3001, and Trial CP543.5001 for a total of 732 days. After the partial hold was imposed by the FDA, the subject received deuruxolitinib 8 mg BID. On Day 142 of deuruxolitinib 8 mg BID, the subject developed palpitations and inability to speak coherently. Evaluation with multiple modalities (brain magnetic resonance imaging [MRI], a computed tomography angiography of the brain and neck [no evidence for carotid stenosis or aneurysm, and no evidence for intracranial large vessel occlusion], 48-hour Holter monitor, and an echocardiogram) was negative. The subject received a diagnosis of possible transient ischemic attack but a stroke assessment revealed normal findings (National Institutes of Health Stroke Score of 0). The event was considered resolved on follow up. The last platelet count prior to the event was 248 $x10^9$/L (range 239-311 $x10^9$/L). In the investigator's opinion, the possible transient ischemic attack was severe (Grade 3), and probably related to use of study drug, and possibly related by the clinical reviewer. No other contributing factors were identified except a history of hypothyroidism.

Since thrombosis is a known class effect of JAK inhibitors, and thrombotic events occurred in the deuruxolitinib development program, labeling will include thrombosis in the Boxed Warning, and Section 5 of labeling. In addition, this reviewer proposes the following language to be included in Section 6 of labeling: "Additional Adverse Reactions Observed after 52 weeks:

Venous thromboembolic events considered related to study treatment were reported in four subjects treated with deuruxolitinib 12 mg twice daily between Week 52 and Week 98. These four subjects experienced 7 thrombotic events (0.2 per 100 patient years), including DVT, bilateral PE, pulmonary embolism, and cerebral venous sinus thrombosis."

8.3.4.3. Malignancy

The JAK-STAT signaling pathway is reported to play a key role in the development of cancer cells, and their proliferation, differentiation, and survival (Harrison 2012). Labeling for JAK inhibitors carry a Boxed Warning for malignancy, including higher rate of lymphomas and lung cancers. There were no reports of lymphomas nor lung cancers in the deuruxolitinib program; however, there were reports of other malignancies which are described below.

In the Placebo-controlled Safety Pool up to Week 24, no subjects who received deuruxolitinib developed malignancies and two subjects who received placebo ((b) (6) developed malignancies (clear renal cell carcinoma and basal cell carcinoma).

In the Overall Exposure Pool (which includes all subjects enrolled in Phase 2 and Phase 3 trials who received active treatment), a total of 10 subjects experienced malignancies. Of these, 4 malignancies (colon cancer, signet-ring cell carcinoma, metastatic pancreatic carcinoma, and clear cell renal cell carcinoma) had no clear temporal association with the study product and are unlikely related. However, the remaining six AEs of malignancy were considered possibly related (malignant melanoma in situ [n =2], basal cell carcinoma [n =1], nasal neoplasm [n =1], testicular cancer [n =1], and salivary gland tumor [n =1]). Brief narrative summaries for these subjects are provided below.

- Colon cancer: A 45-year-old male ((b) (6)) with a history of alcohol use, anogenital warts, hemorrhoids, psoriasis, and a family history of colon cancer, was enrolled in trial CP543.2003 and received 12-mg BID deuruxolitinib for 168 days, followed by 36 days of 12 mg BID in OLE trial CP543.5001. He experienced hematochezia 44 days after initiating treatment with 12-mg BID deuruxolitinib. Colon adenocarcinoma was confirmed 216 days after initiating treatment (OLE Day 36), study drug was discontinued, and he underwent low anterior colon resection. The event was considered unlikely related by both the investigator and the clinical reviewer due to history of alcohol use and a family history of colon cancer.
- Malignant melanoma (n=2):
  - A 45-year-old female ((b) (6)) with a history of juvenile idiopathic arthritis, anemia, anxiety and depression, uterine leiomyoma, autoimmune thyroiditis, and Fitzpatrick skin type II was enrolled in trial CP543.2004 (which evaluated maintenance of hair regrowth following dose reduction). She received 12-mg BID deuruxolitinib for 132 days and then on Day 170 was reduced to 8 mg for 142 days. 141 days after initiating treatment with 12 mg BID physical exam revealed a neoplasm on the right upper cheek (she reported she had a previous neoplasm in the same location years earlier which had disappeared, and not reappeared). On Day 150 a shave biopsy revealed melanoma in situ, extending to peripheral margin and focally to deep margin within follicular epithelium. The study drug was interrupted (to minimize infection prior to surgery) and

she underwent Mohs micrographic surgery and immediate advancement flap reconstruction on Day 164, with pathology revealing clear margins. The subject resumed treatment with 8 mg BID on Day 170. The event was considered resolved in Day 176 post suture-removal. The event was considered possibly related by the Applicant and the clinical reviewer.

- A 61-year-old female ([redacted]) with a history of hyperlipidemia and atrophic vulvovaginitis received 8-mg BID deuruxolitinib in trial CP543.2004 for 170 days and then enrolled in the OLE trial in which she received the same dose. On Day 95 in the OLE trial (265 days after initiation with 8 mg BID) the subject was diagnosed with melanoma in situ of the left superior helix of the ear, which was completely excised. No action was taken with the study drug. The subject had Fitzpatrick skin type II, no previous history of suspicious skin lesions, and average sun exposure. The event was considered possibly related by the investigator and the clinical reviewer.

- Signet-ring cell carcinoma: A 39-year-old male ([redacted]) with a history of hypertension and smoking received 8-mg BID deuruxolitinib in trial CP543.2004 for 170 days and then enrolled in the OLE trial during which he received placebo through Day 337. While on placebo he was diagnosed with severe Crohn's disease (Day 325). He then enrolled in OLE trial CP543.5001 receiving 8-mg BID deuruxolitinib and on OLE Day 11 he was hospitalized for intestinal blockage, underwent resection with diagnosis of stage III signet cell carcinoma. Signet-ring cell carcinoma was considered by the investigator and clinical reviewer to be unlikely related to study drug (since possible contributing factors include smoking history and due to temporal relationship not supporting causality). Study drug was discontinued, and further medical records were unable to be obtained after multiple attempts to contact the subject.
- Metastatic pancreatic carcinoma: A 52-year-old female ([redacted]) with a history of diabetes mellitus, hypothyroidism, anxiety, and hypercholesterolemia received 8-mg BID deuruxolitinib in trial CP543.2004 for 105 days at which point she presented to the emergency room with acute right upper quadrant pain and nausea. CT at the time was normal, however she had persistent flank pain, and on Day 131 repeat CT and MRI revealed a 43-mm mass at the pancreatic neck with upstream main duct dilation suspicious of pancreatic malignancy. A liver biopsy was positive for metastatic pancreatic cancer (stage IV disease), and she began chemotherapy on Day 153. Study drug was discontinued. The event was considered by the investigator and clinical reviewer to be unlikely related to study drug due to temporal relationship not supporting causality and other risk factors including a medical history of diabetes and obesity.
- Nasal neoplasm: A 47-year-old female ([redacted]) with a history of asthma, Raynaud's phenomenon, eczema, cystic acne attention deficit hyperactivity disorder and autoimmune thyroiditis received 12-mg BID deuruxolitinib in trial CP543.2004. On Day 85 the subject was diagnosed with "nasal neoplasm." The lesion was not biopsied per the narrative summary and the event was considered by the investigator to be not related to study drug. However, this reviewer concludes that there is insufficient information to perform a causality assessment. No action was taken with the study drug.

- Testicular cancer: A 31-year-old male ([(b) (6)]) with a history of keratoconus, received placebo in trial CP543.3001 and then 12-mg BID deuruxolitinib in OLE trial CP543.5001. On Day 57 the subject notified study staff of a new testicular lump identified on self-exam. He was referred to urology, and underwent ultrasound and testicular biopsy, followed by right testis and proximal spermatic cord radical orchiectomy on Day 78. Final pathology revealed malignant germ cell tumor consisting of pure classical seminoma with associated moderate host lymphocytic reaction. The event was considered not related by the investigator, and unlikely related by the clinical reviewer (the temporal onset of the malignancy at Day 57 suggests unlikely causation to active). Study drug was discontinued.
- Salivary gland tumor: A 57-year-old female ([(b) (6)]) with a history of C-section, received 12-mg BID deuruxolitinib in trial CP543.3001 for 166 days then received 12 mg BID in OLE trial CP543.5001. On OLE Day 121 the subject noticed a growing palatal mass. Prior to this, in 2020, the subject noted a small palatal mass that was under observation for 2 years. On exam, the mucosa of the soft and hard palates was dull with a palpable sub-centimeter fullness in the soft palate. On OLE Day 226 the subject was diagnosed with grade 2 salivary gland neoplasm; CT scan revealed 7.5 × 7.5 × 5.6 mm well-circumscribed enhancing lesion of the soft palate and core biopsy revealed mucoepidermoid carcinoma of the soft and hard palate. The gland was surgically excised on OLE Day 226. The event was considered by the investigator to be not related to study drug. However, since no alternative contributing factors were cited, it is considered possibly related by the clinical reviewer. Study drug was interrupted.
- Basal cell carcinoma: A 49-year-old female ([(b) (6)]) with a history of menopause received 8-mg BID deuruxolitinib in trial CP543.3001 for 24 weeks, and then enrolled in OLE trial CP543.5001 at the same dose. On OLE Day 62 the subject underwent biopsy of a nasal lesion with biopsy revealing basal cell carcinoma. The subject noted she had developed an unusual spot on her nose in the previous months that was described as a “slow to heal pimple.” She subsequently underwent Mohs surgery. The subject’s risk factors for basal cell carcinoma included fair skin and chronic sun exposure. The event was considered by the investigator and clinical reviewer to be possibly related. No action was taken with study drug.
- Clear cell renal carcinoma: A 48-year-old male ([(b) (6)]) with a history of seasonal allergy, arthritis, hypertension, hypercholesterolemia, melanocytic nevus, and cystic nodules, received placebo in trial CP543.3001. Prior to enrollment in the OLE trial, he underwent an MRI back after a fall at home, with incidental finding of renal lesion. He then received 8-mg BID deuruxolitinib in OLE trial CP543.5001. On Day 27 he underwent right robotic partial nephrectomy, pathology report revealed cell carcinoma, clear cell papillary type, grade 2. The event was considered by the investigator and clinical reviewer to be unlikely related to study drug, with a possible contributor being smoking history and due to temporal relationship of study drug not supporting causality. Study drug was discontinued.

The 120-day Safety Report included five additional reports of malignancy. Of the 5 malignancies, 3 were considered possibly related by the investigator. Brief narrative summaries for these subjects are provided below:

- Basal cell carcinoma (BCC; n=2):
  - A 49-year-old male ([(b) (6)]) with a history of allergies, oral herpes, tinnitus, and rosacea received treatment with placebo in trial CP543.3001. Subsequently the subject enrolled in OLE trial CP543.5001 and received 8-mg BID deuruxolitinib for 363 days and then with 12-mg BID deuruxolitinib for an additional 297 days. On Day 589 (while being dosed with 12 mg BID) a lesion of the left cheek was noted on exam and biopsy revealed basal cell carcinoma, infiltrative type. On Day 667 he underwent Mohs surgery with reconstruction. The event was considered by the investigator to be unlikely related to study drug. However, in the absence of additional information regarding risk factors, the clinical reviewer considered the adverse event of BCC as possibly related. No action was taken with study drug.
  - A 55-year-old female ([(b) (6)]) with a history of lymphoid tissue hyperplasia received deuruxolitinib 24 mg once daily (QD) in trial CP543.2003 and then received 12-mg BID deuruxolitinib in OLE trial CP543.5001. On Day 1043 of the OLE a biopsy of the left nasal area revealed basal cell carcinoma, which was fully excised. The subject's risk factors for basal cell carcinoma included sun exposure. The AE of BCC was considered not related by the investigator. However, in the absence of additional information regarding risk factors, the clinical reviewer considered the adverse event of BCC as possibly related. No action was taken with study drug.
- Gastric cancer: A 52-year-old female with history of hypothyroidism received 8-mg BID deuruxolitinib in trial CP543.3002 for 24 weeks and continued on the same dose in OLE trial CP543.5002. On approximately Day 330 of the OLE the subject experienced dysphagia. She completed the trial on Day 365, and approximately 60 days later she was admitted to the hospital where laparoscopy confirmed a diagnosis of gastric cancer with peritoneal metastasis, stage IV, and she initiated palliative chemoterhapy. The event was considered by the investigator and clinical reviewer to be possibly related to study drug. No action was taken with the study drug since the subject had completed the trial prior to the site being informed of the event.
- Planoepithelia cancer of tongue: A 61-year-old male ([(b) (6)]) with no relevant medical history received 12-mg BID deuruxolitinib in trial CP543.3001 and continued on this dose in OLE trial CP543.5002 for 421 days. At the Week 60 visit (Day 420) the subject reported to the site that he had noticed a "change" on his tongue (suspected cancer), without any other signs or symptoms. A biopsy confirmed diagnosis of Grade 3 "planoepithelial cancer." He began radiotherapy and chemotherapy. The event was considered not related by the investigator. However, since the subject did not have a history of smoking and no other risk factors were identified, the clinical reviewer considers the event as possibly related by the. Study drug was discontinued.
- Squamous cell carcinoma of skin: A 65-year-old male ([(b) (6)]) with history of varicella and aerophobia, who received 16 mg QD deuruxolitinib in trial CP543.2002. He then entered OLE CP543.5001 in which he received 12-mg BID deuruxolitinib for 1264 days. On Day 1148 biopsy results of an area on the subject's right temple confirmed a well

differentiated squamous cell carcinoma of skin. He underwent Mohs surgery. He subsequently reported 2 additional events of squamous cell carcinoma after completion of the OLE (back and right temple). Risk factors for squamous cell carcinoma included age, fair skin, and sun exposure. The event was considered by the investigator to be not related to study drug and possibly related by the clinical reviewer No action was taken with study drug.

Overall, the incidence rates for malignancies (tabulated in Table 50) were low. In addition, a substantial number of the narratives lacked key information to allow a definitive causality assessment. Therefore, the number of events was not sufficient to draw meaningful conclusions regarding risk or dose-response for malignancies.

Since malignancy is a known class effect of JAK inhibitors, and malignancies occurred in the deuruxolitinib development program, "Malignancy and lymphoproliferative disorders" will be included in labeling in the Boxed Warning and Section 5.

8.3.4.4. Hypersensitivity

In the trials for deuruxolitinib, anaphylaxis, angioedema, and hypersensitivity reactions were evaluated as AESIs.

Potential hypersensitivity reactions were assessed with a narrow search using SMQs which included the Anaphylaxis SMQ, Angioedema SMQ and Hypersensitivity Reactions adjusted SMQ (which included the following preferred terms: Anaphylactic reaction, Angioedema, Drug eruption, Hypersensitivity, Multiple allergies, Periorbital swelling, Rash, Rash pruritic, Rash pustular, Rash vesicular, Swelling of eyelid, Swollen tongue, Urticaria, and Vulvovaginitis allergic).

In the Week 0-24 placebo-controlled period, there were no reports of anaphylaxis in any treatment arm and no significant imbalances among the treatment arms in reports of angioedema, or hypersensitivity. Specifically, in the placebo-controlled safety pool (Week 0-24), angioedema was reported in 2 (0.7%) subjects who received placebo, 5 (0.8%) subjects who received 8 mg, and in 2 (0.6%) subjects who received 12 mg. Hypersensitivity reactions were reported in 7/299 subjects (2.1%) who received placebo, 6/640 (0.9%) of subjects who received 8 mg, and in 4/380 subjects (0.7%) who received 12 mg. None of the events in subjects who received deuruxolitinib were considered treatment related by the Investigator and none were considered as serious.

In the Week 0-52 period, anaphylaxis was reported in 1 (0.1%) subject who received 8 mg and in 1 (0.1%) subject who received 12 mg; angioedema was reported in 8 (0.9%) subjects who received 8 mg and in 2 (0.2%) subjects who received 12 mg; and hypersensitivity reactions were reported in 13 (1.5%) subjects who received 8 mg and in 11 (1.1%) subjects who received 12 mg. Analysis of the hypersensitivity events suggested no apparent causal relationship between deuruxolitinib and hypersensitivity based on a temporal relationship. All subjects with

hypersensitivity reactions continued to receive the drug without a recurrence of the event (negative re-challenge).

Given the lack of imbalance in hypersensitivity reports amongst the three treatment arms in the Week 0-24 placebo-controlled period and the low number of reports of hypersensitivity in the Week 0-52 period without apparent causal relationship, hypersensitivity will not be included in labeling.

8.3.4.5. Infection

Due to the known immunosuppressive effects of deuruxolitinib and the class of JAK inhibitors, the Applicant identified infection as an AESI and the risk of serious infection will be included in labeling as a boxed warning. In the deuruxolitinib development program, the Applicant analyzed all infections using the PTs from the MedDRA "Infections and infestations" SOC, opportunistic infections from SMQ of "opportunistic infections," and herpes zoster and herpes simplex utilizing CMQs.

During the 24-week placebo-controlled period, the exposure-adjusted incidence rate (EAIR) for overall infections was 88/100 patient-years in the placebo group, 101.5/100 patient-years in the deuruxolitinib 8-mg group, and 117/100 patient-years in the deuruxolitinib 12-mg group. Through Week 52, the EAIR for overall infections was 50.1/100 patient-years in the deuruxolitinib 8-mg group and 41.2/100 patient-years in the deuruxolitinib 12-mg group. Incidence rates for overall infections for the period from Baseline to Week 52 were generally comparable between treatment groups (Refer to Table 50), with the exception of herpes zoster (which was reported in 3[0.5%] subjects on deuruxolitinib 8 mg, 3[0.9%] subjects on deuruxolitinib 12 mg and in no subjects on placebo during the Week 0-24 period).

Serious Infections

During the 26-week placebo-controlled period, the EAIR for serious infections was 0.8 /100 patient-years for the placebo group, 1.8/100 patient-years in the deuruxolitinib 8-mg group, and 1.2/100 patient-years in the deuruxolitinib 12-mg group. Through Week 52, the EAIR for serious infections was 0.7/100 patient-years in the deuruxolitinib 8-mg group, and 0.5/100 patient-years in the deuruxolitinib 12-mg group.

Serious infections reported during the 24-week placebo-controlled period included appendicitis (two subjects on 8 mg and one subject on 12 mg), meningitis (one subject on 8 mg), COVID-19 (one subject on 8 mg), influenzal pneumonia (one subject on 8 mg) and cellulitis (one subject on 12 mg). Additional serious infections in the long-term safety pool from Week 24-52 included: peritonsillar abscess (one subject on 8 mg), postoperative wound infection (one subject on 8 mg) and pyomyositis (one subject on 8 mg).

Select narratives for subjects with serious infections who received deuruxolitinib 8 mg are provided below. The clinical reviewer agreed with the investigator's causality assessments. None of these subjects reported events of leukopenia or neutropenia in association with the infection.

- A 55-year-old female ([(b) (6)]) with a history of type 2 diabetes mellitus, hypothyroidism, hyperlipidemia, hypertension, neuralgia, back pain, spinal fusion surgery and spinal nerve stimulator implantation, developed meningitis and pyrexia on Day 42. On Day 43 the subject presented to the emergency room with fever, altered mental status and worsened back pain after injection of an unknown drug to the back on the previous day. She was admitted to the critical care unit, where a lumbar puncture revealed cloudy exudate of cerebrospinal fluid suspicious for infection (negative polymerase chain reaction and cultures for bacteria). An infectious source was not identified. The subject received intravenous antibiotics and her status improved. Neurosurgery removed the nerve stimulator due to concern for infection. The investigator assessed the SAE of meningitis as possibly related due to the immunosuppressant effect of study drug.
- A 35-year-old male ([(b) (6)]) with no relevant medical history developed pneumonia on Day 133. The subject presented to the emergency room with respiratory distress and was admitted to the hospital for pneumococcal pneumonia of the lower left lobe and superinfection due to influenza A (pneumonia influenzal) confirmed with polymerase chain reaction testing. He was treated with antibiotics and ipratropium bromide inhalation and was discharged from the hospital on Day 136. The event of pneumonia influenzal was considered by the investigator to be possibly related to study drug, which was discontinued. The subject discontinued from the trial due to the SAE.

Because serious infections occurred in subjects who received deuruxolitinib and it is a known class effect of JAK inhibitors serious infections will be included in the Boxed Warning and Section 5 of labeling.

Tuberculosis and Non-Tuberculosis Atypical Mycobacterial Infection

In the clinical trials for deuruxolitinib, subjects with a positive TB test or history of incompletely treated or untreated tuberculosis were excluded. Assessment for active signs and symptoms of infection including tuberculosis was performed periodically throughout the trials.

In the original NDA submission, there were no reports of the development of TB in any treatment arm during Weeks 0-24 or Weeks 0-52.

The 120-day safety update included a report of a previously undiagnosed case of disseminated non-tuberculosis mycobacterial infection with lytic bone lesions in a subject who was receiving 8 mg BID during the open label long-term extension trial, the narrative summary of which is below:

- A 59-year-old postmenopausal African American female ([(b) (6)]) with a history of obesity, type 2 diabetes mellitus, peripheral neuropathy, depression, iron deficiency

anemia, and atopic dermatitis developed disseminated mycobacterium avium on Day 159. The subject received deuruxolitinib 8 mg BID for 24 weeks in Trial CP543.3001 and extension Trial CP543.5001. On Day 159, the subject experienced severe left intercostal back pain, and was admitted to the hospital. An X-ray showed lytic bone lesions and a bone biopsy confirmed granulomatous disease with disseminated atypical mycobacterium infection (mycobacterium avium species). She was discharged from the hospital on Day 164 and followed up with oncology who ruled out multiple myeloma and metastatic malignancy. Subsequent bone biopsy also did not reveal malignancy but was acid fast bacteria positive without evidence of mycobacterium tuberculosis. Study medication was discontinued on Day 197. The subject reported no ex-U.S. travel over the past few years and no history of frequent or recurrent infections. HIV status is not reported. The subject began treatment with rifampin, ethambutol, and azithromycin, and per narrative summary had improvement in her intractable back pain. The event of non-tuberculosis mycobacterial infection was considered possibly related to the study drug by the Investigator, and by the clinical reviewer.

Labeling will include language in Section 2 regarding pretreatment evaluation for active and latent tuberculosis. A Boxed Warning and Section 5.1 (Serious Infections) will convey the increased risk of tuberculosis in patients treated with the proposed product.

Skin and Soft Tissue Infections

The review team analyzed the pooled term of “Skin and soft issue infections” to include the preferred terms: folliculitis, impetigo, skin infection, subcutaneous abscess, furuncle, paronychia, and pustule. In the Week 0-24 period, pooled skin and soft tissue infections were reported in 2 (0.8%) subjects on placebo, 11 (1.6%) subjects on deuruxolitinib 8 mg BID, and 15 (4%) subjects on deuruxolitinib 12 mg BID.

Of these pooled skin and soft tissue infections, folliculitis was reported in 2 (0.7%) subjects on placebo, in 8 (1.3%) of subjects on 8 mg BID, and in 10 (2.6%) of subjects on 12 mg BID.

Among the TEAEs of folliculitis, approximately 25% of events had information provided on the case report forms (verbatim term) that involved the scalp. However, the location of folliculitis was not systematically collected, and investigators were not specifically asked to comment if these events occurred in areas of hair regrowth, therefore it is not possible to accurately determine if folliculitis was associated with hair regrowth in the scalp region.

Pooled “Skin and soft tissue infections” is proposed for inclusion in Section 6.1 of labeling.

Herpes

There was not a significant imbalance between treatment arms in subjects who reported herpes zoster or herpes simplex in the placebo-controlled period Week 0-24. In the Week 0-24 period, herpes zoster was reported in zero subjects on placebo, 3 (0.5%) subjects on deuruxolitinib 8 mg BID, and 3 (0.9%) subjects on deuruxolitinib 12 mg BID. The reports of herpes zoster included only the general anatomic area not dermatome. Therefore, it was not

possible to identify the distribution of subjects who reported AEs of herpes zoster by dermatome. In the Week 0-24 period, herpes simplex was reported in 3 (1%) subjects on placebo, 8 (1.2%) subjects on deuruxolitinib 8 mg BID, and 6 (1.6%) subjects on deuruxolitinib 12 mg BID. Of the six subjects who reported herpes zoster in the Week 0-24 period, the mean age in years [SD] was 39.2 [15.45]. In the long-term extension trials during the Week 0-52 period, herpes zoster was reported in 10 (1.2%) subjects on deuruxolitinib 8 mg BID and in 15 (1.5%) subjects on deuruxolitinib 12 mg BID, and similar rates were observed for herpes simplex. Of the 25 subjects who reported herpes zoster, the mean age in years [SD] was 44.3 [12.17].

However, when the pooled term of "herpes" was analyzed (which included the preferred terms of oral herpes, herpes simplex, genital herpes simplex, and nasal herpes), there was an imbalance between treatment arms for the Week 0-24 period: 2 (0.6%) subjects on placebo, 8 (1.2%) subjects on deuruxolitinib 8 mg, and 6 (1.6%) subjects on deuruxolitinib 12 mg (Refer to Table 49). Therefore, the pooled term of herpes is proposed for inclusion in labeling Section 6.

There were two reports of ophthalmic herpes in the Week 0-52 period, described below in "Opportunistic Infection."

Increased risk of viral and opportunistic infections will be conveyed in the Boxed Warning, and Section 5 Serious infection of labeling, as is the pooled term of herpes described above.

Opportunistic Infection

No subjects in any treatment arm reported opportunistic infection as defined by the Applicant in the placebo-controlled Week 0-24 period. In the long-term extension trials during the Week 0-52 period, opportunistic infection was reported in 1 (0.1%) subject on deuruxolitinib 8-mg BID (ophthalmic herpes) and in 2 (0.2%) subjects on deuruxolitinib 12 mg BID (Epstein-Barr virus infection reactivation and ophthalmic herpes). All three events were considered possibly related by the investigators and this reviewer. The narrative for the subject who received 8-mg deuruxolitinib BID is below:

- A 51-year-old female ([redacted] (b) (6)) with a history of autoimmune thyroiditis and hypertension developed grade 1 (mild) ophthalmic herpes zoster (TEAESI category: opportunistic infection, herpes zoster) on Day 21 of the OLE trial. The subject received 8-mg deuruxolitinib BID for 24 weeks in Trial CP543.3002 and in the same dose in OLE trial CP543.5002 for 21 days. Ophthalmic herpes zoster resolved on Day 28 and was considered possibly related by the Investigator, and clinical reviewer. No action was taken with the study drug. At the time of the event, the subject also developed grade 2 (moderate) bacterial infection of the eye which resolved on Day 27 of the OLE trial.

Candida Infections

Using the MedDRA dictionary high-level term of 'Candida infections', there were eight cases of candidiasis for subjects on deuruxolitinib in the integrated safety database (four subjects on 8 mg BID and four subjects on 12 mg BID). Preferred terms for these cases include vulvovaginal

candidiasis (four subjects on 8 mg BID [1 related], two subjects on 12 mg BID) and oral candidiasis (two subjects on 12 mg BID [1 related]).

In addition to the above preferred terms, the following preferred terms were reported by subjects on active treatment: vulvovaginal mycotic infection (five subjects on 8 mg BID [none related] and seven subjects on 12 mg BID [2 related)], fungal infection (two subjects on 8 mg BID [1 related] and one subject on 12 mg BID [related]), and genital infection fungal (one subject on 8 mg BID [not related]).

COVID-19

Phase 3 trials were conducted during the height of the COVID-19 pandemic. Therefore, testing for COVID-19 was required at each visit in Europe and any positive test was considered a TEAE. During Weeks 0-24, a similar number of placebo subjects reported the TEAE of COVID-19 as deuruxolitinib subjects, which suggests that the development of COVID-19 infections is not impacted by deuruxolitinib treatment.

8.3.4.6. Gastrointestinal Perforation

Gastrointestinal (GI) perforation is a known risk associated with treatment with other JAK inhibitors documented in the literature, and reflected in labeling under Warnings and Precautions for JAK inhibitors that treat certain chronic inflammatory conditions (Hoisnard et al. 2022).

The Applicant reported one TEAE of GI perforation in the original NDA submission. In the 120-day Safety Update Report, the Applicant reported one additional TEAE of GI perforation. Brief narratives for these subjects are below:

- A 49-year-old female ([(b) (6)]) with a history of abdominoplasty developed a GI fistula and underwent GI fistula repair on Day 120 of treatment with deuruxolitinib 8 mg. The investigator attributed the development of the fistula to an abdominoplasty that was performed five years prior to the AE. The investigator considered the fistula in the category of GI perforations and as not related to study drug. The drug was interrupted due to the event for 6 days, and the subject completed the trial and enrolled in open label extension. No further details are provided in the narrative.
- A 45-year-old male ([(b) (6)]) with a history of dyspepsia, and back pain, developed a colonic abscess on Day 382 of treatment with 12 mg of deuruxolitinib. At the time of the event, the subject also reported Grade 2 (moderate) constipation, and Grade 2 (moderate) diverticulum. The event was considered in the AESI category of GI perforation. The investigator assessed the event as not related to the drug. No action was taken with the drug. No further details are provided in the narrative.

Both subjects with GI perforation had other risk factors for this AE which confounded the assessment of causality (e.g., history of previous abdominal surgery and diverticular disease). In addition, the subjects continued to receive deuruxolitinib after the diagnosis of gastrointestinal perforation and reported no further similar AEs. However, since gastrointestinal perforation is a

known risk with JAK inhibitors and the two gastrointestinal perforation events occurred while the subjects were actively receiving treatment with deuruxolitinib, the review team could not definitively exclude an association of gastrointestinal perforations with exposure to the drug and the events are considered possibly related. Therefore, "Gastrointestinal perforations" will be included in Section 5 of labeling.

8.3.4.7. Suicidal Ideation and Behavior, Depression and Anxiety

Suicidal Ideation and Behavior

There was one death by suicide in the development program. (Discussed in Section 8.3.3 of this review). The subject was a 34-year-old male ([redacted] (b) (6)) with a history of deficit hyperactivity disorder who died of suicide two weeks after discontinuing deuruxolitinib 8 mg. The subject received deuruxolitinib twice daily for approximately 30 weeks. Both the Applicant and the FDA psychiatry consultant considered this SAE as not related to the use of study drug. Potential contributing factors to the suicide as documented in the autopsy report were an ongoing lawsuit, paranoia, and relationship issues. In addition, the subject expressed dissatisfaction with his response to treatment with deuruxolitinib.

The AE data did not support an association of drug exposure with the development of suicidal ideation and behavior. The psychiatry review concluded "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." However, there was no active assessment for suicidal ideation and behavior using an appropriate prespecified scale (e.g., C-SSRS).

Depression and Anxiety

Because of the elevated risk of depression and anxiety among patients with alopecia areata, the safety monitoring for the Phase 3 trials included an instrument to assess these psychiatric adverse events at every visit. As such, the review team consulted with the Division of Psychiatry to provide interpretation and analysis of the AE data related to psychiatric disorders and the results of the safety monitoring.

The study population enrolled in the 24- week controlled Phase 3 clinical trials excluded subjects with a "clinically significant" psychiatric disease. The OLE trials excluded subjects with any "psychiatric condition" that is "likely to unfavorably affect the risk-benefit of continued study participation, interfere with study compliance, or confound safety or efficacy assessments." This study population with limited psychiatric restrictions is likely to allow detection of any clinically meaningful signal related to anxiety and depression.

The protocols specified safety monitoring for anxiety and depression throughout the trials using the HADS. As described by the psychiatry reviewer, Dr. Zimri Yaseen, the HADS is a subject-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. Total scores range from 0 to 42.

There is no specified recall period and items appear to refer to a general current state (e.g., "Worrying thoughts go through my mind") (Psychiatry Review dated March 22, 2024, by Dr. Zimri Yaseen).

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." (Bjelland et al. 2002) The psychiatry reviewer states "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." According to Lemay et al., "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 (Lemay et al. 2019).

The review team conducted an analysis of the mean and mean change from baseline in HADS total score for all subjects in the placebo-controlled trials from Weeks 0 to 24. The psychiatry reviewer stated that "The review of HADS data from the registration trials did not indicate any negative effect of CTP-543 (deuruxolitinib) on mood as assessed by the HADS."

In addition, the review team performed custom MedDRA queries to capture pertinent treatment emergent AE related to depression and anxiety. This analysis did not reveal any significant imbalances between treatment groups. The psychiatry reviewer stated that "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."

8.3.4.8. Liver Enzyme Elevations

Hepatotoxicity is a labeled class effect of JAK inhibitors. Warnings regarding the potential for "elevated liver enzymes" are included in Section 5 (Warnings and Precautions, Laboratory Abnormalities) and Section 6 (Adverse Reactions) of labeling for JAK inhibitors indicated for the treatment of chronic inflammatory conditions. In the deuruxolitinib development program, the Applicant identified DILI as an AESI.

The review team consulted with the Drug-induced Liver Injury Team from the Division of Hepatology and Nutrition to review the narrative summaries for subjects with elevated liver enzymes, potential DILI cases, and potential Temple's Corollary cases. The DILI team provided a causality assessment and recommendations for language to be included in labeling. The review team, in consultation with the DILI team, evaluated the available information regarding hepatotoxicity associated with JAK inhibitor use, performed additional analyses of changes in liver analytes and reviewed relevant narratives.

One additional analysis was an examination of the shift in liver analytes by treatment arm. In the Week 0-24 placebo-controlled period, elevations in aminotransaminases (AT; ALT or AST) occurred more frequently in the deuruxolitinib arms compared to placebo arm. However, the elevations were typically mild, the rates were low, and the elevations in aminotransaminases were not observed with concurrent elevations in total bilirubin (i.e., no potential Hy's Law

cases). The differences in Ats elevations compared to placebo were driven by AST elevations. In the open-label long-term extension period, while elevations in bilirubin of >2x upper limit of normal (ULN) occurred, none were associated with AT levels >3x ULN. Therefore, none had the potential to fulfill Hy's law.

There were no cases of jaundice or other signs or symptoms of hepatotoxicity associated with AT elevations. Case level analyses of narrative summaries and laboratory data suggest the AT elevation imbalance was due to concurrent myopathy (high CPK levels with concurrent AT increases), not DILI (refer to the DNR review by Dr. Eileen Navarro Almario and Dr. Paul Hayashi dated April 15, 2024).

The DILI team concluded that deuruxolitinib does not appear to be associated with an increased risk of DILI based on the safety data to date. Therefore, the review team does not propose to include language in labeling related to hepatotoxicity or liver enzyme elevations in Sections 5 or 6.

However, the protocols excluded subjects with positive screening results for hepatitis B surface antigens (HbsAg), antibodies to hepatitis B core antigens (anti-HBc), or hepatitis C virus (HCV) with detectable HCV RNA. Therefore, the impact of the drug on viral hepatitis is not known. The DILI team proposed that Section 5 of labeling include a statement that deuruxolitinib should not recommended for use in patients with active hepatitis B or hepatitis C (HCV RNA detected). The labeling recommendations are as follows:

"2.1 Recommended Evaluations and Immunizations Prior to and During Treatment

- Viral hepatitis screening in accordance with clinical guidelines: LEQSELVI treatment is not recommended in patients with active hepatitis B or hepatitis C.
- Screen for hepatitis B infection before treatment with LEQSELVI; if hepatitis B infection is discovered, follow hepatitis B clinical guidelines, or refer to a liver specialist. Monitor patients for reactivation in accordance with clinical guidelines during treatment. [*see Warnings and Precautions (5.1)*].

5.1 Serious Infections

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) were reported in clinical trials with LEQSELVI *[see Adverse Reactions (6.1)].* If a patient develops herpes zoster, consider interrupting LEQSELVI treatment until the episode resolves.

The impact of LEQSELVI on chronic viral hepatitis reactivation is unknown. Subjects with positive results for hepatitis B surface antigens (HbsAg), antibodies to hepatitis B core antigens (anti-HBc), or HCV with detectable HCV RNA at screening were excluded from LEQSELVI clinical trials. Perform screening for viral hepatitis before treatment with LEQSELVI. LEQSELVI is not recommended for use in patients with active hepatitis B or hepatitis C (HCV RNA detected).

If non-active hepatitis B infection is discovered, monitoring for reactivation or prophylactic treatment is recommended. Follow hepatitis B clinical guidelines or refer to a liver specialist."

8.3.4.9. Elevated Creatine Phosphokinase

The Applicant designated CPK elevation as an AESI because there are reports of both asymptomatic and symptomatic CPK elevations in subjects who have received JAK inhibitors for a variety of inflammatory disorders (e.g., atopic dermatitis, rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis). While neuromuscular causes maybe most likely, increases in CPK may occur in association with many other conditions (endocrine disorders, connective tissue diseases, cardiac and renal disease, viral diseases, pregnancy, celiac disease medications, metabolic disease, and surgery.) (Moghadam-Kia et al. 2016). Although CPK increases can be indicative of muscle damage, there do not appear to be other indicators of muscle pathology associated with JAK inhibitors, suggesting that there may be another mechanism behind the increased CPK levels. The exact mechanism of elevated CPK is unknown, though some studies suggest the increase in serum CPK upon treatment with JAK inhibitors may represent recovery of muscle development via reversal of inflammation-associated inhibition of myoblast differentiation (Queeney et al. 2019).

In the deuruxolitinib development program, there was an imbalance in the incidence of elevated CPK in the active groups compared with the placebo group. Many of these cases were associated with strenuous exercise and were transient. In the placebo-controlled safety pool (Week 0-24) for the deuruxolitinib development program, elevated CPK was reported in 7/299 (2.2%) of subjects who received placebo, 35/640 (5.3%) of subjects who received deuruxolitinib 8 mg BID, and 27/380 (7.4%) of subjects who received deuruxolitinib 12 mg BID. In the Week 0-52 long-term exposure safety pool, elevated CPK was reported in 49/868 (5.6%) of subjects who received deuruxolitinib 8 mg BID, and 46/991 (4.6%) of subjects who received deuruxolitinib 12 mg BID. In addition, mean changes from baseline in CPK levels at Week 24 were greater in the active groups (+43 U/L for subjects who received 8 mg BID and +74 U/L for subjects who received 12 mg BID) than for subjects who received placebo (-35 U/L). CPK levels appeared to increase in the first 4 weeks of treatment and then plateau for subjects who received either dose of deuruxolitinib. For subjects who received placebo, CPK levels generally remained stable.

The review team noted similar findings in the analysis of shift tables. The number of subjects who shifted from Grade 0 at baseline to Grade 4 (>10 x ULN) at Week 24 was higher in the deuruxolitinib groups (13/640, 2.3% of subjects who received 8 mg BID, and 7/380, 2.1% of subjects who received 12 mg BID) compared to placebo group (2/299, 0.8% of subjects who received placebo). In the OLE safety pool, there were similar shift rates from Grade 0 at baseline to Grade 4 after >52 weeks (10/460 [2.5%] of subjects who remained on 8 mg BID, and 17/678 [2.9%] of subjects who remained on 12 mg BID).

The Applicant and review team investigated whether subjects with elevations of CPK were identified in the rhabdomyolysis/myopathy SMQ (narrow scope, MedDRA v23.1). Preferred terms in this SMQ include the following: Muscle necrosis, Myoglobin blood increased,

Myoglobin blood present, Myoglobin urine present, Myoglobinaemia, Myoglobinuria, Myopathy, Myopathy toxic, Necrotizing myositis, Rhabdomyolysis, and Thyrotoxic myopathy. No subjects reported TEAEs from the Rhabdomyolysis/myopathy SMQ.

As discussed in Section 8.3.3, "Blood creatine phosphokinase increased" will be included in Section 6.1 of labeling.

Creatine Phosphokinase Elevations

During the 24-week treatment period, CPK elevations were reported in 7 subjects (5.4 per 100 subject -years) treated with placebo, 35 subjects (12.9 per 100 subject -years) treated with LEQSELVI 8 mg twice daily and 27 subjects (16.6 per 100 subject -years) treated with deuruxolitinib 12 mg twice daily. During the 0–52-week period, CPK elevations were reported in 49 subjects (7.6 per 100 subject -years) treated with LEQSELVI 8 mg twice daily and 46 subjects (6.1 per 100 subject -years) treated with deuruxolitinib 12 mg twice daily.

8.3.4.10. Hematologic Abnormalities

Erythropoietin, granulocyte colony-stimulating factor, and granulocyte-macrophage colony stimulating factor are modulated by JAK2 signaling. Therefore, inhibition of JAK2 may result in reduced production of erythrocytes and leukocytes (Brizzi et al. 1996). Neutropenia, lymphopenia, and anemia are known risks associated with treatment with other JAK inhibitors.

During this development program, the Applicant monitored hematologic parameters periodically. The review team conducted analyses of abnormalities in hematologic parameters for the 24-week placebo- controlled period as well as the long-term safety population through Week 52, including analyses of shift tables from baseline NCI-CTCAE grades to worst postbaseline NCI-CTCAE grades. Results of these analyses are discussed below.

Leukopenia

As discussed in Section 8.3.3 of this review, leukopenia (consisting of the pooled preferred terms neutropenia, white blood cell count decreased, neutrophil count decreased, lymphopenia, and leukopenia) will be included as an AR in Section 6.1 of labeling.

During the 24-week placebo-controlled period, leukopenia of any NCI-CTCAE grade was generally reported more frequently in the deuruxolitinib 8-mg and 12-mg groups than in the placebo group. The proportion of subjects with leukopenia of NCI-CTCAE Grade 1 was similar for deuruxolitinib 8 mg BID and 12 mg BID. The proportion of subjects with leukopenia of NCI-CTCAE Grade 2 and 3 was higher for deuruxolitinib 12 mb BID compared to 8 mg BID. No subjects experienced Grade 4 leukopenia in the 24-week placebo-controlled period.

From Week 0-52 in the long-term exposure safety pool (in which there was no placebo arm comparator), the proportion of subjects with leukopenia of NCI-CTCAE Grade 1 was similar for deuruxolitinib 8 mg and 12 mg. The proportion of subjects with leukopenia of NCI-CTCAE Grade

2 and 3 was higher for deuruxolitinib 12 mg BID compared to 8 mg BID. No subjects experienced Grade 4 leukopenia in the Week 0-52 period.

Incidence and exposure-adjusted incidence rates of treatment-emergent adverse events by NCI-CTCAE grade for leukopenia for the 24-week placebo-controlled period and the Week 0-52 period is presented below.

Table 53. Leukopenia by CTCAE Grade

Leukopenia by CTCAE Grade 24-Week placebo-controlled period CTCAE Grade	Placebo n(%) [EAIR] (N = 299)	DEURUX 8 mg BID n(%) [EAIR] (N = 640)	DEURUX 12 mg BID n(%) [EAIR](N = 380)
Grade 1 (<LLN - 3.0 x 10^9/L)	4 (1.0) [3.0*]	14 (2.0) [5.1*]	9 (2.5) [5.4*]
Grade 2 (<3.0 - 2.0 x 10^9/L)	1 (0.3) [0.8*]	2 (0.3) [0.7*]	6 (1.7) [3.6*]
Grade 3 (<2.0 - 1.0 x 10^9/L)	0	1 (0.2) [0.4*]	6 (1.7) [3.6*]
Grade 4 (<1.0 x 10^9/L)	0	0	0
Week 0-52 long term exposure safety pool CTCAE Grade	**Placebo n(%) [EAIR] (N = 0)**	**DEURUX 8 mg BID n(%) [EAIR] (N = 868)**	**DEURUX 12 mg BID n(%) [EAIR] (N = 991)**
Grade 1 (<LLN - 3.0 x 10^9/L)	N/A	16 (1.8) [2.4*]	14 (1.4) [2.1*]
Grade 2 (<3.0 - 2.0 x 10^9/L)	N/A	3 (0.3) [0.5*]	7 (0.7) [1.0*]
Grade 3 (<2.0 - 1.0 x 10^9/L)	N/A	1 (0.1) [0.2*]	7 (0.7) [1.0*]
Grade 4 (<1.0 x 10^9/L)	N/A	0	0

n = number of subjects with event; N = number of subjects in the analysis
BID = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; N/A = not applicable
* Unadjusted EAIR, which equals 100 * incidence / (sum of the individual risk-times in years)
NOTE: Adverse events are coded according to MedDRA version 23.1.
NOTE: Percentages for the placebo-controlled pool are adjusted for study size. Adjusted EAIRs come from a Poisson regression model with study and treatment as explanatory variables and are reported if estimable. Unadjusted EAIRs are reported if the model fails to converge or provide meaningful results.
NOTE: Subjects are only counted once at the subject's maximum grade.
NOTE: Leukopenia is a grouped preferred term consisting of the following preferred terms: Neutropenia, White blood cell count decreased, Neutrophil count decreased, Lymphopenia, Leukopenia.

Source: Applicant's response to information request dated March 13, 2024 (SDN 28)

As discussed in Section 8.3.4.5, no serious infections were associated with leukopenia. EAIRs for leukopenia through Week 52 were not increased compared to the 24-week placebo-controlled period.

Neutropenia

During the 24-week placebo-controlled period, the proportion of subjects with neutropenia of NCI-CTCAE Grade 1 was higher for deuruxolitinib 8 mg BID compared to placebo and 12 mg BID. The proportion of subjects with neutropenia of NCI-CTCAE Grade 2 and Grade 3 was higher for deuruxolitinib 12 mg BID compared to placebo and 8 mg BID. No subjects experienced Grade 4 neutropenia in the 24-week placebo-controlled period.

From Week 0-52 in the long-term exposure safety pool, there was no clear dose response in the proportion of subjects with leukopenia of NCI-CTCAE Grade 1, Grade 2, or Grade 3 for deuruxolitinib 8 mg BID and 12 mg BID. No subjects experienced Grade 4 neutropenia in the Week 0-52 period. Incidence and exposure-adjusted incidence rates of treatment-emergent

adverse events by NCI-CTCAE grade for neutropenia for the 24-week placebo-controlled period and the Week 0-52 period is presented below is presented below.

Table 54. Neutropenia by CTCAE Grade

Neutropenia by CTCAE Grade

24-Week placebo-controlled period CTCAE Grade	Placebo n(%) [EAIR] (N = 299)	DEURUX 8 mg BID n(%) [EAIR] (N = 640)	DEURUX 12 mg BID n(%) [EAIR](N = 380)
Grade 1 (<LLN - 1.5 x 10^9/L)	2 (0.4) [1.5*]	8 (1.1) [2.9*]	2 (0.6) [1.2*]
Grade 2 (<1.5 - 1.0 x 10^9/L)	1 (0.3) [0.8*]	1 (0.2) [0.4*]	2 (0.6) [1.2*]
Grade 3 (<1.0 - 0.5 x 10^9/L)	0	1 (0.2) [0.4*]	6 (1.7) [3.6*]
Grade 4 (<0.5 x 10^9/L)	0	0	0
Week 0-52 long term exposure safety pool CTCAE Grade	**Placebo n(%) [EAIR] (N = 0)**	**DEURUX 8 mg BID n(%) [EAIR] (N = 868)**	**DEURUX 12 mg BID n(%) [EAIR] (N = 991)**
Grade 1 (<LLN - 1.5 x 10^9/L)	N/A	9 (1.0) [1.4*]	7 (0.7) [1.0*]
Grade 2 (<1.5 - 1.0 x 10^9/L)	N/A	1 (0.1) [0.2*]	2 (0.2) [0.3*]
Grade 3 (<1.0 - 0.5 x 10^9/L)	N/A	1 (0.1) [0.2*]	6 (0.6) [0.9*]
Grade 4 (<0.5 x 10^9/L)	N/A	0	0

n = number of subjects with event; N = number of subjects in the analysis
BID = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; N/A = not applicable
* Unadjusted EAIR, which equals 100 * incidence / (sum of the individual risk-times in years)
NOTE: Adverse events are coded according to MedDRA version 23.1.
NOTE: Percentages for the placebo-controlled pool are adjusted for study size. Adjusted EAIRs come from a Poisson regression model with study and treatment as explanatory variables and are reported if estimable. Unadjusted EAIRs are reported if the model fails to converge or provide meaningful results.
NOTE: Subjects are only counted once at the subject's maximum grade.
NOTE: Neutropenia is a grouped preferred term consisting of the following preferred terms: Neutropenia, Neutrophil count decreased.

Source: Applicant's response to information request dated March 13, 2024 (SDN 28)

As discussed in Section 8.3.4.5, no serious infections were associated with neutropenia. There were no events of Grade 4 neutropenia. In the Week 0-24 period, neutropenia led to treatment discontinuation in one subject (0.2%) on placebo, one subject (0.2%) on 8 mg BID, and two subjects (0.6%) on 12 mg BID.

Lymphopenia

During the 24-week placebo-controlled period, lymphopenia of Grade 1 severity was reported more frequently in the deuruxolitinib 12-mg BID group compared to placebo. During this period lymphopenia of Grade 2 severity was reported more frequently in the deuruxolitinib 8-mg bid and 12-mg BID group compared to placebo. There were no events of Grade 3 or Grade 4 lymphopenia.

From Week 0-52 in the long-term exposure safety pool the proportion of subjects with lymphopenia of NCI-CTCAE Grade 1, Grade 2, and Grade 3 was higher for deuruxolitinib 12 mg BID compared to 8 mg BID. No subjects experienced grade 4 leukopenia in the Week 0-52 period. Incidence and exposure-adjusted incidence rates of TEAEs by NCI-CTCAE grade for lymphopenia for the 24-week placebo-controlled period and the Week 0-52 period is presented below is presented below.

Table 55. Lymphopenia by CTCAE Grade

Lymphopenia by CTCAE Grade 24-Week placebo-controlled period CTCAE Grade	Placebo n(%) [EAIR] (N = 299)	DEURUX 8 mg BID n(%) [EAIR] (N = 640)	DEURUX 12 mg BID n(%) [EAIR](N = 380)
Grade 1 (<LLN - 0.8 x 10^9/L)	2 (0.6) [1.5*]	1 (0.2) [0.4*]	3 (0.8) [1.8*]
Grade 2 (<0.8 - 0.5 x 10^9/L)	0	1 (0.2) [0.4*]	4 (1.2) [2.4*]
Grade 3 (<0.5 - 0.2 x 10^9/L)	0	0	0
Grade 4 (<0.2 x 10^9/L)	0	0	0
Week 0-52 long term exposure safety pool CTCAE Grade	**Placebo n(%) [EAIR] (N = 0)**	**DEURUX 8 mg BID n(%) [EAIR] (N = 868)**	**DEURUX 12 mg BID n(%) [EAIR] (N = 991)**
Grade 1 (<LLN - 0.8 x 10^9/L)	N/A	3 (0.3) [0.5*]	5 (0.5) [0.7*]
Grade 2 (<0.8 - 0.5 x 10^9/L)	N/A	1 (0.1) [0.2*]	4 (0.4) [0.6*]
Grade 3 (<0.5 - 0.2 x 10^9/L)	N/A	0	1 (0.1) [0.1*]
Grade 4 (<0.2 x 10^9/L)	N/A	0	0

n = number of subjects with event; N = number of subjects in the analysis
BID = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; N/A = not applicable
* Unadjusted EAIR, which equals 100 * incidence / (sum of the individual risk-times in years)
NOTE: Adverse events are coded according to MedDRA version 23.1.
NOTE: Percentages for the placebo-controlled pool are adjusted for study size. Adjusted EAIRs come from a Poisson regression model with study and treatment as explanatory variables and are reported if estimable. Unadjusted EAIRs are reported if the model fails to converge or provide meaningful results.
NOTE: Subjects are only counted once at the subject's maximum grade.
NOTE: Lymphopenia is a grouped preferred term consisting of the following preferred terms: Lymphopenia, Lymphocyte count decreased.

Source: Applicant's response to information request dated March 13, 2024 (SDN 28)

Anemia

As discussed in Section 8.3.3 of this review, anemia (consisting of the pooled preferred terms anaemia, haematocrit decreased, haemoglobin decreased, and red blood cell count decreased) is proposed for inclusion as an AR in Section 6.1 of labeling.

During the 24-week placebo-controlled period, anemia of Grade 1 and Grade 2 was reported more frequently in the deuruxolitinib groups compared to placebo. There were no events of Grade 3 or Grade 4 anemia.

Mean hemoglobin levels (and, correspondingly, hematocrit and red blood cell [RBC] count) initially decreased for subjects who received deuruxolitinib 12 mg BID or deuruxolitinib 8 mg BID and then plateaued by about Week 12 (mean change from baseline at Week 12 for hemoglobin: -0.9 g/dL for total deuruxolitinib [-0.7 g/dL for 8 mg BID and -1.1 g/dL for 12 mg BID]. Placebo subjects did not develop a decrease (-0.1 g/dL mean change from baseline at Week 12).

From Week 0-52 in the long-term exposure safety pool, the proportion of subjects with anemia of NCI-CTCAE Grade 1 was higher for deuruxolitinib 12 mg BID compared to 8 mg BID. No subjects experienced Grade 3 or 4 anemia in the Week 0-52 period. Incidence and exposure-adjusted incidence rates of treatment-emergent adverse events by NCI-CTCAE grade for anemia for the 24-week placebo-controlled period and the Week 0-52 period is presented below.

Table 56. Anemia by CTCAE Grade

Anemia by CTCAE Grade 24-Week placebo-controlled period CTCAE Grade	Placebo n(%) [EAIR] (N = 299)	DEURUX 8 mg BID n(%) [EAIR] (N = 640)	DEURUX 12 mg BID n(%) [EAIR](N = 380)
Grade 1 (<LLN - 10.0 g/dL)	3 (1.0) [3.5]	14 (2.0) [9.4]	15 (3.1) [16.4]
Grade 2 (<10.0 - 8.0 g/dL)	0	4 (0.6) [1.4*]	1 (0.2) [0.6*]
Grade 3 (<8.0 g/dL, transfusion indicated)	0	0	0
Grade 4 (life threatening, urgent action needed)	0	0	0
Week 0-52 long term exposure safety pool CTCAE Grade	**Placebo n(%) [EAIR] (N = 0)**	**DEURUX 8 mg BID n(%) [EAIR] (N = 868)**	**DEURUX 12 mg BID n(%) [EAIR] (N = 991)**
Grade 1 (<LLN - 10.0 g/dL)	N/A	12 (1.4) [1.8*]	30 (3.0) [4.5*]
Grade 2 (<10.0 - 8.0 g/dL)	N/A	5 (0.6) [0.8*]	6 (0.6) [0.9*]
Grade 3 (<8.0 g/dL, transfusion indicated)	N/A	0	0
Grade 4 (life threatening, urgent action needed)	N/A	0	0

n = number of subjects with event; N = number of subjects in the analysis
BID = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; N/A = not applicable
* Unadjusted EAIR, which equals 100 * incidence / (sum of the individual risk-times in years)
NOTE: Adverse events are coded according to MedDRA version 23.1.
NOTE: Percentages for the placebo-controlled pool are adjusted for study size. Adjusted EAIRs come from a Poisson regression model with study and treatment as explanatory variables and are reported if estimable. Unadjusted EAIRs are reported if the model fails to converge or provide meaningful results.
NOTE: Subjects are only counted once at the subject's maximum grade.
NOTE: Anemia is a grouped preferred term consisting of the following preferred terms: Anaemia, Haematocrit decreased, Haemoglobin decreased, Red blood cell count decreased.

Source: Applicant's response to information request dated March 13, 2024 (SDN 28)

In the Week 0-24 period, anemia led to treatment discontinuation in no subjects in placebo, two subjects (0.3%) on 8 mg BID, and two subjects (0.6%) on 12 mg BID.

Summary and Conclusion

No unexpected or unique safety concerns were identified in the hematologic laboratory findings given mechanism of action of deuruxolitinib as a JAK inhibitor.

Anemia, neutropenia, and leukopenia were reported more commonly in the deuruxolitinib 8-mg BID dose compared to placebo in the 24-week placebo-controlled period. Anemia, neutropenia, leukopenia, and lymphopenia were reported more commonly in the deuruxolitinib 12-mg dose compared to placebo in the 24-week placebo-controlled period. There were adverse event reports of neutropenia, and anemia that led to treatment discontinuation.

A possible dose response is apparent in the 24-week placebo period for leukopenia and lymphopenia but to a lesser degree in the 0–52-week period. A dose response for anemia is less apparent. No evidence of a dose response is apparent for neutropenia.

As discussed in Section 8.3.3 of this review, neutropenia, lymphopenia, and anemia are proposed for inclusion in Section 6.1 (Adverse Reactions) of labeling. In addition, safety monitoring will be proposed for Section 5 Laboratory Abnormalities to add the statement "Perform a CBC prior to and periodically during treatment with LEQSELVI [see Dosage and Administration (2.1)]. (b) (4) ."

8.3.4.11. Hyperlipidemia

Hyperlipidemia is a known risk associated with the class of JAK inhibitors. During the clinical trials, the Applicant evaluated lipid profiles periodically and designated lipid elevations as an AESI. In the 24-week placebo-controlled period, mean (SD) change from Baseline to Week 24 for lipid parameters are displayed below.

Table 57. Mean (SD) Change From Baseline to Week 24, Lipid Parameters

Parameter	Placebo (N = 299) mean (SD)	DEURUX 8 mg BID (N = 640) mean (SD)	DEURUX 12 mg BID (N = 380) mean (SD)
Cholesterol (mg/dL)	-2.1 (25.16)	16.4 (27.89)	21.3 (28.33)
HDL Cholesterol (mg/dL)	0.6 (9.39)	8.0 (10.99)	8.5 (11.20)
LDL Cholesterol (mg/dL)	-1.6 (20.56)	9.1 (24.29)	12.8 (25.27)
LDL/HDL ratio	-0.06 (0.487)	-0.11 (0.687)	-0.02 (0.571)
Triglycerides (mg/dL)	-4.4 (57.45)	-3.8 (56.42)	0.4 (58.15)

Source: Applicant response to information request dated March 18, 2024 (SDN 29)

Compared with subjects who received placebo, subjects who received deuruxolitinib developed increases in mean total cholesterol, LDL cholesterol and HDL cholesterol. Total cholesterol and LDL cholesterol decreased for subjects who received placebo and increased for subjects who received deuruxolitinib 8 mg BID or deuruxolitinib 12 mg BID. HDL cholesterol was stable for placebo subjects and increased for subjects who received deuruxolitinib at either dose. The LDL/HDL ratio was stable for all treatment groups. Triglycerides decreased slightly for subjects who received placebo or deuruxolitinib 8 mg BID; triglycerides appeared stable for subjects who received deuruxolitinib 12 mg BID.

Analyses of shift tables revealed no apparent clinically significant dose-related change in total cholesterol, triglycerides, LDL cholesterol or HDL cholesterol in either the placebo-controlled safety pool or in the 0-52 long-term exposure pool.

For total cholesterol, HDL cholesterol, and LDL cholesterol, the values tended to increase during the first 4 weeks of the trials and plateau at 8 weeks with some expected fluctuations throughout the trial period.

For the Week 0-24 placebo-controlled period, treatment emergent adverse reaction of hyperlipemia was reported in 7 subjects (2.3%, EAIR 5.4) who received placebo, in 22 subjects (3.3%, EAIR 8.0) who received 8 mg, and in 16 subjects (4.4%, EAIR 9.6) who received 12 mg. For the Week 0-52 safety pool, hyperlipemia was reported in 36 subjects (4.1%, EAIR 4.4) who received 8 mg, and in 55 subjects (5.4%, EAIR 6.9) who received 12 mg. (Refer to Table 50).

As discussed in Section 8.3.4.1 MACE of this review, there were no events of MACE in the deuruxolitinib development program. Therefore, at this time, a correlation between

deuruxolitinib associated hyperlipidemia and increased cardiovascular risk cannot be determined.

The potential for hyperlipidemia will be included in two sections of deuruxolitinib labeling: Section 6.1 (Adverse Reactions) as a pooled term including blood cholesterol increased, low density lipoprotein increased, blood triglycerides increased, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, and dyslipidemia and in Section 5 Laboratory Abnormalities. The healthcare provider will be instructed to "Perform assessment of lipid parameters at baseline and periodically during treatment with LEQSELVI. Manage patients according to clinical guidelines for hyperlipidemia." Refer to Section 8.3.3 of this review.

8.3.4.12. Thrombocytosis

Because thrombocytosis is a known risk associated with treatment with JAK inhibitors, the Applicant evaluated thrombocytosis (PTs of "Thrombocytosis", "Secondary thrombocytosis", "Essential thrombocythaemia" or "Platelet count increased") as an AESI.

During the placebo-controlled period Week 0-24, treatment-emergent thrombocytosis was reported in 0/299 (0%) of subjects treated with placebo, 18/640 (2.7%) of subjects treated with deuruxolitinib 8 mg, and 6/380 (1.6%) of subjects treated with deuruxolitinib 12 mg.

Mean platelet count increased while mean platelet volumes correspondingly decreased in subjects who received either dose of deuruxolitinib. The increase in platelet count and decrease in platelet volume was seen at Week 2. Levels plateaued by Weeks 12 to 16. The mean change from baseline at Week 16 for platelet count was 71.2 $x10^9$/L for the deuruxolitinib 8-mg group and 89.3 $x10^9$/L for the deuruxolitinib 12 mg group; the mean platelet volume was -0.3 fL for the deuruxolitinib 8-mg group and -0.6 fL for the deuruxolitinib 12 mg group. The placebo group did not show changes over time in platelet count or platelet volume (mean change from baseline at Week 16 of -0.5 $x10^9$/L and 0 fL, respectively).

As discussed in Section 8.3.4.2 of this review, there was no clear relationship between platelet count elevations and thrombotic events. There were no TEAEs of bleeding, bruising, or clotting abnormalities associated with abnormal platelet count reported in any of the placebo-controlled trials.

As discussed in Section 8.3.3 of this review, thrombocytosis will be included in Section 6.1 (Adverse Reactions) of labeling.

8.3.4.13. Increased Risk of Higher Plasma Concentrations in CYP2C9 Poor Metabolizers and Patients on Concomitant Moderate or Strong CYP2C9 Inhibitors

During the course of the review, the clinical pharmacology team identified a clinically significant difference in the PK of deuruxolitinib when coadministered with multiple doses of fluconazole (a dual CYP3A4 and CYP2C9 moderate inhibitor) and sulphaphenazole (a strong CYP2C9

inhibitor), resulting in increased deuruxolitinib total exposure greater than 2 and 3-fold respectively. In addition, based on the simulations using PBPK modeling, total exposure to deuruxolitinib in the CYP2C9 poor metabolizers is estimated to be increased to 2-fold when compared to CYP2C9 normal metabolizers. (Refer to Section 6.2.1 and 6.3.2 of this review).

The importance of the clinical pharmacology findings is related to the safety profile of the drug. Thrombosis is a key safety signal that was identified only in subjects who received deuruxolitinib 12 mg. (Refer to Section 8.3.4.2 of this review) Given the possible dose-response relationship of deuruxolitinib and the incidence of serious adverse reactions, an increase in the plasma concentration may substantially increase the risk of thrombosis and other SAEs. In the placebo-controlled clinical trials for deuruxolitinib, review of the data suggested a possible dose-response relationship for other adverse reactions. Between Weeks 0 to 24, a greater proportion of subjects who received deuruxolitinib 12 mg also developed the following adverse reactions compared to those who received deuruxolitinib 8 mg (Refer to Section 8.3.3 of this review):

- Neutropenia: 2.8% for 12 mg BID vs. 1.4% for 8 mg BID
- Anemia: 3.4% for 12 mg BID vs. 2.6% for 8 mg BID
- Skin and soft tissue infections: 4% for 12 mg BID vs. 1.6% for 8 mg BID

Therefore, there is a concern that increased plasma concentrations of deuruxolitinib due to the pharmacologic properties of the drug may result in an increased risk of serious adverse reactions. However, the protocols did not provide for PK sampling in all subjects; SAEs could not be correlated with increased exposure to deuruxolitinib in most cases. In a single subject who developed a thrombotic event ((b) (6)), PK at steady state is available (mean exposure [AUC] was 1740 ng*h/mL). Using the PopPK model predicted mean values, the exposure in this subject was 1.34-fold higher than the mean exposure after 12-mg BID dosing and 2-fold higher when compared to mean exposure after 8-mg BID dosing. But the extent of the clinical impact on the overall target population with AA is uncertain. According to the Applicant, the number of subjects receiving concomitant administration of moderate or strong CYP2C9 inhibitors during the clinical trials was limited. In addition, the proportion of the population with genetic variants of CYP2C9 conferring poor metabolizer status is small (<1-4%) and varies with race. A detailed discussion of the results of clinical pharmacology analyses in subjects who are CYP2C9 poor metabolizers and those who are receiving concomitant moderate or strong CYP2C9 inhibitors, the implications of those findings, and the information to be included in labeling is provided below.

Increased Risk of Higher Plasma Concentrations in CYCP2C9 Poor Metabolizers

Deuruxolitinib is a CYP2C9 substrate and is primarily metabolized by CYP2C9 (76%). Since CYP2C9 is the major metabolizing enzyme for deuruxolitinib, CYP2C9 activity is expected to be decreased in individuals with genetic variants such as CYP2C9*2 and CYP2C9*3 alleles (i.e., poor metabolizers). Such individuals are expected to have in higher plasma concentrations of deuruxolitinib (i.e., increased exposure-response and increased risk of serious adverse events).

Using PBPK modeling, the simulated mean AUC and maximum concentration (C_{max}) values following a single oral dose of deuruxolitinib in normal metabolizer subjects and CYP2C9*3*3 genotyped subjects (i.e., poor metabolizers) is estimated to be increased to 2-fold in CYP2C9 poor metabolizers compared to normal metabolizer subjects (Refer to Section 6.3.2).

Increased Risk of Higher Plasma Concentrations When Administered With Moderate or Strong CYP2C9 Inhibitors

When deuruxolitinib was co-administered with moderate or strong CYP2C9 inhibitors, AUC and C_{max} were increased greater than 2 and 3-fold, respectively.

Specifically,

1. Population pharmacokinetics (PopPK) model predicted geometric mean steady state AUC_{0-12} following 12 mg BID was 1300 ng*h/mL compared to 869 ng*h/mL for 8-mg BID regimens, representing an approximately 1.47-fold increase in AUC with a 1.50-fold increase in dose (PopPK modeling report: conc-pmx-ctp543-3280),
2. Clinically significant differences in the PK of deuruxolitinib were observed when coadministered with multiple doses of fluconazole (a dual moderate CYP3A4 and CYP2C9 inhibitor), resulting in increased deuruxolitinib total exposure by 140% and peak exposure by 21% relative to deuruxolitinib dose given alone (Clinical Study CP543.1015), and
3. Clinically significant differences in the PK of deuruxolitinib were observed when coadministered with multiple doses of sulphaphenazole (a strong CYP2C9 inhibitor), resulting in increased deuruxolitinib total exposure by greater than 200% and peak exposure by 25% relative to deuruxolitinib dose given alone (Refer to Section 6.2 of this review).

In the clinical trials that evaluated deuruxolitinib, concomitant use of CYP2C9 inhibitors was not excluded. In an analysis of 1223 randomized subjects in the Phase 3 trials, the Applicant identified 13 subjects who received a moderate CYP2C9 inhibitor as a concomitant medication: six subjects who received 8 mg, four subjects who received 12 mg, and three subjects who received placebo. No subjects received a strong CYP2C9 inhibitor. Moderate (i.e., amiodarone, fluconazole, metronidazole, phenylbutazone) or strong (i.e., sulphaphenazole) CYP2C9 inhibitors were identified using the Flockhart Table and from the literature (Flockhart et al. 2021). Indications for use of a concomitant moderate CYP2C9 inhibitor in these 13 subjects included yeast infections, rosacea, folliculitis, colitis, bacterial intestinal infection, and dental infection. The most utilized moderate CYP2C9 inhibitors were metronidazole and fluconazole. No new TEAEs were reported for these subjects during administration of concomitant administration of the CYP2C9 inhibitor.

One subject who developed a cerebral venous sinus thrombosis received one dose of fluconazole prior to the SAE. However, the subject reported headaches approximately 9 days prior to receiving fluconazole. (Refer to Section 8.3.4.2 of this review for subject narrative). Therefore, the contribution of the fluconazole to the SAE of thrombosis is unclear. None of the

subjects who developed a thrombosis on 12 mg were receiving concomitant moderate or strong CYP2C9 inhibitors at the time of thrombosis events.

Summary of Increased Risk of Higher Plasma Concentrations in CYP2C9 Poor Metabolizers and Patients on Concomitant Moderate or Strong CYP2C9 Inhibitors and Recommendations for Labeling

Deuruxolitinib is metabolized by CYP2C9 and the gene encoding CYP2C9 has polymorphisms that impact metabolic function. CYP2C9 poor metabolizers are individuals with two nonfunctional alleles, which results in no CYP2C9 enzyme activity (e.g., *3/3, *3/*11). CYP2C9 metabolizer status has a significant impact on deuruxolitinib metabolism and based on drug-drug interaction data, CYP2C9 poor metabolizers (e.g., *2/*3, *3/*3) are expected to have 2-fold higher concentrations of deuruxolitinib, when compared to normal metabolizers (Refer to Section 6.3 of this review).

Of note, there is currently no FDA approved companion diagnostic genotyping assay for CYP2C9 genotype determination, and there is no available PK data in subjects with specific CYP2C9 genotypes who received deuruxolitinib. Therefore, the FDA will require the Applicant to conduct a PK study in CYP2C9 normal metabolizers, intermediate metabolizers, and poor metabolizers. In addition, a PMC will be issued recommending that the Applicant agree to develop an in-vitro diagnostic device test to guide the use of deuruxolitinib in patients with severe AA. (Refer to Section 13 of this review and Center for Devices and Radiological Health review dated June 27, 2024).

Despite the lack of a currently available FDA approved companion diagnostic genotyping assay, there are other widely commercially available assays which prescribers can utilize to determine genotyping prior to initiating treatment with deuruxolitinib while awaiting development of an assay from the Applicant.

Labeling

To inform the prescriber of the increased risk of adverse events from higher plasma concentrations in CYCP2C9 poor metabolizers and patients on concomitant moderate or strong CYP2C9 inhibitors, the following risk mitigation measures are proposed for multiple sections of labeling:

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8.3.5. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

There were no patient-reported outcome assessments that evaluated safety parameters. Refer to Section 8.1.3 for COA analyses informing efficacy.

8.3.6. Safety Analyses by Demographic Subgroups

To assess potential drug-demographics interactions, the review team analyzed TEAEs for the placebo-controlled safety pool for the following subgroups: Sex at birth (male, female), age (<50 years and ≥50 years age), race (White, Black or African American, Asian, and Other), and ethnicity (Hispanic or Latino, not Hispanic or Latino). There were no clinically meaningful differences in the frequency of TEAEs by demographic subgroup after accounting for the individual subgroup sample size. TEAEs in the placebo-controlled safety pool with respect to sex, race, and ethnicity that occurred in ≥1% of subjects on active and greater than placebo are summarized below.

SUBGROUP ANALYSIS BY SEX

	Placebo		DEURUX 8 mg BID		DEURUX 12 mg BID	
	M (N = 100)	F (N = 199)	M (N = 226)	F (N = 414)	M (N = 138)	F (N = 242)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Severe infections	1 (1.1)	1 (0.5)	1 (0.4)	6 (1.4)	2 (1.5)	2 (0.6)
Herpes simplex	2 (2.0)	1 (0.5)	2 (0.9)	2 (0.9)	1 (0.7)	1 (0.7)
CPK increased	3 (2.9)	4 (1.8)	23 (9.9)	12 (2.8)	15 (10.8)	12 (5.4)
Thrombocytosis	0	0	3 (1.2)	15 (3.5)	1 (0.7)	5 (2.1)
Lymphopenia	1 (0.9)	1 (0.5)	0	2 (0.5)	2 (1.4)	5 (2.3)
Neutropenia	0	3 (1)	3 (1.2)	7 (1.5)	3 (2.2)	7 (3.2)
Lipid Elevation	5 (4.9)	5 (2.2)	10 (4.1)	20 (4.6)	8 (5.9)	10 (4.3)
Liver enzyme elevations	0	0	1 (0.4)	2 (0.5)	2 (1.0)	1 (0.4)

Source: Reviewer table adapted from ISS Post-text Table 4.3.1.3
M = Male, F = Female
NOTE: Percentages are adjusted for study size.

SUBGROUP ANALYSIS BY RACE

	Placebo				DEURUX 8 mg BID				DEURUX 12 mg BID			
	W	B/AA	A	O	W	B/AA	A	O	W	B/AA	A	O
	(N = 219)	(N = 31)	(N = 18)	(N = 10)	(N = 467)	(N = 63)	(N = 27)	(N = 30)	(N = 284)	(N = 36)	(N = 29)	(N = 8)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Severe infections	1 (0.5)	1 (2.6)	0	0	5 (1.0)	2 (3.2)	0	0	4 (1.2)	0	0	0
Herpes zoster	0	0	0	0	3 (0.6)	0	0	0	3 (1.1)	0	0	0
Herpes simplex	3 (1.4)	0	0	0	6 (1.3)	1 (1.5)	0	1 (3.4)	6 (2.2)	0	0	0
CPK increased	4 (1.8)	1 (2.3)	0	1 (12.5)	23 (4.8)	1 (1.6)	4 (14.8)	3 (10.3)	21 (7.6)	3 (8.5)	2 (6.8)	0
Thrombocytosis	0	0	0	0	12 (2.4)	1 (1.6)	0	2 (6.8)	5 (1.8)	0	0	1 (9.4)
Lymphopenia	2 (0.8)	0	0	0	2 (0.4)	0	0	0	7 (2.6)	0	0	0
Neutropenia	2 (0.7)	1 (2.3)	0	0	6 (1.2)	3 (3.5)	0	0	8 (3.0)	2 (4.7)	0	0
Lipid Elevation	7 (3.0)	1 (4.0)	0	0	27 (5.5)	2 (2.7)	0	0	14 (5.1)	0	0	1 (9.4)
Anemia	3 (1.4)	0	0	0	12 (2.3)	6 (8.6)	0	0	9 (2.3)	4 (10)	0	1 (9.4)
Liver enzyme elevations	0	0	0	0	2 (0.4)	0	0	1 (3.4)	2 (0.5)	0	1 (3.4)	0

Source: Reviewer table adapted from ISS Post-text Table 4.3.1.4
W = White, B/AA= Black or African American, A = Asian, O = other
NOTE: Percentages are adjusted for study size.

SUBGROUP ANALYSIS BY ETHNICITY

	Placebo		DEURUX 8 mg BID		DEURUX 12 mg BID	
	H/L* (N = 24)	N** (N = 254)	H/L (N = 57)	N (N = 525)	H/L (N = 25)	N (N = 332)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Severe infections	0	2 (0.8)	0	7 (1.3)	0	4 (1.1)
Herpes zoster	0	0	0	3 (0.6)	0	3 (1.0)
Herpes simplex	0	3 (1.2)	1 (1.7)	7 (1.3)	0	6 (1.8)
CPK increased	0	6 (2.2)	3 (5.1)	28 (5.2)	0	26 (8.1)
Thrombocytosis	0	0	2 (3.4)	13 (2.3)	0	6 (1.8)
Lymphopenia	0	2 (0.7)	1 (1.8)	1 (0.2)	0	7 (2.2)
Neutropenia	0	3 (0.8)	1 (1.8)	8 (1.3)	2 (9)	8 (2.5)
Lipid Elevation	1 (3.7)	7 (2.6)	1 (1.7)	28 (5.0)	1 (3.9)	14 (4.4)
Anemia	0	3 (1.2)	0	18 (3.1)	3 (6.4)	11 (2.7)

Source: Reviewer table adapted from ISS Post-text Table 4.3.1.5
*H/L = Hispanic or Latino, **N= Not Hispanic or Latino
NOTE: Percentages are adjusted for study size.

8.3.7. Specific Safety Studies/Clinical Trials

The thorough QT study and other pharmacokinetic trials to evaluate safety in subpopulations are discussed in Section 6.1 and 6.2 of this review.

The Applicant conducted no other specific trials to evaluate safety issues.

However, to address the FDA request to evaluate the durability of effect after drug discontinuation/ dose reduction and response after retreatment (potential for tachyphylaxis),

the Applicant submitted additional data from Part A of Trial CP543.2004. Part A of Trial CP543.2004 was a double-blind, randomized, two- arm, uncontrolled trial of deuruxolitinib 8 mg and 12 mg to evaluate maintenance of hair regrowth following dose reduction or discontinuation in 403 adult subjects with moderate to severe AA for up to 24 weeks. Part B was intended to evaluate response after retreatment over 24 weeks. Refer to Section 8.1.2 of this review for the data regarding the maintenance of SALT score ≤20 after 24 weeks with dose reduction (68-72%) or drug discontinuation (17-20%).

8.3.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct a dedicated trial to assess human carcinogenicity. The Applicant did conduct carcinogenicity studies in two animal species, rats and mice. These studies evaluated the carcinogenic potential of the test article, deuruxolitinib (CTP-543), when administered daily via oral gavage to rats for up to 104 weeks, and to mice for up to 26 weeks. The analysis did not show any statistically significant findings in tumor data for male and female mice or rats (Statistical Review and Evaluation of Carcinogenicity Studies by Dr. Hepei Chen dated January 30, 2024.) Refer to Sections 5.5.3 and 16.3.1 of this review for a description and analysis of the nonclinical data related to carcinogenicity.

Refer to Section 8.3.4.3 for a discussion of the malignancies reported by subjects who received deuruxolitinib in the clinical trials.

Human Reproduction and Pregnancy

In the development of language for Section 8 USE IN SPECIFIC POPULATIONS of labeling, the review team considered both the clinical data related to lactation and pregnancy outcomes and the nonclinical data related to embryofetal toxicity. The labeling in Section 8 for deuruxolitinib will reflect the greater systemic exposure to this drug compared to the formulations of ruxolitinib (oral and topical.) According to the nonclinical reviewer, when comparing the animal reproductive toxicity data for ruxolitinib and deuruxolitinib, the NOAELs identified in these studies were generally comparable, but the toxicity findings noted in doses higher than the NOAEL were generally more severe in the studies for deuruxolitinib. Therefore, the reviewers recommended a more conservative approach in labelling with consideration of family planning and contraception. Refer to Section 5.5.4.

The Applicant identified ten cases of females of childbearing potential who reported pregnancy during treatment with deuruxolitinib and one case of paternal exposure resulting in a healthy full-term baby to the unexposed female partner. The Maternal Health Team analyzed the pregnancy and lactation data from the Applicant and conducted a search of FDA Adverse Event Reporting System and comprehensive review of the literature for additional cases (Review by

Jane Liedtka, MD, Medical Officer, Maternal Health Team dated February 14, 2024). The Maternal Health Team review includes the following summary of the outcomes and cases:

"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."

Table 58. 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: MHT Table *Pregnancy occurred after cut-off date 11/21/22

Both the Applicant (May 14, 2023) and the Division of Pediatric and Maternal Health reviewer searched the medical literature for cases or information regarding deuruxolitinib exposure during pregnancy and lactation. Neither search identified any relevant publications. The reviewer commented:

> "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 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."

The Division of Pediatric and Maternal Health reviewer identified no relevant literature regarding deuruxolitinib and effects on reproduction. However, nonclinical data in rats demonstrate adverse effects on fertility in female animals at high multiples of the maximum recommended human dose (MRHD). Fertility studies in human are not available. The reviewer concludes, "At these high multiples it is reasonable not to include this in Section 8.3 as it is unlikely to be relevant."

Division of Pediatric and Maternal Health Provides the Following Labeling Recommendations:

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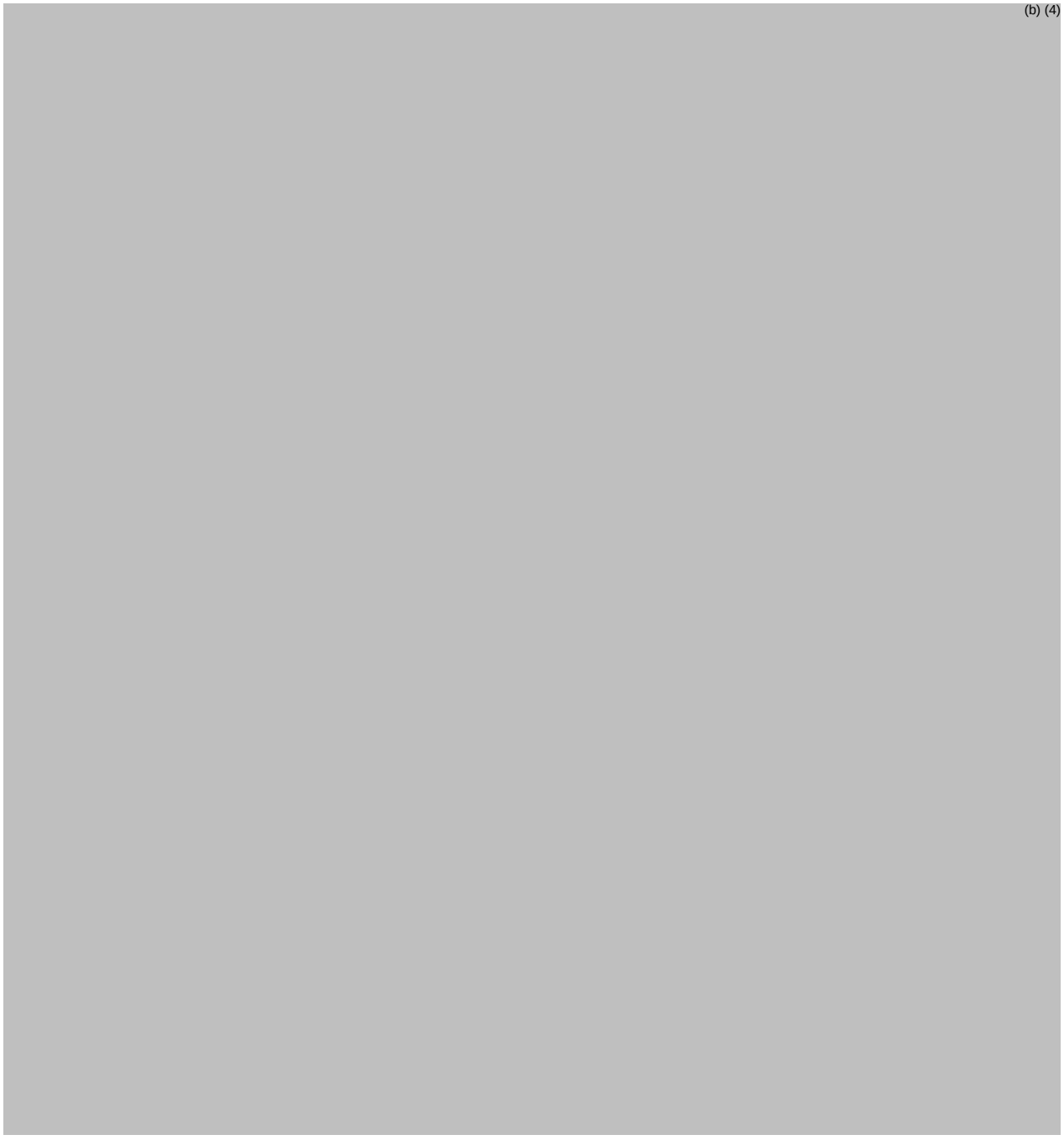

Division of Pediatric and Maternal Health Recommends the Following Postmarketing Requirements (PMRs):

- Conduct prospective pregnancy exposure registry cohort analyses in the U.S. 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 though 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, 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.

Review Team Conclusions

Alopecia areata occurs in females of reproductive potential and requires chronic dosing. Because exposures to deuruxolitinib during pregnancy are likely to occur and the available data are insufficient to characterize the associated risk in pregnant women, the FDA will require two postmarketing studies (PMRs): a Pregnancy Exposure Registry for collection of detailed patient information and a complementary study for more rapid collection of human data.

Labeling (Section 8.2 Lactation) informs the healthcare provider that deuruxolitinib is present in the milk of lactating female rats after exposure and that it is likely that the drug will be present in human milk. Labeling states, “Because of the potential for serious adverse reactions in nursing infants, advise women not to breastfeed during treatment with LEQSELVI and for one day after the last dose (approximately 5 to 6 elimination half-lives).” In view of the information in current labeling, the absence of a known threshold for adverse events, the absence of information on assay sensitivity, and the benefit risk of deuruxolitinib in this patient population, even negative data from a lactation study is unlikely to result in a recommendation for change in labeling regarding breastfeeding. Therefore, the FDA will not require the conduct of a lactation study.

Pediatrics and Assessment of Effects on Growth

During drug development, the Applicant did not evaluate the safety and efficacy of deuruxolitinib in the pediatric population. The product triggered the Pediatric Research Equity Act (2003) (21 U.S.C. 355c) as a new active ingredient. Per the Food and Drug Administration Safety and Innovation Act, the Applicant submitted an Initial Pediatric Study Plan (iPSP) on May 29, 2020 (Agreement Letter issued October 30, 2021). The Agreed iPSP (under IND 131423) provided for the following:

- In accordance with 21 CFR 314.55(c)(3)(ii), the Applicant planned to request a partial waiver of pediatric assessments for the population with AA from birth to <6 years old as necessary studies are impossible or highly impractical to conduct because the number of patients with moderate to severe AA in this age group is so small (Caldwell et al. 2017; Ali et al. 2022).
- In accordance with 21 CFR 314.55(b), the Applicant planned to request a deferral of pediatric assessments in the population ages ≥6 to ≤17 years. Specifically, the Applicant requested a deferral of assessments in the population ≥12 to ≤17 years old “until the data

from adults with AA have been submitted, reviewed and the benefit-risk has been determined", and a deferral of assessments in the population ≥6 to <12 years old with AA "until after a favorable benefit-risk has been demonstrated in adolescents with AA."

In addition, the Applicant also requested a deferral of a planned juvenile toxicology study (JTS) in rats, designed to support the clinical trials in subjects ≥6 to <12 years old. The Applicant proposed to conduct the JTS (7-Week toxicity study in juvenile animals with a 6-week recovery period) in parallel with the proposed clinical trial in adolescents. The assessments in the younger cohort (6 to <12 years old) would not be initiated until final results of the juvenile toxicology study are available.

The Division discussed the iPSP with Pediatric Review Committee (PeRC) on August 4, 2020. PeRC agreed with the recommendations from the Division regarding the proposed pediatric waiver and deferral. However, the PeRC initially argued that the nonclinical study should be completed prior to submission of the NDA and not deferred. However, PeRC ultimately agreed that the JTS could be conducted as a deferred study with an accelerated timeline. PeRC reviewed the final agreed iPSP on October 5, 2021, to ensure that the Applicant had fully addressed the additional comments regarding the accelerated timeline for the JTS. In the meeting minutes, PeRC "concurs with the plan to request partial waiver and deferral as outlined in the Agreed iPSP" (See Clinical Reviews under IND 131423 dated August 6, 2021, and October 15, 2024).

With this NDA submission, the Applicant provided the Agreed Initial Pediatric Study Plan and timelines. The Division discussed the pediatric study plan and the proposed postmarketing requirements (PMRs) with PeRC on July 9, 2024. Refer to Section 13 for a description of the required pediatric assessments under PREA.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no data to support an association of JAKi including deuruxolitinib with the potential for addiction, abuse, withdrawal or rebound. Therefore, the Applicant did not evaluate abuse potential. Although drug discontinuation effects were not formally assessed, no specific drug withdrawal or rebound effects have been observed in the clinical development program.

8.3.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

LEQSELVI is not marketed in any jurisdiction. Therefore, postmarketing safety data is not available.

Expectations on Safety in the Postmarket Setting

The comprehensive analysis of the deuruxolitinib safety data identified no new safety signals. However, drug-drug interaction studies and PBPK simulations showed that deuruxolitinib

exposure could be affected by both CYP2C9 induction and strong and moderate CYP2C9 inhibition. In addition, based on the simulations using PBPK modeling, total exposure to deuruxolitinib in the CYP2C9 poor metabolizers is estimated to be increased when compared to subjects with normal CYP2C9 metabolizers. Refer to Section 6.2.1 and 6.3.2 of this review. Given the potential for dose-dependent adverse events, there is clinical concern that higher plasma concentrations of deuruxolitinib may increase the risk of serious adverse reactions, including thrombosis. Therefore, labeling will include contraindications for use of deuruxolitinib by patients who are CYP2C9 poor metabolizers and are using strong or moderate CYP2C9 inhibitors.

Because the impact of CYP2C9 genetic variants on the pharmacokinetics of deuruxolitinib has not been directly evaluated in a clinical trial, there is some uncertainty about the impact on safety. Therefore, the FDA will manage these potential risks through labeling and by requiring a postmarketing study to assess systemic deuruxolitinib exposure in CYP2C9 intermediate and poor metabolizers. Currently, there are no safety concerns that are expected to change the favorable risk/benefit assessment in the general population with AA.

As part of routine pharmacovigilance, the Office of Surveillance and Epidemiology Division of Epidemiology-I will use Sentinel Initiative capabilities to monitor incidence during treatment of thrombosis and other safety events of interest.

However, additional data are needed to characterize the safety profile of the proposed product in special populations (pregnant females, pediatric population, and those with reduced CYP2C9 activity). Refer to Section 13 of this review for the postmarketing requirements and commitments.

8.3.10. Integrated Assessment of Safety

The safety profile for deuruxolitinib for the treatment of severe AA was adequately characterized during the development program. The primary safety database consisted of pooled data from subjects from the 24-week placebo-controlled period of Trials CP543.3001, CP543.3002, and CP543.2001. The primary safety database included 640 subjects exposed to deuruxolitinib 8 mg BID and 380 subjects exposed to deuruxolitinib 12 mg BID. Overall exposure, as reported in the 120-day Safety Update Report, included 414 subjects exposed to deuruxolitinib 16 mg total daily dose for ≥52 weeks and 208 subjects exposed for ≥76 weeks. Overall exposure to deuruxolitinib 24 mg total daily dose included 666 subjects exposed for ≥52 weeks and 388 subjects exposed for ≥76 weeks.

Deuruxolitinib did not appear to be associated with increased mortality in subjects with AA. Only one death occurred during the development program, which was a completed suicide in a subject who was receiving deuruxolitinib 8 mg BID. The suicide was adjudicated by both the Applicant and Psychiatry consultant as not related to the study drug. The review team concluded that there is no evidence in the submitted safety data to support an association of deuruxolitinib with an increased risk of psychiatric adverse events including suicidal ideation and behavior (Refer to Section 8.3.4.7 for further details)

During the 24-week placebo-controlled period, SAEs were reported at a comparable rate in subjects who received deuruxolitinib compared to placebo. SAEs were reported in 7/640 (1.1%) of subjects who received deuruxolitinib 8 mg BID, 4/380 (0.9%) of subjects who received deuruxolitinib 12 mg BID, and 4/299 (1.5%) of subjects who received placebo. Most SAE preferred terms (PTs) were reported by single subjects in any treatment group. The majority of SAEs were in the Infections and infestations SOC across both deuruxolitinib treatment groups.

For subjects who remained on deuruxolitinib from Weeks 0-52, SAEs were reported at a similar frequency for subjects who received deuruxolitinib 8 mg compared to 12 mg. During this period, a total of 14 SAEs were reported by 7 (1.1%) subjects who received 8 mg and 4 (0.9%) subjects who received 12 mg. Most SAEs were in the Infections and infestations SOC across both deuruxolitinib 8 mg and 12-mg treatment groups. During this period, SAEs were reported in 16/868 (1.8%) of subjects who received 8 mg and 18/991 (1.8%) of subjects who received 12 mg. Most SAE PTs were reported by single subjects in any treatment group. The majority were in the same SOCs irrespective of deuruxolitinib dose: Infections and infestations SOC; Neoplasms benign, malignant, and unspecified; and Musculoskeletal and connective tissue disorders system organ class.

During the Weeks 0-24, AEs leading to permanent discontinuation of study drug were reported more commonly in subjects treated with either dose of deuruxolitinib than subjects treated with placebo. During this period, permanent discontinuations of treatment because of an AE were reported in 19/640 (2.8%) of subjects who received deuruxolitinib 8 mg, 9/380 (2.4%) of subjects who received deuruxolitinib 12 mg, and 5/299 (1.5%) of subjects who received placebo. The most frequent reason for treatment discontinuation in any group was headache (reported in five subjects, 0.8%, who received 8 mg BID). For subjects who received deuruxolitinib 8 mg, the most common SOCs for AEs leading to discontinuation were: Nervous system disorders, Blood and lymphatic system disorders, and Infections and infestations.

For subjects who remained on deuruxolitinib from Weeks 0-52, the distribution of AEs leading to discontinuation by SOC included more discontinuations due to Neoplasms benign, malignant, and unspecified compared to the 24-week placebo-controlled period. During this period, permanent discontinuations of treatment because of an AE were reported in 6/868 (0.7%) of subjects who received with deuruxolitinib 8 mg BID and 11/991 (1.1%) of subjects who received deuruxolitinib 12 mg BID.

Based on the established risk profile for the class of Janus Kinase Inhibitors, the Applicant identified AESI for close monitoring during the Phase 3 trials. No subjects receiving treatment with deuruxolitinib developed AESI of MACE, DILI, or retinal detachment during Weeks 0-24 or Week 0-52. During Weeks 0-24, AESIs that were reported more frequently in either of the deuruxolitinib groups than the placebo group included infections, herpes zoster, herpes simplex, gastrointestinal perforation (deuruxolitinib 8-mg BID group, n=1), elevated creatine phosphokinase, lipid elevation, liver enzyme abnormalities, and hematologic abnormalities including thrombocytosis, lymphopenia, neutropenia, and anemia. AESIs are discussed in more detail in Section 8.3.4 of this review.

The adverse reaction profile was similar to other products in this class. During Weeks 0-24, the most common ARs in subjects treated with deuruxolitinib were acne, headache, nasopharyngitis, blood CPK increased, hyperlipidemia, fatigue, skin and soft tissue infections, anemia, weight increased), neutropenia, thrombocytosis, lymphopenia, and herpes. ARs reported <1% included vulvovaginal candidiasis (n=1, 8 mg BID) and oral candidiasis (n=1, 12 mg BID). The review team recommends inclusion of these ARs in Section 6.1 (Adverse Reactions) of labeling. Analysis of adverse events for subjects who remained on deuruxolitinib through Week 52 did not reveal any new safety signals. ARs are discussed in more detail in Section 8.3.3 of this review.

For some treatment emergent AEs, the review team observed a dose-response relationship with a greater number of AEs in subjects receiving 12 mg versus 8 mg. These TEAEs included: thrombosis, acne, blood CPK increased, hyperlipidemia, pooled fatigue, lymphopenia, leukopenia, anemia, skin and soft tissue infections, folliculitis, pooled neutropenia, herpes, HDL increased and bronchitis (Refer to Section 8.3.3 for details).

During the course of the review, the clinical pharmacology team identified a clinically significant difference in the PK of deuruxolitinib when coadministered with moderate or strong CYP2C9 inhibitors resulting in increased deuruxolitinib total exposure, and an increased risk of total exposure to deuruxolitinib in CYP2C9 poor metabolizers. Given the potential for dose-dependent adverse events, there is clinical concern that higher plasma concentrations of deuruxolitinib may increase the risk of serious adverse reactions, including thrombosis (Refer to Sections 6.2.1, 6.3.2, and 8.3.4.13 of this review for details).

During the development program, ten females of childbearing potential reported pregnancy during treatment with deuruxolitinib. There was one case of paternal exposure which resulted in a healthy full-term baby to the unexposed female partner. Of the ten maternal exposures, outcomes included four elective terminations, three spontaneous abortions (including one pregnancy exposed to placebo), one lost to follow-up, one unknown outcome, and one live birth of a healthy infant. Refer to Section 8.3.8 in this review. Because exposures to deuruxolitinib during pregnancy are likely to occur and the available data are insufficient to characterize the associated risk in pregnant women, the FDA will require the Applicant to conduct a postmarketing assessment to characterize the drug associated risk. Refer to Section 13 for further details.

The use of deuruxolitinib is associated with a number of potential toxicities that have been observed with the JAK-inhibitor class of products. Deuruxolitinib labeling will carry a Boxed Warning for increased risk of serious infection, all-cause mortality, including sudden cardiovascular death, malignancies (including lymphoma and lung cancers), MACE (defined as cardiovascular death, myocardial infarction, and stroke) and thrombosis. In addition, based on the data from the deuruxolitinib development program, labeling will include product-specific contraindications for CYP2C9 poor metabolizers and patients using moderate or strong CYP2C9 inhibitor medications.

As part of routine pharmacovigilance, the Office of Surveillance and Epidemiology Division of Epidemiology-I will use Sentinel Initiative capabilities to monitor (a) deuruxolitinib uptake and use patterns, (b) baseline risk factor profiles for patients who start treatment with deuruxolitinib, and (c) incidence of certain sentinel safety events (acute myocardial infarction, acute stroke, deep vein thrombosis, and pulmonary embolism) that occur during treatment with deuruxolitinib.

Currently available data support a favorable safety profile for deuruxolitinib 8 mg BID in the treatment of adult patients with severe AA.

8.4. Statistical Issues

The key statistical issues addressed during the review included:

Site Excluded From Trial CP543.3002

Site 102 in Trial CP543.3002 was placed on enrollment hold and eventually terminated due resistance to an onsite audit by the Applicant. Remaining subjects were terminated. The decision to exclude 17 randomized subjects from the efficacy analyses was made prior to unblinding. The Modified Efficacy Population and the Safety Population includes subjects from site 102.

Results of the analysis of the primary efficacy endpoint using the Modified Efficacy Population (including subjects from Site 102) were similar to results from the Efficacy Population (not including subjects from Site 102).

Summary of Final Labeling Recommendation

The Applicant proposed to include the following endpoints in labeling: SALT ≤10, (b) (4) [redacted]. Although SALT ≤10 was not included in the multiplicity hierarchy, this endpoint is closely related to the primary endpoint and has been included in other product labeling for alopecia areata.

8.5. Conclusions and Recommendations

To establish the effectiveness of deuruxolitinib (CTP-543) for the treatment of AA, the Applicant submitted data from two adequate and well-controlled clinical trials. The trials included subjects 18 years of age and older with "moderate to severe AA", defined as a SALT score of 50 or greater at Baseline, which corresponds to loss of 50% or greater loss of scalp hair. Subjects may also have had loss of eyebrow or eyelash hair. The clinical trials evaluated deuruxolitinib 8 mg and 12 mg for the primary endpoint of SALT ≤20 response (i.e., no more than 20% missing hair) at Week 24. For both trials, both deuruxolitinib 8 mg and 12 mg were statistically superior

to placebo for the primary endpoint. In Trial CP543.3001, the proportion of subjects who received deuruxolitinib 8 mg, deuruxolitinib 12 mg, and placebo and achieved SALT ≤20 at Week 24 was 29.2%, 39.8% and 0.8%, respectively. In Trial CP543.3002, the proportion of subjects who received deuruxolitinib 8 mg, deuruxolitinib 12 mg, and placebo and achieved SALT ≤20 at Week 24 was 32.1%, 36.7%, and 0.8%, respectively.

The efficacy of the 8-mg and 12-mg BID dosage were additionally supported by key secondary endpoints SPRO responders at Week 24, SALT scores ≤20 at Week 12, Week 16 and Week 20, and the exploratory endpoints SALT scores ≤10 at Week 24, the eyebrow (BETA) and eyelash (BELA) hair loss measures. However, content validity and other measurement properties of the BETA and BELA were not reviewed since they were considered exploratory endpoints. Results from the BETA and BELA scores are not proposed for inclusion in labeling.

SALT ≤20 response rates were higher in all dose groups in subjects with baseline SALT 50 to 94 versus SALT 95 to 100. Thus, while the 12-mg dose had consistently higher response rates than the 8-mg dose for the primary endpoint across the range of baseline SALT scores, approximately 46% of subjects with baseline SALT score <95 were able to achieve SALT ≤20 response on the 8-mg dose.

To support the safety of deuruxolitinib, the Applicant submitted pooled data from the Phase 3 Trials CP543.3001 and CP543.3002, and data from the proposed doses in Phase 2 Trial CP543.2001. The Applicant and review team conducted a comprehensive assessment of the safety of deuruxolitinib in the target population. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent adverse reactions. The review identified no unexpected safety signals. However, because of the potential for increased exposure to deuruxolitinib, labeling will contraindicate use in the subpopulations of patients with AA who are CYP2C9 poor metabolizers and are using moderate or strong CYP2C9 inhibitors.

The Applicant sought an indication of the treatment of adults with “moderate to severe alopecia areata.” However, the study population in the trials to support efficacy was defined as SALT ≥50 and literature indicates that patients and clinicians consider SALT ≥50 to represent "severe" disease, not "moderate to severe” (Wyrwich et al. 2020). Therefore, the review team concluded the indication should be for the treatment of “severe alopecia areata.”

Based on our review, the review team concludes that the benefit-risk of deuruxolitinib is favorable in the population of patients with severe alopecia areata with appropriate labeling and recommend approval of this application.

9 Advisory Committee Meeting and Other External Consultations

The FDA conducted no advisory committee meeting regarding this application because there were no complex regulatory issues that warranted discussion with external experts.

10 Pediatrics

Refer to the following sections of this review for information regarding the proposed development program for deuruxolitinib in the pediatric population:

1. Section 8.3.8 for a discussion regarding the Pediatric Study Plan
2. Section 13 for the deferred pediatric studies, which are required under the PREA (21 CFR 314.55(b) and 601.27(b)).

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

The Applicant submitted proposed prescribing information, medication guide (MG) and carton/container labels for LEQSELVI™ (deuruxolitinib) tablets. The Office of Prescription Drug Promotion reviewed and provided comments regarding the prescribing information and MG. These comments are reflected in final labeling (Refer to Section 11.2 of this review). Division of Medication Error Prevention and Analysis 1 reviewed the LEQSELVI prescribing information, MG, and container labels for areas of vulnerability that may lead to medication errors. The reviewer identified medication error issues, provided a rationale for concern, and proposed recommendations for labeling to be conveyed to the Applicant to minimize the risk for medication error (review by Madhuri R. Patel, PharmD dated February 14, 2024).

Table 59. Location of Reviewer Comments on Proposed Labeling

Section	Location of Reviewer Comments on Proposed Labeling
1 INDICATIONS AND USAGE	Clinical Team: Section 1, 7
2 DOSAGE AND ADMINISTRATION	Clinical Pharmacology Team: Section 6.1, 6.2
5 WARNINGS AND PRECAUTIONS	Clinical Team: Section 8.3.4
6 ADVERSE REACTIONS	Clinical Team: Section 8.3.3
7 DRUG INTERACTIONS	Clinical Pharmacology Team: Section 6.1, 6.2
8 USE IN SPECIFIC POPULATIONS	Clinical & DPMH: Section 8.3.8,
12 CLINICAL PHARMACOLOGY	Clinical Pharmacology Team: Section 6.3.2
14 CLINICAL STUDIES	Statistical Team/ COA Team: Section 8.3
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling, Sections 4, 5, 6 and 14.

Source: Reviewer's Table

11.2. Patient Labeling

The Applicant submitted a MG for LEQSELVI (deuruxolitinib) for the proposed indication of the treatment of adults with moderate to severe alopecia areata. The Division of Medical Policy Programs and the Office of Prescription Drug Promotion reviewed and provided comments on the Medication Guide for LEQSELVI. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by (Susan Redwood, MPH, BSN, RN, and David Foss, PharmD dated June 18, 2024.

12 Risk Evaluation and Mitigation Strategies (REMS)

Based on the safety profile of deuruxolitinib, which is consistent with other JAK inhibitors, the proposed labeling (prescribing information and patient labeling via a Medication Guide) and routine pharmacovigilance are considered adequate to manage risks of this product in the treatment of moderate to severe AA. A REMS would not reduce the known risks associated with treatment with deuruxolitinib and is not warranted at this time. The benefits of treatment with deuruxolitinib were demonstrated in adequate and well controlled trials. Potential risks in the target population and subgroups will continue to be evaluated using standard surveillance tools and postmarketing assessments.

13 Postmarketing Requirements and Commitment

Clinical postmarketing requirements are intended to characterize the risks of deuruxolitinib use in special populations (pregnancy, pediatrics and reduced CYP2C9 activity) and address the safety of this product with long-term use in the target population with AA. Because the Applicant is conducting open-label extension trials of adequate design and sample size, a PMR to inform long- term safety will not be needed.

As part of routine pharmacovigilance, the Office of Surveillance and Epidemiology will use Sentinel Initiative capabilities to monitor (a) deuruxolitinib uptake and use patterns, (b) baseline risk factor profiles for patients who start treatment with deuruxolitinib, and (c) incidence during treatment of certain sentinel safety events (acute myocardial infarction, acute stroke, deep vein thrombosis, and pulmonary embolism).

The available safety data regarding deuruxolitinib use during pregnancy are limited. The study population as defined by the entry criteria excluded pregnant and breastfeeding females, and females planning to become pregnant or breastfeed during the trials. The risks will be conveyed in labeling (Section 8.2). However, because exposures to deuruxolitinib during pregnancy are likely to occur and the available data are insufficient to characterize the associated risk in pregnant women, the FDA will require the Applicant to conduct postmarketing assessments to characterize the drug associated risk.

In addition, exposure to deuruxolitinib is predicted to be increased by approximately 2-fold in CYP2C9 poor metabolizers (CYP2C9 *3/*3 genotyped subjects), when compared to heathy subjects, using PBPK modeling. CYP2C9 activity is expected to be decreased in individuals with genetic variants such as the CYP2C9*2 and CYP2C9*3 alleles. There is no available data to characterize the risks of dose dependent serious adverse events in individuals with the potential for increased plasma levels of deuruxolitinib due to genetic variants of CYP2C9 activity. To verify the modeling data and assess possible impacts on PK and safety, this PMR will characterize the PK in subjects that are CYP2C9 normal metabolizers, intermediate metabolizers and PM. Therefore, the FDA will require an assessment of PK in the population with the relevant genotypes for both IMs and PMs including, but not limited to *1/*2, *1/*3, *2/*2, *2/*3, and *3/*3. In addition, the FDA will request the development of a diagnostic device to detect the presence of nonfunctional alleles of CYP2C9.

PMRs, PMCs and milestone dates are currently under negotiation with the Applicant.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the Federal Food, Drug, and Cosmetic Act will not be sufficient to identify the unexpected serious risk of adverse maternal, fetal, and infant outcomes of women exposed to deuruxolitinib during pregnancy. Furthermore, the active postmarket risk identification and analysis system as available under Section 505(k)(3) of the Federal Food, Drug, and Cosmetic Act will not be sufficient to assess this serious risk. Therefore, based on appropriate scientific data, FDA has determined that the Applicant is required to conduct the following:

Pregnancy

PMR 4655-4

Collect global data from prospective pregnancy exposure registry/registries, preferably disease-based multiproduct pregnancy registry/registries, using a registry-based cohort study design to compare the maternal, fetal, and infant outcomes of women with Alopecia Areata exposed to deuruxolitinib during pregnancy with unexposed comparator population(s).The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, pregnancy terminations, preterm births, small for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

Draft Protocol Submission:	01/2025
Final Protocol Submission:	01/2026
Study/Trial Completion:	01/2036
Final Report Submission:	01/2037

PMR 4655-5

Conduct an additional pregnancy study that uses a different design from the pregnancy exposure registry (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, stillbirths, pregnancy terminations, preterm births, and small for gestational age infants in women exposed to deuruxolitinib during pregnancy compared to an unexposed comparator population(s).

Draft Protocol Submission:	01/2025
Final Protocol Submission:	01/2026
Study/Trial Completion:	01/2036
Final Report Submission:	01/2037

Clinical Pharmacology

PMR 4655-6

Conduct a PK study in subjects who are CYP2C9 Normal Metabolizers (NM), Intermediate Metabolizers (IM)), and Poor Metabolizers (PM) in order to characterize the systemic exposure of deuruxolitinib in these subgroups.

Draft Protocol Submission:	10/2024
Final Protocol Submission:	04/2025
Study/Trial Completion:	04/2026
Final Report Submission:	10/2026

PMC 4655-7

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.

Draft Protocol Submission:	10/2024
Final Protocol Submission:	04/2025
Study Completion:	04/2026
Final Report Submission:	10/2026

REQUIRED PEDIATRIC ASSESSMENTS: PREA (21 U.S.C. 355c)

We are waiving the pediatric study requirement for ages 0 to less than 6 years because the studies are impossible or highly impractical.

We are deferring submission of your pediatric study for ages 6 years to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric studies required by Section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and Section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act.

PMR 4655-1

Conduct a juvenile toxicity study to evaluate the potential toxicity of deuruxolitinib, including the potential effects on growth, development, and reproduction, when administered orally to juvenile rats.

Final Protocol Submission:	Completed (01/2024)
Study/Trial Completion:	08/2025
Final Report Submission:	02/2026

PMR 4655-2

Conduct a randomized, controlled trial to evaluate the safety, efficacy, and pharmacokinetics of deuruxolitinib in the adolescent population (12 years to less than 18 years) with severe alopecia areata. Evaluate at least 300 subjects exposed to deuruxolitinib for a minimum of 52 weeks.

Draft Protocol Submission:	08/2024
Final Protocol Submission:	02/2025
Study Completion:	04/2029
Final Report Submission:	10/2029

PMR 4655-3

Conduct a randomized, controlled trial to evaluate the safety, efficacy, and pharmacokinetics of deuruxolitinib in the pediatric population (6 years to less than 12 years) with severe alopecia areata. Evaluate at least 100 subjects exposed to deuruxolitinib for a minimum of 52 weeks.

This trial should not be initiated until you have submitted for review clinical data from your trial in subjects 12 years to less than 18 years and nonclinical data from your juvenile toxicology study.

Draft Protocol Submission:	04/2030
Final Protocol Submission:	10/2030
Study Completion:	01/2035
Final Report Submission:	07/2035

14 Division Director (Clinical) Comments

I concur with the review team's recommendation to approve NDA 217900 for LEQSELVI (deuruxolitinib) tablets, 8 mg for the treatment of adults with severe alopecia areata (AA). Recommended dosage is 8 mg orally twice daily, with or without food. Before initiation of treatment, the patient should be evaluated for CYP2C9 genotype, use of concomitant CYP2C9 inhibitors, active and latent tuberculosis (TB) infection, viral hepatitis screening, and complete blood count. Additionally, immunizations should be updated according to current immunization guidelines. LEQSELVI is contraindicated in patients who are CYP2C9 poor metabolizers and who are using concomitant moderate or strong CYP2C9 inhibitors.

Alopecia areata is a chronic, relapsing autoimmune, T-cell mediated disease that targets anagen hair follicles and causes nonscarring hair loss. Alopecia most commonly occurs on the scalp but may be found on any hair-bearing area. Approximately 10 percent of patients progress to alopecia totalis or alopecia universalis. The estimated prevalence of AA is approximately 1 in 1000 people, with a lifetime risk of approximately 2 percent. For most patients the onset is before age 30 years; however, the disorder may occur at any age. Men and women are equally affected. Alopecia areata can negatively affect quality of life and is associated with increased prevalence of anxiety and depression.

Deuruxolitinib, a deuterated form of ruxolitinib, is a new-molecular-entity, and is a Janus kinase (JAK) inhibitor. Serious adverse reactions have been observed with use of the JAK-inhibitor products. Therefore, labeling for deuruxolitinib will carry a Boxed Warning for increased risk of serious infection, all-cause mortality, including sudden cardiovascular death, malignancies (including lymphoma and lung cancers), MACE (defined as cardiovascular death, myocardial infarction, and stroke) and thrombosis (pulmonary embolism, venous and arterial thrombosis).

The efficacy and safety of deuruxolitinib were evaluated in two identically designed multicenter, randomized, double-blind, placebo-controlled phase 3 clinical trials. A total of 1,209 adult subjects with AA, who had at least 50% scalp hair loss as measured by the Severity of Alopecia Tool (SALT) for more than six months, received deuruxolitinib 8 mg twice daily, deuruxolitinib 12 mg twice daily, or placebo twice daily for 24 weeks. Upon completion of the 24-week trials, subjects were eligible to enroll in a long-term extension trial.

During the conduct of phase 3 clinical trials and open label trial, Applicant submitted safety reports for 8 serious adverse events of thromboembolism that occurred in 5 subjects receiving deuruxolitinib 12 mg twice daily (including bilateral pulmonary embolism, pulmonary embolism, deep vein thrombosis and cerebral venous sinus thrombosis; 1 subject had 1 event at Week 41, and 4 subjects had 7 events between Week 52 and Week 98). No thromboembolic events were reported in any subject treated with deuruxolitinib 8 mg twice daily. This resulted in regulatory action – partial clinical hold under 21 CFR 312.42 (b)(2)(i) for the 12 mg dose for the treatment of alopecia areata because the continued use of the deuruxolitinib 12 mg dose

would expose human subjects to an unreasonable and significant risk of illness or injury (May 17, 2023).

The primary efficacy endpoint for both trials assessed the proportion of subjects who achieved at least 80% scalp hair coverage (SALT score of ≤ 20) at Week 24. The primary endpoint for both the 8 mg versus placebo (29.2% v 0.8%; 32.1% v 0.8%) and the 12 mg versus placebo (39.8% v 0.8%; 36.7 v 0.8%) comparisons were statistically significant.

The safety profile for deuruxolitinib for the treatment of severe AA was adequately characterized during the development program. The treatment emergent adverse events (TEAEs) observed in the deuruxolitinib development program were consistent with the known safety profile for other JAK inhibitors used to treat chronic inflammatory conditions. In the placebo- controlled period (Weeks 0 to 24), subjects who received either dose of deuruxolitinib reported higher observed rates of headache, acne, nasopharyngitis, blood creatine phosphokinase (CPK) increased, hyperlipidemia, fatigue, anemia, increased weight, neutropenia, and herpes infection compared to subjects who received placebo. For some TEAEs such as thrombosis, lymphopenia, leukopenia, anemia, neutropenia, skin and soft tissue infections neutropenia, herpes, bronchitis, hyperlipidemia and blood CPK increased, the review team observed a dose-response relationship with greater numbers of AEs in subjects receiving deuruxolitinib 12 mg versus 8 mg.

Deuruxolitinib is primarily metabolized by CYP2C9 (76%) and CYP3A4 (21%) and to a lesser extent by CYP1A2 (3%). Based on drug interaction studies (clinical studies and Model-Informed Approaches), deuruxolitinib AUC increased by 140% and C_{max} by 21% following concomitant use of multiple dosages of 200 mg fluconazole (dual moderate CYP2C9 and CYP3A4 inhibitor) with a single dose of 12 mg deuruxolitinib (1.5 times the 8 mg dose), and deuruxolitinib AUC is predicted to be increased by 200% and C_{max} by 25% following concomitant use of multiple dosages of a strong CYP2C9 inhibitor with a single dose of 12 mg deuruxolitinib (1.5 times the 8 mg dose). CYP2C9 activity is reduced in patients with genetic variants in CYP2C9, such as the CYP2C9*2 and CYP2C9*3 alleles. The impact of CYP2C9 genetic variants on the pharmacokinetics of deuruxolitinib has not been directly evaluated. Based on drug-drug interaction modeling data, CYP2C9 poor metabolizers (e.g., *2/*3, *3/*3) may have up to 2-fold higher concentrations of deuruxolitinib, when compared to normal metabolizers. Because the potential for dose-dependent serious adverse events at those exposure levels, there is concern that higher plasma concentrations of deuruxolitinib may increase the risk of deuruxolitinib - associated serious/life-threatening adverse reactions (e.g., thrombosis) in CYP2C9 poor metabolizers or with concomitant use of moderate or strong CYP2C9 inhibitors. Therefore, deuruxolitinib should be contraindicated in patients who are CYP2C9 poor metabolizers or patients who are on concomitant moderate or strong CYP2C9 inhibitors. Consequently, prior to initiation of treatment, the patient should be evaluated for CYP2C9 genotype and use of concomitant CYP2C9 inhibitors.

Approval of deuruxolitinib will include postmarketing requirements (PMRs) for:

1. Conduct a PK study in subjects who are CYP2C9 Normal Metabolizers, Intermediate Metabolizers, and Poor Metabolizers to characterize the systemic exposure of deuruxolitinib in these subgroups.
2. Conduct of a juvenile toxicology study to evaluate the potential toxicity of deuruxolitinib, including the potential effects on growth, development, and reproduction, when administered orally to juvenile rat.

Additionally, PMRs will focus on the collection of safety data in populations that have not yet been studied (e.g., pregnant females, and pediatric subjects age ≥ 6 years).

As a postmarking commitment (PMC), the Agency will request that the Applicant Establish an in-vitro diagnostic device to guide the use of deuruxolitinib in patients with severe AA. The device should detect, at a minimum, the presence of the nonfunctional alleles in cytochrome P450 2C9 (CYP2C9) relevant to the US population.

15 Office Director (or Designated Signatory Authority) Comments

I concur with the recommendation of the Division of Dermatology and Dentistry to approve NDA 217900 for Leqselvi (deuruxolitinib) tablets, 8 mg twice daily, for the treatment of adults with severe alopecia areata (AA). Deuruxolitinib, a deuterated form of ruxolitinib, is a new-molecular-entity, and is a Janus kinase (JAK) inhibitor. There are currently two other oral JAK inhibitors, baricitinib and ritlecitinib, approved for the same indication.

The effectiveness of deuruxolitinib was demonstrated in two phase 3 adequate and well-controlled clinical trials of similar design, in a total of 1,209 adult subjects with AA, who had at least 50% scalp hair loss as measured by the Severity of Alopecia Tool (SALT) for more than six months. Subjects were randomized to deuruxolitinib 8 mg twice daily, deuruxolitinib 12 mg twice daily, or placebo twice daily for 24 weeks. Due to accruing serious safety events, i.e., thromboembolism, the 12 mg dose arm was placed on clinical hold and the Applicant has proposed the 8 mg twice daily dose in the NDA. The agreed upon primary endpoint, the proportion of subjects who achieved at least 80% scalp hair coverage (SALT score of ≤ 20) at Week 24, was statistically significant for the 8 mg versus placebo in both studies (Table 24). Secondary endpoints were also supportive of the efficacy of deuruxolitinib.

The safety profile of deuruxolitinib is consistent with that of other JAK inhibitors and included dose-dependent changes in laboratory parameters and safety events, including serious ones, i.e., thromboembolism when comparing the 8 mg and 12 mg twice daily dose levels. Respectively, labeling for deuruxolitinib will carry a Boxed Warning for increased risk of serious infection, all-cause mortality, including sudden cardiovascular death, malignancies (including lymphoma and lung cancers), MACE (defined as cardiovascular death, myocardial infarction, and stroke) and thrombosis (pulmonary embolism, venous and arterial thrombosis).

While the analysis of the deuruxolitinib safety data through Week 52 has not identified new safety signals, the review team identified a safety concern related to CYP2C9 metabolism of deuruxolitinib. Specifically, meaningful increases in deuruxolitinib exposures when co-administered with moderate or strong CYP2C9 inhibitors, and higher estimated total exposure to deuruxolitinib in CYP2C9 poor metabolizers, as detailed in Clinical Pharmacology section. Given the potential for dose-dependent serious adverse events at those exposure levels, the review team has determined that these potential risks will be addressed through labeling, including a requirement for CYP2C9 genotype status testing and a contraindication statement for CYP2C9 poor metabolizers and for patients using moderate or strong CYP2C9 inhibitors. A postmarketing study will be required to assess systemic deuruxolitinib exposure in CYP2C9 poor metabolizers to potentially inform labeling in the future. The review team also recommends the Applicant develop an in-vitro diagnostic genotyping assay to determine CYP2C9 genotype status. I agree with these assessments and recommendations.

In summary, the review team concluded, and I agree, that the benefit-risk of deuruxolitinib 8 mg twice daily is favorable in the population of adult patients with severe alopecia areata, with the agreed labeling and the above-mentioned post-marketing requirements and commitments, to support approval of NDA 217900.

16 Appendices

16.1. References

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Queeney, K, W Housley, J Sokolov, and A Long, 2019, Elucidating the Mechanism Underlying Creatine Phosphokinase Upregulation With Upadacitinib, Annual European Congress of Rheumatology, EULAR 2019, Madrid, 12-15 June 2019, Madrid, 78: 734.732-735.

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March, 2018, The Voice of the Patient: Alopecia Areata Center for Drug Evaluation and Research (CDER).

16.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical trials for deuruxolitinib. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical trials as defined in 21 CFR 54.2(e) were Trials CP543.3001 and CP543.3002.

Table 60. Financial Disclosure Information From Trials CP543.3001 and CP543.3002

Study Phase	Study #	Study Title	Financial Disclosure Information
3	CP543.3001	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	Form 3454: no interests Form 3455: completed for 3 investigators
3	CP543.3002	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	Form 3454: no interests

Source: Table 1. 1.3. Administrative Information.

It should be noted that Concert Pharmaceuticals, Inc. (Concert) was the sponsor for both Covered Studies conducted under the U.S. IND. No clinical investigators/sub-investigators were full-time or part-time employees of Concert. After the completion of the Covered Studies, CP543.3001 and CP543.3002, Concert merged with Sun Pharmaceutical Industries (Sun), Inc. (March 31, 2023), the Applicant for this NDA. In view of this merger, investigators in the Covered Studies were asked to disclose any financial interests in Sun. No clinical investigators/sub-investigators disclosed equity interest in the Applicant.

Clinical investigators /sub-investigators who disclosed significant payments of other sorts made by the Applicant are tabulated below. The submission includes Forms 3455 for these investigators /sub-investigators and Form 3454.

Table 61. Investigators Disclosing Significant Payments of Other Sorts

Study #	Investigator/Sub-Invest Name	Institution	Disclosure
CP543.3001 (Site# (b) (6) subjects)	(b) (6)		Consultancy Payments
CP543.3001 (Site# (b) (6) subjects)			Consultancy Payments
CP543.3001 (Site# (b) (6) subjects)			Consultancy Payments

Steps Taken to Minimize Bias

This distribution of subjects across multiple sites, as well as the study design, minimized the potential for bias in the assessment of trial outcomes. The two Covered Studies CP543.3001 and CP543.3002 were Phase 3, double-blind, randomized, placebo-controlled trials conducted at multiple sites across the United States, Canada, and countries in the European Union. Trial CP543.3001 enrolled 706 subjects across 73 study sites and CP543.3002 enrolled 517 subjects across 63 study sites. All investigators and site study staff, including raters, were blinded to study drug assignment for the duration of the studies. In both trials, the randomization schedule was generated prior to trial initiation. Also, for both trials the tablets and packaging of CTP-543 and placebo were identical in appearance.

In addition, the Applicant performed an assessment of efficacy data from investigators (Drs. (b) (6)) who disclosed "Significant payments of other sorts" and these efficacy results were similar to the overall efficacy results.

Table 62. Covered Clinical Trial CP543.3001

Was a list of clinical investigators provided:	Yes X	No (Request list from Applicant)
Total number of investigators identified: 73 sites		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes N/A	No (Request explanation from Applicant)

Table 63. Covered Clinical Trial CP543.3002

Was a list of clinical investigators provided:	Yes X	No (Request list from Applicant)
Total number of investigators identified: 63 sites		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes N/A	No (Request explanation from Applicant)

Refer to NDA 217900 Section 1.3.4 for a list of the investigators and subinvestigators that participated in the covered clinical trials.

16.3. Nonclinical Pharmacology/Toxicology

16.3.1. Carcinogenicity Study Review

Study title: 104-week oral gavage carcinogenesis study with CTP-543 in rats

Study no.:	8400790 (sponsor reference# CTP-543 TX-107)
Study report location:	SD 1, NDA 217900
Conducting laboratory and location:	(b) (4)
Date of study initiation:	05/31/2019 (experiment start date: 06/03/2019)
GLP compliance:	Yes
Drug, lot #, and % purity:	CTP-543, lot# M024443-CA18-0754, purity 99.9%
Prior Executive Carcinogenicity Assessment Committee (ECAC) concurrence:	Yes

Study title: 104-week oral gavage carcinogenesis study with CTP-543 in rats

Basis for Dose Selection: The high dose was based on hematology changes at 37.5 mg/kg/day in the 13-week toxicity study.

Reviewer Carcinogenicity Conclusion (Negative/Positive): Negative

ECAC Carcinogenicity Conclusion (Negative/Positive): Negative

Tumor Findings

There was no treatment-related effect on mortality. A complete list of tissues was examined histopathologically. No significant deuruxolitinib-related neoplastic findings were noted in this study.

Methods

Doses:	0 (water), 0 (vehicle), 3, 10, and 30 mg/kg/day for both males and females
Frequency of dosing:	Once daily
Number/Sex/Group:	65
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose in reverse osmosis water
Species/Strain:	Rat / Sprague-Dawley
Age:	~8 weeks at the start of dosing
Comment on Study Design and Conduct:	The sponsor added a water control group in addition to the vehicle control group, although the ECAC did not recommend it.
Dosing Comments (Dose Adjustments or Early Termination):	All surviving animals from all groups were terminated early per the early termination criteria that was recommended by the ECAC (males were sacrificed during Week 91 and females during Week 92).
Dosing Solution Analysis:	CTP-543 dosing formulations were in the range of 88-102% of nominal concentrations (within the target range of ±15%).

Observations and Results

Mortality

All surviving animals from all groups, including water and vehicle controls, were sacrificed early due to declining survival (males during Week 91 and females during Week 92). In the statistical reviewer's analysis, there was no statistically significant dose response relationship or pairwise comparisons in mortality for either male or female rats. Therefore, there was no test article-related effect on mortality.

Table 64. Animal Survival at the End of the 2-Year Oral Rat Carcinogenicity Study

Sex	Survival Parameter	Group 1 (Water)	Group 2 (Vehicle)	Group 3 (Low Dose)	Group 4 (Mid Dose)	Group 5 (High Dose)
Male	Survival number	29	20	25	19	22
	Survival rate	45%	31%	38%	29%	34%
Female	Survival number	19	21	16	17	18
	Survival rate	29%	32%	25%	26%	28%

Clinical Observations

There was no significant test article-related effect.

Body Weights

Body weight was measured weekly for the first 14 weeks and once every 2 weeks thereafter. A decrease in body weight gain was noted in high dose males at Week 90 (-12% and -11% compared with water and vehicle controls, respectively). No significant changes were noted in females.

Feed Consumption

Food consumption was measured weekly for the first 14 weeks and once every 2 weeks thereafter. High dose males had a higher incidence of lower mean food consumption intervals, compared with controls. There were no significant changes in low or mid dose males or females at any doses.

Gross Pathology

There were no significant test article-related findings.

Histopathology

Peer Review: Yes

Historical Control Provided for Tumor Incidence: Not provided

Neoplastic:

A complete tissue list was examined for all main study animals. The tumor incidence data were analyzed by the statistical reviewer, Dr. Hepei Chen. A dose-response relation test (trend test) was conducted across the vehicle control group, low, mid, and high dose groups. Pairwise comparison tests were conducted for water control group and three dose groups against the vehicle control group. A Poly-k method was used for the data analysis (k =3). Statistical significance levels used for the tumor data analysis in this study were 0.005 and 0.025 for common and rare tumors, respectively, in trend tests and 0.05 and 0.1 for common and rare tumors, respectively, in pairwise comparisons.

Per Dr. Chen's analysis, the tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons are shown in the following table.

Table 65. Tumor Types With p-Values ≤0.05 for Dose-Response Relation Tests and/or Pairwise Comparison Tests in the 2-Year Oral Rat Carcinogenicity Study

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 3 mg P - VC vs. L	Mid (M) 10 mg P - VC vs. M	High (H) 30 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Male						
Testis	B-Interstitial Cell Tumor (C)	0/65 (30)	0/65 (31)	0/65 (29)	4/65 (29)	0/65 (32)
		0.0030 $	NC	NC	0.0522	NC
Female						
Thyroid	B-Adenoma, Follicular Cell/	0/65 (29)	1/65 (27)	1/65 (28)	3/65 (30)	3/65 (29)
	M-Carcinoma, Follicular Cell (R)	0.0480 @	0.4821	0.4912	0.1249	0.1184

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.
$ = Statistically significant at 0.005 level for test of dose response relationship in common tumor;
@ = Not statistically significant at 0.025 level for test of dose response relationship in rare tumor;

Statistical significance was noted in the trend test for interstitial cell tumor in testis in males (p=0.003). However, there was no statistical significance in any of the pairwise comparisons for this tumor type. Usually for a neoplastic finding considered to be biologically significant, statistical significance should be achieved in both the trend test and pairwise comparison test. Overall, there were no significant test article-related neoplastic findings in either sex.

Non-neoplastic:

Test article-related microscopic findings were noted in the liver and spleen. In the liver, mixed cell foci characterized by generally eosinophilic and clear cell types were seen at all doses. In the spleen, decreased lymphocytes were noted at mid and high doses.

Toxicokinetic Analysis

TK parameters were measured for deuruxolitinib and its metabolites C-21714 and C-21717, for Days 1 and 176. TK parameters for deuruxolitinib are shown in the table below. The exposure to deuruxolitinib was higher in females than males. $AUC_{0\text{-}24hr}$ values of deuruxolitinib increased with dose in a greater than dose-proportional manner. Drug accumulation was noted after repeated dosing.

Table 66. Summary of Toxicokinetic Results of Deuruxolitinib in the 2-Year Oral Rat Carcinogenicity Study

Day	Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)
1	3	3	M	20.5	0.500	44.8	1.67
			F	39.6	0.500	63.8	NR
			MF	30.1	0.500	54.3	2.58
	4	10	M	72.8	0.500	183	NR
			F	184	0.500	325	0.824
			MF	128	0.500	254	1.24
	5	30	M	368	0.500	872	0.878
			F	899	0.500	2490	NR
			MF	634	0.500	1680	1.89
176	3	3	M	32.2	0.500	60.8	0.862
			F	113	0.500	164	NR
			MF	72.8	0.500	112	3.42
	4	10	M	175	0.500	315	NR
			F	373	0.500	856	2.89
			MF	274	0.500	586	NR
	5	30	M	773	0.500	1210	1.26
			F	2780	0.500	6050	NR
			MF	1780	0.500	3630	NR

NR = Not reported due to the lack of a distinct elimination phase.
Notes: Combined male and female (MF) parameters were calculated by combining concentration data for all animals (male and female) at each dose level on each interval and using these data as a separate composite profile for toxicokinetic analysis. These parameters are not an average of the values calculated for males and females separately.
Due to sex differences observed, MF combined results are presented for informational purposes only.

Study title: 26-week oral gavage carcinogenesis study with CTP-543 in 001178-T (hemizygous) rasH2 and 001178-W (wild type) rasH2 Mice, respectively

Study no.:	8452442 (sponsor reference# CTP-543 TX-120)
Study report location:	SD 1, NDA 217900
Conducting laboratory and location:	(b) (4)
Date of study initiation:	03/02/2021 (experiment start date: 03/04/2021)
GLP compliance:	Yes
Drug, lot #, and % purity:	CTP-543, lot# PRPL2019-125, purity 99.8%
Prior ECAC concurrence:	Yes
Basis for Dose Selection:	The high dose was based on mortality at 300 mg/kg/day in the 4-week toxicity study.

Reviewer Carcinogenicity Conclusion (Negative/Positive): Negative

ECAC Carcinogenicity Conclusion (Negative/Positive): Negative

Tumor Findings

There was no treatment-related effect on mortality. A complete list of tissues was examined histopathologically. No significant deuruxolitinib-related neoplastic findings were noted in this study.

Methods

Doses:	0 (vehicle), 10, 30, and 100 mg/kg/day for both males and females
Frequency of dosing:	Once daily
Number/Sex/Group:	25
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose in reverse osmosis water
Species/Strain:	Mouse / CB6F1-TgN (RasH2)
Age:	~8 weeks at the start of dosing
Comment on Study Design and Conduct:	A positive control group (10/sex) is included [receiving a single intraperitoneal dose of 75 mg/kg (b) (4) on Day 1]
Dosing Comments (Dose Adjustments or Early Termination):	This study was conducted as planned with no dosing adjustment or early termination.
Dosing Solution Analysis:	CTP-543 dosing formulations were in the range of 95-101% of nominal concentrations (within the target range of ±15%).

Observations and Results

Mortality

In Dr. Chen's analysis, there were no statistically significant findings in mortality for either male or female mice treated with deuruxolitinib. Therefore, there was no deuruxolitinib-related effect on mortality.

Survival in the (b) (4)-treated positive control animals at the end of the dosing Phase was 0%. The early death rate in the positive control animals is in line with expectations using this model and it was attributed primarily to the presence of malignant neoplasms (mainly malignant lymphoma).

Table 67. Animal Survival at the End of the 6-Month Oral Mouse Carcinogenicity Study

Sex	Survival Parameter	Group 1 (Vehicle)	Group 2 (Low Dose)	Group 3 (Mid Dose)	Group 4 (High Dose)	Group 5 (Positive Control)
Male	Survival number	25	25	24	23	0
	Survival rate	100%	100%	96%	92%	0%
Female	Survival number	24	24	23	25	0
	Survival rate	96%	96%	92%	100%	0%

Clinical Observations

There was no significant test article-related effect.

Body Weights

Body weight was measured weekly. There was no significant test article-related effect.

Feed Consumption

Food consumption was measured weekly. There was no significant test article-related effect.

Gross Pathology

There were no significant test article-related findings.

Histopathology

Peer Review: No

Historical Control Provided for Tumor Incidence: Not provided

Neoplastic:

A complete tissue list was examined for all main study animals. The tumor incidence data were analyzed by Dr. Chen. A dose-response relation test (trend test) was conducted across the vehicle control group, low, mid, and high dose groups. Pairwise comparison tests were conducted for the positive control group and three dose groups against the vehicle control group. Statistical significance level used for the tumor data analysis in this study was 0.05 in both the trend tests and pairwise comparisons.

Per Dr. Chen's analysis, there were no statistically significant findings in tumor data for either male or female mice treated with deuruxolitinib. There were no significant deuruxolitinib-related neoplastic findings in either sex.

In the positive control group, all animals developed neoplasms (malignant lymphoma in 7/10 males and 8/10 females, squamous cell papilloma/carcinoma in 2/10 males and 1/10 female, and hemangiosarcoma in 1/10 male and 1/10 female), demonstrating validity of this study.

Non-neoplastic:

The microscopic findings of decreased lymphocytes in the spleen, thymus, and/or mesenteric lymph node were observed across deuruxolitinib-treated and vehicle control groups (with no significant differences among groups) and was considered related to stress. However, a pharmacologic effect of deuruxolitinib cannot be ruled out.

Toxicokinetic Analysis

TK parameters were measured for deuruxolitinib and its metabolites C-21714 and C-21717, for Days 1 and 182. TK parameters for deuruxolitinib are shown in the table below. The exposure to deuruxolitinib was higher in females than males. $AUC_{0\text{-}24hr}$ values of deuruxolitinib increased

with dose in a greater than dose-proportional manner. Drug accumulation was not noted after repeated dosing (exposure decreased after repeated dosing).

Table 68. Summary of Toxicokinetic Results of Deuruxolitinib in the 6-Month Oral Mouse Carcinogenicity Study

Interval (Day)	Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)
1	2	10	M	1090	0.500	1020	0.650
			F	2070	0.500	1910	0.825
			MF	1580	0.500	1460	0.779
	3	30	M	4860	0.500	5150	0.693
			F	5740	0.500	6250	0.635
			MF	5300	0.500	5700	0.650
	4	100	M	16600	0.500	38800	0.832
			F	28400	0.500	45300	1.02
			MF	22500	0.500	42100	0.926
182	2	10	M	555	0.500	553	0.856
			F	977	0.500	1370	1.30
			MF	766	0.500	975	1.20
	3	30	M	2330	0.500	2410	1.13
			F	3850	0.500	4270	1.03
			MF	2940	0.500	3270	1.07
	4	100	M	5080	0.500	14600	0.967
			F	9520	0.500	15600	1.83
			MF	7300	0.500	15300	1.29

Note: Combined male and female (MF) parameters were calculated by combining concentration data for all animals (male and female) at each dose level on each interval and using these data as a separate composite profile for TK analysis. These parameters are not an average of the values calculated for males and females separately.

16.3.2. Multiples of Human Exposure Calculation

The multiples of human exposure based on AUC comparison between the NOAELs identified in pivotal toxicology studies and the maximum recommended human dose (MRHD, 8 mg BID) are shown in the table below.

The human AUC_{0-24h} value at the MRHD used in the calculation is 2020 ng·hr/ml. This value is provided by the clinical pharmacology reviewer, Dr. Rakesh Gollen. This value is based on the steady state AUC_{0-12h} value of 1010 ng·hr/ml (refer to Section 6).

Table 69. Multiples of Human Exposure for NOAELs Identified in Pivotal Toxicology Studies

Study	Route	NOAEL (mg/kg/day)	AUC[a] (ng·hr/ml)	Multiples of Human Exposure[b] (Based on AUC Comparison)
26-week rat study	Oral	37.5	1640	0.8
52-week dog study	Oral	3	2850	1.4

Study	Route	NOAEL (mg/kg/day)	AUC[a] (ng·hr/ml)	Multiples of Human Exposure[b] (Based on AUC Comparison)
2-year carcinogenicity study in rats	Oral	30[c]	1210	0.6
Fertility study in male rats	Oral	Paternal: 30	761	0.4
		Male fertility: 100	4540	2.2
Fertility and early embryonic development study in female rats	Oral	Maternal: 30	1860[d]	0.9
		Female fertility: 100	27800[d]	14
		Early embryonic: 10	492[d]	0.2
Embryo-fetal development study in rats	Oral	Maternal: 60	9700[d]	4.8
		Embryo-fetal: 30	2070[d]	1.0
Embryo-fetal development study in rabbits	Oral	Maternal: 30	96	0.05
		Embryo-fetal: 30	96	0.05
Pre- and postnatal development study in rats	Oral	Maternal: 30	1600[d]	0.8
		Developmental: 30	1600[d]	0.8

[a] The lower AUC value between males and females was used for the calculation.
[b] Compared with the estimated steady state human $AUC_{0\text{-}24h}$ value: 2020 ng·hr/ml
[c] Dose level of no neoplastic findings in the carcinogenicity study
[d] AUC_{Tlast} value

16.3.3. Recommended Revisions to the Nonclinical Portions of Labeling

Revisions to the Applicant's proposed wording for the nonclinical portions of labeling are provided below. It is recommended that the underlined wording be inserted into, and the ~~strikethrough~~ wording be deleted from the LEQSELVI label proposed by the Applicant. The subheadings in Section 8.1 should be in underlined format. It is recommended that the Applicant proposed Section 8.3 be deleted as the study findings in the female rat fertility and early embryonic study are described in Section 13.1 and the addition of Section 8.3 is not considered necessary. A clean copy of the recommended nonclinical portions of labeling is also provided.

(b) (4)

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

16.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

16.4.1. Population Pharmacokinetics (PopPK) Modeling Analysis

Executive Summary

The FDA's Assessment

The objective of this review is to evaluate the adequacy of the Applicant's Population Pharmacokinetics (PopPK) modeling analysis and to evaluate the impact of intrinsic and extrinsic factors on the PK of deuruxolitinib. The Division of Pharmacometrics has reviewed the PopPK report (conc-pmx-ctp543-3280) and the modeling supporting files and concluded that:

Article VII. The PK of deuruxolitinib following oral administration in AA patients and healthy adults was adequately described by a 2-compartment model with rate of absorption, ALAG1, and linear elimination.

Article VIII. ALT, BMI, male sex were considered statistically significant covariates on CL/F, body weight was statistically significant covariate on the central volume of distribution (V2/F) and food status was considered a statistically significant covariate on rate of absorption. However, none of these covariate effects is considered clinical meaningful. There was also no effect of race, ethnicity, age, or eGFR on the PK of deuruxolitinib. Thus, no dose adjustments were recommended based on intrinsic factors or for specific populations.

Article IX. Exposure was largely proportional to doses between 4 and 12 mg BID and with an estimated terminal elimination half-life independent of dose and with a geometric mean between 3.97 and 4.54 hours for 4-mg to 12-mg BID regimens.

Article X. PopPK modeling is applicable to produce individual EBE estimates for exposure prediction and covariate identification for subjects with moderate to severe AA. The individual estimated exposure metrics derived for exposure-response analysis was considered reliable.

PopPK Review Summary

The goal of PopPK analysis is to characterize the PK profile of deuruxolitinib and explore the source of PK variability for the potential need of individualized dosing as well as predict the individual exposure for E-R assessment. The summary of all continuous and categorical covariates is presented Table 71. The summary of population PK model is outlined in and goodness of fit plots for the final PK model are given in Figure 15 and Figure 16, as well as the visual predictive check plots is given in Figure 17. The model predicted parameter estimates for deuruxolitinib final 2 compartment PopPK model with rate of absorption, ALAG1, and linear elimination is given in Table 72 and model predicted summary of plasma steady-state AUC_{0-12} estimates of deuruxolitinib by dose is given in Figure 18.

Table 70. Summary of Population PK Model

Study Included	**Phase I: CP543.1001, CP543.1002, CP543.1003, CP543.1006** **Phase II: CP543.2001, CP543.2004** **Phase III: CP543.3001 CP543.3002**	
Dose(s) included	Single dose: 8, 16, 32, 48 mg Multiple doses: 8, 24, and 32 mg QD, and 4, 8, 12, and 16 mg BID	
Dosage form included	capsule, tablet	
Population Included	Healthy adults, adults with hepatic and renal impairment, patients with moderate-to-severe AA. A total of 868 PK observations and 19 subjects were excluded from the analysis.	
No. of patients, PK samples, BLQ	The full dataset included 4854 PK observations from 670 subjects. BLQ observations after administration of the first dose ("post-treatment BLQ") account for 10.4% of all observations. the analysis was conducted on the PK analysis set containing 651 subjects and 3986 PK observation records.	
Covariates evaluated	A total of eleven continuous covariates and 5 categorical covariates were tested in the PopPK analysis, which includes age, BW, height, BMI, ideal body weight, serum creatinine, creatinine clearance (CLcr), eGFR, ALT, AST, albumin, bilirubin, ALP(U/L) as continuous covariates, and food (fasted/fed), drug formulation type (capsule /tablet), sex (male/female), dose (4, 8, 12, 16, 24, 32, and 48 mg), subject status (healthy subjects/subjects with AA), race (white/African American, Asian, American Indian/Alaskan native/ native Hawaiian or other pacific islander, ethnicity (not Hispanic or Latino/Hispanic or Latino, etc.).	
Final Model	**Summary**	**Acceptability/Comment**
Software (version)	NONMEM software (Ver 7.4.3) R (Version 4.2.0) Perl-speaks-NONMEM (Version 4.8.1)	Yes
Estimation algorithm	first-order conditional estimation with INTERACTION	Yes
Model structure	2-compartment model with first order absorption with an absorption lag time, and linear elimination.	Acceptable.
Model parameter estimates	Table 72	N/A
Uncertainty and variability (RSE, IIV, shrinkage, bootstrap)	- For the parent drug, key parameters were estimated with good precision (|%RSE| <40%). Unexplained IIV (coefficient of variation percentage [CV%]) was reduced by 11.2% for CL/F, 12.7% for V2/F, and 1% for KA compared to the base model. The magnitude of the IIV was moderate for CL (59.6% CV) but high for KA	Generally acceptable. Steady-state exposures were derived from individual EBE estimates for E-R analysis of AA patients.

Study Included	**Phase I: CP543.1001, CP543.1002, CP543.1003, CP543.1006** **Phase II: CP543.2001, CP543.2004** **Phase III: CP543.3001 CP543.3002**	
	(192% CV) and bioavailability (130% CV). Shrinkages are reasonable, ranging from 7.4 to 52.5%.	The large eta-shrinkage of V2 will impact the accuracy of predicting peak of deuruxolitinib concentrations.
BLQ for parameter accuracy	BLQ excluded in PopPK analysis.	Yes. Postinfusion BLQ is ~10% of all observations. Considering the timing of the majority of the BLQ records (>24 hours postdose) and the short half-life for deuruxolitinib (<4 hours), the M3 likelihood imputation was not used.
Goodness of Fit (GOF), Visual Predicted Check (VPC) and boxplots of steady-state AUC_{0-12} by dose.	Figure 15 and Figure 16 are GOF plots showing overall agreement between observed and model-predicted concentrations. Figure 17 VPC plot showed a good agreement between observed and model predicted values. Figure 18 containing boxplots of steady-state AUC_{0-12} by dose (mg) shows change in AUC at each dose level studied.	Acceptable.
Significant covariates and clinical relevance	CL of the deuruxolitinib: Positive factors: ALT, BMI, male sex V2 of the deuruxolitinib: Positive factors: body weight KA of the deuruxolitinib: Positive factors: food status	Yes. None of these covariates are likely to have clinically meaningful impact on exposure of deuruxolitinib.
Labeling Language	**Description**	**Acceptability/Action**
12.3 Pharmacokinetics	Specific population information was based on the impact of covariates assessed in PopPK or results from dedicated studies. No dose adjustment is suggested.	Yes

Table 71. Summary of Continuous and Categorical Covariates – PK Analysis Set

Variable Type	Study Number	Total (N=651)
Continuous covariates[a]	Age (years)	37.8 (12.9)
	Baseline body weight (kg)	77.8 (18.7)
	Baseline body height (cm)	168 (9.89)
	Baseline body mass index (kg/m²)	27.4 (6.08)
	Baseline ideal body weight (kg)	62.9 (7.62)
	Baseline serum creatinine (µmol/L)	71.8 (15.2)
	Baseline creatinine clearance mL/min	126 (37.2)
	Baseline eGFR (mL/min/1.73)	95.9 (19.7)
	Baseline ALT (U/L)	20.1 (12.9)
	Baseline AST (U/L)	19.2 9.94)
	Baseline bilirubin (mg/dL)	0.566 (0.295)
Categorical covariates[b]	Food status	
	Fasted	87 (13.4%)
	Fed	14 (2.20)
	Unknown	550 (84.5%)
	Study drug formulation	
	Capsule	60 (9.2%)
	Tablet	591 (90.80%)
	Sex	
	Male	225 (34.60%)
	Female	426 (65.40%)
	Dose (mg)	
	4 mg	30 (4.60%)
	8 mg	322 (49.50%)
	12 mg	232 (35.60%)
	16 mg	40 (6.10%)
	24 mg	8 (1.20%)
	32 mg	14 (2.20%)
	48 mg	5 (0.80%)
	Subject status	
	Healthy subject	101 (15.50%)
	Subject with AA	550 (85.50%)

Variable Type	Study Number	Total (N=651)
	Race	
	White	485 (74.50%)
	African American	108 (16.60%)
	Asian	41 (6.30%)
	American Indian/Alaskan Native	4 (0.60%)
	Native Hawaiian or other Pacific Islander	2 (0.30%)
	Other	11 (11.70%)
	Ethnicity	
	Non-Hispanic or Latino	575 (88.30%)
	Hispanic or Latino	73 (11.20%)
	Missing	3 (0.50%)

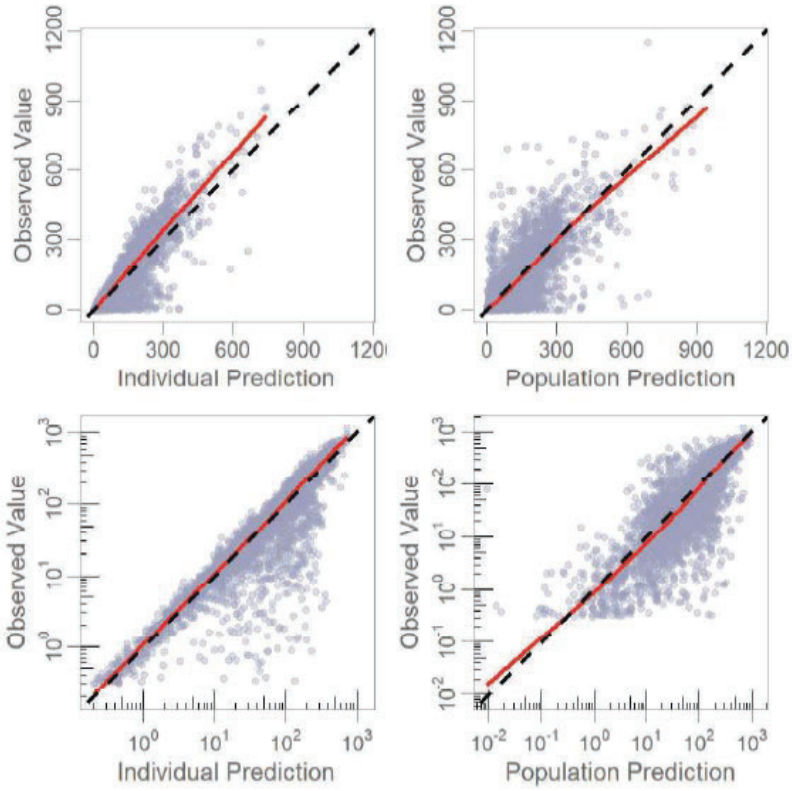
Source: EDA-CTP543_07Dec2022.Rmd (continuous variables), EDA-CTP543_07Dec2022.Rmd (categorical variables)
[a] Data is presented as Mean (SD)
[b] Numeric columns are formatted as count (% of total).
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; N, number of subjects with available information; PK, pharmacokinetic

Table 72. Parameter Estimates for Deuruxolitinib Final PopPK Model

Parameter	Estimate	RSE%	95%CI	Shrinkage
Typical Values				
CL/F (L/h)	7.9	3.36	7.38, 8.42	
V2/F (L)	47.2	2.76	44.7, 49.8	
KA (1/h)	2.65	10.3	2.12, 3.18	
Q (L/h)	0.736	38.5	0.180, 1.29	
V3/F (L)	3.48	21.5	2.01, 4.94	
F1	1.00 Fixed	N/A	N/A	
ALAG1	0.0659	0.81	0.0648, 0.0669	
Covariate				
ALT on CL/F	-0.228	21.8	(-0.326, -0.131)	
BMI on CL/F	0.56	22.8	0.309, 0.81	
Male on CL/F	0.487	15.5	0.339, 0.635	
Fed on F1	-0.138	20.7	(-0.194, -0.0821)	
Capsule on F1	-0.229	13.1	(-0.288, -0.17)	
Fed on KA	-0.793	5.48	(-0.879, -0.708)	
Fasted on KA	1.07	25.3	0.539, 1.6	
Body weight on V2/F	1.16	7.22	0.993, 1.32	
Between-subject variability				
On V2/F	22.5	8.71	18.3, 26.1	52.50%
Correlation on CL/F and V2/F	0.0276	37.7	0.00724, 0.048	
On CL/F	59.6	4.63	54.1, 65	12.90%
Correlation on KA and CL/F	-0.48	13.7	(-0.608, -0.351)	
On KA	192	13	146, 245	23.50%
Residual error				
Proportional error %	0.408	1.44	0.396, 0.419	7.40%

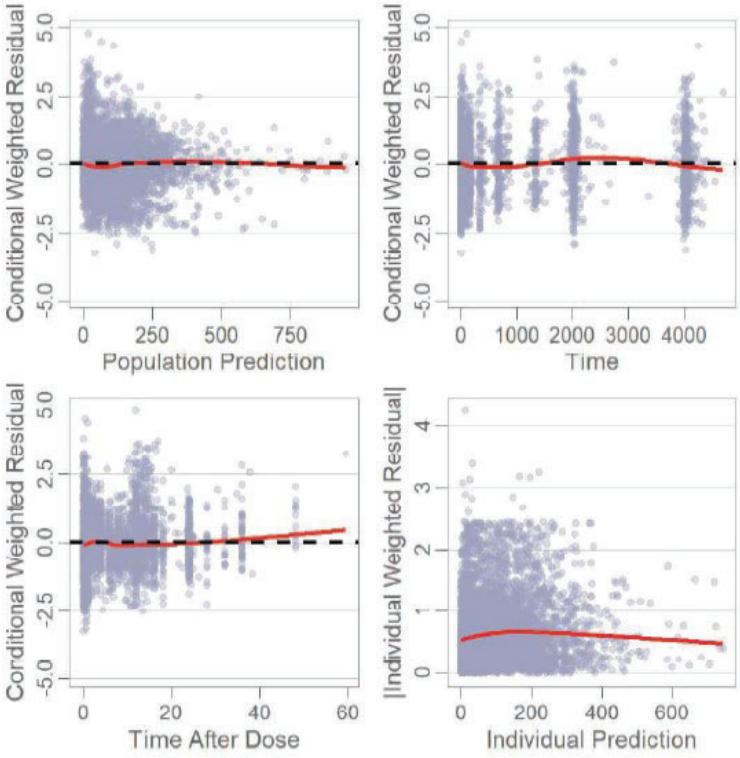
Source: Concert-PopPK_Cov Model Diagnostics_Run21014_v2.Rmd
Estimates shown are CV%.
Abbreviations: ALAG1, absorption lag time; ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; CL/F, apparent clearance; CV%, coefficient of variation percentage; F1, relative bioavailability; I, individual subject parameter; KA, first-order absorption rate constant; N/A, not applicable; PopPK, population pharmacokinetic; Q, intercompartmental clearance; RSE%, relative standard error percentage; V/F and V2/F, apparent central volume of distribution; V3/F, apparent peripheral volume of distribution

Figure 15. Observed vs. Predicted Concentration GOF Plots for the Final PK Model



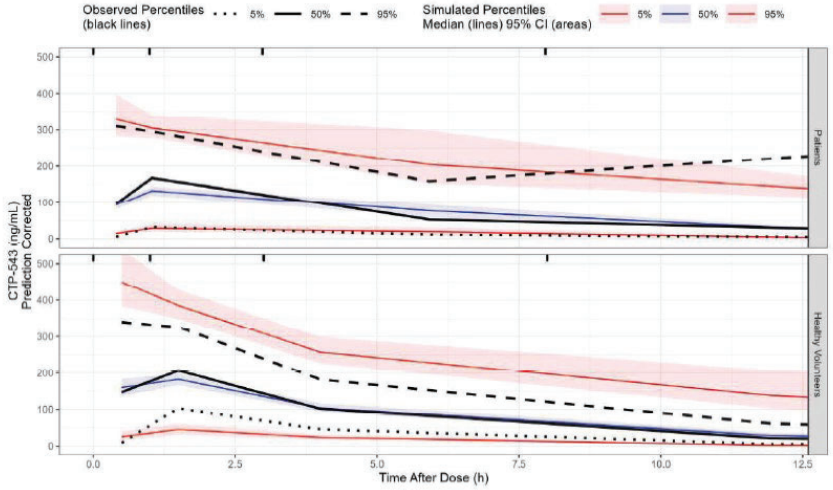
Source: Concert-PopPK_Cov Model Diagnostics_Run21014_v2.Rmd
Notes: Dots are individual data points, and solid red lines are smoothed LOESS lines. The dashed lines are lines of identity.
Abbreviations: GOF, goodness-of-fit; LOESS, locally weighted scatterplot smoothing

Figure 16. Residual GOF Plots for the Final PopPK Model



Source: Concert-PopPK_Cov Model **Diagnostics_Run21014_v2.Rmd**
Notes: Dots are **individual data points, and solid red lines are smoothed LOESS lines. The dashed lines are at 0.**
Abbreviations: GOF = goodness-of-fit; LOESS = locally weighted scatterplot smoothing

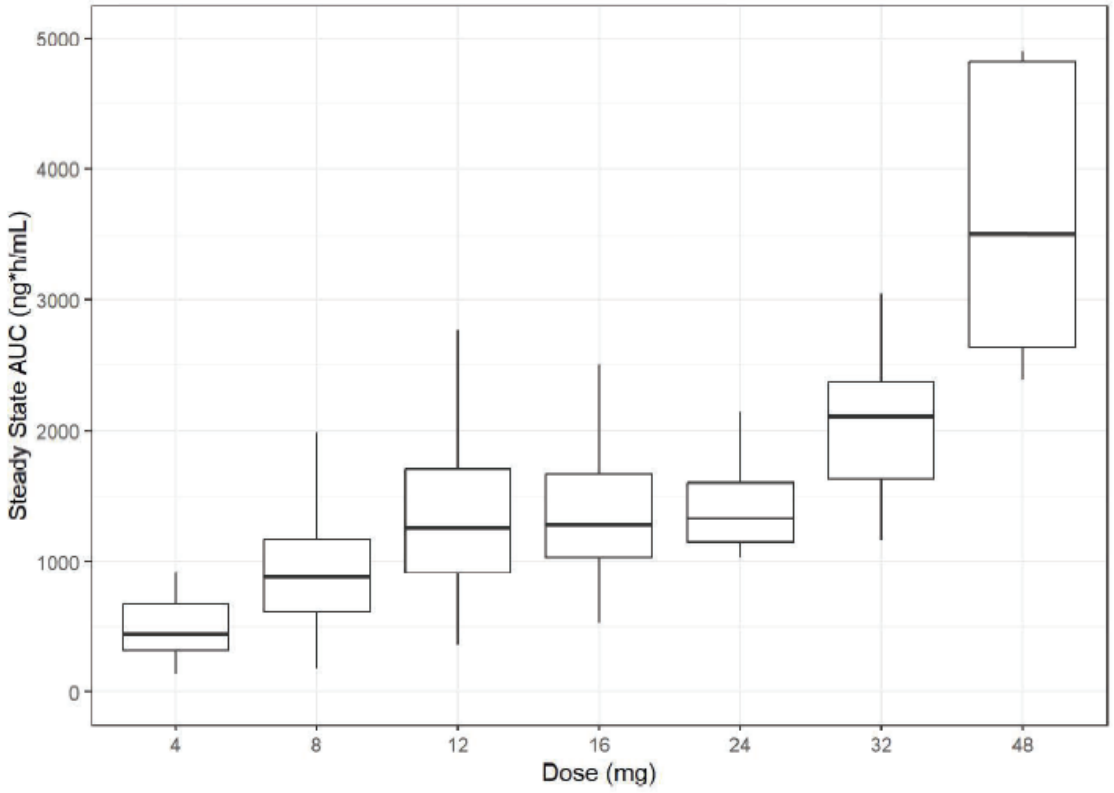
Figure 17. VPC for Deuruxolitinib Final PopPK Model by Subjects Status Linear



APPEARS THIS WAY ON ORIGINAL

Source: run21014vpc.r
Notes: The black solid line is the observed median, the black dashed line is the observed 95th percentile, and the black dotted line is the 5th percentile. The blue area is the 95% PI of the simulated median, and red areas are the 95% PIs of the simulated 5th and 95th percentiles.
Abbreviations: CI, confidence interval; pcVPC, prediction-corrected visual predictive check; PI, prediction interval

Figure 18. Boxplots of Steady-State AUC_{0-12} by Dose



Source: Concert-PopPK_Covariate Model Run21014-Simulated Exposures_v3.Rmd
Notes: Outliers are not included in the boxplots.
Abbreviations: AUC, area under the plasma concentration-time curve; $AUC_{0-12,}$ AUC over the dosing interval

16.4.2. Exposure-Response Analysis

Executive Summary

The FDA's Assessment

- E-R efficacy models adequately describe dose/exposure-dependent change in efficacy endpoints which includes 1) the probability of achieving a SALT score </=20 at week 24 as a binary endpoint and 2) the change from baseline in SALT score as a continuous variable. Results from both analyses support a near plateauing of the exposure-effect relationship at C_{avg} associated with an 8-mg BID regimen which falls on the steep portion of the E-R curve.
- For E-R safety analysis of select AEs, there were an increasing trend of platelets and a decreasing trend of hemoglobin versus time and with increased deuruxolitinib exposure. PK-PD indirect response models were developed for both endpoints.
- E-R relationship for efficacy and safety provide support for the proposed dosing regimen of 8 mg BID.

E-R Review Summary

Goal of E-R analysis is to evaluate/explore the E-R relationship for efficacy and safety for potential dose optimization. C_{avg} was chosen as the exposure metric due to the assumption it was related to the pharmacologic activity of deuruxolitinib and the observation that the secondary exposure parameters largely correlated with each other (coefficients of determination >0.8 for AUC_{0-12}, C_{max}, and C_{min}).

In the E-R efficacy analysis, SALT score at Week 24 was selected for the exposure-efficacy analysis as efficacy endpoint. The subjects who were included in the exposure-efficacy analysis had valid exposure values, baseline SALT scores, and a Week 24 SALT score and 2 endpoints were analyzed, which includes 1) Binary endpoint: whether the subject had a SALT score ≤20 at week 24 and 2) Continuous endpoint: % change from baseline SALT score, which are outlined in Table 73. Out of a total of 662 subjects, SALT score ≤20 at week 24 was achieved in 4 subjects (2.5%) for the placebo group, 4 subjects (14.3%) for the 4-mg group, 74 subjects (26.8%) for the 8-mg group, and 80 subjects (40.8%) for the 12-mg group respectively. The summary of exposure-efficacy analysis using population PK approach is outlined in Table 73. The baseline SALT on E0 covariate effect is a linear relationship on E0. The predicted probability for achieving a SALT score ≤20 at week 24 for the median C_{avg} for 8 mg (75.8 ng/mL) for a subject with the median baseline SALT score (98.6) is 0.225.

For the E-R safety analysis, increasing trend of platelets and a decreasing trend of hemoglobin versus time and with increased deuruxolitinib exposure are selected as safety endpoints. The summary of exposure-safety model for platelets and hemoglobin versus time and with increased deuruxolitinib exposure using population PK approach is also outlined in Table 73 below. The median increase in platelet count was estimated to be $<100 \times 10^3$ µL over the course of 24 weeks of treatment. The median decrease in hemoglobin was estimated to be approximately 1 g/dL over the course of 24 weeks of treatment. Out of the 658 subjects, AEs of at least Grade 2 severity were reported in one subject (0.2%) for any AE related to platelet count, one subject (0.2%) for any AE related to absolute neutrophil count, five subjects (0.8%) for any AE related to hemoglobin, seven subjects (1.1%) for any AE related to creatine kinase, and one subject (0.2%) for any AE related to lipase.

Table 73. Summary of Exposure-Response (Both Efficacy and Safety) Analysis Using Population PK Approach

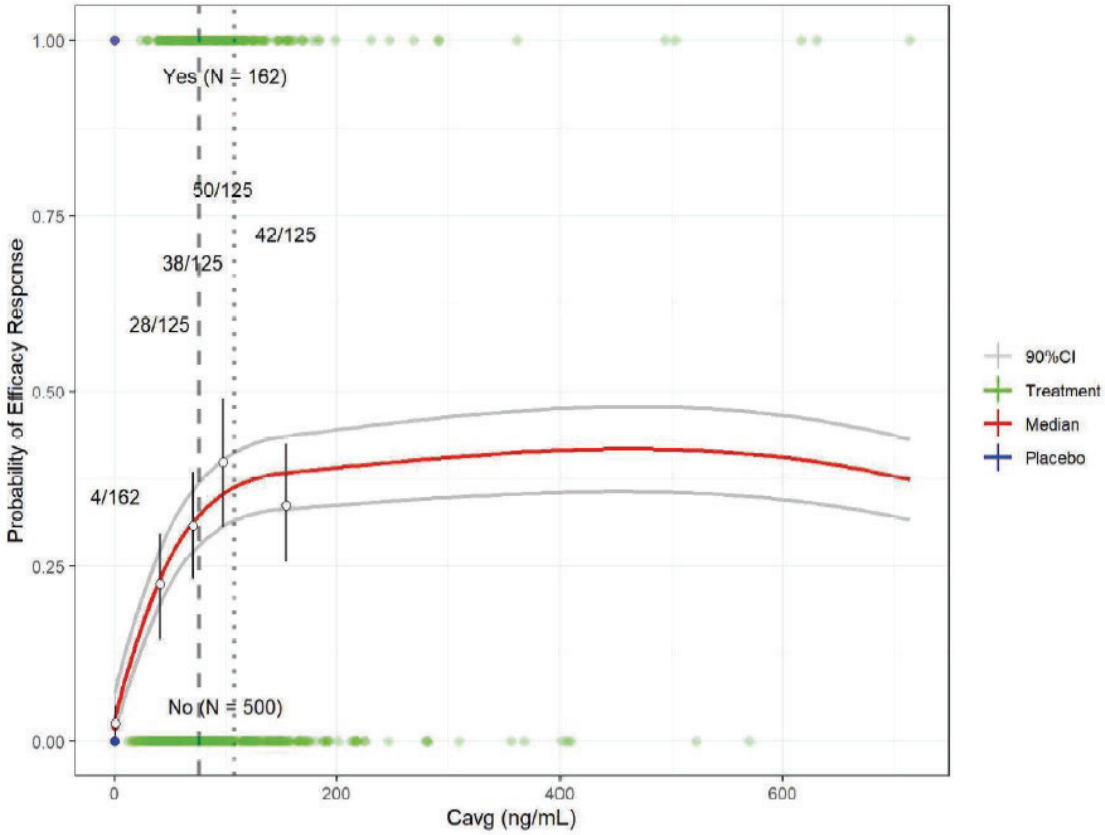
		General Information	
Study included		Phase II: CP543.2001, CP543.2004 Phase III: CP543.3002	
Exposure variable		C_{min}ss, C_{max}ss, C_{avg}ss were used	
Endpoint		Efficacy: SALT score Safety: platelet count, hemoglobin,	
No. of patients in treatment arm		662	
Dose(s) included		162 subjects for placebo, 28 subjects for a dose of 4 mg, 276 subjects for a dose of 8 mg, and 196 subjects for a dose of 12 mg.	
Covariates evaluated		For exposure efficacy model: Baseline SALT on E0, E_{max}, Age on E0 and E_{max}, Sex (male) on E0 and E_{max}, current duration of episode on E0 and E_{max} For exposure-safety model: Baseline Body weight, sex, age, dose level are tested for Platelet Model and Hemoglobin Model	
E-R Model		**Summary**	
		Estimation algorithm	Acceptability/comments
Efficacy: binary endpoint (whether the subject had a SALT score ≤20 at week 24)	Model structure	E_{max} model was chosen as the base model	Yes. Based on the trends shown over time, E_{max} model is acceptable. P_{event} is the probability of a certain outcome/event (response), E0 is the response at 0 concentration, E_{max} is the maximum response, EC_{50} is the exposure producing half maximal response, and Exposure is the exposure metric chosen to best describe the observed responses (C_{avg}), which is acceptable.
	Model parameter estimates	E_{max} model was chosen as the base model. The EC_{50} was fixed to 16.7 ng/mL due to the lack of precision in estimating that parameter, RSE of 47%.	The predicted probability for achieving a SALT 24 for the median C_{avg} for 8 mg (75.8 ng/mL) for a subject with the median baseline SALT score (98.6) is 0.225.

		General Information	
	Significant covariates for efficacy binary endpoint SALT score ≤20 at week 24 for E-R Model	Baseline SALT on E0	Based on a p-value of <0.001 significance, a drop in OFV of >10.828 is considered statistically significant, which is acceptable.
	Visualization of E-R (efficacy binary endpoint): SALT score ≤20 at week 24	Figure 19; 8-mg median exposure is on the steeper portion of the E-R curve, which is consistent with dose-response observations.	The model accurately predicts the observed responders for each C_{avg} quartile and the placebo group.
Efficacy: continuous endpoint (% change from baseline SALT score)	Model structure	E_{max} model was chosen as the base model	Yes. Based on the trends shown over time, E_{max} model is acceptable. E is % change from baseline SALT score at Week 24 (response), E0 is the response at 0 concentration, E_{max} is the maximum response, EC_{50} is the exposure producing half maximal response, and Exposure is exposure metric chosen to best describe the observed responses (C_{avg}), which is acceptable.
	Model parameter estimates	The estimated E_{max} (-63.77) suggests that the typical baseline SALT score at Week 24 will have a maximum decrease by 63.77%.	The predicted percent change from baseline in SALT score for the median C_{avg} for 8 mg (75.8 ng/mL) is a decrease by 44.8%.
	Significant covariates for efficacy continuous endpoint: % change from baseline SALT score for E-R Model	No covariates were accepted as a statistically significant covariate on the model	Based on a p-value of <0.001 significance, a drop in OFV of >10.828 is considered statistically significant, which is acceptable.
	Visualization of E-R (efficacy continuous endpoint): % change from baseline	Figure 20; 8-mg median exposure falls on the steeper portion of the E-R curve, which is consistent with dose-response observations as well as the logistic regression E-R analysis.	The model accurately predicts the observed response for the range of predicted C_{avg}.

		General Information	
Safety: platelet as endpoint	Model structure – platelet as endpoint	Indirect response model, where a standard indirect response PD model with DE stimulating turnover rate (Kin) was used. Linear, power, E_{max}, and sigmoidal E_{max} DEs were tested with an E_{max} model providing the best model fit. The goodness of fit plots for final platelet model are shown in Figure 21	Yes. Based on the trends shown over time, E_{max} model is reasonable. R is the response; Kin is the turnover rate; Kout is the fractional turnover rate; BLc(baseline value) is the ratio of Kin to Kout; E_{max} is the maximum response; Cp is the predicted plasma concentration; and EC_{50} is the exposure producing half maximal response.
	Summary of endpoints	The model parameters are estimated with high precision based on the low RSE% for all parameters. The IIV for Kin has moderately high shrinkage (47.3%). The ϵ-shrinkage was low (7.70%). Table 74	Yes. There are no trends of model misspecification observed within the GOF plots.
	Significant covariates	Based on scatterplots (for continuous covariates) and boxplots (for categorical covariates), no covariates were tested on the base model.	Yes
	Visualization of E-R	Figure 22	There are no trends of model misspecification observed when model simulated values were compared with clinical observed values.

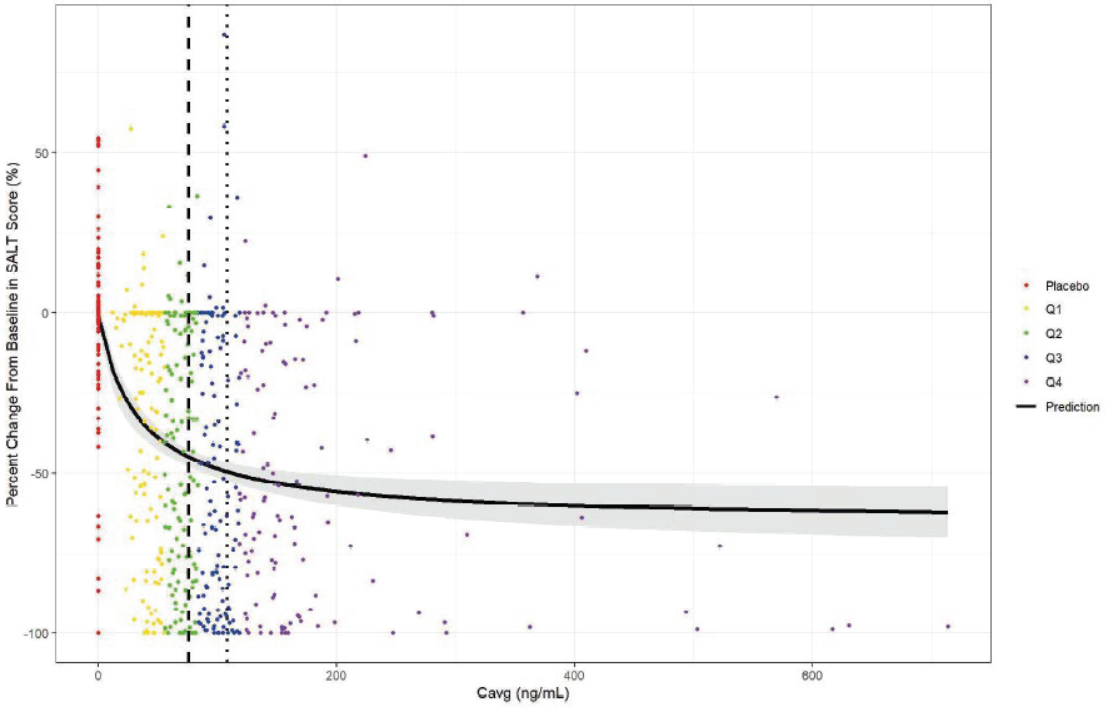
		General Information	
Safety: hemoglobin as endpoint	Model structure	Indirect response model, where a standard indirect response PD model with DE stimulating turnover rate (Kin) was used. R is the response; Kin is the turnover rate; Kout is the fractional turnover rate; BL (baseline value) is the ratio of Kin to Kout; E_{max} is the maximum response; Cp is the predicted plasma concentration; and EC_{50} is the exposure producing half maximal response.	Yes. Based on the trends shown over time, E_{max} model is reasonable. Also, among linear, power, E_{max}, and sigmoidal E_{max} DEs were tested with an E_{max} model providing the best model fit. Different error models including proportional, additive, and additive-proportional error models were tested. Additive error providing the best model fit.
	Summary of endpoints	All parameters except for concentration at which 50% of the response is observed (EC_{50}) were estimated with good precision (RSE% <25%). EC_{50} was estimated with higher uncertainty (RSE% 33.1%). The ϵ-shrinkage was low (9.30%). Table 75	The IIV shrinkage for the base model was low for baseline hemoglobin. The IIV for Kin and E_{max} has moderately high shrinkage (75.0% and 33.1%). No marked systematic trends were seen in the GOF plots (Figure 24).
	Significant covariates	Based on scatterplots (for continuous covariates) and boxplots (for categorical covariates), sex on baseline hemoglobin was tested on the base model.	Yes, Following inclusion of sex on baseline hemoglobin, the OFV decreased by 451 signifying statistical significance of this covariate effect.
	Visualization of E-R	Figure 25	There are no trends of model misspecification observed when model simulated values were compared with clinical observed values.

Figure 19. Visual Predictive Plot for the Efficacy Binary Endpoint Final Model



Source: CTP543_ER_Efficacy_12Dec2022_v2.Rmd
Notes: The dashed line represents the median C_{avg} for the 8-mg dose group and the dotted line represents the median C_{avg} for the 12-mg dose group. The open circles represent observed responses by the exposure (C_{avg}) quartile or placebo grouping. The solid red line is the LOESS smooth line through the median response from the 1000 replicates with the gray lines representing the 90% CI.
Abbreviations: C_{avg}, average plasma concentration; CI, confidence interval; LOESS, locally weighted scatterplot smoothing; N, number of subjects with available information

Figure 20. Visual Predictive Plot for the Efficacy Continuous Endpoint Final Model



Source: CTP543_ER_Efficacy_12Dec2022_v2.Rmd
Notes: The dashed line represents the median C_{avg} for the 8-mg dose group and the dotted line represents the median C_{avg} for the 12-mg dose group. The dots represent observed individual data that are colored by the exposure (C_{avg}) quartile or placebo grouping. The solid black line is the median response from the 1000 replicates with the gray shaded region representing the 90% CI.
Abbreviations: C_{avg}, average plasma concentration; CI, confidence interval; Qx, quartile x; SALT, Severity of Alopecia Tool

For E-R safety analysis of select AEs, there were an increasing trend of platelets and a decreasing trend of hemoglobin versus time and increased deuruxolitinib exposure. For other laboratory data, there was no clear longitudinal or deuruxolitinib exposure trend. PK-PD indirect response models were developed for both endpoints.

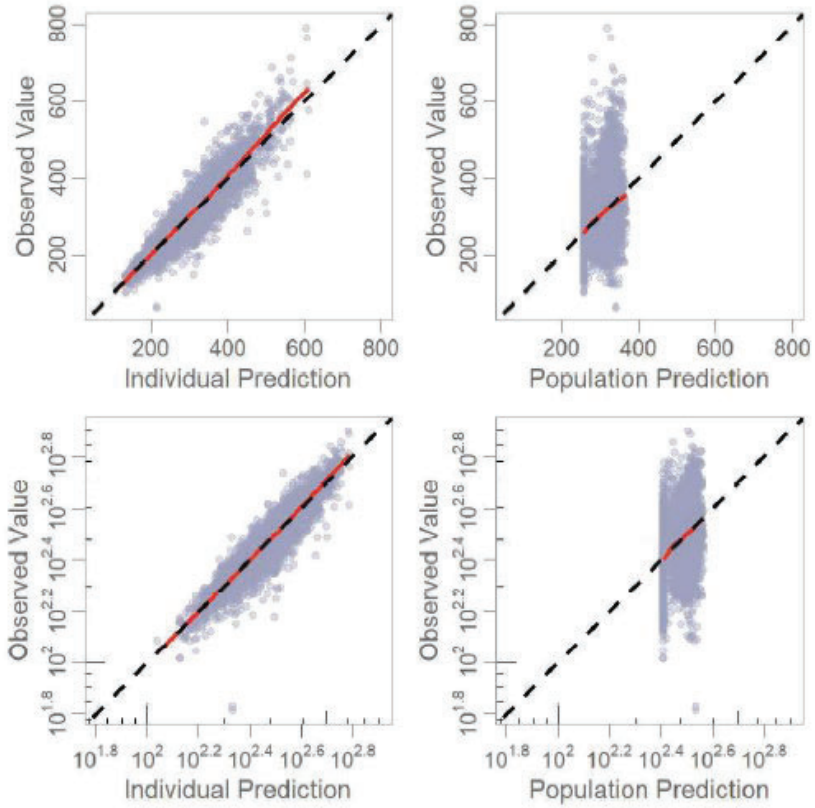
E-R safety analysis for an increasing trend of platelets versus time and increased deuruxolitinib exposure: Predicted plasma concentrations and hemoglobin were selected to be modeled as an indirect response model due to the trends shown in exploratory analysis. A standard indirect response PD model with DE stimulating fractional turnover rate (Kout) was used. The final platelet model parameter estimates are listed in Table 74. Figure 21 and Figure 22 shows the goodness of fit plots and visual predictive check plots for the final model. The predicted responses after 8-mg BID regimen resulted in elevations of platelet counts, with a maximum effect typically within the normal range of 150 × 10^3/µL to 450 × 10^3/µL across 8- and 12- mg dosing regimen. The median increase in platelet count was estimated to be <100 × 10^3/ µL over the course of 24 weeks of treatment period as shown in Figure 23. Minimal differences were predicted between the 8-mg and 12-mg BID regimens.

Table 74. Final Platelet Model Parameter Estimates

Parameter	Estimate	RSE%	95%CI	Shrinkage
Typical values				
Kin (1/h)	1.02	0.788	1.01, 1.04	
Baseline platelets ($\times 10^3/\mu L$)	256	0.380	254, 257	
Emax (-)	0.474	1.42	0.461, 0.487	
Hill (-)	1.00 fixed	N/A	N/A	
EC50 (ng/mL)	54.9	2.29	52.4, 57.3	
Between-subject variability[a]				
On Kin	307	21.6	196, 463	47.3%
On baseline platelets	22.5	2.95	21.2, 23.8	1.40%
Residual error				
Additive error ($\times 10^3/\mu L$)	0.00100 fixed	N/A	N/A	7.70%
Proportional error (%)	0.105	0.393	0.104, 0.106	7.70%

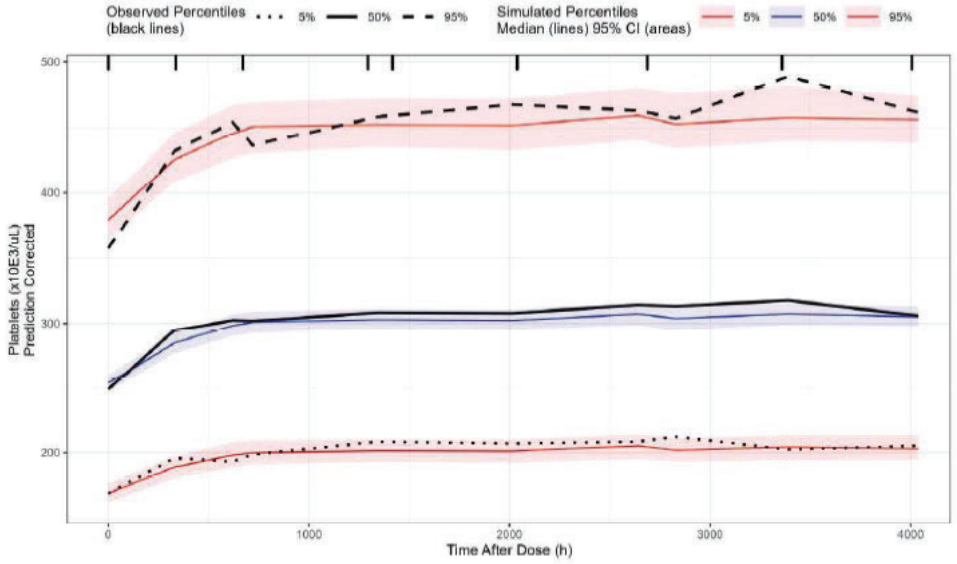
Source: CTP543-PKPD_Model Diagnostics_Run052.Rmd
[a] Estimates shown are CV%.
Abbreviations: CI, confidence interval; CV%, coefficient of variation percentage; EC_{50}, concentration at which 50% of the response is observed; E_{max}, maximum response; Kin, turnover rate; N/A, not applicable; RSE%, relative SE percentage

Figure 21. Observed vs. Predicted Concentration GOF Plots for the Final Platelet Model



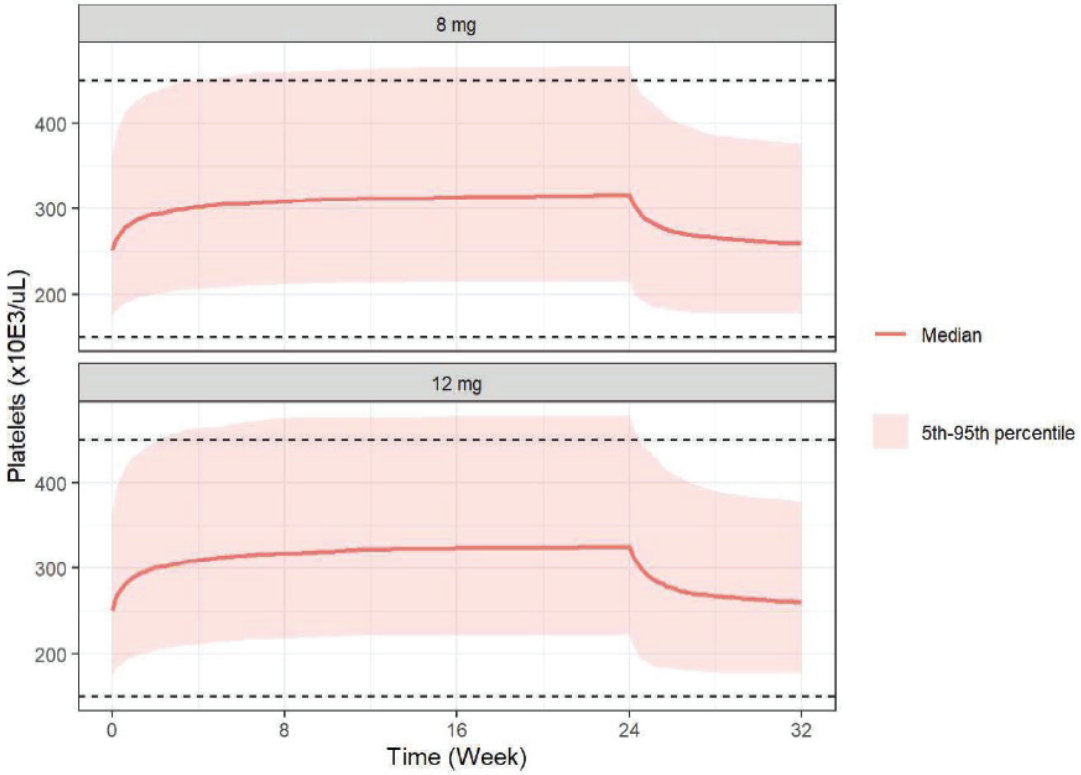
Source: CTP543-PKPD_Model Diagnostics_Run052.Rmd
Notes: Dots are individual data points, and solid red lines are smoothed LOESS lines. The dashed lines are lines of density.
Abbreviations: GOF, goodness-of-fit; LOESS, locally weighted scatterplot smoothing

Figure 22. VPC for Platelet Final Model Platelet Model



Source: run052vpc.r
Notes: The black solid line is the observed median, the black dashed line is the observed 95th percentile, and the black dotted line is the 5th percentile. The blue area is the 95% PI of the simulated median, and red areas are the 95% PIs of the simulated 5th and 95th percentiles.
Abbreviations: CI, confidence interval; pcVPC, prediction-corrected visual predictive check; PI, prediction interval

Figure 23. Predicted Platelets Following 24 Weeks of Treatment After 8-mg BID (Top), and 12-mg BID (Bottom) Dosing Regimen



Source: CTP543-PKPD Platelets Model Simulation.Rmd
Notes: The red solid line is the predicted median. The red areas are the simulated 5th and 95th percentiles. The dashed lines are at 150 × 103/µL and 450 × 103/µL.

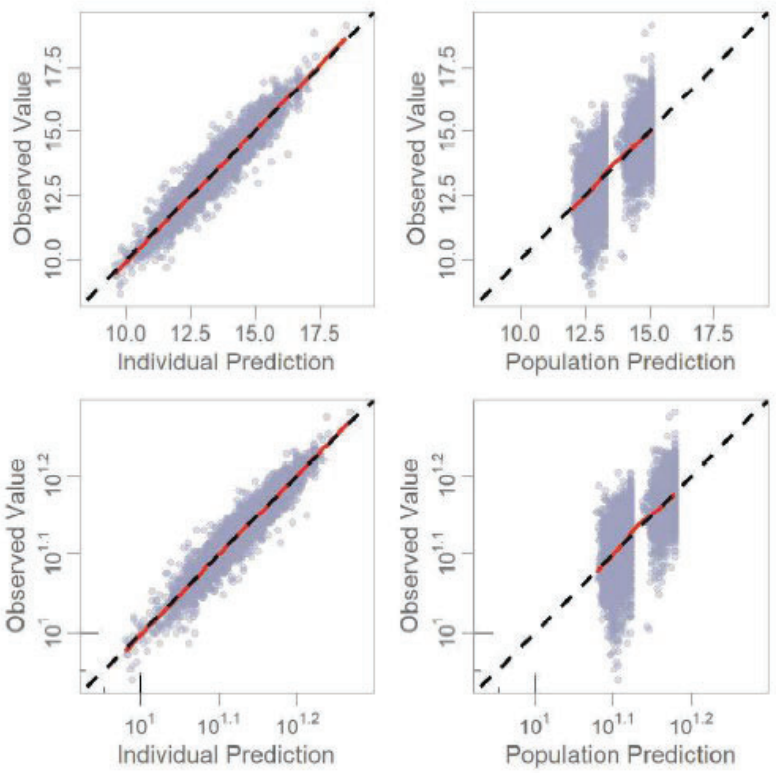
E-R safety analysis for a decreasing trend of hemoglobin versus time and increased deuruxolitinib exposure: Predicted plasma concentrations and hemoglobin were selected to be modeled as an indirect response model due to the trends shown in exploratory analysis. A standard indirect response PD model with DE stimulating fractional turnover rate (Kout) was used. The final hemoglobin model parameter estimates are listed in Table 75. Figure 24 and Figure 25 shows the goodness of fit plots and visual predictive check plots for the final model. The predicted median response after 8-mg BID regimen resulted in a median hemoglobin that was >12 g/dL over the entire course of 24 weeks of therapy for females and males, respectively. These predicted median responses by sex do not meet the threshold for a Grade 2 anemia (hemoglobin <10 g/dL) as per the NCI-CTCAE. The median decrease in hemoglobin was estimated to be approximately 1 g/dL over the course of 24 weeks of therapy in both females and males as shown in Figure 26 and Figure 27 respectively. Minimal differences were predicted between the 8-mg and 12-mg BID doses.

Table 75. Final Hemoglobin Model Parameter Estimates

Parameter	Estimate	RSE%	95%CI	Shrinkage
Typical values				
Kin (1/h)	0.0112	5.56	0.0100, 0.0125	
Baseline hemoglobin (g/dL)	13.3	0.304	13.2, 13.3	
Emax (-)	0.118	14.1	0.0858, 0.151	
Hill (-)	1.00 fixed	N/A	N/A	
EC50 (ng/mL)	59.7	33.1	21.0, 98.3	
Covariate effects				
Male on baseline hemoglobin	0.139	4.18	0.127, 0.150	
Between-subject variability[a]				
On Kin	33.2	22.6	13.0, 46.1	75.0%
On baseline hemoglobin	5.97	3.02	5.61, 6.31	4.20%
On Emax	72.9	6.69	63.1, 82.3	33.1%
Residual error				
Additive error (g/dL)	0.427	1.11	0.418, 0.437	9.30%

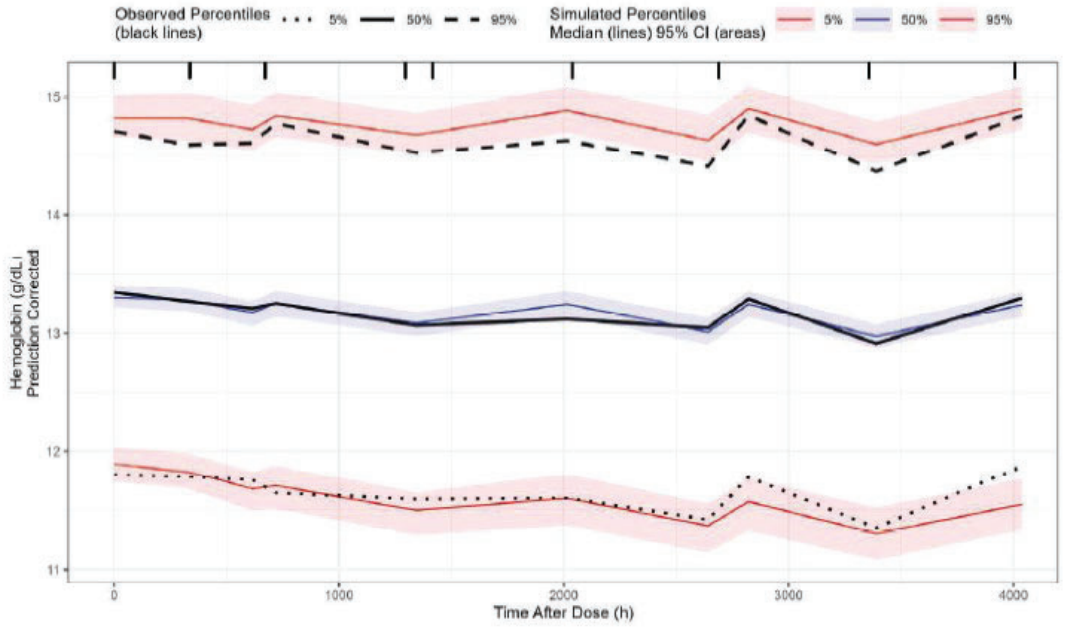
Source: CTP543-PKPD_Model Diagnostics_Run161.Rmd
[a] Estimates shown are CV%.
Abbreviations: CI, confidence interval; CV%, coefficient of variation percentage; EC_{50}, concentration at which 50% of the response is observed; E_{max}, maximum response; Kin, turnover rate; N/A, not applicable; RSE%, relative SE percentage

Figure 24. Observed vs. Predicted Concentration GOF Plots for the Final Hemoglobin Model



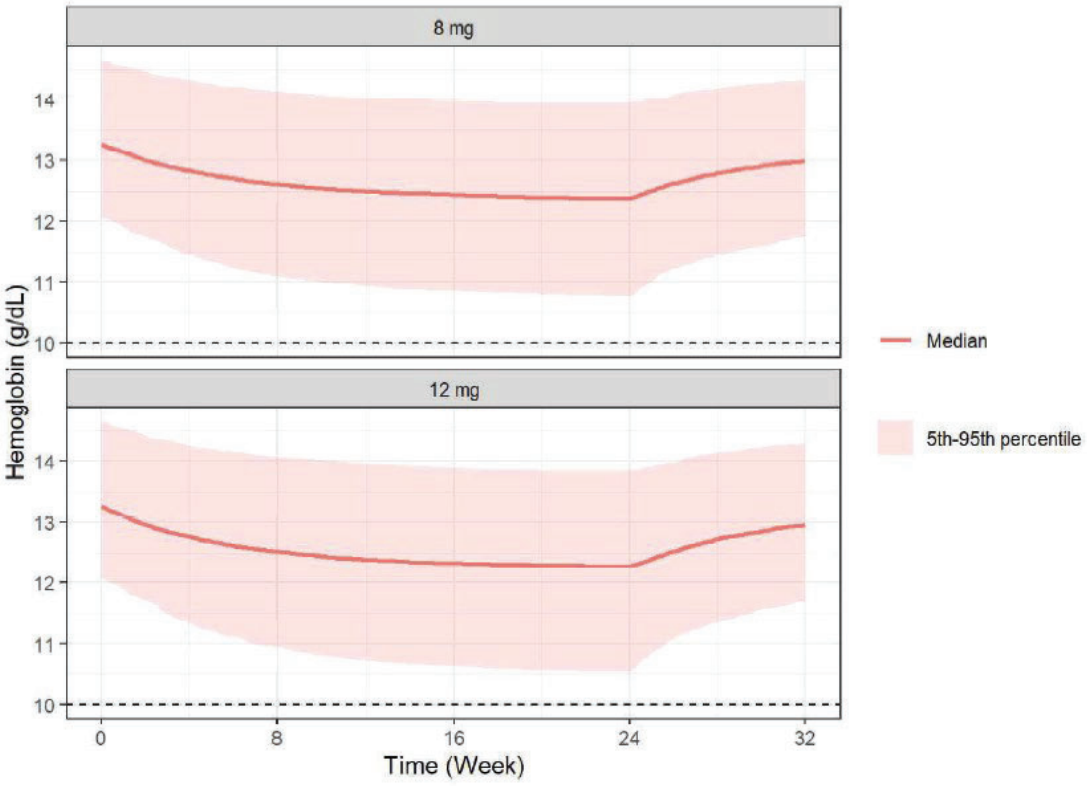
Source: CTP543-PKPD_Model Diagnostics_Run161.Rmd
Notes: Dots are individual data points, and solid red lines are smoothed LOESS lines. The dashed lines are lines of identity.
Abbreviations: GOF, goodness-of-fit; LOESS, locally weighted scatterplot smoothing

Figure 25. Visual Predictive Plot for the Hemoglobin Final Model



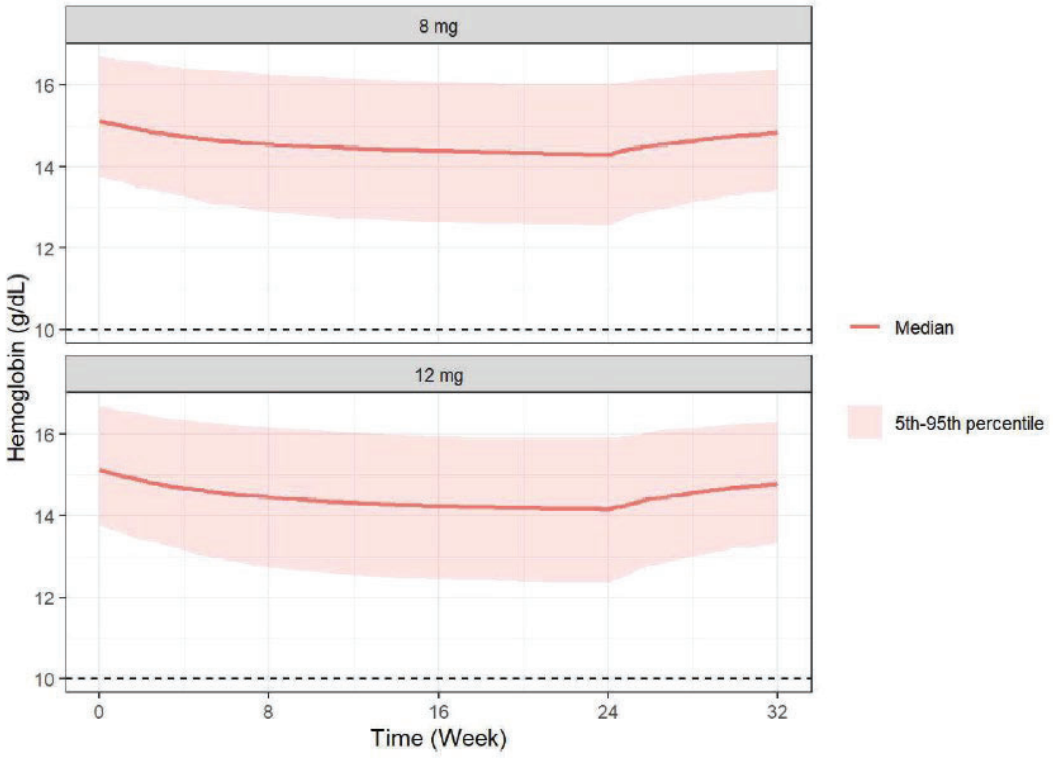
Source: run161vpc.r
Notes: The black solid line is the observed median, the black dashed line is the observed 95th percentile, and the black dotted line is the 5th percentile. The blue area is the 95% PI of the simulated median, and red areas are the 95% PIs of the simulated 5th and 95th percentiles.
Abbreviations: CI, confidence interval; pcVPC, prediction-corrected visual predictive check; PI, prediction interval

Figure 26. Predicted Hemoglobin Following 24 Weeks of Therapy for Females After 8-mg BID (Top), and 12-mg BID (Bottom) Dosing Regimens



Source: CTP543-PKPD Hemoglobin Model Simulation.Rmd
Notes: The red solid line is the predicted median. The red areas are the simulated 5th and 95th percentiles. The dashed line is at 10 g/dL to note the CTCAE definition for a Grade 2 anemia.
Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events

Figure 27. Predicted Hemoglobin Following 24 Weeks of Therapy for Males After 8-mg BID (Top), and 12-mg BID (Bottom) Dosing Regimens



Source: CTP543-PKPD Hemoglobin Model Simulation.Rmd
Notes: The red solid line is the predicted median. The red areas are the simulated 5th and 95th percentiles. The dashed line is at 10 g/dL to note the CTCAE definition for a Grade 2 anemia.
Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events

16.4.3. Physiological Based Pharmacokinetics Modeling Analysis

Executive Summary

The FDA's Assessment

The objective of this review is to evaluate the adequacy of the Applicant's PBPK analyses to evaluate the DDI potential of deuruxolitinib as a victim of strong CYP2C9 inhibitors and strong/moderate CYP3A4 inducers on the PK of deuruxolitinib in a non-genotyped population and in CYP2C9*3*3 genotyped subjects (CYP2C9 poor metabolizers) at 12-mg dose.

The Division of Pharmacometrics has reviewed the PBPK report (dm-116-conc-2-c), the modeling supporting files and Response to FDA's Information Requests (IRs) and concluded that the deuruxolitinib PBPK model can be used to inform dosing modifications in individuals with different CYP2C9 genotypes when co-administered with CYP3A4 and CYP2C9 inhibitors and inducers.

- The PBPK model predicts that concomitant use of multiple doses of a strong CYP2C9 inhibitor with a single 12-mg dose of deuruxolitinib would increase the AUC and C_{max} of

deuruxolitinib by 100% and 13%, respectively. CYP2C9 poor metabolizers are expected to have a similar magnitude of increases in deuruxolitinib exposure.

- The PBPK model supports that concomitant use of multiple doses of a dual CYP2C9 and CYP3A4 inhibitor (e.g., fluconazole) with a single 12-mg dose of deuruxolitinib would increase the AUC and C_{max} of deuruxolitinib by 140% and 12%, respectively. CYP2C9 poor metabolizers are expected to have a similar magnitude of increases in deuruxolitinib exposure.
- No clinically significant differences in deuruxolitinib pharmacokinetics are expected when used concomitantly with itraconazole (strong CYP3A4 inhibitor) or efavirenz (moderate CYP3A4 inducer)
- The PBPK analysis predicted that deuruxolitinib exposure (AUC_{0-12}) can increase 2-fold in CYP2C9 poor metabolizers (CYP2C9*3*3 genotyped) compared to subjects with CYP2C9 normal metabolizers (CYP2C9*1*1 genotyped).

Background

Deuruxolitinib (CTP-543) is a deuterated selective Janus kinase (JAK) inhibitor that modulates an immune response through intracellular JAK1 and JAK2 signaling. Deuruxolitinib is being developed as a potential oral treatment for adults with moderate to severe AA. Janus kinases bind to the intracellular domains of cytokine receptor subunits that dimerize or oligomerize upon cytokine binding. Juxtaposition of JAKs results in their phosphorylation, which activates the kinases and triggers phosphorylation of STAT proteins (signaling pathway referred to as JAK/STAT). The proposed dosing regimen is 8 mg BID with or without food.

The Applicant evaluated the PK of Deuruxolitinib in eleven separate Phase 1 studies, and 3 studies in the target patient population with AA. Additional studies conducted to obtain clinical information include a thorough QT study, a dose-ranging study, a mass-balance study, a renal impairment study, a hepatic impairment study, five clinical drug-drug interaction studies, two Food effect and two bioavailability studies. Population PK analyses and the exposure-response (E-R) analyses were also performed to support the dose selection as discussed in Section 16.4.1 and 16.4.2 respectively.

A single dose ranging from 8 to 48 mg and multiple oral doses ranging from 8 to 32 mg once daily and 8 to 16 mg BID for 7 days under fasted conditions have been evaluated in HV subjects.

The exposure of deuruxolitinib showed a rapid and close to complete absorption and systemic exposure parameters were largely proportional to dose between 4 mg BID and 12-mg BID regimens in patient population (Report CONC-PMX-CTP543-3280). The mean terminal half-life of deuruxolitinib following once daily and BID dosing of tablet formulation in healthy subject was 2.9 and 4.2 hr. The geometric mean accumulation ratio for the AUC following repeat dosing of deuruxolitinib ranged from 0.92 – 1.16 (Study CP543.1001) which is consistent with short terminal half-life of 4 hours following twice daily dosing. There was minimal accumulation of deuruxolitinib after multiple dose and the PK of deuruxolitinib was comparable between healthy subjects and subjects with AA. Compared to the fasted state, the mean C_{max} of

deuruxolitinib decreased by 30-40% and no corresponding decrease in AUC respectively following oral administration of a single oral dose of 16 mg deuruxolitinib in healthy subjects (Study CP543.1003) and deuruxolitinib is recommended to be administered with or without food.

The results from the human absorption, distribution, metabolism, excretion (ADME) study in healthy male subjects (Study CP543.1004), conducted with a single oral dose of 20 mg deuruxolitinib, showed that 90% of administered radioactivity was recovered with 70% recovered in urine and 20% recovered in feces, and no single component contributed more than 25% of the radiolabeled dose in either urine or feces respectively. The mean deuruxolitinib plasma C_{max} and AUC_{0-12} were approximately 72% and 62% those of TRA in plasma, respectively, indicating that the parent drug accounted for most of the radioactivity in systemic circulation over the first 12 hours postdose compared to metabolites. Mean C_{max} were 8.984 and 8.424 ng/mL for the metabolites C-21714 and C-21717, respectively, which is approximately 50 times lower than the mean C_{max} of deuruxolitinib (434.1 ng/mL). Considering total exposure (AUC_{0-inf}), C-21714 and C-21717 constituted about 6% and 5% of the parent drug, respectively. Deuruxolitinib predicted total plasma clearance of 9.04 L/h is comparable to observed median CL/F of 8.85 L/h obtained from healthy subjects following a single oral dose of 12-mg deuruxolitinib (Study CP543.1007).

Based on in vitro studies, deuruxolitinib is not an inhibitor or inducer to CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6. deuruxolitinib did not induce CYPs 1A2 or 2B6 (Report CTP-543DM-102) or CYPs 2C8, 2C9 or 2C19, whereas an induction response for CYP3A4 is reported in 1 out of 3 donors (Report DM-106). The DDI effect of multiple doses of deuruxolitinib on the PK of single dose of midazolam was evaluated in Clinical Study CP543.1012. The geometric mean of AUC_{0-inf} and peak plasma concentration (C_{max}) exposure of midazolam was decreased minimally by 15% and 16%, respectively. As for transporters, deuruxolitinib does not inhibit organic anion transporting polypeptides (OATPs), OAT and OCTs. Deuruxolitinib inhibited human BCRP and BSEP efflux transporters with IC_{50} values of 21.4 and 33.2 µg/mL.

Based on these *in-vitro* data which shows CYP3A4 as the main enzyme metabolizing deuruxolitinib, the Applicant proposed to study the impact of CYP3A4's strong inhibitors and inducers on deuruxolitinib's PK in clinical trials, then using this data to model the effects of mild and moderate CYP3A4 inhibitors and inducers. This approach was approved by the agency (EOP2 meeting package Question 5). *In vitro* assays in MDCKII cells indicated that deuruxolitinib was a substrate of both BCRP and P-gp, with efflux ratios >2 (Report CTP-543 DM-101). However, at comparable concentrations in Caco-2 cells, a lack of active transport was observed (efflux ratio ~1; Reports CTP-543 DM-093; CTP-543DM-073). Deuruxolitinib is not a substrate of uptake transporters OATP1B1/3 (Report CTP-543 DM-101).

Clinical DDI studies were conducted to evaluate the PK of deuruxolitinib in the presence and absence of itraconazole (a strong CYP3A4 inhibitor; Study CP543.1007), rifampin (a strong CYP3A4 and moderate CYP2C9 inducer; Study CP543.1008), fluconazole (a moderate CYP2C9 and CYP3A4 inhibitor; Study CP543.1015) and midazolam (marker of CYP3A4 activity) as a

substrate; Study CP543.1012), which are summarized in Table 76. Refer to the Clinical Pharmacology review Section 6 (above) for the detail information on deuruxolitinib regarding ADME properties, *in vitro* and clinical studies used in PBPK modeling.

Table 76. Summary of Clinical DDI Studies for Deuruxolitinib

Clinical Study #	Inhibitor/Inducer	Substrate	Sub's C_{max} Ratio	Sub's AUC ratio
CP543.1007	Itraconazole	Deuruxolitinib	1.13	1.27
CP543.1015	Fluconazole	Deuruxolitinib	1.21	2.2
CP543.1008	Rifampin	Deuruxolitinib	0.59	0.22
CP543.1012	Deuruxolitinib	Midazolam	0.85	0.84

Methods

Schemes of the PBPK modeling and simulation strategy are shown in Figure 28, which summarizes the studies used for deuruxolitinib model development and verification, and model applications in predicting DDI of deuruxolitinib as a victim of CYP2C9 and CYP3A4-mediated metabolism in healthy subjects with all CYP2C9 genotypes and specifically CYP2C9*3*3. The final model input parameters were summarized in Table 77.

The deuruxolitinib PBPK model consists of first order absorption, and the fraction of deuruxolitinib absorbed was estimated from in vitro permeability data and was essentially complete (fraction absorbed, fa =1.00). This is in agreement with *in vitro* permeability data (Report CTP-543 DM-073) and the mass balance data from the [14C] human ADME study (Clinical Study CP543.1004) as no unchanged deuruxolitinib was detected in feces. Distribution was described by a minimal PBPK model, which considers liver and intestinal metabolism. The reported renal clearance was negligible in healthy subjects (CP543.1004) so was assumed negligible (0) in the model. Observed median CL/F data obtained from healthy subjects following a single oral dose of 12-mg deuruxolitinib was used to optimize intrinsic clearance (CLint) values in order to recover the observed deuruxolitinib plasma concentration-time profiles. In vitro recombinant human CYP (rhCYP) data combined with the clinical DDI study with itraconazole were used to assign the relative contribution of CYPs 3A4, 2C9 and 1A2 to the clearance of deuruxolitinib. To account for any auto-induction, CYP3A4 induction data were included within the PBPK model but had a negligible effect on PK is reported. The Simcyp library files for itraconazole, fluconazole, efavirenz, and sulphaphenazole were used without any modification unless otherwise noted. For rifampin a revised CYP3A4 induction with value of 30.6 in conjunction with a reduced fu_{gut} value of 0.116 (equal to fu) is used, which are based on the clinical studies between rifampin and 2 CYP3A4 sensitive index substrates, 9 CYP3A4 clinical substrates and 22 metabolically stable CYP3A4 substrates.

Reviewer's Note

Given deuruxolitinib is not a sensitive CYP3A4 substate, the Applicant's conclusion of a negligible CYP3A4 TDI effect on deuruxolitinib pharmacokinetics cannot be used to inform CYP

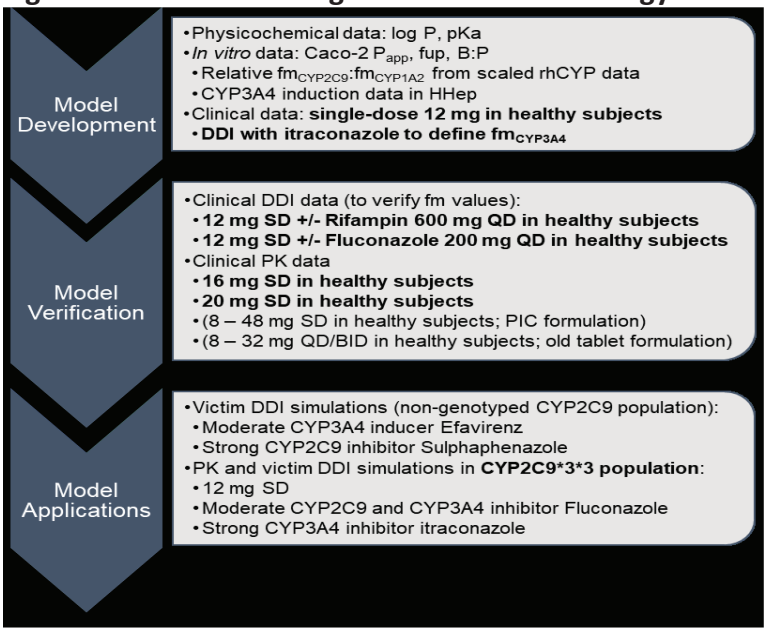
TDI parameter. Reviewer relied on the findings of clinical study CP543-1012, where the effect of multiple doses of deuruxolitinib on the PK of single dose of midazolam resulted in a decrease of 15% and 16% in the total ($AUC_{0\text{-}inf}$) and peak exposure (C_{max}) of midazolam (clinical study CP543-1012) and thus concluded that the TDI effect is not clinically significant. This is consistent with a slightly higher clearance of midazolam, and the primary metabolite (1-hydroxymidazolam) exposures were slightly increased following administration of midazolam with deuruxolitinib, with geometric mean AUC increased by approximately 14% and geometric mean C_{max} increased by only 5%.

The Applicant used the revised values of maximal fold induction (Ind_{max}) in the revised rifampin model for the CYP3A4 induction, which were based on one donor, using E_{max} model, where $Ind_{max} = E_{max} +1$ is reasonable.

Although the highest *in vitro* turnover of deuruxolitinib was observed with CYP3A4 (Report CTP-543 DM107), the weak interaction observed in the clinical DDI study with itraconazole indicated a smaller role for CYP3A4 in the elimination of deuruxolitinib. The contribution of CYP3A4 elimination ($f_{mCYP3A4}$) was calculated using the observed AUC ratio (AUCR), where Fm =1-(1/AUCR). This indicated that CYP3A4 was not the major metabolism enzyme for deuruxolitinib in vivo. In-vitro data suggested that CYP2C19 values were very low in comparison to the other two and therefore excluded. The relative contribution of other CYPs including 2C9 and 1A2 were considered relevant for calculation of fm. These relative contributions were applied to the non-CYP3A4 fm calculated from the itraconazole study (1/AUCR) to provide fmCYP1A2 and fm_{CYP2C9} values, which resulted in 3, 76 and 21% for CYP1A2, CYP2C9 and CYP3A4 respectively.

Applicant recalculation of $f_{mCYP3A4}$ using the clinical data and assigning the remaining fm to CYP2C9 and CYP1A2 based on the relative contribution of substrate depletion data from study CTP-543 DM107 appears reasonable. All modeling and simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Versions 21, Certara, Sheffield, UK). Simulations were performed using healthy subject population (sim-Healthy Volunteers) models. The minimal PBPK model was selected for prediction of deuruxolitinib plasma concentration-time profiles. The model described the disposition of deuruxolitinib with reasonable accuracy when compared with observed clinical data following dosing of 12 mg of deuruxolitinib to healthy subjects (Clinical Study CP543.1007). Fasted condition was selected as input in model for studies conducted after overnight fasting. Age, sex ratio, subject number, and dosing regimens were consistent with the actual individual trial design. Ten trials were simulated for each simulation scenario.

Figure 28. PBPK Modeling and Simulation Strategy



Source: Figure 1 in the PBPK report dm-116-conc-2-c

Table 77. Final Input Parameters in the Deuruxolitinib PBPK Model

PARAMETER	Value	Reference
Physicochemical and Binding Parameters		
Molecular Weight (g/mol)	314.42	
log P	2.33	Report N16-11528-20170215
pKa (basic)	4.2	Report N16-11528-20170215
B:P	1.30	Clinical Study CP543.1004
fu	0.085	Report CTP-543 DM-082
Main binding protein	HSA	Assumption
Absorption model – first order model		
fu_{gut}	1	Assumption
Caco-2 P_{app} ($x10^{-6}$ cm/s)	38.1	Report CTP-543 DM-073
Calibrator P_{app} ($x10^{-6}$ cm/s)	20.8	Propranolol; Report CTP-543 DM-073
$P_{eff,man}$ ($x10^{-4}$ cm/s)	7.98	Predicted (on-screen value)
Q_{gut} (L/h)	17.5	Predicted (on-screen value)
ka (1/h)	3.48	Predicted (on-screen value)
fa	1.00	Predicted (on-screen value)
Distribution model – minimal PBPK model		
V_{SS} (L/kg)	0.342	Method 3; optimised (on screen value)
K_p scalar	0.5	Optimised
Elimination parameters		
CL/F (L/h)	8.85	Clinical Study CP543.1007
fm_{CYP3A4}	21%	Clinical Study CP543.1007 (from AUCR)
fm_{CYP2C9}	76%	Relative fm calculated from Study CTP-543 DM-107, corrected for *in vivo* 3A4 fm
fm_{CYP1A2}	3%	
CYP3A4 CL_{int} (µL/min/pmol)	0.05	Retrograde model. CL/F obtained from Clinical Study CP543.1007; fm values as above
CYP2C9 CL_{int} (µL/min/pmol)	0.40	
CYP1A2 CL_{int} (µL/min/pmol)	0.02	
CL_R (L/h)	0	Clinical Study CP543.1004
Interaction parameters		
CYP3A4 Ind_{max}	32.3	Report CTP-543 DM-106; calibrated against rifampin
CYP3A4 $IndC_{50}$ (µM)	27.3	Report CTP-543 DM-106
fu_{hep}	0.608	Predicted, then corrected for substrate loss

Source: Table 3 in the PBPK report dm-116-conc-2-c

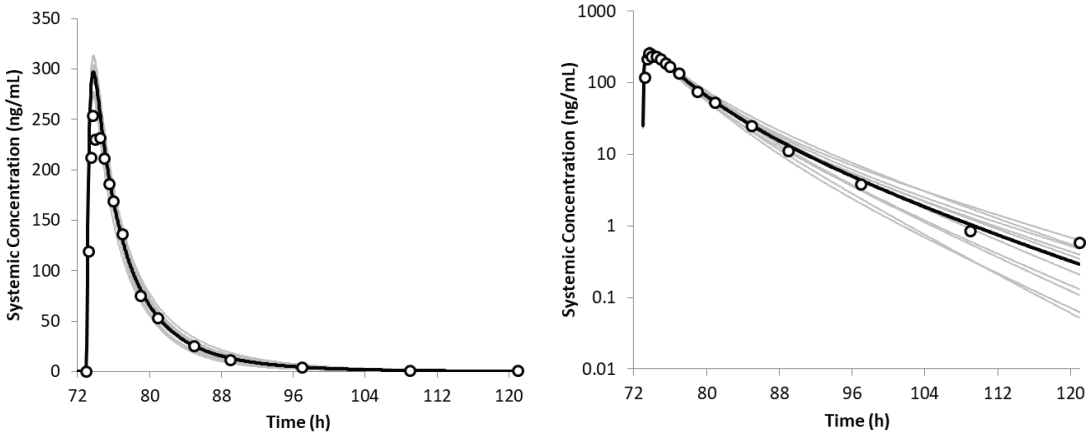
PBPK Review Questions

Was the contribution of CYP3A4, CYP2C9, and CYP1A2 to the overall clearance of deuruxolitinib verified?

Defining the Fm_{CYP3A4}

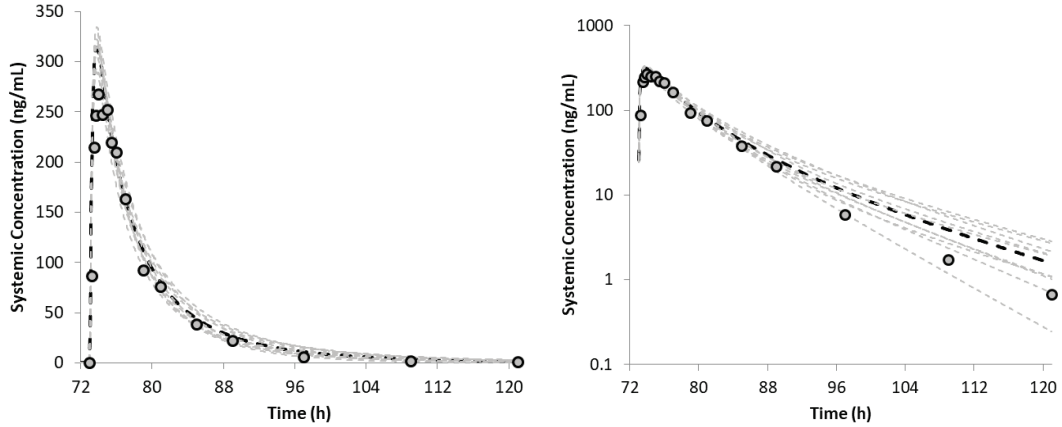
To define the Fm_{CYP3A4} in healthy volunteers, Applicant use the data from clinical study CP543.1007, where subjects received 200 mg itraconazole alone QD for 5 days; on Day 4, subjects also received a single dose of 12-mg deuruxolitinib, approximately 1 hour after the itraconazole dose (n=22). The comparison of the simulated and observed plasma-concentration time profile after a single oral dose of 12-mg deuruxolitinib administered alone and with Itraconazole in healthy volunteers are presented in Figure 29 and Figure 30 and their respective PK parameters are tabulated in Table 78 below.

Figure 29. Simulated and Observed Mean Plasma Concentrations of Deuruxolitinib Following Single Dose Administration of 12-mg Deuruxolitinib Alone in Healthy Subjects (Linear Scale on Left and Semi-Log Scale on Right)



Source: Figure 3 in PBPK report (dm-116-conc-2)
Depicted are simulated (lines) and observed data (circles; mean of n=22* individuals; Clinical Study CP543.1007). The grey lines represent mean values of simulated individual trials and the black lines portray the mean data of the simulated population (n=220) Left graph, y-axis in linear scale; right graph, y-axis in log-scale. *exceptions for: 36 h postdose (109 h on plot) where n=13 and 48 h postdose (121 h on plot) where n=1

Figure 30. Simulated and Observed Mean Plasma Concentrations of Deuruxolitinib Following Single Dose Administration of 12-mg Deuruxolitinib in the Presence of Multiple Doses of Itraconazole (200 mg QD) in Healthy Subjects (Linear Scale on Left and Semi-Log Scale on Right)



Source: Figure 4 in PBPK report (dm-116-conc-2)
Depicted are simulated (lines) and observed data (circles; mean of n=22* individuals; Clinical Study CP543.1007). The grey lines represent mean values of simulated individual trials and the black lines portray the mean data of the simulated population (n=220). *exceptions for: 36 h postdose (109 h on plot) where n=17 and 48 h postdose (121 h on plot) where n=6. Left graph, y-axis in linear scale; right graph, y-axis in log-scale.

Table 78. Simulated and Observed Geometric Mean PK Parameters for Deuruxolitinib Following Single Dose Administration of 12-mg Deuruxolitinib Alone and in the Presence of Multiple Doses of Itraconazole (200 mg QD) in Healthy Subjects

	CTP-543			CTP-543 + Itraconazole			GMR	
	$AUC_{0\text{-}inf}$ (h.ng/mL)	C_{max} (ng/mL)	t_{max}* (h)	$AUC_{0\text{-}inf}$ (h.ng/mL)	C_{max} (ng/mL)	t_{max}* (h)	$AUC_{0\text{-}inf}$	C_{max}
Simulated	1241	287	0.75	1583	305	0.80	1.29	1.06
CV%	70	30	0.45 - 1.10	83	30	0.45 - 1.30		
90% CI							1.27 - 1.31	1.06 - 1.06
Observed	1333	266	0.75	1687	301	1	1.27	1.13
CV%	33	26	0.50 - 2.50	32	27	0.50 - 2.50		
90% CI							1.20 - 1.33	1.07 - 1.20
S/O	0.93	1.08	1.00	0.94	1.01	0.80	1.02	0.94

Source: Table 4 in PBPK report (dm-116-conc-2)
Source observed data: Clinical Study CP543.1007
*t_{max}: median, min, max
Abbreviations: CI, confidence interval; CV, coefficient of variation; S/O, simulated/observed

The in vitro reaction phenotyping study suggested that deuruxolitinib was predominantly metabolized by CYP3A4 (with an fm of approximately 87%) and to a lesser extent, by CYP2C9 and CYP1A2 with fm values of 5.6% and 6.0%, respectively. However, the weak interaction observed in the clinical DDI study with itraconazole (CP543.1007) indicated that CYP3A4 may not be the major CYP metabolizing enzyme as the resulted AUCR is 1.27. The results from CP543.1007 study suggested the in-vivo contribution of CYP3A4 to deuruxolitinib elimination (fm_{CYP3A4}) is 0.21. The revised fm_{CYP3A} value in the deuruxolitinib model was further verified by its ability to reproduce the inhibitory effects of itraconazole on deuruxolitinib (Table 78) using PBPK

model, where the observed and model simulated values were comparable (the simulated and observed ratio of PK parameters are within 80- 125%). The model simulated $AUC_{0\text{-}inf}$ and C_{max} GMRs following administration of itraconazole with deuruxolitinib were 1.29 and 1.06, which are within 10% of the observed values of 1.27 and 1.13, respectively. Therefore, based on the observed clinical data from study CP543.1007 and using the recalculated fm for CYP3A4 to verify the PBPK model with clinical data, the recalculated fm_{CYP3A} value are considered verified.

Verification of Contribution of CYPs 3A4, 2C9 and 1A2 to the Overall Clearance of Deuruxolitinib

The results of Clinical DDI study with itraconazole (Study CP543.1007) suggested that in vitro data may have overestimated the involvement of CYP3A4 in the metabolism of deuruxolitinib. Based on these findings, Applicant revised fmCYPs values by rescaling in-vitro phenotyping data and proposed that CYP2C9 (75.6%) was the major metabolizing CYP enzyme for deuruxolitinib, followed by CYP3A4 (21%) and CYP1A2 (3.4%) and CYP2C19 contributed to <1%. This contribution of CYPs 3A4, 2C9, and 1A2 to the overall clearance of deuruxolitinib was verified by comparing the model predicted and clinical observed DDI data from the clinical DDI Study CP543.1008 with multiple dose rifampicin (600 mg QD) and clinical study CP543.1015 with multiple dose (200 mg QD) fluconazole, which has not been used previously in the model development.

Comparing the Observed and Simulated DDI With Rifampin

The simulated single oral dose deuruxolitinib data in the absence of rifampin (Day 1) and administered with rifampin on the 11th day of 12 days of dosing (600 mg QD) to healthy subjects are illustrated in Figure 31 for the updated rifampin model. The kinetics parameters for CYP3A4 induction (Ind_{max}) were higher in the default model (32.3) compared to the Ind_{max} value of 30.6 in the updated model. Simulated and observed geometric mean $AUC_{0\text{-}inf}$ and C_{max} values and corresponding GMRs for deuruxolitinib in the absence and presence of rifampin are listed in Table 79 using the default and Table 80 using the updated model.

Table 79. Simulated and Observed Geometric Mean $AUC_{0\text{-}inf}$ and C_{max} Values and Corresponding GMRs for Deuruxolitinib in the Absence and Presence of Rifampin (Default Model)

	CTP-543			CTP-543 + Rifampin			GMR	
	$AUC_{0\text{-}inf}$ (ng/mL.h)	C_{max} (ng/mL)	t_{max}* (h)	$AUC_{0\text{-}inf}$ (ng/mL.h)	C_{max} (ng/mL)	t_{max}* (h)	$AUC_{0\text{-}inf}$	C_{max}
Simulated	1190	279	0.75	346	174	0.55	0.29	0.62
CV%	67	26	0.45 - 1.15	69	37	0.35 - 0.85		
90% CI							0.28 - 0.30	0.61 - 0.64
Observed	1550	304	0.75	342	180	0.50	0.22	0.59
CV%	29	27	0.25 - 2.50	22	32	0.25 - 1.00		
S/O	0.77	0.92	1.00	1.01	0.97	1.10	1.31	1.05

Source observed data: Clinical Study CP543.1008; Source: Table 5 in PBPK report (dm-116-conc-2).
*t_{max}: median, min, max
Abbreviations: CI, confidence interval; CV, coefficient of variation; GMR, geometric mean ratio; S/O, simulated/observed

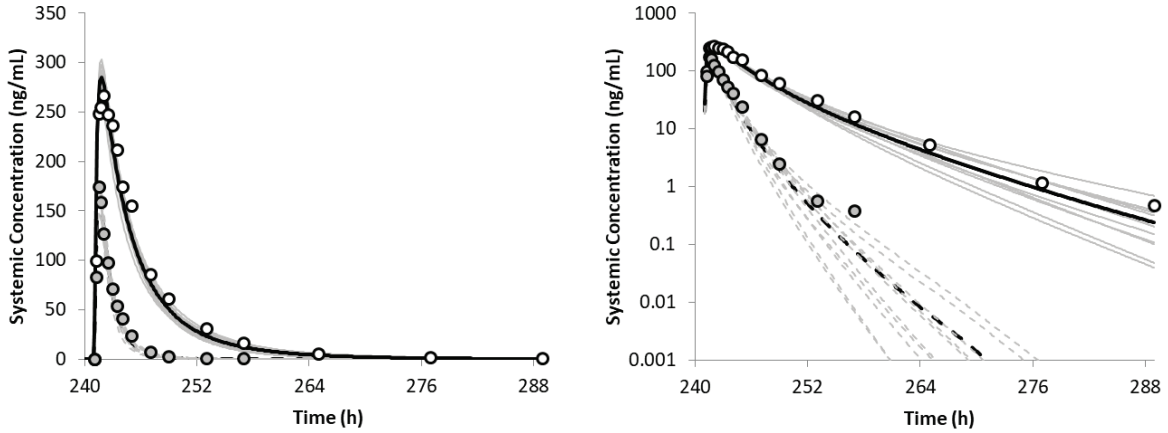
Table 80. Simulated and Observed Geometric Mean $AUC_{0\text{-}inf}$ and C_{max} Values and Corresponding GMRs for Deuruxolitinib in the Absence and Presence of Rifampin (Updated Model)

	CTP-543			CTP-543 + Rifampin			GMR	
	$AUC_{0\text{-}inf}$ (ng/mL.h)	C_{max} (ng/mL)	t_{max}* (h)	$AUC_{0\text{-}inf}$ (ng/mL.h)	C_{max} (ng/mL)	t_{max}* (h)	$AUC_{0\text{-}inf}$	C_{max}
Simulated	1190	279	0.75	274	154	0.50	0.23	0.55
CV%	67	26	0.45 - 1.15	68	38	0.30 - 0.80		
90% CI							0.22 - 0.24	0.54 - 0.57
Observed	1550	304	0.75	342	180	0.50	0.22	0.59
CV%	29	27	0.25 - 2.50	22	32	0.25 - 1.00		
S/O	0.77	0.92	1.00	0.80	0.86	1.00	1.02	0.93

Source observed data: Clinical Study CP543.1008; Source: Table 6 in PBPK report (dm-116-conc-2).
*t_{max}: median, min, max
Abbreviations: CI: Confidence Interval; CV: Coefficient of Variation; CI: Confidence Interval; GMR, geometric mean ratio; S/O: Simulated/Observed

The model simulated geometric mean $AUC_{0\text{-}inf}$ and C_{max} ratios for deuruxolitinib in the presence of rifampin was reported to be improved using the updated rifampin model (within 0.8- and 1.25-fold of the observed values).

Figure 31. Simulated and Observed Plasma Concentration Time Profiles of Deuruxolitinib Coadministered With Rifampin (Updated Model, Linear Scale on Left and Semi-Log Scale on Right)



Source: Figure 6 in PBPK report (dm-116-conc-2)
Depicted are simulated (lines) and observed (circles; mean of n=22* individuals; Clinical Study CP543.1008) plasma concentration-time profiles of deuruxolitinib following a single oral dose of deuruxolitinib in the absence of rifampin (solid line) and on the 11th day of 12 days of dosing of rifampin (dashed line). The grey lines represent mean values of simulated individual trials (10 trials of n=2) and the black lines portray the mean data of the simulated population (n=220). *exceptions: in absence of rifampin for 36 h postdose (277 h on plot) where n=14 and 48 h postdose (289 h on plot) where n=4; in the presence of rifampin where n=21 for all except 12 h postdose (253 h on plot) where n=12 and 16 h postdose (257 h on plot) where n=4. Left graph, y-axis in linear scale; right graph, y-axis in log-scale.

The reviewer concluded that the revised fm values for CYP2C9, CYP3A4 and CYP1A2 calculated based on the findings from clinical DDI study (study (CP543.1007) in combination with the relative contribution from the in vitro data (DM-114 and DM-107), which were further verified

using the clinical DDI data when deuruxolitinib is co-administered with fluconazole and rifampin is reasonable.

Clinical DDI results from literature showed that rifampin would result in 90% reduction in AUC of omeprazole, a sensitive index substrate of CYP2C19, compared to a 65% reduction in tolbutamide, CYP2C9 index substrate. Given that rifampin decreased the AUC of deuruxolitinib by 78% (Clinical DDI Study CP543.1008), it is possible that both CYP2C19 and CYP2C9 could be major contributor in metabolism of deuruxolitinib. Additional discuss can be found below.

Simulation of a Single Oral Dose of 12-mg Deuruxolitinib Co-Administered With Fluconazole (a Moderate CYP2C9 and CYP3A4 Inhibitor) in Healthy Subjects

The simulation after single oral dose of deuruxolitinib in the absence of fluconazole (Day 1) as shown by solid lines and when administered with fluconazole on the 5th day of 6 days of continuous dosing (200 mg fluconazole QD) as shown by dashed line to healthy subjects, when compared with observed data of deuruxolitinib in the absence of fluconazole (Day 1) as shown by open circle and when administered with fluconazole on the 5th day of 6 days of continuous dosing (200 mg fluconazole QD) as shown by grey circle are illustrated in Figure 32. Simulated and observed geometric mean $AUC_{0\text{-}inf}$ and C_{max} values and corresponding GMRs for deuruxolitinib in the absence and presence of fluconazole are listed in Table 81.

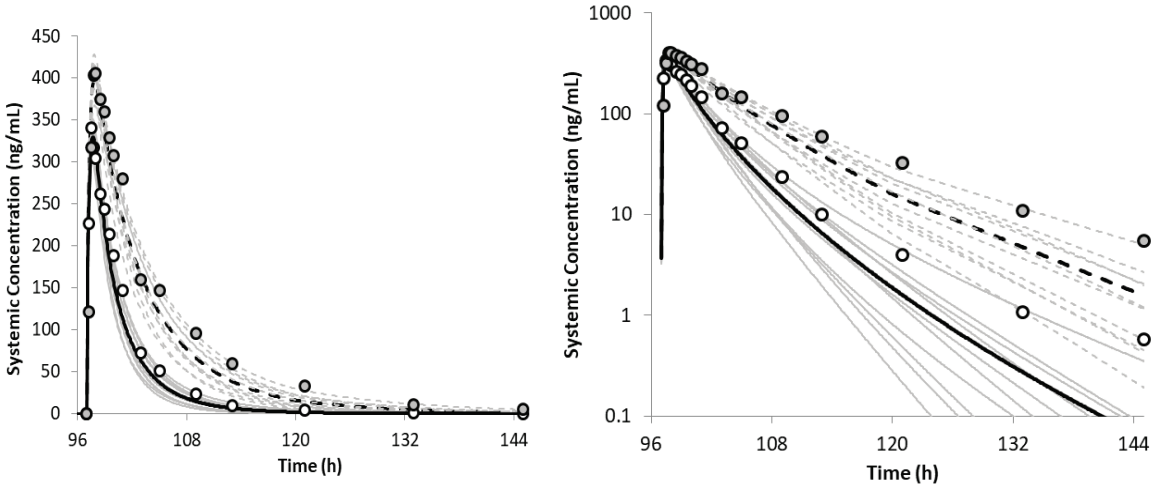
Table 81. Simulated and Observed Geometric Mean $AUC_{0\text{-}inf}$ and C_{max} Values and Corresponding GMRs for Deuruxolitinib in the Absence and Presence of Fluconazole

	CTP-543			CTP-543 + Fluconazole			GMR	
	$AUC_{0\text{-}inf}$ (ng/mL.h)	C_{max} (ng/mL)	t_{max}* (h)	$AUC_{0\text{-}inf}$ (ng/mL.h)	C_{max} (ng/mL)	t_{max}* (h)	$AUC_{0\text{-}inf}$	C_{max}
Simulated	1120	318	0.70	2430	383	0.90	2.19	1.20
CV%	62	32	0.35 - 1.05	61	32	0.50 - 1.30		
90% CI							2.17 - 2.22	1.19 - 1.21
Observed	1383	357	0.50	3312	431	0.75	2.40	1.21
CV%	41.5	28.2	0.25 - 1.00	35.8	27	0.50 - 2.50		
90% CI							2.17 - 2.65	1.09 - 1.33
S/O	0.81	0.89	1.40	0.73	0.89	1.20	0.91	1.00

Source observed data: Clinical Study CP543.1008; Source: Table 7 in PBPK report (dm-116-conc-2).
*t_{max}: median, min, max; CI: Confidence Interval; CV: Coefficient of Variation; CI: Confidence Interval; GMR, geometric mean ratio; S/O: Simulated/Observed

The model simulated geometric mean $AUC_{0\text{-}inf}$ and C_{max} ratios for deuruxolitinib in the presence of fluconazole were within 0.8- and 1.25-fold of the observed values.

Figure 32. Simulated and Observed Plasma-Concentration Time Profiles of Deuruxolitinib Coadministered With Fluconazole (Linear Scale on Left and Semi-Log Scale on Right)



Source: Figure 9 in PBPK report (dm-116-conc-2)
Depicted are simulated (lines) and observed (circles; mean of n=18* individuals; Clinical Study CP543.1015) plasma concentration-time profiles of deuruxolitinib following a single oral dose of deuruxolitinib in the absence of fluconazole (solid line) and on the 5th day of 6 days of dosing of fluconazole (dashed line). The grey lines represent mean values of simulated individual trials (10 trials of n=18) and the black lines portray the mean data of the simulated population (n=180) * *exceptions: in absence of fluconazole for 24 h postdose (121 h on plot) where n=15, 36 h postdose (133 h on plot) where n=7 and 48 h postdose (145 h on plot) where n=1; in the presence of fluconazole for 48 h postdose (145 h on plot) where n=17. Left graph, y-axis in linear scale; right graph, y-axis in log-scale.

Since the coadministration of 200 mg QD fluconazole with omeprazole, which is sensitive index substrate of CYP2C19, resulted in 8.22-fold change in AUC GMR while with s-warfarin which is CYP2C9 index substrate, it resulted in approximately 2-fold change in AUC (AUCR is 1.86). The study results (Study CP543-1015) show that when deuruxolitinib is administered in the presence of fluconazole similar magnitude of change in AUC ratio (AUCR of 2.4 was observed, which support that CYP2C9 maybe the main metabolic enzyme not CYP2C19, as in case of later, a much higher change is AUC ratio would have been expected (~8 fold) as in case of Omeprazole.

These revised fm values were further verified using the PBPK model for deuruxolitinib when co-administered with fluconazole where the predicted $AUC_{0\text{-}inf}$ and C_{max} GMR are 2.19 and 1.20, which were somewhat similar (within 1.1 -fold) to the observed values of 2.40 and 1.21 $AUC_{0\text{-}inf}$ and C_{max} respectively (Table 81).

The incorporation of new derived fm values in the PBPK model and verifying using the clinical data from Study CP543-1015, and Study CP543-1008 gives some degree of confidence in the revised fm values and on the model predictability using the revised fm values for deuruxolitinib. Thus, these findings further support that the revised fmCYP values can predict the CYP3A4 and CYP2C9 DDIs. Nevertheless, FDA issued an information request on 2/08/2024 to justify the rationale for allocating major contribution to CYP2C9 and not to other CYP2C's given the known discrepancy between the *in-vitro* and *in-vivo* finding. In response to information request, Applicant stated that 'if the main metabolic enzyme for deuruxolitinib was CYP2C19 instead of CYP2C9, much larger magnitude of clinical DDIs would have been expected for deuruxolitinib with both fluconazole and rifampin.' Overall, the proposed fm values is acceptable.

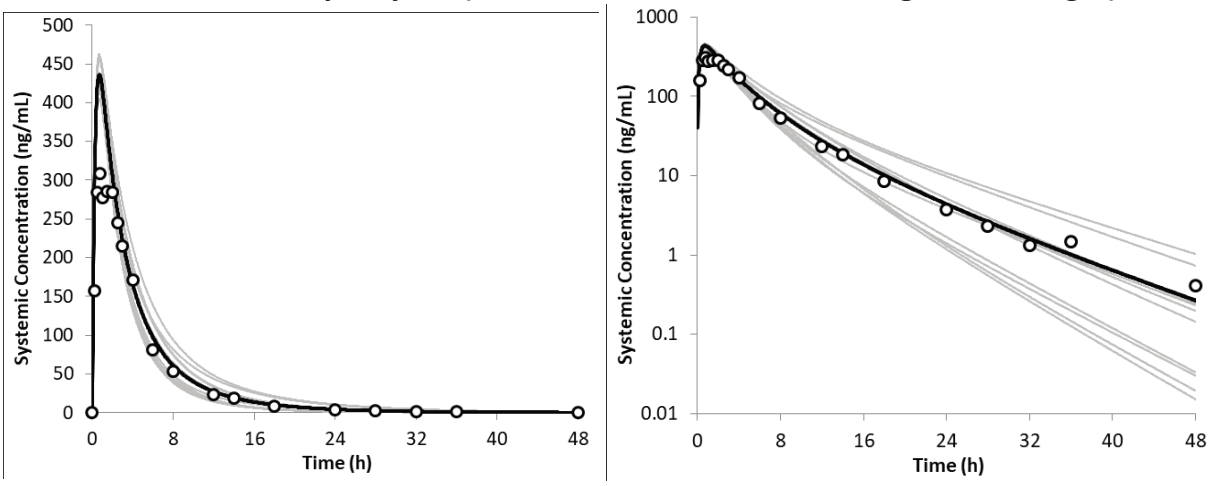
Can the PBPK model adequately describe the PK profiles of deuruxolitinib?

Clinical PK data that had not been used in model development was used to verify the deuruxolitinib PBPK model both after single and multiple doses of deuruxolitinib in healthy subjects.

PBPK Model for Single Dose Using Tablet Formulation Under Fasted Conditions

The model could reasonably describe the plasma concentration-time profiles of deuruxolitinib following single oral doses of deuruxolitinib in healthy subjects, and the model-estimated AUC and C_{max} were mostly within 0.8- and 1.25-fold of the observed values. The maximum observed concentration is over predicted by the model at both dose levels. Simulated and observed deuruxolitinib PK profiles and parameters after 16 and 20 mg singles dose are summarized in Figure 33 and Figure 34, and Table 82 and Table 83 respectively.

Figure 33. Plasma Concentrations of Deuruxolitinib After a Single Oral Dose 16-mg Deuruxolitinib in Healthy Subjects (Linear Scale on Left and Semi-Log Scale on Right)



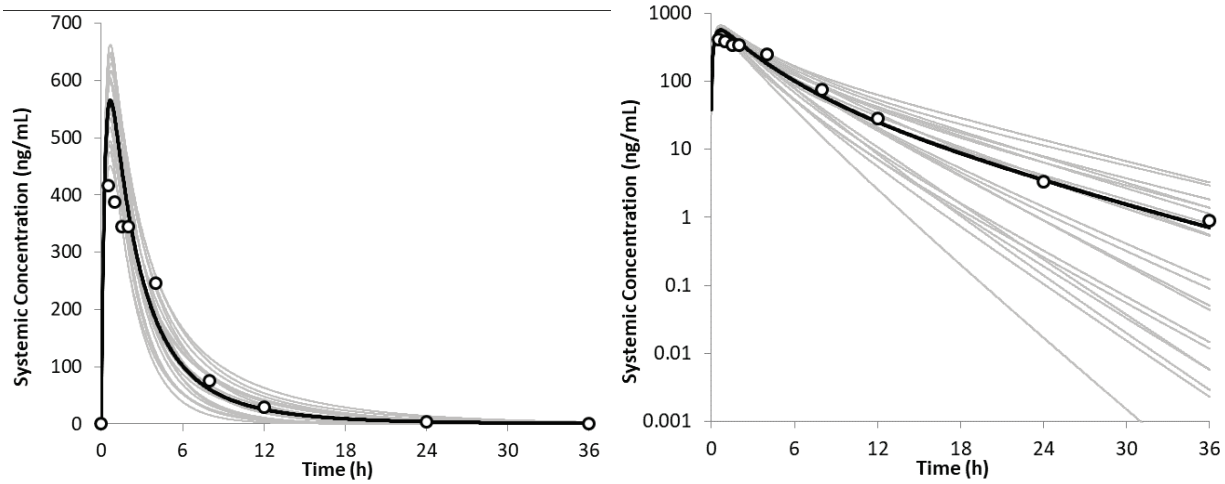
Source: Figure 9 in PBPK report (dm-116-conc-2)
Depicted are mean simulated (lines) and observed data (circles, mean of n=14* individuals; Clinical Study CP543.1003). The grey lines represent mean values of simulated individual trials (10 trials of n=14) and the black lines portray the mean data of the simulated population (n=140)

Table 82. Simulated and Observed Geometric Mean PK Parameters for Deuruxolitinib After a Single 16-mg Oral Dose in Healthy Subjects

	$AUC_{0\text{-inf}}$ (ng/mL.h)	C_{max} (ng/mL)	t_{max}* (h)
Simulated	1595	423	0.72
CV%	69	30	0.41 - 1.03
Observed	1568	343	0.63
CV%	33	27	0.25 - 2.00
S/O	1.02	1.23	1.15

Source: Table 8 in the PBPK report (dm-116-conc-2)

Figure 34. Plasma Concentrations of Deuruxolitinib After a Single Oral Dose 20-mg Deuruxolitinib in Healthy Subjects (Linear Scale on Left and Semi-Log Scale on Right)



Source: Figure 12 in the PBPK report (dm-116-conc-2)
Depicted are mean simulated (lines) and observed data (circles, mean of n=6 individuals, except at 36 hours where n=3; Clinical Study CP543.1004). The grey lines represent mean values of simulated individual trials (20 trials of n=6) and the black lines portray the mean data of the simulated population (n=120).

Table 83. Simulated and Observed Geometric Mean PK Parameters for Deuruxolitinib After a Single 20-mg Oral Dose in Healthy Subjects

	$AUC_{0\text{-inf}}$ (ng/mL.h)	C_{max} (ng/mL)	t_{max}^* (h)
Simulated	1894	551	0.70
CV%	61	28	0.32 - 1.04
Observed	2254	434	0.76
CV%	27	27	0.50 - 1.50
S/O	0.84	1.27	0.92

Source: Table 9 in the PBPK report (dm-116-conc-2)

Overall, the reviewer conclude that the model could reasonably describe the plasma concentration-time profiles of deuruxolitinib following single oral doses of deuruxolitinib in healthy subjects, and the model-estimated AUC and C_{max} were mostly within 0.8- and 1.25-fold of the observed values.

<u>PBPK Model After Multiple Doses Using Tablet (Not Clinical) Formulation Under Fasted Conditions</u>

Although a different tablet formulation was used in early Phase 1 study, which resulted in an overprediction of C_{max} and an underprediction of T_{max} but overall, the model could reasonably describe the plasma concentration-time profiles of deuruxolitinib following multiple oral doses of deuruxolitinib twice a day for seven consecutive days in healthy subjects, and the model-

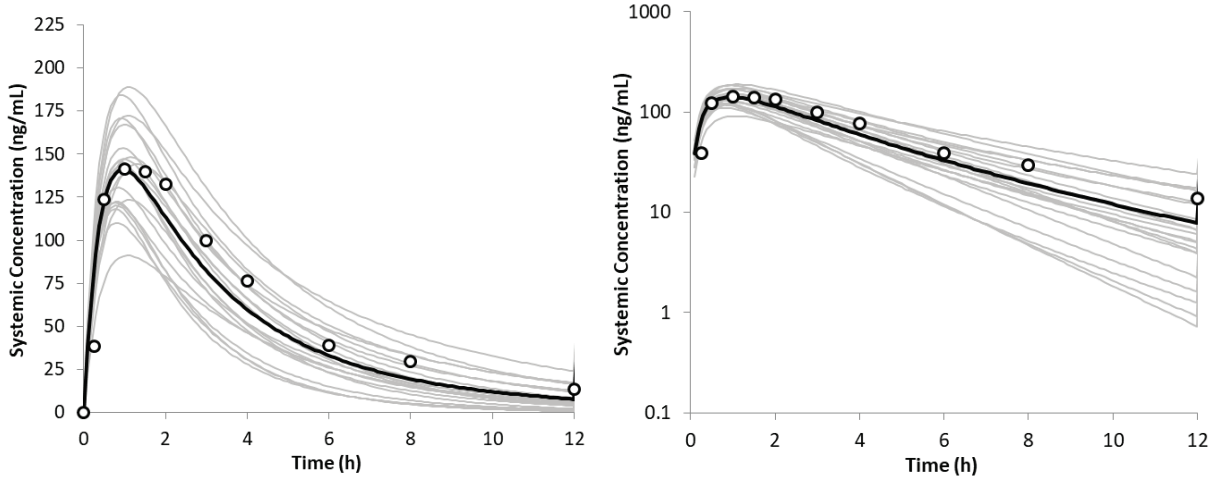
estimated AUC and C_{max} were mostly within 0.75- and 1.25-fold of the observed values. Simulated and observed deuruxolitinib PK profiles and parameters after 8-mg BID dose for 7 days are summarized in Figure 35 for Day 1 (for both linear and semi-log scale) and Figure 36 for Day 7 (for both linear and semi-log scale), whereas the PK Parameters are summarized in Table 84. Also, the Simulated and observed deuruxolitinib PK profiles and parameters after 16 mg BID dose for 7 days are summarized in Figure 37 for Day 1 (for both linear and semi-log scale) and Figure 38 for Day 7 (for both linear and semi-log scale), whereas the PK Parameters are summarized in Table 85.

Table 84. Simulated and Observed Arithmetic Mean PK Parameters for CTP-543 After the First and Multiple Oral Doses of 8-mg Deuruxolitinib BID for 7 Days in Healthy Subjects

	Day 1			Day 7		
	AUC_{0-12} (ng/mL.h)	C_{max} (ng/mL)	t_{max}* (h)	AUC_{tau} (ng/mL.h)	C_{max} (ng/mL)	t_{max}* (h)
Simulated	594	146	1.00	629	151	1.00
CV%	57	32	0.50 - 2.05	64	34	0.50 - 1.80
Observed	703	160	1.00	844	183	1.50
CV%	25	18	0.50 - 1.50	40	26	0.25 - 2.00
S/O	0.85	0.91	1.00	0.75	0.83	0.67

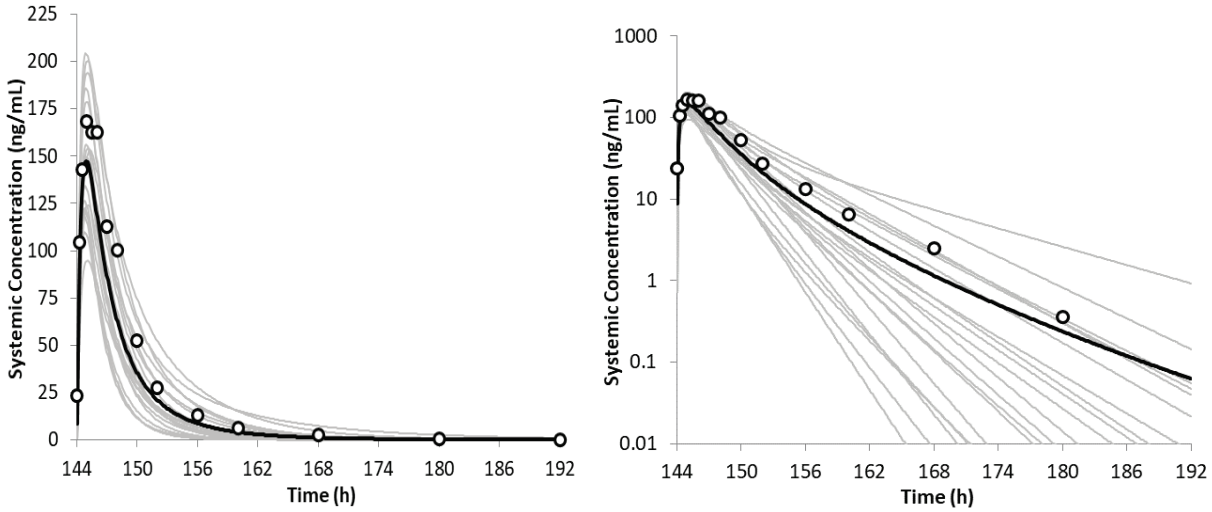
Source: Table 22 in the PBPK report (dm-116-conc-2) Source observed data: Clinical Study CP543.1001, Part B
Source simulated data: conc2b-ver-10a.xlsx
*t_{max}: median, min, max;
Abbreviations: CV, coefficient of variation; S/O, simulated/observed

Figure 35. Linear (Left) and Log-Linear (Right) Simulated and Observed Plasma Concentration-Time Profiles of the First Oral Dose of 8-mg Deuruxolitinib BID on Day 1



Source: Figure 31 in the PBPK report (dm-116-conc-2)
[Source simulated data: conc2b-ver-10a.xlsx].
Depicted are simulated (lines) and observed data (circles, mean of n=4 individuals; Clinical Study CP543.1001 Part B). The grey lines represent mean values of simulated individual trials (20 trials of n=4) and the black lines portray the mean data of the simulated population (n=80)

Figure 36. Linear (Left) and Log-Linear (Right) Simulated and Observed Plasma Concentration-Time Profiles of the First Oral Dose of 8-mg Deuruxolitinib BID on Day 7



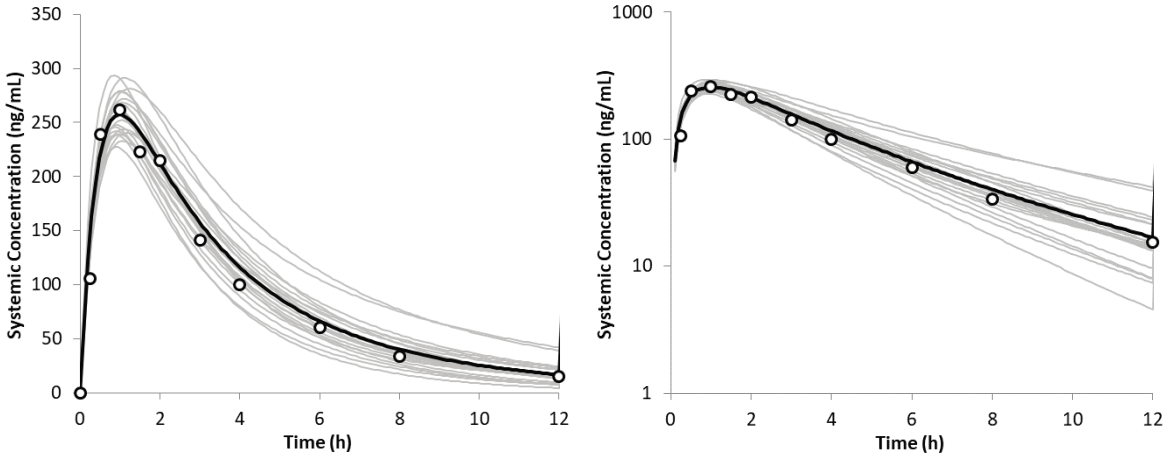
Source: Figure 32 in the PBPK report (dm-116-conc-2)
[Source simulated data: conc2b-ver-10a.xlsx].
Depicted are simulated (lines) and observed data (circles, mean of n=4 individuals; Clinical Study CP543.1001 Part B). The grey lines represent mean values of simulated individual trials (20 trials of n=4) and the black lines portray the mean data of the simulated population (n=80)

Table 85. Simulated and Observed Arithmetic Mean PK Parameters for CTP-543 After the First and Multiple Oral Doses of 16-mg Deuruxolitinib BID for 7 Days in Healthy Subjects

	Day 1			Day 7		
	AUC_{0-12} (ng/mL.h)	C_{max} (ng/mL)	t_{max}* (h)	AUC_{tau} (ng/mL.h)	C_{max} (ng/mL)	t_{max}* (h)
Simulated	1137	264	1.05	1203	276	1.05
CV%	60	35	0.55 - 2.05	67	38	0.55 - 1.95
Observed	1062	290	1.00	1127	288	0.75
CV%	23	20	0.50 - 2.00	27	36	0.50 - 2.00
S/O	1.07	0.91	1.05	1.07	0.96	1.40

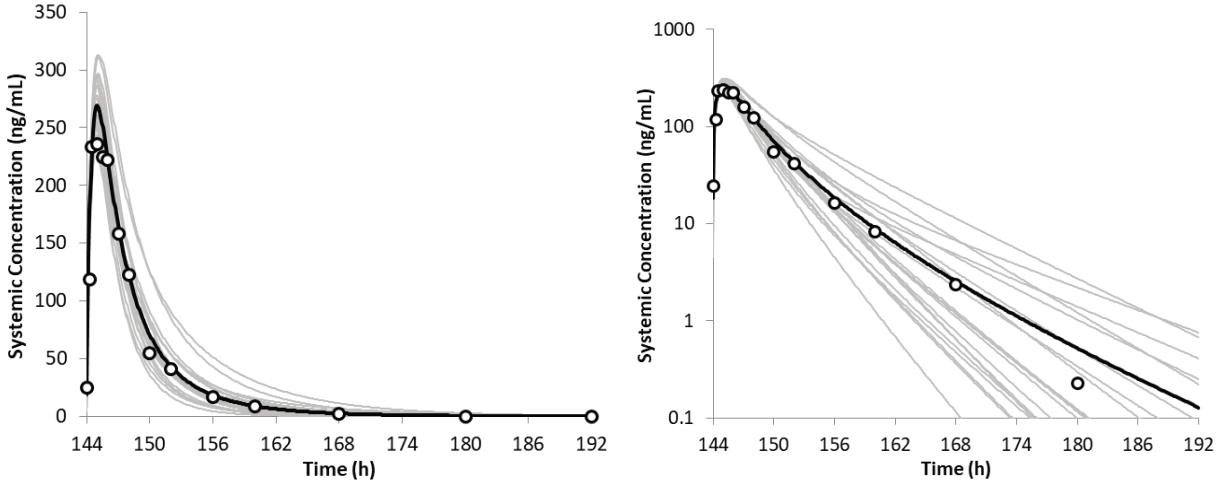
Source: Table 25 in the PBPK report (dm-116-conc-2) Source observed data: Clinical Study CP543.1001, Part B
Source simulated data: conc2b-ver-13a.xlsx
*t_{max}: median, min, max;
Abbreviations: CV, coefficient of variation; S/O, simulated/observed

Figure 37. Linear (Left) and Log-Linear (Right) Simulated and Observed Plasma Concentration-Time Profiles of the First Oral Dose of 16-mg Deuruxolitinib BID on Day 1



Source: Figure 37 in the PBPK report (dm-116-conc-2)
[Source simulated data: conc2b-ver-13a.xlsx].
Depicted are simulated (lines) and observed data (circles, mean of n=8 individuals; Clinical Study CP543.1001 Part B). The grey lines represent mean values of simulated individual trials (20 trials of n=8) and the black lines portray the mean data of the simulated population (n=160)

Figure 38. Linear (Left) and Log-Linear (Right) Simulated and Observed Plasma Concentration-Time Profiles of Multiple Oral Doses of 16-mg Deuruxolitinib BID on Day 7



Source: Figure 37 in the PBPK report (dm-116-conc-2)
[Source simulated data: conc2b-ver-13a.xlsx]
Depicted are simulated (lines) and observed data (circles, mean of n=8 individuals; Clinical Study CP543.1001 Part B). The grey lines represent mean values of simulated individual trials (20 trials of n=8) and the black lines portray the mean data of the simulated population (n=160)

The Applicant noted two formulations of deuruxolitinib were used during the drug development. The Clinical formulation with batch No.: 200058 and 210083 was used in DDI studies. The clinical formulation is bioequivalence with the to-be-marketed formulation in study CP543-1009 using batch number 200198. Since the active pharmaceutical ingredient is highly soluble and the drug product is an immediate release product, the comparative dissolution data of the batches indicates similarity in their dissolution profiles (≥85% dissolution of batches at the 10-minute time-point in the Guidance method). Furthermore, all three batches of clinical

formulation along with to-be-marketed formulation comply with the acceptance criterion of "Q = (b) (4)% in 30 minutes" thus are considered similar. In-vitro data suggested deuruxolitinib is not an inhibitor or inducer to CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6. As for transporters, deuruxolitinib does not inhibit OATPs, OAT and OCTs. Deuruxolitinib inhibited human BCRP and BSEP efflux transporters with IC_{50} values of 21.4 and 33.2 µg/mL.

Only single dose data to the model for deuruxolitinib alone using the current tablet formulation and the multiple dose models are based on previous formulations which has different absorption characteristics leading to overpredicting the C_{max}. To adjust for the change in PK parameters among different formulations used in earlier clinical studies including powder in capsule and uncoated tablet formulations, when compared to the formulation used in the later clinical studies including coated tablet and solution, the Applicant model has adjusted fa and Ka parameter values empirically just to fit the decreased AUC values observed for the early formulations including powder in capsule and uncoated tablet. Reviewer noted that this is not the appropriate approach and is not recommended. Given that the studies used for model development (Study CP543.1007) and model verification (Study CP543.1008, CP543.1003, CP543.1004 and CP543.1015), used the final proposed coated tablet formulations, which resulted in similar PK parameters. The fa and ka values that were predicted from permeability data, resulting in same absorption parameters (ka =3.48/h, fa =1.00) were used across all these studies as input parameter in the model is acceptable. The findings from the sensitive analysis of absorption parameters (Ka, fa) on the exposure (C_{max}, AUC), supporting the exposure in presence and absence of itraconazole are not affected by the absorption parameters (Ka, fa) of deuruxolitinib is acceptable.

Can PBPK analyses predict the effects of moderate CYP3A4 inducer and strong CYP2C9 inhibitor as well as subjects genotyped as CYP2C9*3*3 on the PK of deuruxolitinib?

Yes, the deuruxolitinib PBPK model can be used to predict the effects of moderate CYP3A4 inducer Efavirenz and strong CYP2C9 inhibitor sulphaphenazole, as well as subjects genotyped as CYP2C9*3*3 on the PK of deuruxolitinib.

Predictions of the Effect of Moderate CYP3A4 Inducer Using Efavirenz as Probe Drug on the PK of Deuruxolitinib

The moderate CYP3A4 inducer Efavirenz, was predicted to decrease deuruxolitinib exposure (AUC) up to ~30% and maximum exposure (C_{max}) up to 10% following multiple dose of efavirenz (600 mg QD) to healthy subjects on Day 13 of dosing, when compared to the PK of a single 12-mg oral dose of deuruxolitinib in the absence of efavirenz (Day 1) (Table 86.).

Table 86. Predicted Geometric Mean With 90% CI for AUC_{0-t} and C_{max} Values and Corresponding GMRs for Deuruxolitinib in the Absence and Presence of Efavirenz

	CTP-543		CTP-543 + Efavirenz		GMR	
	AUC_{0-t} (ng/mL.h)	C_{max} (ng/mL)	AUC_{0-t} (ng/mL.h)	C_{max} (ng/mL)	AUC_{0-t}	C_{max}
GM	1179	324	793	290	0.67	0.90
CV%	64	33	58	33		
90% CI					0.65 - 0.70	0.89 - 0.91

Source: Table 9 in the PBPK report (dm-116-conc-2)
Abbreviations: CI, confidence interval; GM, geometric mean; GMR, geometric mean ratio

Predictions of the Effect of Strong CYP2C9 Inhibitor Using Sulphaphenazole as Probe Drug

Mean simulated plasma deuruxolitinib concentrations following a single 12-mg oral dose of deuruxolitinib in the absence of strong CYP2C9 inhibitor sulphaphenazole (Day 1) and on the 6th day of 8 days of dosing of sulphaphenazole (500 mg BID) to healthy subjects shows a 3-fold increase in the deuruxolitinib exposure (AUC) and maximum exposure (C_{max}) increases up to 25% following multiple doses of suphaphenazole as shown in Table 87. These changes in exposure are similar as GMR for AUC_{0-t} is 3.02 after 500 mg bid dose (Table 87) when compared to 3.62 after 2000 mg QD dosing of sulphaphenazole dosing on the 6th day of 8 days as shown in Table 88.

Table 87. Simulated Geometric Mean AUC_{0-t} and C_{max} Values and Corresponding GMRs for Deuruxolitinib in the Absence and Presence of Sulphaphenazole (500 mg BID)

	CTP-543		CTP-543 + Sulphaphenazole		GMR	
	AUC_{0-t} (ng/mL.h)	C_{max} (ng/mL)	AUC_{0-t} (ng/mL.h)	C_{max} (ng/mL)	AUC_{0-t}	C_{max}
GM	1180	324	3567	404	3.02	1.25
CV%	64	33	50	31		
90% CI					2.86 - 3.18	1.23 - 1.27

Source: Table 11 in the PBPK report (dm-116-conc-2)
Abbreviations: CI, confidence interval; GM, geometric mean; GMR, geometric mean ratio

Table 88. Simulated Geometric Mean AUC_{0-t} and C_{max} Values and Corresponding GMRs for Deuruxolitinib in the Absence and Presence of Sulphaphenazole (2000 mg QD)

	CTP-543		CTP-543 + Sulphaphenazole		GMR	
	AUC_{0-t} (ng/mL.h)	C_{max} (ng/mL)	AUC_{0-t} (ng/mL.h)	C_{max} (ng/mL)	AUC_{0-t}	C_{max}
GM	1180	324	4265	414	3.62	1.28
CV%	64	33	47	32		
90% CI					3.38 - 3.86	1.25 - 1.31

Source: Table 12 in the PBPK report (dm-116-conc-2)
Abbreviations: CI, confidence interval; GM, geometric mean; GMR, geometric mean ratio

The Applicant proposed simulating the DDI effect of a strong CYP2C9 inhibitor on deuruxolitinib using sulphaphenazole as a probe drug. Reviewer conducted additional simulations to assess the performance of sulphaphenazole PBPK model on CYP2C9 pathway.

Verification of Sulphaphenazole PBPK Model

The SV-sulphaphenazole model was obtained from Simcyp compound database. The model validation was performed by the software developer and is summarized as follows. The SV-sulphaphenazole model has been validated using the observed sulphaphenazole PK data after the single dose of 1000 mg for one subject were reported by (Riess et al. 1965)and after multiple dose of 2000 mg on Day 1 followed by 500 mg BID for 4 more days. The Ki value for CYP2C19 was derived from in vitro data reported by(Rasmussen et al. 1998). For CYP2C9, Ki was optimized to recover the change in tolbutamide AUC and half-life described by Veronese et al. (Veronese et al. 1990). Simulated DDIs with CYP2C9 substrates were compared to observed studies. The input parameters of sulphaphenazole PBPK model are presented in Table 90. Reviewers conducted additional analysis to evaluate the DDI potential of sulphaphenazole as the sensitive index CYP2C9 perpetrator using sensitive CYP2C9 substrate such as tolbutamide and warfarin, both of which are index CYP2C9 substrates. Perkins et. al. reported the change of tolbutamide AUC to ≥5-fold with sulphaphenazole and Tasisulam (strong index inhibitors of CYP2C9) in clinical DDI studies (Perkins et al. 2018). The assigned fraction metabolized (fm) was approximately 0.85, which based on published clinical and *in-vitro* data (Thomas and Ikeda 1966; Veronese et al. 1990).

To verify these findings, Reviewer conducted additional simulation to evaluate the inhibition potential of sulphaphenazole on sensitive CYP2C9 substrate (such as tolbutamide and warfarin) and concluded that sulphaphenazole is a strong index inhibitor of CYP2C9 as it resulted in the change of AUC ≥5-fold both tolbutamide and warfarin using virtual healthy subjects. The results of these simulations are summarized in Table 89.

Table 89. Model Simulation PK Parameters for Tolbutamide and Warfarin Alone and in the Presence of Sulphaphenazole 2000 mg QD

DDI scenario	Tolbutamide alone (500 mg)			Tolbutamide + Sulphaphenazole (2000 mg QD)			GMR (90% CI)	
PK parameters	AUC (ng/mL.h)	C_{max} (ng/mL)	T_{max} (h)*	AUC (ng/mL.h)	C_{max} (ng/mL)	T_{max} (h)*	AUC Ratio	C_{Max} Ratio
Geometric mean	586790.05	37734.02	3.98	2996442.09	55368.41	8.4	5.11 (4.67-5.58)	1.47 (1.42-1.51)
DDI scenario	**Warfarin alone (10 mg QD)**			**Warfarin+ Sulphaphenazole (2000 mg QD)**			**GMR (90% CI)**	
PK parameters	AUC (ng/mL.h)	C_{max} (ng/mL)	T_{max} (h)*	AUC (ng/mL.h)	C_{max} (ng/mL)	T_{max} (h)*	AUC Ratio	C_{Max} Ratio
Geometric mean	40609.25	1019.53	2.28	309210.65	1102.33	3.7	7.6 (7.05-8.22)	1.08 (1.07-1.09)

Table 90. Input Parameters (ADME) for SV-Sulphaphenazole

Parameter	Value	Method/Reference
Molecular weight (g/mol)	314.36	PubChem
logP	1.52	PubChem
Compound type	Monoprotic Acid	
pKa	5.91	Simcyp
B/P	0.62	Simcyp
fu	0.0275	Predicted
fa	1	Assumed
ka (1/h)	1.86	Simcyp
fugut	0.0275	fu
Qgut (L/h)	4.642853	Predicted
Distribution model	Minimal	PBPK Model
Vss (L/kg)	0.162	Boger (1959)
Clpo (L/h)	0.382	Boger (1959)
CLR (L/h)	0.084	Boger (1959)
Enzyme CYP2C9		
Ki	1.5	(Veronese et al. 1990)
fumic	1	
Enzyme CYP2C19		
Ki	12	(Rasmussen et al. 1998)
fumic	0.945	

Predictions of Plasma Concentrations of Deuruxolitinib in Subjects Genotyped as CYP2C9*3*3 (Poor Metabolizers) Following a Single Oral Dose of 12-mg Alone and in the Presence of Fluconazole and Itraconazole at Steady State

To simulate deuruxolitinib exposure in CYP2C9 PM subjects, the Applicant assigned the proportion of CYP2C9 poor metabolizers (PMs) as 1 and used the CYP2C9*3*3 mean abundance values (25.2 pmol/mg) and coefficient of variation (79%) for the CYP2C9 PM population. The

mean fmCYP values of each isoform for deuruxolitinib in the CYP2C9*3*3 population were fmCYP1A2=7%, fmCYP2C9=52% and fmCYP3A4=41%. Although the extent of CYP2C9 metabolism was reduced, but CYP2C9 is still the major enzyme involved in deuruxolitinib elimination in CYP2C9*3*3 subjects.

Simulated mean AUC_{0-t} and C_{max} values following a single oral dose of deuruxolitinib in normal metabolizers and CYP2C9*3*3 genotyped subjects are given in Table 91, where the exposure in predicted to be increased to 2 fold in CYP2C19 poor metabolizers (CYP2C9*3*3 genotyped subjects), when compared to normal metabolizers subjects.

Table 91. Simulated Geometric Mean PK Parameters for Deuruxolitinib After a Single 12-mg Oral Dose in Normal Metabolizers and CYP2C9*3*3 Genotyped Subjects

Population	CTP-543 in Normal Metabolizers		CTP-543 in CYP2C9*3*3 Genotyped Subjects	
Parameters	AUC_{0-t} (ng/mL.h)	C_{max} (ng/mL)	AUC_{0-t} (ng/mL.h)	C_{max} (ng/mL)
GM	1180	324	2425	379
CV%	64	33	55	31

Simulated mean AUC_{0-t} and C_{max} values following a single oral dose of deuruxolitinib in normal metabolizers alone and in the absence of itraconazole (Day 1) and on the 4th day of 5 days of dosing of itraconazole (200 mg QD) to healthy CYP2C9*3*3 subjects are illustrated in Table 92 where a weak DDI was predicted.

Table 92. Simulated Geometric Mean AUC_{0-t} and C_{max} Values for Deuruxolitinib in Normal Metabolizers Alone in the Absence and Presence of Itraconazole (200 mg QD) in CYP2C9*3*3 Subjects

Population	Deuruxolitinib in Normal Metabolizers		Deuruxolitinib in CYP2C9*3*3 Genotyped Subjects		Deuruxolitinib + Itraconazole in CYP2C9*3*3 Genotyped Subjects	
Parameters	AUC_{0-t} (ng/mL.h)	C_{max} (ng/mL)	AUC_{0-t} (ng/mL.h)	C_{max} (ng/mL)	AUC_{0-t} (ng/mL.h)	C_{max} (ng/mL)
GM	1180	324	2416	379	3975	409
CV%	64	33	55	31	68	31

Simulated mean AUC_{0-t} and C_{max} values following a single oral dose of deuruxolitinib in normal metabolizers alone and in the absence of fluconazole (Day 1) and on the 5th day of 6 days of dosing of fluconazole (200 mg QD) to healthy CYP2C9*3*3 subjects are given in Table 93, where a moderate DDI was predicted.

Table 93. Simulated Geometric Mean AUC_{0-t} and C_{max} Values for Deuruxolitinib in Normal Metabolizers Alone and in the Absence and Presence of Fluconazole (200 mg QD) in CYP2C9*3*3 Subjects

Population	Deuruxolitinib in Normal Metabolizers		Deuruxolitinib in CYP2C9*3*3 Genotyped Subjects		Deuruxolitinib + Fluconazole in CYP2C9*3*3 Genotyped Subjects	
Parameters	AUC_{0-t} (ng/mL.h)	C_{max} (ng/mL)	AUC_{0-t} (ng/mL.h)	C_{max} (ng/mL)	AUC_{0-t} (ng/mL.h)	C_{max} (ng/mL)
GM	1180	324	2417	379	5096	426
CV%	64	33	55	31	50	32

The magnitude of DDI effect (such as AUC ratio) of deuruxolitinib in the poor metabolizer (CYP2C9*3*3 genotyped) subjects is estimated to be similar to other CYP2C9 genotypes subjects when administered with strong and moderate inhibitor (Table 92 and Table 93). However, the total exposure (AUC_{0-t}) is estimated to increase 2-fold in CYP2C9 poor metabolizers (CYP2C9*3*3 genotype) (Table 91), compared to normal metabolizers (CYP2C91/*1 genotype) and may warrant a dose adjustment or contraindication in patients who are poor metabolizers.

16.4.4. GLP Validated Bioanalytical Methods for the Measurement of Deuruxolitinib and the Two Most Abundant Metabolites, C-21714 and C-21717

Deuruxolitinib was quantified by a validated bioanalytical method to quantitate deuruxolitinib its 2 most abundant (human) metabolites, C-21714 and C-21717 in human plasma utilizing liquid-liquid extraction of 100 µL of human K2 EDTA plasma followed by LC-MS/MS detection. The method used nondeuterated ruxolitinib and nondeuterated versions of the 2 ruxolitinib human metabolites C-21708 and C-21636 as internal standards for deuruxolitinib, C-21714 and C-21717, respectively. For deuruxolitinib, the calibration curve comprised 9 levels of nonzero standards, ranging from 0.300 to 150 ng/mL. QC samples for validation of precision and accuracy were prepared at 4 concentrations: 0.300, 0.900, 7.50, and 105 ng/mL. Dilution integrity was verified with samples diluted up to 50-fold. For both C-21714 and C-21717, the calibration curve comprised 9 levels of nonzero standards, ranging from 0.100 to 50.0 ng/mL. QC samples for the validation of precision and accuracy were prepared at 4 concentrations: 0.100, 0.300, 2.50, and 35.0 ng/mL. Dilution integrity was verified with samples diluted up to 50-fold. The validation summary for the determination of Deuruxolitinib, C-21714, and C-21717 plasma concentrations are given in Table 94 below.

Table 94. Validation Summary for the Determination of Deuruxolitinib, C-21714 and C-21717 Plasma Concentrations

Validation Report	Clinical Studies	Performance
CTP-543 and 2 metabolites, C-21714 and C-21717 human plasma (EDTA) (final method) (b) (4) **Title**: Validation of an LC-MS/MS Method for the Determination of CTP-543, C-21714, and C-21717 in Human Plasma (EDTA)	CP543.1003 CP543.1004 CP543.1005 CP543.1006 CP543.1007 CP543.1008 CP543.1009 CP543.1010 CP543.1011 CP543.1012 CP543.1013 CP543.1014 CP543.1015 CP543.2004 CP543.3002	**Analyte: deuruxolitinib (CTP-543)** LLQ: 0.300 ng/mL Validated range: 0.300 to 150 ng/mL QC levels: 0.300, 0.900, 7.50, and 105 ng/mL Within-run precision (CV%): between 0.9 and 6.3% Between-run precision (CV%): between 1.9 and 6.3% Within-run accuracy (% Bias): between -4.8 and 8.0% Stability in human plasma: 5 freeze-thaw cycles each at -20°C or -80°C 300 days at -20°C, 711 days at -80 °C 5 hours in an ice water bath Stability in human blood: up to 2 hours at ambient temperature Processed sample integrity: 180 hours at 5°C Multiple analytes: deuruxolitinib (CTP-543) at 0.900 ng/mL fortified with C-21714 at 50 ng/mL and C-21717 at 50 ng/mL Stability in human plasma: 5 freeze-thaw cycles at -20°C or -80°C 61 days at -20°C or -80°C 5 hours in an ice water bath **Analyte: C-21714** LLQ: 0.100 ng/mL Validated range: 0.100 to 50 ng/mL QC levels: 0.100, 0.300, 2.50, and 35.0 ng/mL Within-run precision (CV%): between 2.1 and 13.1% Between-run precision (CV%): between 3.1 and 9.6% Within-run accuracy (% Bias): between -12.7 and 1.7% Stability in human plasma: 5 freeze-thaw cycles at -20°C or -80°C 182 days at -20°C, 711 days at -80 °C 5 hours in an ice water bath Stability in human blood: up to 2 hours at ambient temperature Processed sample integrity: 132 hours at 5°C Multiple analytes: C-21714 at 0.300 ng/mL fortified with deuruxolitinib (CTP-543) at 150 ng/mL and C-21717 at 50 ng/mL Stability in human plasma: 5 freeze-thaw cycles at -20°C or -80°C 5 hours in an ice water bath 6 days at -20°C or -80°C **Analyte: C-21717**

Validation Report	Clinical Studies	Performance
		LLQ: 0.100 ng/mL Validated range: 0.100 to 50 ng/mL QC levels: 0.100, 0.300, 2.50, and 35.0 ng/mL Within-run precision (CV%): between 1.2 and 13.1% Between-run precision (CV%): between 3.1 and 14.0% Within-run accuracy (% Bias): between -6.3 and 19.0% Stability in human plasma: 5 freeze-thaw cycles at -20°C or -80°C 98 days at -20°C, 711 days at -80 °C 5 hours in an ice water bath Stability in human blood: up to 2 hours at ambient temperature Processed sample integrity: 180 hours at 5°C Multiple analytes: C-21717 at 0.300 ng/mL fortified with deuruxolitinib (CTP-543) at 150 ng/mL and C-21714 at 50 ng/mL Stability in human plasma: 5 freeze-thaw cycles at -20°C or -80°C 5 hours in an ice water bath 56 days at -20°C or -80°C

CV% = coefficient of variation percentage; EDTA = ethylenediaminetetraacetic acid; LC-MS/MS = liquid chromatography tandem mass spectrometry; LLQ = lower limit of quantification; QC = quality control.

16.5. Additional Clinical Safety Tables

Table 95. Mean and Mean Change From Baseline in HADS Total Score, With Observed HADS Scores at Baseline and Week 24

Parameter Visit [1] Statistic	Placebo (N=267)	Pooled CTP-543 8 mg BID (N=600)	Pooled CTP-543 12 mg BID (N=342)	Pooled CTP-543 Total (N=942)	Pooled Total (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.

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