NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	215830
Priority or Standard	Standard
Submit Date(s)	June 24, 2022
Received Date(s)	June 24, 2022
PDUFA Goal Date	June 24, 2023
Division/Office	Division of Dermatology and Dentistry
Review Completion Date	June 22, 2023
Established/Proper Name	Ritlecitinib
(Proposed) Trade Name	Litfulo
Pharmacologic Class	Kinase Inhibitor
Code name	PF-06651600
Applicant	Pfizer, Inc.
Dosage form	Capsule
Applicant proposed Dosing Regimen	50 mg once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of alopecia areat (b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	N/A
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	LITFULO is indicated for the treatment of severe alopecia areata in adults and adolescents ≥ 12 years of age
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	68225006 | Alopecia areata (disorder) |
Recommended Dosing Regimen	50 mg once daily

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRM=Division of Risk Management
DPMH=Division of Pediatric and Maternal Health
DPV=Division of Pharmacovigilance
PLT=Patient Labeling Team

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The Applicant, Pfizer, Inc., submitted a new drug application for NDA 215830 to support the

following indication for LITFULO (ritlecitinib) 50 mg daily capsule:

"LITFULO is a kinase inhibitor indicated for the treatment of severe alopecia areata (AA) in adults and adolescents 12 years and older ".

Ritlecitinib is an oral covalent irreversible inhibitor of the 5 TEC family kinases (BMX,

BTK, ITK, TEC, TXK and JAK3, with high selectivity over JAK isoforms (JAK1, JAK2 and TYK2) and the broader kinome. According to the Applicant, ritlecitinib is differentiated from all approved JAK inhibitors by its lack of activity against JAK1 and JAK2 leading to a narrower spectrum of cytokine inhibition; inhibiting only the 6 ϒ-common cytokines IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. In human whole blood, ritlecitinib inhibits signaling of the common-ϒ- chain receptors but does not inhibit signaling of JAK3-independent cytokines such as the JAK1-dependent cytokines (including type 1 & 2 interferons, the IL-6 family of cytokines, the IL-10 family of cytokines) or the JAK2-dependent hematopoietic factors such as EPO and TPO. Ritlecitinib's inhibition of the TEC family kinases leads to the inhibition of cytolytic functions in CD8+ T cells and NK cells. Ritlecitinib inhibits signaling of the JAK3-dependent cytokines and the TEC-kinase-dependent immune receptors, which contribute to the immunopathogenesis of AA.

The use of LITFULO is associated with a number of potential toxicities. LITFULO labeling will carry a Boxed Warning (for JAK-inhibitor class of products) 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.

The proposed dosage of LITFULO "for the treatment of severe AA in adults and adolescents 12 years and older" is 50 mg orally once daily with or without food.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant provided substantial evidence of effectiveness for ritlecitinib 50 mg in the treatment of severe alopecia areata. This was supported by an adequate and well-controlled large multicenter Phase 2b/3 trial (B7981015, N=718), with very persuasive results which were consistent with those suggested by the Phase 2a trial, B7931005 (N=142). Trial B7981015 evaluated 5 doses of ritlecitinib (with or without a loading dose of 200 mg during the first 4 weeks: 200/50 mg, 200/30 mg, 50 mg, 30 mg, 10 mg) and placebo. The applicant is proposing use of the 50 mg dose without the loading dose. Trial B7981015 demonstrated that ritlecitinib 50 mg was superior to

placebo for the primary endpoint of SALT ≤20 at Week 24 under appropriate multiplicity control across dosing regimens. Multiplicity control was not extended to the set of secondary endpoints, which included additional endpoints based on SALT at each visit, and eyebrow and eyelash assessments. The efficacy results from this trial are consistent across centers, demographic subgroups, and methods of handling missing data, though the estimated magnitude of the treatment effect varied somewhat across gender and baseline disease severity subgroups. Even though the secondary endpoints were not included under the multiplicity control, the results of the secondary endpoints are consistent with the results of the primary endpoint and are supportive of the primary endpoint findings. The primary efficacy endpoint results from Trial B7981015 for the 50 mg dose are presented in Table 1.

Table 1 – Primary Efficacy Endpoint: SALT ≤ 20 at Week 24 (FAS/Analysis #4)

Ritlecitinib 50 mg N=130 %	Placebo N=131 %	Difference from Placebo (95% CI) p-value
23.0	1.6	21.4 (13.4, 29.5) <0.00001[a]

[a] Statistically significant under the prespecified multiplicity control scheme at α=0.00125.
FAS=full analysis set; Analysis #4 = multiple imputation for missing data due to COVID-19 and non-responder imputation for other reasons for missing data.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Ritlecitinib is not currently approved in any country. Ritlecitinib is an orally administered, small molecule that is proposed as a covalent irreversible inhibitor of Janus kinase 3 (JAK3) and 5 TEC family kinases (BMX, BTK, ITK, TEC, TXK). 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. Ritlecitinib has selectivity over the remaining three JAK isoforms (JAK1, JAK2 and TYK2) and greater inhibitory potency at JAK3, compared to other JAK isozymes in human whole blood. However, the relevance of inhibition of specific JAK enzymes to the therapeutic effectiveness or safety is not currently known.

The Applicant submitted NDA 215830 to support the use of ritlecitinib for the indication of treatment of patients with severe alopecia areata (AA) in adult and adolescent patients 12 years and older.

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)[1]. The most common presentation of AA in adults and children is patchy hair loss. However, in severe cases, hair loss may involve the entire scalp (alopecia totalis) or all hair-bearing areas (alopecia universalis). Among patients with AA, approximately 5% will develop alopecia totalis and 1% will develop alopecia universalis. The marked change in physical appearance caused by severe hair loss is frequently associated with loss of self-esteem and the development of psychiatric disorders including depression and anxiety. In one review (Toussi et al. 2020[2]), nearly 80% of patients with AA reported impaired health related quality of life based on Dermatology Life Quality Index survey results. FDA approved therapies for AA include intralesional corticosteroids (which provides limited efficacy in the population with severe disease, defined as ≥50% hair loss), and baricitinib (Olumiant), a JAK inhibitor approved for the treatment of adult patients with severe alopecia areata in June 2022. Therefore, a variety of therapies are used off-label, including other JAK inhibitors, to address this unmet medical need with variable treatment effect and potential risks. In a public meeting organized by the FDA to explore the perspectives of patients with alopecia areata, their caregivers, and other patient representatives, participants voiced frustration with the variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of these treatments.

The Applicant provided substantial evidence of effectiveness of ritlecitinib for the treatment of adult and adolescent patients with severe AA with data from an adequate and well-controlled large multicenter Phase 2b/3 trial, B7981015 (N=718), with very persuasive results which were consistent with those suggested by the Phase 2a trial, B7931005 (N=142). Trial B7981015 was a randomized, double-blind, trial with a placebo-controlled period (weeks 0-24) followed by an extension period (weeks 24-48). Trial B7981015 evaluated ritlecitinib 50 mg once daily and 30 mg once daily (with or without a loading dose of 200 mg QD during weeks 0-4), compared with ritlecitinib 10 mg once daily (without a loading dose) and placebo once daily in adult and adolescent subjectswith severe AA (defined as at least 50% hair loss). Efficacy was evaluated using the Severity of Alopecia Tool (SALT) which assesses the percentage of missing scalp hair in each of four areas of scalp (total scores range from 0 to 100). The primary efficacy endpoint in trial B7981015 was the proportion of subjects achieving SALT ≤20 (i.e., no more than 20% missing hair) at Week 24. For the primary efficacy endpoint, a ritlecitinib dose of 50 mg once daily was superior to placebo ($p<0.00001$). The results on the primary efficacy endpoint were consistent across subgroups.

In trial B7981015, the proportion of subjects who received ritlecitinib 50 mg once daily or placebo once daily, and achieved SALT ≤20 at Week 24 were 23.0% and 1.6%, respectively. Secondary endpoints included clinician-reported outcomes (ClinRO)s for the eyebrow (eyebrow assessment [EBA]) and the eyelash (eyelash assessment [ELA]) hair loss. Although the results were favorable, there were issues with the measurement properties of the instruments that limited interpretability of the data, as well as their statistical analyses. Therefore, the efficacy results for these secondary endpoints will not be included in the product labeling.

The safety database (All Exposure Pool, AEP) for the ritlecitinib AA development program included 1523 subjects (including 133 adolescents) who received at least one dose of ritlecitinib ≥ 50 mg once daily, and 1048 subjects who received treatment for ≥ 12 months (48 weeks); and was adequate to characterize the safety profile of ritlecitinib in the target patient population with AA.

In the Placebo-controlled safety pool for AA (PCPAA, Weeks 0-24), 130 subjects received ritleicitinib 50 mg once daily and 213 subjects received placebo. Review of the safety data in the AA development program identified no serious safety concerns. There were no deaths up to Week 48. Adverse reactions in the PCPAA safety pool reported in ≥1% of subjects treated with ritlecitinib 50/50 mg once daily (and at a higher frequency than placebo-treated subjects), compared to the placebo group respectively, were headache (10.8% v. 8.5%), diarrhea (10.0% v. 3.8%), acne (6.2% v. 4.7%), rash (5.4% v. 0.9%), urticaria (4.6% v. 1.4%), folliculitis (3.1% v. 1.9%), pyrexia (3.1% v. 0), dermatitis atopic (2.3% v. 0.5%), dizziness (2.3% v. 1.4%), blood creatine phosphokinase increased (1.5% v. 0), herpes zoster (1.5% v. 0), red blood cell count decreased (1.5% v. 0), and stomatitis (1.5% v. 0).

Adverse events reported under Safety Areas of Interest or adjudicated as Adverse Events of Special Interest (AESI) for the AEP (refer to Sec. 8.2.5 of this review) included opportunistic infections of multidermatomal herpes zoster (2), non-melanoma skin cancer (NMSC) (5), malignancies excluding NMSC (7), myocardial infarction (1), retinal artery occlusion (1), pulmonary embolism (1), no deep vein thrombosis [DVT], and death (1) related to acute cardiopulmonary arrest. No neuroaudiology safety signals were identified from the clinical safety data in the Phase 2b/3 trial B7981015 or the neuroaudiology safety trial, B7981037 (which was conducted following a finding of axonal dystrophy reported in the nonclinical 9-month dog toxicity studies of ritlecitinib [deemed as a species specific finding]).

There is limited long-term data to support the chronic use of ritlecitinib. Safety data from the ongoing, long-term (3-year) safety trial B7981032 (N=1052, including 805 patients continuing in the study, up to data cutoff date of 2/28/2022) were submitted under this NDA. Additionally, Sentinel's Active Postmarket Risk Identification and Analysis System (ARIA), established under section 505(k)(3) of the FDCA, will be used to identify unexpected serious risks (myocardial infarction, stroke, and thrombosis) possibly related to ritlecitinib during long-term use for AA.

Overall, the safety profile adverse reactions observed in subjects with AA treated with LITFULO was consistent with the safety profile of adverse reactions in subjects treated with other JAKi products.

Ritlecitinib will carry the labeled risks (Boxed Warning and Warning and Precautions) associated with JAKi class of products, including serious infections, mortality, malignancy (including lymphoma and lung cancer), major adverse cardiovascular events (MACE: including cardiovascular death), thrombosis (including deep venous thrombosis and pulmonary embolism). Our understanding of the off-target effects of JAKi is evolving. Data from PMR Study A3921133 in subjects with rheumatoid arthritis (RA) who received tofacitinib, prompted the Division of Rheumatology and Transplant Medicine (DRTM) to initiate a safety labeling change (SLC) for tofacitinib and other JAKi for the treatment of inflammatory conditions (sNDA-004 approved December 2, 2021). These data identified a new safety signal of MACE, confirmed the safety signal of malignancy noted in the original tofacitinib program, and confirmed the safety signals of all-cause mortality and thrombosis. While these JAK inhibitors are different products with potentially different in vitro selectivity for different Janus kinases, there is currently insufficient information to link a specific mechanism of action or target selectivity to an adverse event. Thus, it is not possible to rule out that these findings with tofacitinib are a class effect.

Labeled and potential safety signals will be characterized in special populations (pregnant patients and pediatrics) with severe AA

with targeted clinical post-marketing requirements (PMRs). Under 505(o), the Applicant will be required to conduct two studies of maternal, fetal, and infant outcomes of women exposed to ritlecitinib during pregnancy. The first study, a Pregnancy Exposure Registry, is a registry based observational exposure cohort study comparing women exposed to ritlecitinib during pregnancy and an unexposed control population. The second study will use a different design from the Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data or a case control study). Both studies will record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes.

NDA 215830 for ritlecitinib triggered the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) as a new active ingredient. Assessments in the pediatric population younger than 6 years of age are waived on the basis that necessary studies are impossible or highly impracticable. The Applicant will be required to conduct the following 6 studies as PMR/PMCs:

For pediatric patients (as PREA PMRs):

1. Study B7981031 (1 week)- Ongoing: An open-label, multiple-dose, PK/PD study (N=12) in patients (6 years to <12 years of age) with moderate to severe AA
2. Study B7981027 (24-week): A phase 3 randomized, double-blind, placebo-controlled study (N=168) to investigate the efficacy and safety of ritlecitinib in patients (6 years to <12 years of age) with AA and ≥50% scalp hair loss
3. Study B7981028 (3 years): A long-term extension study to investigate the efficacy and safety of ritlecitinib (N=140) in patients (6 years to <12 years of age) with AA and ≥50% scalp hair loss

For pediatric (adolescent) or pregnant patients (as FDAAA PMRs):

4. Study B7981032 (3 years)- Ongoing: A long-term open-label extension study to investigate the efficacy and safety of ritlecitinib (N= 1050) in patients (≥12 years of age) with AA and ≥50% scalp hair loss.
5. A Pregnancy Exposure Registry Study
6. A Retrospective Pregnancy Cohort Study

Safety and efficacy data submitted by the Applicant support approval of this NDA for LITFULO® (ritlecitinib) capsule, 50 mg once daily for the indication of "the treatment of severe alopecia areata in adults and adolescents 12 years and older".

[1] Xing L, Dai Z, Jabbari A, Cerise JE, Higgins CA, Gong W, de Jong A, Harel S, DeStefano GM, Rothman L, Singh P, Petukhova L, Mackay-Wiggan J, Christiano AM, Clynes R. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. Nat Med. 2014 Sep;20(9):1043-9. doi: 10.1038/nm.3645. Epub 2014 Aug 17. PMID: 25129481; PMCID: PMC4362521.
[2] Toussi A, Barton VR, Le ST, Agbai ON, Kiuru M. Psychosocial and psychiatric comorbidities and health-related quality of life in alopecia areata: A systematic review. J Am Acad Dermatol. 2021 Jul;85(1):162-175. doi: 10.1016/j.jaad.2020.06.047. Epub 2020 Jun 17. PMID: 32561373; PMCID: PMC8260215.

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	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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	experiencing social isolation, and bullying as a result of their condition.	
IND Current Treatment Options	• There is no cure and limited FDA-approved treatments (corticosteroids) for AA. Olumiant was Approved in June 2022 for adult patients with severe AA. • There are a number of treatments used off-label to manage AA. The selection of treatment depends on the extent of disease. For limited disease, the most common treatment is corticosteroids, either administered as an intradermal injection, or applied topically as a cream, ointment, or gel. • Second-line treatment options include calcineurin inhibitors, immunotherapies, and topical products to stimulate hair growth. Systemic therapies are considered for patients who have more extensive hair loss, or who have a rapid progression of AA	There is a significant unmet medical need for effective treatment for patients with AA. There are limited approved therapies; existing therapies that are used off-label do not adequately manage the condition for most patients with severe AA. Participants at the Patient-Focused Drug Development meeting emphasized the lack of approved and effective therapies for AA, describing their condition as poorly managed by existing off-label therapies.
Benefit	• To establish the efficacy of ritlecitinib in the treatment of AA in patients with ≥50% scalp hair loss (including AT/AU) who were ≥12 years of age, the Applicant submitted data from an adequate and well-controlled large multicenter R, DB, PC Phase 2b/3 trial, B7981015 (N=718), with very persuasive results which were consistent with those suggested by the Phase 2a trial, B7981005 (N=142). • The primary efficacy endpoint in the Phase 2b/3 trial was the proportion of subjects achieving SALT ≤20 (i.e., no more than 20% missing hair) at Week 24. Ritlecitinib 50 mg daily was superior to placebo for the primary efficacy endpoint of treatment success (achieved SALT ≤20) of (23.0%) compared to placebo (1.6%), a treatment effect of 21.4% (95% CI of (13.4, 29.5)).	The submitted data has met the evidentiary standard for providing substantial evidence of effectiveness in subjects with AA and ≥50% scalp hair loss (including AT/AU). Ritlecitinib will provide patients with an approved therapeutic option with well- characterized benefits and risks and reduced uncertainty regarding access to treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• For the all-exposure (AEP) safety pool, the safety database included 1628 subjects treated with any dose of ritlecitinib, including 1523 subjects who received at least one dose of ritlecitinib ≥ 50 mg. There were no deaths for up to 12 months (48 weeks) of exposure. Two subjects died during the long-term safety (LTS) study B7981032 (both deaths were deemed as not related to ritlecitinib). In patients treated with any dose of ritlecitinib, SAEs by PT reported in ≥2 subjects included appendicitis (5), breast cancer and invasive lobular breast carcinoma (3 and 1, respectively), abortion spontaneous (3), acute respiratory failure (3), COVID-19 (2), COVID-19 pneumonia (2), migraine (2), and suicidal behavior (2). • In the PCPAA safety pool (weeks 0-24), 130 subjects received ritlecitinib 50 mg daily and 213 subjects received placebo. No serious adverse events (SAEs) were reported in subjects who received ritlecitinib 50 mg daily or placebo. SAEs were reported for 2 (3.2%) of subjects who received ritlecitinib 10 mg daily, 1 (0.8%) of subjects who received ritlecitinib 30/30 mg daily, and 4 (1.9%) of subjects who received ritlecitinib 200/50 mg daily. • In the one-year exposure (OYEP) safety pool (weeks 0-48 of trial B7981015), SAEs were reported for (6/261= 2.3%) subjects in the All 50 mg (combined 200/50 mg and 50/50 mg) group and (3/261= 1.1%) of subjects in the All 30 mg (combined 200/30 mg and 30/30 mg) group, including 2 subjects in the 50/50 mg group and 2 subjects in the 200/30 mg group during weeks 24-48 (not included in PCPAA pool). • In the PCPAA safety pool (Week 0-24), Adverse Reactions reported with a frequency of ≥1% in subjects treated with ritlecitinib 50/50 mg daily (and at a higher frequency than placebo-treated subjects) were headache (10.8% v. 8.5%), diarrhea (10.0% v. 3.8%), acne (6.2% v. 4.7%), rash (5.4% v. 0.9%), urticaria (4.6% v. 1.4%), folliculitis (3.1% v. 1.9%), pyrexia (3.1% v. 0), dermatitis atopic (2.3% v. 0.5%), dizziness (2.3% v. 1.4%), blood creatine phosphokinase increased (1.5% v. 0), herpes zoster (1.5% v. 0), red blood cell count decreased (1.5% v. 0), and stomatitis (1.5% v. 0). • Overall, the AE profile reported for subjects who received ritlecitinib for a duration > 24 weeks was consistent with the AE profile reported during	There is an unmet medical need for safe and effective therapies for patients with severe, extensive AA for whom the chronic use of corticosteroids or off-label use of immunosuppressants carries substantial risks. The size of the safety database and the scope of the safety analyses were sufficient to evaluate the safety profile of ritlecitinib in subjects with AA. Sentinel's Active Postmarket Risk Identification and Analysis System (ARIA), established under section 505(k)(3) of the FDCA, will be used to identify unexpected serious risks (myocardial infarction, stroke, and thrombosis) possibly related to ritlecitinib during long-term use for alopecia areata. To address the benefit and risk assessment in the pediatric population with moderate to severe AA, the Applicant will be required to conduct: 1. An open- label, once daily dose (for 7 days), PK/PD study (B7981031) in 12 pediatric patients between 6 to <12 years of age with moderate to severe AA. 2. A randomized, controlled trial (B7981027) to evaluate the safety, efficacy, and pharmacokinetics of ritlecitinib in the pediatric population (6 years to <12 years)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	weeks 0-24 in the PCPAA safety pool. • No additional serious safety concerns were identified that warranted consideration of a Risk Evaluation and Mitigation Strategy (REMS). • Prescribing Information and a Medication Guide adequately addresses the known risks associated with the moiety and those identified during product development as well as mitigation strategies. • The Applicant evaluated subjects ≥ 12 years of age with moderate to severe AA. Because moderate to severe AA occurs in pediatric population < 12 years of age, the effects of ritlecitinib on pediatric patients between 6 to < 12 years of age will be evaluated as post-marketing requirements. Pregnant and breastfeeding women, and women planning to become pregnant and breastfeed during the trial were excluded from participation. Therefore, the effects of ritlecitinib on pregnant women will be evaluated as a post- marketing requirement. The use of ritlecitinib during lactation is addressed in Applicant's proposed labeling.	with moderate to severe AA (≥50% scalp hair loss). Evaluate at least 168 subjects exposed to ritlecitinib for a minimum of 24 weeks. 3. A long-term extension study (B7981028) to evaluate the safety and efficacy of ritlecitinib in pediatric population (6 to <12 years of age) with moderate to severe AA (50% or greater scalp hair loss). Approximately 140 subjects will be enrolled for up to 3 years. 4. A long-term open-label extension study (B7981032) to investigate the efficacy and safety of ritlecitinib (N= 1050) in patients (≥12 years of age) with AA and ≥50% scalp hair loss (up to 3 years). 5. Because the uptake of the drug is expected to be substantial, the Applicant will be required to evaluate pregnancy outcomes in two studies. The first study will be a registry based observational exposure cohort study comparing women exposed to ritlecitinib during pregnancy and an unexposed control population. The second study will use a different design (e.g., a retrospective cohort study using claims or electronic medical record data or a case control study). Both studies will record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		for gestational age, preterm birth, and any other adverse pregnancy outcomes. Per Applicant's proposed labeling, ritlecitinib is present in the milk of lactating rats. Because of the potential for serious adverse reactions in nursing infants advise women not to breastfeed during treatment with LITFULO and for approximately 14 hours after the last dose (approximately 6 elimination half-lives). A lactation study will not be conducted because Applicant's proposed labeling advised women not to breastfeed and without an identified threshold for harm, data from a lactation study would not inform healthcare provider decisions.

1.4. Patient Experience Data

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

☐	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		Sec. 8
✓		X	Patient reported outcome (PRO)	PGI-C, P-Sat
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	SALT, EBA, ELA
		☐	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.			

SALT: Severity of Alopecia Tool
EBA: eyebrow assessment
ELA: eyelash assessment
PGI-C: Patient Global Impression of Change
P-Sat: Patient Satisfaction with Hair Growth

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 (PDUFA V) to more systematically gather patient perspectives 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. (The Voice of the Patient: Alopecia Areata, report dated March 2018.)

2 Therapeutic Context

2.1. Analysis of Condition

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)[1]. 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)[2]. 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%[3]. 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[1] of the prevalence of AA in the United States as of 2020 suggests

that the AA prevalence in the US is approximately 0.21% (700,000 persons) with the current prevalence of "moderate to severe" disease being approximately 0.09% (300,000 persons). 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[2]. 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[3]. 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)[4].

Psychiatric co-morbidities occur more frequently in patients with AA. In one review of the world wide literature, the authors (Hon et al. 2020)[5], state that patients with AA have an increased prevalence of personality disorders, paranoid disorders, stress, depression and anxiety disorders, varying from 17-22%. In another review (Toussi et al. 2020)[6], nearly 80% of patients with AA reported impaired health related quality of life based on Dermatology Life Quality Index survey results. 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[7].

According to Toussi et al[6]., pediatric patients with AA also have a higher psychiatric burden than age-matched controls, with higher prevalence of anxiety, depression, and psychiatry appointments. 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 K through 8, misunderstand the nature of AA and can perceive children with AA as sick or dying[8].

[1] Xing L, Dai Z, Jabbari A, Cerise JE, Higgins CA, Gong W, de Jong A, Harel S, DeStefano GM, Rothman L, Singh P, Petukhova L, Mackay-Wiggan J, Christiano AM, Clynes R. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. Nat Med. 2014 Sep;20(9):1043-9. doi: 10.1038/nm.3645. Epub 2014 Aug 17. PMID: 25129481; PMCID: PMC4362521.

[2] UpToDate. Messenger AG. Alopecia areata: Clinical manifestations and diagnosis. Accessed March 10, 2022.

[3] Strazzulla LC, Wang EHC, Avila L, Lo Sicco K, Brinster N, Christiano AM, Shapiro J. Alopecia areata: Disease characteristics, clinical evaluation, and new perspectives on pathogenesis. J Am Acad Dermatol. 2018 Jan;78(1):1-12. doi: 10.1016/j.jaad.2017.04.1141. PMID: 29241771.

[4] Tan E, Tay YK, Giam YC. A clinical study of childhood alopecia areata in Singapore. Pediatr Dermatol. 2002 Jul-Aug;19(4):298-301. doi: 10.1046/j.1525-1470.2002.00088.x. PMID: 12220271.

[5] Hon KL, Luk DCK, Leung AKC, Ng C, Loo SKF. Childhood Alopecia Areata: An Overview of Treatment and Recent Patents. Recent Pat Inflamm Allergy Drug Discov. 2020;14(2):117-132. doi:

10.2174/1872213X14999200728145822. PMID: 32723274.

[6] Toussi A, Barton VR, Le ST, Agbai ON, Kiuru M. Psychosocial and psychiatric comorbidities and health-related quality of life in alopecia areata: A systematic review. J Am Acad Dermatol. 2021 Jul;85(1):162-175. doi: 10.1016/j.jaad.2020.06.047. Epub 2020 Jun 17. PMID: 32561373; PMCID: PMC8260215.

[7] On September 11, 2017, FDA held a public meeting to hear perspectives from patients with alopecia areata, their caregivers, and other patient representatives regarding the aspects of alopecia areata and its treatment that are most important to patients. The meeting was conducted as part of the Patient-Focused Drug Development initiative, an FDA commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V).

[8] Hankinson A, McMillan H, Miller J. Attitudes and perceptions of school-aged children toward alopecia areata. JAMA Dermatol. 2013 Jul;149(7):877-9. doi: 10.1001/jamadermatol.2013.601. PMID: 23864089.

2.2. Analysis of Current Treatment Options

Currently, the only FDA-approved therapies for AA are intralesional corticosteroid injection and oral baricitinib. Use of intralesional corticosteroid injection is recommended for limited disease where, according to a literature report, roughly 80% of patients treated in one series showed >50% improvement after intralesional triamcinolone acetate injections for 12 weeks. Patients with moderate to severe disease had poorer results, 25% to 50% regrowth after 6 months[1]. Adverse events include pain, skin atrophy, telangiectasias, hypopigmentation among others.

Baricitinib (Olumiant), a Janus kinase (JAK) inhibitor, was approved on 6/13/2022 for the treatment of adult patients with severe AA. Olumiant carries a boxed warning and is not recommended as a first-line treatment for AA.

Treatment options for AA which have been used off-label include corticosteroids (topical and oral), immunosuppressants (such as cyclosporine A and azathioprine), pimecrolimus, minoxidil, anthralin, ultraviolet B and psoralen/ultraviolet A therapy, and contact immunotherapy. Success with these approaches is variable and may be limited by the side effect profile, size of the treatment area, concomitant medical conditions and patient preferences.

Extent of hair loss and patient age are the most important factors that determine the approach to treatment. In some instances it may be appropriate not to medically treat AA because the

rates of spontaneous remission can be significant[2], ranging from approximately 8% for extensive disease (>50% scalp involvement) to as high as 68% for limited alopecia (<25% scalp involvement)[3].

For limited disease (less than 50% scalp involvement) and for patients under age 10 years, the most common treatment is corticosteroids, either administered as an intradermal injection, or applied topically as a cream, ointment, or gel. Intralesional corticosteroids may be considered to be first line treatment for patchy alopecia, however, the procedure for administration is painful and impractical for extensive hair loss. Other adverse effects can include local skin atrophy, telangiectasias, and hypopigmentation. Regarding the use of topical corticosteroids, literature reports that two double-blind, randomized, placebo- controlled trials showed regrowth of ≥25% with the use of highly potent topical corticosteroids[4]. Adverse effects of topical corticosteroids include mild itching, burning, acneiform eruption of the face (more common with ointment preparations than foam), striae, telangiectasia, and skin atrophy[10].

Second-line unapproved treatment options for limited disease include hair-growth-stimulating solutions such as minoxidil), anthralin, immunotherapies and calcineurin inhibitors.

For patients with more than 50% scalp involvement or who have rapid progression of AA, healthcare providers prescribe a variety of treatments including topical immunotherapy, oral corticosteroids, and JAK inhibitors. Data to support the use of these unapproved treatments comes from case reports, small uncontrolled trials and rare randomized, controlled trials.

- Topical immunotherapy agents include Diphenylcyclopropenone (DPCP) and squaric acid dibutylester (SADBE). These are sensitizers and induce allergic contact dermatitis. Two RCTs showed ≥75% hair regrowth in severe AA[12]. Other authors, Strazulla et al., also

state there is evidence to support use of topical immunotherapy in extensive AA, even for pediatric patients 10 years of age[10]. Patients who do not respond to diphenylcyclopropenone may be treated with squaric acid dibutylester. Topical sensitizers should not be used in pregnant women because the teratogenic effects and degree of systemic absorption of these compounds are unknown. Side effects can include severe eczema and cervical and occipital lymphadenopathy[10].

- Short courses (6 weeks) of oral corticosteroids are often adequate to stimulate hair regrowth. Per the literature, a single RCT demonstrated treatment effect. Prednisolone 200 mg Q week x 12 weeks, in subjects with ≥40% baseline hair loss, showed ≥30% hair regrowth in 40% of subjects at 3 months, and in 20% of subjects at 6 months[12]. Side effects for oral corticosteroids, however, are not favorable for long term use and can include suppression of the pituitary-adrenal axis, effects on bone growth or integrity, ocular changes, and worsening of hypertension or diabetes[10].

- In the literature, oral Janus kinase inhibitors such as tofacitinib, ruxolitinib, and baricitinib, have been used off-label for the treatment of AA with some evidence of treatment effect. It was reported that the durability of response to these medications is variable, and most patients experience recurrence of hair loss after discontinuation. In a retrospective study of 90 adult patients who received oral tofacitinib (a JAK 1/ JAK3 inhibitor) for severe AA, AT or AU, 77% achieved a clinical response including 58% of patients who achieved ≥50% change in SALT score over 4 to 18 months of treatment[5]. In general, side effects of JAKi include (potentially serious) infections, viral reactivation, bone marrow disruption, transaminase changes, and a theoretical risk for malignancy[10]. Topical JAKi may also be effective but have not been fully evaluated[10].

- Methotrexate may be considered for off-label use in patients who have failed other

treatments such as topical immunotherapy and oral corticosteroids. Treatment benefit has also been reported in pediatric patients[10]. A systematic review and meta-analysis of primarily retrospective observational studies (16 total, mean number of subjects =16) suggests benefits of methotrexate, particularly when used in adults or in conjunction with systemic glucocorticoids. Doses were between 7.5 and 25 mg per week. The pooled rate of good or complete response (at least 50% hair regrowth) was 63%. Recurrence appears common upon tapering of methotrexate[6]. Adverse events associated with low dose (7.5 to 25 mg weekly) methotrexate (MTX) can include; gastrointestinal problems (e.g., nausea, stomach upset, and loose stools), stomatitis, abnormal liver chemistries, a macular punctate cutaneous eruption, central nervous system symptoms (including headache, fatigue, malaise, or impaired ability to concentrate), alopecia, fever, and hematologic abnormalities[7].

Other unapproved therapies used for the treatment of AA include:

- Azathioprine may induce hair regrowth in some patients with moderate to severe AA as suggested by data from small, uncontrolled studies. Adverse effects can include diarrhea, liver enzyme elevation, pancreatitis, and bone marrow suppression.

- Cyclosporine may promote hair growth in patients with AA however, efficacy data are limited and the potential for serious side effects generally precludes long-term use.

- Photochemotherapy with psoralen plus ultraviolet A (PUVA) in patients with AA, as shown in several uncontrolled series, may have efficacy rates of 60 to 65%, though with a high relapse rate. Other series have found efficacy rates no higher than might be expected without therapy. Potential long-term adverse effects, include cutaneous malignancy. Because of these concerns, PUVA is generally avoided in children[8].

Ritlecitinib will be the second kinase inhibitor, following the approval of baricitinib[9] , for the

indication of treatment of AA[10].

[1] Tan E, Tay YK, Goh CL, Chin Giam Y. The pattern and profile of alopecia areata in Singapore--a study of 219 Asians. Int J Dermatol. 2002 Nov;41(11):748-53. doi: 10.1046/j.1365-4362.2002.01357.x. PMID: 12452996.

[2] Strazzulla LC, Wang EHC, Avila L, Lo Sicco K, Brinster N, Christiano AM, Shapiro J. Alopecia areata: An appraisal of

new treatment approaches and overview of current therapies. J Am Acad Dermatol. 2018 Jan;78(1):15-24. doi:

10.1016/j.jaad.2017.04.1142. PMID: 29241773.

[3] Tosti A, Bellavista S, Iorizzo M. Alopecia areata: a long term follow-up study of 191 patients. J Am Acad Dermatol. 2006 Sep;55(3):438-41. doi: 10.1016/j.jaad.2006.05.008. Epub 2006 Jun 27. PMID: 16908349.

[4] Hordinsky M, Donati A. Alopecia areata: an evidence-based treatment update. Am J Clin Dermatol. 2014

Jul;15(3):231-46. doi: 10.1007/s40257-014-0086-4. PMID: 25000998.

[5] Liu LY, Craiglow BG, Dai F, King BA. J Am Acad Dermatol. 2017 Jan;76(1):22-28. doi: 10.1016/j.jaad.2016.09.007. Epub 2016 Nov 2.

[6] Phan K, Ramachandran V, Sebaratnam DF. Methotrexate for alopecia areata: A systematic review and metaanalysis. J Am Acad Dermatol. 2019;80(1):120. Epub 2018 Jul 10.

[7] UpToDate. Kremer JM. Major side effects of low-dose methotrexate. Accessed March 23, 2022.

[8] UpToDate. Messenger AM. Alopecia Areata: Management. Accessed March 28, 2022.

[9] <*https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=866e9f35-9035-4581-a4b1-75a621ab55cf&type=display*>

[10] Parts of Sections on “Benefit-Risk Summary and Assessment”, “Analysis of Condition”, and “Alalysis of current treatment options” of this review were adapted from Clinical Review of the Multi-disciplinary Review and Evaluation of NDA 207924/S-007 (Olumiant) by Drs. Kevin Clark, MD; Patricia Brown, MD; and Melinda McCord, MD.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

To date, ritlecitinib has not been approved for use in any country.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed ritlecitinib for oral treatment of AA under IND 131503 (submitted to FDA on 10/3/2016) and submitted their marketing application for NDA 215830 under 505(b)(1) regulatory pathway on 6/24/2022. No pre-IND meeting was requested by the sponsor. Milestone interactions with the Applicant included the following:

1. Study may proceed letter- 12/15/2016

2. Type C Guidance meeting- 3/14/2018

Target population, seriousness of AA, primary efficacy endpoint (EEP) of SALT10, week 24 for evaluation of primary EEP, SALT50, SALT90, eyelash assessment (ELA) and eyebrow assessment (EBA), size of safety database, real world evidence (RWE), and mAASIS (PRO) were discussed.

3. Breakthrough Therapy Designation Granted- 7/31/2018

4. Advice/Information Request (IR)- 8/23/2018

SALT50, NRS for ELA/EBA, Sponsor's proposals for a delphi panel for clinician global impression (CGI) assessment as a CRO and mAASIS (PRO) for psychosocial symptoms of AA and their COA measurement strategy were discussed.

5. End of Phase 2 meeting- 8/8/2018

Adequacy of the development program to file an NDA, SALT10 as the primary EEP, target population, additional PRO EEPs, planned iPSP, dose ranging strategy, statistical analysis for the primary EEP, and safety assessments were discussed.

6. Model Informed Drug Development (MIDD) meetings- 12/19/2018, 3/11/2019

Exposure-response (E-R) analysis for dose selection, Bayesian approach to E-R modeling, and

Sponsor's proposed methodology for characterization of E-R for emerging safety endpoints and planned simulations were discussed.

7. iPSP (10/8/2018) Advice/IR- 7/30/2019

8. Type C Guidance meeting- 4/8/2020

Discussed potential serious risks related to JAK Inhibitor class of drugs, FDA agreed to change the primary EEP to SALT20 at week 24, discussed broad outlines of a patient preference study (PPS), discrete choice experiment (DCE) method and potential safety attributes for PPS (as informative, not determinative for regulatory decisions), target population for a PPS, content and format of the ISS/ISE and narratives in the NDA, and timing of the submission of safety update.

9. TQT Waiver request- Advice/IR- 8/11/2020

Study B7981001 for a concentration-QTc analysis appear adequate as an alternative to a TQT study.

10. Type C Guidance meeting- 11/4 /2020

Discussed potential impact of missing data from subjects affected by COVID-19 pandemic and subjects/tabular listings in the CSR, statistical comments regarding Amendment 3 to trial B7981015 (submitted on 9/11/2020), one-year exposure defined as 48+/-1 weeks, PPS: B7981048/SAP and mapping risk attributes comments.

11. Agreed iPSP Agreement 3/10/2021

Waiver < 6 years of age, deferral between 6 to < 12 years of age, inclusion between 12 to < 18 years of age.

12. Pre-NDA meeting- 6/14/2021

Discussed presentation of efficacy data in SCE, statistical commentsfor Protocol B7981015 Amendment (4/29/2021), size of the safety database (≥1000 subjects exposed to the to-be-marketed dose for ≥1 year), potential safety concerns for JAK inhibitor class of products, pooling strategy for safety data, and presentation of safety data in SCS.

13. Amendment to Ageed iPSP (submitted to IND 131503, SDN 220)- 3/3/2022

The Applicant's proposed new timeline for completion of planned pediatric studies (discussed at PeRC meetings on 7/12/2022 and 5/2/2023 and was agreed to by PeRC).

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. The Division requested that the Office of Scientific Investigations conduct clinical inspections of the following 3 clinical sites for trial B7981015:

1) Site #1045 (n=18) Saint-Cyr Proulx, Etienne: 3530 Boulevard Saint- Laurent Montreal, QUEBEC H2X 2V1, CANADA
2) Site#1024 (n=12) Lugo-Somolinos, Aida: 410 Market St, Chapel Hill, NC 27516, USA
3) Site#1037 (n=16) Nossa, Robert: 60 Pompton Ave Verona, NJ 07044, USA

The criteria used to select these sites were enrollment of large numbers of study subjects and high treatment responders (for domestic sites), and highest enrollment at Site #1045 in Canada. All inspections were conducted on site.

In the Clinical Inspection Summary, the review team concluded that the conduct of the trial appears to be adequate, and that the data generated appear to be acceptable to support the use of this product for the proposed indication. In her Clinical Inspection Summary of

1/10/2023, Stephanie Coquia, MD (GCPAB/DCCE/OSI), made the following overall assessment of findings and recommendations regarding the findings of the Clinical Site Inspections:

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

On 2/3/2023, letters of no action indicated (NAI) were issued by the FDA’s GCP assessment branch to these 3 sites, which included the following statement: “We have reviewed the FDA Establishment Inspection Report and the documents submitted with that report, and we did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance”.

The Clinical Review Team for NDA 215830 concurs with the conclusions by the Office of Scientific Investigation clinical inspection team that the data quality from the inspected sites are acceptable in support of this application and did not identify any safety concerns that would preclude a recommendation for an “Approval Action” for this NDA.

4.2. Product Quality

The complete Integrated Quality Assessment (IQA) review, dated April 23, 2023, is archived in the CDER Informatics Platform and DARRTS (Document Archiving, Reporting, and Regulatory Tracking System).

4.3. Clinical Microbiology

Not Applicable

4.4. Devices and Companion Diagnostic Issues

Not Applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The applicant submitted a 505(b)(1) application for LITFULO (ritlecitinib) tablets for the treatment of alopecia areata. Ritlecitinib is a new molecular entity kinase inhibitor.

The applicant submitted the following nonclinical studies to support the NDA. Oral repeat dose toxicity studies in rats (up to 26 weeks in duration); oral repeat dose toxicity studies in dogs (up to 39 weeks in duration); a battery of in vitro and in vivo genetic toxicity studies; a 6-month oral carcinogenicity study in transgenic mice; a 2-year oral carcinogenicity study in rats; a fertility and early embryonic development study in rats; embryofetal development studies in rats and rabbits; a pre- and postnatal development study in rats. The applicant also submitted several studies to support the safety of potential impurities, including a 13-week oral repeat dose toxicity study in rats and in vitro genotoxicity studies.

Ritlecitinib is a kinase inhibitor. In vitro, ritlecitinib inhibits Janus kinase 3 (JAK3) and tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family members (i.e., BMX, BTK, ITK, TEC, and TXK) without clinically relevant in vitro activity at other Janus kinases (JAK1, JAK2, and tyrosine kinase 2 [TYK2]). Ritlecitinib inhibited JAK3-dependent STAT phosphorylation in vitro and displayed little or no activity in in vitro assays that do not signal through JAK3.

At clinically relevant concentrations in vitro, ritlecitinib did not inhibit hERG currents (IC_{50} >300 µM). A single oral dose of ritlecitinib did not produce acute CNS or respiratory effects in male rats (doses: 0, 75, 175, and 400 mg/kg; NOEL: 400 mg/kg). In a cardiovascular safety pharmacology study in male dogs (doses: 0, 3, 15, and 45 mg/kg), a single oral dose of ritlecitinib increased heart rate (and consequently decreased the QT interval without affecting QTc) at the HD, but not at lower doses (NOEL: 15 mg/kg). Additionally, up to 39 weeks of oral dosing in dogs did not affect cardiovascular measures (NOAEL: 40 mg/kg/day). Ritlecitinib did not demonstrate cutaneous or ocular phototoxic potential in a 3-day phototoxicity study in female Long Evans rats.

Ritlecitinib had oral bioavailability of approximately 61%, 85%, and 100% in mice, rats, and dogs, respectively. In mouse, rabbit, rat, dog, and human plasma, the unbound fraction was 0.22, 0.29, 0.67, 0.82, and 0.86, respectively. Given the differences in plasma protein binding between species, ritlecitinib exposure will be presented as (and compared using) unbound AUC and C_{max} values. No unique human metabolites were identified. The major human metabolite, M2 (PF-07034562), did not display appreciable binding to plasma proteins in humans or nonclinical species. Ritlecitinib was concentrated in the milk of lactating rats.

In the pivotal 26- and 39-week oral repeat dose toxicity (RDT) studies in rats and dogs, respectively, ritlecitinib displayed reversible effects consistent with its intended pharmacology (i.e., decreasing circulating lymphocytes [typically including total T cells, T helper cells, cytotoxic

T cells, B cells, NK cells, basophils, and eosinophils] and decreasing cellularity in lymphoid tissues [typically including spleen, thymus, GALT, lymph nodes, and sternal bone marrow]). Additionally, ritlecitinib-related reversible, non-adverse clinical pathology changes without correlates were noted (generally including decreased red blood cells, albumin, phosphorous, total cholesterol, and serum creatinine; increased platelets, fibrinogen, and globulin; and increased or decreased reticulocytes). For concision, these findings will not be discussed in detail in each of the following summaries.

In the 26-week oral RDT study in rats with 3-month recovery (doses: 0, 50, 100, and 200 mg/kg/day), no clearly ritlecitinib-related mortalities were noted. At the HD, ritlecitinib decreased food consumption and body weight gain, resulting in slightly decreased mean body weights; these findings were non-adverse. In addition to the common ritlecitinib-related effects noted above, ritlecitinib reversibly increased hyaline droplet accumulation in renal tubular epithelial cells in a dose-related manner (in males and females at doses ≥50 mg/kg/day and ≥100 mg/kg/day, respectively). The NOAEL was 200 mg/kg/day, corresponding to a combined sex Day 176 $AUC_{24.u}$ and $C_{max.u}$ of 53700 hr·ng/mL and 16800 ng/mL, respectively.

In the first 39-week oral RDT study in dogs with 3-month recovery (doses: 0, 5, 20, and 40 mg/kg/day), no ritlecitinib-related effects were noted on mortality, ECG, or ophthalmology. At the HD, ritlecitinib-related immunosuppression was adverse because of skin mites and lung inflammation. At doses ≥20 mg/kg/day, microscopic axonal dystrophy was noted in the olivary nucleus of the brainstem. Treatment-related microscopic findings were generally reversible, except for axonal dystrophy, which was present in HD recovery animals. Auditory testing during the recovery period demonstrated mild to severe hearing loss and waveform defects in brainstem auditory evoked potential (BAEP) testing in 2/2 HD recovery males (auditory testing was not conducted during the dosing period). Brain tissues from terminal and recovery HD dogs were examined via transmission electron microscopy, revealing reversible ultrastructural findings of axosomatic bouton enlargement in the olivary nucleus, which correlated with the microscopic findings of axonal dystrophy. This finding was not observed in brain tissue after a 3-month recovery. Synapses between these bouton enlargements and adjacent neuronal cell bodies were morphologically intact. The NOAEL was 5 mg/kg/day based on microscopic findings in the brainstem at doses ≥20 mg/kg/day and adverse immunosuppressive effects and effects on hearing at the HD.

In the second 39-week oral RDT study in dogs with 6-month recovery (doses: 0, 10, 20, 10 [BID, 6 hours apart] and 40 mg/kg/day), ritlecitinib exposure was similar between sexes and increased dose-proportionally without accumulation. No ritlecitinib-related mortality was noted. Findings were generally similar to the prior study. Ritlecitinib similarly decreased lymphocytes (and cellularity in lymphoid tissues) and similar clinical pathology effects were noted as in the first dog study. At doses ≥20 mg/kg/day, ritlecitinib caused adverse clinical signs (related to skin mites) and reversibly decreased food consumption and body weight. In contrast to the previous study, brainstem auditory evoked potential (BAEP) was evaluated at baseline, during Months 2, 4, 7, and 9 of dosing, and during Recovery Months 3 and 6. At the HD, adverse threshold and waveform BAEP deficits were first noted during Month 7 of dosing;

similar deficits persisted through the end of dosing and Recovery Month 3. However, no auditory threshold deficits were noted at Recovery Month 6. Microscopic findings included axonal dystrophy in the rostro-medial aspect of the vermis (lobule centralis) at ≥10 mg/kg/day, autonomic nerves of the adrenal gland in animals at 20 mg/kg/day, and brainstem, spinal cord (white and gray matter), sciatic nerve, nerve branches of the vagus nerve, and myenteric/submucosal plexuses of the GI tract in animals at ≥20 mg/kg/day. Findings at the LD were non-adverse. All ritlecitinib-related findings were fully or partially reversible after 6-month recovery. The NOAEL was 10 mg/kg/day, corresponding to a combined sex $AUC_{24.u}$ and $C_{max.u}$ of 7940 hr·ng/mL and 1910 ng/mL, respectively.

Based on a series of nonclinical studies investigating the potential mechanism, ritlecitinib-related axonal dystrophy appears to be an off-target effect, rather than mediated through inhibition of JAK3 or TEC kinase family members.

Ritlecitinib was aneugenic in vitro, as determined by an in vitro micronucleus assay in TK6 cells and follow-up in vitro mechanism experiments. However, ritlecitinib was not mutagenic in a reverse mutation assay in bacterial cells. Additionally, ritlecitinib was not mutagenic in a micronucleus assay in rats at doses up to 400 mg/kg/day (corresponding to a Day 1 $AUC_{24.u}$ and $C_{max.u}$ of 133000 hr·ng/mL and 19500 ng/mL, respectively).

In a 6-month oral carcinogenicity study in hemizygous RasH2 transgenic mice (doses: 0, 30, 100, and 300 mg/kg/day), ritlecitinib did not increase mortality, affect body weight, produce adverse clinical observations, or increase the incidence of any tumors.

In a 2-year oral carcinogenicity study in rats (doses: 0, 10, 30 and 100 mg/kg/day), ritlecitinib decreased body weights by approximately 15% at the HD, but did not increase mortality or produce adverse clinical observations at any dose level. At the HD, ritlecitinib increased the incidence of thymus tumors (combined benign and malignant thymoma) in females and thyroid tumors (follicular cell adenoma and combined follicular adenoma and carcinoma) in males. No ritlecitinib-related tumors were noted at doses ≤30 mg/kg/day. The Week 26 AUC_{24} at the MD and HD was 10100 and 47000 hr·ng/mL, respectively.

In an oral fertility and early embryonic development study in rats (doses: 0, 20, 60, and 200 mg/kg/day), treated rats were mated with naïve rats to evaluate fertility in each sex. No adverse ritlecitinib-related effects were noted in females. Ritlecitinib caused longer mean estrous cycles in HD females without affecting other parameters. The NOAEL for female fertility and early embryonic development was 200 mg/kg/day. In HD males, body weights were adversely decreased (>10%) compared to controls and pre-implantation loss was markedly increased, resulting in fewer implantation sites and viable embryos. The NOAEL for male fertility was 60 mg/kg/day, corresponding to a Study Day 62 $AUC_{24.u}$ and $C_{max.u}$ of 58600 hr·ng/mL and 17800 ng/mL, respectively.

In an oral embryofetal development (EFD) study in rats (doses: 75, 175, and 325 mg/kg/day), ritlecitinib adversely decreased maternal food consumption and body weight gain at the HD. At

doses ≥175 mg/kg/day, ritlecitinib decreased fetal body weights, increased the incidence of early resorptions without affecting other ovarian or uterine parameters, and increased the incidence of fetal skeletal (vertebrae and/or rib) malformations and variations. The maternal NOAEL was 175 mg/kg/day. The developmental NOAEL was 75 mg/kg/day, corresponding to a maternal $AUC_{24.u}$ and $C_{max.u}$ of 17000 hr·ng/mL and 7770 ng/mL, respectively.

In an oral EFD study in rabbits (doses: 5, 25, and 75 mg/kg/day), no ritlecitinib-related maternal toxicity was noted (maternal NOAEL: 75 mg/kg/day). At the HD, ritlecitinib decreased fetal body weights and increased post-implantation loss without affecting other ovarian or uterine parameters; increased the incidence of fetal skeletal (vertebrae and/or rib) malformations and visceral malformations (malpositioned kidneys) and skeletal variations (delayed ossification and structural changes). Malpositioned kidneys were noted in single fetuses at the LD and MD, but it is unclear if these malformations are ritlecitinib-related or incidental. In the absence of clearly ritlecitinib-related adverse findings at doses ≤25 mg/kg/day, the developmental NOAEL appeared to be 25 mg/kg/day, corresponding to a maternal $AUC_{24.u}$ and $C_{max.u}$ of 13200 hr·ng/mL and 4470 ng/mL, respectively.

In an oral pre- and post-natal development study in rats (doses: 25, 75, and 175 mg/kg/day), no ritlecitinib-related mortality, clinical signs, body weight effects, macroscopic findings, or reproductive effects were noted in F_0 dams. At doses ≥75 mg/kg/day, ritlecitinib reduced maternal food consumption during lactation in a dose-related manner, which did not affect maternal body weight but corresponded to decreased F_1 pre-weaning weight gain. In F_1 offspring: HD pups had decreased birth weight by approximately 20% and reduced survival through postnatal day (PND) 7; MD and HD pups had dose-related decreased body weight gain through PND 21 (pre-weaning); HD offspring displayed delayed vaginal patency and balanopreputial separation (secondary to lower body weights). No ritlecitinib-related effects were noted on F_1 sensory function, motor activity, learning and memory, estrous cycle lengths, pre-coital intervals, or mating, fertility, and copulation or conception indices. In pregnant HD F_1 females, ritlecitinib reduced corpora lutea, resulting in fewer implantation sites and viable embryos, but did not affect F_2 intrauterine survival. The maternal F_0 NOAEL was 175 mg/kg/day. The F_1 developmental NOAEL was 75 mg/kg/day, corresponding to a maternal (F_0) $AUC_{24.u}$ and $C_{max.u}$ of 15400 hr·ng/mL and 7910 ng/mL, respectively.

The applicant proposes to control six specified impurities and degradants [redacted] (b) (4) at levels requiring qualification; these compounds are qualified at the proposed specification limits based on the nonclinical data. The specified impurity [redacted] (b) (4) was identified as potentially mutagenic in silico, but was not mutagenic in vitro. A potential [redacted] (b) (4) impurity, [redacted] (b) (4) was mutagenic in vitro. However, per the applicant's [redacted] (b) (4) risk assessment, there is no risk of [redacted] (b) (4) formation or presence in the drug substance.

This NDA is approvable from a nonclinical perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

There are 4 members of the Janus kinase (JAK) family, including JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). There are 5 members of the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family, including bone marrow tyrosine kinase gene in chromosome X protein (BMX), Bruton's tyrosine kinase (BTK), interleukin-2-inducible T-cell kinase (ITK), tyrosine protein kinase (TXK), and TEC.

Ritlecitinib inhibited JAK3 and TEC kinase family members in vitro, but did not display clinically relevant inhibition of other JAK family members. In vitro, ritlecitinib covalently binds to JAK3, TEC kinase family members (BMX, BTK, ITK, TEC, and TXK), and BLK, which each have cysteine in their ATP binding pockets (Cys909 in JAK3). The in vitro 50% occupancy (OC_{50}) concentrations for JAK3 and TEC kinase family members in human peripheral blood mononuclear cell lysate was generally similar to in vitro ritlecitinib kinase inhibition when the ATP concentration was at the K_m value; in the presence of a physiologically relevant ATP concentration (1 mM), ritlecitinib was generally less potent. The following table summarizes in vitro ritlecitinib inhibition and occupancy of JAK kinaes and TEC family kinases.

Kinase	Ritlecitinib IC_{50} (nM)[1]		Ritlecitinib OC_{50} (nM)[2]
	ATP @ 1 mM	ATP @ K_m	
JAK3	33.1	0.346	73
TXK	194	34.5	161
TEC	592	219	58
BMX	606	29	67
BTK	608	38.2	89
ITK	8510	ND	176
JAK1	>9710	1640	-
JAK2	>10000	1510	-
TYK2	>10000	3780	-

ND, not determined
[1]in vitro using recombinant human enzymes
[2]in vitro using human peripheral blood mononuclear cell lysate

At 1 mM ATP in vitro, M2 (PF-07034562) did not display clinically relevant inhibition (IC_{50}: >9000 nM) of recombinant human JAKs (JAK1, JAK2, JAK3, and TYK2) or TEC kinase family kinases (BMX, BTK, ITK, TEC, and TXK).

In vitro, ritlecitinib selectively inhibited JAK3-dependent STAT phosphorylation with little-to-no inhibition of STAT phosphorylation through other JAKs. Ritlecitinib inhibited JAK1/JAK3-dependent STAT phosphorylation, including IL-15-induced STAT5 phosphorylation and IL-21-induced STAT3 phosphorylation in human, rat, and dog whole blood and human peripheral

blood mononuclear cells (IC_{50} values ranging from 52 nM to 362 nM) and IL-4-induced STAT6 phosphorylation in B cells and T cells from human blood (IC_{50} values of 1000 nM and 226 nM, respectively). Ritlecitinib displayed low potency inhibition of JAK1/JAK2-dependent IL-31-induced STAT3 phosphorylation in THP-1 cells (IC_{50}: 4400 nM). However, ritlecitinib did not display any other biologically relevant inhibition (IC_{50} >10 µM) of JAK1/TYK2-, JAK1/JAK2/TYK2-, JAK1/JAK2-, JAK2/TYK2-, or JAK2/JAK2-dependent STAT phosphorylation.

The applicant submitted a series of in vitro studies which provided preliminary evidence of ritlecitinib inhibition of TEC family kinases affecting immune cell activity. When incubated with PBMCs containing activated CD8+ T cells and Natural Killer (NK) cells in vitro, ritlecitinib inhibited surface expression of CD107a (a marker of cytotoxic degranulation; IC_{50}: 210 nM and 509 nM for CD8+ T cells and NK cells, respectively) and IFNγ production (IC_{50}: 188 nM in both cell types); these effects were potentially caused by ITK inhibition. In vitro, ritlecitinib inhibited B cell receptor mediated CD69 upregulation in CD19+ B cells (IC_{50}: 344 nM) and T cell receptor mediated CD69 upregulation in CD4+ T cells (IC_{50}: 380 nM), presumably because of (or related to) BTK and ITK inhibition, respectively.

The applicant evaluated oral ritlecitinib administration in several inflammatory models in rodents, including models of inflammatory bowel disease and multiple sclerosis in mice and a model of adjuvant-induced arthritis in rats. These studies are not relevant to the current NDA and are not reviewed here.

In published literature submitted to the NDA (Dai Z, Chen J, Chang Y, Christiano AM. Selective inhibition of JAK3 signaling is sufficient to reverse alopecia areata. JCI Insight. 2021 Apr 8;6(7):e142205. doi: 10.1172/jci.insight.142205), ritlecitinib (30 mg/kg, delivered via osmotic pump) prevented onset of hair loss and caused hair regrowth in a mouse model of alopecia areata. However, the translatability of these findings to alopecia areata in humans is unknown.

The above pharmacology data support statements made in section 12.1 of the applicant's proposed labeling.

At high concentrations in vitro, ritlecitinib inhibited Abl kinase (IC_{50}: 2800 nM), EGFR kinase (IC_{50}: 2200 nM), and VEGFR2 kinase (IC_{50}: 1300 nM [in a functional assay, no inhibition was noted at concentrations up to 30 µM]).

Safety pharmacology

Neurological and respiratory effects:

Male Wistar Han rats (6 per group) received a single oral dose of ritlecitinib (doses: 0 [0.5% methylcellulose], 75, 175, and 400 mg/kg). One hour post-dose, body temperature was recorded and a functional observation battery was performed, followed by 30 minutes of locomotor activity measurement. In a separate group, pulmonary parameters (respiratory rate,

tidal volume, and minute volume) were assessed using whole body plethysmography for 4 hours post-dose. No ritlecitinib-related effects were noted.

Cardiovascular effects:
In vitro, ritlecitinib did not produce clinically relevant inhibition of the hERG potassium current (IC_{50} >300 µM).

Telementry-implanted male dogs (n=3) received a single oral dose of ritlecitinib (doses: 0 [0.5% methylcellulose], 3, 15, and 45 mg/kg) in a cross-over study with a minimum washout period of 6 days. Cardiovascular parameters were monitored pre-dose through 24 hours post-dose, including arterial blood pressure, heart rate, and ECG (including RR, PR, QRS, QT, and QTc intervals). At the HD, ritlecitinib increased heart rate (and consequently decreased the QT interval without affecting QTc). No ritlecitinib-related effects were noted at lower doses.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Single Dose Pharmacokinetics and Excretion of PF-06651600 in Rats Following Intravenous or Oral Administration / PF-06651600_11Jun14_152020	Rat (single dose) Oral bioavailability (F): 85.4% Clearance (CL): 68.7 mL/min/kg Volume of distribution (V_d): 1.41 L/kg
Single Dose Pharmacokinetics and Oral Bioavailability of PF-06651600 in Mice Following Oral or Intravenous Administration / PF-06651600_23Sep14_145444	Mouse (single dose) F: 61.3% CL: 45.2 mL/min/kg V_d: 0.839 L/kg
Single Dose Pharmacokinetics and Oral Bioavailability of PF-06651600 in Dogs Following Oral or Intravenous Administration / PF-06651600_22May14_132012	Dog (single dose) F: 100% CL: 13.4 mL/min/kg V_d: 1.07 L/kg
Pharmacokinetic Assessment of PF-06651600 and PF-07034562 Following the Oral Administration of PF-06651600 in the Rat JVC/CAC Model / PF-06651600_08APR21_105110	Rat (200 mg/kg/day for 7 days) Ritlecitinib: $AUC_{24.u.Day7}$: 81700 hr·ng/mL $C_{max.u.Day7}$: 48700 ng/mL $t_{max.Day7}$: 0.42 ± 0.33 hr PF-07034562 (M2): $AUC_{24.Day7}$: 75000 hr·ng/mL $C_{max.Day7}$: 16400 ng/mL $t_{max.Day7}$: 1.4 ± 0.53 hr
Distribution	

Type of Study	Major Findings
Protein Binding of PF-06651600 in Rat, Dog, Monkey, and Human Plasma / PF-06651600_22May14_154304	Ritlecitinib (2 µM) displayed low binding to plasma proteins in rat, dog, and human (fraction unbound: 0.67, 0.82, and 0.86, respectively).
Protein Binding of PF-06651600 in Mouse and Rabbit Plasma / YDP067/032	Ritlecitinib (2 µM) displayed moderate binding to plasma proteins in mouse and rabbit (fraction unbound: 0.22 and 0.29, respectively).
Protein Binding of PF-07034562 in Mouse, Rat, Dog, Rabbit and Human Plasma / YDP/067/368	M2 (2 µM) did not display appreciable binding to plasma proteins (fraction unbound: 0.95, 1.07, 1.11, 1.12, and 1.21 in human, rabbit, rat, mouse, and dog, respectively).
In Vitro Assessment of the Binding of [^{14}C] PF-06651600 to Human Plasma Proteins / PF-06651600_12Apr21_103503	After a 24 hr in vitro incubation, 12.8% to 15.3% of [^{14}C]ritlecitinib (5 µM) was bound to plasma proteins, 6.1% was bound to serum albumin, and platelets, α1-acid glycoprotein, high density lipoprotein, fibrinogen, and γ-globulins each accounted for <1% of binding.
Red Blood Cell to Plasma Partitioning of PF-06651600 in Rat, Dog and Human Whole Blood / YDP/067/018	Ritlecitinib (1 µM) blood:plasma ratios were 0.99, 1.57, and 1.62 in rat, dog, and human, respectively.
Red Blood Cell to Plasma Partitioning of PF-07034562 in Mouse Rat, Rabbit, Dog and Human Whole Blood / YDP/067/369	M2 (1 µM) blood:plasma ratios were 0.52, 0.55, 0.55, 0.68, and 0.83 in dog, rat, mouse, human, and rabbit, respectively.
Tissue Distribution in Male Long-Evans Rats Following a Single Oral Administration of [^{14}C]PF-06651600 Using Quantitative Whole Body Autoradiography / 15647	[^{14}C]Ritlecitinib was widely distributed in rats with detectable radioactivity at 672 hr post-dose in the adrenal gland, aorta, blood, eye, heart, lens, liver, lung, kidney, spleen, and uveal tract
Metabolism	

Type of Study	Major Findings
Preliminary Investigation of the In Vitro and In Vivo Biotransformation of PF-06651600 in Human and Preclinical Species / PF-06651600_13Jun14_085839	After a 4 hour incubation with rat, dog, or human liver microsomes and hepatocytes in vitro, similar metabolic clearance pathways were noted across species. No unique human metabolites were identified. Ritlecitinib and an N-acetyl-cysteine metabolite were detected in rat urine and bile. Ritlecitinib and a cysteine conjugate were detected in dog urine and glutathione, N-acetyl-cysteine, cysteine-glycine, cysteine, and hydroxyl-thiol conjugates in dog bile.
Preliminary Investigation of the Circulating Metabolite Profile of PF-06651600 in Human Plasma (B7981001) / PF-06651600_13Dec17_040703	M1 (PF-07034563), M2 (PF-07034562, a cysteine conjugate), and M3 (PF-07034468, an N-acetylcysteine conjugate), were the main circulating metabolites in human subjects (from trial #B7981001, after 400 mg/day oral dosing for 14 days); similar or higher metabolite levels were noted in rats and mice. Ritlecitinib, M1, M2, and M3 were detected in urine of all species examined and in rat bile.
Metabolite Scouting of Plasma and Brain Tissue From the 3-Day Oral Gavage Toxicokinetic Study of PF-06651600 in Female Beagle Dogs / PF-06651600_14Mar18_092809	After 3 days of oral 40 mg/kg/day dosing in dogs, no marked differences in ritlecitinib metabolites were detected between plasma and brain tissue (from the superior olivary nucleus, cochlear nucleus, and hippocampus); M2 was the only major metabolite detected.
In Vitro Biotransformation of PF-06651600 in Bacterial Incubation Media / PF-06651600_09Aug21_111222	After incubating ritlecitinib for 3 hours in the same media preparation as used for bacterial reverse mutation assays, the human metabolites M2 (PF-7034562) and M4 (PF-07297983) were observed with and without metabolic activation.
Excretion	
Lacteal Excretion of PF-06651600 Following Administration of a Single Oral Dose to Rats / 8448335	Ritlecitinib (30 mg/kg) was concentrated in milk of lactating Sprague-Dawley rats. The highest milk:plasma concentration ratio was 3.63 at 1 hour post-dose. The AUC_{0-t} milk:plasma ratio of 2.21.

Type of Study	Major Findings
TK data from general toxicology studies A 6-Month Oral Gavage Toxicity Study of PF-06651600 in Rats with a 3-Month Recovery Period / 14MA142	<u>Rat @ NOAEL (HD; 200 mg/kg/day) on Day 176</u> t_{max}: 1.0 hr $AUC_{24.u}$: 53700 hr·ng/mL $C_{max.u}$: 16800 ng/mL Accumulation: No clear accumulation Dose proportionality: Exposure increased approximately dose-proportionally
A 9-Month Oral Gavage Toxicity Study of PF-06651600 in Dogs with a 3-Month Recovery Period / 14MA143	<u>Dog @ NOAEL (LD; 5 mg/kg/day) on Day 273</u> t_{max}: 1 hr $AUC_{24.u}$: 4020 hr·ng/mL $C_{max.u}$: 1120 ng/mL Accumulation: None Dose proportionality: Exposure increased approximately dose-proportionally
A 9-Month Oral Gavage Toxicity Study of PF-06651600 in Dogs with a 6-Month Recovery Period / 16MA106	<u>Dog @ NOAEL (LD; 10 mg/kg/day) on Day 273</u> t_{max}: 1 hr $AUC_{24.u}$: 7940 hr·ng/mL $C_{max.u}$: 1910 ng/mL Accumulation: None Dose proportionality: Exposure increased approximately dose-proportionally

Type of Study	Major Findings
TK data from reproductive toxicology studies An Oral (Gavage) Study of the Effects of PF-06651600 on Male and Female Fertility and Early Embryonic Development to Implantation in Rats / 18GR019	<u>Male rat @ NOAEL on Study Day 62</u> Male NOAEL (60 mg/kg/day): $AUC_{24.u}$: 14700 hr·ng/mL $C_{max.u}$: 7200 ng/mL Female NOAEL (200 mg/kg/day): $AUC_{24.u}$: 58600 hr·ng/mL $C_{max.u}$: 17800 ng/mL *Note: Male TK data is presented for both sexes because TK assessment was not conducted on females in this study.*
An Embryo-fetal Development Study of PF-06651600-15 by Oral Gavage in Rats / 15GR148	<u>Rat @ NOAEL on GD 17</u> Developmental (75 mg/kg/day): $AUC_{24.u}$: 17000 hr·ng/mL $C_{max.u}$: 7770 ng/mL Maternal (175 mg/kg/day): $AUC_{24.u}$: 52900 hr·ng/mL $C_{max.u}$: 13700 ng/mL
An Embryo-Fetal Development Study of PF-06651600-15 by Oral Gavage in Rabbits / 15GR149	<u>Rabbit @ NOAEL on GD 19</u> Developmental (25 mg/kg/day): $AUC_{24.u}$: 13200 hr·ng/mL $C_{max.u}$: 4470 ng/mL Maternal (75 mg/kg/day): $AUC_{24.u}$: 58600 hr·ng/mL $C_{max.u}$: 14900 ng/mL
An Oral (Gavage) Study of the Effects of PF-06651600 on Pre- and Postnatal Development, Including Maternal Function in Wistar Rats / 19GR230	<u>Rat @ NOAEL on GD 17</u> Developmental (F_1; 75 mg/kg/day): $AUC_{24.u}$: 15400 hr·ng/mL $C_{max.u}$: 7910 ng/mL Maternal (F_0; 175 mg/kg/day): $AUC_{24.u}$: 44000 hr·ng/mL $C_{max.u}$: 16100 ng/mL
TK data from Carcinogenicity studies 6-Month Oral Gavage Carcinogenicity Study of PF-06651600 in Hemizygous rasH2 Transgenic (tg/wt) Mice / 19GR034	<u>Mouse @ HD (300 mg/kg/day)</u> $AUC_{24.u}$: 12100 hr·ng/mL
104-Week Oral Gavage Carcinogenicity Study with PF-06651600 in Rats / 18MA002	<u>Rat @ MD and HD (30 and 100 mg/kg/day)</u> MD: $AUC_{24.u}$: 6770 hr·ng/mL HD: $AUC_{24.u}$: 31500 hr·ng/mL

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: A 6-Month Oral Gavage Toxicity Study of PF-06651600 in Rats with a 3-Month Recovery Period / 14MA142

- No ritlecitinib-related mortalities or clinical signs were noted. At the HD, ritlecitinib caused a non-adverse decrease in overall body weight compared to controls.
- Consistent with its intended pharmacology, ritlecitinib decreased circulating white blood cells, lymphocytes, basophils, monocytes, and eosinophils, which correlated to decreased thymus and spleen weights and microscopically decreased lymphoid cellularity in lymphoid organs (thymus, spleen, and mesenteric and inguinal lymph nodes) minimally decreased sternal bone marrow cellularity. These effects were reversible and generally dose-related.
- The NOAEL was the HD (200 mg/kg/day), which corresponds to a Day 176 combined sex AUC_{24} of 80100 hr·ng/mL and C_{max} of 25100 ng/mL.

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

Methods

Dose and frequency of dosing:	0, 50, 100, and 200 mg/kg/day, once daily
Route of administration:	ORAL GAVAGE
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	RAT/WISTAR HAN
Number/Sex/Group:	15
Age:	7 weeks old at dosing initiation
Satellite groups/ unique design:	5/sex control and HD animals for 3-month recovery; TK assessment was conducted using the toxicity group, with 12 animals/sex/group each having one TK sample collected on Day 91 and 176 (samples were collected from 3/sex/group/time point [1, 3, 7, and 24 hours post-dose]); TK sampling on Day 91 was conducted after clinical pathology sampling
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control
[Do not enter text here. Use the table]

Parameters	Major findings
Mortality	No ritlecitinib-related effects.
Clinical Signs	No ritlecitinib-related effects.
Body Weights	HD: Ritlecitinib decreased body weight by approximately 10%; reversible in males, but not females.

Ophthalmoscopy	No ritlecitinib-related effects.
Hematology	At all dose levels, ritlecitinib decreased white blood cells, monocytes, and eosinophils and decreased lymphocytes and basophils in a dose-related manner. At the HD, ritlecitinib decreased red blood cells (by up to 10%) and caused transient poikilocytosis, hypochromasia, and increased reticulocytes. All ritlecitinib-related effects were reversible and non-adverse.
Clinical Chemistry	At all dose levels and without dose relationship, ritlecitinib decreased aspartate transaminase (by up to 37%) and potassium (by up to 18%). At the MD and HD, ritlecitinib decreased glucose (by up to 17%) and triglycerides (by up to 56%). All ritlecitinib-related effects were reversible and non-adverse.
Urinalysis	At all dose levels, ritlecitinib reversibly increased urine protein in males without dose relationship or corresponding adverse findings.
Gross Pathology	Reversibly small thymuses were noted in males at all dose levels and in females at the MD and HD.
Organ Weights	At all dose levels in both sexes, ritlecitinib reversibly decreased thymus weights (by up to approximately 80%) in a dose-related manner. Spleen weights reversibly decreased (by approximately 20%) at all dose levels in males and in MD and HD females.
Histopathology Adequate battery: Yes	At all dose levels, ritlecitinib decreased lymphoid cellularity in the thymus (minimal to severe) and spleen (minimal to mild) in a dose-related manner. At the HD, ritlecitinib decreased lymphoid cellularity in the mesenteric lymph node (minimal to moderate) and inguinal lymph node (minimal to mild) and minimally decreased sternal bone marrow cellularity. At all dose levels in males and in MD and HD females, ritlecitinib increased hyaline droplet accumulation in tubular epithelial cells of the kidney in a dose-related manner. All ritlecitinib-related effects were reversible and non-adverse.

MD: mid dose; HD: high dose.

Study title/ number: A 9-Month Oral Gavage Toxicity Study of PF-06651600 in Dogs with a 3-Month Recovery Period / 14MA143

- No ritlecitinib-related mortalities were noted. At doses ≥20 mg/kg/day, ritlecitinib slightly decreased mean body weights.
- At all dose levels, ritlecitinib reversibly decreased circulating lymphocytes, basophils, and eosinophils and reversibly decreased lymphoid cellularity in lymphoid organs (thymus, spleen, GALT, and mesenteric and popliteal lymph nodes) and minimally decreased sternal bone marrow cellularity in males.
- At doses ≥20 mg/kg/day, ritlecitinib caused dose-related microscopic axonal dystrophy in the olivary nucleus of the brain. Axosomatic bouton enlargement was noted in the olivary nucleus via transmission electron microscopy at the end of dosing, but not observed at the end of recovery.

- Mild to severe hearing loss and waveform defects in brainstem auditory evoked potential (BAEP) testing was noted in both HD recovery males; testing was not conducted during dosing or on MD animals.
- At the HD, ritlecitinib also caused adverse immunosuppression and infections, lung inflammation, and progressive skin inflammation.
- The NOAEL was 5 mg/kg/day, which corresponds to a Day 273 combined sex AUC_{24} of 4900 hr·ng/mL and C_{max} of 1360 ng/mL. These data support proposed reviewer additions to section 13.2 of labeling.

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

Methods

Dose and frequency of dosing:	0, 5, 20, and 40 mg/kg/day, once daily
Route of administration:	ORAL GAVAGE
Formulation/Vehicle:	0.5% methylcellulose in water
Species/Strain:	DOG/BEAGLE
Number/Sex/Group:	4
Age:	11 to 12 months old at dosing initiation
Satellite groups/ unique design:	2/sex control and HD groups for 3-month recovery. Brainstem auditory evoked potential (BAEP) testing was conducted during recovery after microscopic findings were noted in the olivary nucleus of the brainstem. Transmission electron microscopy was used on brain tissues from 2 HD males and 3 recovery animals.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No ritlecitinib-related effects.
Clinical Signs	HD: Non-adverse red skin and focal scabs/papules were noted during dosing which progressed during recovery to adverse generalized red skin, thin fur, interdigital cysts, and ear infections.
Body Weights	MD and HD: Ritlecitinib slightly (<10%) decreased mean body weights compared to controls.
Ophthalmoscopy	No ritlecitinib-related effects.
ECG	No ritlecitinib-related effects.
Hematology	Ritlecitinib decreased lymphocytes, basophils, eosinophils, and red blood cells (and related parameters). At the HD, ritlecitinib increased neutrophils, white blood cells, monocytes, platelets, and fibrinogen. All ritlecitinib-related effects displayed reversibility.

Clinical Chemistry	Ritlecitinib decreased albumin, albumin:globulin ratio, phosphorus, creatinine, and cholesterol and increased globulin. All ritlecitinib-related effects displayed reversibility.
Urinalysis	No ritlecitinib-related effects.
Gross Pathology	HD: Ritlecitinib caused reversible scabs/nodules in the skin and discolored foci in the lung.
Organ Weights	HD: Ritlecitinib reversibly reduced spleen weights.
Histopathology Adequate battery: Yes	Ritlecitinib caused dose-related minimal to moderate axonal dystrophy in the olivary nucleus of the brain of both sexes at the MD and HD; reversibility was not observed at the HD. At all dose levels in a dose-related manner, ritlecitinib reversibly decreased lymphoid cellularity in lymphoid organs (thymus, spleen, GALT, and mesenteric and popliteal lymph nodes) and minimally decreased sternal bone marrow cellularity (males only). At the HD, ritlecitinib caused reversible chronic inflammation in the skin and in lung foci.
Immunophenotyping	Ritlecitinib decreased total T cells, helper T cells, cytotoxic T cells, NK cells, and B cells. All ritlecitinib-related effects displayed reversibility.
Brainstem auditory evoked potential (BAEP)	Mild to severe hearing loss and waveform defects in BAEP testing in both HD recovery males.
Transmission Electron Microscopy	HD: Axosomatic bouton enlargement was noted in the olivary nucleus (in 2/2 examined) at the end of dosing, but not at the end of the recovery period.

MD: mid dose; HD: high dose.

Study title/ number: A 9-Month Oral Gavage Toxicity Study of PF-06651600 in Dogs with a 6-Month Recovery Period / 16MA106

- No ritlecitinib-related mortalities were noted.
- At doses ≥20 mg/kg/day, ritlecitinib slightly decreased mean body weights, caused adverse clinical signs, and caused reversible microscopic axonal dystrophy in the brainstem, spinal cord, sciatic nerve, nerve branches of the vagus nerve, and myenteric/submucosal plexuses of the GI tract.
- Axonal dystrophy in the rostral vermis was noted at all dose levels, but was non-adverse at the LD.
- At the HD, adverse threshold and waveform BAEP deficits were noted during Month 7 of dosing, persisted through the end of dosing, and worsened by Recovery Month 3. However, no auditory threshold deficits were noted at Recovery Month 6.
- The NOAEL was 10 mg/kg/day, corresponding to a combined sex $AUC_{24.u}$ and $C_{max.u}$ of 7940 hr·ng/mL and 1910 ng/mL, respectively. These data support proposed reviewer additions to section 13.2 of labeling.

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

Methods

Dose and frequency of dosing:	0, 10, 20, 10 (twice daily, 6 hours apart), and 40 mg/kg/day, once daily (except as noted otherwise)
Route of administration:	ORAL GAVAGE
Formulation/Vehicle:	0.5% methylcellulose in water
Species/Strain:	DOG/BEAGLE
Number/Sex/Group:	4
Age:	9 months old at dosing initiation
Satellite groups/ unique design:	3/sex control and 20 and 40 mg/kg/day groups for 6-month recovery. Ophthalmic examination and ECG were not conducted because ritlecitinib did not affect either in the prior 9-month oral repeat dose toxicity study in dogs. Brainstem auditory evoked potential (BAEP) was evaluated in all groups at baseline, during Months 2, 4, 7, and 9 of dosing, and during Recovery Months 3 and 6. To determine background incidence of spheroids in the rostral vermis of dogs, 95 additional brain sections from control dogs (age-matched or older and unrelated to the study) were examined microscopically, revealing 1 to 5 spheroids in the rostral vermis of 25% of the controls (and increasing numbers with age).
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No ritlecitinib-related effects.
Clinical Signs	At doses ≥20 mg/kg/day, ritlecitinib caused adverse reversible red skin, thin fur, and skin papules.
Body Weights	Reversible, non-adverse, slightly (<5%) lower body weights were noted at doses ≥20 mg/kg/day (10 mg/kg BID).
Hematology	Ritlecitinib reversibly decreased lymphocytes, basophils, eosinophils, and red blood cells (and related parameters).
Clinical Chemistry	Ritlecitinib decreased albumin, albumin:globulin ratio, calcium, phosphorus, creatinine, and cholesterol and increased globulin. All ritlecitinib-related effects displayed reversibility.
Urinalysis	No ritlecitinib-related effects.
Gross Pathology	At doses ≥20 mg/kg/day, reversible skin nodules, masses, or cysts were noted (correlated to infection and inflammation). At the HD, reversible pale foci were noted in lungs.
Organ Weights	No ritlecitinib-related effects.

Histopathology Adequate battery: Yes	At all dose levels, axonal dystrophy was noted in the rostro-medial aspect of the vermis (lobule centralis); this finding was non-adverse at the LD based on background incidence (in age-matched control dogs from unrelated studies), low severity, and lack of adverse correlates or impairment. At doses ≥20 mg/kg/day, adverse axonal dystrophy (spheroids) was noted in the brainstem, spinal cord (white and gray matter), sciatic nerve, nerve branches of the vagus nerve, and myenteric/submucosal plexuses of the GI tract. Axonal dystrophy was noted in autonomic nerves of the adrenal gland of females at the 20 mg/kg/day (QD) dose level. At all dose levels in a dose-related manner, ritlecitinib reversibly decreased lymphoid cellularity in lymphoid organs (thymus, spleen, GALT, and mesenteric and popliteal lymph nodes) and minimally decreased sternal bone marrow cellularity. Ritlecitinib increased the incidence of mixed cell inflammation in the lung at all dose levels in males and at 10 mg/kg BID and 40 mg/kg/day doses in females. Adverse skin findings consistent with skin infection and mites were noted at 10 mg/kg BID (both sexes) and 40 mg/kg/day (males only). All ritlecitinib-related effects were fully or partially reversible at the end of a 6-month recovery.
Immunophenotyping	Ritlecitinib decreased total T cells, helper T cells, cytotoxic T cells, and NK cells. All ritlecitinib-related effects displayed reversibility.
Brainstem auditory evoked potential (BAEP)	At the HD, adverse threshold and waveform BAEP deficits were first noted during Month 7 of dosing; similar deficits persisted through the end of dosing and through Recovery Month 3. However, no auditory threshold deficits were noted at Recovery Month 6.

LD: low dose; HD: high dose.

General toxicology; additional studies

The applicant conducted a series of studies to probe the mechanism underlying axonal dystrophy in dogs. These studies examined select brain tissues, including: the superior olivary nucleus and rostral cerebellar vermis because these were sites of ritlecitinib-related axonal dystrophy in chronic dog studies; the cochlear nucleus because it has a similar location and relationship to the auditory pathway; and the hippocampus because it is anatomically and functionally different from the superior olivary nucleus.

In a 3-day oral repeat dose toxicity study in female dogs (4/group; 2-3 years old), ritlecitinib (40 mg/kg/day) was administered once daily followed by blood sampling and determination of ritlecitinib concentrations in brain tissues. The mean ritlecitinib concentration in plasma was 11300 ng/mL; concentrations in the superior olivary nucleus, cochlear nucleus, and hippocampus were 1080, 1090, and 1340 ng/g, respectively. As noted in the Distribution table in section 5.4, no differences in ritlecitinib metabolites were noted in plasma or brain in this study.

In control male dogs (n=3, approximately 4 years old), brain tissues were collected to determine relative mRNA expression of select kinases (JAKs, TEC family kinases, LRRK2, SLK, KDR, NTRK2, ABL2, and FLT3) and oxidative stress genes based on the hypothesis that differences in expression might contribute to toxicity being observed in the superior olivary nucleus but not the other brain tissues. However, no differences in kinase expression were noted, JAK3 expression in dog brain was low, and no clear, consistent differences in oxidative stress genes were noted between the superior olivary nucleus and cochlear nucleus or hippocampus.

In a separate study, rostral cerebellar vermis and hippocampus from control dogs were homogenized and incubated with 10 µM ritlecitinib and 1 µM PF-06789402, an alkyne-containing ritlecitinib analog, to identify off-target binding sites in dog brain tissues. BTK, BMX, DOCK10, and MAP2K7 were identified as apparent high binding affinity targets; MAP2K7 was the only high affinity target noted in rostral cerebellar vermis. Based on the lack of similar findings with ibrutinib (a more potent inhibitor of BTK and BMX) and presence in both brain regions, BTK and BMX do not appear likely to be responsible for ritlecitinib-related axonal dystrophy. However, DOCK10 and MAP2K were identified as off-target proteins potentially relevant to axonal dystrophy in dogs.

In subsequent studies, MAP2K7 binding affinities and cerebellar expression of DOCK10 were evaluated in humans and nonclinical species. Using lysate from HEK293F cells overexpressing dog, rat, or human MAP2K7, ritlecitinib displayed similar binding across species (OC_{50} values were 7.45, 11.1, and 14.3 µM for dog, rat, and human MAP2K7, respectively). Using RNAseq datasets containing cerebellar expression data from humans (20 samples), dogs (5 samples), rats (7 samples), and mice (23 samples), DOCK10 expression was found to be significantly higher in nonclinical species compared to humans.

These studies did not identify the mechanism of ritlecitinib-related axonal dystrophy. However, they provide support for this finding being an off-target effect. These data support proposed reviewer additions to section 13.2 of labeling.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)
Study title/ number: PF-06651600 Salmonella-E. Coli/Mammalian Microsome Reverse Mutation Assay / 14GR129
Key Study Findings:

- Ritlecitinib was not mutagenic under the conditions of the assay. These data support statements made in section 13.1 of labeling.

GLP compliance: Yes
Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA* pKM101; up to 5000 µg/plate; ±S9
Study is valid: Yes

In Vitro Assays in Mammalian Cells
Study title/ number: PF-06651600 *In Vitro* Micronucleus Assay In TK6 Cells / 14GR130
Key Study Findings:

- Ritlecitinib induced micronuclei in vitro after a 27-hour incubation without metabolic activation.
- In a subsequent mechanistic study, ritlecitinib was identified as an in vitro aneugen.

GLP compliance: Yes
Test system: TK6 cells; up to 285 µg/mL (4-hour incubation, ±S9) or 125 µg/mL (27-hour incubation, -S9)
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Study title/ number: 8-Week Oral Gavage Toxicity and Micronucleus Assessment Study of PF-06651600 in Wistar Han Rats / 14GR132
Key Study Findings:

- Ritlecitinib did not induce bone marrow micronuclei at doses up to 400 mg/kg/day (corresponding to a Day 1 $AUC_{24.u}$ and $C_{max.u}$ of 133000 hr·ng/mL and 19500 ng/mL, respectively). These data support statements made in section 13.1 of labeling.

GLP compliance: Yes
Test system: Rat, bone marrow micronuclei; four consecutive days of oral dosing of 0 (0.5% methylcellulose), 75, 175, or 400 mg/kg/day; assessments on the 4th day of dosing
Study is valid: Yes

5.5.3. Carcinogenicity

In a 6-month oral carcinogenicity study in hemizygous RasH2 transgenic mice (doses: 0, 30, 100, and 300 mg/kg/day), ritlecitinib did not increase mortality, affect body weight, produce adverse clinical observations, or increase the incidence of any tumors.

In a 2-year oral carcinogenicity study in rats (doses: 0, 10, 30 and 100 mg/kg/day), ritlecitinib decreased body weights by approximately 15% at the HD, but did not increase mortality or produce adverse clinical observations at any dose level. At the HD, ritlecitinib increased the incidence of thymus tumors (combined benign and malignant thymoma) in females and thyroid tumors (follicular cell adenoma and combined follicular adenoma and carcinoma) in males. No ritlecitinib-related tumors were noted at doses ≤30 mg/kg/day. The Week 26 AUC_{24} at the MD and HD was 10100 and 47000 hr·ng/mL, respectively.

Refer to Section 19.3.3 for complete review of conducted carcinogenicity studies.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: An Oral (Gavage) Study of the Effects of PF-06651600 on Male and Female Fertility and Early Embryonic Development to Implantation in Rats / 18GR019

Key Study Findings

- No adverse ritlecitinib-related effects were noted in females. Ritlecitinib caused longer mean estrous cycles in HD females without affecting other parameters. The NOAEL for female fertility and early embryonic development was 200 mg/kg/day, corresponding to a Study Day 62 $AUC_{24.u}$ and $C_{max.u}$ of 58600 hr·ng/mL and 17800 ng/mL, respectively, in males (see Study design).
- In HD males, body weights were adversely decreased (>10%) compared to controls and pre-implantation loss was markedly increased, resulting in fewer implantation sites and viable embryos. The NOAEL for male fertility was 60 mg/kg/day, corresponding to a Study Day 62 $AUC_{24.u}$ and $C_{max.u}$ of 14700 hr·ng/mL and 7240 ng/mL, respectively. These data support statements made in section 13.1 of labeling.

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

Methods

Dose and frequency of dosing:	0, 20, 60, and 200 mg/kg/day, once daily
Route of administration:	ORAL GAVAGE
Formulation/Vehicle:	0.5% methylcellulose in water
Species/Strain:	RAT/WISTAR HAN
Number/Sex/Group:	20
Satellite groups:	None
Study design:	Females were dosed beginning 2 weeks prior to mating (with naïve males) and continuing through gestation day (GD) 7. Males were dosed beginning 4 or 12 weeks prior to first and second mating phases, respectively (with naïve females) and continuing for at least 15 weeks. Cesarean sections were performed on surviving animals on GD 14. Blood samples were collected from males on Study Day 62 for toxicokinetic assessment. TK assessment was not conducted on females. However, there were no marked sex differences were noted in rat exposure in other studies and pregnancy does not appear to markedly alter exposure in

	females based on TK parameters from pregnant female rats in other developmental and reproductive toxicology studies. As such, TK parameters from males in this study are used to provide an estimate of female exposure.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No ritlecitinib-related effects.
Clinical Signs	No ritlecitinib-related effects.
Body Weights	HD males: Body weight was adversely decreased (-10.9%) compared to controls. No ritlecitinib-related effects at lower doses or in females.
Necropsy findings	HD males: Naïve mated females had increased (>20%) pre-implantation loss, resulting in decreased implantation sites and viable embryos. HD females: Mean estrous cycle length increased. No other ritlecitinib-related effects in either sex.

HD: high dose

Embryo-Fetal Development

Study title/ number: An Embryo-fetal Development Study of PF-06651600-15 by Oral Gavage in Rats / 15GR148

Key Study Findings

- Ritlecitinib exposure increased approximately dose-proportionally.
- No ritlecitinib-related mortality or clinical signs were noted. However, ritlecitinib caused adversely decreased food consumption and decreased maternal body weight gain at the HD.
- Ritlecitinib decreased fetal body weights in a dose-related manner at the MD and HD and increased the incidence of early resorptions, but did not affect other ovarian or uterine parameters.
- Ritlecitinib increased the incidence of fetal skeletal malformations and variations at doses ≥175 mg/kg/day; vertebrae and/or rib malformations were noted in 1 MD fetus and 3 HD fetuses. Ritlecitinib did not increase the incidence of fetal visceral or external malformations or variations.
- The maternal NOAEL was 175 mg/kg/day, corresponding to a maternal GD 17 $AUC_{24.u}$ and $C_{max.u}$ of 52900 hr·ng/mL and 13700 ng/mL, respectively.

- The developmental NOAEL was 75 mg/kg/day, corresponding to a maternal GD 17 $AUC_{24.u}$ and $C_{max.u}$ of 17000 hr·ng/mL and 7770 ng/mL, respectively. These data support statements made in section 8.1 of labeling.

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

Methods

Dose and frequency of dosing: 0, 75, 175, and 325 mg/kg/day, once daily
Route of administration: ORAL GAVAGE
Formulation/Vehicle: 0.5% methylcellulose in water
Species/Strain: RAT/WISTAR HAN
Number/Group: 22 females
Satellite groups: 3 control and 5/group from ritlecitinib-treated groups for toxicokinetic assessment
Study design: Females were dosed daily from GD 6 through 17 and euthanized on GD 21. Blood samples were collected on GD 17.
Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	No ritlecitinib-related effects.
Clinical Signs	No ritlecitinib-related effects.
Body Weights	HD: Body weight gain was decreased (-19%) compared to controls during dosing, resulting in lower mean body weights (by up to -7%). No ritlecitinib-related effects at lower doses.
Necropsy findings Cesarean Section Data	Dose-related decreased fetus weights (by approximately -6% and -18% for MD and HD) compared to controls. Increased incidence of early resorptions at the HD. No other ritlecitinib-related effects.
Necropsy findings Offspring	Dose-related increased incidence of skeletal malformations (of ribs and/or vertebrae) and skeletal variations in MD and HD fetuses. No other ritlecitinib-related effects.

MD: mid dose; HD: high dose

Study title/ number: An Embryo-Fetal Development Study of PF-06651600-15 by Oral Gavage in Rabbits / 15GR149

Key Study Findings

- Ritlecitinib exposure increased approximately dose-proportionally.

- No ritlecitinib-related mortality, clinical signs, or primary body weight effects were noted.
- At the HD, ritlecitinib decreased fetal body weights and increased post-implantation loss, but did not affect litter size or other ovarian or uterine parameters.
- At the HD, ritlecitinib increased the incidence of fetal skeletal malformations (vertebrae and/or rib) and visceral malformations (malpositioned kidneys) and skeletal variations (delayed ossification and structural changes). Malpositioned kidneys were noted in single fetuses at the LD and MD, but it is unclear if these malformations are ritlecitinib-related or incidental.
- Ritlecitinib did not increase the incidence of fetal visceral or external malformations or variations.
- The maternal NOAEL was 75 mg/kg/day, corresponding to a maternal GD 19 $AUC_{24.u}$ and $C_{max.u}$ of 58600 hr·ng/mL and 14900 ng/mL, respectively.
- In the absence of clearly ritlecitinib-related adverse findings at the MD or LD, the developmental NOAEL appeared to be 25 mg/kg/day, corresponding to a maternal GD 19 $AUC_{24.u}$ and $C_{max.u}$ of 13200 hr·ng/mL and 4470 ng/mL, respectively. These data support statements made in section 8.1 of labeling.

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

Methods

Dose and frequency of dosing:	0, 5, 25, and 75 mg/kg/day, once daily
Route of administration:	ORAL GAVAGE
Formulation/Vehicle:	0.5% methylcellulose in water
Species/Strain:	RABBIT/NEW ZEALAND WHITE
Number/Group:	20 females
Satellite groups:	3 control and 5/group from ritlecitinib-treated groups for toxicokinetic assessment
Study design:	Females were dosed daily from GD 7 through 19 and euthanized on GD 29. Blood samples were collected on GD 19.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No ritlecitinib-related effects.
Clinical Signs	No ritlecitinib-related effects.
Body Weights	No primary ritlecitinib-related effects on maternal body weight.

Necropsy findings Cesarean Section Data	HD: Decreased fetus weights (by approximately -12%) compared to controls and increased incidence of post-implantation loss. No other ritlecitinib-related effects.
Necropsy findings Offspring	HD: Increased incidence of skeletal malformations (of ribs and/or vertebrae), visceral malformations (malpositioned kidney) and skeletal variations (delayed ossification and structural changes). No clearly ritlecitinib-related findings at the LD or MD.

HD: high dose

Prenatal and Postnatal Development

Study title/ number: An Oral (Gavage) Study of the Effects of PF-06651600 on Pre- and Postnatal Development, Including Maternal Function in Wistar Rats / 19GR230

Key Study Findings

- Ritlecitinib exposure increased dose-proportionally. F_0 dam milk was not analyzed for the presence of ritlecitinib.
- No ritlecitinib-related mortality, clinical signs, body weight effects, macroscopic findings, or reproductive effects were noted in F_0 dams.
- At doses ≥75 mg/kg/day, ritlecitinib reduced food consumption during lactation in a dose-related manner, which did not affect maternal body weight but corresponded to decreased F_1 pre-weaning weight gain.
- In F_1 offspring:
    - HD pups had decreased birth weight by approximately 20% and reduced survival through PND 7;
    - MD and HD pups had dose-related decreased body weight gain through PND 21 (pre-weaning);
    - HD offspring displayed delayed vaginal patency and balanopreputial separation secondary to lower body weights;
    - No ritlecitinib-related effects were noted on sensory function, motor activity, learning and memory, estrous cycle lengths, pre-coital intervals, or mating, fertility, and copulation/conception indices;
    - At the HD, ritlecitinib reduced corpora lutea in pregnant F_1 females, resulting in fewer implantation sites and viable embryos without affecting F_2 intrauterine survival.
- The maternal F_0 NOAEL was 175 mg/kg/day, corresponding to a maternal GD 17 $AUC_{24.u}$ and $C_{max.u}$ of 44000 hr·ng/mL and 16100 ng/mL, respectively.
- The F_1 developmental NOAEL was 75 mg/kg/day, corresponding to a maternal (F_0) GD 17 $AUC_{24.u}$ and $C_{max.u}$ of 15400 hr·ng/mL and 7910 ng/mL, respectively. These data support statements made in section 8.1 of labeling.

Conducting laboratory and location: [redacted] (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 25, 75, and 175 mg/kg/day, once daily
Route of administration:	ORAL GAVAGE
Formulation/Vehicle:	0.5% methylcellulose in water
Species/Strain:	RAT/WISTAR HAN
Number/Sex/Group:	F_0: 22 females F_1: 18-21/sex/group
Satellite groups:	F_0: 5 females/group for toxicokinetic assessment
Study design:	F_0 dams were dosed once daily from GD 6 through lactation day (LD) 20. On postnatal day 4, F_1 animals were selected for the next generation (18-21/sex/group). The following parameters were evaluated in the selected F_1 animals: mortality, clinical observations, body weight, food consumption, developmental landmarks (balanopreputial separation and vaginal patency), neurobehavioral evaluations (auditory function, motor activity, and learning and memory), sexual maturation, estrous cycles, reproductive performance, macroscopic observations, and F_2 intrauterine survival.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Generation	Major Findings
F_0 Dams	HD: Ritlecitinib decreased food consumption during lactation without affecting body weight. No other ritlecitinib-related effects.
F_1 Generation	HD: Adversely decreased birth weights (approximately -20%); decreased survival through PND 7; decreased pre-weaning body weight gain; and lower mean body weights throughout study (which caused delayed vaginal patency and balanopreputial separation). MD: Non-adverse decrease in pre-weaning body weight gain. LD: No ritlecitinib-related effects.
F_2 Generation	HD: Decreased corpora lutea (and implantation sites and viable embryos). No ritlecitinib-related effects on intrauterine survival.

5.5.5. Other Toxicology Studies

In vivo phototoxicity:

Study title/ number: A 3-Day Dose Phototoxicity Study to Determine the Effects of Oral Gavage Administration of PF-06651600 on Eyes and Skin in Pigmented Rats / 15MA032

Ritlecitinib (doses: 0 [vehicle: 0.5% methylcellulose], 50, 100, and 200 mg/kg/day) or positive control (15 mg/kg 8-methoxypsoralen) was orally administered to female Long Evans pigmented rats once daily for 3 days, followed by irradiation with 9.8 to 10.78 J/cm^2 UVA, then 138 to 152 mJ/cm^2 UVB. Vehicle and positive control produced expected results. Ritlecitinib did not display evidence of cutaneous or ocular phototoxicity potential.

Impurities:

The following organic impurities are listed in the drug substance specification: (b) (4)

Individual unspecified impurities will be NMT (b) (4)% each and total impurities will be NMT (b) (4)%.
The following degradation products are listed in the drug product specification: (b) (4)

The following potential impurities were not mutagenic in GLP in vitro bacterial reverse mutation assays: (b) (4)

The specified impurity (b) (4) was identified as potentially mutagenic in silico (DEREK v6.1.0, KB 2020 1.0 and SARAH v3.1.0, model 2020.1), but was not mutagenic in a non-GLP in vitro bacterial reverse mutation assay (using a design consistent with OECD Guideline 471). A potential (b) (4) impurity, (b) (4) was positive in a non-GLP bacterial reverse mutation assay. However, per the applicant's (b) (4) risk assessment, there is no risk of (b) (4) formation or presence in the drug substance.

The following potential impurities were not mutagenic in non-GLP in vitro bacterial reverse mutation assays, including: (b) (4) (a specified impurity); (b) (4) and a geometric isomer mixture of (b) (4)

was weakly positive in a non-GLP in vitro bacterial reverse mutation assay.

In a GLP 13-week oral repeat dose toxicity study, Wistar Han rats (n=10/sex/group) received vehicle (0.5% methylcellulose), a 200 mg/kg/day dose of ritlecitinib without impurities (lot #19-AP-00204), or a 200 mg/kg/day dose of ritlecitinib spiked with impurities (lot #00705980-0749-03). The spiked lot contained (b) (4)% total impurities, including the following: (b) (4) No ritlecitinib-related effects were noted on mortality, clinical signs, or ophthalmic examinations. Body weight gain was lower in ritlecitinib and spiked ritlecitinib groups than controls. This effect was slightly more pronounced in the spiked ritlecitinib groups and resulted in 4% and 10% lower body weights in females and males given spiked ritlecitinib. All other ritlecitinib-related effects (i.e., hematology, clinical chemistry, and urinalysis effects; organ weight changes; and gross and microscopic findings) were of similar incidence and magnitude and/or consistent with findings in prior repeat dose toxicity studies in rats. The NOAEL was 200 mg/kg/day, without or with impurities.

Notably, of these specified impurities and degradants, (b) (4) are controlled at levels requiring qualification. Based on the above 13-week oral repeat dose toxicity study in rats, the NOAEL doses for (b) (4) are (b) (4) mg/kg/day (formula: [Ritlecitinib NOAEL dose] x [% impurity] = [impurity NOAEL dose]). Based on a 50 mg/day maximum recommended human dose (MRHD) and an adolescent body weight of 40 kg, the maximum human exposure for these impurities (formula: [50 mg/day ÷ 40 kg] x [maximum % impurity] = [maximum human exposure]) will be more than 100 times lower than the nonclinical NOAEL dose. Because (b) (4) is a (b) (4) (b) (4) the applicant used (b) (4) to qualify it using a read-across approach; this is acceptable from a nonclinical perspective. As such, (b) (4) are qualified at the proposed specification limits based on the nonclinical data.

6 Clinical Pharmacology

6.1. Executive Summary

Ritlecitinib (also known as PF-06651600) is a new molecular entity, orally administered inhibitor of Janus kinase 3 (JAK3) and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family. Ritlecitinib is proposed for the oral treatment of alopecia areat (b) (4) Proposed dose of ritlecitinib is 50 mg once daily (QD) with or without food as an immediate-release capsule.

The Applicant evalutated the safety and efficacy of ritlecitinib, in one randomized, double-blind, placebo-controlled, dose ranging study in patients 12 years of age and older with alopecia areata with ≥ 50% scalp hair loss, including alopecia totalis (AT) and alopecia universalis (AU).

Key review findings with specific recommendations and comments are summarized in Table 1.

Table 1: Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Efficacy is established in a Phase 2b/3 trial (B7981015). See section 8.1 for efficacy results.
General dosing instructions	The efficacy data from Phase 2b/3 trial support the proposed dosing regimen of 50 mg once daily (QD). See section 8.1 and 8.2 for efficacy and safety results.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Not recommended in patients with severe hepatic impariment. • No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. • Not recommended in patients with end-stage renal disease or in patients with renal transplants. • No dose adjustment is required in patients with mild, moderate, or severe renal impairment. • Additional monitoring and dose adjustment of CYP3A and CYP1A2 substrates should be considered where small concentration changes of these substrates may lead to serious adverse reactions. The dose adjustment of these substrates should be made as per their approved labeling. • Avoid concomitant use of strong inducers of CYP3A.

Bridge between to-be-marketed and clinical trial formulations	The clinical bridge between the to-be-marketed capsule formulation and the tablet formulation used in Phase 2b/3 trials was demonstrated by establishing bioequivalence in pivotal relative bioavailability study B7981029.

6.1.1. Recommendations

From a clinical pharmacology standpoint, data submitted in this NDA is acceptable to support the approval of ritlecitinib 50 mg once daily for the treatment of alopecia areata (b) (4)

6.2. Summary of Clinical Pharmacology Assessment

6.2.0. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action
Ritlecitinib irreversibly inhibits Janus kinase 3 (JAK3) and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family. Ritlecitinib primary metabolite M2 is pharmacologically inactive against JAK1, JAK2, JAK3, TYK2 and TEC family kinases.

Pharmacodynamics
A dose-dependent early decrease in absolute lymphocyte levels, T lymphocytes (CD3) and T lymphocyte subsets (CD4 and CD8) was associated with ritlecitinib treatment in patients with alopecia areata. There was also a dose-dependent early decrease in NK cells (CD16/56) which remained stable at the lower level up to Week 48. For the 50 mg QD dose, there was an initial decrease in median lymphocyte levels by approximately 30% and this remained in that range upto 48 weeks. There was no change observed in B lymphocytes (CD19) in any treatment group.

QT Prolongation
Up to a dose of 800 mg (recommended dose is 50 mg) ritlecitinib does not prolong the QT interval to any clinically relevant extent.

Pharmacokinetics
Oral doses of ritlecitinib were rapidly absorbed following single doses of 5 mg to 200 mg with median Tmax values of ≤0.75 hours. Absorption following single doses was slightly prolonged at doses >200 mg. Following multiple oral doses ritlecitinib is rapidly absorbed with Tmax values of ≤1 hour for doses of 50 mg QD, 200 mg BID and 400 mg QD. No dedicated dose proportionality study was conducted by the sponsor. Based on the PK results from single ascending dose study (5 mg to 800 mg) increase in Ritlecitinib Cmax was observed to be in dose-proportional manner, however AUCinf increase was more than dose proportional especially at doses greater than 200 mg (See section 19.4.1 for more details). Additionally the

Applicant's PopPK analysis showed that the median dose normalized geometric mean ratios of Cmax from 10 mg to 800 mg compared to 50 mg QD were within 0.8 to 1.25 and median geometric mean ratios of AUCtau from 30 mg to 200 mg compared to 50 mg QD steady-state were within 0.8 to 1.25. This data are supportive of the results shown in the single ascending dose study showing approximate dose proportionality upto 200 mg (See section 19.4.16 for more details). Overall data suggests that PK increased in approximately dose proportional manner upto 200 mg dose.

Administration of ritlecitinib with food decreased the rate of absorption which resulted in a reduction in Cmax of ~32% with a median Tmax of 3 hours with no impact on extent of ritlecitinib absorbed as the AUC increased by a marginal amount of ~10%. Overall, food does not have a clinically meaningful impact on the extent of ritlecitinib absorbed. Ritlecitinib was administered without regard to food in the safety and efficacy clinical trials.

Drug Interaction Studies:

Effect of Other Drugs on Ritlecitinib

- CYP3A Inducers: Rifampin (strong CYP3A inducer) decreased AUCinf and Cmax of ritlecitinib 50 mg dose by 0.44 and 0.25 fold, respectively.
- *CYP3A Inhibitor:* In presence of itraconazole (strong CYP3A inhibitor), no clinically relevant change in the systemic exposure of 30 mg dose ritlecitinib was observed.

Effect of ritlecitinib on other drugs:

- *CYP3A Substrates:* Midazolam (CYP3A substrate) $AUC_{0\text{-}inf}$ increased 2.7fold and C_{max} 1.8fold following concomitant use with multiple doses of 200 mg ritlecitinib once daily (4 times the recommended dosage).
- *CYP1A2 Substrates:* Caffeine (CYP1A2 substrate) $AUC_{0\text{-}inf}$ increased 2.7fold and C_{max} 1.1fold following concomitant use with multiple doses of 200 mg ritlecitinib once daily (4 times the recommended dosage).
- *Oral Contraceptive:* No clinically relevant changes in the systemic exposure of oral conraceptive (ethinyl estradiol or levonorgestrel) was observed when used concomitantly with ritlecitinib at 50 mg QD.
- *CYP Substrates:* In presence of 200 mg dose of ritlecitinib, no clinically relevant change in the systemic exposure of CYP2B6 substrates (e.g., efavirenz), CYP2C substrates (e.g., tolbutamide).
- *Transporter Substrates:* In presence of 200 mg dose of ritlecitinib, no clinically relevant change in the systemic exposure of rosuvastatin which is a substrate of organic anion transporter (OAT)P1B1, breast cancer resistance protein (BCRP), and OAT3 was observed.
- *OCT1 Substrates:* Sumatriptan (OCT1 substrate) AUC_{inf} increased approximately 1.3 to 1.5-fold following concomitant use with a single 400 mg dose of ritlecitinib (8 times the approved recommended dosage).

Effect of Gastric Acid Reducing Agents on Ritlectinib

Ritlecitinib is a highly soluble drug with high solubility across the physiological pH range of 1.0 to 6.8. Co-administration of ritlecitinib with acid reducing agents is highly unlikely to impact its solubility and subsequent absorption given its solubility profile across a range of pH levels (see section 19.4.15 for more details). A clinical study evaluating the impact of acid reducing agents was therefore not conducted and this is deemed acceptable.

Systemic Safety-Incidence of Thrombocytopenia
A mean reduction of changes in platelets from baseline counts of less than 25% was observed for all ritlecitinib doses with respect to placebo. All doses demonstrated a similar response without a clear dose-response relationship.

6.2.1. General Dosing and Therapeutic Individualization

General Dosing

The efficacy results in Phase 3 trial overall support the acceptability of the proposed dosing regimen of 50 mg QD.

The results of the food effect study support that ritlecitinib can be taken with or without food which is consistent with the design of the Phase 3 clinical trials.

Therapeutic Individualization

Renal Impairment: No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment. Ritlecitininb has not been studied in patients with end-stage renal disease (ESRD) or in patients with renal transplants.

Hepatic Impairment: No dose adjustments are recommended for patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. Ritlecitinib has not been studied in patients with severe (Child-Pugh C) hepatic impairment and hence, it is not recommended for use in these patients.

Drug Interaction:

- Additional monitoring and dose adjustment of CYP3A substrate and CYP1A2 substrate is recommended especially for those substrates where small concentration changes may lead to serious adverse events.
- Concomitant use of strong inducers of CYP3A is not recommended.

Outstanding Issues

There are no outstanding issues other than the requested PREA PMR study that would preclude the approval of ritlecitinib from the Clinical Pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

General clinical pharmacology, PK, and PD characteristics of ritlecitinib are summarized in Table 2.

Table 2: Summary of Clinical Pharmacology, Pharmacokinetics and Pharmacodynamics of Ritlecitinib

	Pharmacology
Mechanism of Action	Ritlecitinib irreversibly inhibits Janus kinase 3 (JAK3) and tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family. Ritlecitinib primary metabolite M2 is pharmacologyically inactive against JAK1, JAK2, JAK3, TYK2 and TEC family kinases.
Pharmacodynamics	A dose-dependent early decrease in absolute lymphocyte levels, T lymphocytes (CD3) and T lymphocyte subsets (CD4 and CD8) was associated with ritlecitinib treatment in patients with alopecia areata. There was also a dose-dependent early decrease in NK cells (CD16/56) which remained stable at the lower level up to Week 48. For the 50 mg QD dose, there was an initial decrease in median lymphocyte levels by approximately 30% and this remained in that range upto 48 weeks. There was no change observed in B lymphocyte levels (CD19) in any treatment group.
QT Prolongation	The results from the concentration-QT analysis using data from study B7981001 (combined SAD and MAD with intensive PK and triplicate ECG assessments) suggest that ritlecitinib is not expected to have any clinically significant effect on QT prolongation up to 800 mg, the highest dose administered in human. The upper bound of 90% CI for ΔΔQTcF estimate at the mean Cmax of the proposed dose of 50 mg QD was 1.98 msec. The upper bound of 90% CI for ΔΔQTcF estimate at supratherapeutic concentration (2-fold of 200 mg QD; 200 mg is highest dose studied in pivotal Phase 3 study) was 3.06 msec, and at the highest concentration after 800 mg SD (12.5-fold of mean Cmax at 50 mg QD) was 4.13 msec, which are all below 10 msec threshold.
	General Information
Bioanalysis	Ritlecitinib concentrations in human plasma were quantified using high performance LC/MS/MS assays with sensitivity upto 0.5 ng/ml. See section 19.4 for details of the method validation.
Exposure Response Analysis	The model predicted concentration response relationship demonstrated an increase in the incidence rate of infections and rash with increased concentration. Increase in dose from 30 mg to 50 mg leads to marginal increase in incidence rate.
Dose Proportionality	In healthy subjects (B7981001), Cmax increase was approximately dose proportional from 3 mg to 800 mg when administered as an oral solution. However, the AUC increase was approximately dose proportional only upto 200 mg. Applicant's PopPK analysis showed that the median dose normalized geometric mean ratios of Cmax from 10 mg to 800 mg compared to 50 mg QD were within 0.8 to 1.25 and median geometric mean ratios of AUCtau from 30 mg to 200 mg compared to 50 mg QD steady-state were within 0.8 to 1.25. This data are

	supportive of the results shown in the single ascending dose study showing approximate dose proportionality upto 200 mg.
	ADME
Absorption	Oral doses of ritlecitinib were rapidly absorbed following single doses of 5 to 200 mg with median Tmax values of ≤0.75 hours. Absorption following single doses was slightly prolonged at doses >200 mg. Following multiple oral doses ritlecitinib is rapidly absorbed with Tmax values of ≤1 hour for doses of 50 mg QD, 200 mg BID and 400 mg QD. The absolute bioavailability estimated in the radiolabeled ADME study was approximately 64% with an estimated fraction absorbed of approximately 89%.
Food Effect	Administration of ritlecitinib with food decreased the rate of absorption which resulted in a reduction in Cmax by approximately 32% with median Tmax of 3 hours with no impact on extent of ritlecitinib absorbed as the AUC increased by approximately 10%.
Distribution	The steady-state volume (Vss) for ritlecitinib estimated after IV administration was estimated to be approximately 74 L. The plasma protein binding in human plasma was determined to be 14%. The blood to plasma ratio was estimated to be 1.62.
	Elimination
Metabolism	Ritlecitinib is metabolised through multiple CYPs (CYP3A, CYP2C8, CYP1A2, and CYP2C9) and GSTs (cytosolic GST A1/3, M1/3/5, P1, S1, T2, Z1 and microsomal GST 1/2/3) pathways with no single route contributing more than 25% of the total metabolism.
Excretion	Following a 200 mg oral administration of [14C]-ritlecitinib in humans, total recovery of radioactivity was 86%, with 66% recovered in urine and 20% in feces. Ritlecitinib was the major component of drug-related material in plasma, while its metabolites including M2 were predominant in pooled urine. Approximately 4% of the ritlecitinib dose is excreted unchanged drug in urine.
Drug-Drug Interaction	<u>Effect of other drugs on ritlecitinib:</u> *CYP3A Substrates:* Midazolam (CYP3A substrate) AUC0-inf increased 2.7 fold and Cmax 1.8 fold following concomitant use with multiple doses of 200 mg ritlecitinib once daily (4 times the approved recommended dosage). *CYP1A2 Substrates:* Caffeine (CYP1A2 substrate) AUC0-inf increased 2.7 fold and Cmax 1.1 fold following concomitant use with multiple doses of 200 mg ritlecitinib once daily (4 times the approved recommended dosage). *CYP3A Inducers:* Rifampin (strong CYP3A inducer) decreased AUCinf and Cmax of ritlecitinib by 0.44 and 0.25 fold, respectively. *CYP3A Inhibitor:* In presence of itraconazole (strong CYP3A inhibitor), no clinically relevant change in the systemic exposure of ritlecitinib was observed. *OCT1 Substrates:* Sumatriptan (OCT1 substrate) AUCinf increased approximately 1.3 to 1.5-fold following concomitant use with a single 400 mg dose of ritlecitinib (8 times the approved recommended dosage). <u>Effect of ritlecitinib on other drugs:</u> *Oral Contraceptive:* No clinically relevant change in the systemic exposure of oral conraceptive (ethinyl estradiol or levonorgestrel) was observed when used concomitantly with ritlecitinib. *CYP Substrates:* In presence of ritlecitinib, no clinically relevant change in the systemic exposure of CYP2B6 substrates (e.g., efavirenz), CYP2C substrates (e.g., tolbutamide).

	Transporter Substrates: In presence of ritlecitinib, no clinically relevant change in the systemic exposure of rosuvastatin which is a substrate of organic anion transporter (OAT)P1B1, breast cancer resistance protein (BCRP), and OAT3 was observed.
Pediatric Subjects	Pediatric patients aged 12-17 years were enrolled in the pivotal Phase 3 study (B7981015) and clinically meaningful scalp hair regrowth was observed (see section 8 clinical review). The systemic exposure in adolescent subjects 12-17 years was similar to adults.

Abbreviations: AUCinf=area under the curve to infinity, Cmax=maximum concentration, Tmax=time of Cmax, LC/MS/MS=liquid chromatography with tandem mass spectrometry

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The efficacy of ritlecitinib for the treatment of alopecia areata was demonstrated in one pivotal Phase 2b/3 study (B7981015). See Section 8 of this multidisciplinary review for details of study design and efficacy results of the Phase 3 study.

Dose-Response for Severity of Alopecia Tool (SALT): The pivotal and dose-ranging study B7981015 tested 4 ritlecitinib dosingregimens for statistical significance versus placebo. The 10 mg dose was not expected to be efficacious, but it was included in study B7981015 to support the characterization of the dose/exposure response.

- 200/50 mg: Loading dose of 200 mg QD for 4 weeks followed by maintenance dosing of 50 mg QD
- 50 mg: 50 mg QD without loading dose
- 200/30 mg: Loading dose of 200 mg QD for 4 weeks followed by maintenance dosing of 30 mg QD
- 30 mg: 30 mg QD without loading dose

Treatment with all the 4 dosing regimens of ritlecitinib mentioned above, demonstrated clinically meaningful hair regrowth (ie, SALT ≤20). The proportion of participants with a SALT ≤20 response was statistically significantly higher than in placebo in all 4 groups. The benefits of treatment were consistently maintained through Month 24.

Table 3: SALT ≤ 20 at week 24 (Primary Endpoint) in Pivotal Efficacy Study B7981015

	Ritlecit 200/50 N=132	Ritlecit 200/30 N=130	**Ritlecit 50/50 N=130**	Ritlecit 30/30 N=132	Ritlecit 10/10 N=63	**Placebo N=131**
n/N1[a]	38/124	27/121	**29/124**	17/119	1/59	**2/130**
(%)	(30.65)	(22.31)	**(23.39)**	(14.29)	(1.69)	**(1.54)**
p-value	<0.000001[b]	<0.000001[b]	**<0.000001[b]**	0.000154[b]	0.936441	
95% CI	(21.17, 37.91)	(13.65, 29.18)	**(14.65, 30.23)**	(6.69, 20.36)	(-4.05, 7.58)	

a N1 excludes subjects with missing assessments due to COVID-19. Subjects with other sources of missing data are imputed as non-responders.
b Statistically significant at the 0.00125 level under the multiplicity control scheme.
Source: Adapted from Table 3, Summary of Clinical Efficacy 2.7.3

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

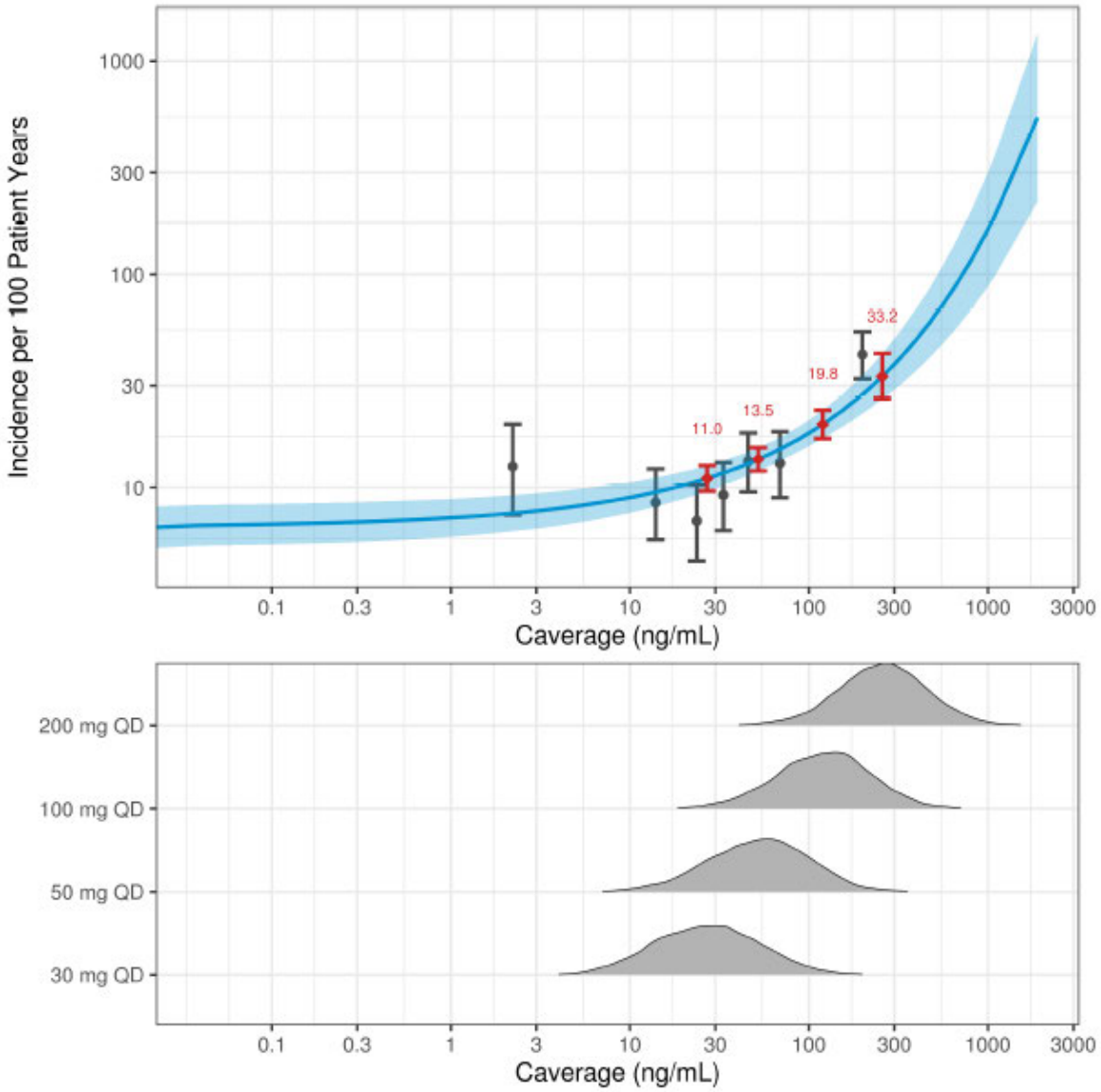
Yes. The efficacy data from Phase 2b/3 study (B7981015) indicate that the 50 mg QD dose of ritlecitinib demonstrated clinically meaningful scalp hair regrowth on the clinician-assessed primary endpoint (SALT ≤20 response) with a placebo corrected response rate of 21.85% (p-value < 0.00125) at Week 24.

The 200 mg QD loading dose regimen was associated with achieving statistical separation from placebo based on SALT ≤20 response earlier than the regimens without loading dose, but this difference in efficacy was not sustained over longer duration of treatment i.e., 48 weeks. The longitudinal concentration response analysis of total lymphocyte counts demonstrated an acceptable safety profile and a lower risk for lymphopenia without a loading dose as compared to with a loading dose.

The longitudinal concentration response analysis also demonstrated that the doses of 50 mg and 30 mg are in the ascending linear part of the dose response curve, with the concentrations associated with 50 mg approximating the EC50. Hence, 50 mg is predicted to provide more benefit over the 30 mg dose in terms of efficacy response.

Exposure-Response for Safety: The relationship between ritlecitinib concentration and treatment-emergent clinical safety endpoints such as infections, herpes zoster, and rash were characterized using Poisson regression. Approximately 10-fold increase in ritlecitinib concentration (geometric mean Cav of 27 ng/mL [30 mg QD] vs. 257 ng/mL [200 mg QD]), was predicted to demonstrate an approximately 3-fold increase in the mean incidence of infections per 100 patient years (11.0 vs. 33.2, respectively). Similarly, an approximately 10-fold increase in ritlecitinib exposure (geometric mean Cav of 27 ng/mL [30 mg QD] vs. 257 ng/mL [200 mg QD]), was predicted to demonstrate approximately 4.4-fold increase in the mean incidence of rash per 100 patient years (18.3 vs. 80.1, respectively). Increase in dose from 30 mg to 50 mg leads to marginal increase in incidence rate of infection and rash.

Figure 1: Incidence of Infections per 100 Patient Years Over the Range of Time-Weighted Observed Caverage

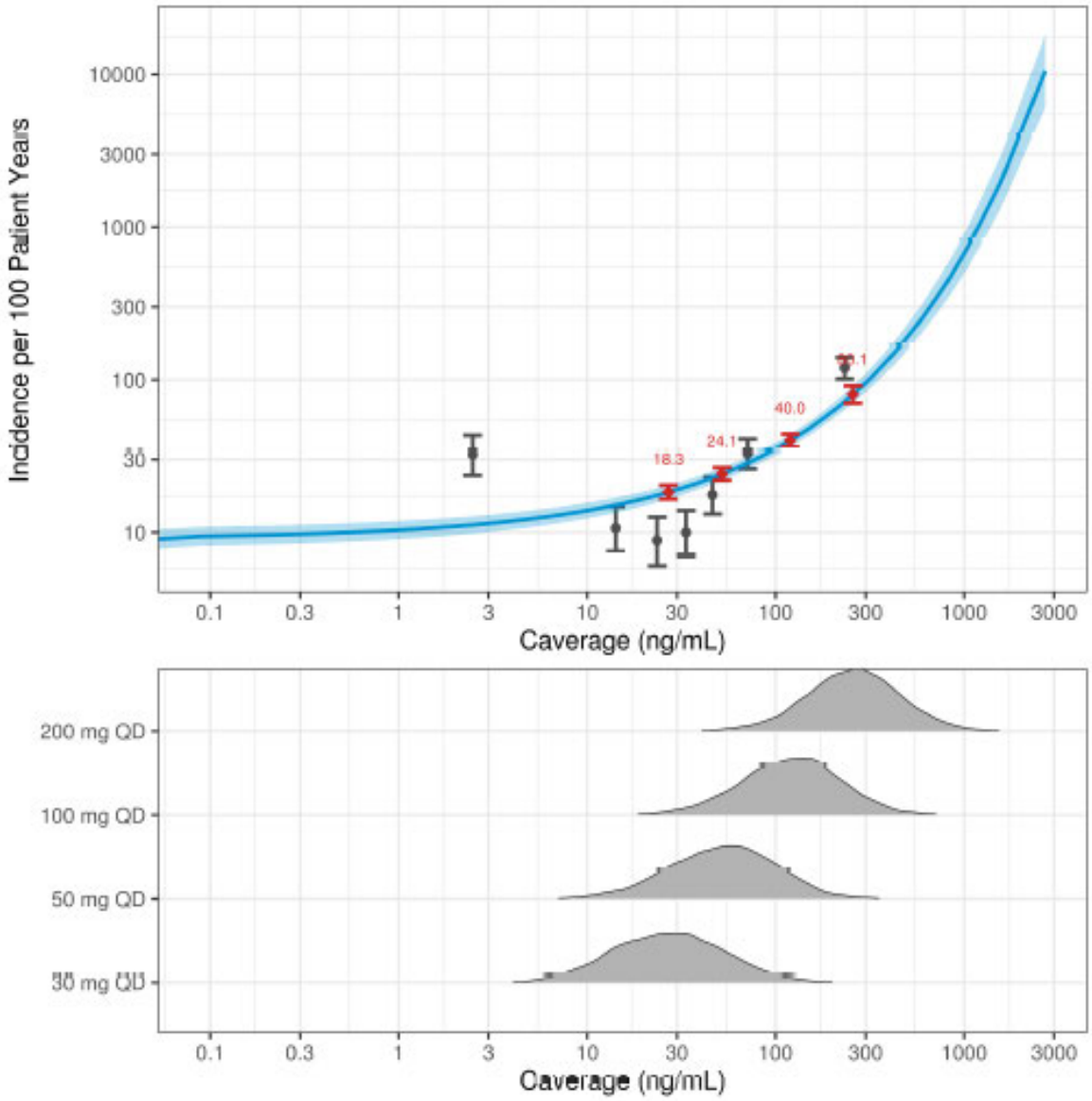


Repository artifact ID FI-29771746.

Top: Gray circles and error bars are the observed mean and 95% CI, respectively, of the incidence of infections (moderate, severe, leading to discontinuation) per 100 patient years for each bin of C_{ave} in the analysis population (n = 7). The blue line, (and blue shaded area) are the model-predicted mean (and 95% CI) incidence per 100 patient years for the range of observed C_{ave} in the analysis population. Red circles and error bars are the model-predicted mean and 95% CI, respectively, incidence of infection per 100 patients years at the geometric mean steady-state C_{ave} for 30 mg, 50 mg, 100 mg, and 200 mg QD in AA patients. *Bottom*: Gray distributions represent the predicted distribution of steady-state C_{ave} for 10,000 AA patients chronically administered 30 mg, 50 mg, 100 mg, and 200 mg QD with randomly drawn random effect parameters for CL/F and Vc/F as described by the final population PK model [2] and body weights sampled from those observed in B7981015.

Source: Figure 3, PMAR-EQDD-B798d-DP4-1306-Amendment-1

Figure 2: Incidence of Rash per 100 Patient Years Over Range of Time-Weighted Observed Caverage



Repository artifact ID FI-29771758.

Top: Gray circles and error bars are the observed mean and 95% CI, respectively, of the incidence of rash (all types) per 100 patient years for each bin of C_{ave} in the analysis population (n = 7). The blue line, (and blue shaded area) are the model-predicted mean (and 95% CI) incidence per 100 patient years for the range of observed C_{ave} in the analysis population. Red circles and error bars are the model-predicted mean and 95% CI, respectively, incidence of rash per 100 patients years at the geometric mean steady-state C_{ave} for 30 mg, 50 mg, 100 mg, and 200 mg QD. *Bottom*: Gray distributions represent the predicted distribution of steady-state C_{ave} for 10,000 AA patients chronically administered 30 mg, 50 mg, 100 mg, and 200 mg QD with randomly drawn random effect parameters for CL/F and Vc/F as described by the final population PK model [2] and body weights sampled from those observed in B7981015.

Source: Figure 6, PMAR-EQDD-B798d-DP4-1306-Amendment-1

Hence, looking at the benefit/risk profile, the proposed dosing regimen of 50 mg QD is acceptable.

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

Yes. Ritlecitinib is not recommended in patients with severe hepatic impairment (Child Pugh C) and end-stage renal disease or in patients with renal transplants as it has not been studied in these patient subpopulations.

No dose adjustment is recommended in patients with mild (Child Pugh A), or moderate (Child Pugh B) hepatic impairment.

No dose adjustment is required in patients with mild, moderate, or severe renal impairment.

Table 4: Effect of Hepatic and Renal Impairment on the Exposure of Ritlecitinib.

Factor	Ritlecitinib Ratio as Percent		Dose Recommendation
	AUC_{inf} or AUC_{tau}	C_{max}	
Intrinsic Factors*			
Moderate Hepatic Impairment	118.50 (87.96, 159.64)	104.00 (74.48, 145.23)	No dose adjustment
Severe Renal Impairment	155.15 (122.83, 195.98)	144.48 (114.24, 182.73)	No dose adjustment

Reference: Adapted from Table 11, Summary ClinPharm, 2.7.2

Effect of Hepatic Impairment

Ritlecitinib was not evaluated in patients with severe hepatic impairment, as immunomodulator such as ritlecitinib is not recommended to be administered in patients with severe hepatic insufficiency. The overall systemic exposures in patients with moderate hepatic impairment (defined as patients with Child-Pugh Class B, scores 7-9 points) as measured by the AUCtau and the peak exposure as measured by the Cmax were 18.5% and 4.0% higher, respectively, compared with those in matched participants with normal hepatic function. The Applicant proposed no dose adjustment for patients with mild or moderate HI which is reasonable. Refer to Individual Study Review in OCP appendices 19.4.4 for more details.

Effect of Renal Impairment

The overall systemic exposures in patients with severe renal impairment (defined as patients with eGFR < 30 mL/min, but not requiring hemodialysis) (B7981020) as measured by AUCtau and Cmax were 55.2% and 44.5% higher, respectively, compared with those in matched participants with normal renal function which were obtained from the hepatic impairment study (B7981016). For the renal impairment study, after severe renal impairment cohort was completed, the healthy participants cohort was not completed due to COVID-19 pandemic. The applicant reviewed healthy participant data from hepatic impairment study (B7981016) and decided that additional healthy participant data were not needed to be collected as it was determined that there was an adequate demographic match to the subjects with severe renal

impairment. Hence, the healthy participant cohort from hepatic impairment study was used as the reference cohort for severe renal impairment study. The PK parameters of ritlecitinib for healthy participant's were assessed for 30 mg dose at steady state in Study B7981016 as compared to 50 mg dose at steady state in Study B7981020. Ritlecitinib PK is dose proportional between 30 mg and 50 mg doses. Hence, the PK parameters of AUC0-24 and Cmax, for healthy participants at 30 mg dose were adjusted to 50 mg assuming linearity. The Applicant's cross-study comparison and proposal of no dose adjustment for patients with mild, moderate, or severe renal impairment is deemed reasonable. Refer to Individual Study Review in OCP appendices 19.4 for more details.

Other Intrinsic Factors from Population PK Analysis

Age (12-73 years), gender, and race were not identified as significant covariates in the population PK analysis. Body weight was identified as a significant covariate on PK, however the applicant proposed no weight-based dosing for adolescents and adult age groups as the impact of body weight was not clinically relevant. The applicant conducted popoulation PK simulation for lower body weight (47 kg, representative of the fifth percentile of the analysis population) which demonstrated 45% increase in AUCtau and 52% increase in Cmax at steady-state when compared to a 70 kg individual. Simulations for higher body weight (101 kg, representative of the 95th percentile of the analysis population) demonstrated 30% decrease in AUCtau and 32% decrease in Cmax at steady-state when compared to a 70 kg individual. The applicant's proposal for no dose adjustment based on body weight for adult and adolescents age group is acceptable.

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

Yes. Ritlecitinib can be administered with or without food. Additional monitoring and dose adjustment of CYP3A and CYP1A2 substrates are recommended especially for those substrates where small concentration changes may lead to serious adverse events. Concomitant use of moderate to strong inducers of CYP3A should be avoided.

Food-Drug Interaction

In a dedicated food effect study (Study B7981029), a single 100 mg dose of ritlecitinib to-be-marketed (TBM) capsule formulation was administered under fasting and fed conditions. A high-fat, high-calorie (approximately 800-1000 calories containing 50% fat) meal consumption decreased ritlecitinib Cmax by approximately 32% and increased AUC0-inf by approximately 10%, respectively, as compared to fasting condition. This change was not considered clinically meaningful and the participants in the pivotal safety/efficacy study (B7981015) were instructed to take study drug without regard to food. Therefore, ritlecitinib capsule can be administered with or without food.

Effect of CYP3A substrates on Ritlecitinib PK:

Co-administration of multiple doses of ritlecitinib increased the AUCinf and Cmax of midazolam (CYP3A substrate) by 2.7 and 1.8-fold, respectively. Hence, ritlecitinib is likely a moderate

inhibitor of CYP3A. Based on the trial results, additional monitoring and dose adjustment of CYP3A substrates are recommended especially for substrates where small concentration changes may lead to serious adverse reactions.

Effect of CYP1A2 substrates on Ritlecitinib PK:

Co-administration of caffeine 100 mg in the presence of steady-state levels of ritlecitinib (200 mg QD) increased caffeine (CYP1A2 substrate) exposure compared to caffeine given alone. The AUCinf and Cmax of caffeine increased by approximately 2.7 fold and 1.1 fold, respectively, when coadministered with ritlecitinib. Based on the trial results, additional monitoring and dose adjustment of CYP1A2 substrates are recommended especially for substrates whee small concentration changes may lead to serious adverse reactions.

Effect of CYP3A inducers on Ritlecitinib PK:

Rifampin (600 mg QD), a potent CYP inducer, reduced the AUCinf of ritlecitinib by approximately 44% and the Cmax by approximately 25%, when ritlecitinib (50 mg) was co-administered with multiple doses of rifampin. Based on the trial results, the exposure of ritlecitinib is reduced by approximately 44%, which brings its exposure below expected exposure of ritlecitinib after administration of 30 mg (lowest efficacious dose observed in pivotal clinical safety/efficacy study B7981015) assuming linear dose proportional decrease in AUC (the systemic exposure can be even lower in case of high body weight patients i.e., more than 101 Kg, see section 19.4.7 for more details). The exposure response relationship indicates that the decrease in exposure will likely lead to loss of efficacy. Hence, it has been recommended to avoid concomitant use of strong inducers of CYP3A (CYP3A is major CYP involved in metabolism of ritlecitinib).

Refer to Individual Study Review in OCP appendices 19.4 for more details.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

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Listing of Clinical Trials Relevant to NDA215830

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								
B7981015	NCT03732807	Phase 2b/3 Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging	<u>Placebo-controlled Weeks 0-24:</u> Induction dose (4 weeks) + Maintenance dose (20 weeks) A: 200 mg/50 mg QD B: 200 mg/30 mg QD C: 50 mg/50 mg QD D: 30 mg/30 mg QD E: 10 mg/10 mg QD F: Placebo G: Placebo <u>Extension Weeks 24-48</u> A, C, and G: 50 mg QD	Primary Endpoint: Response based on an absolute SALT Score ≤20 at Week 24. Secondary Endpoints: response based on an absolute SALT score ≤10 at Week 24 was included for EMA and VHP countries (not FDA)	Treatment: 48 Weeks Folllow-up: 24 Weeks	N=718 Groups: A: 132 B: 130 C: 130 D: 132 E: 63 F: 65 G: 66	Male or female subjects ≥12 years of age with a clinical diagnosis of AA and ≥50% scalp hair loss (measured by SALT), including alopecia totalis (AT) and alopecia universalis (AU) and a duration of ≤10 years	128 sites in 18 countries: (Argentina, Australia, Canada, Chile, China, Colombia, Czech Republic, Germany, Hungary, Japan, Republic of Korea, Mexico, Poland, Russian Federation, Spain, Taiwan, United Kingdom, United States)

			B and D: 30 mg QD E: 10 mg QD F: 200 mg QD/50 mg QD					
B7931005	02974868	Phase 2a Randomized, Double-Blind, Placebo-Controlled (Ritlecitinib and Brepocitinib)	<u>Placebo-Controlled weeks 0-24</u> Ritlecitinib 200 mg/50 mg QD vs. placebo OR Brepocitinib 60 mg/30 mg vs. placebo	Primary Endpoint: Change from baseline in SALT score at Week 24 Multiple Secondary Endpoints, including: Change from baseline in SALT score at intermediate time points up to Week 24	113 weeks Treatment: 24 Weeks Ritlecitinib Single-Blind Extension Period: 48 weeks Cross-Over Open-Label Extension Period: 24 weeks	N=142 Groups: ritlecitinib: 48 Placebo: 24 Brepocitinib:47 Placebo: 23	Male or female subjects between 18-75 years of age with a clinical diagnosis of moderate to severe alopecia areata (≥50% scalp hair: SALT ≥50), no hair regrowth within 6 months, and a duration of ≤7 years	31 sites in Australia, Canada, United States
		Studies to Support Safety						
B7981037	04517864	Phase 2a, Randomized, Double-Blind, Placebo-Controlled	<u>Placebo-Controlled: months 0-9</u> Ritlecitinib 200/50 mg QD vs. Placebo	Primary Endpoint (safety): Change from baseline (CFB) in I-V interwave	26 months	N=71 36 vs. 35	Male or female subjects between 18-50 years of age with a clinical diagnosis of AA and ≥25% scalp hair loss (SALT ≥25) (including AT and AU)	27 sites in Australia, Canada, Poland, United States

		(Neuroaudio-logy safety)	Extension: Months 9-24 Ritlecitinib 50 mg QD or 200/50 mg QD	latency on BAEP at a stimulus intensity of 80 dB at Month 9 Multiple Secondary Endpoint (safety) including: CFB in I-V interwave latency on BAEP at a stimulus intensity of 80 dB at Months 6, 9E, and 15E.				
B798 1032	040064 57	(ongoing) Phase 3 open-label, multicenter, long-term Interim CSR: Data cutoff date: 28 February 2022	Rollover subjects from trials - 1005/-1015: Ritlecitinib 50 mg QD De novo subjects: Ritlecitinib 200 mg/50 mg QD	Primary (safety) Endpoints: Incidence of TEAEs, SAEs, AEs leading to Discontinuation (AELD), clinically significant abnormal vital signs and laboratory values multiple Secondary	36 months	As of data cutoff: N= 1052 Treated (805 continuing)	Male or female subjects ≥12 years of age with a clinical diagnosis of AA and ≥25% scalp hair loss (SALT ≥25) (including AT and AU), no hair regrowth within 6 months, and AA duration of ≤10 years (De novo subjects)	Argentina, Australia, Canada, Chile, China, Colombia, Czech Republic, Germany, Japan, Republic of Korea, Mexico, Poland, Russian

				(efficacy) Endpoints, including absolute SALT score ≤20 response at Month 36				Federation, Spain, Taiwan, United Kingdom, United States)
B798 1019	037158 29	Phase 2b Randomized , Double-Blind, Placebo-Controlled, Multicenter, Dose-Ranging (DR) trial in subjects with nonsegmantal Vitiligo	DR Period (24 weeks): Ritlecitinib Groups: 200/50 mg QD, 100/50 mg QD, 50/50 mg QD, 30/30 mg QD, 10/10 mg QD, Placebo QD Extension Period (24 weeks): Ritlecitinib Groups: 200/50 mg QD+ nbUVB, 200/50 mg QD, 50/50 mg QD, 30/30 mg QD, placebo	Primary Endpoint: Percent change from Baseline (%CFB) in central facial-vitiligo area scoring index (F-VASI) at Week 24. Key secondary Endpoint: Proportion of subjects achieving central read F-VASI75 at Week 24. Safety Endpoints: Incidence of TEAEs, SAEs,	48 months	N=364	Male or female subjects between 18-65 years of age with a diagnosis of active nonsegmental vitiligo of duration >= 3 months. Body surface area (BSA) involvement 4% - 50% excluding palms, dorsal fingers and thumbs/MCP joints, soles or dorsal feet. BSA ≥0.25% involvement on the face	(United states, Canada, Australia, Italy, Japan, Spain, Taiwan, Germany, Belgium, Republic of Korea)

				abnormal laboratory values at Week 24				

7.2. Review Strategy

Data Sources
The applicant provided CSR and datasets by electronic submission at the following network path: EDR Location: \\CDSESUB1\evsprod\NDA215830\0001

A consultation for review of data fitness was obtained from CDER Office of Computational Sciences (OCS). OCS performed exploratory safety analysis and data fitness analysis for this NDA and found the data quality acceptable.

Data and Analysis Quality

In collaboration with the OCS (JumpStart Data Fitness Consult Response dated 8/23/2022), the review team held the following meetings with the OCS clinical services team:

1. 7/15/2022 Core data fitness assessment
   9/1/2022 Annotated SDTM to ADaM traceability assessment
   9/2/2022 ISS overview assessment
   9/6/2022 Annotated ISS traceability assessments
   9/7/2022 Exploratory safety analysis bundles assessment

Assessments evaluated the data fitness, whether certain common analyses could be performed, and other data quality metrics including:

- Availability of appropriate variables
- Variables populated by expected data points
- Appropriate use of standard terminology
- Data well described by metadata

In general, the data submitted by the Applicant to support the efficacy and safety of LITFULO oral capsule for the proposed indication appeared adequate.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study B7981015

Trial Design

Study B7981015 is a randomized, double-blind, dose-ranging placebo-controlled phase 2b/3 trial in subjects with ≥50% scalp hair loss due to alopecia areata (AA) without evidence of terminal scalp hair regrowth within the previous 6 months and with the current episode of scalp hair loss ≤10 years. The trial included a 24-week placebo-controlled period followed by a 24-week extension period where all subjects received an active dose of ritlecitinib. The study enrolled subjects 12 years of age and older. In some European countries, all subjects were to be between 18 and 74 years of age. Subjects with 100% scalp hair loss were classified as Alopecia Totalis/Alopecia Universalis (AT/AU)

The treatment arms were as follows:

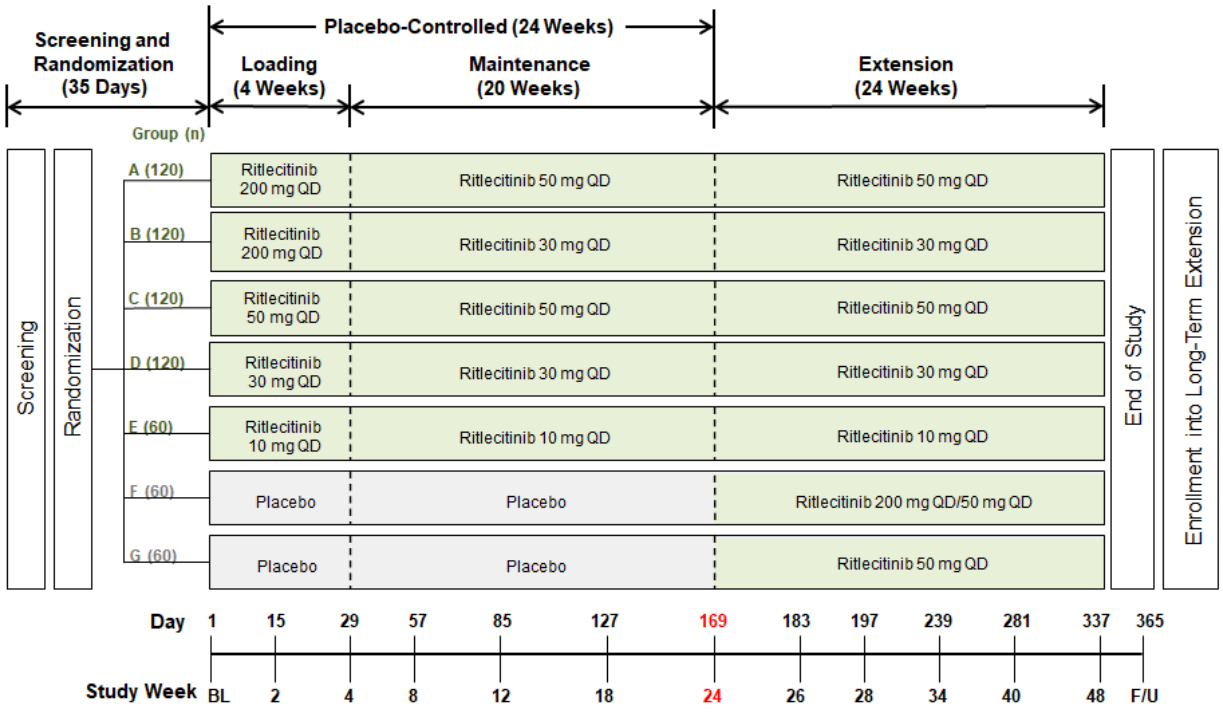
A. Ritlecitinib 200 mg once daily (QD) for 4 weeks followed by ritlecitinib 50 mg QD (200/50 mg)
B. Ritlecitinib 200 mg QD for 4 weeks followed by ritlecitinib 30 mg QD (200/30 mg)
C. Ritlecitinib 50 mg QD (50 mg)
D. Ritlecitinib 30 mg QD (30 mg)
E. Ritlecitinib 10 mg (QD (10 mg)
F. Placebo for 24 weeks followed by ritlecitinib 200 mg QD for 4 weeks followed by ritlecitinib 50 mg QD (placebo/200/50 mg)
G. Placebo for 24 weeks followed by ritlecitinib 50 mg QD (placebo/50 mg)

Subjects were randomized in a 2:2:2:2:1:1:1 ratio to the above treatment arms. Randomization was stratified by age group (<18 years and ≥18 years) and AT/AU status (yes/no). In countries that only enrolled adult subjects, randomization was stratified on AT/AU status. The targets for enrollment were approximately 40% AT/AU and approximately 15% adolescents.

The study was designed to provide substantial evidence of effectiveness as a an adequate and well-controlled large multicenter trial using a significance level of 0.00125.

The study design schema is presented in Figure 1.

Figure 1 – Study Design (B7981015)



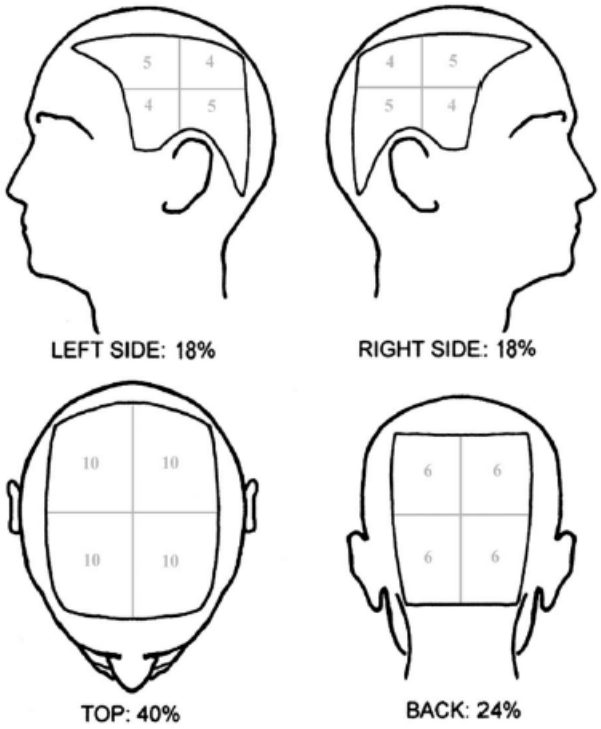
Source: pg 59 of Protocol B7981015 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7981015\b7981015-protocol.pdf)

Study Endpoints

Efficacy was assessed using the clinician-reported Severity of Alopecia Tool (SALT), an Eyelash Assessment (ELA) scale, and an Eyebrow Assessment (EBA) scale.

SALT measures the percentage of scalp hair loss assessed by determining the sum of the scalp hair loss in each region for the four areas of the scalp (left, right, top, back). See Figure 2. Possible values on the SALT range from 0 (no hair loss) to 100 (complete hair loss).

Figure 2 – Severity of Alopecia Tool (SALT)



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The Eyelash and Eyebrow Assessment tools are presented in Table 2.

Table 2 – Eyelash Assessment (ELA) and Eyebrow Assessment (EBA) Tools

Score	Eyelash Assessment (ELA)	Eyebrow Assessment (EBA)
0	None Eyelash • No eyelashes of both right and left upper and lower eyelashes.	None Eyebrow • No eyebrow hair.
1	Minimal Eyelash • Modestly or severely decreased density of and/or large gap(s) in one or both upper eyelashes.	Minimal Eyebrow • Normal or decreased density of one or both eyebrows with large gap(s). • Severely decreased density of one or both eyebrows with or without gap(s).
2	Moderate Eyelash	Moderate Eyebrow

	• Normal density of both upper eyelashes without gap(s), and decreased density or gap(s) is present in one or both lower eyelashes, OR • Normal density of both upper eyelashes with short gap(s), OR • Mildly decreased density of one or both upper eyelashes with or without short gap(s).	• Normal density of both eyebrows with short gap(s) that does not significantly distort the appearance of the eyebrows, OR • Mildly decreased density of eyebrows with or without short gap(s), OR • Moderately decreased density of eyebrows without short gap(s). There is visual definition of eyebrows at a distance of 3 feet.
3	Normal Eyelash • Normal density of both right and left upper and lower eyelashes from near medial canthus to near lateral canthus without any gap(s).	Normal Eyebrow • Normal density of both right and left eyebrows spanning usual length (ie, from glabella to near temple) and width. There are no gap(s).
	NOTE: • Density of lower eyelashes is usually less than upper eyelashes. • A short gap does not significantly distort the appearance of the eyelash(es). • Moderate Eyelash score does not require presence of lower eyelashes.	NOTE: • Density of lateral aspect of eyebrows may be mildly less than medial eyebrows. • A short gap does not significantly distort the appearance of the eyebrow(s).

Source: pg 107 of Protocol B7981015 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7981015\b7981015-protocol.pdf)

The protocol specified different sets of primary and secondary endpoints and analysis plans by regulatory region. One list was prepared for FDA and Pharmaceuticals and Medical Devices (PMDA) regulatory submissions, and one was specified for European Medicines Agency (EMA) regulatory submissions. The list of primary and key secondary endpoints specified for FDA regulatory submissions is as follows.

Primary Endpoint

- SALT ≤ 20 at Week 24

Secondary Endpoints

- SALT ≤ 10 at Week 24
- SALT ≤ 20 at Weeks 4, 8, 12, 18, 28, 34, 40, and 48
- SALT ≤ 10 at Weeks 4, 8, 12, 18, 28, 34, 40, and 48

- Response based on 75% improvement in SALT score from baseline (SALT75) at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48
- Change from baseline in SALT scores at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
- Response based on at least a 2-grade improvement from baseline or a score of 3 in EBA score at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48
- Response based on at least a 2-grade improvement from baseline or a score of 3 in ELA score at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48

The key difference between the EMA submission plan and the FDA/PMDA submission plan was that for EMA submission, the primary efficacy endpoint was SALT ≤ 10 at Week 24, rather than SALT ≤ 20, and that the overall significance level was 0.01, rather than 0.00125. In addition, the primary method of handling missing data due to COVID-19 was different for EMA submissions.

Statistical Analysis Plan

The primary analysis population is the full analysis set (FAS) defined as all randomized subjects.

The primary analysis for binary endpoints, including the primary endpoint, used the Miettinen and Nurminen (MN) method to calculate 95% confidence intervals (CI) for the difference in the proportion of responders between each active treatment group and placebo. The MN confidence intervals are computed by inverting score tests for the risk difference. This analysis does not include stratification factors.

For FDA/PMDA regulatory submissions, the protocol-specified method of handling missing data excluded subjects with missing SALT score at Week 24 due to COVID-19 related reasons from the analysis. Subjects with missing SALT scores due to other reasons were counted as non-responders. This method of handling missing data is referred to as Analysis #1.

In addition to the primary analysis, the statistical analysis plan included several supplementary analyses using multiple imputation and/or non-responder imputation to handle missing data, depending on whether the missing data was due to COVID-19 or other reasons. The following table summarizes the alternative approaches for handling the missing data due to COVID-19 vs other reasons, which are referred to Analysis #2 through Analysis #4.

Analysis #	Missing due to COVID-19	Missing due to other reasons
2	MI/MAR	MI/MAR
3	Non-responders	Non-responders
4	MI/MAR	Non-responders

MI=multiple imputation, MAR=missing at random

The multiple imputation analyses used the Missing at Random (MAR) assumption. For the multiple imputation, SALT≤20 response up to Week 24 was modeled with a generalized linear mixed model (GLMM) using a logistic-normal distribution with fixed factors of treatment, visit, and treatment-by-visit interaction with a subject-specific random intercept. The modeling also

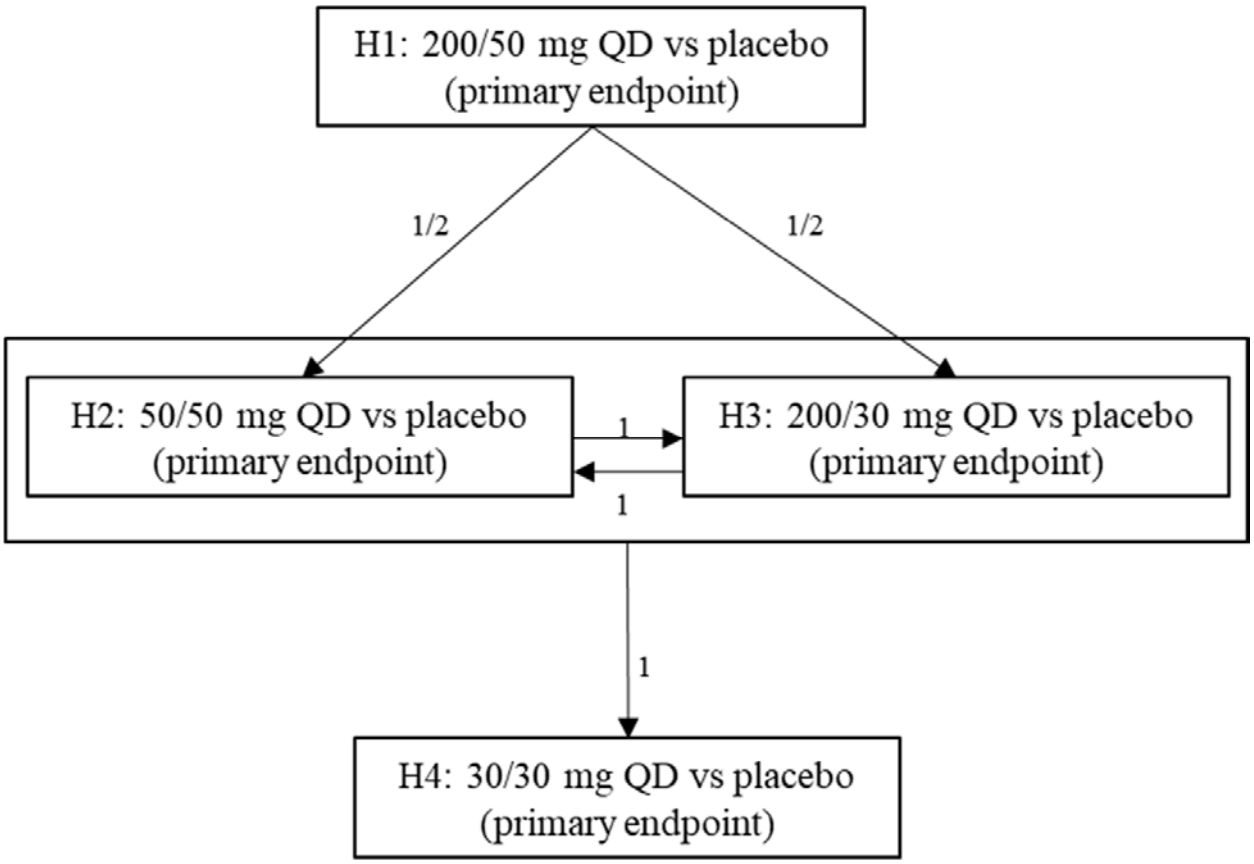
included Bayesian estimation with diffusive priors for the placebo response probability due to the expected negligible placebo response. The SAP specified that the multiple imputation would use at least 100 imputations. The programs submitted by the applicant use 500 imputations. Each imputation the data was analyzed using the MN method and combined using Rubin's rules. In addition, a tipping point analysis was planned using multiple imputation for all sources of missing data (i.e., using missing data handling as in Analysis #2). Note that Analysis #4 was the prespecified primary method of handling missing data for submissions to EMA.

Reviewer Comment
FDA and the applicant discussed handling of subjects with missing data due to COVID-19 during development (Type C meeting Preliminary Comments dated 10/29/2020). FDA acknowledged the difficulty in handling subjects with missed in person assessment visits due to the COVID-19 pandemic and noted that efficacy should be established based on data for subjects with complete in-person visits. Following establishing a treatment effect, sensitivity analyses can be conducted to investigate the impact of missed visits on the overall efficacy assessment. Thus, the applicant proposed excluding such subjects from the primary analysis and defined supplementary analyses with alternate handling of such subjects.

Note that while Analysis #1 (excluding missing data due to COVID-19) was the pre-specified primary analysis, Analysis #4 (using multiple imputation for missing data due to COVID-19) may be a more justifiable method for handling missing data, as it relies on the MAR assumption for subjects who missed visits due to COVID-19, rather than the missing completely at random (MCAR) assumption. Key analyses in Study B7981015 will be presented using both Analysis #1 and Analysis #4 in this review.

For FDA regulatory submissions, the protocol proposed strong control of the type I error rate for the primary endpoint (SALT ≤ 20) across the multiple dosing regimens at $\alpha = 0.00125$. The multiplicity control method included the 4 higher dose comparisons (200/50 mg, 200/30 mg, 50 mg, and 30 mg) versus placebo. The lowest dose (10 mg) was not included in the multiplicity control scheme. Multiplicity was controlled using the following graphical procedure (Figure 3). At the first stage the hypothesis H1 (200/50 mg vs. placebo) is tested at level α. At the second stage, multiplicity was controlled across the hypotheses H2 (50 mg vs. placebo) and H3 (200/30 mg vs. placebo) using Holm's method. If both the tests for the 50 mg arm and the 200/30 mg doses are rejected at the $\alpha/2$ level, then the final hypothesis H4 (30 mg vs. placebo) can be tested at level α.

Figure 3 – Graphical Procedure used to Control Multiplicity for the Primary Efficacy Endpoint



Source: pg 31 of SAP B7981015 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7981015\b7981015-sap.pdf)

Once the procedure for assessing statistical significance of the primary endpoint was completed using the graphical procedure, the key secondary endpoint of SALT ≤10 at Week 24 was to be tested at the same significance level as the primary endpoint for any dose comparison that was statistically significant for the primary endpoint. The SAP notes that the proposed procedure does not protect the Type I error for the family of all possible comparisons. If any of the primary endpoint tests were not significant, then no alpha would be available to pass to the secondary endpoints. In addition, even if all of the primary endpoint tests were significant, the secondary endpoint testing scheme would still need to be designed to control the type I error across the eight primary and key secondary dose comparisons in order to adequately control the type I error rate against all key hypotheses.

The protocol included the possibility that an interim analysis "for internal decision-making purposes" could be conducted when ≥90% of subjects have reached 24 weeks post-randomization. Unblinded personnel were to be kept separate from the rest of the team. No adjustments in the conduct, analysis, or reporting were planned. The applicant decided not to conduct the interim analysis, and the trial was not unblinded until all subjects completed the trial.

Protocol Amendments

Protocol B7981015 was amended five times. The first subject was enrolled on December 3, 2018. Amendment 3 was a significant amendment in which the final determination was made about the definition of the primary and key secondary endpoints (i.e., that SALT ≤20 would be the primary endpoint for FDA regulatory submissions.) The key changes to the protocol impacting the design and analysis were as follows:

1. Amendment 1 (2/28/2019) – An exploratory endpoint was added: the Clinician Global Impression – Alopecia Areata (CGI-AA). The summary used for two exploratory endpoints (Patient's Global Impression of Change (PGI-C) and Patient Satisfaction with Hair Growth (P-Sat)) were clarified as "absolute score".
2. Amendment 2 (5/30/2019) – Clarification of study procedures. No endpoint or analysis changes proposed.
3. Amendment 3 (7/14/2020) – The primary endpoint for FDA regulatory submissions was changed from SALT ≤ 10 to SALT ≤ 20. SALT ≤ 10 was added as a secondary endpoint. The secondary endpoint of 90% improvement in SALT was removed. A secondary endpoint defined as Patient's Global Impression of Change (PGI-C) response (score of " moderately improved" or "greatly improved") was added. Some secondary endpoints were converted to exploratory endpoints. An interim analysis at 90% enrollment was added to support internal decision making.
4. Amendment 4 (10/20/2020) – Clarifications were made regarding the endpoints and analyses that will be used to support EMA regulatory submissions.

Amendment 5 (4/13/2021) – Clarification that SALT ≤ 10 was to be a key secondary endpoint. The objectives of the proposed interim analysis were clarified and that the results would have no impact on the study conduct, analysis, or reporting. The definition of the Full Analysis Set was updated to include all subjects. The methods for handling subjects missing visits due to COVID-19 were added. Clarifications were provided about how secondary endpoints that were not under multiplicity control would be analyzed.

8.1.2. Study Results

Compliance with Good Clinical Practices

The following Good Clinical Practice (GCP) statement by the Applicant is included in the clinical trial reports for all clinical trials in the LITFULO development program: "This study was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents".

Financial Disclosures

See Section 19.2 of this review.

Patient Disposition

Study B7981015 randomized 718 subjects. Three subjects did not receive treatment. Approximately 14% of subjects discontinued treatment during the trial, including 7% who discontinued during the first 24 weeks of the trial. The most common reasons for treatment discontinuation were withdrawal by participant and physician decision. See Table 3 through Table 5.

Table 3 – Subject Disposition in Study B7981015

	Ritlecitinib 200/50 mg N=132	Ritlecitinib 200/30 mg N=130	Ritlecitinib 50 mg N=130	Ritlecitinib 30 mg N=132	Ritlecitinib 10 mg N=63	Placebo N=131
Randomized (FAS)	132	130	130	132	63	131
Treated (SAS)	131 (99.2)	129 (99.2)	130 (100)	132 (100)	62 (98.4)	131 (100)
Completed	116 (87.9)	112 (86.2)	113 (86.9)	103 (78.0)	53 (84.1)	117 (89.3)
Discontinued	15 (11.4)	17 (13.1)	17 (13.1)	29 (22.0)	9 (14.3)	14 (10.7)
Not Treated	1 (0.8)	1 (0.8)	0	0	1 (1.6)	0
Discontinued	1 (0.8)	1 (0.8)	0	0	1 (1.6)	0

FAS = Full Analysis Set, SAS=Safety Analysis Set
Source: pg 59 of Study Report B7981015 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7981015\b7981015-report-body.pdf) and reviewer analysis.

Table 4 – Reasons for Discontinuation up to Week 24 inStudy B7981015

	Ritlecitinib 200/50 mg N=132	Ritlecitinib 200/30 mg N=130	Ritlecitinib 50 mg N=130	Ritlecitinib 30 mg N=132	Ritlecitinib 10 mg N=63	Placebo N=131
Discontinued up to Week 24	10 (7.6)	6 (4.6)	9 (6.9)	15 (11.4)	5 (7.9)	7 (5.3)
Adverse Event	3 (2.3)	0	2 (1.5)	4 (3.0)	2 (3.2)	1 (0.8)
Lack of Efficacy	0	0	0	0	0	1 (0.8)
Lost to Follow-up	1 (0.8)	0	1 (0.8)	2 (1.5)	1 (1.6)	0
Physician Decision	0	1 (0.8)	2 (1.5)	5 (3.8)	0	1 (0.8)
Pregnancy	1 (0.8)	0	0	0	1 (1.6)	1 (0.8)
Protocol Deviation	1 (0.8)	1 (0.8)	0	0	0	0
Withdrawal by Participant	4 (3.0)	4 (3.1)	4 (3.1)	4 (3.0)	1 (1.6)	3 (2.3)

Source: pg 61 of Study Report B7981015 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7981015\b7981015-report-body.pdf) and reviewer analysis.

Table 5 – Reasons for Discontinuation during Extension Period (Weeks 25-48) in Study B7981015

	Ritlecitinib 200/50 mg N=132	Ritlecitinib 200/30 mg N=130	Ritlecitinib 50 mg N=130	Ritlecitinib 30 mg N=132	Ritlecitinib 10 mg N=63	Placebo/ 200/50 mg N=65	Placebo/ 50 mg N=66
Discontinued Week 25-48	6 (4.5)	11 (8.5)	5 (3.8)	9 (6.8)	5 (7.9)	3 (4.6)	4 (6.1)
Adverse Event	0	2 (1.5)	2 (1.5)	1 (0.8)	0	0	2 (3.0)
Lack of Efficacy	2 (1.5)	1 (0.8)	0	3 (2.3)	3 (4.8)	0	1 (1.5)
Lost to Follow-Up	0	0	2 (1.5)	1 (0.8)	1 (1.6)	2 (3.1)	0
Non-Compliance With Study Drug	0	1 (0.8)	0	0	0	0	0
Physician Decision	0	1 (0.8)	0	1 (0.8)	1 (1.6)	0	0
Withdrawal By Participant	3 (2.3)	2 (1.5)	1 (0.8)	1 (0.8)	0	1 (1.5)	1 (1.5)
Other	1 (0.8)	4 (3.1)	0	2 (1.5)	0	0	0

Source: pg 62-63 of Study Report B7981015 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7981015\b7981015-report-body.pdf) and reviewer analysis.

For the efficacy analyses, subjects with missing data at Week 24 were classified as either having missing data due to COVID-19 or missing due to other reasons. The primary and supplementary methods for handling missing data used different methods of handling the missing data from these two categories, as discussed above in the Statistical Analysis Plan Section. Approximately 6% of subjects had missing data at Week 24 due to COVID-19 and approximately 4% of subjects had missing data due to other reasons. The ritlecitinib 30 mg arm had a higher proportion of subjects with missing data due to COVID-19 and the placebo arm had a lower proportion. The proportion of subjects with missing data due to other reasons was generally consistent across the treatment arms. See Table 6.

Table 6 – Missing Data Category for Week 24 Efficacy Analyses in Study B7981015

	Ritlecitinib 200/50 mg N=132	Ritlecitinib 200/30 mg N=130	Ritlecitinib 50 mg N=130	Ritlecitinib 30 mg N=132	Ritlecitinib 10 mg N=63	Placebo N=131
Missing due to COVID-19	8 (6.1)	9 (6.9)	6 (4.6)	13 (9.8)	4 (6.3)	1 (0.8)
Missing due to other reasons	6 (4.5)	2 (1.5)	5 (3.8)	5 (3.8)	4 (6.3)	5 (3.8)
Total	14 (10.6)	11 (8.5)	11 (8.5)	18 (13.6)	8 (12.6)	6 (4.6)

Source: pg 74 of Study Report B7981015 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7981015\b7981015-report-body.pdf) and reviewer analysis.

Protocol Violations/Deviations

The most common protocol violations related to investigational product use (e.g., drug product accountability and subject compliance violations) and procedures and tests not done. See Table 7.

Table 7 - Protocol Deviation Categories Observed in **≥1%** of Subjects in Study B7981015

	Ritlecitinib 200/50 mg N=132	Ritlecitinib 200/30 mg N=130	Ritlecitinib 50 mg N=130	Ritlecitinib 30 mg N=132	Ritlecitinib 10 mg N=63	Placebo/ 200/50 mg N=65	Placebo/ 50 mg N=66
Concomitant Meds	11 (8.3)	11 (8.5)	14 (10.8)	13 (9.8)	3 (4.8)	7 (10.8)	7 (10.6)
Inclusion/Exclusion	14 (10.6)	11 (8.5)	16 (12.3)	10 (7.6)	10 (15.9)	8 (12.3)	8 (12.1)
Investig. Product	50 (37.9)	54 (41.5)	65 (50.0)	51 (38.6)	31 (49.2)	27 (41.5)	31 (47.0)
Laboratory	18 (13.6)	25 (19.2)	13 (10.0)	23 (17.4)	9 (14.3)	14 (21.5)	10 (15.2)
Procedures/Tests	35 (26.5)	54 (41.5)	36 (27.7)	39 (29.5)	23 (36.5)	20 (30.8)	17 (25.8)
Visit Schedule	1 (0.8)	2 (1.5)	3 (2.3)	1 (0.8)	0	3 (4.6)	0

Source: pg 168-177 of Study Report B7981015 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7981015\b7981015-report-body.pdf).

Table of Demographic Characteristics

The demographics were generally balanced across the treatment groups. See Table 8. Approximately 15% of subjects were 12-17 years of age, and 3% were 65 years of age and older, Approximately 62% of subjects were female, and 38% were male. Approximately 68% of subjects were White, 26% were Asian, and 4% were Black or African American, and 12% were Hispanic or Latino.

Table 8 – Demographics in Study B7981015

	Ritlecitinib 200/50 mg N=132	Ritlecitinib 200/30 mg N=130	Ritlecitinib 50 mg N=130	Ritlecitinib 30 mg N=132	Ritlecitinib 10 mg N=63	Placebo N=131
Age (years)						
Mean	34.5	33.7	32.4	33.7	34.3	32.0
Range	12, 71	12, 65	13, 70	12, 73	13, 58	12, 71
<18 years	20 (15.2)	19 (14.6)	18 (13.8)	20 (15.2)	9 (14.3)	19 (14.5)
18-64 years	108 (81.8)	110 (84.6)	109 (83.8)	105 (79.5)	54 (85.7)	107 (81.7)
≥ 65 years	4 (3.0)	1 (0.8)	3 (2.3)	7 (5.3)	--	5 (3.8)
Gender						
Female	81 (61.4)	85 (65.4)	71 (54.6)	80 (60.6)	43 (68.3)	86 (65.6)

Male	51 (38.6)	45 (34.6)	59 (45.4)	52 (39.4)	20 (31.7)	45 (34.4)
Race						
White	92 (69.7)	90 (69.2)	79 (60.8)	91 (68.9)	42 (66.7)	94 (71.8)
Black or Afric.-Amer.	6 (4.5)	7 (5.4)	5 (3.8)	3 (2.3)	2 (3.2)	4 (3.1)
Asian	33 (25.0)	28 (21.5)	43 (33.1)	34 (25.8)	17 (27.0)	31 (23.7)
Am. Ind./ AK Native	--	1 (0.8)	--	2 (1.5)	--	--
Native HI/ Pac. Isl.	--	--	--	--	1 (1.6)	--
Multiracial		3 (2.3)	1 (0.8)	2 (1.5)		2 (1.5)
Not reported	1 (0.8)	1 (0.8)	2 (1.5)	--	2 (1.5)	--
Ethnicity						
Hispanic or Latino	18 (13.6)	16 (12.3)	11 (8.5)	23 (17.4)	8 (12.7)	11 (8.4)
Not Hispanic or Latino	113 (85.6)	114 (87.7)	116 (89.2)	109 (82.6)	55 (87.3)	119 (90.8)
Unknown	1 (0.8)	--	3 (2.3)	--	--	1 (0.8)

Note: ages are approximate, as only birth year, rather than full birthdate was recorded.
Source: pg 69-70 of Study Report B7981015 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7981015\b7981015-report-body.pdf) and reviewer analysis.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline disease characteristics were generally balanced across treatment arms. Approximately 46% of subjects had complete scalp hair loss at baseline (AT/AU). Approximately 83% of subjects had some eyebrow involvement (other than "normal eyebrow") and approximately 75% of subjects had some eyelash involvement (other than "normal eyelash"). See Table 9.

Table 9 – Baseline Disease Characteristics in Study B7981015

	Ritlecitinib 200/50 mg N=132	Ritlecitinib 200/30 mg N=130	Ritlecitinib 50 mg N=130	Ritlecitinib 30 mg N=132	Ritlecitinib 10 mg N=63	Placebo N=131
Baseline Severity						
AT/AU	60 (45.5)	60 (46.2)	60 (46.2)	61 (46.2)	29 (46.0)	60 (45.8)
Not AT/AU	72 (54.5)	70 (53.8)	70 (53.8)	71 (53.8)	34 (54.0)	71 (54.2)
Episode Duration (years)						
Mean	3.4	3.4	3.2	3.6	3.3	3.2
Range	0.02, 9.97	0.03, 13.02	0.18, 9.89	0.25, 9.97	0.28, 9.68	0.04, 9.97
Eyebrow Assessment						
0=None Eyebrow	66 (50.0)	59 (45.4)	59 (45.4)	59 (44.7)	27 (42.9)	58 (44.3)
1=Minimal Eyebrow	32 (24.2)	31 (23.8)	31 (23.8)	38 (28.8)	17 (27.0)	33 (25.2)
2=Moderate Eyebrow	12 (9.1)	19 (14.6)	16 (12.3)	15 (11.4)	8 (12.7)	16 (12.2)
3=Normal Eyebrow	22 (16.7)	21 (16.2)	24 (18.5)	20 (15.2)	11 (17.5)	24 (18.3)
Eyelash Assessment						
0=None Eyelash	55 (41.7)	48 (36.9)	56 (43.1)	51 (38.6)	21 (33.3)	52 (39.7)
1=Minimal Eyelash	36 (27.3)	30 (23.1)	25 (19.2)	37 (28.0)	15 (23.8)	24 (18.3)
2=Moderate Eyelash	11 (8.3)	17 (13.1)	14 (10.8)	14 (10.6)	9 (14.3)	21 (16.0)
3=Normal Eyelash	30 (22.7)	35 (26.9)	35(26.9)	30 (22.7)	18 (28.6)	34 (26.0)

AT/AU = Alopecia Totalis/Alopecia Universalis
Source: reviewer analysis.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

A total of 7 subjects use concomitant medications for alopecia areata through Week 24, though none of these subjects were on the ritlecitinib 50 mg arm (3 subjects on the ritlecitinib 200/50 mg arm, 3 subjects on the ritlecitinib 200/30 mg arm, and 1 subject on the ritlecitinib 10 mg arm. Approximately 97% of subjects had treatment compliance between 80% and 120%, with the remaining subjects having < 80% compliance, with similar levels of compliance across treatment arms (range: 96.1% to 98.5%).

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was SALT ≤ 20 at Week 24 and the overall significance was controlled at α=0.00125. The endpoint was analyzed using the Miettinen and Nurminen (MN) method. Subjects with missing SALT score at Week 24 due to COVID-19 related reasons were excluded from the analysis. Subjects with missing SALT scores due to other reasons were counted as non-responders (Analysis #1).

The hypothesis tests for the four highest doses (200/50 mg, 200/30 mg, 50 mg, and 30 mg) versus placebo were included in the multiplicity control scheme for the primary endpoint. (See Figure 3 above). The first test in the graphical procedure was the comparison with the 200/50 mg dose. Since the p-value for this comparison was significant at α=0.00125, the 200/30 mg and 50 mg dose comparisons were tested at α/2 = 0.000625. Since both of these comparisons were significant at that level, the 30 mg dose comparison was tested at α=0.00125. All four of the tested dose comparisons were statistically significant under the prespecified analysis. See Table 10. The applicant is proposing to market the 50 mg dose.

Table 10 - SALT ≤ 20 at Week 24 in Study B7981015 (FAS/Analysis #1)

	Ritlecitinib 200/50 mg N=132	Ritlecitinib 200/30 mg N=130	Ritlecitinib 50 mg N=130	Ritlecitinib 30 mg N=132	Ritlecitinib 10 mg N=63	Placebo N=131
n/N1[a] (%)	38/124 (30.65)	27/121 (22.31)	29/124 (23.39)	17/119 (14.29)	1/59 (1.69)	2/130 (1.54)
p-value	<0.000001[b]	<0.000001[b]	<0.000001[b]	0.000154[b]	0.936441	
95% CI[c]	(21.17, 37.91)	(13.65, 29.18)	(14.65, 30.23)	(6.69, 20.36)	(-4.05, 7.58)	

[a] N1 excludes subjects with missing assessments due to COVID-19. Subjects with other sources of missing data are imputed as non-responders.
[b] Statistically significant at the 0.00125 level under the multiplicity control scheme.
[c] 95% Confidence interval for the treatment difference
FAS= Full Analysis Set
Source: pg 74-75 of Study Report B7981015 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7981015\b7981015-report-body.pdf) and reviewer analysis.

The applicant conducted three supplementary analyses for handling missing data, as discussed above in the Statistical Analysis Plan section. For these analyses, different combinations of multiple imputation and non-responder imputation were used for data missing due to COVID-19 or due to other reasons. The results for the 50 mg dose and placebo arms were similar across all the planned analyses and are presented in Table 11. All of the p-values computed from the tipping point analysis, which used multiple imputation for all missing data across a range of plausible missing not at random assumptions, remained <0.00125 for the 50 mg versus

placebo comparison. Thus, the handling of missing data did not impact the conclusions about the efficacy.

Table 11 - SALT ≤ 20 at Week 24 in Study B7981015 (Primary and Supplementary Missing Data Analyses - FAS)

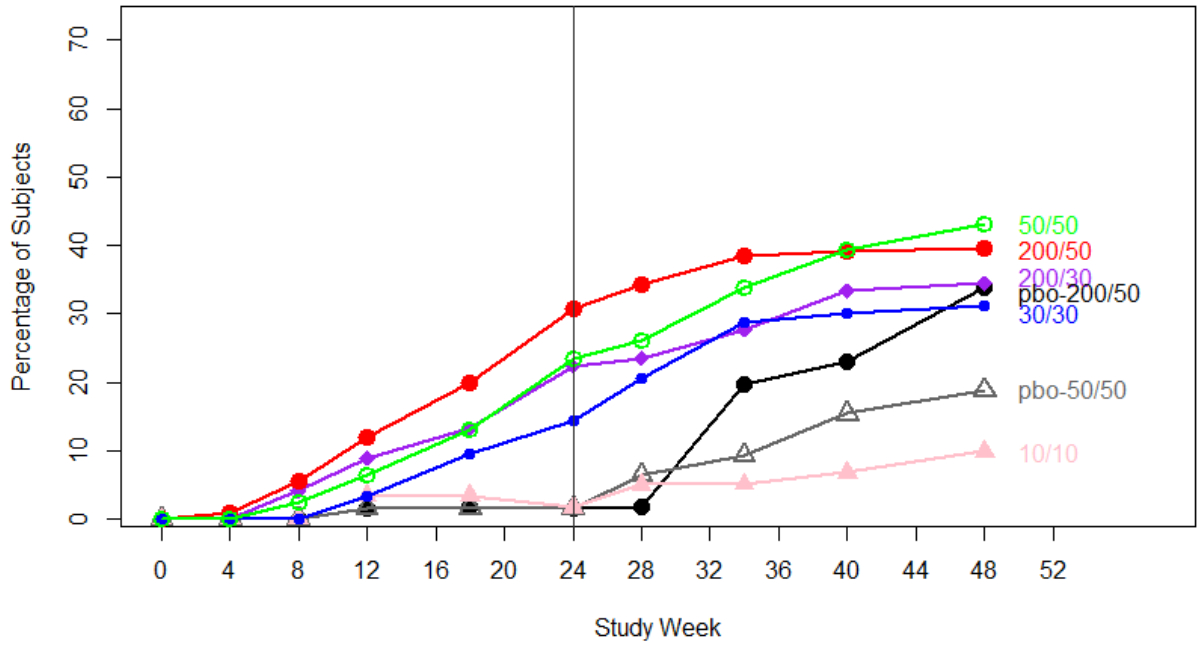
Missing Data Handling			Ritlecitinib 50 mg N=130 %	Placebo N=131 %	Treatment Difference and 95% CI	P-value
Analysis	COVID-19	Other Reasons				
#1	Excluded	NRI	23.39	1.54	21.85 (14.65, 30.23)	<0.000001
#2	MI	MI	23.68	1.63	22.05 (13.74, 30.36)	<0.000001
#3	NRI	NRI	22.31	1.53	20.78 (13.84, 28.88)	<0.000001
#4	MI	NRI	22.98	1.55	21.43 (13.37, 29.48)	<0.000001

FAS=Full Analysis Set; MI=Multiple Imputation; NRI=Non-responder Imputation; CI = Confidence Interval
Source: pg 74, 75, 359, 368, 369 of Study Report B7981015 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7981015\b7981015-report-body.pdf) and reviewer analysis.

Efficacy over Time

The SALT ≤ 20 response rates by visit for the evaluated dosing regimens are presented in Figure 4. The proportion of responders among subjects who received the 200 mg loading dose during the first 4 weeks (200/50 mg and 200/30 mg regimens) was higher at Week 24 than for the subjects who received either 50 mg or 30 mg throughout the first 24 weeks. However, by Week 48, the proportion of responders for the 200/50 mg and 50 mg dosing regimens were similar, as were the proportion of responders for the 200/30 mg and 30 mg dosing regimens. Subjects who received placebo during the first 24 weeks were randomized at baseline to switch to either 200/50 mg or 50 mg at Week 24.

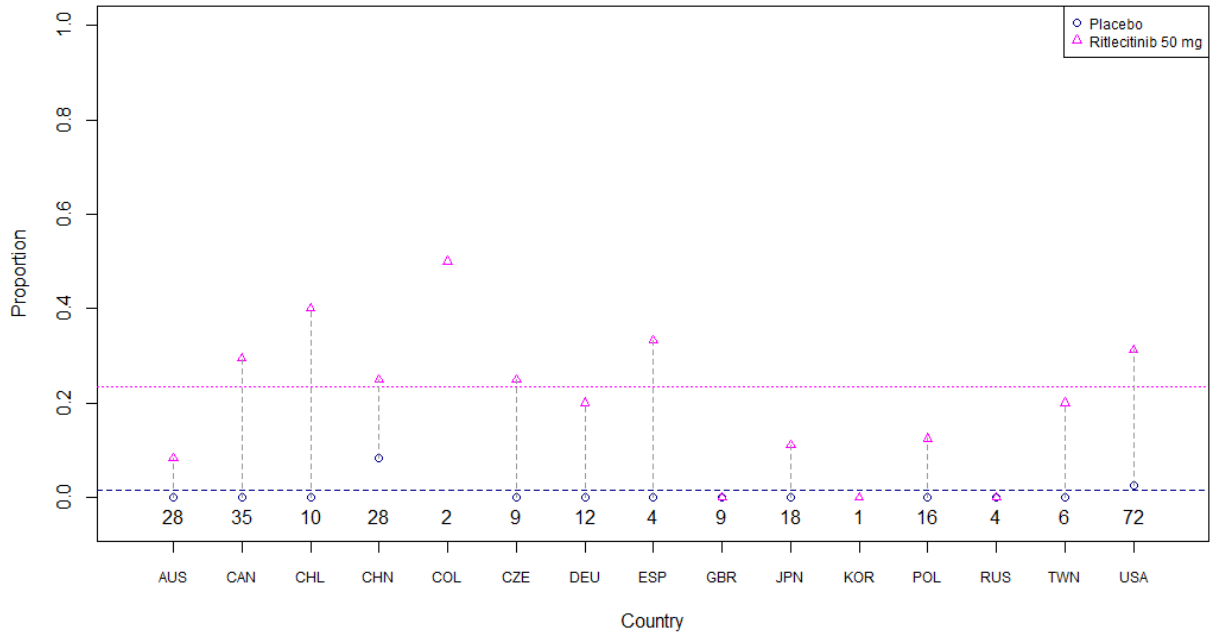
Figure 4 - SALT ≤ 20 by Visit in Study B7981015 (FAS-Analysis #1)



FAS= Full analysis set, pbo=Placebo
Source: reviewer analysis

Findings in Subgroup Populations
Study B7981015 enrolled 718 subjects across 6 dosing regimens in 128 centers. The trial enrolled subjects in 18 countries. Of these subjects, 195 (27%) subjects were enrolled in the U.S. at 31 centers. The primary endpoint results were generally consistent across countries for the 50 mg dosing regimen versus placebo (Figure 5).

Figure 5 - SALT ≤ 20 at Week 24 by Country in Study B7981015 (FAS-Analysis #1)



Numbers at the bottom represent the number of subjects per country enrolled in the ritlecitinib 50 mg or placebo arm.
Source: reviewer analysis.

Treatment effects for the primary endpoint were generally consistent across pediatric and adult age groups. Treatment effects were also consistent across the two larger race groups (White and Asian). Within each dose group, treatment effects were larger in female subjects than in male subjects. Similarly, subjects who did not have AT/AU had larger treatment effects than subjects with AT/AU at baseline within each dose group. See Table 12.

Table 12 - SALT ≤ 20 at Week 24 by Subgroup in Study B7981015 (FAS/Analysis #1)

n/N (%) 95% CI for treatment difference vs. placebo	Ritlecitinib 200/50 mg N=132	Ritlecitinib 200/30 mg N=130	Ritlecitinib 50 mg N=130	Ritlecitinib 30 mg N=132	Placebo N=131
Age (years)					
<18 years	5/18 (27.8) (8.2, 51.2)	3/17 (17.6) (-1.2, 41.4)	4/16 (25.0) (5.5, 49.9)	3/18 (16.7) (-2.0, 39.6)	0/19 (0)
18-64 years	32/102 (31.4) (21.8, 40.1)	24/104 (23.1) (14.6, 31.3)	24/105 (22.9) (14.4, 31.0)	13/95 (13.7) (6.4, 21.2)	1/106 (0.9)
≥ 65 years	1/4 (25.00) (-49.6, 59.8)	0/0	1/3 (33.3) (-46.0, 69.7)	1/6 (16.7) (-53.3, 45.2)	1/5 (20.0)
Gender					
Female	28/77 (36.4) (23.2, 45.5)	21/79 (26.6) (14.6, 35.3)	25/69 (36.2) (22.7, 46.0)	11/70 (15.7) (5.0, 24.0)	2/85 (2.4)

Male	10/47 (21.3) (12.0, 35.0)	6/42 (14.3) (5.8, 27.9)	4/55 (7.3) (-0.9, 17.3)	6/49 (12.2) (3.9, 24.3)	0/45 (0)
Race					
White	25/85 (29.4) (19.2, 38.9)	16/81 (19.8) (10.8, 28.8)	18/74 (24.3) (14.3, 34.3)	12/79 (15.2) (6.9, 23.8)	1/93 (1.1)
Black or Afric.-Amer.	0/5 (0)	0/7 (0)	0/5 (0)	0/3	0/4 (0)
Asian	12/33 (36.4) (15.3, 51.0)	10/28 (35.7) (14.0, 51.8)	10/42 (23.8) (4.8, 36.1)	3/33 (9.1) (-8.4, 21.0)	1/31 (3.2)
Am. Ind./ AK Native	0/0	0/1 (0)	0/0	1/2 (50.0)	0/0
Native HI/ Pac. Isl.	0/0	0/0	0/0	0/0	0/0
Multiracial	0/0	1/3 (33.3)	0/1 (0)	0/0	0/2 (0)
Not reported	1/1 (100)	0/1 (0)	1/2 (50.0)	0/0	0/0
Ethnicity					
Hispanic or Latino	4/15 (26.7) (-3.1, 52.4)	6/16 (37.5) (7.0, 61.8)	5/11 (45.5) (13.1, 72.5)	3/22 (13.6) (-14.2, 33.7)	0/11 (0)
Not Hispanic or Latino	34/108 (31.5) (21.2, 39.3)	21/105 (20.0) (11.0, 27.2)	24/110 (21.8) (12.7, 29.0)	14/97 (14.4) (6.1, 21.3)	2/118 (1.7)
Unknown	0/1 (0)	0/0	0/3 (0)	0/0	0/1 (0)
Baseline Severity					
AT/AU	8/57 (14.0) (7.3, 25.4)	7/57 (12.3) (5.8, 23.3)	4/55 (7.3) (1.0, 17.3)	4/56 (7.1) (0.9, 17.0)	0/60 (0)
Not AT/AU	30/67 (44.8) (29.4, 54.3)	20/64 (31.3) (16.9, 41.0)	25/69 (36.2) (21.7, 45.7)	13/63 (20.6) (7.7, 29.8)	2/70 (2.9)

Note: results from the 10 mg dosing arm are not presented.
Source: reviewer analysis

Data Quality and Integrity

No issues with data quality and integrity were identified in Study B7981015.

Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoint was SALT ≤ 10 at Week 24. The protocol also proposed secondary endpoints based on the SALT score at each visit (Weeks 4, 8, 12, 18, 28, 34, 40, and 48), including SALT ≤ 20, SALT ≤ 10, 75% improvement in SALT, and change from baseline in SALT. The multiplicity control scheme focused on controlling the Type I error rate across the 4 dose comparisons for the primary endpoint and did not extend to the secondary endpoints. SALT ≤ 20 results are presented in Figure 4 above. This section will present the results for the key secondary endpoint SALT ≤ 10 at Week 24 which was analyzed for the dose groups that

demonstrated statistical significance for the primary endpoint (200/50 mg, 200/30 mg, 50 mg, and 30 mg).

The results for SALT ≤ 10 at Week 24 are consistent with the results for the primary endpoint and are presented in Table 13. For the 50 mg dose versus placebo comparison, the results were consistent across the various methods for handling missing data (Table 14)

Table 13 - SALT ≤ 10 at Week 24 in Study B7981015 (FAS/Analysis #1)

	Ritlecitinib 200/50 mg N=132	Ritlecitinib 200/30 mg N=130	Ritlecitinib 50 mg N=130	Ritlecitinib 30 mg N=132	Ritlecitinib 10 mg N=63	Placebo N=131
n/N1[a]	27/124	16/121	17/124	13/119	1/59	2/130
(%)	(21.77)	(13.22)	(13.71)	(10.92)	(1.69)	(1.54)
p-value	<0.0001	0.0003	0.0002	0.0019	0.9364	
95% CI[c]	(13.23, 28.49)	(5.82, 19.07)	(6.27, 19.53)	(3.86, 16.46)	(-4.05, 7.58)	

[a] N1 excludes subjects with missing assessments due to COVID-19. Subjects with other sources of missing data are imputed as non-responders.
[c] 95% Confidence interval for the treatment difference
FAS= Full Analysis Set
Source: reviewer analysis

Table 14 - SALT ≤ 10 at Week 24 in Study B7981015 (Primary and Supplementary Missing Data Analyses - FAS)

Missing Data Handling			Ritlecitinib 50 mg N=130 %	Placebo N=131 %	Treatment Difference and 95% CI	P-value
Analysis	COVID-19	Other Reasons				
#1	Excluded	NRI	13.71	1.54	12.17 (6.27, 19.53)	0.0002
#2	MI	MI	13.85	1.60	12.25 (5.60, 18.90)	0.0003
#3	NRI	NRI	13.08	1.53	11.55 (5.83, 18.63)	0.0002
#4	MI	NRI	13.42	1.54	11.88 (5.42, 18.33)	0.0003

FAS=Full Analysis Set; MI=Multiple Imputation; NRI=Non-responder Imputation; CI = Confidence Interval
Source: pg 77, 395 of Study Report B7981015 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7981015\b7981015-report-body.pdf) and reviewer analysis.

Dose/Dose Response

Study B7981015 evaluated 5 dosing regimens, including two regimens with a 4-week loading

dose (200/50 mg and 200/30 mg) and three regimens without a loading dose (50 mg, 30 mg, 10 mg). The observed SALT ≤ 20 response rates followed the expected dose response pattern with 200/50 mg having a higher response rate than 200/30 mg at Week24, and 50 mg having a higher response rate than 30 mg and 10 mg. Subjects receiving the loading dose of 200 mg for the first 4 weeks followed by either 50 mg or 30 mg had slightly higher response rates at Week 24 for the primary endpoint than subjects who received either 50 mg or 30 mg through Week 24, though by Week 48, the response rates for the 200/50 mg and 50 mg arms were similar, as were the response rates for the 200/30 mg and 30 mg arms. See Figure 4 above. The applicant is seeking approval for the 50 mg dosing regimen, without the loading dose.

Durability of Response

At Week 24, all subjects on an active ritlecitinib dosing regimen continued the same dosing regimen through Week 48. At baseline, subjects randomized to placebo were randomized to either switch to the 200/50 mg or 50 mg dosing regimen starting at Week 24. SALT ≤ 20 response rates continued to increase after Week 24 among subjects receiving ritlecitinib, but the response rates generally were plateauing by Week 48. See Figure 4 above. Study B7981015 did not evaluate treatment withdrawal of alternate maintenance regimens.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Study B7981015 evaluated eyebrows and eyelashes using the Eyebrow Assessment (EBA) and Eyelash Assessment (ELA) tools. Each tool is a 4-point ordinal assessment and efficacy was assessed defining response as at least a 2-grade improvement from baseline or a score of 3 (normal) on the corresponding scale, among subjects without normal eyebrow or eyelash at baseline. Table 15 shows that responses on the EBA and ELA were generally consistent with the primary endpoint results. However, Study B7981015 did not include multiplicity adjustments among the secondary endpoints, and the EBA and ELA endpoints were among a list of 6 endpoints evaluated at up to 9 timepoints. Because the study was not designed to permit multiplicity-controlled assessment among the secondary endpoints, response on the EBA and ELA tools would not be appropriate for labeling.

Table 15 – Eyebrow and Eyelash Assessment Response at Week 24 in Study B7981015 (FAS/Analysis #1)

	Ritlecitinib 200/50 mg N=132	Ritlecitinib 200/30 mg N=130	Ritlecitinib 50 mg N=130	Ritlecitinib 30 mg N=132	Ritlecitinib 10 mg N=63	Placebo N=131
Eyebrow						
n/N1[a] (%)	35/103 (33.98)	26/102 (25.49)	29/100 (29.00)	17/102 (16.67)	4/48 (8.33)	5/107 (4.67)
p-value	<0.000001	0.000023	0.000002	0.004741	0.367601	
95% CI[c]	(19.47, 39.50)	(11.70, 30.67)	(14.82, 34.48)	(3.89, 21.02)	(-4.04, 15.33)	

Eyelash						
n/N1[a] (%) p-value 95% CI[c]	29/96 (30.21) 0.000005 (15.00, 35.56)	19/89 (21.35) 0.000999 (6.86, 26.49)	26/90 (28.89) 0.000013 (13.61, 34.50)	24/92 (26.09) 0.000066 (11.15, 31.43)	2/41 (4.88) 0.946052 (-7.75, 11.44)	5/97 (5.15)

[a]N1=number of subjects with score 0, 1, or 2 at baseline and excludes subjects with missing assessments due to COVID-19. Subjects with other sources of missing data are imputed as non-responders.
[c] 95% Confidence interval for the treatment difference
FAS= Full Analysis Set
Source: pg 498, 502 of Study Report B7981015 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7981015\b7981015-report-body.pdf) and reviewer analysis.

8.1.3. Assessment of Efficacy Across Trials

In addition to Study B7981015, the applicant conducted a Phase 2a study (Study B7931005) that evaluated ritlecitinib 200/50 mg, another test product (PF-06700841) and placebo in subjects with moderate to severe AA. The primary endpoint was percent change in SALT from baseline to Week 24, and the protocol did not evaluate SALT ≤20. Although Study B7931005 only evaluated the 200/50 mg dosing regimen, which is higher than the proposed 50 mg dose without loading dose, it provided preliminary data which were generally consistent with what was seen in the Phase 2b/3 trial. The percent reduction in SALT from Studies B7931005 and B7981015 for the 200/50 mg dosing regimen are presented in Table 16. The results for the secondary endpoint in Study B7981015 and the primary endpoint in Study B7931005 for the 200/50 mg dosing regimen are similar. The efficacy results from Study B7931005 are not further discussed in this review.

Table 16 – Percent Reduction in SALT at Week 24 across Trials (Studies B7931005 and B7981015)

	Ritlecitinib 200/50 mg Mean (SE)	Placebo Mean (SE)	Treatment Difference and 95% CI
Study B7931005	N=44 32.54 (4.34)	N=35 1.41 (4.49)	(18.78, 43.50)
Study B7981015	N= 132 36.5 (2.55)	N=131 5.1 (2.52)	(24.41, 38.49)

Source: pg 474 of Study Report B7981015 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7981015\b7981015-report-body.pdf) and pg 145 of Study Report B7931005 (\\CDSESUB1\EVSPROD\nda215830\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alopecia-areata\5351-stud-rep-contr\b7931005\b7931005-synopsis.pdf).

8.1.4. Integrated Assessment of Effectiveness

The applicant provided substantial evidence of effectiveness for ritlecitinib 50 mg in the treatment of severe alopecia areata. This was supported by an adequate and well-controlled large multicenter Phase 2b/3 trial (B7981015, N=718), with very persuasive results which were consistent with those suggested by the Phase 2a trial, B7931005 (N=142). Trial B7981015 was designed to control the Type I error rate across the hypothesis tests for the primary endpoint for the four highest doses (200/50 mg, 200/30 mg, 50 mg, 30 mg) versus placebo. Multiplicity control was not extended to the set of secondary endpoints, which included additional endpoints based on SALT at each visit, and eyebrow and eyelash assessments. The key secondary endpoint of SALT ≤10 at Week 24 is closely related to the primary endpoint, as it is based on a different dichotomization of the SALT score. Estimates of this endpoint may be useful to patients and prescribers, even though the multiplicity control scheme did not fully incorporate this endpoint across all doses. However, beyond the key secondary endpoint, the set of secondary endpoints included additional endpoints based on SALT and endpoints based on the Eyebrow and Eyelash Assessment tools at each study visit through Week 48. While the results on the eyebrow and eyelash assessments at Week 24 were generally consistent with the primary endpoint, due to the structuring of the secondary endpoints in Study B7981015, the eyelash and eyebrow assessments did not have adequate multiplicity control to support any claims related to these assessments. The prespecified method of handling missing data in the protocol involved excluding subjects with missing visits due to COVID-19 from the analyses. However, in order to incorporate all randomized subjects into the analyses, the recommended presentation of the key efficacy results uses data imputation that uses less restrictive assumptions on subjects with missing data (i.e. Analysis #4, that uses multiple imputation for subjects with missing data due to COVID-19). The key efficacy results from Study B7981015 for the 50 mg dose using Analysis #4 are presented in Table 17. The efficacy results from this trial are consistent across centers, demographic subgroups, and methods of handling missing data.

Table 17 – Key Efficacy Results at Week 24 in Study B7981015 (FAS/Analysis #4)

	Ritlecitinib 50 mg N=130 %	Placebo N=131 %	Difference from Placebo (95% CI)
SALT ≤20 response	23.0	1.6	21.4 (13.4, 29.5)
SALT ≤10 response	13.4	1.6	11.9 (5.4, 18.3)

FAS=full analysis set; Analysis #4 = multiple imputation for missing data due to COVID-19 and non-responder imputation for other reasons for missing data.

8.2. Review of Safety

8.2.1. Safety Review Approach

Safety data to support the safety and tolerability of ritlecitinib oral capsule, 50 mg once daily for the treatment of adult (≥ 18 years of age) and adolescent (≥12 to <18 years of age) (b) (4) includes safety data from 5 clinical studies (4 AA studies (B7931005, B7981015, B7981032, B7981037) and 1 vitiligo study (B7981019)) grouped into the following 4 safety data pools:

1. PCPAA pool

Includes safety data from the placebo-controlled periods (PCP) (weeks 0-24) of 3 AA studies (B7931005, B7981015, B7981037). PCPAA is the focus of the primary review of safety for ritlecitinib for this NDA. Of the 881 subjects randomized, 345 were included in the All 50 mg dose group (combined treatment group for the 200/50 mg and 50/50 mg dose groups).

2. PCPAAV pool

Includes the placebo-controlled period of the vitiligo study (B7981019) and the PCPAA safety pool. Of the 1245 subjects randomized, 544 were included in the All 50 mg dose group (combined treatment group for the 200/50 mg, 100/50 mg, and 50/50 mg dose groups).

3. OYEP (One-year exposure) pool

Includes safety data, up to one year, from study B7981015. Of the 584 subjects in this pool, 261 were included in the All 50 mg dose group (combined treatment group for the 200/50 mg and 50/50 mg dose groups).

4. All exposure pool (AEP)

Includes safety data from 5 studies in the AA and vitiligo development programs (including long term safety data from the long-term safety (LTS) study B7981032). Of the 1628 subjects enrolled, 1521 were included in the All 50 mg dose group (combined treatment group for the 200/50 mg, 100/50 mg, and 50/50 mg dose groups). In the 120-day safety update, 2 additional subjects were included in the AEP.

To determine the safety profile of ritlecitinib oral capsule, 50 mg once daily for the treatment of AA (b) (4) the review team analyzed the following types of pooled data: exposure, demographics, baseline characteristics, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, adverse events of special interest (AESIs), clinical laboratory results, vital signs, and findings from physical examinations.

Additionally, the Applicant submitted incidence rates (IR) data for selected AEs from external cohorts of AA patients enrolled in two epidemiological studies (US study B7981051 and Danish Study B7981049) to provide contextualization of the safety data from the ritlecitinib AA trials.

8.2.2. Review of the Safety Database

[Do not insert text here]

Overall Exposure

Overall exposure to ritlecitinib in terms of frequency, duration and target population was adequate for the evaluation of safety.

In the AEP, 1521 subjects were exposed to a ritlecitinib does of ≥ 50 mg daily (1763.3 patient-years of exposure (PYE)) including 1011 subjects (133 of whom were adolescents) with ≥ 12 months (48 weeks) of exposure. In the 120-day safety update, 1523 subjects were reported as exposed to a ritlecitinib does of ≥ 50 mg daily (1981.4 PYE) including 1048 subjects with ≥ 12 months (48 weeks) of exposure .

In the PCPAA pool, of the 345 subjects exposed to a ritlecitinib does of ≥ 50 mg daily (154.4 PYE), 327 (95%) subjects received treatment for ≥ 16 weeks.

The demographics of the safety population were similar to the ITT population and was comparable across treatment groups. For subjects in the PCPAA pool, the median age was 33.0 years (age groups included 88.1% adults, 11.9% adolescents, and 2.5% were≥ 65 years of age). Most subjects were female (63.6%), white (70.7%).

Exposure in Adolescent Subjects
Adolescent subjects were included in 2 of the 5 clinical trials in the AA development program. Trial B7981015 enrolled 98 adolescent subjects. Trial 7981032 included 73 rollover and 72 de novo adolescent subjects.

The AEP All 50 mg dose group included 172 adolescent subjects exposed to a ritlecitinib dose of ≥ 50 mg daily; 133/172 adolescent subjects were exposed for ≥ 12 months (48 weeks).

Refer to the tabular summary of the baseline characteristics for the ITT population in the review of efficacy (Sec. 8) of this review.

Adequacy of the safety database:

The total subject exposure to ritlecitinib capsule, 50 mg once daily for the treatment of AA (b) (4) 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 one year (48 weeks) are sufficient to characterize the safety of the product over longer treatment periods. Safety assessments were reasonable and consistent with known adverse events for Janus Kinase inhibitor class of products.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of data submitted is adequate to characterize the safety and efficacy of oral ritlecitinib capsule, 50 mg daily for the treatment of subjects ≥ 12 years of age with AA (b) (4) The review team discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

An Adverse Event (AE) was defined as any untoward medical occurrence, including illness, sign, symptoms, clinically significant laboratory abnormalities, or disease temporally associated with the use of the drug, in a subject administered the drug product. AEs did not necessarily have a causal relationship to the study drug.

AEs were recorded from the time of signing the informed consent to the last study visit, and followed up by the investigators until the AE or its sequelae resolve or stabilize. Treatment Emergent Adverse Events (TEAEs) were AEs that occurred after the first administration of the study drug.

The investigators categorized AEs by system-organ-class (SOC) and preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. The Applicant assessed TEAEs by the number of subjects reporting one or more adverse events. Each subject reporting a TEAE was counted once at each level of MedDRA summarization (PT or SOC). Both verbatim terms and preferred terms were included in the data files for trials. There was good correlation between the verbatim and preferred terms used. The investigators categorized AEs for seriousness, causality, event name (diagnosis/signs and symptoms), duration, maximum intensity (severity), action taken regarding the study drug (including any treatment given), and outcome of AEs.

Serious Adverse Events (SAEs) were any AE that resulted in death, was immediately life-threatening, required (or prolonged) hospitalization, resulted in persistent disability or incapacity, resulted in a congenital anomaly or birth defect, or a medically important event that may have required medical or surgical intervention to prevent one of the outcomes listed above. SAEs were reported from the time of signing the informed consent to 35 days after the last does of study drug.

Severity of AEs were assessed by investigators as mild (does not interfere with subject's usual function), moderate (interferes to some extent with subject's usual function), or severe (interferes significantly with subject's usual function).

Causality of AEs (relationship to study drug assessed by investigators as probably related, possibly related, or unrelated) were based on a reasonable temporal sequence from study drug administration, whether the AE could be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies; and whether the AE followed a known pattern of response to the study drug, disappeared or decreased on cessation or reduction in dose and/or reappeared or worsened upon re-challenge with the study drug.

Adverse Events of Special Interest (AESIs) were prespecified and adjudicated by blinded, external, independent adjudication committees for AESIs of opportunistic infections (OI), malignancies, cardiovascular AEs (MACE, thromboembolic AEs), neurological and audiological AEs of interest.

The Applicant's assessment of AEs conducted for trials in the AA development program appears reasonable and appropriate. The Applicant reported accurate definitions of TEAEs, SAEs, and severity of AEs.

Routine Clinical Tests

The trial safety assessments included clinical evaluation of AEs, SAEs, AEs leading to discontinuation (AELDs), vital signs, height and weight measurements, physical examinations, clinical laboratory evaluation (chemistry, fasting lipid panel, hematology, and urinalysis), 12-lead electrocardiograms (ECGs), audiological evaluations, pregnancy testing, HBV DNA (for subjects testing positive at screening for hepatitis B core antibody (HBcAb) if applicable to country, psychiatric assessments (using the Columbia Suicide Severity Rating Scale (C-SSRS), HADS, SF36v2 Acute, EQ-5D-5l/Y forms).

Subjects received pre-treatment screening evaluations for HIV, hepatitis B/C, VZV IgG Ab, tuberculosis (TB) and chest radiography. Subjects considered at high-risk for acquiring TB or reactivation of latent TB were monitored according to local guidelines.

8.2.4. Safety Results

Deaths

No deaths were reported in the PCPAA, PCPAAV, and OYEP safety pools (up to week 48). Two subjects died during the LTS study B7981032 (Subject IDs: B7981032/(b) (6) and B7981032(b) (6)) and were reported in the AEP:

1. Subject B7981032/(b) (6) SAE of breast cancer (spindle cell carcinoma)

A 64-year-old Asian female subject treated with 200/50 mg dose was reported with a SAE of breast cancer (diagnosed by a routine mammogram and confirmed on biopsy of the right

breast) on study Day 90 and led to discontinuation from study. She was treated with lumpectomy, mastectomy and chemotherapy. The investigator and sponsor assessed this SAE as unrelated to study drug. Subject died due to breast cancer approximately 8 months after discontinuation from the study. This SAE was reviewed by an external Malignancy Adjudication Committee and was determined to meet criteria for breast cancer, and by an external Cardiovascular Event Adjudication Committee and was determined to meet criteria for non-cardiovascular death (due to cancer).

2. Subject B7981032 (b) (6) SAEs of acute respiratory failure and cardiorespiratory arrest.

A 51-year-old female subject from Chile with history of asthma and smoking was enrolled in Trial B7981015 and treated with ritlecitinib 10 mg daily for 337 days, followed by roll-over into LTS study B7981032 and treatment with ritlecitinib 50 mg daily for 233 days. On Day 234, subject was found unresponsive and transported to the emergency department and pronounced dead. An autopsy was not performed. The investigator and sponsor assessed these SAEs as unrelated to study drug. The SAEs were reviewed by an external Cardiovascular Event Adjudication Committee and was determined to meet criteria for sudden cardiac death.

Serious Adverse Events

PCPAA

The highest frequency of SAEs was reported in the SOC of Infections and Infestations. No PTs for an SAE was reported in > 1 subject in any group. Three (3) SAEs led to discontinuation from study (eczema (10 mg group), invasive lobular breast carcinoma (200/50 mg group), and sepsis (200/50 mg group). More SAEs were reported in the 200/50 mg group compared to 50/50 mg group as summarized in the following table.

Summary of Serious TEAEs- PCPAA

System Organ Class - Preferred Term	Placebo (N=213) n (%)	Ritlecitinib 10 mg (N=62) n (%)	Ritlecitinib 200/30 mg (N=129) n (%)	Ritlecitinib 200/50 mg (N=215) n (%)	Ritlecitinib 30/30 mg (N=132) n (%)	Ritlecitinib 50/50 mg (N=130) n (%)
Subjects with any SAE	**4 (1.9)**	**2 (3.2)**	**0**	**4 (1.9)**	**1 (0.8)**	**0**
Infections and infestations	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.9)**	**1 (0.8)**	**0 (0.0)**
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Diverticulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Empyema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	**1 (0.5)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Humerus fracture	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**	**0 (0.0)**

Invasive lobular breast carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	**1 (0.5)**	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**	**0 (0.0)**
Abortion spontaneous	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Psychiatric disorders	**1 (0.5)**	**1 (1.6)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Conversion disorder	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicidal behaviour	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	**1 (0.5)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Heavy menstrual bleeding	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**1 (1.6)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Eczema	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: M 2.7.4, Table 28. Consistent with clinical reviewer's analysis by OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Ri lecitinib 10 mg" and SAFFL = "Y" (Ritlecitinib 10 mg); TRT01A = "Ritlecitinib 200/30 mg" and SAFFL = "Y" (Ritlecitinib 200/30 mg); TRT01A = "Ritlecitinib 200/50 mg" and SAFFL = "Y" (Ritlecitinib 200/50 mg); TRT01A = "Ri lecitinib 30/30 mg" and SAFFL = "Y" (Ritlecitinib 30/30 mg); TRT01A = "Ritleci inib 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); TRTEMFL = "Y" and AESER = "Y" (Adverse Events).

Narratives for SAEs in the PCPAA pool

- Treatment Group: Ritlecitinib 200/50 mg QD
  - Subject ID: B7981015 (b) (6) SAE of invasive lobular breast carcinoma

A 46-year-old white female subject from Australia with history of smoking and alcohol use diagnosed with SAE of left breast cancer on study Day 68 which led to discontinuation of study drug. Subject underwent bilateral mastectomy, superficial cavity shave, breast conserving surgery, and sentinel lymph node biopsy, treated with tamoxifen, and discontinued from the study on study Day 114. The investigator and sponsor considered SAE as not related to the study drug. This SAE was reviewed by an external Malignancy Adjudication Committee and was determined to meet criteria for breast cancer.

  - ,Subject ID: B7981015 (b) (6) SAEs of sepsis and empyema

A 64-year-old Asian male subject from Canada with no smoking history normal hematologic parameters at baseline was reported with a severe (nonserious) AE of viral pneumonia (without pleural effusion) on study Day 45 which led to discontinuation of study drug on study Day 48 and was considered by the investigator as related to study drug. On study Day 50, subject was hospitalized with progressive respiratory symptoms and fever and reported with SAEs of left sided empyema and sepsis. A CT scan showed massive loculated left pleural effusion. Chest tube was inserted and drained 300 mL of fluid which led to a (+) culture for multiple bacterial species. Subject was also treated with antithrombotic agents (tissue plasminogen activator), IV piperacillin/tazobactam, and sodium chloride. A nonserious AE of hyponatraemia with possible SIADH related to pulmonary infection was reported as resolved on Day 60.
On study Day 63, the SAE of sepsis was considered resolved and subject was discharged home. The SAE of empyema, and AE of pneumonia viral was reported as resolved on study Day 73. Subject was discontinued from study on study Day 113 due to the SAE of sepsis. The

Investigator and the sponsor considered the SAEs of empyema and sepsis as related to the study drug based on the compatible temporal association and a possible increased susceptibility to
infection associated with the mechanism of action of the study drug.
The SAEs of sepsis and empyema were reviewed by an external Opportunistic Infections Adjudication Committee and was determined not to meet criteria for an opportunistic infection.

- Subject ID: B7981015 (b) (6) SAE of Appendicitis

A 31-year-old white male subject from Chile hospitalized on study Day 173 for abdominal pain, abnormal abdominal ultrasound, and a diagnosis of acute appendicitis. Study drug was interrupted and emergency appendectomy was performed. Subject discharged from hospital and SAE reported as resolved on Day 174. Subject resumed study drug on Day 175. The Investigator and the sponsor considered the SAE as unrelated to the study drug.
The SAE of acute appendicitis was reviewed by an external Opportunistic Infections Adjudication Committee and was determined not to meet criteria for an opportunistic infection.
Subject completed Trial B7981015 on Day 333 and enrolled in the LTS Study B7981032.

- Subject ID: B7981015 (b) (6) SAE of abortion spontaneous

A 30-year-old Asian female subject from China was reported with a nonserious AE of pregnancy on study Day 172 which led to treatment discontinuation with the study drug (estimated date of conception on study Day 156). On Day 156, subject was not abstinent and did not use contraceptive methods as required and received levonorgestrel for emergency contraception on study Day 157. Gestation was first trimester at the time of initial exposure to study drug. A SAE of "abortion spontaneous" was reported on study Day 198, and subject was discontinued from study on study Day 200 due to pregnancy. The Investigator and the sponsor considered the SAE of "abortion spontaneous" as unrelated to the study drug (abortion was considered as elective abortion- related to emergency contraception).

- Treatment Group: Ritlecitinib 30/30 mg QD
  - Subject ID: B7981015 (b) (6) SAE of diverticulitis

A 57-year-old white female subject from Germany diagnosed with diverticulitis on Day 46 and continued to receive study drug. On Day 56, subject reported diarrhea, abdominal pain, emesis, and fever and hospitalized with diagnosis of diverticulitis and treated with oral metronidazole and IV piperacillin sodium/ tazobactam sodium. Study drug was interrupted on Day 57. Colonoscopy on Day 61 confirmed the diagnosis of idiopathic diverticulitis and ruled out infectious colitis. On Day 64, the SAE was reported as resolved and subject discharged home. The Investigator and the sponsor considered the SAE as unrelated to the study drug. This SAE was reviewed by an external Opportunistic Infections Adjudication Committee and was determined not to meet criteria for an opportunistic infection. Subject completed Trial B7981015 on Day 336 and enrolled in the LTS Study B7981032.

- Treatment Group: Ritlecitinib 10 mg QD
    - Subject ID: B7981015 (b) (6) SAE of suicidal behavior

A 17-year-old white female subject from the United States with history of ADHD, anxiety, and depression (no suicidal ideation or behavior (SIB) on her C-SSRS at screening or baseline visits) was reported on Day 123 with a SAE of SIB following treatment at an emergency department for taking 40 mg of fluoxetine hydrochloride and 25 mg of hydroxyzine. Subject was evaluated by a psychotherapist, who confirmed the diagnosis of suicidal gesture. Subject received several psychotherapy sessions and discharged with no changes in her C-SSRS responses throughout trial. The SAE of SIB was reported as resolved on Day 123. The Investigator and the sponsor considered the SAE of SIB as unrelated to the study drug (related to history of depression). Subject continued treatment with the study drug to Day 295 and was discontinued from the study on Day 350 due to Physician's decision.

    - Subject ID: B7981015 (b) (6) SAE of eczema

A 16-year-old Black/African American female subject from the United States with history of atopic dermatitis, alopecia areata, and asthma reported a new onset painful and pruritic rash on Day 147. Study drug was discontinued on Day 148 due to the SAE of eczema and skin infection, and subject was hospitalized on Day 149 for further evaluation of vesiculobullous eruption on the face, trunk, and extremities. Skin biopsy showed spongiotic dermatitis. Viral cultures were (-) for HSV/VZV, bacterial culture was (+) for *Staphylococcus aureus* resistant to Penicillin. Subject was treated with steroids, intravenous acyclovir, and oral doxycycline and discharged home on Day 151. The SAE of eczema and AE of skin infection were reported as resolved on Day 172. On Day 174, a dermatologist assessed rash as "positive Staph overgrowth. Favor staph superinfected exacerbation of underlying atopic dermatitis independent of or as a side effect of the experimental drug, cannot rule out eczematous drug eruption- experimental drug". Subject was discontinued from the study on Day 202 due to SAE of eczema. The Investigator considered the SAE of eczema and AE of skin infection as related to the study drug. Based on temporal association, the sponsor concurred with the Investigator's assessment, and reported the SAE as related to subject's underlying atopic dermatitis with a possibility of a *Staphylococcus aureus* superinfection.

PCPAAV

In addition to the SAEs reported for subjects in the PCPAA pool, the following 4 additional subjects (in the vitiligo trial B7981019, included in the PCPAAV pool) were reported with SAEs:

- Treatment Group: Ritlecitinib 10 mg QD
    - Subject ID: B7981019 (b) (6) SAE of Migraine

A 48-year-old male subject of an unknown race with history of headaches, dyslipidemia, and coronary artery disease was evaluated at the emergency department with worsening of intermittent headaches on Day 56 and hospitalized for a SAE of migraine on Day 57. Study drug was discontinued on Day 55. Subject was evaluated by a neurologist and imaging studies, received treatment for migraine, and discharged home on Day 59. The investigator empirically

diagnosed left forehead pain/numbness as herpes zoster on Study Day 60 and treated subject with valacyclovir. However, the investigator later ruled our herpes Zoster based on negative viral tests at baseline and Days 56, 91 and reported SAE as migraine, reported resolved on Day 91. Subject declined follow-up with neurologist. The Investigator and the sponsor considered the SAE as unrelated to study drug.

- Treatment Group: Ritlecitinib 50/50 mg QD
  - Subject ID: B7981019 (b) (6) SAE of Migraine

A 31-year-old white female with history of migraine hospitalized and was treated for SAE of migraine on Day 43. Study drug was continued and SAE resolved on Day 43. The Investigator and the sponsor considered the SAE as unrelated to study drug.

- Treatment Group: Ritlecitinib 30/30 mg QD
  - Subject ID: B7981019 (b) (6) SAE of esophageal spasm

A 53-year-old white female subject with surgical history of gastric banding was evaluated at the emergency department for chest pain on Day 135 and diagnosed with SAE of esophageal spasm after cardiac and pulmonary chest pain was ruled out. Study drug was interrupted for 1 day and was resumed at hospital discharge on Day 136. The Investigator assessed the SAE of esophageal spasm (secondary to gastric band device associated complication) as not related to study drug.

- Treatment Group: placebo
  - Subject ID: B7981019 (b) (6) SAE of neurogenic bladder

OYEP

OYEP included safety data from weeks 0-48 of trial B7981015. The proportion of subjects reported with SAEs in OYEP for the All 50 mg group (6/261= 2.3%) and All 30 mg group (3/261= 1.1%) was similar to those reported for the PCPAA and PCPAAV pools. SAEs from weeks 0-24 of OYEP were included in the PCPAA pool. The following narratives include 4 additional SAEs reported during weeks 24-48 of OYEP:

- Treatment Group: Ritlecitinib 50/50 mg QD
  - Subject ID: B7981015 (b) (6) SAE of Breast cancer

A 58-year-old white female subject from the Great Britain with history of smoking, alcohol use, and unknown family history noted a left breast mass on Day 195 and underwent ultrasound guided biopsy on Day 205 which showed invasive Grade 2 carcinoma. Study drug was discontinued on Day 209 and was she was treated with chemotherapy. Subject discontinued from study on Day 281 due to SAE of breast cancer and underwent mastectomy on Day 391.
The SAE of breast cancer was reported as resolved on Day 566.
The Investigator considered the SAE of breast cancer as related to the study drug. The sponsor considered the SAE of breast cancer as not related to the study drug, with the underlying relevant risk factors of gender, advanced age, having no children, and alcoholism. The SAE of breast cancer was reviewed by an

external Malignancy Adjudication Committee and was determined to meet criteria for breast cancer.

- Subject ID: B7981015 (b) (6) SAE of Pulmonary embolism

A 54-year-old (weight: 118 kg; BMI: 46.09 kg/m2) white female subject from Spain with history of Monoclonal gammopathy of undetermined significance (MGUS), morbid obesity, sleep apnea syndrome, hypertension and hyperlipidemia. Subject had an AE of SARS-CoV-2 test positive and upper respiratory infection on Day 60, resolved on Day 86.
Subject was evaluated at an emergency department on Day 169 for right leg pain, lateral right chest pain for 24 hours, left rib pain without respiratory failure or hypoxemia. On Day 170, an axial CT of pulmonary arteries revealed acute bilateral pulmonary embolism. Subject was discontinued from study drug treatment and from trial on Day 170. SAE of pulmonary embolism was resolved on Day 178 and she was discharged home. The investigator considered the SAE as not related to study drug. The sponsor considered the SAE as related to the study drug, with subject's underlying medical history of MGUS, morbid obesity, and cardiovascular disease as confounding factors. The SAE of pulmonary embolism was reviewed by an external Cardiovascular Event Adjudication Committee and was determined to meet criteria for cardiovascular event of pulmonary embolism.

- Treatment Group: Ritlecitinib 200/30 mg QD

- B7981015 (b) (6) SAE of Appendicitis

A 13-year-old white female subjects from the US was hospitalized on Day 241 for localized right lower quadrant pain and mild fever. She was treated with intravenous cefoxitin and underwent laparoscopic appendectomy, which confirmed acute appendicitis. she was discharged from hospital on Day 242. Study drug was interrupted on Day 240 and resumed on Day 252. The SAE was reported resolved on Day 261. Per investigator and sponsor, the SAE of appendicitis was not considered related to the study drug. This SAE was reviewed by an external Opportunistic Infections Adjudication Committee and was determined not to meet criteria for an opportunistic infection. Subject completed study treatment on Day 336 and enrolled into the long-term Study B7981032.

- B7981015 (b) (6) SAEs of Chemical poisoning, Suicidal behavior

A 38-year-old Asian female subject from China (with no reported suicidal ideation or behavior on the Columbia Suicide Severity Rating Scale (C-SSRS) at screening or baseline) informed the investigator on Day 296 that she had quarreled with her family and as an emotional impulse, consumed about 50 mL of phosphorus octoate. After gastric lavage in the emergency department, she was hospitalized for SAEs of suicidal behaviour and chemical poisoning (organophosphorus poisoning) which led to permanent discontinuation of study drug and a positive C-SSRS for suicidal behavior on Day 297. She was discharged from hospital on Day 300. The SAE of chemical poisoning, suicidal behaviour, and AE of gastric mucosal lesion were considered resolved on Day 307. her mental status was evaluated on Day 311 and reported as

not clinically abnormal. She was discharged from trial on Day 338 for SAE of suicidal behavior. The investigator and sponsor considered the SAEs of suicidal behavior and chemical poisoning as not related to the study drug.

AEP

The frequency and incidence rate (IR) of SAEs for subjects in Any ritlecitinib group of the AEP was 57/1628 (3.5%, 2.61/100 PYE), and in the All 50 mg group was 50/1521 (3.3%, 2.72/100 PYE); which was comparable to the reported frequency/IR of SAEs in the PCPAA All 50 mg dose group for 4 subjects (1.2%, 2.69/100 PYE), and in the OYEP All 50 mg dose group for 6 subjects (2.3%, 2.60/100 PYE).

The following SAEs by PT were reported in ≥2 subjects in Any ritlecitinib dosing group for the AEP: appendicitis (5), breast cancer and invasive lobular breast carcinoma (3 and 1, respectively), abortion spontaneous (3), acute respiratory failure (3), COVID-19 (2), COVID-19 pneumonia (2), migraine (2), and suicidal behavior (2).

Refer to the Study B7981032 section of this review for the narratives of SAEs reported during Study B7980132. Narratives for SAEs deemed to be AESIs are included under AESI section of this review.

SAEs reported for the AEP are summarized in the following table:

Summary of SAEs in the AEP (grouped by treatment received during the initial treatment period)

System Organ Class - Preferred Term	Ritlecitinib 10 mg (N=111) n (%)	Ritlecitinib 30 mg (N=311) n (%)	Ritlecitinib 50 mg (N=1206) n (%)
Infections and infestations	**0 (0.0)**	**5 (1.6)**	**9 (0.7)**
Appendicitis	0 (0.0)	2 (0.6)	3 (0.2)
Covid-19	0 (0.0)	0 (0.0)	2 (0.2)
Covid-19 pneumonia	0 (0.0)	1 (0.3)	1 (0.1)
Empyema	0 (0.0)	0 (0.0)	1 (0.1)
Sepsis	0 (0.0)	0 (0.0)	1 (0.1)
Septic shock	0 (0.0)	0 (0.0)	1 (0.1)
Staphylococcal sepsis	0 (0.0)	0 (0.0)	1 (0.1)
Vulval abscess	0 (0.0)	0 (0.0)	1 (0.1)
Diverticulitis	0 (0.0)	1 (0.3)	0 (0.0)
Pyelonephritis	0 (0.0)	1 (0.3)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.9)**	**0 (0.0)**	**7 (0.6)**
Breast cancer	0 (0.0)	0 (0.0)	3 (0.2)
Basal cell carcinoma	0 (0.0)	0 (0.0)	1 (0.1)

Invasive lobular breast carcinoma	0 (0.0)	0 (0.0)	1 (0.1)
Papillary thyroid cancer	0 (0.0)	0 (0.0)	1 (0.1)
Testis cancer	0 (0.0)	0 (0.0)	1 (0.1)
Uterine leiomyoma	1 (0.9)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	**1 (0.9)**	**2 (0.6)**	**3 (0.2)**
Meniscus injury	0 (0.0)	0 (0.0)	1 (0.1)
Tendon rupture	0 (0.0)	0 (0.0)	1 (0.1)
Thermal burn	0 (0.0)	0 (0.0)	1 (0.1)
Chemical poisoning	0 (0.0)	1 (0.3)	0 (0.0)
Joint dislocation	0 (0.0)	1 (0.3)	0 (0.0)
Ligament rupture	0 (0.0)	1 (0.3)	0 (0.0)
Subdural haematoma	1 (0.9)	0 (0.0)	0 (0.0)
Psychiatric disorders	**1 (0.9)**	**1 (0.3)**	**3 (0.2)**
Bipolar disorder	0 (0.0)	0 (0.0)	1 (0.1)
Bipolar i disorder	0 (0.0)	0 (0.0)	1 (0.1)
Delirium	0 (0.0)	0 (0.0)	1 (0.1)
Suicidal ideation	0 (0.0)	0 (0.0)	1 (0.1)
Suicidal behaviour	1 (0.9)	1 (0.3)	0 (0.0)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**1 (0.3)**	**2 (0.2)**
Foot deformity	0 (0.0)	0 (0.0)	1 (0.1)
Intervertebral disc protrusion	0 (0.0)	0 (0.0)	1 (0.1)
Flank pain	0 (0.0)	1 (0.3)	0 (0.0)
Nervous system disorders	**1 (0.9)**	**0 (0.0)**	**2 (0.2)**
Bell's palsy	0 (0.0)	0 (0.0)	1 (0.1)
Migraine	1 (0.9)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	**1 (0.9)**	**1 (0.3)**	**2 (0.2)**
Acute respiratory failure	1 (0.9)	1 (0.3)	1 (0.1)
Pulmonary embolism	0 (0.0)	0 (0.0)	1 (0.1)
Vascular disorders	**0 (0.0)**	**1 (0.3)**	**2 (0.2)**
Takayasu's arteritis	0 (0.0)	0 (0.0)	1 (0.1)
Varicose vein	0 (0.0)	0 (0.0)	1 (0.1)
Aortic aneurysm	0 (0.0)	1 (0.3)	0 (0.0)
Cardiac disorders	**1 (0.9)**	**0 (0.0)**	**1 (0.1)**
Acute myocardial infarction	0 (0.0)	0 (0.0)	1 (0.1)
Cardio-respiratory arrest	1 (0.9)	0 (0.0)	0 (0.0)
Eye disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**
Retinal artery occlusion	0 (0.0)	0 (0.0)	1 (0.1)
Gastrointestinal disorders	**0 (0.0)**	**1 (0.3)**	**1 (0.1)**
Ileus	0 (0.0)	0 (0.0)	1 (0.1)

Oesophageal spasm	0 (0.0)	1 (0.3)	0 (0.0)
General disorders and administration site conditions	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**
Cyst rupture	0 (0.0)	0 (0.0)	1 (0.1)
Hepatobiliary disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**
Cholelithiasis	0 (0.0)	0 (0.0)	1 (0.1)
Immune system disorders	**0 (0.0)**	**1 (0.3)**	**1 (0.1)**
Hypersensitivity	0 (0.0)	0 (0.0)	1 (0.1)
Anaphylactic reaction	0 (0.0)	1 (0.3)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	**1 (0.9)**	**1 (0.3)**	**1 (0.1)**
Abortion spontaneous	1 (0.9)	1 (0.3)	1 (0.1)
Renal and urinary disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**
Calculus urinary	0 (0.0)	0 (0.0)	1 (0.1)
Reproductive system and breast disorders	**0 (0.0)**	**1 (0.3)**	**1 (0.1)**
Cervical dysplasia	0 (0.0)	0 (0.0)	1 (0.1)
Cervical polyp	0 (0.0)	1 (0.3)	0 (0.0)
Skin and subcutaneous tissue disorders	**1 (0.9)**	**0 (0.0)**	**0 (0.0)**
Eczema	1 (0.9)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Ritlecitinib 10 mg" and SAFFL = "Y" (Ri lecitinib 10 mg); TRT01A = "Ritlecitinib 30 mg" and SAFFL = "Y" (Ritlecitinib 30 mg); TRT01A = "Ri lecitinib 50 mg" and SAFFL = "Y" (Ritlecitinib 50 mg); TRTEMFL = "Y" and AESER = "Y" (Adverse Events).

Refer to the Study B7981032 section of this review for a summary of SAEs reported during the LTS study.

Dropouts and/or Discontinuations Due to Adverse Effects

PCPAA

The proportion of subjects with AEs leading to discontinuation (AELD) from study or study drug was similar across the ritlecitinib and placebo groups. Urticaria was the only AELD reported in > 1 subject. Number (%) of subjects with any AELDs were 5 (2.3%) in the placebo group, 2 (3.2%) in Ritlecitinib 10 mg group, 4 (1.5%) in the All 30 mg dose group, 6 (2.8%) in the Ritlecitinib 200/50 mg group, 2 (1.5%) in Ritlecitinib 50/50 mg group, and 8 (2.3%) in the All 50 mg group.

Summary of Subjects with TEAEs Leading to Discontinuation (AELDs)- PCPAA

System Organ Class - Preferred Term	Placebo (N=213) n (%)	Ritlecitinib 10 mg (N=62) n (%)	Ritlecitinib 200/30 mg (N=129) n (%)	Ritlecitinib 200/50 mg (N=215) n (%)	Ritlecitinib 30/30 mg (N=132) n (%)	Ritlecitinib 50/50 mg (N=130) n (%)
Number of subjects with AE	**5 (2.3)**	**2 (3.2)**	**0 (0.0)**	**6 (2.8)**	**4 (3.0)**	**2 (1.5)**
Skin and subcutaneous tissue disorders	**1 (0.5)**	**1 (1.6)**	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**	**2 (1.5)**

Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)
Angioedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Alopecia areata	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eczema	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	**1 (0.5)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Sinus tachycardia	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	**1 (0.5)**	**1 (1.6)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Deafness neurosensory	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear discomfort	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.8)**	**0 (0.0)**
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
General disorders and administration site conditions	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**1 (0.8)**	**0 (0.0)**
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Infections and infestations	**0 (0.0)**	**1 (1.6)**	**0 (0.0)**	**1 (0.5)**	**1 (0.8)**	**0 (0.0)**
Pneumonia viral	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Skin infection	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**2 (1.5)**	**0 (0.0)**
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Blood pressure increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Platelet count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**	**0 (0.0)**
Invasive lobular breast carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Nervous system disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**2 (1.5)**	**0 (0.0)**
Headache	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.8)	0 (0.0)
Hypoaesthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	**1 (0.5)**	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**	**0 (0.0)**
Pregnancy	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Renal and urinary disorders	**1 (0.5)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Nephrolithiasis	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: M 2.7.4, Table 31 and M 5.3.5.3 scs-pcpaa-supportingTable PCPAA.14.3.1.2.4.1 .
Consistent with clinical reviewer's analysis by OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Ri lecitinib 10 mg" and SAFFL = "Y" (Ritlecitinib 10 mg); TRT01A = "Ritlecitinib 200/30 mg" and SAFFL = "Y" (Ritlecitinib 200/30 mg); TRT01A = "Ritlecitinib 200/50 mg" and SAFFL = "Y" (Ritlecitinib 200/50 mg); TRT01A = "Ritlecitinib 30/30 mg" and SAFFL = "Y" (Ritlecitinib 30/30 mg); TRT01A = "Ritlecitinib 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); TRTEMFL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

In the PCAAV pool, additional AELDs reported in ≥2 subjects by PT included Blood creatine

phosphokinase increased (2) and Urticaria (4).

AEP

Most frequent AELDs were in the SOC of Investigations. Most frequent AELDs in the All 50 mg group were reported for the following PTs: pregnancy (9, 0.6%), urticaria (6, 0.4%), and blood creatinine phosphokinase increased (4, 0.3%).

Summary of AELDs in AEP (grouped by treatment received during the initial treatment period)

System Organ Class - Preferred Term	Ritlecitinib 10 mg (N=111) n (%)	Ritlecitinib 30 mg (N=311) n (%)	Ritlecitinib 50 mg (N=1206) n (%)
Investigations	**1 (0.9)**	**5 (1.6)**	**15 (1.2)**
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	3 (0.2)
Blood creatine phosphokinase increased	0 (0.0)	1 (0.3)	3 (0.2)
Lymphocyte count decreased	0 (0.0)	0 (0.0)	3 (0.2)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	2 (0.2)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	1 (0.1)
Interferon gamma release assay	0 (0.0)	0 (0.0)	1 (0.1)
Liver function test increased	0 (0.0)	1 (0.3)	1 (0.1)
Sars-cov-2 test positive	0 (0.0)	1 (0.3)	1 (0.1)
Transaminases increased	1 (0.9)	0 (0.0)	1 (0.1)
Blood pressure increased	0 (0.0)	1 (0.3)	0 (0.0)
Platelet count decreased	0 (0.0)	1 (0.3)	0 (0.0)
Skin and subcutaneous tissue disorders	**1 (0.9)**	**2 (0.6)**	**10 (0.8)**
Urticaria	0 (0.0)	1 (0.3)	6 (0.5)
Rash	0 (0.0)	0 (0.0)	2 (0.2)
Acne	0 (0.0)	0 (0.0)	1 (0.1)
Angioedema	0 (0.0)	0 (0.0)	1 (0.1)
Eczema	1 (0.9)	1 (0.3)	0 (0.0)
Infections and infestations	**1 (0.9)**	**3 (1.0)**	**6 (0.5)**
Covid-19	0 (0.0)	0 (0.0)	1 (0.1)
Covid-19 pneumonia	0 (0.0)	1 (0.3)	1 (0.1)
Herpes zoster	0 (0.0)	0 (0.0)	1 (0.1)
Latent tuberculosis	0 (0.0)	0 (0.0)	1 (0.1)
Pneumonia viral	0 (0.0)	0 (0.0)	1 (0.1)
Staphylococcal sepsis	0 (0.0)	0 (0.0)	1 (0.1)
Nasopharyngitis	0 (0.0)	1 (0.3)	0 (0.0)
Pyelonephritis	0 (0.0)	1 (0.3)	0 (0.0)
Skin infection	1 (0.9)	0 (0.0)	0 (0.0)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0.0)**	**0 (0.0)**	**6 (0.5)**
Breast cancer	0 (0.0)	0 (0.0)	3 (0.2)
Invasive lobular breast carcinoma	0 (0.0)	0 (0.0)	1 (0.1)
Papillary thyroid cancer	0 (0.0)	0 (0.0)	1 (0.1)
Testis cancer	0 (0.0)	0 (0.0)	1 (0.1)
Nervous system disorders	**2 (1.8)**	**4 (1.3)**	**6 (0.5)**
Dizziness	0 (0.0)	0 (0.0)	3 (0.2)
Headache	0 (0.0)	2 (0.6)	2 (0.2)
Myoclonus	0 (0.0)	0 (0.0)	1 (0.1)
Neuropathy peripheral	0 (0.0)	0 (0.0)	1 (0.1)
Paraesthesia	0 (0.0)	0 (0.0)	1 (0.1)
Dysaesthesia	0 (0.0)	1 (0.3)	0 (0.0)
Hypoaesthesia	0 (0.0)	1 (0.3)	0 (0.0)
Mental impairment	1 (0.9)	0 (0.0)	0 (0.0)
Migraine	1 (0.9)	0 (0.0)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	**1 (0.9)**	**3 (1.0)**	**6 (0.5)**
Pregnancy	1 (0.9)	3 (1.0)	6 (0.5)
Abortion spontaneous	0 (0.0)	1 (0.3)	0 (0.0)
Blood and lymphatic system disorders	**0 (0.0)**	**1 (0.3)**	**3 (0.2)**
Anaemia	0 (0.0)	1 (0.3)	1 (0.1)
Neutropenia	0 (0.0)	1 (0.3)	1 (0.1)
Thrombocytopenia	0 (0.0)	1 (0.3)	1 (0.1)
Leukopenia	0 (0.0)	1 (0.3)	0 (0.0)
Lymphopenia	0 (0.0)	1 (0.3)	0 (0.0)
Gastrointestinal disorders	**0 (0.0)**	**2 (0.6)**	**3 (0.2)**
Crohn's disease	0 (0.0)	0 (0.0)	1 (0.1)
Diarrhoea	0 (0.0)	2 (0.6)	1 (0.1)
Nausea	0 (0.0)	0 (0.0)	1 (0.1)
Vomiting	0 (0.0)	0 (0.0)	1 (0.1)
General disorders and administration site conditions	**0 (0.0)**	**1 (0.3)**	**3 (0.2)**
Asthenia	0 (0.0)	1 (0.3)	1 (0.1)
Fatigue	0 (0.0)	0 (0.0)	1 (0.1)
Pyrexia	0 (0.0)	0 (0.0)	1 (0.1)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**1 (0.3)**	**2 (0.2)**
Muscle spasms	0 (0.0)	0 (0.0)	1 (0.1)
Spinal ligament ossification	0 (0.0)	0 (0.0)	1 (0.1)
Myalgia	0 (0.0)	1 (0.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**1 (0.3)**	**2 (0.2)**

Acute respiratory failure	0 (0.0)	1 (0.3)	1 (0.1)
Pulmonary embolism	0 (0.0)	0 (0.0)	1 (0.1)
Congenital, familial and genetic disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**
Atrial septal defect	0 (0.0)	0 (0.0)	1 (0.1)
Eye disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**
Vision blurred	0 (0.0)	0 (0.0)	1 (0.1)
Immune system disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**
Hypersensitivity	0 (0.0)	0 (0.0)	1 (0.1)
Psychiatric disorders	**0 (0.0)**	**1 (0.3)**	**1 (0.1)**
Bipolar i disorder	0 (0.0)	0 (0.0)	1 (0.1)
Suicidal behaviour	0 (0.0)	1 (0.3)	0 (0.0)
Reproductive system and breast disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**
Prostatitis	0 (0.0)	0 (0.0)	1 (0.1)
Vascular disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**
Takayasu's arteritis	0 (0.0)	0 (0.0)	1 (0.1)
Ear and labyrinth disorders	**3 (2.7)**	**1 (0.3)**	**0 (0.0)**
Deafness	0 (0.0)	1 (0.3)	0 (0.0)
Deafness neurosensory	1 (0.9)	0 (0.0)	0 (0.0)
Deafness unilateral	1 (0.9)	0 (0.0)	0 (0.0)
Ear discomfort	1 (0.9)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**
Chemical poisoning	0 (0.0)	1 (0.3)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer. Consistent with M 2.7.4, Table 31.

Filters: TRT01A = "Ritlecitinib 10 mg" and SAFFL = "Y" (Ri lecitinib 10 mg); TRT01A = "Ritlecitinib 30 mg" and SAFFL = "Y" (Ritlecitinib 30 mg); TRT01A = "Ri lecitinib 50 mg" and SAFFL = "Y" (Ritlecitinib 50 mg); TRTEMFL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

Refer to the Study B7981032 section of this review for a summary of AELDs reported during the LTS study.

Significant Adverse Events

Significant AEs included adverse events of special interest (AESIs) and AEs for which a significant imbalance between the active treatment arms and the placebo arm was observed.

Treatment Emergent Adverse Events and Adverse Reactions

PCPAA

In general, the proportion of subjects reported with TEAEs, severe AEs, and treatment-related (per sponsor) AEs was similar across the ritlecitinib dose groups and placebo group in the PCPAA pool during weeks 0-24, as summarized in the following Table:

Table- TEAEs by overall frequency and severity – PCPAA pool:

Treatment dose group	Ritlecitinib 200/50 mg QD (N=215) n (%)	Ritlecitinib 50/50 mg QD (N=130) n (%)	Ritlecitinib All 50 mg QD (N=345) n (%)	Ritlecitinib 30 mg QD (N=261) n (%)	Ritlecitinib 10 mg QD (N=62) n (%)	Placebo QD (N=213) n (%)
Number of TEAEs	404	243	647	513	113	370
Number of subjects with TEAE	151 (70.2)	98 (75.4)	249 (72.2)	186 (71.3)	43 (69.4)	148 (69.5)
Number of subjects with severe TEAE	4 (1.9)	2 (1.5)	6 (1.7)	10 (3.8)	2 (3.2)	5 (2.3)
Number of subjects with treatment-related TEAEs	71 (33.0)	47 (36.2)	118 (34.2)	91 (34.9)	19 (30.6)	68 (31.9)

Source: M 2.7.4, Tables 21 and 25; and M 5.3.5.3 AA PCPAA.14.3.1.1.2. Consistent with clinical reviewer's JMP Clinical 8.0 analysis.

Most TEAEs were mild or moderate in severity and no PT was reported as a severe AE in > 1 subject.

The most frequent (in ≥2% of subjects in any treatment group) TEAEs by PT reported at a greater frequency in any ritlecitinib group than placebo group, and with a dose-related increase in frequency were diarrhea, acne, urticaria, rash, dizziness, and blood creatine phosphokinase (CK) increased. An apparent dose-dependent increase in frequency of TEAE for herpes zoster (HZ) was also reported at 2 (1.6%) in the Ritlecitinib 200/30 mg and 2 (1.5%) in the Ritlecitinib 50/50 mg groups) and will be discussed further in a later section of this review. The following table summarizes TEAEs reported at a frequency ≥2% (sorted in decreasing frequency in the 50/50 mg group):

Summary of TEAEs frequency (≥2% in any group) and higher than placebo- PCPAA (Weeks 0-24)

System Organ Class - Preferred Term	Placebo (N=213) n (%)	Ritlecitinib 10 mg (N=62) n (%)	Ritlecitinib 200/30 mg (N=129) n (%)	Ritlecitinib 200/50 mg (N=215) n (%)	Ritlecitinib 30/30 mg (N=132) n (%)	Ritlecitinib 50/50 mg (N=130) n (%)
Infections and infestations	**66 (31.0)**	**20 (32.3)**	**48 (37.2)**	**88 (40.9)**	**48 (36.4)**	**43 (33.1)**
Nasopharyngitis	15 (7.0)	6 (9.7)	18 (14.0)	21 (9.8)	16 (12.1)	13 (10.0)
Upper respiratory tract infection	16 (7.5)	2 (3.2)	10 (7.8)	21 (9.8)	11 (8.3)	8 (6.2)
Folliculitis	4 (1.9)	2 (3.2)	8 (6.2)	12 (5.6)	3 (2.3)	4 (3.1)
Covid-19	2 (0.9)	0 (0.0)	0 (0.0)	1 (0.5)	2 (1.5)	3 (2.3)
Gastroenteritis	0 (0.0)	2 (3.2)	3 (2.3)	3 (1.4)	0 (0.0)	2 (1.5)
Herpes simplex	4 (1.9)	1 (1.6)	2 (1.6)	0 (0.0)	3 (2.3)	2 (1.5)
Influenza	3 (1.4)	2 (3.2)	0 (0.0)	6 (2.8)	1 (0.8)	2 (1.5)
Viral upper respiratory tract infection	3 (1.4)	1 (1.6)	2 (1.6)	4 (1.9)	3 (2.3)	1 (0.8)
Laryngitis	1 (0.5)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngitis	1 (0.5)	0 (0.0)	3 (2.3)	1 (0.5)	0 (0.0)	0 (0.0)

Rhinitis	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.3)	0 (0.0)
Urinary tract infection	6 (2.8)	0 (0.0)	2 (1.6)	8 (3.7)	5 (3.8)	0 (0.0)
Gastrointestinal disorders	**40 (18.8)**	**10 (16.1)**	**20 (15.5)**	**38 (17.7)**	**26 (19.7)**	**30 (23.1)**
Diarrhoea	8 (3.8)	0 (0.0)	4 (3.1)	14 (6.5)	6 (4.5)	12 (9.2)
Abdominal pain upper	2 (0.9)	0 (0.0)	3 (2.3)	1 (0.5)	2 (1.5)	4 (3.1)
Nausea	15 (7.0)	3 (4.8)	2 (1.6)	12 (5.6)	10 (7.6)	3 (2.3)
Vomiting	5 (2.3)	0 (0.0)	3 (2.3)	6 (2.8)	3 (2.3)	2 (1.5)
Abdominal discomfort	6 (2.8)	0 (0.0)	2 (1.6)	1 (0.5)	0 (0.0)	1 (0.8)
Constipation	3 (1.4)	0 (0.0)	0 (0.0)	1 (0.5)	5 (3.8)	0 (0.0)
Skin and subcutaneous tissue disorders	**38 (17.8)**	**10 (16.1)**	**27 (20.9)**	**45 (20.9)**	**29 (22.0)**	**28 (21.5)**
Acne	10 (4.7)	3 (4.8)	7 (5.4)	12 (5.6)	7 (5.3)	8 (6.2)
Urticaria	3 (1.4)	1 (1.6)	6 (4.7)	11 (5.1)	4 (3.0)	6 (4.6)
Rash	2 (0.9)	0 (0.0)	3 (2.3)	3 (1.4)	1 (0.8)	5 (3.8)
Dermatitis atopic	1 (0.5)	0 (0.0)	0 (0.0)	5 (2.3)	1 (0.8)	3 (2.3)
Dermatitis acneiform	0 (0.0)	0 (0.0)	4 (3.1)	2 (0.9)	1 (0.8)	1 (0.8)
Pruritus	5 (2.3)	1 (1.6)	6 (4.7)	4 (1.9)	2 (1.5)	1 (0.8)
Dermatitis contact	2 (0.9)	3 (4.8)	0 (0.0)	1 (0.5)	3 (2.3)	0 (0.0)
Nervous system disorders	**29 (13.6)**	**12 (19.4)**	**19 (14.7)**	**40 (18.6)**	**26 (19.7)**	**20 (15.4)**
Headache	17 (8.0)	11 (17.7)	10 (7.8)	20 (9.3)	20 (15.2)	12 (9.2)
Dizziness	3 (1.4)	1 (1.6)	7 (5.4)	11 (5.1)	3 (2.3)	3 (2.3)
Investigations	**14 (6.6)**	**5 (8.1)**	**12 (9.3)**	**21 (9.8)**	**20 (15.2)**	**13 (10.0)**
Sars-cov-2 test positive	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.0)	4 (3.1)
Blood creatine phosphokinase increased	0 (0.0)	2 (3.2)	3 (2.3)	7 (3.3)	3 (2.3)	2 (1.5)
Platelet count decreased	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	3 (2.3)	1 (0.8)
General disorders and administration site conditions	**13 (6.1)**	**3 (4.8)**	**9 (7.0)**	**9 (4.2)**	**17 (12.9)**	**11 (8.5)**
Fatigue	5 (2.3)	2 (3.2)	6 (4.7)	1 (0.5)	6 (4.5)	4 (3.1)
Pyrexia	0 (0.0)	1 (1.6)	0 (0.0)	4 (1.9)	3 (2.3)	4 (3.1)
Respiratory, thoracic and mediastinal disorders	**20 (9.4)**	**5 (8.1)**	**9 (7.0)**	**17 (7.9)**	**9 (6.8)**	**11 (8.5)**
Oropharyngeal pain	6 (2.8)	0 (0.0)	6 (4.7)	3 (1.4)	1 (0.8)	4 (3.1)
Cough	2 (0.9)	0 (0.0)	0 (0.0)	4 (1.9)	3 (2.3)	2 (1.5)
Nasal congestion	3 (1.4)	0 (0.0)	1 (0.8)	2 (0.9)	3 (2.3)	2 (1.5)
Injury, poisoning and procedural complications	**13 (6.1)**	**2 (3.2)**	**9 (7.0)**	**11 (5.1)**	**8 (6.1)**	**10 (7.7)**
Ligament sprain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	3 (2.3)	3 (2.3)
Fall	2 (0.9)	2 (3.2)	1 (0.8)	1 (0.5)	0 (0.0)	2 (1.5)
Musculoskeletal and connective tissue disorders	**21 (9.9)**	**8 (12.9)**	**10 (7.8)**	**20 (9.3)**	**16 (12.1)**	**7 (5.4)**
Back pain	0 (0.0)	2 (3.2)	2 (1.6)	3 (1.4)	2 (1.5)	2 (1.5)
Arthralgia	6 (2.8)	2 (3.2)	3 (2.3)	2 (0.9)	3 (2.3)	1 (0.8)

Myalgia	3 (1.4)	5 (8.1)	1 (0.8)	5 (2.3)	5 (3.8)	1 (0.8)
Reproductive system and breast disorders	**6 (2.8)**	**2 (3.2)**	**5 (3.9)**	**3 (1.4)**	**3 (2.3)**	**5 (3.8)**
Cardiac disorders	**3 (1.4)**	**1 (1.6)**	**2 (1.6)**	**2 (0.9)**	**2 (1.5)**	**3 (2.3)**
Vascular disorders	**1 (0.5)**	**1 (1.6)**	**0 (0.0)**	**3 (1.4)**	**2 (1.5)**	**3 (2.3)**
Blood and lymphatic system disorders	**6 (2.8)**	**1 (1.6)**	**7 (5.4)**	**3 (1.4)**	**1 (0.8)**	**2 (1.5)**
Ear and labyrinth disorders	**10 (4.7)**	**3 (4.8)**	**4 (3.1)**	**10 (4.7)**	**2 (1.5)**	**2 (1.5)**
Tinnitus	2 (0.9)	1 (1.6)	0 (0.0)	6 (2.8)	1 (0.8)	0 (0.0)
Eye disorders	**6 (2.8)**	**2 (3.2)**	**3 (2.3)**	**0 (0.0)**	**2 (1.5)**	**2 (1.5)**
Metabolism and nutrition disorders	**4 (1.9)**	**2 (3.2)**	**4 (3.1)**	**4 (1.9)**	**4 (3.0)**	**2 (1.5)**
Psychiatric disorders	**13 (6.1)**	**2 (3.2)**	**2 (1.6)**	**9 (4.2)**	**4 (3.0)**	**2 (1.5)**
Insomnia	5 (2.3)	1 (1.6)	0 (0.0)	4 (1.9)	0 (0.0)	1 (0.8)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer. Consistent with M 2.7.4, Table 22.

Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Ri lecitinib 10 mg" and SAFFL = "Y" (Ritlecitinib 10 mg); TRT01A = "Ritlecitinib 200/30 mg" and SAFFL = "Y" (Ritlecitinib 200/30 mg); TRT01A = "Ritlecitinib 200/50 mg" and SAFFL = "Y" (Ritlecitinib 200/50 mg); TRT01A = "Ri lecitinib 30/30 mg" and SAFFL = "Y" (Ritlecitinib 30/30 mg); TRT01A = "Ritleci inb 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); TRTEMFL = "Y" (Adverse Events).

Percent Threshold: Any Column ≥ 2%.

Reviewer's Comment

The following Information request (IR) was conveyed to the Applicant in the FDA filing communication letter of 9/7/2022:

"FDA QUESTION 1:
Submit a revised Table 2 in Sec. 6.1 of your proposed labeling (and a revised source Table 22 in M 2.7.4 SCS) for Adverse Reactions occurring at ≥1% in the treated group and at a higher rate than the placebo group (b) (4)

Applicant Response (submitted under SDN 8 on 10/24/2022):
A table of treatment-emergent adverse events (TEAEs) occurring in ≥1% of participants in any treatment group by system organ class (SOC) and preferred term (PT) from the Placebo-Controlled Pool Alopecia Areata (PCPAA) pool is provided in Table 1.

Additionally, as requested, a table of TEAEs occurring in ≥1% of participants in ritlecitinib 200/50 mg or 50/50 mg treatment groups and at a higher rate than placebo in the PCPAA pool is provided in Table 2.

While the above information has been provided per FDA request, the Sponsor has updated Table 2 in Section 6.1 of the proposed labeling to provide more concise and meaningful information in the label than that in the table above. Specifically, Table 3 includes grouping of some PTs (among those occurring at ≥1% in either of the treated groups and at a higher rate than the placebo group) into medical concepts. The PTs contributing to each medical concept are included as a footnote to Table 3. The source table is provided in Table 3 and draft labeling with a revised Table 2 in Section 6.1 is included in this submission".
The following Table summarizes the frequency of TEAEs reported (at ≥1% in any treatment group and greater than placebo) for the Ritlecitinib 50/50 mg QD and 200/50 mg QD dose

groups in the PCPAA pool, and are generally consistent with the frequency reported by the Applicant under SDN 8 (M 1.11.3, Table 3 and revised Table 2 in section 6.1 of the label). Some CMQ groupings of PTs conducted by the clinical reviewer contains additional PTs, leading to slightly different percentages for some grouped terms than those reported above by the Applicant:

Summary of TEAEs frequency (≥1% in any group) – by Grouped Terms or by PT- PCPAA (Weeks 0-24)

Preferred Term	Placebo (N=213) n (%)	Ritlecitinib 200/50 mg (N=215) n (%)	Ritlecitinib 50/50 mg (N=130) n (%)
URTI*	47 (22.1)	58 (27.0)	29 (22.3)
Headache*	19 (8.9)	24 (11.2)	14 (10.8)
diarrhea*	8 (3.8)	14 (6.5)	13 (10.0)
Acne*	10 (4.7)	17 (7.9)	10 (7.7)
Rash*	3 (1.4)	5 (2.3)	8 (6.2)
Abdominal pain*	5 (2.3)	2 (0.9)	7 (5.4)
COVID-19*	3 (1.4)	2 (0.9)	4 (3.1)

Urticaria	3 (1.4)	11 (5.1)	6 (4.6)
Fatigue	5 (2.3)	1 (0.5)	4 (3.1)
Folliculitis	4 (1.9)	12 (5.6)	4 (3.1)
Pyrexia	0 (0.0)	4 (1.9)	4 (3.1)
Dermatitis atopic	1 (0.5)	5 (2.3)	3 (2.3)
Dizziness	3 (1.4)	11 (5.1)	3 (2.3)
Ligament sprain	0 (0.0)	1 (0.5)	3 (2.3)
Nausea	15 (7.0)	12 (5.6)	3 (2.3)
Abdominal pain	2 (0.9)	1 (0.5)	2 (1.5)
Back pain	0 (0.0)	3 (1.4)	2 (1.5)
Blood creatine phosphokinase increased	0 (0.0)	7 (3.3)	2 (1.5)
Contusion	0 (0.0)	3 (1.4)	2 (1.5)
Cough	2 (0.9)	4 (1.9)	2 (1.5)
Deafness neurosensory	1 (0.5)	0 (0.0)	2 (1.5)
Dry skin	2 (0.9)	0 (0.0)	2 (1.5)
Ear infection	0 (0.0)	0 (0.0)	2 (1.5)
Fall	2 (0.9)	1 (0.5)	2 (1.5)
Flatulence	0 (0.0)	0 (0.0)	2 (1.5)
Gastroenteritis	0 (0.0)	3 (1.4)	2 (1.5)
Herpes simplex	4 (1.9)	0 (0.0)	2 (1.5)
Herpes zoster	0 (0.0)	0 (0.0)	2 (1.5)
Hypoaesthesia	2 (0.9)	1 (0.5)	2 (1.5)

Mouth ulceration	2 (0.9)	0 (0.0)	2 (1.5)
Nasal congestion	3 (1.4)	2 (0.9)	2 (1.5)
Red blood cell count decreased	0 (0.0)	0 (0.0)	2 (1.5)
Stomatitis	0 (0.0)	0 (0.0)	2 (1.5)
Vomiting	5 (2.3)	6 (2.8)	2 (1.5)
Abdominal discomfort	6 (2.8)	1 (0.5)	1 (0.8)
Anxiety	2 (0.9)	3 (1.4)	1 (0.8)
Arthralgia	6 (2.8)	2 (0.9)	1 (0.8)
Asthma	3 (1.4)	1 (0.5)	1 (0.8)
Dermatitis	4 (1.9)	0 (0.0)	1 (0.8)
Gingivitis	3 (1.4)	0 (0.0)	1 (0.8)
Insomnia	5 (2.3)	4 (1.9)	1 (0.8)
Muscle spasms	2 (0.9)	4 (1.9)	1 (0.8)
Myalgia	3 (1.4)	5 (2.3)	1 (0.8)
Natural killer cell count decreased	1 (0.5)	3 (1.4)	1 (0.8)
Pruritus	5 (2.3)	4 (1.9)	1 (0.8)
Alopecia areata	3 (1.4)	1 (0.5)	0 (0.0)
Constipation	3 (1.4)	1 (0.5)	0 (0.0)
Depression	3 (1.4)	0 (0.0)	0 (0.0)
Dyspepsia	3 (1.4)	3 (1.4)	0 (0.0)
Ear pain	2 (0.9)	3 (1.4)	0 (0.0)
Liver function test increased	0 (0.0)	3 (1.4)	0 (0.0)
Pain in extremity	3 (1.4)	2 (0.9)	0 (0.0)
Pain in jaw	1 (0.5)	3 (1.4)	0 (0.0)
Seasonal allergy	3 (1.4)	2 (0.9)	0 (0.0)
Seborrhoeic dermatitis	3 (1.4)	1 (0.5)	0 (0.0)
Syncope	3 (1.4)	1 (0.5)	0 (0.0)
Tinnitus	2 (0.9)	6 (2.8)	0 (0.0)
Urinary tract infection	6 (2.8)	8 (3.7)	0 (0.0)

Source: Clinical Reviewer's analysis in OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Ri lecitinib 200/50 mg" and SAFFL = "Y" (Ritlecitinib 200/50 mg); TRT01A = "Ri lecitinib 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); TRTEMFL = "Y" (Adverse Events).

Percent Threshold: Any Column ≥ 1%.

Abdominal pain* includes: Abdominal pain, Abdominal pain lower, Abdominal pain upper.

Acne* includes: Acne, Acne cystic, Acne pustular, Dermatitis acneiform.

COVID-19* includes: Covid-19, Sars-cov-2 antibody test positive, Sars-cov-2 test positive.

diarrhea* includes: Diarrhoea, Frequent bowel movements.

Headache* includes: Headache, Migraine, Tension headache.

Rash* includes: Dermatitis allergic, Rash, Rash erythematous, Rash maculo-papular.

URTI* includes: Influenza, Laryngitis, Nasopharyngitis, Oropharyngeal pain, Pharyngitis, Rhinitis, Sinusitis, Tonsillitis, Upper respiratory tract infection, Viral upper respiratory tract infec ion.

No clinically significant difference between the proportion of subjects in the 30/30 mg and the 50/50 mg dose groups were reported for TEAEs, severe AEs, SAEs, or AELDs. In the 50/50 mg dose group, diarrhea was more frequently reported. In 30/30 mg dose group, nausea, nasopharyngitis, URTI, myalgia and headache were more frequently reported. Most TEAEs were mild and did not lead to study drug discontinuation. The following tables compare TEAE and AELD profiles between these groups:

Summary of TEAEs (≥2% in any group)- Comparison between 50/50 mg and 30/30 mg dose groups-PCPAA:

Preferred Term	Ritlecitinib 50/50 mg (N=130) n (%)	Ritlecitinib 30/30 mg (N=132) n (%)	Risk Difference RD (95% CI)	Forest Plot
Nasopharyngitis	13 (10.0)	16 (12.1)	-2.12 (-9.71, 5.47)	
Diarrhoea	12 (9.2)	6 (4.5)	4.69 (-1.43, 10.80)	
Headache	12 (9.2)	20 (15.2)	-5.92 (-13.81, 1.96)	
Acne	8 (6.2)	7 (5.3)	0.85 (-4.78, 6.48)	
Upper respiratory tract infection	8 (6.2)	11 (8.3)	-2.18 (-8.45, 4.09)	
Urticaria	6 (4.6)	4 (3.0)	1.59 (-3.06, 6.23)	
Rash	5 (3.8)	1 (0.8)	3.09 (-0.53, 6.71)	
Abdominal pain upper	4 (3.1)	2 (1.5)	1.56 (-2.07, 5.19)	
Fatigue	4 (3.1)	6 (4.5)	-1.47 (-6.10, 3.16)	
Folliculitis	4 (3.1)	3 (2.3)	0.80 (-3.10, 4.71)	
Oropharyngeal pain	4 (3.1)	1 (0.8)	2.32 (-1.00, 5.64)	
Pyrexia	4 (3.1)	3 (2.3)	0.80 (-3.10, 4.71)	
Sars-cov-2 test positive	4 (3.1)	4 (3.0)	0.05 (-4.12, 4.21)	
Covid-19	3 (2.3)	2 (1.5)	0.79 (-2.52, 4.11)	
Dermatitis atopic	3 (2.3)	1 (0.8)	1.55 (-1.42, 4.53)	
Dizziness	3 (2.3)	3 (2.3)	0.03 (-3.59, 3.66)	
Ligament sprain	3 (2.3)	3 (2.3)	0.03 (-3.59, 3.66)	

Nausea	3 (2.3)	10 (7.6)	-5.27 (-10.47, -0.07)
Blood creatine phosphokinase increased	2 (1.5)	3 (2.3)	-0.73 (-4.04, 2.57)
Cough	2 (1.5)	3 (2.3)	-0.73 (-4.04, 2.57)
Herpes simplex	2 (1.5)	3 (2.3)	-0.73 (-4.04, 2.57)
Nasal congestion	2 (1.5)	3 (2.3)	-0.73 (-4.04, 2.57)
Vomiting	2 (1.5)	3 (2.3)	-0.73 (-4.04, 2.57)
Arthralgia	1 (0.8)	3 (2.3)	-1.50 (-4.46, 1.45)
Myalgia	1 (0.8)	5 (3.8)	-3.02 (-6.61, 0.57)
Platelet count decreased	1 (0.8)	3 (2.3)	-1.50 (-4.46, 1.45)
Viral upper respiratory tract infection	1 (0.8)	3 (2.3)	-1.50 (-4.46, 1.45)
Constipation	0 (0.0)	5 (3.8)	-3.79 (-7.04, -0.53)
Dermatitis contact	0 (0.0)	3 (2.3)	-2.27 (-4.82, 0.27)
Rhinitis	0 (0.0)	3 (2.3)	-2.27 (-4.82, 0.27)
Urinary tract infection	0 (0.0)	5 (3.8)	-3.79 (-7.04, -0.53)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Ritlecitinib 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); TRT01A = "Ritlecitinib 30/30 mg" and SAFFL = "Y" (Ritlecitinib 30/30 mg); TRTEMFL = "Y" (Adverse Events).

Percent Threshold: Any Column ≥ 2%.

Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Summary of TEAEs (≥2% in any group)- Comparison between 50/50 mg and 30/30 mg dose groups- PCPAA:

Preferred Term	Ritlecitinib 50/50 mg (N=130) n (%)	Ritlecitinib 30/30 mg (N=132) n (%)	Risk Difference RD (95% CI)	Forest Plot
Nasopharyngitis	13 (10.0)	16 (12.1)	-2.12 (-9.71, 5.47)	
Diarrhoea	12 (9.2)	6 (4.5)	4.69 (-1.43, 10.80)	
Headache	12 (9.2)	20 (15.2)	-5.92 (-13.81, 1.96)	
Acne	8 (6.2)	7 (5.3)	0.85 (-4.78, 6.48)	
Upper respiratory tract infection	8 (6.2)	11 (8.3)	-2.18 (-8.45, 4.09)	
Urticaria	6 (4.6)	4 (3.0)	1.59 (-3.06, 6.23)	
Rash	5 (3.8)	1 (0.8)	3.09 (-0.53, 6.71)	
Abdominal pain upper	4 (3.1)	2 (1.5)	1.56 (-2.07, 5.19)	

Fatigue	4 (3.1)	6 (4.5)	-1.47 (-6.10, 3.16)
Folliculitis	4 (3.1)	3 (2.3)	0.80 (-3.10, 4.71)
Oropharyngeal pain	4 (3.1)	1 (0.8)	2.32 (-1.00, 5.64)
Pyrexia	4 (3.1)	3 (2.3)	0.80 (-3.10, 4.71)
Sars-cov-2 test positive	4 (3.1)	4 (3.0)	0.05 (-4.12, 4.21)
Covid-19	3 (2.3)	2 (1.5)	0.79 (-2.52, 4.11)
Dermatitis atopic	3 (2.3)	1 (0.8)	1.55 (-1.42, 4.53)
Dizziness	3 (2.3)	3 (2.3)	0.03 (-3.59, 3.66)
Ligament sprain	3 (2.3)	3 (2.3)	0.03 (-3.59, 3.66)
Nausea	3 (2.3)	10 (7.6)	-5.27 (-10.47, -0.07)
Blood creatine phosphokinase increased	2 (1.5)	3 (2.3)	-0.73 (-4.04, 2.57)
Cough	2 (1.5)	3 (2.3)	-0.73 (-4.04, 2.57)
Herpes simplex	2 (1.5)	3 (2.3)	-0.73 (-4.04, 2.57)
Nasal congestion	2 (1.5)	3 (2.3)	-0.73 (-4.04, 2.57)
Vomiting	2 (1.5)	3 (2.3)	-0.73 (-4.04, 2.57)
Arthralgia	1 (0.8)	3 (2.3)	-1.50 (-4.46, 1.45)
Myalgia	1 (0.8)	5 (3.8)	-3.02 (-6.61, 0.57)
Platelet count decreased	1 (0.8)	3 (2.3)	-1.50 (-4.46, 1.45)
Viral upper respiratory tract infection	1 (0.8)	3 (2.3)	-1.50 (-4.46, 1.45)
Constipation	0 (0.0)	5 (3.8)	-3.79 (-7.04, -0.53)
Dermatitis contact	0 (0.0)	3 (2.3)	-2.27 (-4.82, 0.27)
Rhinitis	0 (0.0)	3 (2.3)	-2.27 (-4.82, 0.27)
Urinary tract infection	0 (0.0)	5 (3.8)	-3.79 (-7.04, -0.53)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Ritlecitinib 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); TRT01A = "Ritlecitinib 30/30 mg" and SAFFL = "Y" (Ritlecitinib 30/30 mg); TRTEMFL = "Y" (Adverse Events).

Percent Threshold: Any Column ≥ 2%.

Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Summary of AELDs- Comparison between 50/50 mg and 30/30 mg dose groups- PCPAA:

Preferred Term	**Ritlecitinib 50/50 mg (N=130)**	**Ritlecitinib 30/30 mg (N=132)**	**Risk Difference**

	n (%)	n (%)	RD (95% CI)	Forest Plot
Asthenia	0 (0.0)	1 (0.8)	-0.76 (-2.24, 0.72)	
Blood pressure increased	0 (0.0)	1 (0.8)	-0.76 (-2.24, 0.72)	
Diarrhoea	0 (0.0)	1 (0.8)	-0.76 (-2.24, 0.72)	
Headache	0 (0.0)	1 (0.8)	-0.76 (-2.24, 0.72)	
Hypoaesthesia	0 (0.0)	1 (0.8)	-0.76 (-2.24, 0.72)	
Nasopharyngitis	0 (0.0)	1 (0.8)	-0.76 (-2.24, 0.72)	
Platelet count decreased	0 (0.0)	1 (0.8)	-0.76 (-2.24, 0.72)	
Urticaria	2 (1.5)	0 (0.0)	1.54 (-0.58, 3.65)	

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Ritlecitinib 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); TRT01A = "Ritlecitinib 30/30 mg" and SAFFL = "Y" (Ritlecitinib 30/30 mg); TRTEMFL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Laboratory Findings

Adverse reactions (AR) related to laboratory findings which were reported in >1% of subjects included: blood creatine phosphokinase (CK) increased, liver function test increased, red blood cell count decreased, lymphocyte CD15/56 (Natural Killer cell) count decreased. These ARs will be included in product labeling (Section 6 Adverse Reactions).

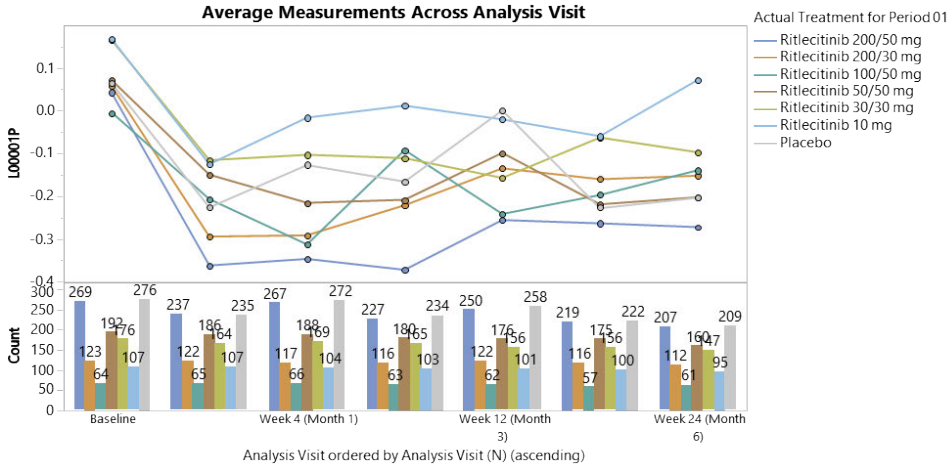
Hemoglobin (Hgb)

For the PCPAA and PCPAAV pools, a transient change from baseline (CFB) of a decrease in the mean Hgb was reported during initial 2-4 weeks of treatment for all groups (greater CFB in the 200/50 mg group) with a trend towards return to near baseline values at Week 24.

For the OYEP pool, CFB in Hgb (g/dL) at Week 48 were -0.39 (for all 50 mg), -0.25 (for all 30 mg), and -0.14 (for 10 mg) dose groups.

The following figure depicts time trends for CFB of Hgb in the PCPAAV pool.

Change from Baseline for Hemoglobin (g/dL)- PCPAAV pool- safety analysis population



Source: Clinical reviewer's JMP Clinical 8.1 analysis. Consistent with M 2.7.4, Table 55 and Figure 8.

No subject was reported with a CTCAE Grade ≥3 (Hgb <8.0 g/dL) anemia or was discontinued from treatment. TEAE of anemia was reported with similar frequency among treatment groups and placebo group in the PCPAAV and OYEP pools.

In the OYEP pool, one subject (ID: B7981015 (b) (6), a 37-year-old male subject from Germany was discontinued from treatment with the study drug for (multiple) non-serious, moderate TEAEs of anemia (ongoing)(D 246), leukopenia (resolved), lymphopenia (resolved), neutropenia (ongoing), and thrombocytopenia (ongoing) (D 239) based on the Investigator's decision (no individual TEAE met protocol-defined criteria for subject discontinuation). Subject received no treatment. TEAEs were deemed related to study drug per investigator.

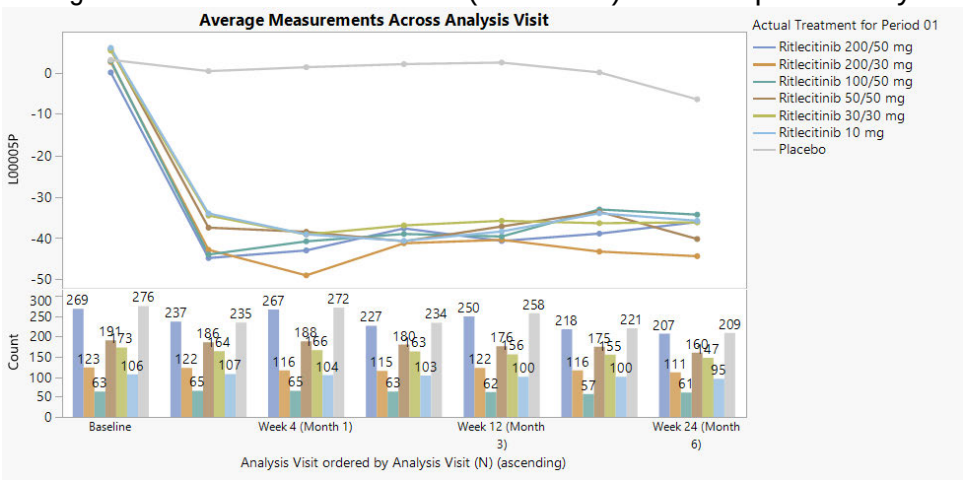
Platelets

For the PCPAA and PCPAAV pools, a similar decrease (of approximately 40,000/mm ^{3}) in the mean platelet counts was reported for all ritlecitinib dose groups at Week 2, which remained stable at the lower count to week 24.

For the OYEP pool, the CFB in platelet counts at Week 2 remained stable to week 48 for the all 50 mg, all 30 mg, and the 10 mg dose groups.

The following figure depicts time trends for CFB of platelet counts in the PCPAAV pool.

Change from Baseline for Platelets (x10^3/mm^3)- PCPAAV pool- safety analysis population



Source: Clinical reviewer's JMP Clinical 8.1 analysis. Consistent with M 2.7.4, Table 75 and Figure 17.

No subject was reported with a CTCAE Grade ≥3 (platelet count <50,000/mm ^{3}) or met subject discontinuation criteria.

In the PCPAAV pool, TEAEs of thrombocytopenia (2) or platelet count decreased (5) , including temporary discontinuation (1) (ID: B7981015 (b) (6) minimum platelet count of 131,000/mm^3 at Week 12) and AELD (1) (ID: B7981015 (b) (6) minimum platelet count of 115,000/mm^3 at Week 16) were reported.

In the OYEP, TEAEs of thrombocytopenia (2) or platelet count decreased (6) , including an AELD (1) (same subject (ID: B7981015 (b) (6) reported as AELD for anemia).

Leukocytes

Leukocyte counts showed small varable changes from baseline during weeks 2-4 for all ritlecitinib dose groups, and remained stable up to Week 48.

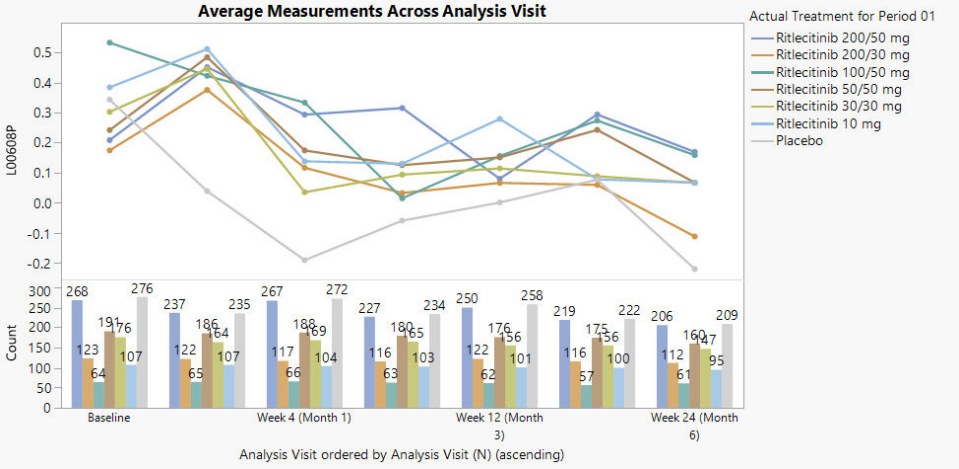
Neutrophils

For the PCPAA and PCPAAV pools, a small transient increase from baseline in absolute neutrophil count (ANC) at Week 2 (greater CFB among groups with a loading dose and in higher dose groups compared to the placebo group). ANC returned towards baseline at week 4 and remained stable to week 24.

Similarly, for the OYEP pool, the increase in ANC at Week 2 returned to baseline and remained stable to week 48.

The following figure depicts time trends for CFB of ANC in the PCPAAV pool.

Change from Baseline for ANC (x10^3/mm^3)- PCPAAV pool- safety analysis population



Source: Clinical reviewer's JMP Clinical 8.1 analysis. Consistent with M 2.7.4, Table 62 and Figure 11.

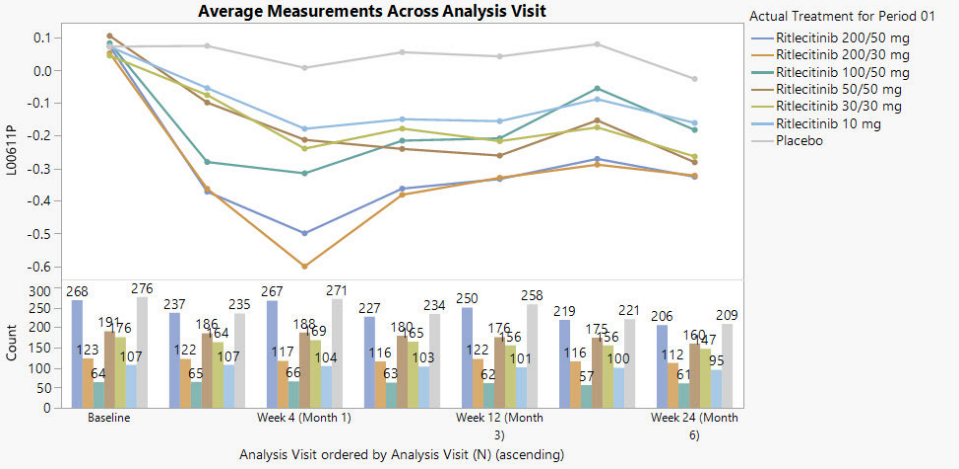
In the PCPAAV pool, Grades 1 or 2 CTCAE for ANC were reported with similar frequency among all dose groups. Two (2) subject with a CTCAE Grade 3 (ANC beween 500 to < 1000/mm ^{3}) and no subject with CTCAE Grade 4 (ANC< 500/ mm ^{3}) were reported. No subject met subject discontinuation criteria.

In the PCPAAV pool, TEAEs of neutropenia (3) or neutrophil count decreased (2) did not lead to temporary or permanent discontinuation as AELD.
In the OYEP, two (2) subject were reported with a CTCAE Grade 3. TEAEs of neutropenia (1) or neutrophil count decreased (3) , including an AELD (1) (same subject (ID: B7981015 (b) (6)) reported as AELD for anemia).

Lymphocyte counts

For the PCPAA and PCPAAV pools, a decrease in the mean absolute lymphocyte counts (ALC) was reported during initial 2-4 weeks of treatment for all groups (greater CFB among groups with a loading dose and in higher dose groups compared to the placebo group) which plateaued at a lower level than their baseline values at Week 24.
For the OYEP pool, CFB in ALC (x10^3/mm^3) at Week 48 were -0.42 (for all 50 mg), -0.34 (for all 30 mg), and -0.1 (for 10 mg) dose groups.
The following figure depicts time trends for CFB of ALC in the PCPAAV pool.

Change from Baseline for ALC (x10^3/mm^3)- PCPAAV pool- safety analysis population



Source: Clinical reviewer's JMP Clinical 8.1 analysis. Consistent with M 2.7.4, Table 68 and Figure 14.

In the PCPAAV pool, 8 subjects (200/50 mg (6), 50 mg (1), 30 mg (2)) were reported with a CTCAE Grade ≥3 (200 ≤ to <500 /mm^3).

- Subject (ID: B7981015/ (b) (6), a 38-year-old female subject in 200/50 mg group) was reported with a CTCAE Grade 4 (<200/mm^3) which was not confirmed by retesting, and a nonserious TEAE of lymphopenia (190 /mm^3) on Day 171 (mild, not related). No treatment was reported and no action was taken with study drug. On Day 176, ALC (1,170/mm^3) was within reference range and the AE of lymphopenia was considered resolved on Day 182. Other hematologic parameters were reported as normal.

No subject was discontinued from trial or met protocol-specified discontinuation criteria for ALC. TEAEs were reported for PTs of lymphopenia (6), lymphocyte count decreased (8), and lymphocyte count abnormal (1).
In the OYEP pool, CTCAE Grade ≥3 was reported for 3/260 (1.2%) subjects in the 50 mg group and 2/257(0.8%) in the 30 mg group. TEAEs were reported for PTs of lymphopenia (7), lymphocyte count decreased (6), and lymphocyte count abnormal (1).

- Subject (ID: B7981015/ (b) (6) was discontinued from trial (same subject discussed above under Hgb heading).

The frequency of AEs reported for any infection, moderate or severe infections, and HZ were similar between subjects with ALC- CTCAE Grade 1 (0.8 × 10 ^{3}/mm^3 to < LLN) or Grade 2 (0.5 × 10 ^{3}/mm^3 to <0.8 × 10 ^{3}/mm^3), compared to subjects with ALC > lower limit of normal (LLN) prior to occurrence of AEs. No subject with ALC <LLN was reported with a serious infection or an infection as an AELD. In the AEP, No concurrent AE of an infections was reported for any subject who was discontinued from trial because of AE of decreased ALC.

Lymphocyte subset counts were measured for CD3+ (T cells), CD4+ (T helper), CD8+ (T cytotoxic), CD19+ (B cells), and CD16+/CD56+ (NK cells) collected in ritlecitinib clinical trials. In the PCPAA pool:

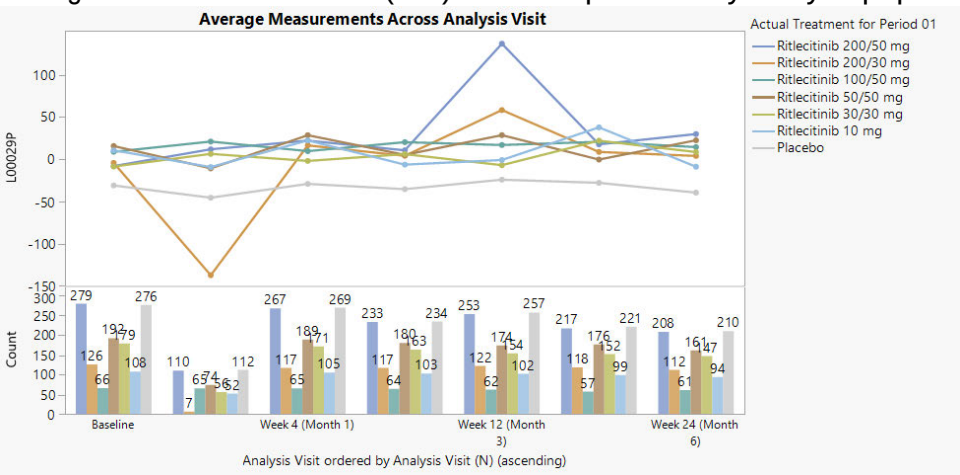
- T cell counts decreased in the first 2-4 weeks (greater decrease for higher dose groups) and remained stable at lower counts with continued treatment to week 24.
  - CD3+ (T cells): median CFB of -200/mm^3 (50/50 mg group) vs. placebo (0).
  - CD4+ (T helper): median CFB of -134/mm^3 (50/50 mg group) vs. placebo (10/mm^3).
  - CD8+ (T cytotoxic): median CFB of -68/mm^3 (50/50 mg group) vs. placebo (-6/ mm^3).
- No significant decreases was reported for B cell counts:(median CFB of 0 (50/50 mg) vs. placebo (0).
- NK cell count decreased in the first 2-4 weeks (greater decrease with 200 mg daily loading dose) and returned to baseline: median CFB of 0 (50/50 mg) vs. placebo (0).

Creatinine Kinase (CK)

For the PCPAAV pool, no clinically significant CFB in CK was reported in any group. The median CFB to week 24 in the 50/50 mg group (8.0) and placebo group (0) were similar.

The following figure depicts time trends for CFB of CK in the PCPAAV pool.

Change from Baseline for CK (U/L)- PCPAAV pool- safety analysis population



Source: Clinical reviewer's JMP Clinical 8.1 analysis. Consistent with M 2.7.4, Figure 22.

The proportion of subjects with CK increases considered CTCAE Grade 3 (between 5× ULN to <10× ULN) or Grade 4 (>10× ULN) was generally similar among the ritlecitinib groups (ranging between 1.2% to 3.7%) but higher compared to placebo (0.5%).

The proportion of subjects reported with TEAEs of blood creatine phosphokinase increased was higher in ritlecitinib groups: 200/50 mg (3.6%), 50/50 mg (2.5%), All 30 mg (2.6%), and 10 mg (2.7%) compared to the placebo group (0.7%). No AEs of rhabdomyolysis were reported in any groups. The following 3 subjects were reported with AEs of CK elevation that led to discontinuation from trial:

1. Subject ID: B7931005 (b) (6) (200/50 mg group): a 23-year-old male subject with a normal baseline CK (98 U/L; reference range 39-308 U/L). On Day 1, CK was 3212 U/L that led to temporary discontinuation of study drug. On Day 8, CK was 200 U/L and dosing resumed on Day 10. An AE of blood creatine phosphokinase increased was reported on Day 43 due to CK of 2324 U/L. Study drug was discontinued on Day 47 and subject was discontinued from the study on Day 49. The AE was considered unrelated to study drug (due to strenuous exercise) and considered resolved on Day 55.

1. Subject ID: B7981019/ (b) (6) - (200/50 mg group): a 49-year-old male subject with a normal baseline CK (111 U/L). On Day 85 an AE of CK increased (78,054 U/L [>3× ULN], urine myoglobin not measured) was reported (severe, related); on Day 85, additional AEs of ALT increased (moderate, related), AST increased (severe, related), and abnormal urinalysis (+ for Hgb) (moderate, related) were reported. No treatment was given for the AEs and study drug was continued. On Day 91, CK value was 3,441 U/L (>3× ULN) and subject was discontinued from the study on Study Day 92 due to the AE of blood creatine phosphokinase increased. The AE of abnormal urinalysis was considered resolved on Day 91. On Day 96, CK value was 327 U/L and AE was considered resolved, ALT and AST values were normal and AEs considered resolved.

2. Subject ID: B7981019/ (b) (6) - (Placebo group): a 56-year-old male subject with normal CK at baseline (100 U/L) was reported with AE of blood creatine phosphokinase increased (2258 U/L [>3× ULN])on Day 86 (severe, related) which led to discontinuation of study drug. On Day 91, CK level was 349 U/L and AE was considered resolved.

For the OYEP, no clinically significant CFB in mean CK values to week 48 was reported in any groups.

The proportion of subjects with CK increases considered CTCAE Grade 3 or 4 was higher in All 50 mg group (6.6%) compared to All 30 mg group (3.9%) and 10 mg group (3.2%).

The proportion of subjects rported with TEAEs of blood creatinine phosphokinase increased was also higher in All 50 mg group (3.8%) compared to All 30 mg group (3.1%) and 10 mg group (3.2%).

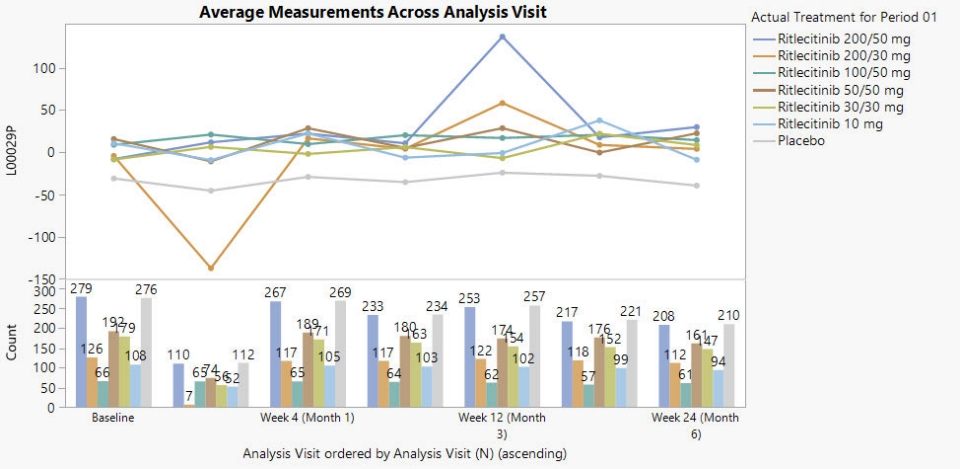
No AEs of rhabdomyolysis were reported, and no subjects was discontinued from treatment with study drug due to an AE of blood creatine phosphokinase increased.

Hepatic Function Tests (AST, ALT, Total bilirubin (Tbili))

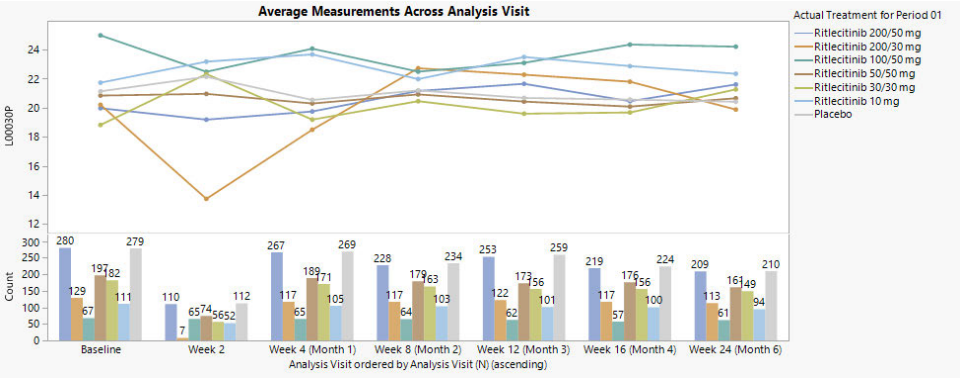
For the PCPAA pool, no clinically significant CFB in median AST, ALT, alkaline phosphatase (ALP), or total bilirubin to week 24 were reported. ALT and AST increases of >3× and >5× ULN and TBili increase of >2× and >3× ULN were reported in the ritlecitinib groups at a frequency of between 0 to 1.6% compared to placebo (0).

In the PCPAAV pool, one additional subject was reported with ALT >3× ULN in the vitiligo trial - 1019. The following figure depicts time trends for values of AST, ALT, and Tbili in the PCPAAV pool.

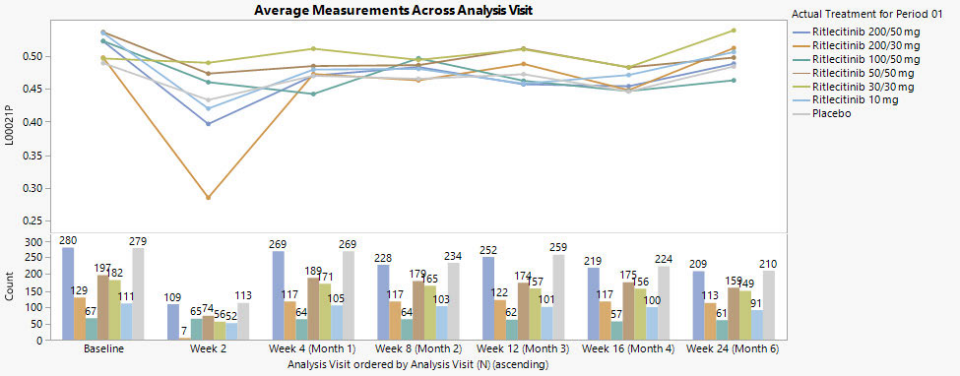
Time trend for AST (U/L)- PCPAAV pool- safety analysis population



Time trend for ALT(U/L)- PCPAAV pool- safety analysis population



Time trend for Tbili (mg/dL)- PCPAAV pool- safety analysis population



Source: Clinical reviewer's analysis by JMP Clinical 8.1.

For the PCPAA pool, AEs were reported for hyperbilirubinemia (1) and liver function test increased for (3); none led to discontinuation from treatment by study drug.

For the PCPAAV pool, three (3) AELDs (reported in the vitiligo trial) were hepatic steatosis (1), ALT increased (1) and AST increased (1); summarized in the following narratives:

1. Subject ID: B7981019 (b) (6) - All 50 mg group:

A 57-year-old Asian female subject was reported with an AE of AST increased (96 U/L [>2.5× ULN]) on Day 58 (not related, resolved). Retest on Day 71 showed AST of 100 U/L. On Day 81, AST was 82 which led to study drug discontinuation, subject's withdrawal of consent and discontinuation from the study.

2. Subject ID: B7981019 (b) (6) - All 50 mg group:

A 50-year-old Asian male subject was reported on Day 31 with an AE of ALT increased (109 U/L [>2.5× ULN]) (nonserious, mild, related). ALT values were 112 U/L on Day 36, 150 U/L on Day 58, and 119 U/L on Day 86. Study drug was discontinued on Day 39 and the AE of ALT increased was reported as resolved on Study Day 86.

3. Subject ID: B7981019 (b) (6) All 30 mg:

A 25-year-old white female with normal liver function tests at baseline was reported with an AE of liver function test increased (moderate) on Day 142. ALT of 89 U/L (>2.5× ULN) and AST of 50 U/L. Study drug was discontinued on Day 164. The investigator assessed the AE as not related to study drug, but due to "other fatty liver" (confirmed by ultrasound on Study Day 206; nonserious AE of hepatic steatosis; mild, unrelated).

In the LTS study -1032, an adolescent subject who had completed trial B7981015 was reported with an AELD of elevated liver function tests and underwent a liver biopsy, according to the following narrative.

- Subject ID: B7981032 (b) (6) (B7981015 (b) (6)):

A 14-year-old female subject from the U.S. completed trial -1015 (50 mg group) at Day 330 and enrolled in study -1032 with normal hepatic enzymes. On Day

184 of study -1032, an AE of hepatic enzyme increased (AST >3× ULN and >5× ULN) (non-serious, mild, not related) which led to discontinuation from study drug on Day 358. No treatment was reported for this AE. A liver biopsy was performed on Day 329. From Day 183, liver enzymes remained elevated through Day 377. The event of hepatic enzyme increased was ongoing at the time of subject's Discontinuation from study on Day 358 .

Reviewer's comment

An Information request (IR) was sent to the Applicant on 12/1/2022 to submit any additional information available regarding this subject (the following information was submitted by the Applicant under SDN 13 on 12/14/2022).

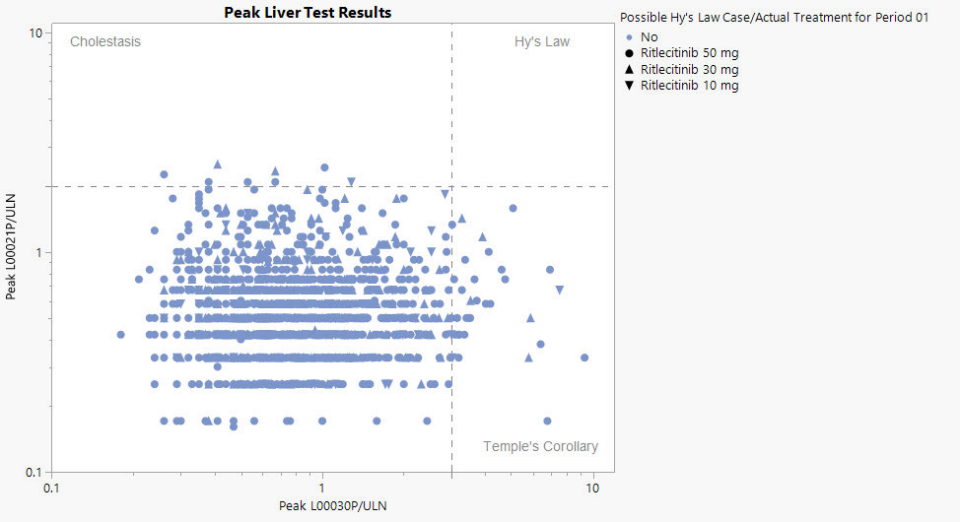
A pediatric gastroenterologist evaluated the subject (hepatic AEs were not adjudicated). The investigator and the Applicant consider the increase in liver function values and associated AE as not related to the study drug based on the following:

- Histological findings of fatty liver disease with steatohepatitis in a patient with obesity
- Obesity increased significantly from the end of trial -1015, from trial -1032 Day 1 (Weight of 84.5 Kg/ BMI of 33.4 Kg/m^2) to Day 183 (Weight of 100.2 Kg/ BMI of 39.0 Kg/m^2); increases in weight and BMI of 15.7 kg and 5.6 kg/m^2.
- Histological findings in the liver biopsy on 16 Nov 2021 (Study-1032, Day 329) demonstrated features of steatosis, active steatohepatitis, fibrosis, and bridging structures.
- Liver test elevation of hepatocellular pattern, primarily starting more than 330 days after initiating ritlecitinib 50 mg QD.
- Liver function values and weight/BMI remained elevated to Day 713. Continued increases in ALT, AST, and GGT for over 500 days after study drug discontinuation (last dose taken on study -1032, Day 202; remained elevated to Day 713), with peak elevations on Day 454 (252 days after study drug discontinuation).

Hy's Law screen/ eDISH plot

No hepatic laboratory changes associated with potential DILI or Hy's Law were reported in any ritlecitinib studies, as depicted in the following Hy's law screening plot for the AEP pool.

Liver Test Elevation plot- peak Tbili vs. peak ALT- AEP pool- safety analysis population



Source: Clinical reviewer's analysis by JMP Clinical 8.1. Consistent with M 2.7.4, Figure 21 (Plot of eDISH Analysis – AEP).

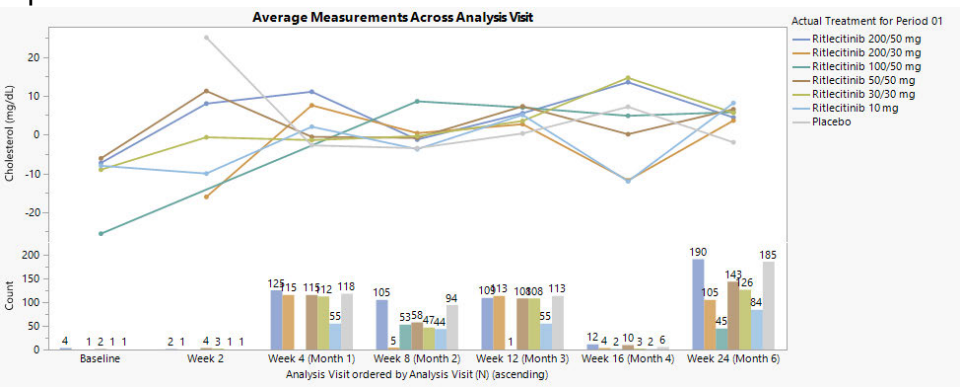
Lipids

For the PCPAA and PCPAAV pools, small increases from baseline to week 4 in median TC, HDL-C, and LDL-C; and variable changes in TG were reported in all ritlecitinib groups compared to the placebo group. At week 24, for all ritlecitinib groups compared to the placebo group, median CFB for HDL-C was similar, but median CFB in TC, LDL-C, and TG showed small increases.

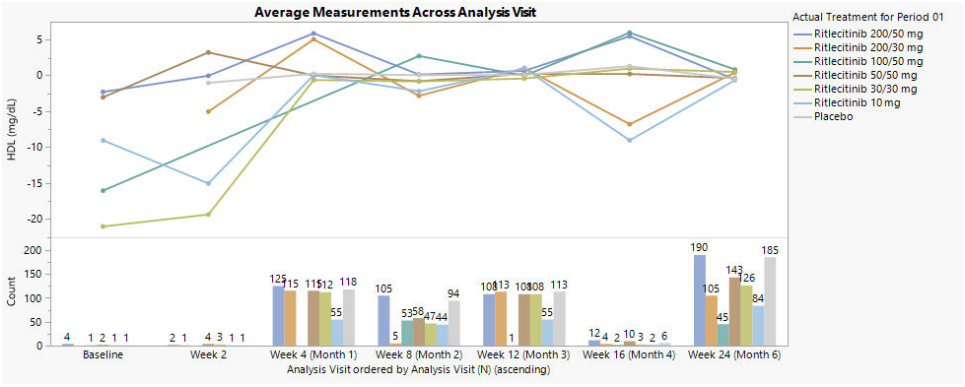
For the OYEP pool, CFB in TC, HDL-C, LDL-C and TG at Week 48 were small and variable with no relation to dose group.

The following figure depicts time trends for CFB of lipids in the PCPAAV pool.

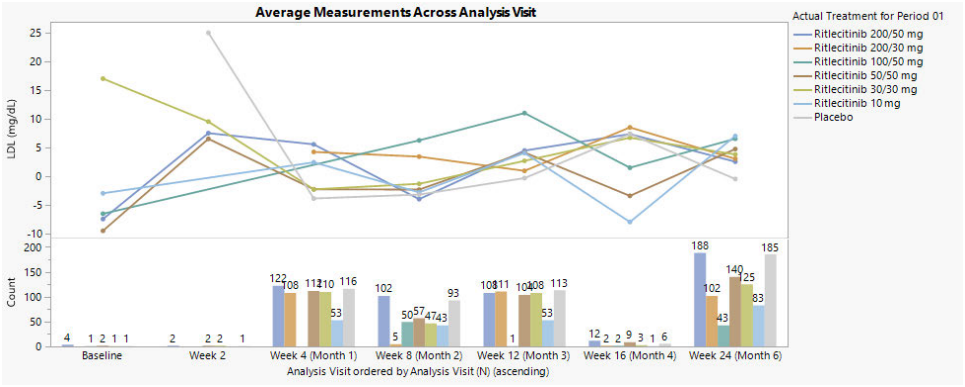
Change from Baseline for fasting Cholesterol (mg/dL)- PCPAAV pool- safety analysis population



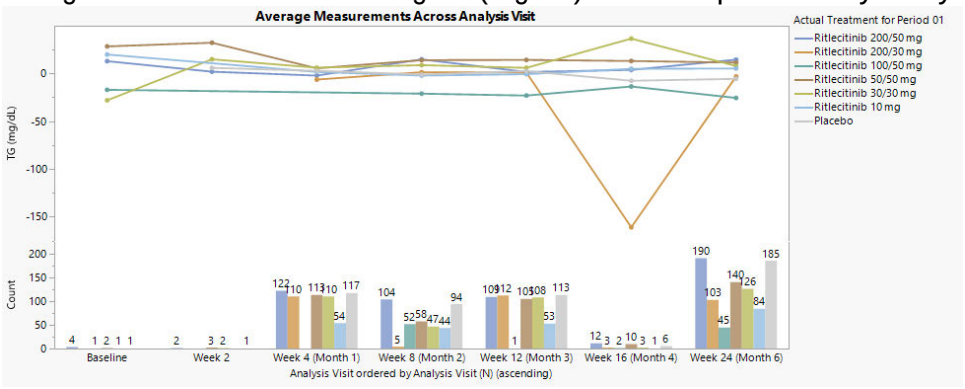
Change from Baseline for fasting HDL-C (mg/dL)- PCPAAV pool- safety analysis population



Change from Baseline for fasting LDL-C (mg/dL)- PCPAAV pool- safety analysis population



Change from Baseline for fasting TG (mg/dL)- PCPAAV pool- safety analysis population



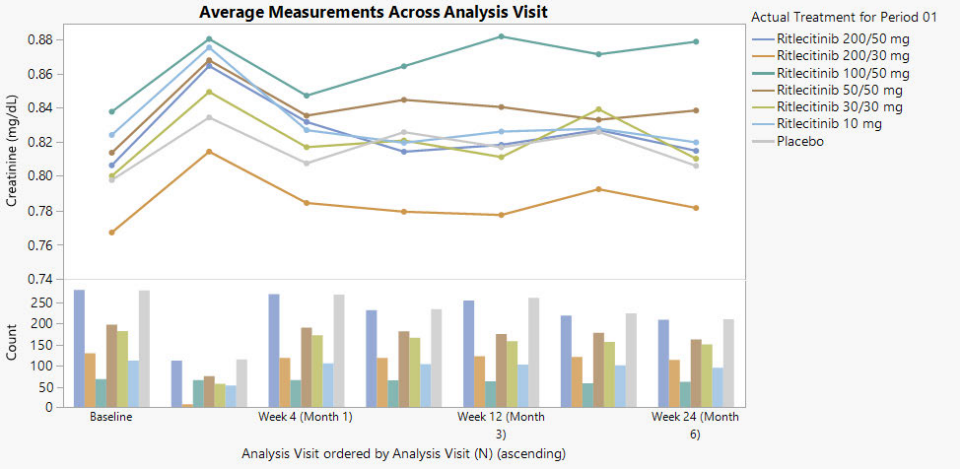
Source: Clinical reviewer's JMP Clinical 8.1 analysis. Consistent with M 2.7.4, Figure 20, and Table 79.

TEAEs of hyperlipidemia were reported for 2 subjects in the PCPAAV pool and 3 subjects in the OYEP (none were AELD).

<u>Serum Creatinine</u>

For the PCPAAV pool, no clinically significant CFB in serum creatinine in the ritlecitinib or placebo groupswere reported at week 24; and no TEAEs associated with blood creatinine increase or renal injury were reported. Similar results were reported for the AEP pool.

Time trend for Creatinine (mg/dL)- PCPAAV pool- safety analysis population



Source: Clinical reviewer's analysis by JMP Clinical 8.1. Consistent with M 2.7.4.3.2.3.1.

Vital Signs

No clinically significant changes in the systolic blood pressure (SBP), diastolic blood pressure (DBP), or pulse rate were reported for any subject in any safety pools. For the PCPAA pool, the following maximum changes from baseline to week 24 were reported: SBP (+2 mm Hg) for the 10 mg dose group, DBP (+0.5 mm Hg) for 50/50 mg dose group, and pulse rate (+2.5 BPM) for the 10 mg dose group.

Electrocardiograms (ECGs)

No clinically significant changes in ECG measurements were reported for any subjects in ritlecitinib treatment or placebo groups in the AA development program.

QT

The Applicant conducted a concentration-QT (C-QT) Study B7981001, a Phase 1, randomized, double-blind, third-party open, placebo-controlled, single- and multiple-dose escalation, parallel-group study in healthy adult subjects, and reported no evidence of a clinically significant QTc interval prolongation. Refer to the Clinical Pharmacology review section of this review for additional detail.

Immunogenicity

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

8.2.5. Analysis of Submission-Specific Safety Issues

Safety Areas of Interest/Adverse Events of Special Interest (AESI)

Safety areas of interest were based on Applicant's review of the nonclinical and clinical safety data for ritlecitinib and other immunomodulators (including JAK and TEC inhibitors) and included the following categories:

- Serious infections (SAEs in SOC of Infections and infestations)
- Opportunistic infections (OI) (including TB)- reviewed by adjudication committee
- Herpes zoster (HZ)
- Herpes simplex (HS)
- Malignancies (NMSC/non-NMSC)- reviewed by adjudication committee
- Cerebrovascular (MACE) and thromboembolic- reviewed by adjudication committee
- Bleeding events and atrial fibrillation- associated with TEC/BTK (not JAK) inhibitors
- Neurologic and audiologic- reviewed by adjudication committee
- Dermatologic
- Growth and development (adolescents)
- Laboratory abnormalities
- Hypersensitivity
- Exposure during pregnancy

Epidemiological Studies

The Applicant conducted the following two population-based external cohort studies and submitted the incidence rates (IR) for selected AESIs for trial-similar (TS) cohorts of each observational study for comparison to their corresponding IRs in the All 50 mg dose group of the ritlecitinib AEP (M 2.7.4, Table 52):

1. Study B7981051: A US retrospective cohort study conducted in persons ≥12 years of age diagnosed with AA embedded within the Optum Claims Database with a study period of 10/1/2016 to 9/30/2020.
2. Study B7981049: A retrospective cohort study conducted between 1/1/1995 and 2016, which utilized the Danish national population health registries.

DDD requested a consultation from DEPI/OSE on 12/13/2022 to review Studies B7981049/-51. The Executive Summary section of the epidemilogy consult review of the final study reports on 2/14/2023 stated the following:

"DEPI found general alignment between evidence presented in the NDA Summary of Clinical Safety (SCS) and the reports from the two observational studies. DEPI advised that DDD might reasonably choose to include—in the Multi-Disciplinary Review and Evaluation for NDA 215830—a cautiously interpreted presentation of evidence enabled by the two observational studies. But DEPI also advised that DDD not use this evidence to eliminate certain AEs from consideration as identified or potential risks from ritlecitinib treatment. ".

The following table (source: Table 2 of the above DEPI draft review, consistent with Table 52 M.2.7.4 (SCS), and Clinical Information Amendment on 11/14/2022) lists the Incidence Rates (IR) for the safety events of interest in the AEP All 50 mg Group and Two External AA Cohorts

(US and Danish Trial-Similar Cohorts), by Age Category.

Incidence Rates for Safety Events of Interest in AEP All 50 mg Group and Two External AA Cohorts (US and Danish Trial-Similar Cohorts), by Age Category.

Safety Events	Categories	AEP All 50 mg IR/100 PY (95% CI)	US TS AA Cohort IR/100 PY (95% CI) (n=5370)	Danish TS AA Cohort IR/100 PY (95% CI) (n=2232)
Serious Infection	All ages	0.66 (0.35, 1.14)	1.15 (0.95, 1.39)	1.8 (1.61, 2)
	≥12 to <18 years	0.81 (0.13, 2.79)	0.35 (0.09, 1.39)	1.54 (1.06, 2.17)
	≥18 years	0.64 (0.32, 1.16)	1.2 (0.99, 1.45)	1.83 (1.63, 2.05)
HZ	All ages	1.17 (0.74, 1.76)	0.55 (0.42, 0.73)	1.14 (0.99, 1.3)
	≥12 to <18 years	No observed cases	No observed cases	0.96 (0.59, 1.46)
	≥18 years	1.34 (0.85, 2.03)	0.59 (0.45, 0.78)	1.16 (1, 1.34)
HS	All ages	1.72 (1.19, 2.41)	1.29 (1.08, 1.55)	Not calculated
	≥12 to <18 years	No observed cases	0.17 (0.02, 1.23)	Not calculated
	≥18 years	1.97 (1.37, 2.77)	1.37 (1.14, 1.64)	Not calculated
Malignancy (excluding NMSC)	All ages	0.37 (0.16, 0.75)	1 (0.82, 1.23)	0.56 (0.46, 0.68)
	≥12 to <18 years	No observed cases	No observed cases	0.17 (0.05, 0.45)
	≥18 years	0.42 (0.18, 0.86)	1.07 (0.87, 1.31)	0.61 (0.5, 0.74)
BCC	All ages	0.16 (0.03, 0.45)	0.59 (0.45, 0.77)	0.11 (0.07, 0.17)
	≥12 to <18 years	No observed cases	No observed cases	No observed cases
	≥18 years	0.18 (0.04, 0.52)	0.63 (0.49, 0.83)	0.13 (0.08, 0.19)
SCC	All ages	0.06 (0.00, 0.29)	0.39 (0.28, 0.54)	0.02 (0.01, 0.05)
	≥12 to <18 years	No observed cases	No observed cases	No observed cases
	≥18 years	0.06 (0.00, 0.33)	0.42 (0.3, 0.58)	0.02 (0.01, 0.06)
Female Breast Cancer	All ages	0.36 (0.11, 0.88)	0.29 (0.17, 0.49)	0.14 (0.08, 0.23)
	≥12 to <18 years	No observed cases	No observed cases	No observed cases
	≥18 years	0.40 (0.12, 0.98)	0.31 (0.18, 0.52)	0.16 (0.09, 0.26)
MACE	All ages	0.15 (0.03, 0.43)	1.2 (0.99, 1.45)	0.58 (0.44, 0.74)
	≥12 to <18 years	No observed cases	0.17 (0.02, 1.23)	No observed cases
	≥18 years	Not calculated	1.27 (1.05, 1.53)	0.65 (0.5, 0.83)
PE	All ages	0.06 (0.00, 0.29)	0.07 (0.03, 0.14)	0.04 (0.01, 0.07)
	≥12 to <18 years	No observed cases	No observed cases	No observed cases
	≥18 years	0.07 (0.00, 0.33)	0.07 (0.03, 0.15)	0.04 (0.02, 0.08)
Arterial Thrombosis	All ages	0.09 (0.01, 0.33)	0.05 (0.02, 0.13)	0.02 (0.01, 0.05)
	≥12 to <18 years	No observed cases	No observed cases	0.04 (0, 0.24)
	≥18 years	0.10 (0.01, 0.37)	0.06 (0.02, 0.14)	0.02 (0, 0.05)
Peripheral Neuropathy	All ages	0.21 (0.06, 0.52)	**4.9 (4.4, 5.3) [2]**	Not calculated
	≥12 to <18 years	No observed cases	**1.6 (0.8, 3.1) [2]**	Not calculated
	≥18 years	0.24 (0.07, 0.59)	**5.1 (4.6, 5.6) [2]**	Not calculated
Paresthesia / Dysesthesia	All ages	1.19 (0.76, 1.78)	**3.2 (2.9, 3.6) [2]**	Not calculated
	≥12 to <18 years	0.46 (0.02, 2.28)	**0.2 (0, 1.2) [2]**	Not calculated
	≥18 years	1.29 (0.82, 1.96)	**3.4 (3.1, 3.9) [2]**	Not calculated
Sensorineural Hearing Loss	All ages	**0.85 (0.49, 1.39) [1]**	2.72 (2.4, 3.09)	0.32 (0.24, 0.41)
	≥12 to <18 years	No observed cases	**1.23 (0.59, 2.59) [3]**	0.09 (0.01, 0.32)
	≥18 years	0.98 (0.57, 1.59)	2.82 (2.49, 3.21)	0.35 (0.26, 0.45)

SOURCE: Clinical Information Amendment, submitted to NDA 215830 (eCTD 0010) on November 14, 2022.
ABBREVIATIONS: AA – alopecia areata cohort; AEP – All Exposure Pool; BCC – basal cell carcinoma; CI – confidence interval; HS – herpes simplex; HZ – herpes zoster; IR – incidence rate; MACE – major adverse cardiovascular event; NMSC – non-melanoma skin cancer; PE – pulmonary embolism; PY – person-years; SCC – squamous cell carcinoma; TS – trial-similar AA cohort
FOOTNOTES:
1. Result not found by DEPI in Integrated Safety Summary (ISS).
2. Result not found by DEPI in final study report from B7981051.
3. Final study report from B7981051 shows result as 1.23 (0.59, 2.58).

8.2.6. Serious infections

Serious infections included infections that required parenteral antimicrobial therapy, hospitalization, or reported as SAEs in the SOC of Infections and Infestation. Per protocol, all serious infections required discontinuation from the trial.

During ritlecitinib Phase 1 Study B7981001, 3 healthy subjects treated with ritlecitinib (at a dose ≥200 mg) were reported with serious infections which were considered treatment-related and led to discontinuation from treatment. Two SAEs (subcutaneous abscess (200 mg) , pilonidal cyst (400 mg) were reported during single-dose period, and 1 SAE of varicella infection (400 mg QD) during multiple-dose period.

PCPAA
In the PCPAA pool, no SAE of as a serious infection was reported in > 1 subject.
Refer to the narratives in the SAE section of this review. No additional seriuos infections were reported for the PCPAAV pool.

Summary of Serious Infections in the PCPAA pool

System Organ Class - Preferred Term	Placebo (N=213) n (%)	Ritlecitinib 10 mg (N=62) n (%)	Ritlecitinib 200/30 mg (N=129) n (%)	Ritlecitinib 200/50 mg (N=215) n (%)	Ritlecitinib 30/30 mg (N=132) n (%)	Ritlecitinib 50/50 mg (N=130) n (%)
Infections and infestations	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.9)**	**1 (0.8)**	**0 (0.0)**
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Empyema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Diverticulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)

Source: Clinical Reviewer's OCS Analysis Studio analysis, Safety Explorer. Consistent with M 2.7.4 Table 34.

Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Ri lecitinib 10 mg" and SAFFL = "Y" (Ritlecitinib 10 mg); TRT01A = "Ritlecitinib 200/30 mg" and SAFFL = "Y" (Ritlecitinib 200/30 mg); TRT01A = "Ritlecitinib 200/50 mg" and SAFFL = "Y" (Ritlecitinib 200/50 mg); TRT01A = "Ri lecitinib 30/30 mg" and SAFFL = "Y" (Ritlecitinib 30/30 mg); TRT01A = "Ritleci inib 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); TRTEMFL = "Y" and AESOC = "Infections and infestations" and AESER = "Y" (Adverse Events).

OYEP
The proportion and IR/100 PYE of subjects reported with serious infections was similar in the

All 50 mg (0.8%, 0.86/100 PYE) and All 30 mg (0.8%, 0.88/100 PYE) dose groups. Appendicitis was the most frequent SAE with 1 subject in each dose group. No events were reported in 10 mg dose group.

AEP

The proportion and IR/100 PYE of subjects reported with serious infections in the All 50 mg (0.8%, 0.66/100 PYE) and Any Ritlecitinib (0.9%, 0.64/100 PYE) dose groups were similar or lower than those reported in the PCPAA and OYEP pools. This trend does not point to an increased risk of serious infections with longer duration of treatment. The following subjects with serious infections were reported in the All 50 mg group: appendicitis (4), COVID-19 (2), and COVID-19 pneumonia (2), vulval abscess (1), empyema (1), sepsis (1), septic shock (1), Staphylococcal sepsis (1), and pyelonephritis (1).

In Any ritlecitinib group, 2 additional serious infections: diverticulitis (1), and appendicitis (1) were reported.

No subject with a reported serious infection had an abnormally low lymphocyte count (ALC< LLN) at baseline or prior to SAE onset.

Narratives for subjects with serious infections reported in the PCPAA(V) and OYEP pools are included under SAE narratives section of this review. Narratives for other subjects with serious infections in the AEP pool are summarized below:

Summary of additional narratives for serious infections in the AEP pool

PT reported as SAE	Study/ Subject ID	Age/ Sex	Dose at onset/ Day	Severity	Causality/ Related per Investigator/ Sponsor/ Adjudicated as OI?	Intervention /Treatment Action	AE outcome/ Day
COVID-19 infection	B7981032/ (b) (6)	71/F	200/50 mg/ D556	severe	No/No/No	Hospitalized/ discontinued	Recovering/ D575
vulval abscess	B7981032 (b) (6)	23/F	200/50 mg/	mild	No/No/No	Hospitalized/ Interrupted D113-118	Recovered/ 65
COVID-19 pneumonia/ acute respiratory failure	B7981032/ (b) (6)	15/M	200/50 mg/ D220	severe	No/possibly related/No	Hospitalized/ discontinued	Recovered/ D251
septic shock/ delirium			200/50 mg/ D227	severe	No/possibly related/No	discontinued	Recovered/ D251
appendicitis	B7981015/ (b) (6)	13/F	200/30 mg/ D240	severe	No/No/No	Hospitalized/ Interrupted	Recovered/ D261
appendicitis	B7981032/ (b) (6)	20/F	50 mg/ D226	severe	No/No/No	Hospitalized/	Recovered/ D226

						None	
appendicitis	B7981032/ (b) (6)	26/M	50 mg/ D368	moderate	No/No/No	Hospitalized/ Interrupted	Recovering / Day 369
appendicitis	B7981032/ (b) (6)	14/F	50 mg/ D297	severe	No/No/No	Hospitalized/ Interrupted D299-308	Recovered/ D302
staphylococcal sepsis	B7981032/ (b) (6)	28/F	50 mg/ D600	severe	No/No/No	Hospitalized/ discontinued	Recovered/ D629
pyelonephritis	B7981032/ (b) (6)	62/F	50 mg/ D172	severe	Yes/Yes/No	Hospitalized/ Discontinued on D182	Recovered/ D177
COVID-19 pneumonia/ Acute respiratory failure	B7981032/ (b) (6)	43/F	50 mg/ D238	Severe/ moderate	No/No/No	Hospitalized/ Discontinued on D290	Recovered/ D266
COVID-19	B7981032/ (b) (6)	52/F	50 mg/ D383	severe	No/No/	Hospitalized/ Interrupted on D383-411	Recovered/ D391

Source: M 2.7.4, Sec. 2.1.5.1.5 and M 5.3.5.2 AA B7981032 CSR Sec. 14.3.3.

8.2.7. Opportunistic infections (OI) and Tuberculosis (TB)

Tuberculosis (TB)-

The Applicant identified TEAEs reported as TB using the following CMQ PTs:

Table 112. Tuberculosis CMQ Terms (PT)

Adrenal gland tuberculosis	Mammary tuberculosis	Tuberculosis of eye
Bone tuberculosis	Meningitis tuberculous	Tuberculosis of genitourinary system
Bovine tuberculosis	Oesophageal tuberculosis	Tuberculosis of intrathoracic lymph nodes

Choroid tubercles	Oral tuberculosis	Tuberculosis of peripheral lymph nodes
Congenital tuberculosis	Pericarditis tuberculous	Tuberculosis ureter
Conjunctivitis tuberculous	Peritoneal tuberculosis	Tuberculous endometritis
Cutaneous tuberculosis	Prostatitis tuberculous	Tuberculous laryngitis
Disseminated Bacillus Calmette-Guerin infection	Pulmonary tuberculoma	Tuberculous pleurisy
Disseminated tuberculosis	Pulmonary tuberculosis	Tuberculous tenosynovitis
Ear tuberculosis	Renal tuberculosis	Mycobacterium tuberculosis complex test
Epididymitis tuberculous	Salpingitis tuberculous	Mycobacterium tuberculosis complex test positive
Erythema induratum	Silicotuberculosis	Tuberculin test
Extrapulmonary tuberculosis	Spleen tuberculosis	Tuberculin test false negative
Female genital tract tuberculosis	Thyroid tuberculosis	Tuberculin test positive
Immune reconstitution inflammatory syndrome associated tuberculosis	Tuberculoma of central nervous system	Interferon gamma release assay
Intestinal tuberculosis	Tuberculosis	Interferon gamma release assay positive
Joint tuberculosis	Tuberculosis bladder	Atypical mycobacterium test positive
Latent tuberculosis	Tuberculosis gastrointestinal	Seroconversion test
Lupus vulgaris	Tuberculosis liver	Seroconversion test positive
Lymph node tuberculosis	Tuberculosis of central nervous system	False positive tuberculosis test
Male genital tract tuberculosis		

Source: M 2.7.4, Table 112 (Appendix 3.3).

The Applicant reported no cases of active TB in any safety pool. TEAEs of latent TB or positive TB test results did not meet reportability criteria of active TB by an OI Review Committee.

Opportunistic infections (OI)- The only infections adjudicated as OI in the PCPAAV pool were HZ (1) and VZV infection (1), as summarized in the following table:

Summary of TEAEs adjudicated as Opportunistic Infections in the PCPAAV pool (Weeks 0-24)

System Organ Class - Preferred Term	Placebo (N=279) n (%)	Ritlecitinib 10 mg (N=111) n (%)	Ritlecitinib 100/50 mg (N=67) n (%)	Ritlecitinib 200/30 mg (N=129) n (%)	Ritlecitinib 200/50 mg (N=280) n (%)	Ritlecitinib 30/30 mg (N=182) n (%)	Ritlecitinib 50/50 mg (N=197) n (%)
Infections and infestations	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.4)**	**0 (0.0)**	**1 (0.5)**
Herpes zoster	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Varicella zoster virus infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Ri lecitinib 10 mg" and SAFFL = "Y" (Ritlecitinib 10 mg); TRT01A = "Ritlecitinib 100/50 mg" and SAFFL = "Y" (Ritlecitinib 100/50 mg); TRT01A = "Ritlecitinib 200/30 mg" and SAFFL = "Y" (Ritlecitinib 200/30 mg); TRT01A = "Ritlecitinib 200/50 mg" and SAFFL = "Y" (Ritlecitinib 200/50 mg); TRT01A = "Ritlecitinib 30/30 mg" and SAFFL = "Y" (Ritlecitinib 30/30 mg); TRT01A = "Ri lecitinib 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); TRTEMFL = "Y" and CRIT4FL = "Y" (Adverse Events).

Refer to the narratives for the 2 subjects with multidermatomal HZ adjudicated as OIs in the HZ section of this review.

8.2.8. Herpes zoster (HZ)

The Applicant identified TEAEs reported as HZ using the following Customized MedDRA Querry (CMQ) PTs:

Table 110. Herpes Zoster CMQ Terms (PT)

Genital herpes zoster	Herpes zoster meningoradiculitis	Varicella zoster gastritis
Herpes zoster	Herpes zoster necrotising retinopathy	Varicella zoster oesophagitis
Herpes zoster cutaneous disseminated	Herpes zoster oticus	Varicella zoster pneumonia
Herpes zoster infection neurological	Herpes zoster pharyngitis	Varicella zoster sepsis
Herpes zoster meningitis	Herpes zoster reactivation	Varicella zoster virus infection
Herpes zoster meningoencephalitis	Ophthalmic herpes zoster	Post herpetic neuralgia
Herpes zoster meningomyelitis		

Source: M 2.7.4, Table 110 (Appendix 3.1).

In the PCPAA pool, TEAEs of HZ were reported for 2 (1.5%) subjects in the ritlecitinib 50/50 mg group compared to 0 in the placebo group (none were SAE, severe AE, or AELD).

Summary of TEAEs for Herpes Zoster (HZ) in the PCPAA pool (Weeks 0-24)

Preferred Term	Placebo (N=213) n (%)	Ritlecitinib 10 mg (N=62) n (%)	Ritlecitinib 200/30 mg (N=129) n (%)	Ritlecitinib 200/50 mg (N=215) n (%)	Ritlecitinib 30/30 mg (N=132) n (%)	Ritlecitinib 50/50 mg (N=130) n (%)
Herpes zoster	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)	2 (1.5)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Ri lecitinib 10 mg" and SAFFL = "Y" (Ritlecitinib 10 mg); TRT01A = "Ritlecitinib 200/30 mg" and SAFFL = "Y" (Ritlecitinib 200/30 mg); TRT01A = "Ritlecitinib 200/50 mg" and SAFFL = "Y" (Ritlecitinib 200/50 mg); TRT01A = "Ri lecitinib 30/30 mg" and SAFFL = "Y" (Ritlecitinib 30/30 mg); TRT01A = "Ritleci inib 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); TRTEMFL = "Y" and AEDECOD = "Herpes zoster" (Adverse Events).

Similarly, in the PCPAAV pool, TEAEs of HZ were reported for 8 subjects, including 3 (1.5%) subjects in the 50/50 mg group, as summarized in the following table:

Summary of TEAEs for Herpes Zoster (HZ) in the PCPAAV pool (Weeks 0-24)

System Organ Class - Preferred Term	Placebo (N=279) n (%)	Ritlecitinib 10 mg (N=111) n (%)	Ritlecitinib 100/50 mg (N=67) n (%)	Ritlecitinib 200/30 mg (N=129) n (%)	Ritlecitinib 200/50 mg (N=280) n (%)	Ritlecitinib 30/30 mg (N=182) n (%)	Ritlecitinib 50/50 mg (N=197) n (%)
Infections and infestations	**1 (0.4)**	**0 (0.0)**	**0 (0.0)**	**2 (1.6)**	**2 (0.7)**	**0 (0.0)**	**3 (1.5)**
Herpes zoster	1 (0.4)	0 (0.0)	0 (0.0)	2 (1.6)	2 (0.7)	0 (0.0)	3 (1.5)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Ri lecitinib 10 mg" and SAFFL = "Y" (Ritlecitinib 10 mg); TRT01A = "Ritlecitinib 100/50 mg" and SAFFL = "Y" (Ritlecitinib 100/50 mg); TRT01A = "Ritlecitinib 200/30 mg" and SAFFL = "Y" (Ritlecitinib 200/30 mg); TRT01A = "Ritlecitinib 200/50 mg" and SAFFL = "Y" (Ritlecitinib 200/50 mg); TRT01A = "Ritlecitinib 30/30 mg" and SAFFL = "Y" (Ritlecitinib 30/30 mg); TRT01A = "Ri lecitinib 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); TRTEMFL = "Y" and AEDECOD = "Herpes zoster" (Adverse Events).

In the PCPAA pool, one subject in ritlecitinib 200/50 mg group was reported with an AE of varicella zoster virus infection (multi-dermatomal herpes zoster) that met criteria as an OI.
In the PCPAAV pool, one additional subject was reported with an OI of multi-dermatomal HZ, as summarized in the following narratives:

- Subject ID: B7981037 (b) (6) (ritlecitinib 200/50 mg group)

not SAE, mild, not related, dose not changed, recovered:
A 39-year-old white female subject from the US with an unknown history of chicken pox infection or varicella vaccination and no history of HZ or herpes zoster vaccination was reported with varicella zoster virus infection on Day 30 located on 3 dermatomes on her back. This AE was reviewed by an external OI Review Committee and met criteria as an opportunistic infection based on the category of multidermatomal HZ (nonadjacent or >2 adjacent dermatomes). The AE wasreported as resolved on Day 40. Subject was continued in the trial with the last reported dose of ritlecitinib taken on D300.

- Subject ID: B7981019/ (b) (6) (ritlecitinib 50 mg group)

not-SAE, moderate, related, drug interrupted, recovered:
A 36-year-old white male subject with a history of chicken pox during childhood, and no previous vaccination for chicken pox or herpes zoster, was reported with herpes zoster on Study Day 98. The event was reviewed by an external OI Review Committee and met criteria as an opportunistic infection based on the category multidermatomal HZ (nonadjacent or >2 adjacent dermatomes). The AE wasreported as resolved on Day 117. Subject withdrew consent on D 166 due to concerns related to COVID 19, and was discontinued from treatment with the last reported dose of ritlecitinib taken on D 164.

<u>HZ frequency by absolute lymphocyte count (ALC) prior to the onset of AE</u>
No association between a decrease in the ALC and TEAEs of HZ were identified. For the ritlecitinib 50 mg dose group in the AEP, 1/21 subjects had an ALC < LLN (= 0.8 x $10^3/mm^3$) and 20/21 subjects had an ALC ≥ LLN prior to the onset of an AE of HZ.

8.2.9. Herpes simplex (HS)

The Applicant identified TEAEs reported as HS using the following CMQ PTs:

Table 111. Herpes Simplex CMQ Terms (PT)		
Colitis herpes	Herpes simplex gastritis	Herpes simplex virus conjunctivitis neonatal
Congenital herpes simplex infection	Herpes simplex hepatitis	Herpes simplex visceral
Gastritis herpes	Herpes simplex meningitis	Herpes virus infection
Genital herpes	Herpes simplex meningoencephalitis	Lower respiratory tract herpes infection
Genital herpes simplex	Herpes simplex meningomyelitis	Meningitis herpes
Herpes dermatitis	Herpes simplex necrotising retinopathy	Meningoencephalitis herpes simplex neonatal
Herpes oesophagitis	Herpes simplex oesophagitis	Meningoencephalitis herpetic
Herpes pharyngitis	Herpes simplex otitis externa	Meningomyelitis herpes
Herpes sepsis	Herpes simplex pharyngitis	Nasal herpes
Herpes simplex	Herpes simplex pneumonia	Neonatal mucocutaneous herpes simplex
Herpes simplex bronchitis	Herpes simplex reactivation	Ophthalmic herpes simplex
Herpes simplex cervicitis	Herpes simplex sepsis	Oral herpes
Herpes simplex colitis	Herpes simplex viraemia	Pneumonia herpes viral
Herpes simplex encephalitis		

Source: M 2.7.4, Table 111 (Appendix 3.2).

In the PCPAA and PCPAAV pools, the frequency of HS reported as TEAES for the ritlecitinib 50/50 mg group and the placebo groups were similar. HS was reported for 2 (1.5%) and 4 (2%) subjects in the ritlecitinib 50/50 mg group, compared to 5 (2.3%) and 6 (2.2%) subjects in their respective placebo group (none were SAE, severe AE, AELD, OI, or genital HS) as summarized in the following table:

Summary of TEAEs for Herpes Simplex (HS) in the PCPAAV pool (Weeks 0-24)

System Organ Class - Preferred Term	Placebo (N=279) n (%)	Ritlecitinib 10 mg (N=111) n (%)	Ritlecitinib 100/50 mg (N=67) n (%)	Ritlecitinib 200/30 mg (N=129) n (%)	Ritlecitinib 200/50 mg (N=280) n (%)	Ritlecitinib 30/30 mg (N=182) n (%)	Ritlecitinib 50/50 mg (N=197) n (%)
Infections and infestations	**6 (2.2)**	**1 (0.9)**	**0 (0.0)**	**3 (2.3)**	**5 (1.8)**	**4 (2.2)**	**4 (2.0)**
Herpes simplex	4 (1.4)	1 (0.9)	0 (0.0)	2 (1.6)	2 (0.7)	3 (1.6)	4 (2.0)
Herpes simplex reactivation	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Oral herpes	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.8)	3 (1.1)	1 (0.5)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Ri lecitinib 10 mg" and SAFFL = "Y" (Ritlecitinib 10 mg); TRT01A = "Ritlecitinib 100/50 mg" and SAFFL = "Y" (Ritlecitinib 100/50 mg); TRT01A = "Ritlecitinib 200/30 mg" and SAFFL = "Y" (Ritlecitinib 200/30 mg); TRT01A = "Ritlecitinib 200/50 mg" and SAFFL = "Y" (Ritlecitinib 200/50 mg); TRT01A = "Ritlecitinib 30/30 mg" and SAFFL = "Y" (Ritlecitinib 30/30 mg); TRT01A = "Ri lecitinib 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); TRTEMFL = "Y" and AEDECOD = "Herpes simplex" or "Herpes simplex reactivation" or "Oral herpes" (Adverse Events).

8.2.10. Malignancy

Malignancies (excluding non-melanoma skin cancers (NMSC))

In the PCPAA pool, one subject (ID: B7981015/ (b) (6) was reported with an adjudicated SAE

of malignancy (lobular carcinoma of the breast).

In the OYEP pool, one additional subject (Subject ID: B7981015(b) (6)) was reported with an adjudicated SAE of malignancy (breast cancer). Refer to the narratives for these 2 subjects in the SAE narratives section of this review.

Five (5) subjects in the long-term trial B7981032 were adjudicated with SAEs of malignancy; including 2 subjects (IDs: B7981032(b) (6) B7981032(b) (6) with breast cancer, 1 subject (ID: B7981032/(b) (6)) with papillary thyroid cancer, 1 subject (ID: B7981032/(b) (6) with testis cancer, and 1 subject (B7981032/(b) (6)) with malignant melanoma.

Non-Melanoma Skin Cancers (NMSC)
No NMSCs were reported in the PCPAA or OYEP pools. In the PCPAAV pool, 2 NMSCs were reported:

- Basal cell carcinoma (BCC) in 1 subject (ID: B7981019(b) (6))- A 50-year-old white female subject with history of vitiligo. The non-serious AE of BCC on scalp (Day 106) was reported as moderate, unrelated to study drug (due to sun exposure) per investigator, and resolved following excision, and did not lead to discontinuation of study drug.

- Squamous cell carcinoma (SCC) in 1 subject (ID: B7981019(b) (6)- 63-year-old white male with history of vitiligo and SCC on bilateral legs. The non-serious AE of SCC on right arm (Day 120) was reported as mild, unrelated to study drug per investigator, and resolved following excision, and did not lead to discontinuation of study drug.

Three (3) subjects in the long-term trial B7981032 were reported with AEs of NMSC, including 2 subjects (IDs: B7981032/(b) (6) B7981032(b) (6) with BCC and 1 subject with Bowen's disease (ID: B7981032(b) (6).

8.2.11. Major Adverse Cardiovascular Events (MACE) and Venous/Arterial Thromboembolic Events (VTE/ATE)

MACE
No TEAEs were reported as a MACE in the PCPAA, PCPAAV, and OYEP pools.
In the LTS B7981032, the following 3 SAEs were adjudicated by an external Cardiovascular Event Adjudication Committee as MACE:

1. Subject ID: B7981032(b) (6)- fatal SAEs of acute respiratory failure/ cardiorespiratory arrest. Refer to the narrative in the Death section of this review.
2. Subject ID: B7981032/(b) (6)- non-fatal SAE of acute myocardial infarction (MI) (severe, not related) on Day 384, followed by a percutaneous transluminal coronary angioplasty/percutaneous coronary intervention (PTCA/PCI) adjudicated as a non-MACE event on Day 385. Subject was a 49-year-old male from the US with history of current smoking, hyperlipidemia, and diabetes mellitus. Study drug was discontinued, and

subject remained in the study.

3. Subject ID: B7981032/ (b) (6) - non-fatal SAE of ischemic stroke (retinal artery occlusion (RAO)) on Day 442 reported as moderate, not related, resolved with sequalae; a nonserious moderate TEAE of vision blurred on Day 442 which led to permanent discontinuation of study drug, and was determined to meet Neurosafety Event Adjudication Committee criteria for visual impairment and blindness; a nonserious moderate TEAE of atrial septal defect (ASD) and a small patent foramen ovale (PFO) with right-to-left (R-L) shunt which led to subject's discontinuation from study on Day 445; and a nonserious moderate TEAE of antiphospholipid syndrome/ANA (+) on Day 463 reviewed by an external Cardiovascular Event Adjudication Committee. Subject was a 48-year-old white female from the US with history of migraine, 3 spontaneous abortions during first trimesters and family history of ASD and systemic lupus erythematosus (SLE).

Thromboembolic Events

The two ATEs reported in the LTS trial B7981032 (MI (1) and RAO (1)) were the same SAEs reported under the MACE section above, and were identified using the following SMQ:

Arterial Thromboembolic Events CMQ Terms (PT)

Acute myocardial infarction	Coronary artery occlusion	Post procedural myocardial infarction
Amaurosis	Coronary artery thrombosis	Postinfarction angina
Amaurosis fugax	Embolism arterial	Precerebral artery occlusion
Aortic embolus	Femoral artery embolism	Precerebral artery thrombosis
Aortic thrombosis	Hepatic artery embolism	Pulmonary artery occlusion
Arterial occlusive disease	Hepatic artery occlusion	Pulmonary artery thrombosis
Arterial thrombosis	Hepatic artery thrombosis	Renal artery occlusion
Basal ganglia infarction	Iliac artery embolism	Renal artery thrombosis
Basilar artery occlusion	Iliac artery occlusion	Renal embolism
Basilar artery thrombosis	Ischaemic cerebral infarction	Retinal artery embolism
Blindness transient	Ischaemic stroke	Retinal artery occlusion
Brachiocephalic artery occlusion	Lacunar infarction	Retinal artery thrombosis
Capsular warning syndrome	Leriche syndrome	Silent myocardial infarction
Carotid arterial embolus	Mesenteric arterial occlusion	Spinal artery embolism
Carotid artery occlusion	Mesenteric artery embolism	Spinal artery thrombosis
Carotid artery thrombosis	Mesenteric artery stenosis	Splenic artery thrombosis
Cerebellar artery occlusion	Mesenteric artery thrombosis	Splenic embolism
Cerebellar artery thrombosis	Myocardial infarction	Subclavian artery embolism
Cerebral artery embolism	Myocardial necrosis	Subclavian artery occlusion
Cerebral artery occlusion	Papillary muscle infarction	Subclavian artery thrombosis
Cerebral artery thrombosis	Penile artery occlusion	Transient ischaemic attack
Cerebral hypoperfusion	Peripheral arterial occlusive disease	Truncus coeliacus thrombosis
Cerebrovascular stenosis	Peripheral artery occlusion	Vertebral artery occlusion
Coeliac artery occlusion	Peripheral artery thrombosis	Vertebral artery thrombosis
Coronary artery embolism	Peripheral embolism	

Source: M 2.7.4, Table 113.

Venous Thromboembolic Events

Adjudicated VTEs included SAEs reported as deep venous thrombosis (DVT) (0), and pulmonary embolism (PE) (1) with the following narrative:

- Subject ID: B7981015/ (b) (6) SAE of PE of moderate severity on Day 169.

A 54-year-old female from Spain with history of monoclonal gammopathy of undetermined significance (MGUS), morbid obesity (weight: 118 kg, BMI: 46 kg/m2), sleep apnea and cardiovascular disease (hypertension, hyperlipidemia).
Subject was reported with nonserious, mild TEAEs of general discomfort and SARS-CoV-2 test positive on Day 60 (resolved on Day 86). Subject evaluated at the Emergency Department Right leg and chest pain on Day 169 including imaging studies which showed (+) acute bilateral pulmonary embolism and no DVTs on Day 170 and led to discontinuation from the trial. The SAE of PE was considered not related to study drug by the investigator but related by the sponsor and the outcome of SAE was reported as resolved on Day 178.

8.2.12. Bleeding Events and atrial fibrillation

Atrial fibrillation
Atrial fibrillation has been reported as an adverse effect for some BTK inhibitors. In the AEP pool, no TEAEs of atrial fibrillation was reported.

Bleeding Events
Increased risk of hemorrhage has been associated with some BTK inhibitors, in the presence or absence of thrombocytopenia. TEAEs associated with bleeding were identified in the PCPAAV and AEP pools using the hemorrhage standardized MedDRA query (SMQ). No clinically significant differences between treatment groups for the frequency of TEAEs in the bleeding SMQ or any association with changes in the platelet counts were identified.

In the PCPAAV pool, the following (nonserious, mild, non-AELD) PTs were reported in > 1 subject: contusion (13), epistaxis (7), hematuria (2), ecchymosis (4), and hematoma (3). Two subjects had platelet counts between CTCAE Grade 2 (> 75,000/mm3) and < LLN.

In the AEP, the following AEs were reported in > 1 subject: contusion (24), epistaxis (22), heavy menstrual bleeding (8), hematuria (5), vaginal hemorrhage (5), intermenstrual bleeding (4), ecchymosis (4), blood urine present (3), conjunctival hemorrhage (2), hematochezia (2), traumatic hematoma (2), and hematoma (2).

One (1) subject was reported with a SAE of subdural hematoma, and four (4) subjects with (nonserious, mild, non-AELD) TEAEs reported in the Hemorrhage SMQ had a CTCAE Grade-1 platelet counts (between 75,000/mm^3 and LLN) prior to the onset of their AEs, as summarized in the following narratives:

1. Subject ID: B7981032 (b) (6) SAE of subdural hematoma

A 44-year-old Japanese male reported with a severe SAE of subdural hematoma on Day 80, considered unrelated to study drug per investigator and sponsor (due to head injury from a fall on Day 56 while under the influence of alcohol), and led to the interruption of study drug on Day 87 following reported mild left lower extremity paralysis. Platelet counts remained abobe the LLN. Subject was hospitalized and underwent surgery (hematoma evacuation) on Day 88,

and discharged from hospital on Day 95. Study drug was restarted on Day 98, and the SAE was reported as resolved on Day 107 and subject continued treatment in the study with last dose on Day 630. This SAE was reviewed by an external Cardiovascular Event Adjudication Committee and was determined not to meet criteria for a cardiovascular event.

2. Subject ID: B7931005/ (b) (6) TEAE of contusion/increased bruising

A 19-year-old white female reported with AE on Day 31 which was attributed to trauma. Platelet count was 140 × 10^3 /mm^3 at baseline, 113 × 10^3 /mm^3 on Day 29 and 148 × 10^3 /mm^3 on Day 34. Study drug was continued and AE was reported as resolved on Day 141.

3. Subject ID: B7981032 (b) (6) TEAE of hematochezia (blood in stool)

The TEAE was reported on Day 340 . Platelet count was 180 × 10^3 /mm^3at baseline, 132 × 10^3 /mm^3 on Day 334, and 140 × 10^3 /mm^3 on Day 350. Study drug was continued and AE was reported as resolved on Day 340.

4. Subject ID: B7981019 (b) (6) TEAE of contusion (left thigh bruise)

The TEAE was reported on Study Day 109. Platelet count was 151 × 10^3 /mm^3 at baseline, 134 × 10^3 /mm^3 on Study Day 83, and 164 × 10^3 /mm^3 on Study Day 142. Study drug was continued and AE was reported as resolved on Day 115.

5. Subject ID: B7981015/ (b) (6) TEAEs of epistaxis and gingival bleeding

The TEAEs was reported on Days 20 and 61 respectively. Platelet count was 160 × 10^3 /mm^3 at baseline, 130 × 10^3 /mm^3 on Day 40, and 148 × 10^3 /mm^3 on Day 64.
Study drug was continued and AEs was reported as resolved on Days 20 and 140 respectively.

8.2.13. Neuro-audiological Adverse Events

Neurologic AEs of interest

A finding of axonal dystrophy was reported in the nonclinical 9-month dog toxicity studies of ritlecitinib (species specific finding). During Phase 2/3 AA trials, neurosafety assessments including auditory assessments by an audiologist and neurological assessments during physical examinations (and a referrals to a neurologist if indicated) were conducted at protocol-specified visits. Neurological and audiological AEs of interest were adjudicated by the Neurosafety Event Adjudication Committee (NSEAC), a blinded external adjudication committee of experts.

In addition, the Applicant conducted Study B7981037, entitled: “A Phase 2a, randomized, double-blind, placebo-controlled study investigating the safety of Ritlecitinib (PF-06651600) in adult participants with AA”, which evaluated brainstem auditory evoked potential (BAEP) and assessed intraepidermal nerve fiber density (IENFD) and axonal swelling in skin punch biopsies over a 9-month placebo-controlled period, followed by a 15-month active-treatment extension. In this study, change from baseline (CFB) to Month 9 in the mean/median IENFD and CFB to Month 9 in the percentage of IENFs with axonal swellings were small and similar between

ritlecitinib 200/50 mg and placebo.

The adjudicated neurological AEs of interest were reported with similar frequencies between the ritlecitinib and placebo groups for the PCPAA, PCPAAV pools, and between ritlecitinib dose groups in the OYEP pool. Paresthesia and dysesthesia were the most frequently adjudicated AEs and reported with similar frequency between ritlecitinib and placebo groups, as summarized in the following table.

Summary of Adjudicated Neurologic TEAEs- PCPAA pool- safety analysis population

Preferred Term	Placebo (N=213) n (%)	Ritlecitinib 10 mg (N=62) n (%)	Ritlecitinib 200/30 mg (N=129) n (%)	Ritlecitinib 200/50 mg (N=215) n (%)	Ritlecitinib 30/30 mg (N=132) n (%)	Ritlecitinib 50/50 mg (N=130) n (%)
Any AE	9 (4.2)	4 (6.5)	5 (3.9)	6 (2.8)	8 (6.1)	2 (1.5)
Dizziness	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Headache	2 (0.9)	0 (0.0)	1 (0.8)	1 (0.5)	3 (2.3)	0 (0.0)
Hyperaesthesia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)
Hypoaesthesia	2 (0.9)	0 (0.0)	2 (1.6)	1 (0.5)	2 (1.5)	2 (1.5)
Lethargy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Orthostatic hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Paraesthesia	1 (0.5)	0 (0.0)	1 (0.8)	1 (0.5)	0 (0.0)	0 (0.0)
Restlessness	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	1 (0.5)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	3 (1.4)	1 (1.6)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Vertigo positional	0 (0.0)	1 (1.6)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Visual impairment	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer. Consistent with M 2.7.4, Table 44.

Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Ri lecitinib 10 mg" and SAFFL = "Y" (Ritlecitinib 10 mg); TRT01A = "Ritlecitinib 200/30 mg" and SAFFL = "Y" (Ritlecitinib 200/30 mg); TRT01A = "Ritlecitinib 200/50 mg" and SAFFL = "Y" (Ritlecitinib 200/50 mg); TRT01A = "Ritlecitinib 30/30 mg" and SAFFL = "Y" (Ritlecitinib 30/30 mg); TRT01A = "Ritlecitinib 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); SAFFL = "Y" and PARCAT1 = "Neurology" (Adverse Events).

For the AEP, 74 (4.9%) subjects in All 50 mg were reported with AEs that met adjudication criteria for neurological safety. Most frequently adjudicated AEs of interest in All 50 mg group included Paresthesia and dysesthesia in 22 (1.4%), headache in 13 (0.9%), and Peripheral neuropathy in 4 (0.3%) subjects.

Audiologic AEs of interest

Audiological testing (pure tone, speech, and immittance audiometry) was conducted in the Phase 2/3 trials at pre-specified visits to assess for potential changes in hearing. TEAEs

adjudicated by the external NSEAC to meet criteria for an audiologic AEs of interest included audiologic tests and subjects' spontaneously reported TEAEs related to hearing loss.

Study B7981037 results did not show an adverse effect of ritlecitinib compared to placebo on BAEP I-V interwave latency (standard test to assess integrity of human brainstem auditory pathway), or on BAEP Wave V amplitude at 80dB nHL.

The Adjudicated AEs did not meet the criteria for a central hearing disorder. The AEs adjudicated as sensorineural hearing loss (SNHL) were reported in 2 subjects in PCPAA pool (1 subject (0.8%) in each of Ritlecitinib 30/30 mg and Ritlecitinib 50/50 mg group), 3 subjects in PCPAAV pool, 5 subjects in the OYEP, and 15 subjects in the AEP. AEs of SNHL were reported in no adolescent subjects, were more frequent in subjects > 65 years of age, and were not consistent with the typical pattern of hearing loss due to ototoxic agents (high-frequency, bilateral, dose-dependent, and progressive).

8.2.14. Dermatologic Adverse Events

The frequency of the reported dermatological AEs of interest (CMQ terms by PT, HLT, M 2.7.4, Table 116) was similar among ritlecitinib and placebo groups. Most dermatologic AEs were mild to moderate in severity, did not lead to treatment discontinuation, and reported as resolved.

In the PCPAA and PCPAAV pools, the most frequently reported dermatologic AEs for ritlecitinib groups (> placebo) which increased with increasing dose were urticaria, folliculitis, acne, and atopic dermatitis. AEs of rashes were more frequent in ritlecitinib group, compared to the placebo group, as summarized in the following tables.

Summary of Dermatologic TEAEs of interest- PCPAA pool- safety analysis population- Grouped Terms

Grouped Term	Placebo (N=213) n (%)	Ritlecitinib 10 mg (N=62) n (%)	Ritlecitinib 200/30 mg (N=129) n (%)	Ritlecitinib 200/50 mg (N=215) n (%)	Ritlecitinib 30/30 mg (N=132) n (%)	Ritlecitinib 50/50 mg (N=130) n (%)
Acnes*	10 (4.7)	3 (4.8)	12 (9.3)	17 (7.9)	8 (6.1)	10 (7.7)
Folliculitis*	4 (1.9)	2 (3.2)	8 (6.2)	12 (5.6)	3 (2.3)	4 (3.1)
Rashes*	3 (1.4)	1 (1.6)	3 (2.3)	5 (2.3)	2 (1.5)	6 (4.6)
urticarias*	3 (1.4)	1 (1.6)	7 (5.4)	12 (5.6)	4 (3.0)	6 (4.6)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Ri lecitinib 10 mg" and SAFFL = "Y" (Ritlecitinib 10 mg); TRT01A = "Ritlecitinib 200/30 mg" and SAFFL = "Y" (Ritlecitinib 200/30 mg); TRT01A = "Ritlecitinib 200/50 mg" and SAFFL = "Y" (Ritlecitinib 200/50 mg); TRT01A = "Ri lecitinib 30/30 mg" and SAFFL = "Y" (Ritlecitinib 30/30 mg); TRT01A = "Ritleci inib 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); TRTEMFL = "Y" (Adverse Events).

Acnes* includes: Acne, Acne cystic, Acne pustular, Dermatitis acneiform.

Folliculitis* includes: Folliculitis.

Rashes* includes: Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash papular.

urticarias* includes: Mechanical urticaria, Urticaria.

Summary of Dermatologic TEAEs of interest- PCPAAV pool- safety analysis population

System Organ Class/HLT or PT	Placebo (N=279) n (%)	Ritlecitinib 10 mg (N=111) n (%)	Ritlecitinib 100/50 mg (N=67) n (%)	Ritlecitinib 200/30 mg (N=129) n (%)	Ritlecitinib 200/50 mg (N=280) n (%)	Ritlecitinib 30/30 mg (N=182) n (%)	Ritlecitinib 50/50 mg (N=197) n (%)
Skin and subcutaneous tissue disorders- HLT= Acnes	11 (3.9)	3 (2.7)	1 (1.5)	11 (8.5)	18 (6.4)	10 (5.5)	15 (7.6)
Skin and subcutaneous tissue disorders- HLT = Rashes, eruptions and exanthems NEC	4 (1.4)	1 (0.9)	2 (3.0)	3 (2.3)	7 (2.5)	2 (1.1)	8 (4.1)
Skin and subcutaneous tissue disorders- HLT = Urticarias	3 (1.1)	4 (3.6)	3 (4.5)	7 (5.4)	14 (5.0)	4 (2.2)	8 (4.1)

Infections and infestations- Preferred Term = Folliculitis	8 (2.9)	2 (1.8)	1 (1.5)	8 (6.2)	12 (4.3)	4 (2.2)	5 (2.5)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Ri lecitinib 10 mg" and SAFFL = "Y" (Ritlecitinib 10 mg); TRT01A = "Ritlecitinib 100/50 mg" and SAFFL = "Y" (Ritlecitinib 100/50 mg); TRT01A = "Ritlecitinib 200/30 mg" and SAFFL = "Y" (Ritlecitinib 200/30 mg); TRT01A = "Ri lecitinib 200/50 mg" and SAFFL = "Y" (Ritlecitinib 200/50 mg); TRT01A = "Ritlecitinib 30/30 mg" and SAFFL = "Y" (Ritlecitinib 30/30 mg); TRT01A = "Ritlecitinib 50/50 mg" and SAFFL = "Y" (Ritlecitinib 50/50 mg); TRTEMFL = "Y" and AESOC = "Skin and subcutaneous tissue disorders" and AEHLT = "Acnes" (Adverse Events- including PT: Acne, Acne cystic, Dermatitis acneiform); TRTEMFL = "Y" and AESOC = "Skin and subcutaneous tissue disorders" and AEHLT = "Rashes, eruptions and exanthems NEC" (Adverse Events including PT: Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic); TRTEMFL = "Y" and AESOC = "Skin and subcutaneous tissue disorders" and AEHLT = “Urticarias”; TRTEMFL = "Y" and AEDECOD = "Folliculitis" (Adverse Events).

In the OYEP pool, most subjects reported with any dermatological AEs of interest were in the All 50 mg (32.6%) and All 30 mg (32.2%) groups, compared to 10 mg (27.4%) group.
The most frequently reported AEs by PT were urticaria, folliculitis, acne, and rash.
AEs of rash were reported for All 50 mg (4.2%) and All 30 mg (1.5%), compared to 10 mg (0).
AEs of urticaria were reported for All 50 mg (6.1%), All 30 mg (5.4%), compared to 10 mg (1.6%). The AEs more frequently reported for the All 30 mg group, compared with the All 50 mg group, were acne (8.4% vs. 6.9%) and pruritis (3.8% vs. 1.9%).

8.2.15. Growth and development (adolescents)

Height and weight measurements for adolescent subjects were converted to the standard deviation score (SDS), and the height SDS (standardized to the US population by age and gender) was calculated at each available visit.

No clinically significant changes were reported in All 50 mg group for subjects' growth curves and the height SDS (ranging from -1.1 to 2.2 with mean and median SDS near 0), and their weight SDS (ranging from -4.0 to 1.7 with median of 0) at months 6 and 12. Tanner staging of adolescent subjects showed progression of puberty from baseline to month 12.

No AEs related to growth disturbance (PTs of growth disorder, growth failure, growth retardation, body height below normal, body height abnormal, body height decreased) were reported in any trials.

Four (4) TEAEs related to fractures (hand, tibia, clavicle, hand) were reported for adolescent subjects in all trials. None were considered as related to the study drug (all were deemed to be related to injury or accidents by investigators).

8.2.16. Laboratory abnormalities

Refer to laboratory results section of this review.

8.2.17. Hypersensitivity

In the AEP safety pool, an SAE of anaphylaxis was reported for one subject (Subject ID: B7981032/ (b) (6)). TEAEs of hypersensitivity were reported for 6 subjects, including 1 SAE/AELD (Subject ID: B7981032 (b) (6)) and 5 nonserious, non-severe AEs (considered by the investigators as not related to study drug, but attributed to allergic conditions) and resolved without study drug interruption. The following narratives describe 2 SAEs of anaphylactic reaction and hypersensitivity.

- Subject ID: B7981032/ (b) (6) SAE of anaphylactic reaction (due to unknown cause)

A 40-year-old white female subject from Australia with past history of drug hypersensitivity to suxamethonium in 2001 and a drug reaction to sulfasalazine with eosinophilia and systemic symptoms (DRESS) syndrome in 2018, completed Trial B7981015 on ritlecitinib 30/30 mg QD (D 336), rolled over into study B7981032 and received ritlecitinib 50 mg QD. On Day 113, subject was reported with hives and swelling in throat, fainted and brought to the emergency department where she was treated with promethazine and prednisolone. The SAE was severe and assessed by the investigator as not related to study drug Study drug was interrupted (last dose of study drug) was on Day 118, and the SAE of anaphylactic reaction was resolved on Study Day 121.

On Day 127, subject developed a nonserious AE of severe eczema, requiring continued prednisolone therapy. Treatment with the study drug was not restarted, and subject was discontinued from study in response to the AELD of eczema.

- Subject ID: B7981032/ (b) (6) SAE of hypersensitivity

A 20-year-old white female subject from Canada a history of drug allergy to cefprozil (reaction described as skin erythema without fever or dyspnea) was enrolled in study B7981032 and received ritlecitinib 200 mg PO QD . She was reported with a SAE of hypersensitivity on Study Day 13, assessed by the investigator as of moderate-severity and as related to study drug.
On Study Day 13, subject experienced a nonserious AE of headache and received paracetamol, followed by redness and red spots all over her body with symptoms of fever and difficulty in breathing. She was treated with diphenhydramine on Day 15 at a walk-in clinic, and was sent to the emergency room (ER) when symptoms did not improve. At the ER, nonserious AEs of nausea, vomiting, dizziness, and headache were reported. Subject received metoclopramide, cetirizine, epinephrine, and prednisone. Study drug was permanently discontinued and the SAE of hypersensitivity was reported as resolved on Day 18. Subject did not meet the definition of anaphylaxis (no hypotension, respiratory distress or anaphylactic shock was reported).

8.2.18. Exposure during pregnancy

Pregnant or lactating patients were excluded from AA trials, and a TEAE of pregnancy reported during trials led to subject discontinuation from the trial (AELD). In the AEP safety pool (as of 2/28/2022), 12 pregnancies (maternal exposure) and 9 partner pregnancies were reported.
Maternal exposure
Pregnancies TEAEs related to maternal exposures were reported for 1 subject in the placebo group (outcome of spontaneous abortion) and the following 11 subjects, across all ritlecitinib dosing groups, with outcomes of elective termination (6), spontaneous abortion (3), outcome unknown (1), and full term normal baby (1). One AE of spontaneous abortion was reclassified as an elective abortion due to the use of emergency contraception. Two SAEs of spontaneous abortion are summarized below:

- Subject ID: B7981032 (b) (6) SAE of spontaneous abortion

A 34-year-old white female subject from Poland received treatment with ritlecitinib 10 mg QD in trial B7981015 for 340 days, followed by 50 mg QD to Day 198 in study B7981032. An AE of pregnancy was reported on Day 201 and led to discontinuation from study (last dose on Day 198). Subject was noncompliant with the additional barrier contraception requirement. An SAE of spontaneous abortion was reported on Day 233 (Gestational age of 13 weeks) followed by hospitalization and uterine curettage and resolved on Day 237. In the opinion of the Investigator and the Sponsor, SAE of abortion spontaneous was considered related to the study drug with the causality confounded by subject's age and use of contraceptive pill.

- Subject ID: B7981032 (b) (6) SAE of spontaneous abortion

A 17-year-old white female subject from the US, with no prior history of pregnancy, received treatment with ritlecitinib 30 mg QD in trial B7981015 for 343 days, followed by 50 mg QD to Day 519 in study B7981032. An AE of pregnancy was reported on Day 495 and led to discontinuation from study. Subject was noncompliant with the oral contraception requirement. An SAE of spontaneous abortion was reported on Day 501. Subject continued receiving the study drug after positive pregnancy test (last dose on Day 519). No treatment was reported for the AE of pregnancy or the SAE of spontaneous abortion. SAE was reported as resolved on Day 506. In the opinion of the Investigator and the Sponsor, SAE of abortion spontaneous was considered related to the study drug with the causality confounded by subject's concomitant use of adapalene/benzoyl peroxide.

Partner exposure

Pregnancies related to partner exposures were reported for 9 subjects across all ritlecitinib dosing groups with outcomes of elective termination (1), full-term/preterm live birth (5), and outcome unknown (3).

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

There were no patient-reported outcome assessments that measured safety parameters.

8.2.20. Safety Analyses by Demographic Subgroups

The Applicant analyzed TEAEs by intrinsic factors, including

- age group (≥12 to <18 years, ≥18 years, ≥65 years)
- sex
- race (Asian, black, white, and other)
- ethnicity (Hispanic/Latino, Not Hispanic/Latino)

Additional analyses by the Applicant included TEAEs by baseline body mass index (<25, ≥25 to <30, ≥30 to <40, ≥40 kg/m2); baseline weight (<median, ≥median), baseline disease severity (AT/AU, Non-AT/AU), and AA disease duration (<median, ≥ median).

The overall safety database and individual subgroup sample sizes were not sufficient to detect clinically meaningful differences in the frequency of TEAEs between individual subgroups.

The following Table summarizes Extent of exposure by overall, age, sex, and race in the PCPAA pool:

Table – PCPA: Duration of Exposure Overall and by Intrinsic Factors

Intrinsic Factor	200/50 mg n (total PY)	50/50 mg n (total PY)	All 50 mg n (total PY)	All 30 mg n (total PY)	10 mg n (total PY)	Placebo n (total PY)
Overall	215 (96.1)	130 (58.3)	345 (154.4)	261 (114.7)	62 (27.6)	213 (94.9)
Age						
Adolescent (12 to <18)	20 (9.3)	18 (8.0)	38 (17.3)	39 (18.2)	9 (4.1)	19 (8.9)
Adult (≥18)	195 (86.9)	112 (50.3)	307 (137.1)	222 (96.4)	53 (23.5)	194 (86.1)
Elderly (≥65)	5 (2.3)	3 (1.4)	8 (3.7)	8 (2.9)	0	6 (2.7)
Sex						
Male	73 (32.9)	59 (25.9)	132 (58.8)	96 (43.8)	20 (8.9)	73 (32.7)
Female	142 (63.2)	71 (32.4)	213 (95.6)	165 (70.9)	42 (18.8)	140 (62.2)
Race						
White	155 (70.2)	79 (35.4)	234 (105.6)	181 (78.2)	41 (18.3)	167 (74.5)
Asian	39 (17.6)	43 (19.2)	82 (36.9)	62 (28.8)	17 (7.6)	33 (14.8)
Black	17 (6.7)	5 (2.2)	22 (8.9)	9 (3.9)	2 (0.9)	8 (3.4)
Other	4 (1.6)	3 (1.4)	7 (3.0)	9 (3.9)	2 (0.9)	5 (2.3)

Source: M 2.7.4, Table 15.

TEAEs by Age Groups

The proportion of subjects by age groups reported with AEs, SAEs, severe AEs, AELDs, and ARs (drug-related AEs) for the PCPAA pool are summarized in the following Table.

Table – PCPAA: Proportion of subjects with TEAEs by Baseline Age

	12 to <18 years old						≥18 years old					
	200/50 mg	50/50 mg	All 50 mg	All 30 mg	10 mg	Placebo	200/50 mg	50/50 mg	All 50 mg	All 30 mg	10 mg	Placebo
Participants evaluable for AEs (n)	20	18	38	39	9	19	195	112	307	222	53	194
Number of adverse events	30	47	77	66	20	34	374	196	570	447	93	336
Participants with AEs (%)	75.0	83.3	78.9	69.2	66.7	78.9	69.7	74.1	71.3	71.6	69.8	68.6
Participants with serious AEs (%)	0	0	0	0	22.2	0	2.1	0	1.3	0.5	0	2.1
Participants with severe AEs (%)	0	0	0	0	0	0	2.1	1.8	2.0	4.5	3.8	2.6
Permanently discontinued from study or study drug due to AE (%)	0	5.6	2.6	0.0	11.1	0	3.1	0.9	2.3	1.8	1.9	2.6
Temporarily discontinued from study drug due to AE (%)	5.0	11.1	7.9	5.1	22.2	10.5	9.2	9.8	9.4	7.2	5.7	3.1
Participants with treatment-related AEs (%)	30.0	44.4	36.8	33.3	55.6	31.6	33.3	34.8	33.9	35.1	26.4	32.0

Source: M 2.7.4, Table 88. Consistent with Clinical reviewer's JMP Clinical 8.1 analysis.

No clinically meaningful differnces between the AE profiles for adolescent and adult subjects were identified.

For the OYEP and AEP safety pools, the AE profiles were similar to that of the PCPAA pool.

For the AEP pool, AEs of nausea and acne were more frequently reported for adolescent subjects and there were no AEs of HZ, HS, or adjudicated events of OI, TB, MACE, malignancy, ATE, or audiologic events of interest reported for adolescent subjects. SAEs were reported for 2 adolescent subjects (appendicitis (1), COVID-19 pneumonia/septic shock (1)). Two adjudicated AEs of Paresthesia and dysesthesia (1) and headache (1) were reported in adolescent subjects.

The number of subjects ≥65 years of age in each treatment group (≤5) was too low to allow for

meaningful comparisons. However, a trend towards a higher frequency of reported TEAEs (UTI, lymphocyte count decreased, arthralgia, and HZ), severe AEs, SAEs (including serious infections), AELDs, and adjudicated AEs of malignancy (excluding NMSC, NMSC, BCC) in subjects ≥65 years of age, compared to adult subjects (≥18 years of age) were reported for the AEP pool.

TEAEs by Sex

Fot the PCPAA and PCPAAV pools, female subjects were reported with a higher frequency of TEAEs and with similar frequency for severe AEs, SAEs, AELDs, and ARs than male subjects in their corresponding ritlecitinib dose groups (and placebo group). No clinically meaningful differnces between the AE profiles for male and female subjects were identified (including safety AEs of interest).

The proportion of subjects by sex reported with AEs, SAEs, severe AEs, AELDs, and ARs (drug-related AEs) for the PCPAA pool are summarized in the following Table.

Table- PCPAA: Proportion of subjects with TEAEs by Sex

	PCPAA					
	200/50 mg	50/50 mg	All 50 mg	All 30 mg	10 mg	Placebo
Male						
Participants evaluable for AEs (n)	73	59	132	96	20	73
Number of adverse events	118	92	210	136	28	94
Participants with AEs (%)	58.9	66.1	62.1	64.6	60.0	54.8
Participants with serious AEs (%)	2.7	0	1.5	0	0	0
Participants with severe AEs (%)	1.4	3.4	2.3	4.2	0	0
Permanently discontinued from study or study drug due to AE (%)	2.7	3.4	3.0	1.0	5.0	0
Temporarily discontinued from study drug due to AE (%)	5.5	6.8	6.1	6.3	0	5.5
Participants with treatment-related AEs (%)	24.7	39.0	31.1	25.0	30.0	30.1
Female						
Participants evaluable for AEs (n)	142	71	213	165	42	140
Number of adverse events	286	151	437	377	85	276
Participants with AEs (%)	76.1	83.1	78.4	75.2	73.8	77.1
Participants with serious AEs (%)	1.4	0	0.9	0.6	4.8	2.9
Participants with severe AEs (%)	2.1	0	1.4	3.6	4.8	3.6
Permanently discontinued from study or study drug due to AE (%)	2.8	0	1.9	1.8	2.4	3.6
Temporarily discontinued from study drug due to AE (%)	10.6	12.7	11.3	7.3	11.9	2.9
Participants with treatment-related AEs (%)	37.3	33.8	36.2	40.6	31.0	32.9

Source: M 2.7.4, Table 91. Consistent with Clinical reviewer's JMP Clinical 8.1 analysis.

For the OYEP and AEP safety pools, the AE profiles were similar to that of the PCPAA pool.

The frequency of reported TEAEs of headache and UTI were higher, and blood creatine

phosphokinase (CK) increased lower in female subjects. No reports of adjudicated TB, OI, NMSC, BCC, SCC, MACE, thromboembolic events, or ATE. AEs of HZ and sensorineural hearing loss were more frequently reported in female subjects in the All 50 mg dose groups.

TEAEs by Race and Ethnicity

Subgroup analysis by race included only White and Asian subjects due to limited number of subjects in other race groups.

For the PCPAA pool, Asian subjects were reported with a higher frequency of upper respiratory tract infections, folliculitis, and urticaria in the All 50 mg dose group. No adjudicated AEs of TB, MACE, thromboembolic events, ATE, or clinically meaningful differences in the frequency of the safety AEs of interest by race were reported.

The proportion of subjects by race (for White and Asian subjects) reported with AEs, SAEs, severe AEs, AELDs, and ARs (drug-related AEs) for the PCPAA pool are summarized in the following Table.

Table- PCPAA: Proportion of TEAEs by Race (White, Asian)

	PCPAA					
	200/50 mg	50/50 mg	All 50 mg	All 30 mg	10 mg	Placebo
White						
Participants evaluable for AEs (n)	155	79	234	181	41	167
Number of adverse events	288	148	436	358	73	292
Participants with AEs (%)	67.7	74.7	70.1	69.6	70.7	70.1
Participants with serious AEs (%)	1.9	0	1.3	0.6	2.4	1.8
Participants with severe AEs (%)	2.6	2.5	2.6	5.5	2.4	1.8
Permanently discontinued from study or study drug due to AE (%)	1.9	0	1.3	1.7	0	1.8
Temporarily discontinued from study drug due to AE (%)	8.4	11.4	9.4	8.8	7.3	4.2
Participants with treatment-related AEs (%)	29.0	29.1	29.1	33.1	19.5	29.9
Asian						
Participants evaluable for AEs (n)	39	43	82	62	17	33
Number of adverse events	86	74	160	112	24	57
Participants with AEs (%)	82.1	76.7	79.3	79.0	64.7	69.7
Participants with serious AEs (%)	2.6	0	1.2	0	0	3.0
Participants with severe AEs (%)	0	0	0	0	5.9	3.0
Permanently discontinued from study or study drug due to AE (%)	5.1	4.7	4.9	1.6	5.9	6.1
Temporarily discontinued from study drug due to AE (%)	2.6	7.0	4.9	1.6	11.8	0
Participants with treatment-related AEs (%)	56.4	48.8	52.4	46.8	47.1	42.4

Source: M 2.7.4, Table 94. Consistent with Clinical reviewer's JMP Clinical 8.1 analysis.

For the OYEP and AEP safety pools, AE profiles were similar to that of the PCPAA pool, and no clinically meaningful differences in the frequency of safety events of interest between White and Asian subjects were reported.

For the AEP pool, comparison of reported AEs for Hispanic/Latino subjects compared to Non-hispanic/Non-latino subjects showed more frequent TEAEs and similar frequency for SAEs, severe AEs, and AELDs. For the PCPAA pool, no meaningful comparison of the AE profiles among dose groups by ethnicity was possible due to limited number of subjects in each subgroup.

TEAEs by Body Mass Index (BMI) and Weight

For the AEP pooll All 50 mg dose group, a similar proportion of subjects were reported with TEAE, SAEs, severe AEs, and AELDs across the BMI (< 25, 25≤ to < 30, 30≤ to < 40 kg/m^2) and weight (< median, ≥median) categories.

TEAEs by AA severity (AT/AU, non-AT/AU) at baseline

For the PCPAA, OYEP, and AEP pools, a similar proportion of subjects were reported with TEAEs, SAEs, severe AEs, and AELDs for AT/AU and non-AT/AU subjects across all ritlecitinib and placebo dose groups.

For the OYEP pool All 50 mg group, TEAE with PT of headache was more frequent in non-AT/AU group.

In AEP, no AEs of MACE or ATE and no clinically significant differences in the proportion of subjects with AEs of interest in subjects with AT/AU and non-AT/AU were reported.

TEAEs by duration of AA since first diagnosis

For the PCPAA, OYEP, and AEP pools, no clinically significant differences were reported in the proportion of subjects with TEAEs, SAEs, severe AEs, and AELDs for subjects with AA duration > or ≤ median duration of AA for all subjects across all ritlecitinib and placebo dose groups.

8.2.21. Specific Safety Studies/Clinical Trials

Long-term Safety Study B7981032

Study B7981032 is an ongoing Phase 3, 36-month, open-label, multi-center, long-term Study of safety and efficacy of ritlecitinib in subjects ≥12 years of age with AA. This Study enrolled 1050 subjects (over the period of 7/18/2019 to 6/10/2021), including 449 de novo subjects and 603 roll-over subjects). Of the 1050 subjects, 247 (23.5%) subjects discontinued (38 (3.6%) of subjects were reported with AELDs). The data cutoff date for the interim CSR submitted with the NDA was 2/28/2022.

Overall, 798 (76.0%) subjects were reported with TEAEs (including 350 (78.3%) de novo and 448 (74.3%) rollover subjects), 43 (4.1%) subjects with SAEs, 52 (5.0%) subjects with severe TEAEs, and 48 (4.6%) subjects with AELDs.

SAEs

The following 51 SAEs were reported in 43 (roll-over and de novo) subjects in the Study B7981032.

Summary of SAE distribution by Group- LTS Study B7981032:

Preferred Term	Ritlecitinib 200/50 mg (de novo) (N=447) n (%)	Ritlecitinib 50 mg (roll-over) (N=603) n (%)	Total (N=1050) n (%)
Acute respiratory failure	1 (0.2)	2 (0.3)	3 (0.3)
Appendicitis	0 (0.0)	3 (0.5)	3 (0.3)
Abortion spontaneous	0 (0.0)	2 (0.3)	2 (0.2)
Breast cancer	1 (0.2)	1 (0.2)	2 (0.2)
Covid-19	1 (0.2)	1 (0.2)	2 (0.2)
Covid-19 pneumonia	1 (0.2)	1 (0.2)	2 (0.2)
Acute myocardial infarction	1 (0.2)	0 (0.0)	1 (0.1)
Anaphylactic reaction	0 (0.0)	1 (0.2)	1 (0.1)
Aortic aneurysm	0 (0.0)	1 (0.2)	1 (0.1)
Basal cell carcinoma	0 (0.0)	1 (0.2)	1 (0.1)
Bell's palsy	0 (0.0)	1 (0.2)	1 (0.1)
Bipolar disorder	0 (0.0)	1 (0.2)	1 (0.1)
Bipolar i disorder	1 (0.2)	0 (0.0)	1 (0.1)
Calculus urinary	0 (0.0)	1 (0.2)	1 (0.1)
Cardio-respiratory arrest	0 (0.0)	1 (0.2)	1 (0.1)
Cervical dysplasia	1 (0.2)	0 (0.0)	1 (0.1)
Cervical polyp	0 (0.0)	1 (0.2)	1 (0.1)

Cholelithiasis	0 (0.0)	1 (0.2)	1 (0.1)
Cyst rupture	1 (0.2)	0 (0.0)	1 (0.1)
Delirium	1 (0.2)	0 (0.0)	1 (0.1)
Flank pain	0 (0.0)	1 (0.2)	1 (0.1)
Foot deformity	1 (0.2)	0 (0.0)	1 (0.1)
Gastrointestinal haemorrhage	1 (0.2)	0 (0.0)	1 (0.1)
Hypersensitivity	1 (0.2)	0 (0.0)	1 (0.1)
Ileus	0 (0.0)	1 (0.2)	1 (0.1)
Intervertebral disc protrusion	1 (0.2)	0 (0.0)	1 (0.1)
Joint dislocation	0 (0.0)	1 (0.2)	1 (0.1)
Ligament rupture	0 (0.0)	1 (0.2)	1 (0.1)
Major depression	1 (0.2)	0 (0.0)	1 (0.1)
Malignant melanoma	0 (0.0)	1 (0.2)	1 (0.1)
Meniscus injury	1 (0.2)	0 (0.0)	1 (0.1)
Papillary thyroid cancer	1 (0.2)	0 (0.0)	1 (0.1)
Pyelonephritis	0 (0.0)	1 (0.2)	1 (0.1)
Retinal artery occlusion	1 (0.2)	0 (0.0)	1 (0.1)
Septic shock	1 (0.2)	0 (0.0)	1 (0.1)
Staphylococcal sepsis	0 (0.0)	1 (0.2)	1 (0.1)
Subdural haematoma	0 (0.0)	1 (0.2)	1 (0.1)
Suicidal ideation	0 (0.0)	1 (0.2)	1 (0.1)
Tendon rupture	0 (0.0)	1 (0.2)	1 (0.1)
Testis cancer	1 (0.2)	0 (0.0)	1 (0.1)
Thermal burn	0 (0.0)	1 (0.2)	1 (0.1)
Varicose vein	1 (0.2)	0 (0.0)	1 (0.1)
Vulval abscess	1 (0.2)	0 (0.0)	1 (0.1)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Ritlecitinib 200/50 mg (de novo" and SAFFL = "Y" (Ritlecitinib 200/50 mg (de novo)); TRT01A = "Ri lecitinib 50 mg (roll-over" and SAFFL = "Y" (Ritlecitinib 50 mg (roll-over)); TRT01A = "Ritlecitinib 50 mg (roll-over" or "Ritlecitinib 200/50 mg (de novo" and SAFFL = "Y" (Total); TRTEMFL = "Y" and AESER = "Y" (Adverse Events).

Source: Clinical Reviewer's analysis. Consistent with Applicant's analysis.

One subject (B7981032 (b) (6) was reported with 4 SAEs, 5 subjects with 2 SAEs each, and 37 subjects with 1 SAE each, as summarized in the following table.

Summary listing of SAEs- LTS Study B7981032:

USUBJID	Age	Sex	PT	Severity	Action taken	AELD?	Causality	Outcome

Roll-over Subjects								
B7931005 (b) (6)	22	F	Cholelithiasis	MILD	DRUG INTERRUPTED	N	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	20	F	Appendicitis	SEVERE	DOSE NOT CHANGED	N	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	28	F	Staphylococcal sepsis	SEVERE	DRUG WITHDRAWN	Y	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	18	F	Bipolar disorder	SEVERE	NOT APPLICABLE	N	NOT RELATED	RECOVERED/RESOLVED
	18	F	Suicidal ideation	SEVERE	NOT APPLICABLE	N	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	50	F	Malignant melanoma	MODERATE	DRUG WITHDRAWN	Y	RELATED	NOT RECOVERED/NOT RESOLVED
B7981015 (b) (6)	17	F	Abortion spontaneous	MILD	DRUG WITHDRAWN	Y	RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	29	M	Calculus urinary	SEVERE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	66	F	Breast cancer	SEVERE	DRUG WITHDRAWN	Y	RELATED	RECOVERING/RESOLVING
B7981015 (b) (6)	26	M	Appendicitis	MODERATE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERING/RESOLVING
B7981015 (b) (6)	51	F	Acute respiratory failure	SEVERE	NOT APPLICABLE	Y	NOT RELATED	FATAL
	51	F	Cardio-respiratory arrest	SEVERE	NOT APPLICABLE	Y	NOT RELATED	FATAL
B7981015 (b) (6)	37	F	Ileus	SEVERE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	70	F	Aortic aneurysm	MODERATE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	62	F	Pyelonephritis	SEVERE	DRUG WITHDRAWN	Y	RELATED	RECOVERED/RESOLVED

	62	F	Flank pain	MODERATE	NOT APPLICABLE	N	NOT RELATED	NOT RECOVERED/NOT RESOLVED
B7981015 (b) (6)	20	M	Joint dislocation	SEVERE	DOSE NOT CHANGED	N	NOT RELATED	RECOVERED/RESOLVED WITH SEQUELAE
	20	M	Ligament rupture	SEVERE	DOSE NOT CHANGED	N	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	40	F	Anaphylactic reaction	SEVERE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	25	F	Tendon rupture	SEVERE	DOSE NOT CHANGED	N	NOT RELATED	NOT RECOVERED/NOT RESOLVED
B7981015 (b) (6)	44	M	Subdural haematoma	SEVERE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	53	F	Bell's palsy	SEVERE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERING/RESOLVING
B7981015 (b) (6)	71	M	Basal cell carcinoma	SEVERE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	60	F	Cervical polyp	MODERATE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	34	F	Abortion spontaneous	SEVERE	NOT APPLICABLE	N	RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	43	F	COVID-19 pneumonia	SEVERE	DRUG WITHDRAWN	Y	NOT RELATED	RECOVERED/RESOLVED
	43	F	Acute respiratory failure	MODERATE	DRUG WITHDRAWN	Y	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	52	F	COVID-19	SEVERE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	14	F	Appendicitis	SEVERE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERED/RESOLVED
B7981015 (b) (6)	66	F	Thermal burn	SEVERE	DOSE NOT CHANGED	N	NOT RELATED	RECOVERED/RESOLVED
De novo Subjects								

B7981032 (b) (6)	49	M	Acute myocardial infarction	SEVERE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERING/RESOLVING
B7981032 (b) (6)	20	F	Hypersensitivity	MODERATE	DRUG WITHDRAWN	Y	RELATED	RECOVERED/RESOLVED
B7981032 (b) (6)	48	F	Retinal artery occlusion	MODERATE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERED/RESOLVED WITH SEQUELAE
B7981032 (b) (6)	25	F	Major depression	SEVERE	DRUG WITHDRAWN	Y	NOT RELATED	NOT RECOVERED/NOT RESOLVED
B7981032 (b) (6)	19	F	Bipolar I disorder	SEVERE	DRUG WITHDRAWN	Y	NOT RELATED	RECOVERING/RESOLVING
B7981032 (b) (6)	71	F	COVID-19	SEVERE	DRUG WITHDRAWN	Y	NOT RELATED	RECOVERED/RESOLVED
B7981032 (b) (6)	23	F	Vulval abscess	MILD	DRUG INTERRUPTED	N	NOT RELATED	RECOVERED/RESOLVED
B7981032 (b) (6)	15	M	COVID-19 pneumonia	SEVERE	DRUG WITHDRAWN	Y	NOT RELATED	RECOVERED/RESOLVED
	15	M	Septic shock	SEVERE	NOT APPLICABLE	N	NOT RELATED	RECOVERED/RESOLVED
	15	M	Delirium	SEVERE	NOT APPLICABLE	N	NOT RELATED	RECOVERED/RESOLVED
	15	M	Acute respiratory failure	SEVERE	DRUG WITHDRAWN	Y	NOT RELATED	RECOVERED/RESOLVED
B7981032 (b) (6)	24	M	Gastrointestinal haemorrhage	SEVERE	DRUG INTERRUPTED	N	NOT RELATED	NOT RECOVERED/NOT RESOLVED
B7981032 (b) (6)	39	F	Intervertebral disc protrusion	SEVERE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERED/RESOLVED
B7981032 (b) (6)	32	F	Varicose vein	MILD	DOSE NOT CHANGED	N	NOT RELATED	RECOVERED/RESOLVED
B7981032 (b) (6)	21	M	Testis cancer	SEVERE	DRUG WITHDRAWN	Y	RELATED	RECOVERED/RESOLVED

B7981032 (b) (6)	40	F	Foot deformity	MILD	DOSE NOT CHANGED	N	NOT RELATED	RECOVERED/RESOLVED
B7981032 (b) (6)	39	F	Cervical dysplasia	MODERATE	DRUG INTERRUPTED	N	NOT RELATED	RECOVERED/RESOLVED
B7981032 (b) (6)	33	F	Cyst rupture	SEVERE	DOSE NOT CHANGED	N	NOT RELATED	RECOVERED/RESOLVED
B7981032 (b) (6)	26	M	Papillary thyroid cancer	SEVERE	DRUG WITHDRAWN	Y	NOT RELATED	NOT RECOVERED/NOT RESOLVED
B7981032 (b) (6)	46	F	Meniscus injury	MILD	DOSE NOT CHANGED	N	NOT RELATED	RECOVERED/RESOLVED
B7981032 (b) (6)	64	F	Breast cancer	SEVERE	DRUG WITHDRAWN	Y	NOT RELATED	FATAL

Source: Clinical Reviewer's JMP Clinical analysis. Consistent with Interim CSR B7981032 Narratives (page 473 of Interim CSR).

AELDS

The following AEs led to drug discontinuation in the LTS study B7981032:

Summary of TEAEs Leading to Discontinuation (AELDs) by Group- LTS Study B7981032:

Preferred Term	Ritlecitinib 200/50 mg (de novo) (N=447) n (%)	Ritlecitinib 50 mg (roll-over) (N=603) n (%)	Total (N=1050) n (%)
Pregnancy	6 (1.3)	3 (0.5)	9 (0.9)
Acute respiratory failure	1 (0.2)	1 (0.2)	2 (0.2)
Blood creatine phosphokinase increased	0 (0.0)	2 (0.3)	2 (0.2)
Breast cancer	1 (0.2)	1 (0.2)	2 (0.2)
Covid-19 pneumonia	1 (0.2)	1 (0.2)	2 (0.2)
Dizziness	2 (0.4)	0 (0.0)	2 (0.2)
Headache	1 (0.2)	1 (0.2)	2 (0.2)
Sars-cov-2 test positive	1 (0.2)	1 (0.2)	2 (0.2)
Abortion spontaneous	0 (0.0)	1 (0.2)	1 (0.1)
Acne	1 (0.2)	0 (0.0)	1 (0.1)
Alanine aminotransferase increased	1 (0.2)	0 (0.0)	1 (0.1)
Anaemia	0 (0.0)	1 (0.2)	1 (0.1)
Atrial septal defect	1 (0.2)	0 (0.0)	1 (0.1)
Bipolar i disorder	1 (0.2)	0 (0.0)	1 (0.1)

Covid-19	1 (0.2)	0 (0.0)	1 (0.1)
Crohn's disease	0 (0.0)	1 (0.2)	1 (0.1)
Dysaesthesia	0 (0.0)	1 (0.2)	1 (0.1)
Eczema	0 (0.0)	1 (0.2)	1 (0.1)
Fatigue	0 (0.0)	1 (0.2)	1 (0.1)
Hepatic enzyme increased	0 (0.0)	1 (0.2)	1 (0.1)
Herpes zoster	0 (0.0)	1 (0.2)	1 (0.1)
Hypersensitivity	1 (0.2)	0 (0.0)	1 (0.1)
Interferon gamma release assay	0 (0.0)	1 (0.2)	1 (0.1)
Latent tuberculosis	1 (0.2)	0 (0.0)	1 (0.1)
Lymphocyte count decreased	0 (0.0)	1 (0.2)	1 (0.1)
Major depression	1 (0.2)	0 (0.0)	1 (0.1)
Malignant melanoma	0 (0.0)	1 (0.2)	1 (0.1)
Muscle spasms	1 (0.2)	0 (0.0)	1 (0.1)
Myalgia	0 (0.0)	1 (0.2)	1 (0.1)
Myoclonus	0 (0.0)	1 (0.2)	1 (0.1)
Nausea	1 (0.2)	0 (0.0)	1 (0.1)
Neuropathy peripheral	1 (0.2)	0 (0.0)	1 (0.1)
Neutropenia	0 (0.0)	1 (0.2)	1 (0.1)
Papillary thyroid cancer	1 (0.2)	0 (0.0)	1 (0.1)
Paraesthesia	0 (0.0)	1 (0.2)	1 (0.1)
Pyelonephritis	0 (0.0)	1 (0.2)	1 (0.1)
Spinal ligament ossification	1 (0.2)	0 (0.0)	1 (0.1)
Staphylococcal sepsis	0 (0.0)	1 (0.2)	1 (0.1)
Testis cancer	1 (0.2)	0 (0.0)	1 (0.1)
Thrombocytopenia	0 (0.0)	1 (0.2)	1 (0.1)
Transaminases increased	0 (0.0)	1 (0.2)	1 (0.1)
Vision blurred	1 (0.2)	0 (0.0)	1 (0.1)
Vomiting	1 (0.2)	0 (0.0)	1 (0.1)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Ritlecitinib 200/50 mg (de novo" and SAFFL = "Y" (Ritlecitinib 200/50 mg (de novo)); TRT01A = "Ri lecitinib 50 mg (roll-over" and SAFFL = "Y" (Ritlecitinib 50 mg (roll-over)); TRT01A = "Ritlecitinib 50 mg (roll-over" or "Ritlecitinib 200/50 mg (de novo" and SAFFL = "Y" (Total); TRTEMFL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

Neuro-Audiology Safety Study B7981037

This Phase 2a, randomized (1:1), Double-Blind, Placebo-Controlled (Months 0-9) with an extension period (Months 9-24) enrolled 71 adult subjects with AA and SALT≥25 at baseline. The primary (safety) endpoint was change from baseline (CFB) in I-V interwave latency on brainstem auditory evoked

potential (BAEP) at a stimulus intensity of 80 dB at Month 9. TEAEs from this trial were reported under the PCPAA and AEP safety pools.

No safety signal was detected from the safety data reported for this trial (refer to Sec. 8.2.13 Neuro-audiological Events of this review for additional discussion).

8.2.22. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

[Insert text here]

Human Reproduction and Pregnancy

[Insert text here]

Pediatrics and Assessment of Effects on Growth

[Insert text here]

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

[Insert text here]

8.2.23. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

[Insert text here]

Expectations on Safety in the Postmarket Setting

[Insert text here]

8.2.24. Integrated Assessment of Safety

The safety profile for ritlecitinib for the treatment of severe AA was adequately characterized during the development program. The primary safety database (PCPAA) consisted of pooled data for subjects from the 24-week placebo-controlled periods of trials B7931005, B7981015, and B7981037; and included 345 subjects exposed to a ritlecitinib does of ≥ 50 mg daily. In the 120-day safety update, the overall safety database (AEP) consisted of 1523 subjects exposed to ritlecitinib does of ≥ 50 mg daily, including 1011 subjects (133/ (b) (6) subjects were adolescents between 12 to < 18 years of age) with ≥ 12 months (48 weeks) of exposure.

Two deaths occurred during the long-term safety study B7981032 (both deaths were considered as unrelated to the study drug by the Investigators and the Sponsor). During the 24-week placebo-controlled period of the PCPAA, SAEs were reported with similar frequency

among the placebo (1.9%) and ritlecitinib dose groups (0 - 3.2%). All SAE preferred terms (PTs) were reported by single subjects in any treatment group. SAEs were more commonly reported in the ritlecitinib groups for the SOC of Infections and Infestations. For the AEP pool, the type and frequency of reported SAEs were generally similar to those reported for the PCPAA and OYEP pools. The exposure-adjusted incidence rates (EAIRs) for subjects reported with any SAE in the All 50 mg dose groups of the AEP (2.72/100 PYE) was similar to the EAIRs in the PCPAA (2.69/100 PYE), and in the OYEP (2.60/100 PYE).

During the 24-week placebo-controlled period of the PCPAA pool, AEs leading to permanent discontinuation of study drug (AELDs) were reported with similar frequency among the placebo (2.3%) and ritlecitinib dose groups (0-3.2%). Urticaria (2) was the only PT reported as AELD in > 1 patient in any group, and the most common AELD was in the SOC of Skin and subcutaneous tissue disorders (5). For the AEP, AELDS were most common in the SOCs of Investigations and Skin and soft tissue disorders.

The Applicant identified Adverse Events of Special Interest (AESI) for close monitoring and adjudication during the phase 3 trials. The pre-specified AESIs included serious infections (including opportunistic infections), major adverse cardiovascular events, venous and arterial thromboembolic events, malignancy (including non-melanoma skin cancer), and neuro-audiologic AEs. During the 24-week placebo-controlled period of PCPAA, AESIs reported in any ritlecitinib group included serious infections (3), Opportunistic infections of herpes zoster (1), malignancy (1), and pulmonary embolism (1). Neurological and audiological AEs were reported with similar frequencies among the placebo and ritlecitinib groups. Adverse reactions (ARs) related to laboratory findings which were reported in >1% of subjects included: blood creatine phosphokinase (CK) increased and red blood cell count decreased. These ARs will be included in product labeling (Section 6, Adverse Reactions). Ritlecitinib treatment was also associated with a decrease in the absolute lymphocyte count (ALC) and platelet count, with no apparent increase in the risk of serious infections or bleeding. The laboratory monitoring guidance (Sec. 2.4 of the label) includes recommendations for thresholds for interruption or discontinuation of treatment by the platelet count and ALC.

The most common adverse reactions (ARs), reported in ≥1% of subjects treated with ritlecitinib 50/50 mg once daily (and at a higher frequency than placebo-treated subjects), compared to the placebo group respectively, were headache (10.8% v. 8.5%), diarrhea (10.0% v. 3.8%), acne (6.2% v. 4.7%), rash (5.4% v. 0.9%), urticaria (4.6% v. 1.4%), folliculitis (3.1% v. 1.9%), pyrexia (3.1% v. 0), dermatitis atopic (2.3% v. 0.5%), dizziness (2.3% v. 1.4%), blood creatine phosphokinase increased (1.5% v. 0), herpes zoster (1.5% v. 0), red blood cell count decreased (1.5% v. 0), and stomatitis (1.5% v. 0). The review team recommends inclusion of these ARs for inclusion in Section 6.1 (Adverse Reactions) of labeling.

Additionally, LITFULO label will carry the boxed warning (including serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis) for the Janus Kinase (JAK)-inhibitor class of products.

Consultants from the Office of Surveillance and Epidemiology (OSE) evaluated the sufficiency of the Active Risk and Identification Analysis system (ARIA) to address the long-term risk of outcomes of interest including pregnancy safety concerns (Refer to the Sentinel ARIA Sufficiency template in DARRTS on 6/16/2023).

During the development program for AA, a total 12 (maternal exposure) pregnancies and 9 partner pregnancies were reported. Because exposures to ritlecitinib 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 post-marketing assessment to characterize the drug-associated risk. Refer to Section 13 (Postmarketing Requirements and Commitments) of this review for further details.

The currently available data support a favorable safety profile for ritlecitinib 50 mg once daily in the treatment of adult and adolescent patients ≥ 12 years of age with AA (b) (4)

8.3. Statistical Issues

The applicant prespecified the primary method of handling missing data in Study B7981015 would be to exclude missing data due to subjects missing visits due to COVID-19 and to use non-responder imputation for other reasons for missing data. One of the key prespecified supplementary analyses used multiple imputation for handling missing data due to COVID-19 and non-responder imputation for other reasons. Excluding data assumes that the data are missing completely at random (MCAR), while the planned multiple imputation procedure assumes data are missing at random (MAR). As the weaker assumption, the MAR assumption is more defensible than the MCAR assumption. Therefore, the recommended analysis for labeling is to use the analysis where multiple imputation was used for missing data due to COVID-19 and non-responder imputation was used for missing data due to other reasons (also referred to as Analysis #4 in this review).

Because the multiplicity control scheme in Study B7981015 only extended across multiple doses for the primary efficacy endpoint, and did not extend to the secondary endpoints, it is difficult to interpret the results of the secondary endpoints. The key secondary endpoint of SALT ≤10 at Week 24 is closely related to the primary endpoint and it does not represent an independent assessment. However, the endpoints based on the Eyebrow and Eyelash Assessment tools were included among a number of secondary efficacy endpoints evaluated at multiple timepoints that had no multiplicity control, and thus the endpoints are not capable of supporting efficacy claims and are not recommended for inclusion in labeling.

8.4. Conclusions and Recommendations

The applicant provided substantial evidence of effectiveness for ritlecitinib 50 mg in the treatment of severe alopecia areata. This was supported by an adequate and well-controlled large multicenter Phase 2b/3 trial (B7981015, N=718), with very persuasive results which were consistent with those suggested by the Phase 2a trial, B7931005 (N=142). Trial B7981015 included subjects 12 years of age and older with SALT≥50 score at baseline, which corresponds to 50% or greater loss of scalp hair. The trial evaluated ritlecitinib doses of 200/50 mg, 200/30 mg, 50 mg, and 30 mg once daily, compared to placebo, for the primary endpoint of SALT ≤20 response (i.e., no more than 20% missing hair) at Week 24. For the to-be-marketed dose of ritlecitinib 50 mg daily, SALT≤20 response was 23.0%, compared to 1.6% for placebo at week 24 (a treatment effect of 21.4% [95% CI: 13.4%, 29.5%], p-value <0.00001).

The efficacy results from this trial are consistent across centers, demographic subgroups, and methods of handling missing data, though the estimated magnitude of the treatment effect varied somewhat across gender and baseline disease severity subgroups. Even though the secondary endpoints were not included under the multiplicity control, and will not be included in labeling, the results of the secondary endpoints are consistent with the results of the primary endpoint and are supportive of the primary endpoint findings.

To support the safety of ritlecitinib in the patient population with severe AA, the review team analyzed safety data from up to 5 clinical studies in the AA (and Vitiligo) development programs pooled by the Applicant into the PCPAA, PCPAAV, OYEP, and AEP safety pools; and conducted a comprehensive assessment of safety. The size of the safety database and the safety evaluations were adequate to identify treatment-emergent adverse reactions and identified no new safety signals. The results of safety assessments support the approval of ritlecitinib 50 mg once daily for the treatment of patients ≥12 years of age with AA (b) (4)

Rationale for selection of 50 mg QD dose (without a loading dose of 200 mg QD x 4 weeks)

The Applicant proposes the ("flat") 50 mg QD ritlecitinib dose (without the loading dose) as the to-be-marketed dose because the 200/50 mg QD dose regimen does not offer a long-term efficacy advantage over the 50 mg QD dose regimen and is associated with more potential safety risks based on the following:

- Efficacy: The 200/50 mg dose group showed a more rapid onset and higher efficacy at week 24 compared to the 50 mg dose. However, the efficacy (SALT ≤20 response and other secondary or PRO-related efficacy endpoints) were similar for both dose groups, at week 48 and at 2 years, based on both observed efficacy data and efficacy exposure-response modeling by the Applicant .
- Safety: The 200/50 mg dose group showed a larger median decrease in lymphocyte counts and more frequently reported TEAEs of tinnitus, nausea, folliculitis, upper respiratory infections, urinary tract infections, and dizziness. The safety exposure-response modeling by the Applicant showed higher rate of lymphopenia and rash.
- DDI: The drug-drug interaction with estradiol in a contraceptive pill was demonstrated for the 200 mg dose (not the 50 mg dose).

Additional post-marketing studies (PREA PMRs and FDAAA PMRs, including pregnancy exposure registry and retrospective cohort study) will be required for further assessment of the potential risks in pediatric patients between 6 to < 12 years of age, pediatric patients between 12 to < 18 years of age, and pregnant patients with AA. The Active Risk and Identification Analysis system (ARIA) will be recommended for further assessment of the potential risks from long-term exposure.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not held because no unexpected significant safety, efficacy, or controversial/challenging issues were identified that would benefit from discussion at an Advisory Committee meeting.

10 Pediatrics

Because ritlecitinib is a new molecular entity (NME), it triggers the requirement under the PREA (21 USC 355c) for an assessment of its safety and effectiveness for the treatment of AA in pediatric patients unless this requirement is waived, deferred, or inapplicable.

In an Agreed iPSP (dated 2/1/2021) agreement letter on 3/10/2021, the Agency agreed with the Applicant's plan to request a waiver for pediatric subjects between ages of 0 to <6 years of age (because necessary studies are impossible or highly impracticable), a request for deferral of pediatric studies for subjects between 6 and < 12 years of age (because clinical studies in adult and adolescent subjects ≥12 years of age will be completed and ready for approval), and inclusion of pediatric (adolescent) subjects between ages of 12 to <18 years of age in the Phase 3 clinical effectiveness and safety studies.

At the time of the NDA submission (6/24/2022), the Applicant submitted safety data for 172 pediatric subjects (between 12 to <18 years of age) who were treated with ritlecitinib ≥50 mg once daily (including 133 subjects exposed for ≥12 months (48 weeks) enrolled in the Phase 3 trial B7981015 and the LTS study B7981032. The safety data for this age group was deemed to be adequate for inclusion of this age group in the Applicant's INDICATIONS AND USAGE Section of
the proposed label, "LITFULO is indicated for the treatment of alopecia areata (b) (4) in adults and adolescents 12 years and older (b) (4) at the time of the expected NDA approval.

In an Amendment to the Agreed iPSP (dated 2/1/2021), the Applicant proposed a new timeline to conduct deferred clinical studies in pediatric subjects between 6 to <12 years of age due to recruitment challenges. The Applicant's PREA Waiver/Deferral/Pediatric Plan request (including their proposal for a revised timeline) was presented and discussed at the Pediatric Review Committee (PeRC) meetings (on 7/12/2022, 5/2/2023). The PeRC agreed with the Applicant's proposed revised timeline to conduct the pediatric deferred studies as PREA PMRs.

The PeRC agreed with the Division's recommendation to:

- Grant a partial waiver for subjects <6 years of age,
- Grant a deferral for subjects between 6 to <12 years of age
- Issue the PREA PMRs outlined in the Postmarketing Requirements and Commitment section (Section 13) of this review.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

The Applicant submitted proposed prescribing information (PI), patient package insert (PPI; also known as patient information), and container labels for LITFULO (ritlecitinib) oral capsule, 50 mg once daily.

The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI, PPI, and the container. These comments will be reflected in final labeling.

Madhuri R. Patel, PharmD, Acting DMEPA 1 Team Leader from the Division of Medication Error Prevention and Analysis (DMEPA) reviewed (Review in DARRTS on 1/13/2023) the proposed PI, MG, and container labeling for LITFULO and concluded that the proposed Prescribing Information (PI) and Medication Guide (MG) were acceptable from a medication error perspective. However, the DMEPA reviewer found the proposed container labels could be improved and provided recommendations for the Applicant to address DMEPA's concerns.

On 3/13/2023, Laurie Buonaccorsi, PharmD (Patient Labeling Reviewer, Division of Medical Policy Programs (DMPP)) and David Foss, PharmD, MPH, BCPS, RAC (Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP)) completed a collaborative review of the Patient Labeling /Medication Guide (MG) and concluded that the MG was acceptable (with their recommended changes).

Other Prescription Drug Labeling

Labeling discussions are ongoing with the Applicant at the time of this review, and the final labeling will reflect all recommendations from the review teams.

12 Risk Evaluation and Mitigation Strategies (REMS)

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling, standard postmarketing surveillance, and ARIA are not warranted at this time (refer to REMS Review by Sarah K. Holman, PharmD, BCPS, Division of Risk Management (DRM) in DARRTS on June 20, 2023) .

13 Postmarketing Requirements and Commitment

Three (3) PREA PMRs and three FDAAA PMRs, including two (2) pregnancy PMRs to conduct the following studies will be issued to the Applicant:

1. Pediatric Pharmacokinetic Study B7981031-Ongoing

Submit the final study report for a PK study which aims to compare the systemic exposures of the dose/regimen in adults and adolescents to that of pediatric subjects ages 6 to <12 years with moderate to severe alopecia areata. Provide data on at least 12 available subjects.

a. Final Protocol Submission: 11/2022 (submitted)
b. Study Completion: 02/2024
c. Final Report Submission: 08/2024

2. Efficacy and Safety Study B7981027

Conduct a randomized, double-blind, placebo-controlled study to investigate the safety of ritlecitinib in pediatric subjects (6 to <12 years of age) with moderate to severe AA (defined by ≥50% scalp hair loss, measured by a SALT score of 50 or greater).

a. Final Protocol Submission: 06/2024
b. Study Completion: 05/2027
c. Final Report Submission: 11/2027

3. Long Term Safety Study B7981028

Conduct the open-label long-term extension (LTE) study to evaluate the safety of ritlecitinib in pediatric subjects 6 to <12 years of age with moderate to severe alopecia areata who have completed previous ritlecitinib studies B7981031 or B7981027 and are eligible to receive ritlecitinib. Study subjects from B7981031 and placebo subjects from B7981027 will be randomly assigned to one of the two dose levels to be administered in this study and study subjects who received active drug in B7981027 will remain on the same dosage level they were assigned. All subjects will receive ritlecitinib for up to an additional 3 years.

a. Final Protocol Submission: 06/2024
b. Study Completion: 06/2030
c. Final Report Submission: 12/2030

4. Long Term Safety Study (B7981032)- Ongoing

Submit the final study report for an ongoing open-label long-term study to investigate the safety of ritlecitinib in adults and adolescents with AA (12 years of age and older).

a. Protocol submission date: 04/2019 (submitted)
b. Study Completion: 02/2026

c. Final Report Submission 08/2026

5. Pregnancy Registry

Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct pregnancy registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women with alopecia areata exposed to ritlecitinib during pregnancy with unexposed comparator population(s). Align the study protocol with protocol(s) outside the US to reach the target sample size. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes described in the protocol 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.

a. Draft Protocol Submission: 12/2023
b. Final Protocol Submission: 06/2024
c. Study Completion: 06/2034
d. Final Report Submission: 06/2035

6. Retrospective Pregnancy Cohort Study

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, and small for gestational age and preterm birth in women exposed to ritlecitinib during pregnancy compared to an unexposed control population.

a. Draft Protocol Submission: 12/2023
b. Final Protocol Submission: 06/2024
c. Study Completion: 06/2034
d. Final Report Submission: 06/2035

14 Office Director Comments

I concur with the recommendation of the Division of Dermatology and Dentistry to approve ritlecitinib, NDA 215830, a kinase inhibitor indicated for the treatment of severe alopecia areata (AA) in adults and adolescents 12 years and older. Ritlecitinib is a new molecular entity that inhibits JAK3- and TEC kinase-mediated signaling, which contribute to the immunopathogenesis of AA. Ritlecitinib will be the second systemic therapy approved for treatment of adults with severe AA and the first systemic therapy for adolescents with this condition. Ritlecitinib is administered orally once daily.

The applicant provided substantial evidence of effectiveness for ritlecitinib 50 mg in the treatment of severe alopecia areata. This was supported by an adequate and well-controlled large multicenter Phase 2b/3 trial (N=718) with very persuasive results which were consistent with those suggested by a Phase 2a trial (N=142). The Phase 2b/3 trial evaluated various doses with and without a loading dose in subjects with at least 50% hair loss. Ritlecitinib 50 mg (without a loading dose) was found to be statistically superior to placebo for the primary endpoint of the proportion of subjects achieving Severity of Alopecia Tool ≤ 20 (i.e., no more than 20% missing hair using the SALT) at Week 24 ($p<0.00001$). Results for SALT ≤ 20 were consistent across pediatric (12 to < 18 years) and adult (18 years and older) subgroups. SALT ≤ 20 response rates continued to increase after Week 24 among subjects continuing on ritlecitinib to Week 48. Although results for the key secondary endpoint (SALT ≤ 10 at Week 24) were not multiplicity-contolled they were consistent with the results for the primary endpoint.

Total subject exposure to ritlecitinib 50 mg once daily for the treatment of AA provides adequate data for the evaluation of safety in subjects 12 years of age and older for up to 48 weeks of treatment. Overall, the safety profile of ritlecitinib was consistent with the safety profile of approved JAK inhibitors. Product labeling for ritlecitinib will include the risks associated with JAK inhibition in a Boxed Warning and in the Warnings and Precautions section, including serious infections, mortality, malignancy (including lymphoma and lung cancer), major adverse cardiovascular events (MACE), and thrombosis (including deep venous thrombosis and pulmonary embolism.

Pediatric studies will be required post-approval to assess PK/PD, efficacy and safety, including long-term safety, in pediatric subjects ages 6 to < 12 years. A prospective pregnancy exposure registry and a retrospective pregnancy cohort study will also be required post-approval.

15 Appendices

15.1. References

References to the literature articles cited were provided as footnotes.

15.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms (FDA Forms 3454 and 3455) in Section 1.3.4 of this sBLA submission for the clinical investigators and sub-investigators who participated in the covered clinical trial. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data. 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 B7931005, B7981015, B7981019, B7981032, and B7981037 which provided the primary data to establish effectiveness and safety of this product in the target population. Refer to Section 8.1 of this review for the trial designs. The Applicant provided the following disclosures for significant payments of other sorts (for payments that exceed threshold amount of (b) (6) for Med AdBoard HCPs, Grants, Speaker honorariums, and clinical trial consultant fees, etc., reported in order for each listed trial, respectively) from the Applicant of the covered studies [21 CFR 54.4 (a)(3)(ii), 54.2 (f)]:

(b) (6)

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(b) (6)

[redacted]

Covered Clinical Study: B7931005

Was a list of clinical investigators provided:	Yes	No (Request list from Applicant)
Total number of investigators identified: 28		
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): 8		
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: Significant payments of other sorts: 8 Proprietary interest in the product tested held by investigator:		

Significant equity interest held by investigator in S Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes	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	No (Request explanation from Applicant)

Covered Clinical Study: B7981015

Was a list of clinical investigators provided:	Yes	No (Request list from Applicant)
Total number of investigators identified: 123		
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): 15		
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: Significant payments of other sorts: 15 Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in S Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes	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	No (Request explanation from Applicant)

Covered Clinical Study: B7981019

Was a list of clinical investigators provided:	Yes	No (Request list from Applicant)
Total number of investigators identified: 79		

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): 9		
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: Significant payments of other sorts: 9 Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in S Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes	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	No (Request explanation from Applicant)

Covered Clinical Study: B7981032

Was a list of clinical investigators provided:	Yes	No (Request list from Applicant)
Total number of investigators identified: 127		
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): 15		
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: Significant payments of other sorts: 15 Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in S Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No (Request details from Applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes	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	No (Request explanation from Applicant)

Covered Clinical Study: B7981037

Was a list of clinical investigators provided:	Yes	No (Request list from Applicant)
Total number of investigators identified: 28		
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): 2		
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: Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in S Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes	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	No (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

15.3.1. Calculations for multiples of exposures

Based on the applicant's population modeling analysis report (#PMAR-EQDD-B798d-DP4-1157, including trial #B7981015, #B7981020, #B7981032, and #B7981036), the unbound AUC at the maximum recommended human dose (MRHD) of 50 mg/day in subjects with alopecia areata is 1070 hr·ng/mL. The following table summarizes the multiples of exposure based on AUC comparisons between the MRHD and AUC values from nonclinical studies referenced in the label.

Study	Species	Dose (mg/kg/day)	Dose Note[a]	$AUC_{24.u}$ (hr·ng/mL)	Multiples of exposure[b]
Embryofetal development	Rat	75	NOAEL (development)	17000	16
		175	LOAEL (development)	52900	49
		325	LOAEL (maternal)	109000	102
	Rabbit	25	NOAEL (development)	13200	12
		75	LOAEL (development)	58600	55
Prenatal and postnatal development	Rat	75	NOAEL (development)	15400	14
		175	NOAEL (maternal)	44000	41
Carcinogenicity	Rat	30	NOAEL	6770	6.3
		100	LOAEL	31500	29
9-Month oral RDT[c] study	Dog	20	TD_{Lo}	14500	14
		40	TD_{Lo}	35200	33
Fertility	Rat (female)	200	NOAEL (female)	58600[d]	55
	Rat (male)	60	NOAEL (male)	14700	14
		200	LOAEL (male)	58600	55

[a]LOAEL (lowest-observed-adverse-effect-level), NOAEL (no-observed-adverse-effect-level), TD_{Lo} (The lowest dose administered that produced a defined toxic effect in dogs)
[b]Calculated by dividing the nonclinical AUC by the estimated AUC at the MRHD (1070 hr·ng/mL)
[c]RDT (repeat dose toxicity)
[d]Using the $AUC_{24.u}$ from males in the same study because blood samples were not collected from females and no sex differences in exposure have been noted in rats

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

15.3.3. Review of Carcinogenicity Studies Conducted with Ritlecitinib

Study Title: 6-Month Oral Gavage Carcinogenicity Study of PF-06651600 in Hemizygous rasH2 Transgenic (tg/wt) Mice

Study no.:	19GR034
Study report location:	SDN 1
Study initiation date:	June 4, 2019
Conducting laboratory and location:	(b) (4)
GLP compliance:	Y
Drug, lot #, and % purity:	PF-06651600 (ritlecitinib tosylate salt), lot #19-AP-00133, 98.8% purity
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	Maximum tolerated dose

Reviewer Carcinogenicity Conclusion (negative/ positive): Negative
ECAC Carcinogenicity Conclusion (negative/ positive): Negative

Tumor Findings:
No ritlecitinib-related tumors were observed in either sex.

Methods	
Doses:	0, 30, 100, and 300 mg/kg/day
Frequency of dosing:	Once daily
Number/Sex/Group:	25 (plus 9/sex control and 12/sex ritlecitinib-treated group for toxicokinetic assessment and 15/sex positive control)
Dose volume:	10 mL/kg
Formulation/Vehicle:	0.5% methylcellulose
Route of administration:	ORAL GAVAGE
Species:	MOUSE
Strain:	CB6F1-TgN (RasH2)
Age:	8 to 9 weeks old at dosing initiation
Comment on Study Design and Conduct:	Positive control (75 mg/kg (b) (4) was administered as a single intraperitoneal injection on Day 1. Two HD females (#M0816 and #M0821) were found dead on Day 5 and replaced (with #M0838 and #M0839). No noteworthy deviations.

Dosing Comments (Dose Adjustments or Early Termination):	No dose adjustments were made. No groups were terminated early.

Dosing Solution Analysis:	Samples from Days 1 and 28 and Weeks 17 and 26 were analyzed. Dosing solutions were homogenous and within 10% of nominal concentrations, except for the HD solution during Week 17, which was 17.8% below the nominal concentration. When protected from light, the current formulation is stable for 1 day at room temperature and up to 18 days at 5°C. Ritlecitinib was not detected in control formulations.

Key Study Findings

- No ritlecitinib-related tumors were noted in either sex.
- Ritlecitinib did not increase mortality, affect body weight, or produce adverse clinical observations.
- Ritlecitinib-related microscopic findings were limited to decreased lymphocyte cellularity in the inguinal lymph node, decreased mixed cell infiltrate in the liver, and decreased mononuclear cell infiltrate in the kidney, harderian gland, and mandibular salivary glands. These findings were non-adverse and related to the intended pharmacological effect.
- Ritlecitinib exposure increased more than dose-proportionally between the LD and MD and approximately dose-proportionally between the MD and HD without marked sex differences. The AUC_{24} at the HD was 55100 hr·ng/mL. These data support statements made in section 13.1 of labeling.

Observations and Results

Mortality

Animals were checked twice daily for health/mortality. As determined by the statistical reviewer, ritlecitinib did not increase overall mortality in males. Per the statistical reviewer, LD and HD females had significantly higher mortality compared to vehicle controls without dose relationship. Based on the lack of dose relationship and ritlecitinib-related and causes of these deaths, they appeared incidental.

Reviewer's Note: A total of 4 LD, 2 MD, and 3 HD females died prematurely. One LD (#M0619 [Day 138]), 1 MD (#M0703 [Day 154]), and 1 HD female (#M0803 [Day 182]) died of unknown causes. Vascular neoplasms (malignant hemangiosarcoma) were the cause of death for the remaining females: 3 LD (M0608 [Day 92], #M0620 [Day 138], #M0622 [Day 110]); 1 MD (#M0713 [Day 169]); and 2 HD (#M0813 [Day 172] and #M0801 [Day 155]). Malignant hemangiosarcoma was found in 5 control females at terminal euthanasia and in a total of 9 LD, 2 MD, and 6 HD females. Because this is a common spontaneous tumor in mice and displayed

no dose relationship in either incidence or relationship to mortality, the premature deaths in the ritlecitinib groups appear incidental.

Clinical Signs
Beginning on Day 1 of dosing, cageside observations were conducted once daily. A detailed physical examination was conducted once weekly beginning on Day 1; beginning during Week 13, detailed examinations included mass observations on each grossly visible or palpable mass. No ritlecitinib-related effects were noted.

Body Weights
Body weights were recorded prior to dosing initiation, once weekly during dosing, and on Day 182. No ritlecitinib-related effects were noted.

Feed Consumption
Food consumption per cage was recorded once weekly beginning on Day 1 and calculated as g/animal/day. No ritlecitinib-related effects were noted.

Gross Pathology
Necropsies were performed on Day 183 and following unscheduled euthanasia or death. No ritlecitinib-related effects were noted.

Histopathology
Peer Review Conducted: Yes, by a Pfizer pathologist
Historical Control Provided for Tumor Incidence: Yes

Neoplastic
No ritlecitinib-related tumor findings were noted in female or male mice.

Non Neoplastic
Ritlecitinib-related microscopic findings were limited to decreased lymphoid cellularity in the inguinal lymph node, decreased mixed cell infiltrate in the liver, and decreased mononuclear cell infiltrate in several tissues (kidney, harderian gland, and mandibular salivary gland). These findings were non-adverse, related to the intended pharmacological effect, and are summarized in the following table.

Toxicokinetics
Blood samples were collected on Day 28 at 1, 3, 7, and 24 hours post-dose. Ritlecitinib exposure increased more than dose-proportionally between the LD and MD and approximately dose-proportionally between the MD and HD without marked sex differences. Ritlecitinib was not detectable in control animals. Combined sex toxicokinetic parameters are summarized in the following table.

Ritlecitinib toxicokinetic parameters in mice (Day 28)			
Dose (mg/kg/day)	AUC_{24} (hr·ng/mL)	C_{max} (ng/mL)	t_{max} (hr)
30	2750	1460	1.0
100	14700	6980	1.0
300	55100	20000	1.0

Study Title: 104-Week Oral Gavage Carcinogenicity Study with PF-06651600 in Rats

Study no.: 18MA002
Study report location: SDN 1
Study initiation date: April 20, 2018
Conducting laboratory and location: (b) (4)
GLP compliance: Y
Drug, lot #, and % purity: PF-06651600 (ritlecitinib tosylate salt),
lot #E010019066, 97.5% purity
lot #19-AP-00089, 0.618 potency factor
lot #19-AP-00106, 0.615 potency factor
lot #19-AP-00168, 0.615 potency factor

Prior Exec CAC Dose Concurrence: Y
Basis for Dose Selection: Maximum tolerated dose

Reviewer Carcinogenicity Conclusion (negative/ positive): Positive
ECAC Carcinogenicity Conclusion (negative/ positive): Positive

Tumor Findings:
A 100 mg/kg/day dose of ritlecitinib increased the incidence of thymus tumors (combined benign and malignant thymoma) in female rats and increased the incidence of thyroid tumors (follicular cell adenoma and combined follicular adenoma and carcinoma) in male rats. No ritlecitinib-related tumors were noted at lower doses.

Methods	
Doses:	0, 10, 30 and 100 mg/kg/day
Frequency of dosing:	Once daily
Number/Sex/Group:	60 (plus 5/sex/group for toxicokinetic assessment)
Dose volume:	10 mL/kg

Formulation/Vehicle:	0.5% methylcellulose
Route of administration:	ORAL GAVAGE
Species:	RAT
Strain:	WISTAR HAN
Age:	6 to 7 weeks old at dosing initiation
Comment on Study Design and Conduct:	Acceptable design. No noteworthy deviations.
Dosing Comments (Dose Adjustments or Early Termination):	No dose adjustments were made. No groups were terminated early.

Dosing Solution Analysis:	Samples from Day 1 and Weeks 13, 25, 39, 55, 69, 72, 85, 96, and 103 were analyzed. Dosing solutions were homogenous and within 11% of nominal concentrations. When protected from light, the current formulation is stable for 1 day at room temperature and up to 18 days at 5°C. Ritlecitinib was not detected in control formulations.

Key Study Findings

- At the HD, ritlecitinib increased the incidence of thymus tumors in females and thyroid tumors in males.
- Ritlecitinib decreased body weights by approximately 15% at the HD, but did not increase mortality or produce adverse clinical observations at any dose level.
- No adverse ritlecitinib-related microscopic findings were noted.
    - Decreased lymphocyte cellularity in lymphoid tissues (thymus, spleen, and mesenteric lymph node) was noted at all dose levels and decreased mononuclear cell infiltrate in liver was noted at the HD, consistent with the intended pharmacology of ritlecitinib.
    - Increased multinucleated hepatocytes in females at doses ≥30 mg/kg/day and increased kidney tubule pigment in both sexes noted at the HD were of low severity and without adverse correlates.
- Ritlecitinib exposure increased approximately dose-proportionally between the LD and MD and more than dose-proportionally between the MD and HD without marked sex differences. The AUC_{24} at the MD and HD was 10100 and 47000 hr·ng/mL, respectively. These data support statements made in section 13.1 of labeling.

Observations and Results

Mortality

Animals were checked twice daily for health/mortality. As determined by the statistical reviewer, ritlecitinib did not increase overall mortality. Unscheduled deaths occurred at similar rates in all groups (female range: 15 to 21; male range: 24 to 29).

Clinical Signs

A detailed physical examination was conducted once weekly, beginning prior to dosing initiation and continuing through study termination. Additional cageside observations were made approximately 1 hour post-dose during dosing. Prior to dosing on Day 1, on Day 176, and weekly thereafter, mass observations were conducted. In females, ritlecitinib generally increased the incidence of thin appearance, corresponding to body weight effects. No clear ritlecitinib-related effects were noted in males.

Body Weights

Body weights were recorded once prior to dosing initiation, once weekly during the first 26 weeks of dosing, and every 4 weeks thereafter. Ritlecitinib decreased weight gain in both sexes, resulting in approximately 15% lower mean body weights in HD females and males. Dose-related body weight effects were noted at lower doses, but without producing marked (>10%) overall body weight differences compared to controls.

Feed Consumption

Food consumption per cage was recorded once weekly for the first 26 weeks, then every 4 weeks thereafter and calculated as g/animal/day. No ritlecitinib-related effects were noted.

Gross Pathology

Necropsies were performed on Day 729/730 (females) or 730/731 (males) and following unscheduled euthanasia or death. Ritlecitinib increased macroscopic thymus abnormalities (abnormal shape, large, and masses) in females at doses ≥30 mg/kg/day and slightly increased thymus abnormalities in males at all dose levels, without dose relationship. Ritlecitinib increased the incidence of macroscopically large thyroids in males at doses ≥30 mg/kg/day. Findings in HD females and males generally corresponded to ritlecitinib-related tumor findings in the thymus and thyroid, respectively.

Histopathology

Peer Review Conducted: Yes, by a Pfizer pathologist

Historical Control Provided for Tumor Incidence: Yes

Neoplastic

In HD females, ritlecitinib increased the incidence of combined benign and malignant thymoma in thymus (trend: $p = 0.0065$; pairwise: $p = 0.0295$). This increased tumor incidence rate did not meet the statistical criteria used by the ECAC for a common tumor (trend: $p < 0.005$; pairwise: $p < 0.01$). However, the incidence at the HD (18/51, mortality weighted, or 35%) was much higher than concurrent controls (8/48, mortality weighted, or 8.3%) and the historical control females (range: 0% to 11.9%). Therefore, this increased incidence rate of combined benign and malignant thymoma in thymus is considered biologically relevant.

In HD males, ritlecitinib increased the incidence of follicular cell adenoma (trend: $p = 0.0055$; pairwise: $p = 0.0047$) and the combined follicular adenoma and carcinoma in thyroid (trend: $p = 0.0020$; pairwise: $p = 0.0013$).

Reviewer's Note: Although the trend for follicular cell adenomas in males did not meet the statistical criteria used by the ECAC for a common tumor, the incidence in HD males (19/49, mortality weighted, or 39%) was significantly higher than concurrent controls (7/50, mortality weighted, or 14%) and nearly twice the historical control (range: 4% to 21.8%). Therefore, the increased rate of follicular cell adenoma in thyroid is considered biologically relevant.

No other ritlecitinib-related tumor findings were noted.

Non Neoplastic

Ritlecitinib-related microscopic findings were limited to lymphoid tissues, liver, and kidney, as summarized in the following table. Decreased lymphocyte cellularity in lymphoid tissues (thymus, spleen, and mesenteric lymph node) of both sexes and decreased mononuclear cell infiltrate in liver at the HD were consistent with the intended pharmacology of ritlecitinib. The increased multinucleated hepatocytes in females at doses ≥30 mg/kg/day and increased kidney tubule pigment in both sexes at the HD appeared non-adverse based on the low severity and lack of correlated adverse findings.

Toxicokinetics

Blood samples were collected during Week 26 at 1, 3, 7, and 24 hours post-dose. Ritlecitinib exposure increased approximately dose-proportionally between the LD and MD and more than dose-proportionally between the MD and HD without marked sex differences. Ritlecitinib was not detectable in control animals. Combined sex toxicokinetic parameters are summarized in the following table.

Ritlecitinib toxicokinetic parameters in rats (Week 26)

Dose (mg/kg/day)	AUC_{24} (hr·ng/mL)	C_{max} (ng/mL)	t_{max} (hr)	AUC_{24}/Dose ([hr·ng/mL]/[mg/kg/day])
10	2990±516	1390±177	1.0±0.0	299±51.6
30	10100±1930	4820±924	1.0±0.0	336±64.4
100	47000±8270	19300±3840	1.0±0.0	470±82.7

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

The clinical pharmacology program for the development of ritlecitinib oral capsule (50 mg QD) comprises of single ascending dose/multiple ascending dose study, radiolabeled ADME study, clinical drug-drug interaction studies, renal impairment study, hepatic impairment study, food effect study and pivotal bioequivalence study. The pivotal BE study was conducted by the Applicant to bridge the to-be-marketed formulation i.e., capsule to tablet formulation that was used during drug development program. Summary of individual studies are provided below.

19.4.1 Study B7981001: Single and multiple asceding dose PK study
Study B7981001 was a Phase 1, randomized, double-blind, open-label, placebo-controlled, single- and multiple-dose escalation, parallelgroup study conducted to evaluate the safety, tolerability, PK, and PD of ritlecitinib in HVs.

Single Ascending Dose (SAD)
During the SAD period (Period 1), participants received single doses of 5, 20, 50, 100, 200, 400, or 800 mg of ritlecitinib. Table 1 summarizes the ritlecitinib PK parameters and Figure 1 provides the median plasma concentration time profile following single oral dose of ritlecitinib.

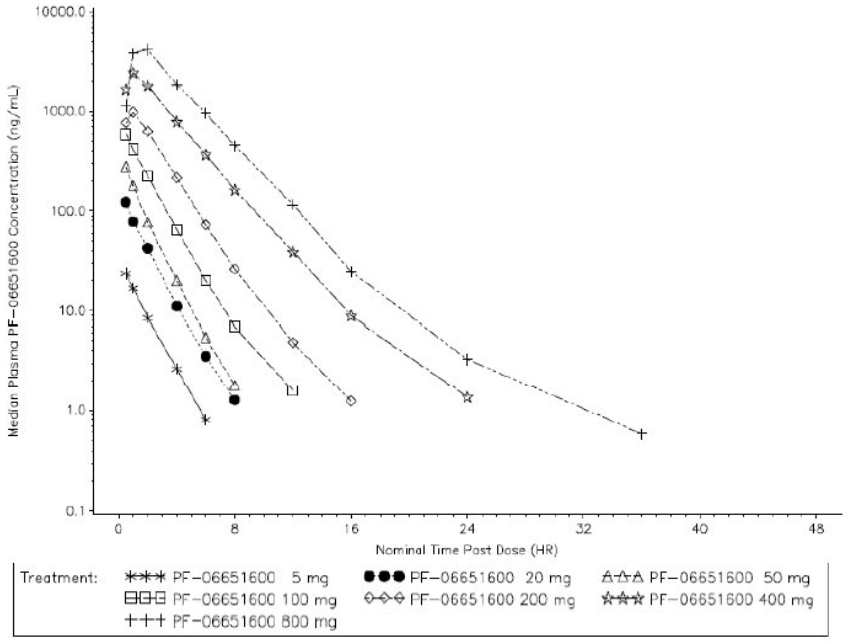
Table 1: Summary of Plasma Ritlecitinib Pharmacokinetic Parameters Following a Single Oral Dose (SAD Period)

	Parameter Summary Statistics[a] by Treatment						
Parameter (units)	**PF-06651600 5 mg**	**PF-06651600 20 mg**	**PF-06651600 50 mg**	**PF-06651600 100 mg**	**PF-06651600 200 mg**	**PF-06651600 400 mg**	**PF-06651600 800 mg**
N, n[b]	6, 6	6, 6	6, 6	6, 6	6, 6	12, 12	6, 6
AUC_{last} (ng•hr/mL)	42.42 (26)	209.3 (40)	382.6 (47)	1081 (23)	2461 (42)	7821 (34)	16760 (18)
AUC_{inf} (ng•hr/mL)	43.86 (26)	211.7 (39)	384.1 (47)	1085 (23)	2464 (42)	7824 (34)	16760 (18)
C_{max} (ng/mL)	27.02 (29)	120.9 (54)	253.3 (45)	647.7 (24)	1039 (40)	2691 (26)	4992 (11)
T_{max} (hr)	0.500 (0.500 - 0.500)	0.500 (0.500 - 1.00)	0.500 (0.500 - 1.00)	0.500 (0.500 - 0.617)	0.750 (0.500 - 2.00)	1.00 (0.500 - 2.00)	1.50 (1.00 - 2.02)
$t_{½}$ (hr)	1.20 ± 0.107	1.20 ± 0.174	1.13 ± 0.166	1.48 ± 0.176	1.75 ± 0.434	2.18 ± 0.337	2.48 ± 0.460
CL/F (L/hr)	113.8 (26)	94.42 (39)	130.0 (47)	92.21 (23)	81.14 (42)	51.10 (34)	47.71 (18)
V_z/F (L)	197.9 (26)	162.6 (28)	211.0 (35)	195.2 (18)	199.5 (30)	159.4 (31)	168.2 (15)
AUC_{last}(dn)[c] (ng•hr/mL/mg)	8.488 (26)	10.48 (40)	7.646 (47)	10.81 (23)	12.32 (42)	19.57 (34)	20.97 (18)
AUC_{inf}(dn)[c] (ng•hr/mL/mg)	8.772 (26)	10.59 (39)	7.684 (47)	10.85 (23)	12.32 (42)	19.57 (34)	20.97 (18)
C_{max}(dn)[c] (ng/mL/mg)	5.404 (29)	6.046 (54)	5.066 (45)	6.477 (24)	5.195 (40)	6.728 (26)	6.240 (11)

Source: Table 14.4.4.1.1
Pharmacokinetic parameters are defined in Table 5.
hr = hour(s); SAD = single ascending dose.
a. Geometric mean (geometric percent coefficient of variation [%CV]) for all except: median (range) for T_{max}; arithmetic mean ± standard deviation for $t_{½}$.
b. N = number of subjects in the treatment group; n = number of subjects where $t_{½}$, AUC_{inf}, CL/F, and V_z/F were determined.
c. Dose-normalized to a 1-mg dose.

Source: Table 12, B7981001 Study Report

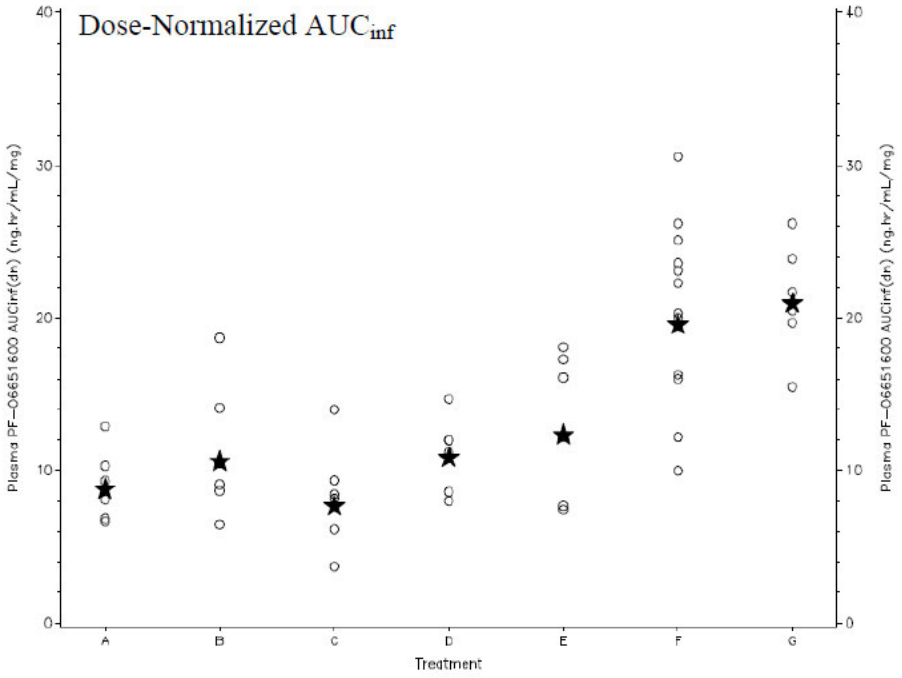
Figure 1: Median Plasma Ritlecitinib Concentration-Time Profiles Following a Single Oral Dose (SAD Period)

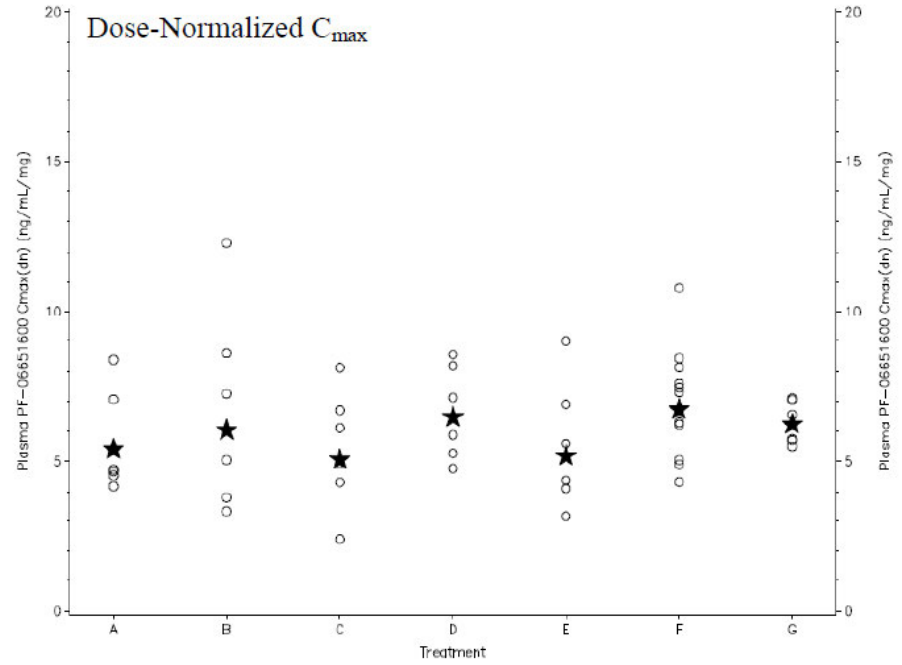


Source: Figure 14.4.3.2.1.1 (linear), Figure 14.4.3.2.2.1 (semi-logarithmic), and Table 14.4.3.1.1
Upper and lower panels are linear and semi-logarithmic scales, respectively.
Summary statistics were calculated by setting concentration values below the lower limit of quantification (LLOQ) to 0. The LLOQ was 0.500 ng/mL.
HR = hour(s); SAD = single ascending dose.

The Cmax of ritlecitinib appears to increase in approximately dose-proportional manner for the 5- to 800-mg dose range (Figure 2). The AUCinf appears to increase in approximately dose-proportional manner upto 200 mg and with greater than proportional increase observed between the 200- and 800-mg doses (Figure 2).

Figure 2: Individual and Geometric Mean Plasma PF-06651600 Dose-Normalized AUCinf and Cmax Following a Single Oral Dose (SAD Period)

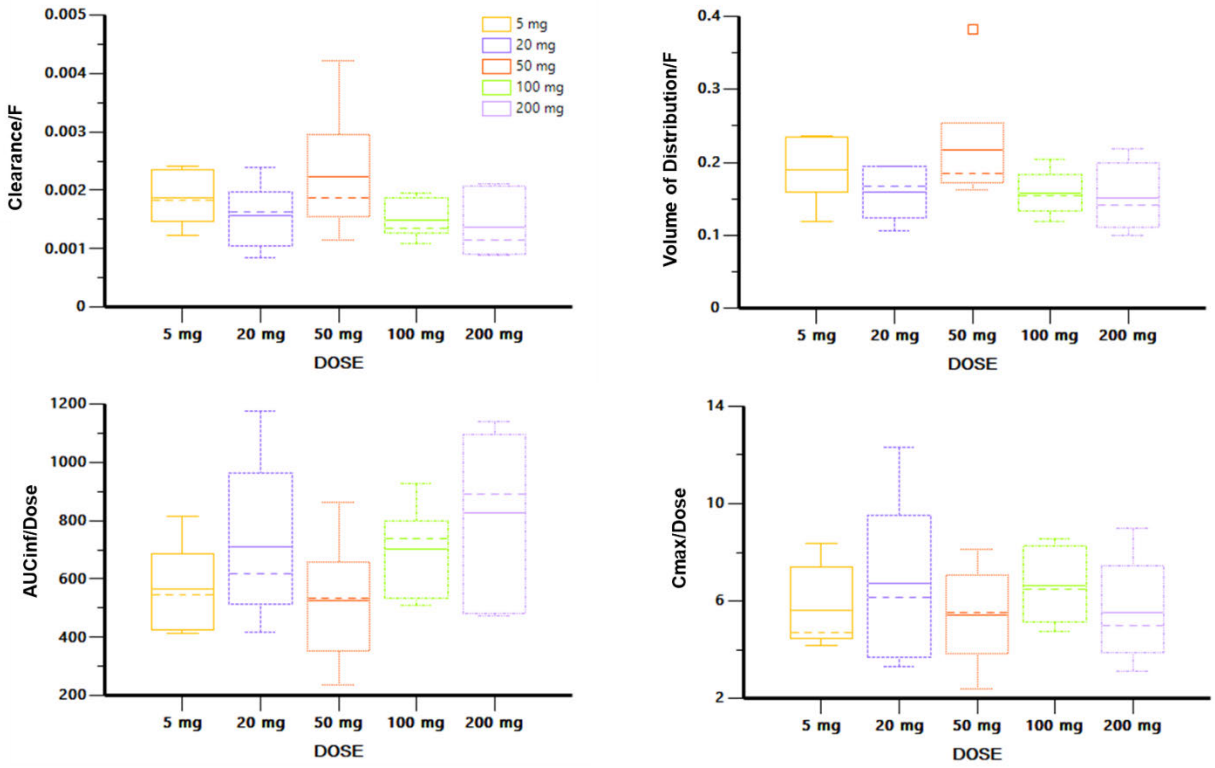




Source: Figure 14.4.4.2.1, Figure 14.4.4.2.3, and Table 16.2.5.4.1.1
Treatments: A = PF-06651600 5 mg; B = PF-06651600 20 mg; C = PF-06651600 50 mg; D = PF-06651600 100 mg, E = PF-06651600 200 mg, F = PF-06651600 400 mg; G = PF-06651600 800 mg.
Notes: The geometric mean was calculated for each treatment group. Stars represent geometric means and circles represent individual values. Pharmacokinetic parameters are defined in Table 5.
SAD = single ascending dose.

Source: Figure 3, Study B7981001

Figure 3: Box plot of Dose Normalized Clearance/F, Volume of Distribution/F, AUCinf and Cmax Following a Single Oral Dose (SAD Period) from 5 mg to 200 mg.



Source: Reviewer's analysis (B7981001, study data)

Reviewer Comments: No dedicated dose proportionality study was conducted by the Applicant. Further analysis was conducted by the reviewer and a truncated box plot was generated for clearance, volume of distribution, dose normalized AUC and Cmax to further assess if PK is linear between the dose of 5 mg to 200 mg. Observations based on the Figure 3 indicate that the apparent clearance and volume of distribution and dose normalized AUC and Cmax are approximately flat in the dose range of 5 mg to 200 mg and the PK can be considered approximately dose proportional up to 200 mg.

Muliple Ascending Dose (MAD)

For Cohorts in the MAD period, participants received doses of 50, 200, or 400 mg QD or 100 or 200 mg BID for 14 days (morning dose only on Day 14). The plasma ritlecitinib accumulation with multiple dosing ranged from 1.0 to 1.8 for the QD dosing. Table 2 summarizes the ritlecitinib PK parameters following multiple oral doses of ritlecitinib on Day 14.

Table 2: Summary of Plasma PF-06651600 Pharmacokinetic Parameters Following Multiple Oral Doses (MAD Period), Day 14

Parameter (units)	Parameter Summary Statistics[a] by Treatment				
	PF-06651600 50 mg QD	PF-06651600 100 mg BID	PF-06651600 200 mg QD	PF-06651600 400 mg QD	PF-06651600 200 mg BID
N, n[b]	6, 6	4, 4	5, 5	15, 14	5, 5
AUC_τ (ng•hr/mL)	540.1 (38)	1984 (15)	4069 (22)	10040 (19)	5207 (24)
C_{max} (ng/mL)	315.2 (38)	663.0 (35)	1422 (28)	3136 (26)	1903 (27)
C_{av} (ng/mL)	22.50 (38)	165.4 (15)	169.4 (22)	418.4 (19)	433.8 (24)
C_{min} (ng/mL)	NR[c]	8.451 (17)	NR[c]	1.501 (42)	23.38 (67)
PTF	NR[c]	3.958 (24)	NR[c]	7.493 (17)	4.327 (5)
T_{max} (hr)	0.500 (0.500 - 1.00)	0.750 (0.500 - 2.00)	1.00 (0.500 - 1.00)	1.00 (0.500 - 2.00)	1.00 (0.500 - 1.00)
$t_{½}$ (hr)	1.30 ± 0.241	2.11 ± 0.341	1.84 ± 0.409	2.16 ± 0.100	2.27 ± 0.212
CL/F (L/hr)	92.56 (38)	50.43 (15)	49.14 (22)	39.85 (19)	38.41 (24)
V_z/F (L)	170.6 (26)	151.4 (27)	128.0 (29)	126.1 (18)	125.3 (18)
Ae_τ (ng)	2044000 (23)	6459000 (4)	10930000 (31)	25840000 (19)	14090000 (20)[d]
Ae_τ%	4.088 (23)	6.459 (4)	5.465 (31)	6.459 (19)	7.042 (20)[d]
CL_r (mL/min)	63.06 (28)	54.33 (12)	44.76 (38)	42.90 (18)	45.46 (17)[d]
AUC_τ(dn)[e] (ng•hr/mL/mg)	10.81 (38)	19.84 (15)	20.33 (23)	25.12 (19)	26.04 (24)
C_{max}(dn)[e] (ng/mL/mg)	6.304 (38)	6.630 (35)	7.118 (29)	7.842 (26)	9.520 (27)

Source: Table 14.4.4.1.2 and Table 14.4.4.1.3
For parameters analyzed on the logarithmic (log) scale, "0" values were substituted with "0.0001" prior to log transformation.
Pharmacokinetic parameters are defined in Table 5.
BID = twice daily; hr = hour(s); MAD = multiple ascending dose; min = minute(s); NR = not reported; QD = once daily.

a. Geometric mean (geometric percent coefficient of variation [%CV]) for all except: median (range) for T_{max}; arithmetic mean ± standard deviation for $t_{½}$.
b. N = number of subjects in the treatment group; n = number of subjects where $t_{½}$ and V_z/F were determined.
c. Summary statistics are not presented where the data include 0 values for C_{min} (geometric mean for C_{min} is biased, and PTF cannot be determined for subjects where $C_{min} = 0$).
d. Data from 4 subjects contributed to this summary statistic.
e. Dose-normalized to a 1-mg dose.

Source: Table 13, B7981001 Study Report

Non-compartmental PK parameters (AUCtau and Cmax) for AA patients receiving multiple doses of ritlecitinib were calculated at Week 4 (after 4 weeks of 200 mg QD) and Week 24 (after 20 weeks of 50 mg QD). AA participants had higher systemic exposures to ritlecitinib compared to HVs, indicative of lower clearance of ritlecitinib in AA patients.The geometric means for the PK parameters are provided in Table 3.

Table 3: Ritlecitinib Non-compartmental PK Parameters in Healthy Participants and AA Patients.

Participant Type	Ritlecitinib 200 mg QD at Steady-state[a]		Ritlecitinib 50 mg QD at Steady-state[a]	
	AUC_{tau} ng•h/ml	C_{max} ng/ml	AUC_{tau} ng•h/ml	C_{max} ng/ml
Healthy Participants*	4069 (22)	1422 (28)	540.1 (38)	315.2 (38)
AA Participants**	6353 (69)	1601 (94)	1411 (47)	397.6 (44)

* Source: Module 5.3.3.1 B7981001 CSR Table 14.4.4.1.2; Table 14.4.4.1.3.
** Source: Module 5.3.5.1 B7931005 CSR Table 14.4.5.5.1.1.
[a] Geometric Mean (Geometric %CV) for all

19.4.2 B7981011 ADME and Absolute Bioavailability Study
Study B7981011 was a Phase 1, open-label, nonrandomized, 2-period, fixed-sequence study conducted to investigate the absorption, distribution, metabolism, and excretion of ritlecitinib ([14C]-ritlecitinib) and to assess the absolute bioavailability and fraction absorbed (Fa) of ritlecitinib in male heatlhy volunteers (HVs) using a [14C]-Microtracer approach. Six male HVs were assigned to receive the investigational product in 2 treatment periods. In Period A, participants received oral dose of [14C]-ritlecitinib 200 mg with 300 nCi dose of radioactivity. In Period B, oral unlabeled 200 mg ritlecitinib was administered approximately 0.5 hour before IV [14C]-ritlecitinib 60 µg. In both periods, the investigational product was administered after an overnight fast of at least 10 hours. In Period A, following a single oral administration of 200 mg 14C-ritlecitinib (290 nCi), the total recovery of the orally administered radioactive dose over a period of 240 hours post dose (mean ±SD) in five subjects was 85.6±9.2%, with 66.1±13.4% in the urine and 19.5±4.0% in the feces. One participant was excluded from dose recovery mean calculations due to incomplete sample collection (urine loss due to leak from the urine container). In Period B, following a single oral dose of 200 mg unlabeled ritlecitinib, an intravenous dose of 60 µg 14C-ritlecitinib (300 nCi) was administered at Tmax (~0.5 hour). The total recovery of the IV administered radioactive dose over a period of 144 hours post dose (mean ±SD) in five subjects was 83.0±4.7%, with 70.5±4.3% in the urine and 12.5±3.7% in the feces.

Following administration of a single 200 mg oral dose of ritlecitinib, the absolute oral bioavailability was 64.30% (90% CI: 58.11%, 71.14%), as measured by the ratio (PO/IV) of adjusted geometric mean plasma dose normalized AUCinf [AUCinf(dn)] values (Table 4).

Table 4: Statistical Analysis for Absolute Oral Bioavailability (F)

Parameter, units	Adjusted Geometric Means		F: Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Unlabeled Ritlecitinib (200 mg PO) Period B (Test)	^{14}C-ritlecitinib (60 µg IV) Period B (Reference)		
AUC_{inf}(dn), ng.hr/mL/mg	14.71	22.87	64.30	(58.11, 71.14)
AUC_{last}(dn), ng.hr/mL/mg	14.69	22.08	66.52	(60.17, 73.54)

Source: Table 14.4.5.2.1
Values were back-transformed from the log scale.
The model was a mixed effect model with treatment as fixed effects and participant as a random effect.
a. The ratios (and 90% CIs) are expressed as percentages.

Source: Table 9, Study Report B7981011

Based on the geometric mean ratio (PO/IV) of dose-normalized Total ^{14}C values for the 5 participants with complete urine data for both PO and IV treatments, Fa was 89.18% (Table 5).

Table 5: Geometric Mean Ratio for Fraction Absorbed (Fa)

Parameter	Geometric Means		F_a: Ratio[a] Test (PO) / Reference (IV)
	^{14}C-ritlecitinib 200 mg PO (Period A)	Unlabeled Ritlecitinib 200 mg PO + ^{14}C-ritlecitinib 60 µg IV (Period B)	
%Total ^{14}C Urine	64.93	72.80	89.18

Source: Table 14.4.5.2.2
a. The ratio is expressed as a percentage.

Radiometric LC-MS analysis of pooled human plasma extract (0-48 hours) revealed 2 major circulating drug-related components: ritlecitinib (30.4% of circulating radioactivity) and cysteine conjugate M2 (PF-07034562, 16.5%). Other minor circulating drug-related components included the glutathione-related M1 (PF-07034563, 4.3%), M3 (PF-07034468, 4.2%), 464 (3.9%) and primary oxidative metabolite M4 (PF-07297983, 5.0%) and downstream oxidations 336-3, 304-4, M5 (PF-07297982), 336-1, 320-1 and 336-2 for 5.9%, 3.5%, 2.8%, 2.2%, 2.1% and 1.2% of circulating radioactivity, respectively. Radiometric LC-MS analysis of pooled urine (0-24 hours representing 66.1 % of recovered 14C) showed 2 major drug-related components: hydroxylated M4 (PF-07297983), and N-acetyl cysteine conjugate M3 (PF-07034468) which represented 16.3% and 10.3 % of the administered dose, respectively. Other minor metabolites observed in urine were the glutathione-related M2 (PF-07034562, 4.6%), M1 (PF-07034563, 4.0%) and 423 (2.0%), downstream oxidative metabolites 336-3 (6.5%), M5 (PF-07297982, 3.3%), 320-1 (2.3%), 318-2 (1.5%), oxidative glucuronide 512 (1.1%) and parent ritlecitinib (2.7%). Metabolic profiling of pooled feces (24-96 hours pool representing 19.5% of recovered 14C) homogenate extract showed a pattern of glutathione-related remnants and various hydrolytic and oxidative metabolites, but no single metabolite was greater than 1% of the administered dose. Figure 4 presents the proposed biotransformation pathways of ritlecitinib in human plasma, urine and feces and Figure 5 shows the composite mass balance and elimination model of ritlecitinib.

Figure 4: Proposed Biotransformation Pathways of Ritlecitinib in Humans after Oral Administration of Ritlecitinib at 200 mg in Plasma (P), Urine (U), and Feces (F)

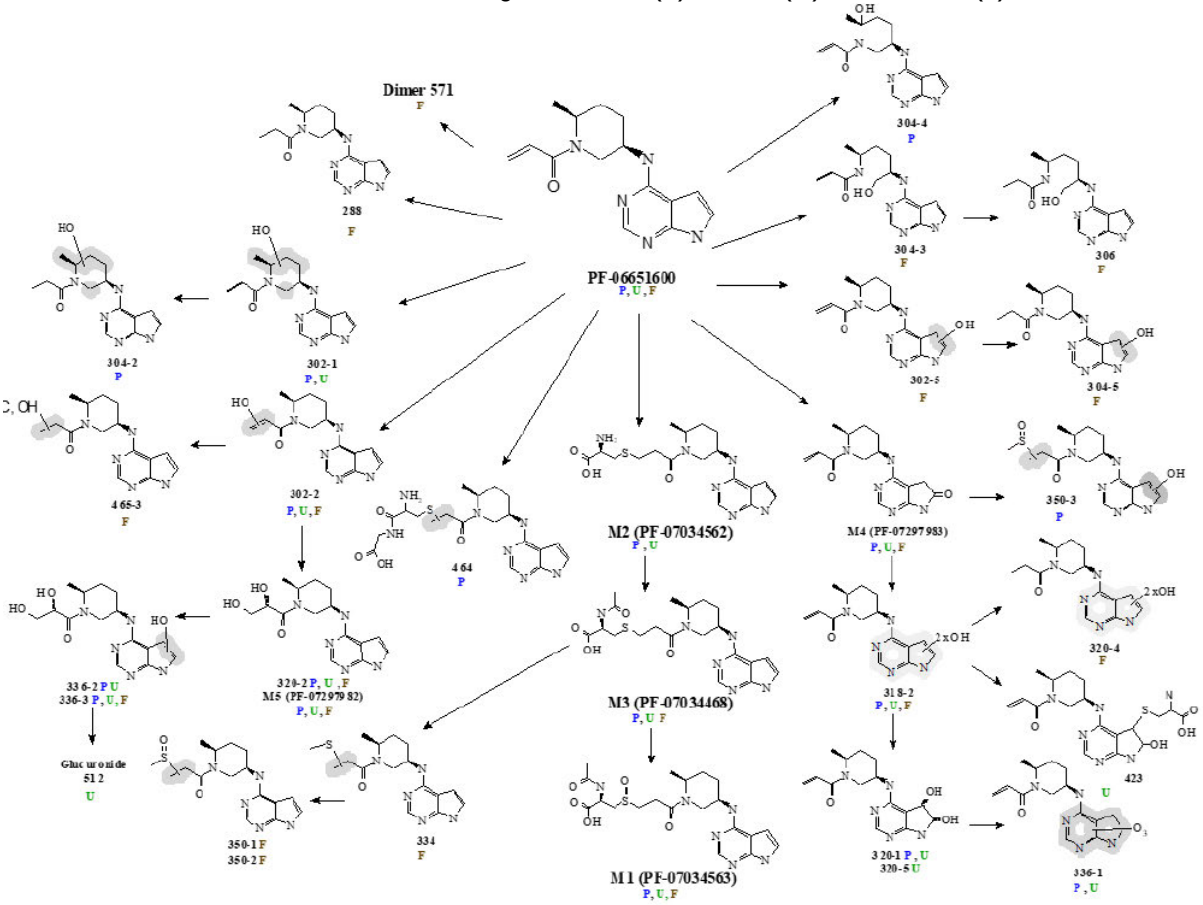
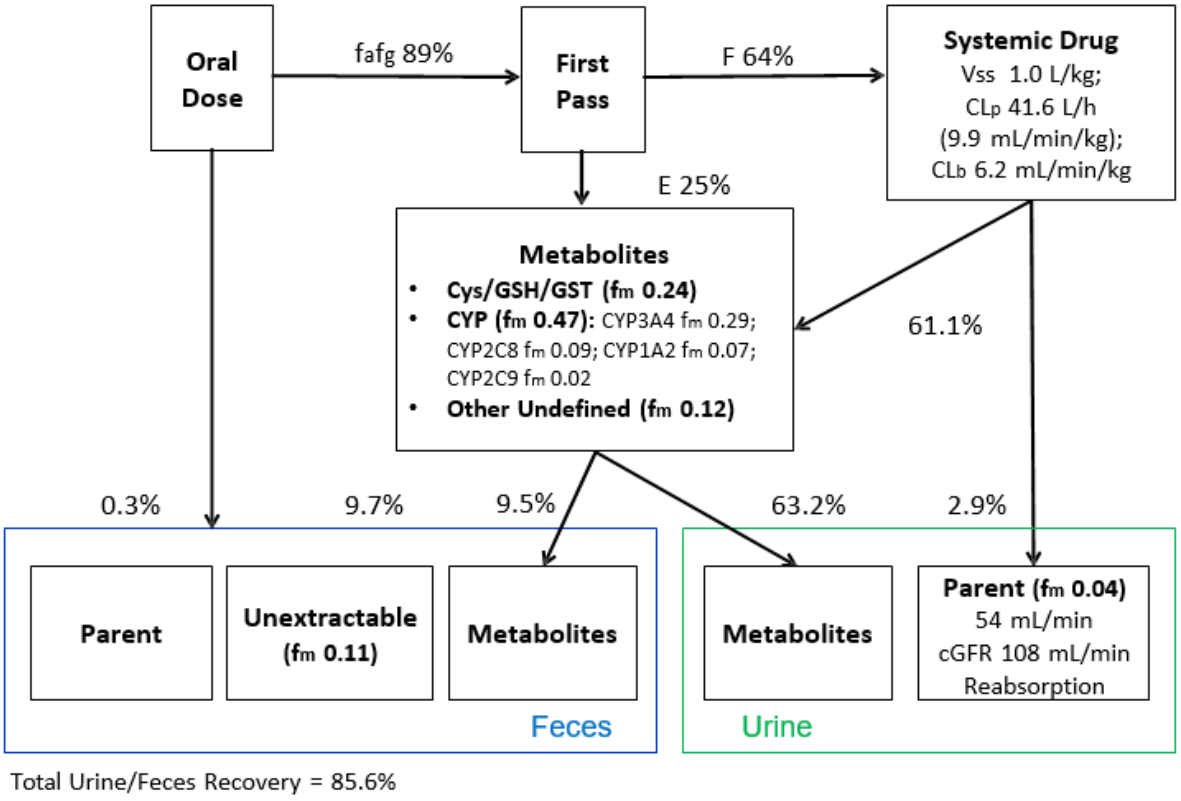


Figure 5: Composite mass balance and elimination model of ritlecitinib.



Note – The ADME of ritlecitinib was characterized following a single dose and represents the most sensitive assessment of potential metabolites. The clearance of ritlecitinib is slightly reduced after multiple doses and no new metabolites are expected to be formed.

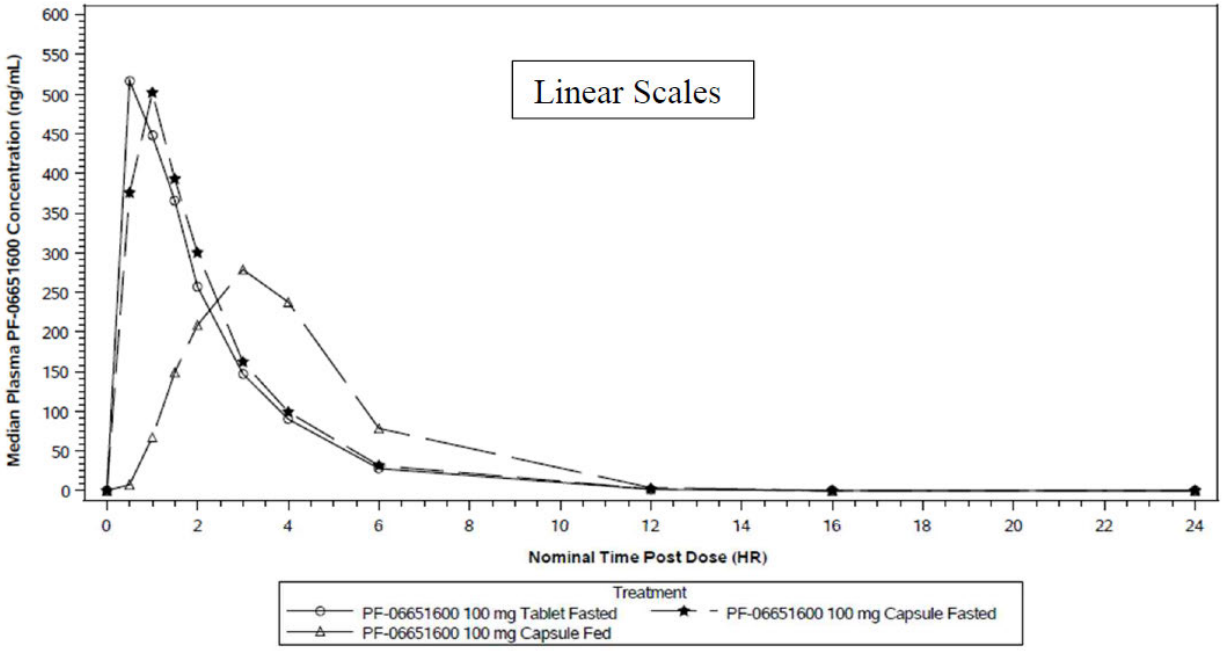
Source: Figure 1, Summary of Clinical Pharmacology Studies

19.4.3 B7981029: Pivotal Bioequivalence Study and Food Effect

The tablet formulation was used in the clinical development and utilized in the pivotal Phase 2b/3 study (B7981015) and other clinical studies in the program, whereas capsule formulation is the to-be-marketed formulation (TBM). Since, the TBM formulation is different than the formulation used in pivotal clinical safety/efficacy study, a pivotal BE study (B7981029) was conducted to establish a scientific bridge. Pivotal bioequivalence (BE) study (B7981029) was conducted using 100 mg capsule and 100 mg (2×50 mg) tablet formulation to establish BE. The Applicant also assessed the effect of food on the TBM capsule formulation in this study. B7981029 study was conducted as a Phase 1, open-label, single-dose, randomized, 2- or 3-period, cross-over design in a single cohort of approximately 118 enrolled (160 actually enrolled) healthy male or female participants at multiple study centers. The applicant noted that the shipment of PK samples from 41 participants to the laboratory was delayed for over a month. Dry ice was not replenished by the courier and consequently the samples thawed and were rendered non evaluable. Therefore, the protocol was amended to allow enrollment additional participants such that number of evaluable participants equaled approximately 118. A total of 123 participants (after discarding the 41 participants with thawed samples) were analyzed for PK concentrations and parameters populations. Median plasma ritlecitinib

concentration-time profiles of all the 3 treatment groups are presented in Figure 6. PK parameters are summarized descriptively in Table 6 and BE analysis is presented in Table 7. Capsule and tablet formulations were bioequivalent and a clinical bridge is considered as established.

Figure 6: Median Plasma Ritlecitinib Concentration-Time Profiles by Treatment Group Following Single Oral Administration



Source: Figure 1, Study B7981029

Table 6: Descriptive Summary of Plasma Ritlecitinib PK Parameters

Parameter (Units)	Parameter Summary Statistics[a] by Treatment Group PF-06651600 100 mg Tablet Fasted (N=122)	PF-06651600 100 mg Capsule Fasted (N=119)	PF -06651600 100 mg Capsule Fed (N=12)
N1,N2	122, 120	119, 119	12, 12
AUC_{inf} (ng.hr/mL)	1223 (42)	1269 (42)	1136 (35)
AUC_{last} (ng.hr/mL)	1215 (43)	1259 (43)	1128 (36)
C_{max} (ng/mL)	614.8 (40)	618.5 (42)	327.9 (25)
T_{max} (hr)	0.500 (0.500-1.58)	1.00 (0.500-2.00)	3.00 (0.500-4.00)
T_{last} (hr)	12.0 (1.50-24.0)	12.0 (6.00-16.1)	12.0 (6.00-16.0)
$t_{1/2}$ (hr)	1.387 ± 0.32328	1.382 ± 0.27664	1.368 ± 0.24391
CL/F (L/hr)	81.74 (42)	78.77 (42)	88.08 (35)
V_z/F (L)	159.7 (34)	153.9 (29)	171.6 (20)

Source: Table 14.4.5.1
N = Total number of participants in the treatment group in the PK parameter population
N1=number of participants contributing to the summary statistics
N2=number of participants contributing to the summary statistics for $t_{1/2}$, AUC_{inf}, CL/F and V_z/F
a. Geometric mean (%CV) for all except: median (range) for T_{max} and T_{last}; arithmetic mean±SD for $t_{1/2}$.
PFIZER CONFIDENTIAL SDTM Creation: 27OCT2021 (03:04) Source Data: adpp Table Generation: 17NOV2021 (01:51)
Output File: ./nda1 cdisc/B7981029 PK/adpp s101 m
Table 14.4.5.1.1 is for Pfizer internal use.

Source: Table 8, Study B7981029

Table 7: Summary of Bioequivalence Analysis following Single Dose of To-be-Marketed 100 mg Capsule (Test, T) and 100 mg (2×50 mg) Tablet Formulation (Reference, R) under fasting conditions

Parameter	Geometric Mean		T/R Ratio (%)	90% CI for Ratio	
	Test	Reference		Lower	Upper
Cmax (ng/mL)	558.96	554.35	100.83	95.61	106.34
AUClast (ng.hr/mL)	1064.78	1101.50	96.67	88.27	105.87
AUCinf (ng.hr/mL)	1089.39	1112.02	97.96	89.61	107.10

Source: Reviewer's analysis using PK data of Study B7981029

When capsule formulation was administered with a high-fat meal, ritlecitinib absorption was delayed with median Tmax occurring at 3 hours post dose. Overall, mean AUCinf between the fed and fasted treatment was similar; however, mean Cmax was approximately ~32% lower for the fed treatment (Table 8).

Table 8: Statistical Summary for Food Effect of Log Transformed Plasma PF-06651600 PK Parameters (AUCinf, AUClast, and Cmax)

	Adjusted Geometric Means			
Parameter (Unit)	PF-06651600 100 mg Capsule Fed (Test)	PF-06651600 100 mg Capsule Fasted (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means	90% CI for Ratio
AUC_{inf} (ng.hr/mL)	1136	1027	110.59	(97.82, 125.03)
AUC_{last} (ng.hr/mL)	1128	1016	111.05	(98.15, 125.65)
C_{max} (ng/mL)	327.9	483.4	67.83	(54.08, 85.08)

Values have been back-transformed from the log scale.
The model is a mixed effect model with sequence and treatment as fixed effects and Participant within sequence as a random effect.
Source: Table 14.4.5.2.2
PFIZER CONFIDENTIAL SDTM Creation: 27OCT2021 (04:04) Source Data: adpp Table Generation: 01NOV2021 (04:56)
Output File: ./nda1 cdisc/B7981029 PK/adpp s202 m
Table 14.4.5.2.4 is for Pfizer internal use.

Source: Table 10, Study B7981029

Reviewer's Comment: The applicant was sent an information request dated 17th October 2022, to provide justification for conducting the pivotal BE study at 100 mg strength and not at proposed TBM strength of 50 mg. (b) (4) *The pivotal BE study B7981029 was then conducted in parallel with the Phase 2b/3 study B7981015.* (b) (4) Based on the approximate dose-proportionality of PK up to 200 mg, in conjunction with demonstrated similarity in dissolution profiles among 30, 50, and 100 mg doses, the BE result established with the 100 mg dose can be considered to be applicable to the dose of 50 mg.

Office of Study Integrity and Surveillance (OSIS) inspection results: OSIS conducted a remote regulatory assessment (RRA) of the analytical portion of studies B7981029 (NDA 215830, ritlecitinib/PF-06651600) conducted at (b) (4) OSIS did not observe any objectionable conditions during the RRA. Therefore, OSIS concluded that data from the audited study is reliable.

19.4.4 B7981016: Hepatic Impairment Study
Study B7981016 was a Phase 1, non-randomized, openlabel, multiple-dose study conducted to evaluate the PK, safety, and tolerability of ritlecitinib in patients with hepatic impairment (HI) and HVs with normal hepatic function (NHF). The study was designed as 2 parts (Part 1 and Part 2). Part 1 consisted of 2 Cohorts (Cohort 1: patients with moderate HI; Cohort 2: demographically matched participants with NHF). Part 2, which would have recruited patients

with mild HI, was to be conducted only if ritlecitinib AUCtau geometric mean ratio for the moderate HI group compared to normal group was ≥2.0 (the decision criterion to proceed to Part 2). HI study was completed after Part 1 because the criterion to proceed to Part 2 was not met. The study was designed to evaluate the PK of ritlecitinib in participants with moderate HI in Part 1 and, if necessary, in participants with mild HI. Participants with severe HI were not studied, as administration of an immunosuppressant such as ritlecitinib to patients with severe HI is generally not recommended. Following multiple 30 mg oral doses of ritlecitinib, the plasma ritlecitinib AUCtau was 18.5% higher and Cmax was comparable for patients with moderate HI relative to participants with NHF.

Table 9: Statistical Summary of Plasma Ritlecitinib PK Parameters, Study B7981016

	Geometric Means			
Parameter (Unit)	Moderate Hepatic Impairment Group Test	Normal Hepatic Function Group Reference	Ratio (Test/Reference) of Geometric Means[a]	90% CI for Ratio[a]
AUC24 (ng.hr/mL)	454.5	383.6	118.50	(87.96, 159.64)
Cmax (ng/mL)	194.3	186.9	104.00	(74.48, 145.23)

Source: Table 14.4.5.2
[a] The ratios (and 90% CIs) are expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: 15MAY2020 (05:15) Source Data: adpp Output
File: ./nda1 cdisc/B7981016 CSR/adpp s102i Date of Generation: 19MAY2020 (03:12)

Source: Table 7, Study Report B7981016

19.4.5 B7981020: Renal Impairment Study

Study B7981020 was a Phase 1, non-randomized, open label, multiple-dose, parallel-cohort, multisite study conducted to investigate the effect of renal impairment on the plasma PK, safety, and tolerability after multiple oral doses of 50 mg QD. Estimated glomerular filtration rate (eGFR) and classification of renal function status of participants was done using the Modification of Diet in Renal Disease (MDRD) formula.The study was designed as 2 parts (Part 1 and Part 2). Part 1 consisted of 2 Cohorts (Cohort 1: patients with severe renal impairment (RI); Cohort 2: demographically matched participants with normal renal function (NRF)). Part 2, which would have recruited participants with mild and moderate RI, was to be conducted only if ritlecitinib AUCtau geometric mean ratio for SRI group compared to NRF was ≥2.0 (the decision criterion to proceed to Part 2). The study was terminated after Part 1 completed participation due to the COVID-19 pandemic and the need to minimize exposure of HV to an immunosuppressant with no benefit. Normal HV data from completed Phase 1 Study B7981016 adequately represented matched NRF (Table 10). Hence, this data was used in place of Cohort 2 (participants with NRF) to avoid unnecessary exposure of HV with NRF to an immunosuppressant. A total of 8 patients with SRI received ritlecitinib 50 mg QD up to Day 9. On Day 10, they received ritlecitinib 50 mg QD after 10-hour fast. The PK data from the patients with SRI were compared with the PK data available for demographically matched participants with NRF from Study B7981016 using ANOVA. Based on the above analysis, the study was considered completed after Part 1 Cohort 1 as the criteria to proceed to Part 2 was not met.

The AUCtau was approximately 55% higher and the Cmax was approximately 44% higher for the patients with SRI relative to the participants with NRF from Study B7981016 using ANOVA (Table 11).

Table 10: Demographic Data

Protocol	Participant Type	N	Age (years)*	Weight (kg)*	BMI (kg/m^2)*	Female/ Male Ratio
B7981020	Severe Renal Impairment	8	59.5 (9.78)	87.8 (4.91)	30.5 (1.65)	3/5
B7981016	Healthy Participant	6	56.7 (7.34)	81 (9.35)	28.8 (3.53)	2/4

*Mean (SD)
Source Tables: 14.1.2.4 and 14.1.2.5

Source: Table 2, PMAR-EQDD-B798D-OTHER-1220 Study Report

Table 11: Statistical Summary (ANOVA) of Log Transformed Plasma Ritlecitinib PK Parameters (AUC0-24, Cmax)

Parameter (Units)	Comparison (Test vs Reference)	Adjusted Geometric Means		Ratio (%) (Test/Reference) of Adjusted Means	90% CI (%) for Ratio
		Test	Reference		
AUC_{0-24} (ng.hr/mL)	Severe Renal Impairment vs Normal Renal Function Group from Study B7981016	986.3	635.7	155.15	(122.83, 195.98)
C_{max} (ng/mL)	Severe Renal Impairment vs Normal Renal Function Group from Study B7981016	445.6	308.4	144.48	(114.24, 182.73)

Values have been back-transformed from the log scale
The model is a one-way ANOVA model based on natural log transformed data.
Parameters from Study B7981016 were dose adjusted to 50 mg by formula '(value/30)*50'
Modified Parameter Analysis Set - SAP defined Parameter Analysis Set for the reference group as participants with eGFR ≥90 mL/min and therefore participants with eGFR <90 mL/min were excluded from the Normal Hepatic Function Group Study B7981016.

Source: Table 3, *PMAR-EQDD-B798D-OTHER-1220 Study Report*

19.4.6 B7981023: Drug-Drug Interaction Study (Ritlecitinib as Victim), Effect of Multiple Doses of Itraconazole 200 mg QD (a Strong CYP3A Inhibitor) on PK of Ritlecitinib
Study B7981023 was a Phase 1, open-label, fixedsequence, 2-period study conducted to investigate the effect of multiple oral doses of itraconazole on the PK of a single oral dose of ritlecitinib in HVs. Twelve HVs were treated and completed the study. The study consisted of 2 treatments in 1 fixed-sequence. Period 1: On Day 1, ritlecitinib single oral dose of 30 mg (as 3 × 10 mg) tablets was given. Period 2: On Day 1 to 3, 200-mg itraconazole was administered as 20 mL Sporanox® 10-mg/mL oral solution once daily. On Day 4, itraconazole 200 mg and 30 mg (as 3 × 10 mg) ritlecitinib tablets were coadministered. The co-administration of multiple 200 mg

doses of itraconazole increased AUCinf of ritlecitinib by approximately 15%, whereas the Cmax of ritlecitinib was similar relative to a single 30 mg ritlecitinib dose given alone (Table 12).

Table 12: Statistical Summary of Plasma Ritlecitinib PK Parameters (Study B7981023)

Parameter (Unit)	Adjusted (Least Squares) Geometric Means: Itraconazole 200 mg MD + PF-06651600 30 mg SD Test	Adjusted (Least Squares) Geometric Means: PF-06651600 30 mg SD Reference	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio[a]
AUC_{inf} (ng.hr/mL)	308.0	267.5	115.11	(104.61, 126.68)
AUC_{last} (ng.hr/mL)	303.9	264.2	115.05	(104.44, 126.74)
C_{max} (ng/mL)	156.5	152.6	102.52	(82.75, 127.02)

Source: Table 14.4.5.3
[a] The ratios (and 90% CIs) are expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: 09JUL2019 (22:40) Date of Table Generation: 14JUL2019 (22:45)

Source: Table 8, Study B7981023

19.4.7 B7981026: Drug-Drug Interaction Study (Ritlecitinib as Victim), Effect of Multiple Doses of Rifampin 600 mg QD (a Strong CYP3A4 inducer) on PK of Ritlecitinib
Study B7981026 (Module 5.3.2.2 B7981026 CSR) was a Phase 1, open-label, fixed-sequence study conducted to evaluate the effect of repeat-dose rifampin on the PK of ritlecitinib in HVs. A total of 12 participants were treated, and 10 participants completed the study. The participants received ritlecitinib and rifampin in a fixed-sequence consisting of 2 periods. In period 1 participants received ritlecitinib 50 mg QD under fasting conditions on Day 1 and in period 2 rifampin 600 mg QD was administered approximately 1 hour before morning meal on Days 1 to 7. On the morning of Day 8, ritlecitinib 50 mg QD was administered under fasting conditions, 2 hours after the morning dose of rifampin. Rifampin, a potent inducer, reduced the AUCinf of ritlecitinib by approximately 44% and the Cmax by approximately 25% (Table 13).

Table 13: Statistical Summary of Plasma Ritlecitinib PK Parameters (Study B7981026)

Adjusted (Least-Square) Geometric Means				
Parameter (Unit)	Rifampin 600 mg QD + PF-06651600 50 mg (single dose) Test	PF-06651600 50 mg (single dose) Reference	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio[a]
AUC_{inf} (ng.hr/mL)	250.5	449.3	55.76	(51.94, 59.87)
AUC_{last} (ng.hr/mL)	249.4	448.1	55.66	(51.87, 59.72)
C_{max} (ng/mL)	204.4	272.3	75.07	(63.25, 89.10)

Source: Table 14.4.5.3.1
a. The ratios (and 90% CIs) are expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: 06NOV2020 (03:48)
Source Data: adpp Table Generation: 12NOV2020 (23:01)
Output File: ./nda1_cdisc/B7981026_PK/adpp_s201_i

Source: Table 8, Study B7981026

Reviewer Comment: Rifampin (600 mg QD), a potent CYP inducer, reduced the AUCinf of ritlecitinib by approximately 44% and the Cmax by approximately 25%, when ritlecitinib (50 mg) was co-administered with multiple doses of rifampin. Based on the trial results, the exposure of ritlecitinib is reduced by approximately 44%, which brings its exposure below expected exposure of ritlecitinib after administration of 30 mg (lowest efficacious dose observed in pivotal clinical safety/efficacy study B7981015) assuming linear dose proportional decrease in AUC. For a scenario of high body weight individuals (the systemic exposure can be even lower in case of high body weight patients i.e., more than 101 kg, 95th percentile in the analysis population, see section 19.4.16 for details) taking strong CYP inducers, the dose (assuming linear dose proportional decrease in AUC with dose) will be likely 19.5 mg (50 mg*0.5576*0.70=19.516). This dose is almost 2/3rd of 30 mg dose studied showing statistically significant clinical effect. In pivotal clinical study, 10 mg dose was not shown to have statistically significant effect at 24 weeks. The exposure response relationship indicates that the decrease in exposure will likely lead to loss of efficacy. Hence it has been recommended to avoid concomitant use of strong inducers of CYP3A (CYP3A is major CYP involved in metabolism of ritlecitinib).

19.4.8 B7981017: Drug-Drug Interaction Study (Ritlecitinib as Perpetrator), Effect of Multiple Doses of Ritlecitinib 200 mg QD on Pharmacokinetics of Midazolam (sensitive CYP3A probe substrate) and Efavirenz (sensitive CYP2B6 Substrate)
Study B7981017 was a Phase 1, randomized, open-label, 2-way, cross-over study conducted to estimate the effect of multiple-dose ritlecitinib on the PK of single-dose midazolam and efavirenz in HVs. A total of 12 HVs were enrolled in the study. Each treatment sequence consisted of 2 periods in a single fixed-sequence. In treatment sequence 1, period 1, midazolam and efavirenz were administered on Day 1. In period 2, ritlecitinib was administered on Days 1 to 11, and midazolam and efavirenz were administered on Day 10. In treatment sequence 2, period 1, ritlecitinib was administered on Days 1 to 11, and midazolam and efavirenz were

administered on Day 10 and in period 2 (after a 10 day washout), midazolam and efavirenz were administered on Day 1. The co-administration of multiple doses of ritlecitinib increased the AUCinf and Cmax of midazolam by 2.7 and 1.8-fold, respectively (Table 14). Hence, ritlecitinib is likely a moderate inhibitor of CYP3A. The exposure (AUC0-72) and peak exposure (Cmax) of efavirenz were similar after the co-administration with multiple doses of ritlecitinib (Table 15). Hence, ritlecitinib does not inhibit or induce the metabolism of drugs metabolized by CYP2B6.

Table 14: Statistical Summary of Log Transformed Plasma Midazolam PK Parameters, Study B7981017

Parameter (Units)	Adjusted Geometric Means: Multiple-dose PF-06651600 200 mg QD + Single-dose of Midazolam and Efavirenz (Test)	Adjusted Geometric Means: Single-dose of Midazolam and Efavirenz (Reference)	Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio[a]
AUC_{inf} (ng.hr/mL)	54.98	20.41	269.41	(216.08, 335.90)
AUC_{last} (ng.hr/mL)	53.32	19.8	269.32	(215.82, 336.08)
C_{max} (ng/mL)	14.44	7.991	180.76	(148.10, 220.63)

Source: Table 10, Study B7981017

Table 15: Statistical Summary of Log Transformed Plasma Efavirenz PK Parameters, Study B7981017

Parameter (Units)	Adjusted Geometric Means: Multiple-dose PF-06651600 200 mg QD + Single-dose of Midazolam and Efavirenz (Test)	Adjusted Geometric Means: Single-dose of Midazolam and Efavirenz (Reference)	Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio[a]
AUC_{0-72} (ng.hr/mL)	5542	5559	99.69	(95.24, 104.36)
AUC_{last} (ng.hr/mL)	5544	5559	99.74	(95.30, 104.39)
C_{max} (ng/mL)	264.5	299.9	88.21	(77.05, 101.00)

Source: Table 12, Study B7981017

19.4.9 B7981054: Drug-Drug Interaction Study (Ritlecitinib as Perpetrator), Effect of Multiple Doses of Ritlecitinib 200 mg QD on Pharmacokinetics of Caffeine (sensitive CYP1A2 substrate)
Study B7981054 was a Phase 1, 2 period, fixed-sequence, multiple-dose, randomized, open-label study conducted to assess the effect of multiple doses of ritlecitinib on the PK of a single, oral dose of caffeine in HVs. PK of ritlecitinib and its metabolite PF-07034562 (M2) at steady-state after multiple doses of ritlecitinib was also evaluated in this study. In period 1, 100 mg caffeine was administered on Day 1 under fasting conditions. In period 2, ritlecitinib 200 mg QD was administered on Day 1 to Day 7 under non-fasting conditions. Ritlecitinib 200 mg QD + Caffeine 100 mg (single-dose) was administered on Day 8. Ritlecitinib 200 mg QD was administered on Day 9. Co-administration of caffeine 100 mg in the presence of steady-state levels of ritlecitinib (200 mg QD) increased caffeine exposure compared to caffeine given alone. The AUCinf and Cmax of caffeine increased by approximately 2.7 fold and 1.1 fold, respectively, when coadministered with ritlecitinib.

Table 16: Statistical Summary of Log Transformed Plasma Caffeine PK Parameters, Study B7981054

Parameter (Unit)	Adjusted Geometric Means: Ritlecitinib (PF-06651600) 200 mg QD + Caffeine 100 mg (SD) (Test)	Adjusted Geometric Means: Caffeine 100 mg (SD) (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI (%) for Ratio[a]
AUC_{inf} (ng.hr/mL)	41530	15660	265.14	(234.12, 300.26)
AUC_{last} (ng.hr/mL)	38580	14780	261.03	(232.49, 293.09)
C_{max} (ng/mL)	2372	2162	109.74	(103.90, 115.91)

Source: Table 8, Study B7981054

PF-07034562 (Metabolite) Pharmacokinetics
Following multiple doses of ritlecitinib (200 mg QD) and a single-dose of caffeine (100 mg), mean PF 07034562 (metabolite) Cmax was reached at median Tmax of 2 hours. The pre-dose concentrations of PF 07034562 (metabolite) on Days 6, 7, 8, and 9 were similar, indicating that steady-state had been achieved when the single-dose of caffeine was administered. The PK parameters for PF 07034562 are provided in Table 17.

Table 17: Descriptive Summary of Plasma Ritlecitinib and PF-07034562 PK Parameters

Parameter (Unit)[a]	Ritlecitinib (N=12)	PF-07034562 (N=12)
N1	12	12
AUC_{tau} (ng•h/ml)	3827 (23)	3091 (30)
C_{av} (ng/ml)	159.5 (23)	128.8 (30)
C_{max} (ng/ml)	1567 (29)	602.7 (25)
$t_{½}$ (h)	2.147 ± 0.4205	ND
T_{max} (h)	1.00 (0.500 - 1.50)	2.00 (1.50 – 3.00)

Source: Module 5.3.2.2 B7981054 CSR Table 14.4.5.1.2; Table 14.4.5.1.3.
N1 = Number of participants contributing to the summary statistics.
a. Geometric Mean (Geometric %CV) for all except: Median (Range) for T_{max} and arithmetic mean ± SD for $t_{½}$.

Source: Table 9, Summary of Clinical Pharmacology

19.4.10 B7981069: Drug-Drug Interaction Study (Ritlecitinib as Perpetrator), Effect of Multiple Doses of Ritlecitinib 200 mg QD on Pharmacokinetics of Tolbutamide (sensitive CYP2C substrate)

Study B7981069 was a Phase 1, 2-period, multiple dose, open label, single fixed sequence study of the effect of ritlecitinib on tolbutamide PK in HVs. A total of 12 male and/or female HVs were enrolled in the study. In period 1, 500 mg tolbutamide was administered as a single dose on Day 1. In period 2, ritlecitinib 200 mg QD was administered on Day 1 to Day 9 under non-fasting conditions. Ritlecitinib 200 mg QD + tolbutamide 500 mg (single-dose) was administered on Day 10. The AUCinf, AUClast and Cmax values of tolbutamide were not affected by multiple doses of ritlecitinib as the 90% CIs for AUCinf, AUClast and Cmax were all contained within 80-125%.

Table 18: Statistical Summary of Log Transformed Plasma Tolbutamide PK Parameters, Study B7981069

Parameter, Unit	Comparison (Test vs. Reference)	Adjusted Geometric Means		Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI (%) for Ratio[a]
		Test	Reference		
AUC_{inf}, ng.hr/mL	Ritlecitinib + Tolbutamide vs. Tolbutamide	602900	608600	99.05	(92.01, 106.62)
AUC_{last}, ng.hr/mL	Ritlecitinib + Tolbutamide vs. Tolbutamide	580700	591000	98.26	(92.77, 104.08)
C_{max}, ng/mL	Ritlecitinib + Tolbutamide vs. Tolbutamide	45570	44240	103.01	(96.66, 109.77)

Source: Table 11, Study B7981069

19.4.11 B7981018: Drug-Drug Interaction Study (Contraceptive Steroids), Effect of Multiple Doses of Ritlecitinib 200 mg QD on Pharmacokinetics of Contraceptive Steroids

Study B7981018 was a Phase 1, randomized, open-label, 2-way, cross-over study conducted to estimate the effect of multiple-dose ritlecitinib on the PK of single-dose oral contraceptive (OC) steroids in female HVs. A total of approximately 12 female HVs (6 in each treatment sequence) were enrolled in the study. Each treatment sequence consisted of 2 periods in a single fixed-sequence. In treatment sequence 1, period 1, PORTIA (ethinyl estradiol (EE) and levonorgestrel (LN)) was administered on Day 1 under fasting conditions. In period 2, ritlecitinib 200 mg QD was administered on Day 1 to Day 11. PORTIA (EE and LN) was administered on Day 10 under fasting conditions. In treatment sequence 2, period 1, ritlecitinib 200 mg QD was administered on Days 1 to Day 11. PORTIA (EE and LN) was administered on Day 10 under fasting conditions. In period 2, (after 10 day washout), PORTIA (EE and LN) was administered on Day 1 under fasting conditions. The AUCinf and Cmax values of EE were decreased by approximately 18% and 12%, respectively, after the co-administration with multiple doses of 200 mg QD ritlecitinib when compared with those of EE administered alone. LN was not affected by multiple doses of ritlecitinib as both 90% CIs for the AUClast and Cmax were wholly contained within the range of 80% to 125%.

Table 19: Statistical Summary of Log Transformed Plasma Ethinyl Estradiol PK Parameters, Study B7981018

Parameter (Units)	Adjusted Geometric Means: Multiple-dose PF-06651600 200 mg QD + Single-dose OC (Test)	Adjusted Geometric Means: Single-dose OC (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio[a]
AUC_{inf} (pg.hr/mL)	656.3	799.9	82.05	(75.80, 88.82)
AUC_{last} (pg.hr/mL)	586.2	679.8	86.23	(81.10, 91.69)
C_{max} (pg/mL)	60.56	68.77	88.05	(77.67, 99.81)

Source: Table 14.4.5.3.1
Values had been back-transformed from the log scale.
The model was a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect.
Abbreviations: CI=confidence interval; OC=oral contraceptive; PK=pharmacokinetic; QD=once daily.
a.The ratios (and 90% CIs) were expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: 31JAN2019 (03:50) Source Data: Table 16.1.9.2.1 Output File: ./nda1_cdisc/B7981018/adpp_s201_m Date of Generation: 31JAN2019 (04:12)

Source: Table 11, Study B7981018

Table 20: Statistical Summary of Log Transformed Plasma Levonorgestrel PK Parameters, Study B7981018

Parameter (Units)	Adjusted Geometric Means: Multiple-dose PF-06651600 200 mg QD + Single-dose OC (Test)	Adjusted Geometric Means: Single-dose OC (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio[a]
AUC_{last} (pg.hr/mL)	26840	23810	112.73	(104.16, 122.01)
C_{max} (pg/mL)	3026	2936	103.07	(97.31, 109.18)

Source: Table 14.4.5.3.2
Values had been back-transformed from the log scale.
The model was a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect.
Abbreviations: CI=confidence interval; OC=oral contraceptive; PK=pharmacokinetic; QD=once daily.
a.The ratios (and 90% CIs) were expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: 31JAN2019 (03:50) Source Data: Table 16.1.9.2.2 Output File: ./nda1_cdisc/B7981018/adpp_s202_m Date of Generation: 31JAN2019 (04:18)

Source: Table 13, Study B7981018

19.4.12 B7981035: Drug-Drug Interaction Study (Contraceptive Steroids), Effect of Multiple Doses of Ritlecitinib 50 mg QD on Pharmacokinetics of Contraceptive Steroids
Study B7981035 was a Phase 1, randomized, open-label, 2-way, cross-over study conducted to demonstrate the lack of an effect of multiple-dose ritlecitinib on the PK of single-dose OC steroids in female HVs. A total of approximately 28 female HVs (14 in each treatment sequence) were enrolled in the study. Each treatment sequence consisted of 2 periods in a single fixed-sequence. In treatment sequence 1, period 1, PORTIA (ethinyl estradiol (EE) and levonorgestrel (LN)) was administered on Day 1 under fasting conditions. In period 2, ritlecitinib 50 mg QD was administered on Day 1 to Day 11. PORTIA (EE and LN) was administered on Day 10 under fasting conditions. In treatment sequence 2, period 1, ritlecitinib 50 mg QD was administered on Days 1 to Day 11. PORTIA (EE and LN) was administered on Day 10 under fasting conditions. In period 2, (after 10 day washout), PORTIA (EE and LN) was administered on Day 1 under fasting conditions. The evaluation of the AUCinf and AUClast for EE and LN, respectively, indicated the lack of an effect of multiple doses of ritlecitinib 50 mg QD on the PK of single dose OC steroids (Table 21 and 22).

Table 21: Statistical Summary of Log Transformed Plasma Ethinyl Estradiol PK Parameters, Study B7981035

Parameter (Units)	Adjusted Geometric Means: Multiple-dose PF-06651600 50 mg QD + Single-dose OC (Test)	Adjusted Geometric Means: Single-dose OC (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio[a]
AUC_{inf} (pg.hr/mL)	733.3	746.6	98.23	(90.63, 106.45)
AUC_{last} (pg.hr/mL)	604.8	658	91.92	(84.40, 100.12)
C_{max} (pg/mL)	63.75	69.1	92.26	(84.02, 101.30)

Source: Table 14.4.5.3.1
Values had been back-transformed from the log scale.
The model was a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect.
a.The ratios (and 90% CIs) were expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: 16JAN2020 (07:52) Source Data: adpp Output
File: ./nda1_cdisc/B7981035_PK/adpp_s201_m Date of Generation: 19JAN2020 (21:50)

Source: Table 11, Study B7981035

Table 22: Statistical Summary of Log Transformed Plasma Levonorgestrel PK Parameters, Study B7981035

Parameter (Units)	Adjusted Geometric Means: Multiple-dose PF-06651600 50 mg QD + Single-dose OC (Test)	Adjusted Geometric Means: Single-dose OC (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio[a]
AUC_{last} (pg.hr/mL)	29580	33670	87.88	(82.72, 93.35)
C_{max} (pg/mL)	2320	2897	80.09	(73.10, 87.75)

Source: Table 14.4.5.3.2
Values had been back-transformed from the log scale.
The model was a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect.
a.The ratios (and 90% CIs) were expressed as percentages.
Statistical summary for AUC_{inf} was not presented because more than 50% of the participants in Multiple-dose PF-06651600 50 mg QD + Single-dose OC treatment group failed to meet the reporting criteria.
PFIZER CONFIDENTIAL SDTM Creation: 16JAN2020 (07:52) Source Data: adpp Output
File: ./nda1 cdisc/B7981035 PK/adpp s202 m Date of Generation: 19JAN2020 (21:52)

Source: Table 11, Study B7981035

Reviewer's Comment:
Ethinyl estradiol AUCinf and Cmax was outside of 80% limit after multiple dose administration of 200 mg ritlecitinib (Study B7981018). However, ethinyl estradiol AUCinf and Cmax was within

the 80-125% limit after multiple dose administration of 50 mg (Study B7981035) ritlecitinib (50 mg is the dose for which approval is being sought). Hence, at currently recommended ritlecitinib dose i.e., 50 mg, no clinically significant impact on ethinyl estradiol PK is anticipated.

Levonorgestrel AUClast was within the 80-125% limit after multiple dose administration of both 50 mg (Study B7981035) and 200 mg (Study B7981018) ritlecitinb. Levonorgestrel Cmax was within 80-125% limit after multiple dose administration of 200 mg ritlecitinib (Study B7981018), however levonorgestrel Cmax was outside of 80% limit after multiple dose administration of 50 mg ritlecitinib (Study B7981035). Although, Cmax of levonorgestrel in study B7981035 was lower than 80% limit, it was within the 80-125% limit in Study B7981018 and AUClast was withing the 80-125% limit in both the studies. Since the PK between 50 mg and 200 mg is approximately dose proportional, we conclude that based on totality of evidence, ritelcitinib may not have clinically significant impact on levonorgestrel PK warranting any dose adjustment.

19.4.13 B7981024: Transporter Interaction Study, Effect of Multiple Doses of Ritlecitinib 200 mg QD on Pharmacokinetics of Rosuvastatin (sensitive substrate for transporters BCRP and OAT3)

Study B7981024 was a Phase 1, 2-period, fixed-sequence, multiple-dose, open-label study conducted to estimate the effect of ritlecitinib on the PK of rosuvastatin in HVs. A total of 12 adult HVs received ritlecitinib and rosuvastatin in a 2-period fixed-sequence. In period 1, rosuvastatin 10 mg tablet was administered only on Day 1 under fasting condition (Day 1-5). In period 2, ritlecitinib 200 mg QD PO was administered under non-fasting conditions on Day 1-7 and Day 9 and 10. On Day 8, the participants received ritlecitinib 200 mg QD PO and 10 mg rosuvastatin tablet under fasting condition. Upon co-administration with ritlecitinib, the plasma exposures of rosuvastatin as measured by the AUC and Cmax were decreased by approximately 13% and 27%, respectively. Ritlecitinib is unlikely to cause a clinically meaningful inhibition of BCRP or OAT3.

Table 23: Statistical Summary of Log Transformed Plasma Rosuvastatin PK Parameters, Study B7981024

Parameter (Units)	Adjusted Geometric Means: PF-06651600 200 mg QD + Rosuvastatin 10 mg (Test)	Adjusted Geometric Means: Rosuvastatin 10 mg (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI (%) for Ratio[a]
AUC_{inf} (ng.hr/mL)	38.09	43.86	86.86	(74.91, 100.71)
AUC_{last} (ng.hr/mL)	36.73	41.78	87.92	(77.08, 100.28)
C_{max} (ng/mL)	3.264	4.496	72.58	(63.25, 83.30)

Source: Table 14.4.5.3.1.1
a.The ratios (and 90% CIs) were expressed as percentages.
Values have been back-transformed from the log scale.
The model is a mixed effect model with treatment as fixed effects and subject within sequence as a random effect.
PFIZER CONFIDENTIAL SDTM Creation: 19MAR2020 (02:46) Source Data: adpp Output File: ./nda1_cdisc/B7981024_PK1/adpp_s201_it Date of Generation: 22MAR2020 (22:15)

Source: Table 8, Study B7981024

19.4.14 B7981025: Transporter Interaction Study, Effect of 400 mg Single Dose Ritlecitinib on the Pharmacokinetics of Sumatriptan (sensitive substrate for transporters OCT1)
Study B7981025 was a Phase 1, fixed-sequence, open-label study conducted to evaluate the effect of ritlecitinib on PK of single-dose sumatriptan in HVs. A total of 10 participants were assigned and completed treatment with ritlecitinib and sumatriptan in 3 consecutive treatment periods without washout periods. In period 1, sumatriptan 25 mg single-dose was administered in the morning on Day 1 under fasted conditions. In period 2, participants received co-administration of single-dose of 400 mg ritlecitinib and sumatriptan 25 mg single-dose in the morning on Day 1 under fasted conditions (referred to as co-administration). In period 3, single-dose of 400 mg ritlecitinib was administered in the evening of Day 1. After a fast of at least 8 to 10 hours, single-dose of 25 mg sumatriptan was administered in the morning of Day 2, approximately 8 (±1) hours after the evening ritlecitinib dose (referred to as staggered administration). The single-dose of 400 mg approximates the exposures of steady state 200 mg QD dose. The sumatriptan Cmax decreased approximately 13% after the co-administration with ritlecitinib, whereas the Cmax increased approximately 50% when the administration of ritlecitinib was staggered. Sumatriptan AUCinf increased when ritlecitinib was coadministered (approximately 30%) or as a staggered dose (approximately 50%). The study results confirm that ritlecitinib can inhibit OCT1 and can increase exposures of sensitive OCT1 substrates (Table 24 and 25).

Table 24: Statistical Summary of Log Transformed Plasma Sumatriptan PK Parameters - Ritlecitinib + D1 Sumatriptan vs Sumatriptan alone, Study B7981025

	Adjusted Geometric Means			
Parameter (Unit)	PF-06651600 + D1 Sumatriptan (Test)	Sumatriptan 25 mg SD (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means	90% CI for Ratio[a]
AUC_{inf} (ng.hr/mL)	86.77	66.89	129.72	(116.84, 144.02)
AUC_{last} (ng.hr/mL)	85.20	63.38	134.42	(123.67, 146.10)
C_{max} (ng/mL)	12.87	14.82	86.87	(73.13, 103.19)

Source: Table 7, Study B7981025

Note: Sumatriptan was administered at the same time as ritlecitinib 400 mg SD (+ D1 Sumatriptan 25 mg SD; referred to as co-administration)

Table 25: Statistical Summary of Log Transformed Plasma Sumatriptan PK Parameters - Ritlecitinib + D2 Sumatriptan vs Sumatriptan alone, Study B7981025 (Staggered Administration)

	Adjusted Geometric Means			
Parameter (Unit)	PF-06651600 + D2 Sumatriptan (Test)	Sumatriptan 25 mg SD (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means	90% CI for Ratio[a]
AUC_{inf} (ng.hr/mL)	100.1	66.89	149.63	(134.77, 166.12)
AUC_{last} (ng.hr/mL)	97.17	63.38	153.31	(141.05, 166.63)
C_{max} (ng/mL)	22.17	14.82	149.63	(125.96, 177.75)

Source table 14.4.5.3.1
a. The ratios (and 90% CIs) were expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: 21OCT2020 (22:20) Source Data: adpp Table Generation: 16NOV2020 (05:06)
Output File: ./nda1_cdisc/B7981025_PK/adpp_s201_2_it

Source: Table 8, Study B7981025

Note: Sumatriptan was administered with an approximate 8-hour delay (+ D2 Sumatriptan 25 mg SD; referred to as staggered administration)

19.4.15 Effect of Acid Reducing Agents

Ritlecitinib is a highly soluble drug with high solubility across the physiological pH range of 1.0 to 6.8. As shown in Table 26, ritlecitinib has adequate solubility over the pH range of 1 to 6.8 where the dose number calculated for the 200 mg dose is <1. Hence, acid reducing agents or other factors that may alter the gastrointestinal pH are unlikely to impact the solubility of ritlecitinib or its bioavailability. Co-administration of ritlecitinib with acid reducing agents is highly unlikely to impact its solubility and subsequent absorption given its solubility profile across a range of pH levels. A clinical study evaluating the impact of acid reducing agents was therefore not conducted and is acceptable.

Table 26: Ritlecitinib Solubility and Sink Level of 100 mg Capsule in 250 mL

Aqueous media	Solubility (mg/mL) 37 °C	Dose Number* (mg/ml)
pH 0.8	28.1	0.028
pH 1.8	25.0	0.032
pH 3.0	31.0	0.026
pH 3.5	34.1	0.023
pH 4.0	35.6	0.022
pH 4.1	32.2	0.025
pH 4.2	30.1	0.027
pH 4.3	26.8	0.030
pH 4.4	25.0	0.032
pH 4.5	22.0	0.036
pH 4.6	18.9	0.042
pH 5.0	13.1	0.061
pH 5.5	8.3	0.096
pH 6.0	7.6	0.105
pH 6.8	6.8	0.118
*Dose Number = Highest dose in mg (200 mg)/ (250 ml*Solubility) in mg/ml; a Dose Number less than 1 indicates that the entire dose is soluble thus meeting the BCS high solubility criteria. Source – Module 3.2.P.2.2		

Source: Table 12, 2.7.2 Summary-ClinPharm

19.4.16 Population PK Analysis (PMAR-EQDD-B798h-Proof of Concept-1091, PMAR-EQDD-B798d-DP4-1157)

Review Summary

The final model described in PMAR-EQDD-B798d-DP4-1157 was developed using PMAR-EQDD-B798h-Proof of Concept-1091 as prior. The prior model was developed based on pooled data from five Phase 1 studies in HV (B7981001, B7981003, B7981008, B7981022) and in participants with moderate hepatic impairment (B7981016), and four Phase 2 studies in patients with moderate-to-severe RA (B7981006), AA (B7931005), moderate-to-severe UC (B7981005), and active non-segmental vitiligo (B7981019). The final model used dataset from pivotal Phase 2b/3 (B7981015), Phase 1 study in patients with severe renal impairment (B7981020), PK study in healthy adult Chinese participants (B7981036) and an ongoing Phase 3 study (B7981032). The structural PK model was same for model developed in PMAR-EQDD-B798h-Proof of Concept-1091 as prior and final model PMAR-EQDD-B798d-DP4-1157.

Intrinsic (patient type, severe renal impairment, hepatic impairment, and body weight) and extrinsic (fed status and formulation) factors were identified as covariates on CL/F, ka and F. The B7981029 pivotal bioequivalence study data in HV was not included for analysis as final

data from that study were available after conclusion of the analysis. Body weight was the covariate on clearance (CL/F, and Q/F) and volume (Vc/F, and Vp/F), with fixed allometric exponents of 0.75 and 1 respectively. Covariates previously assessed in the development of the prior model (PMAR-EQDD-B798h-Proof of Concept-1091) for which no information was available in final model development (PMAR-EQDD-B798d-DP4-1157) analysis dataset, such as the impact of food, the capsule formulation, hepatic impairment, and RA, UC and vitiligo patients, were not re-evaluated.

The applicant's population PK analysis is acceptable for characterization of PK of ritlecitinib. The inter-individual variability (IIV) for CL (18.8%), and Vc (11.5%) were low in the final model. An increase in eta-shrinkage for the random effect on Vc/F relative to the prior model was noted from 20.9% to 33.1%. The applicant attributed this to the validation dataset containing sparse PK sampling compared to the dataset used to generate the prior model. However, the increase in eta-shrinkage on Vc/F was not considered severe to warrant removal of the corresponding random effect from the model. The estimated PK parameters and Eta and epsilon shrinkages are reasonable for empirical bayes estimate (EBE) estimation used in PK/PD analyses. Both goodness-of-fit plots and prediction corrected visual predictive checks indicate that the population PK model is adequate in characterizing the PK profile of ritlocitinib in healthy adults and alopecia areata patients.

Data
The study design, study population, dose, and timing of blood samples varied among the studies and are presented in Table 27, 28, 29, 30 and 31.

Table 27: Summary of Analysis Population by Study (Study PMAR-EQDD-B798d-DP4-1157)

Covariate	B7981015	B7981020	B7981032	B7981036	Total
Age (years)					
Median	32.0	58.5	32.0	30.0	32.0
Minimum	12.0	43.0	12.0	21.0	12.0
Maximum	72.0	72.0	73.0	37.0	73.0
Mean	33.6	59.5	34.0	28.7	33.9
SD	14.2	9.78	14.3	4.90	14.3
n Available	584	8	980	9	1574
n Missing	0	0	0	0	0
Total Body Weight (kg)					
Median	68.1	88.8	68.0	68.9	68.1
Minimum	29.6	81.1	29.6	54.3	29.6
Maximum	131	96.2	200	79.5	200
Mean	70.3	88.3	70.5	70.1	70.4
SD	17.0	4.88	17.7	8.45	17.4
n Available	584	8	980	9	1574
n Missing	0	0	0	0	0
Creatinine Clearance (mL/min)					
Median	117	30.5	114	117	115
Minimum	54.1	14.7	52.3	94.0	14.7
Maximum	288	39.3	413	151	413
Mean	123	29.1	122	120	122
SD	35.5	10.2	37.7	18.3	37.2
n Available	584	8	978	9	1572
n Missing	0	0	2	0	2
eGFR based on MDRD (mL/min)					
Median	113	22.9	113	101	113
Minimum	61.0	10.5	60.0	77.8	10.5
Maximum	508	27.5	508	125	508
Mean	119	21.0	119	101	119
SD	35.7	6.75	35.4	14.9	35.8
n Available	583	8	975	9	1568

Covariate	B7981015	B7981020	B7981032	B7981036	Total
n Missing	1	0	5	0	6
eGFR based on CKD-EPI (mL/min)					
Median	63.7	12.1	62.8	64.3	62.9
Minimum	36.0	5.20	27.5	52.6	5.30
Maximum	101	14.2	97.7	71.3	101
Mean	63.6	10.6	62.7	63.3	62.9
SD	11.0	3.66	11.8	5.88	11.9
n Available	584	8	978	9	1572
n Missing	0	0	2	0	2
Hematocrit (%)					
Median	42.0	35.2	41.0	45.0	41.0
Minimum	32.0	32.2	32.0	36.0	32.0
Maximum	52.0	45.7	55.0	46.0	55.0
Mean	42.0	36.7	41.6	42.8	41.7
SD	3.76	4.56	3.73	3.67	3.76
n Available	583	8	975	9	1569
n Missing	1	0	5	0	5
Albumin (g/dL)					
Median	4.70	3.95	4.70	4.44	4.70
Minimum	3.90	3.90	3.90	4.31	3.90
Maximum	5.80	4.40	5.70	4.81	5.80
Mean	4.70	4.08	4.68	4.49	4.69
SD	0.286	0.225	0.287	0.177	0.288
n Available	584	8	978	9	1572
n Missing	0	0	2	0	2
ALT (U/L)					
Median	16.0	12.5	16.0	12.0	16.0
Minimum	4.00	6.00	5.00	9.00	4.00
Maximum	123	77.0	168	32.0	168
Mean	19.3	23.2	19.5	14.7	19.4
SD	11.7	24.2	12.8	7.70	12.5
n Available	584	8	978	9	1572
n Missing	0	0	2	0	2
AST (U/L)					
Median	19.0	15.5	19.0	16.0	19.0
Minimum	11.0	8.00	9.00	13.0	8.00
Maximum	75.0	65.0	64.0	24.0	75.0
Mean	20.6	20.8	20.5	16.7	20.5
SD	6.47	18.7	6.42	3.71	6.53

Covariate	B7981015	B7981020	B7981032	B7981036	Total
n Available	584	8	978	9	1572
n Missing	0	0	2	0	2
Bilirubin (mg/dL)					
Median	0.500	0.300	0.500	0.610	0.500
Minimum	0.100	0.200	0.100	0.410	0.100
Maximum	2.60	0.600	2.70	1.11	2.70
Mean	0.563	0.300	0.535	0.732	0.546
SD	0.328	0.131	0.328	0.283	0.328
n Available	584	8	978	9	1572
n Missing	0	0	2	0	2
Age Group, *n* (%)					
Adolescent	79 (13.5)	0	137 (14.0)	0	216 (13.7)
Adult	505 (86.5)	8 (100)	843 (86.0)	9 (100)	1365 (86.3)
Geographical Location, *n* (%)					
Asia	124 (21.2)	0	152 (15.5)	9 (100)	285 (18.0)
Europe	127 (21.7)	0	222 (22.7)	0	349 (22.1)
North America	234 (40.1)	8 (100)	451 (46.0)	0	693 (43.8)
Rest of World	99 (17.0)	0	155 (15.8)	0	254 (16.1)
Alopecia Patient Type, *n* (%)					
AT	128 (21.9)	0	188 (19.2)	0	316 (20.0)
AU	113 (19.3)	0	186 (19.0)	0	299 (18.9)
non-AT/AU	343 (58.7)	0	605 (61.7)	0	948 (60.0)
Non-Alopecia	0	8 (100)	0	9 (100)	17 (1.1)
Missing	0	0	1 (0.1)	0	1 (0.1)
Patient Type, *n* (%)					
AA	584 (100)	0	980 (100)	0	1564 (98.9)
Severe RI	0	8 (100)	0	0	8 (0.5)
HV	0	0	0	9 (100)	9 (0.6)
Race, *n* (%)					
Asian	155 (26.5)	0	218 (22.2)	9 (100)	382 (24.2)
Black	22 (3.8)	1 (12.5)	34 (3.5)	0	57 (3.6)
Other	10 (1.7)	0	23 (2.3)	0	33 (2.1)
Unknown	5 (0.9)	0	15 (1.5)	0	20 (1.3)
White	392 (67.1)	7 (87.5)	690 (70.4)	0	1089 (68.9)
Sex, *n* (%)					
Female	358 (61.3)	3 (37.5)	617 (63.0)	3 (33.3)	981 (62.0)
Male	226 (38.7)	5 (62.5)	363 (37.0)	6 (66.7)	600 (38.0)

Source: Table 4, PMAR-EQDD-B798d-DP4-1157

Table 28: Summary of Observed Concentrations in Analysis Population by Dose (Study PMAR-EQDD-B798d-DP4-1157)

Summary Value	10 mg QD	30 mg QD	50 mg QD	200 mg QD
Number of PK Observations	455	1309	4771	2240
Proportion of BLQ Observations (%)	39.8	38.0	37.5	37.8
Time After Dose of BLQ Observation (hours; Median [90% PI])	0 (0, 0)	0 (0, 0)	0 (0, 0.5)	0 (0, 0)
Proportion of BLQ Observations at Pre-Dose (%)	95.0	95.8	93.0	96.3

Source: Table 5, PMAR-EQDD-B798d-DP4-1157

Table 29: Summary of Analysis Population by Patient Type (Study PMAR-EQDD-B798h-Proof of Concept-1091)

Covariate	HV	MoHI	RA	UC	AA	Vitiligo	Total
Dosing Regimen, *n* (%)							
5 mg Single	6 (3.3)	0	0	0	0	0	6 (0.5)
20 mg Single	6 (3.3)	0	0	0	0	0	6 (0.5)
50 mg Single	43 (23.5)	0	0	0	0	0	43 (3.6)
100 mg Single	54 (29.5)	0	0	0	0	0	54 (4.5)
200 mg Single	6 (3.3)	0	0	0	0	0	6 (0.5)
400 mg Single	12 (6.6)	0	0	0	0	0	12 (1.0)
800 mg Single	6 (3.3)	0	0	0	0	0	6 (0.5)
10 mg QD	0	0	0	0	0	96 (16.6)	96 (8.0)
20 mg QD	0	0	0	51 (19.7)	0	0	51 (4.3)
30 mg QD	8 (4.4)	10 (100)	0	0	0	98 (17.0)	116 (9.7)
50 mg QD	6 (3.3)	0	0	108 (41.7)	35 (28.7)	252 (43.6)	401 (33.6)
70 mg QD	0	0	0	49 (18.9)	0	0	49 (4.1)
100 mg QD	0	0	0	0	0	67 (11.6)	67 (5.6)
200 mg QD	9 (4.9)	0	42 (100)	51 (19.7)	87 (71.3)	65 (11.2)	254 (21.3)
400 mg QD	17 (9.3)	0	0	0	0	0	17 (1.4)
100 mg BID	4 (2.2)	0	0	0	0	0	4 (0.3)
200 mg BID	6 (3.3)	0	0	0	0	0	6 (0.5)
Formulation, *n* (%)							
Large API Particle Size Capsule	12 (6.6)	0	0	0	0	0	12 (1.0)
Over-Encapsulated Capsule	12 (6.6)	0	0	0	0	0	12 (1.0)
Capsule	12 (6.6)	0	0	0	0	0	12 (1.0)
Solution	100 (54.6)	0	0	0	0	0	100 (8.4)
Tablet	47 (25.7)	10 (100)	42 (100)	259 (100)	122 (100)	578 (100)	1058 (88.6)
Age (years)							
Median	38.5	57.0	58.5	36.5	37.5	46.0	43.0
Minimum	19.0	51.0	24.0	18.0	19.0	18.0	18.0
Maximum	67.0	68.0	74.0	70.0	65.0	66.0	74.0
Mean	37.3	59.0	55.4	39.6	37.6	44.7	42.6
SD	11.3	6.88	11.7	14.4	12.9	11.5	13.2
n Available	98	10	42	150	70	298	668
n Missing	0	0	0	0	0	0	0
Total Body Weight (kg)							

Covariate	HV	MoHI	RA	UC	AA	Vitiligo	Total
Median	75.5	84.0	82.5	71.7	74.9	75.3	75.0
Minimum	51.6	66.9	63.0	39.0	46.0	35.1	35.1
Maximum	106	108	125	135	164	143	164
Mean	77.1	86.4	84.5	72.6	77.4	76.5	76.5
SD	11.8	14.8	14.8	17.3	20.5	17.3	17.0
n Available	98	10	42	150	70	298	668
n Missing	0	0	0	0	0	0	0
Creatinine Clearance (mL/min)							
Median	124	105	113	112	116	108	113
Minimum	78.1	79.5	73.6	64.4	57.1	45.4	45.4
Maximum	185	130	243	271	248	267	271
Mean	126	107	120	115	122	113	116
SD	23.0	18.1	35.2	30.1	32.4	31.7	30.7
n Available	98	10	42	150	70	297	667
n Missing	0	0	0	0	0	1	1
Hematocrit (%)							
Median	43.0	37.8	39.5	40.0	41.0	42.0	42.0
Minimum	38.0	34.3	32.0	27.0	35.0	30.0	27.0
Maximum	48.0	42.9	49.0	52.0	49.0	51.0	52.0
Mean	42.7	38.3	40.0	39.9	41.2	42.5	41.6
SD	2.58	3.17	3.38	4.85	3.58	3.66	4.00
n Available	98	10	42	150	70	298	668
n Missing	0	0	0	0	0	0	0
Albumin (g/dL)							
Median	4.30	4.20	4.25	4.40	4.50	4.65	4.50
Minimum	3.70	3.00	3.50	2.80	3.70	3.70	2.80
Maximum	5.10	4.50	4.80	5.30	5.20	5.40	5.40
Mean	4.33	4.07	4.23	4.30	4.49	4.66	4.48
SD	0.293	0.422	0.282	0.388	0.291	0.286	0.360
n Available	98	10	42	150	70	298	668
n Missing	0	0	0	0	0	0	0
ALT (U/L)							
Median	23.0	21.5	14.5	16.0	17.5	19.0	18.0
Minimum	10.0	9.00	6.00	7.00	4.00	5.00	4.00
Maximum	68.0	69.0	51.0	91.0	61.0	83.0	91.0
Mean	25.1	29.2	16.4	18.4	20.4	22.2	21.3
SD	10.3	18.9	8.03	11.3	11.0	13.0	12.1
n Available	98	10	42	150	70	298	668
n Missing	0	0	0	0	0	0	0

Covariate	HV	MoHI	RA	UC	AA	Vitiligo	Total
AST (U/L)							
Median	23.0	23.0	15.0	16.0	19.0	20.0	19.0
Minimum	12.0	13.0	9.00	8.00	10.0	10.0	8.00
Maximum	40.0	60.0	27.0	39.0	57.0	94.0	94.0
Mean	24.1	28.1	15.7	16.9	20.7	21.3	20.4
SD	5.36	16.2	3.91	5.89	7.66	8.18	7.72
n Available	98	10	42	150	70	298	668
n Missing	0	0	0	0	0	0	0
Bilirubin (mg/dL)							
Median	0.600	0.950	0.400	0.300	0.400	0.500	0.400
Minimum	0.300	0.200	0.199	0.200	0.200	0.100	0.100
Maximum	1.60	2.00	1.30	1.90	1.30	1.50	2.00
Mean	0.677	0.930	0.409	0.399	0.459	0.515	0.506
SD	0.269	0.629	0.245	0.270	0.243	0.243	0.281
n Available	98	10	42	150	70	298	668
n Missing	0	0	0	0	0	0	0
Japanese Status, *n* (%)	0	0	0	0	0	0	0
Japanese	4 (4.1)	0	0	0	0	17 (5.7)	21 (3.1)
Not Japanese	94 (95.9)	10 (100)	42 (100)	150 (100)	70 (100)	281 (94.3)	647 (96.9)
Race, *n* (%)	0	0	0	0	0	0	0
Asian	5 (5.1)	0	1 (2.4)	4 (2.7)	5 (7.1)	65 (21.8)	80 (12.0)
Other	20 (20.4)	10 (100)	0	140 (93.3)	3 (4.3)	224 (75.2)	397 (59.4)
White	73 (74.5)	0	41 (97.6)	4 (2.7)	58 (82.9)	8 (2.7)	184 (27.5)
Missing	0	0	0	2 (1.3)	0	0	2 (0.3)
Black	0	0	0	0	4 (5.7)	1 (0.3)	5 (0.7)
Sex, *n* (%)	0	0	0	0	0	0	0
Female	5 (5.1)	3 (30.0)	33 (78.6)	60 (40.0)	48 (68.6)	153 (51.3)	302 (45.2)
Male	93 (94.9)	7 (70.0)	9 (21.4)	90 (60.0)	22 (31.4)	145 (48.7)	366 (54.8)

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Source: Table 4, PMAR-EQDD-B798h-Proof of Concept-1091

Table 30: Summary of Studies Included in the Population PK Modeling Analysis (PMAR-EQDD-B798h-Proof of Concept-1091)

Protocol	Phase	Protocol Design	Population	n	Dose Administration	Plasma Sampling[a]
B7981001	1	A Phase 1, Randomized, Double Blind, Third-Party Open, Placebo-Controlled, Single and Multiple Dose Escalation, Parallel Group Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PF-06651600 in Healthy Subjects	HV	80	SAD: Single doses of 5, 20, 50, 100, 200, 400, and 800 mg [b] ritlecitinib or placebo. MAD: Repeated doses of 50, 200, or 400 mg QD or 100 or 200 mg BID for 14 days. Fasted.	SAD: 0 (pre-dose), 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48 hours post-dose. MAD: Pre-dose on Day 1, 4, 6, 8, 10, 12, and 14, and 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48 hours post-dose on Day 14.
B7981003	1	A Phase 1, Open Label, Single-Dose 3-Way Crossover study to Evaluate the Relative Bioavailability of a Solid Dose Formulation of PF-06651600 Under Fasting Conditions and the Effect of a High Fat Meal on the Bioavailability of the Solid Dosage Formulation on PF-06651600 in Healthy Subjects	HV	14	50 mg ritlecitinib tablet[c] under fasted conditions, 50 mg ritlecitinib oral solution[b] under fasted conditions, and 50 mg ritlecitinib tablet[c] under fed conditions, each as a single-dose.	0 (pre-dose), 0.25, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, and 48 hours post-doses.
B7981005	2b	A Phase 2b, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Dose Ranging Study of Oral PF-06651600 and PF-06700841 as Induction and Chronic Therapy in Subjects With Moderate to Severe Ulcerative Colitis	UC	~180	Initial 8-Week Treatment Period: 200 mg, 70 mg, 20 mg of ritlecitinib[c] or matching placebo QD for 8 weeks. 50 mg QD of ritlecitinib[c] for 24 weeks. Fasted.	0 hour (pre-dose) on Days 1, 15, 85, 113, 141, 169 and 225. 0.5 hour post-dose on Day 29, 1 hour post-dose on Days 57, 2 hours post-dose on Day 57, 4 hours post-dose on Day 57, and 2 hours pre-dose on Days 29 and 57.
B7981006	2a	A Phase 2a, Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multi-Center Study to Assess the Efficacy and Safety Profile of PF-06651600 in Subjects With Moderate to Severe Active Rheumatoid Arthritis with an Inadequate Response to Methotrexate	RA	70	200 mg QD[c] of ritlecitinib or matching placebo for 8 weeks. Fasted.	0 hour (pre-dose) on Days 1, 8, 15, 29, 43, and 57. 0.5 hours post-dose on Days 15, 29, 43, and 57. 1 hour post-dose on Days 15, 43, and 57. 2 and 4 hours post-dose on Day 57.
B7981008	1	A Phase 1, Randomized, Double-Blind, Third-Party Open, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics After Multiple Oral Doses of PF-06651600 in Healthy Japanese Subjects	HV	8	200 mg QD of ritlecitinib[c] for 10 days. Fasted.	0 (pre-dose), 0.5, 1, 2, 4, 6, 8, 12, and 16 hours post-dose on Days 1 and 10. Additional 0 hour (pre-dose) samples on Days 2, 4, 6 and 8.
B7981016	1	A Phase 1, Non-Randomized, Open Label, Multiple Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of PF-06651600 in Subjects with Hepatic Impairment and in Healthy Subjects with Normal Hepatic Function	HV, MoHI	16	30 mg QD of ritlecitinib[c] for 10 days. Fasted.	0 hour (pre-dose) on Days 7, 8, 9 and 10. 0.5, 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours post-dose on Day 10.
B7981019	2b	A Phase 2b Randomized, Double-Blind, Placebo-Controlled, Multicenter, Dose-Ranging Study to Evaluate the Efficacy and Safety Profile of PF-06651600 With a Partially Blinded Extension Period to Evaluate the Efficacy and Safety of PF-06651600 and PF-06700841 in Subjects with Active Non-Segmental Vitiligo	Vitiligo	~330	Initial 24-Week Treatment Period: 200 mg QD ritlecitinib[c] for 4 weeks then 50 mg QD for 20 weeks, or 100 mg QD ritlecitinib[c] for 4 weeks then 50 mg QD for 20 weeks, or 50 mg or 30 mg or 10 mg QD ritlecitinib[c] for 24 weeks, or matching placebo.	0 hour (pre-dose) on Days 1, 29, 57, 85, and 169. 0.5 hours post-dose on Days 57 and 85, and 0.5, 1, 2 and 4 hours post-dose on Days 29 and 169.
B7981022	1	A Phase 1, Randomized, Open-Label, Cross-Over, Single Dose Study to Estimate the Relative Bioavailability of Candidate Capsule Formulations of PF-06651600 Relative to Tablets in Healthy Participants	HV	12	100 mg ritlecitinib tablet[c], 100 mg ritlecitinib capsule[d], 100 mg ritlecitinib capsule[e], 100 mg ritlecitinib capsule[f], each as a single-dose under fasted conditions.	0 hour (pre-dose), and 0.25, 0.5, 1, 2, 3, 4, 6, 12, 16, and 24 hours post-dose.
B7931005	2a	A Phase 2a Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety Profile of PF-06651600 and PF-06700841 in Subjects with Moderate to Severe Alopecia Areata With a Single-Blind Extension Period and a Cross-Over Open Label Extension Period	AA	142	Initial 24-Week Treatment Period: 200 mg QD ritlecitinib[c] for 4 weeks, then 50 mg QD ritlecitinib[c] for 20 weeks or matching placebo. Fasted.	0 hour (pre-dose) on Days 1, 15, 29, 43, 57, 85, 113, 141 and 169. 0.5 hours post-dose on Days 29 and 141. 1 hour post-dose on Day 85. 0.5, 1, 2, and 4 hours post-dose on Days 29 and 169.

[a]Ritlecitinib plasma concentrations only, [b]solution, [c]tablet, [d]capsule, [e]capsule (b) (4)

Source: Table 1, PMAR-EQDD-B798h-Proof of Concept-1091

Table 31: Summary of Studies Included in the Final Population PK Modeling Analysis (PMAR-EQDD-B798d-DP4-1157)

Protocol	Phase	Protocol Design	Population	n	Dose Administration	Plasma Sampling
B7981015	2b/3	A Phase 2b/3 Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Investigate the Efficacy and Safety of PF-06651600 in Adult and Adolescent Alopecia Areata (AA) Subjects with 50% or Greater Scalp Hair Loss	AA	718	Period 1: 200 mg QD for 4 weeks then 50 mg QD for 20 weeks ritlecitinib, or 200 mg QD for 4 weeks then 30 mg QD for 20 weeks ritlecitinib, or 50 mg QD or 30 mg QD or 10 mg QD for 24 weeks ritlecitinib, or matching placebo. Period 2: 50 mg QD or 30 mg QD or 10 mg QD ritlecitinib for 24 weeks or 200 mg QD for 4 weeks then 50 mg QD for 20 weeks ritlecitinib. Administered regardless of food.	0 hour (pre-dose), and 0.5, 1 and 3 hours post-dose on Day 29. 0 hour (pre-dose), 0.5 and 2 hours post-dose on Day 57. If samples were not collected on Day 57, then samples are required on Day 85. LLOQ: 3.0 ng/mL.
B7981020	1	A Phase 1, Non-Randomized, Open Label, Multiple Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of PF-06651600 in Participants with Renal Impairment and in Healthy Participants with Normal Renal Function	HV, RI	8	50 mg QD for 10 days ritlecitinib. Fasted.	0 hr (pre-dose) on Days 8, 9 and 10, and, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 16, and 24 hrs post-dose on Day 10. LLOQ: 0.5 ng/mL.
B7981032	3	A Phase 3 Open-Label, Multi-Center, Long-Term Study Investigating the Safety and Efficacy of PF-06651600 in Adult and Adolescent Participants with Alopecia Areata	AA	~960	Participants rolling over from B7931005 or B7981015: 50 mg QD ritlecitinib. *de novo* participants: 200 mg QD for 4 weeks, then 50 mg QD ritlecitinib. Administered regardless of food.	0 hr (pre-dose), and 1 hr post-dose on Day 31, and 0 hr (pre-dose), and 0.5 and 3 hours post-dose on Day 91. LLOQ: 3.0 ng/mL.
B7981036	1	A Single Center, Open Label, Single Arm Study to Investigate the Repeated Dose (For 10 Days) Pharmacokinetics After Oral Administration of 200 mg PF-06651600 in Chinese Healthy Adult Participants	HV	9	200 mg QD for 10 days ritlecitinib. Fasted.	0 hr (pre-dose) on Days 1, 2, 4, 8, 9, 10 and 11, and 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 16 hrs post-dose on Days 1 and 10. LLOQ: 1.0 ng/mL.

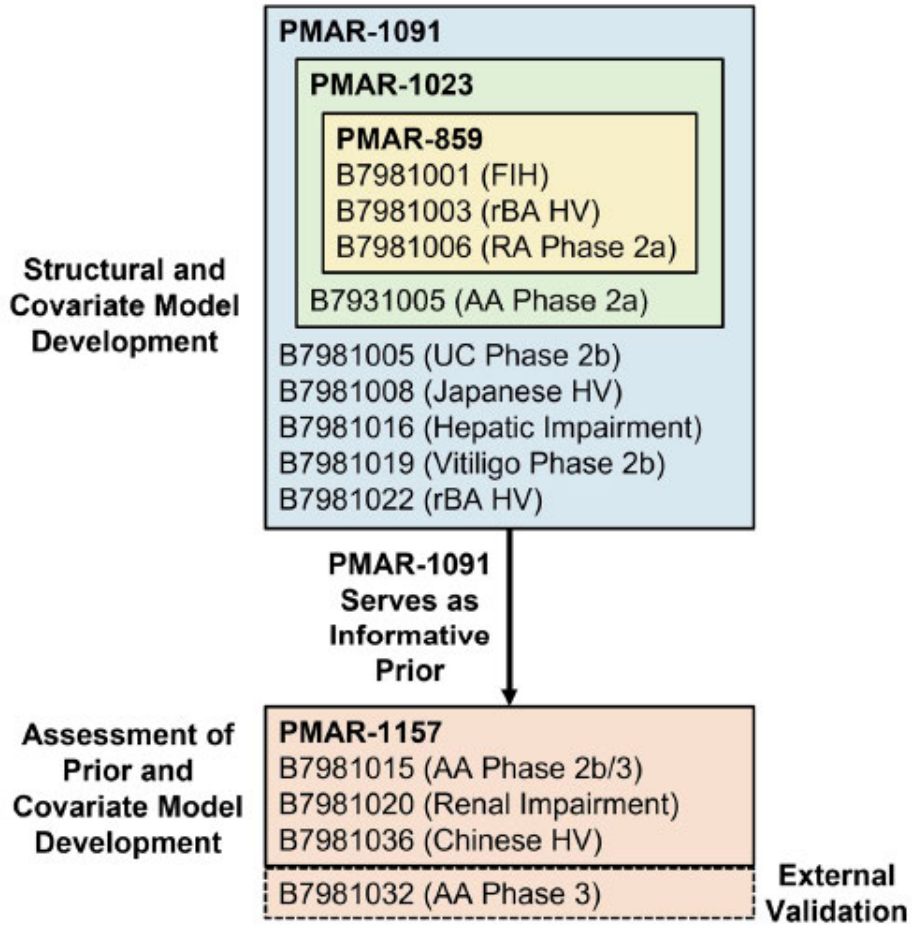
All individuals in B7981015, B7981020, B7981032, and B7981036 were administered the same tablet formulation.

Source: Table 1, PMAR-EQDD-B798d-DP4-1157

Final Population PK Model

Ritlecitinib, population PK analysis was conducted in an iterative manner as ritlecitinib concentration information became available from completed studies. A graphical depiction of the studies included in each of the reported population PK models, and how they were used, is presented in Figure 7.

Figure 7: Evolution of Ritlecitinib Population Pharmacokinetic Models



Source: PMAR-EQDD-B798d-DP4-1157 Figure 1

PMAR-859 = PMAR-EQDD-B798d-PrePoC-859, PMAR-1023 = PMAR-EQDD-B798d-Other-1023, PMAR-1091 =PMAR-EQDD-B798h-Proof of Concept-1091, PMAR-1157 = PMAR-EQDD-B798d-DP4-1157.

Source: Figure 1, PMAR-EQDD-B798d-DP4-1157

The final model described in PMAR-EQDD-B798d-DP4-1157 was developed using PMAREQDD-B798h-Proof of Concept-1091 as prior.

Model development used NONMEM Version VII Level 5.0 (b) (4) [4]. Population parameter estimation used first-order conditional estimation method with interaction (FOCEI) and individual parameters were obtained from empirical Bayes estimates (EBE). The ADVAN13 subroutine with TOL = 9 was used for solving differential equations. PsN 5.2.6 was used for sampling importance resampling (SIR).The final model was a 2-compartment model with first-order absorption with inter-individual variance (IIV) on apparent clearance (CL/F) and apparent central volume of distribution (Vc/F), a proportional random unexplained variability (RUV) model, and non-stationary clearance (CL) and bioavailability (F) directly driven by peripheral concentrations.

Covariates incorporated into the model included:

- Allometric scaling on CL/F and apparent inter-compartmental clearance (Q/F), and Vc/F and apparent peripheral volume of distribution (Vp/F), referenced to a 70 kg individual with exponents of 0.75 and 1, respectively.
- Effect of RA, UC, AA, and vitiligo patients on CL/F (individually estimated covariate effects).
- Effect of inflammatory disease patients (RA, UC, AA, and vitiligo patients) on IIV in CL/F and Vc/F.
- Effect of inflammatory disease patients (RA, UC, AA, and vitiligo patients) on RUV.
- Effect of food on first-order absorption rate constant (ka).
- Effect of 800 mg single-dose on ka.
- Effect of pilot capsule formulation on ka.
- Effect of moderate-to-severe UC on F.
- Effect of moderate hepatic impairment on F.
- Effect of severe renal impairment on F.

Covariates previously assessed in the development of the prior model (PMAR-EQDD-B798h-Proof of Concept-1091) of which no information was available in this analysis data, such as the impact of food, the capsule formulation, hepatic impairment, and RA, UC and vitiligo patients, were not re-evaluated. The parameter estimates from prior model (PMAR-EQDD-B798h-Proof of Concept-1091) and final model (PMAR-EQDD-B798d-DP4-1157) are provided in Table 32 and Table 33 respectively.

Table 32: Parameter Estimates for Prior Model (PMAR-EQDD-B798h-Proof of Concept-1091)

Parameter	Value	95% CI	Bootstrap Median	Bootstrap 95% CI	SHR (%)
Objective Function Value	50373.1				
Condition Number	14.5				
Population Parameter					
Apparent clearance (CL/F; L/hr)	115	(105, 125)	113	(98.7, 131)	
Apparent volume of the central compartment (Vc/F; L)	149	(143, 155)	148	(139, 156)	
Apparent inter-compartmental clearance (Q/F; L/hr)	0.304	(0.264, 0.344)	0.299	(0.243, 0.373)	
Apparent volume of the peripheral compartment (Vp/F; L)	4.67	(4.29, 5.05)	4.70	(3.98, 5.62)	
Maximum non-stationary effect on CL/F and F ($I_{max,P}$; %)	-0.488	(-0.526, -0.450)	-0.482	(-0.535, -0.433)	
Half-maximal concentration for non-stationary effect ($IC_{50,P}$, ng/mL)	15.1	(11.6, 18.6)	15.5	(9.78, 24.8)	
First-order absorption rate constant (k_a; hr^{-1})	8.51	(6.71, 10.3)	8.40	(6.88, 12.5)	
Proportional residual error (σ^2_{res}; SD)	0.359	(0.351, 0.367)	0.355	(0.328, 0.382)	
Effect of inflammatory disease patients on σ^2_{res} (%)	0.306	(0.265, 0.347)	0.324	(0.210, 0.444)	
Effect of inflammatory disease patients on $\omega^2_{CL/F}$ (%)	1.69	(1.18, 2.20)	1.68	(1.21, 2.28)	
Effect of inflammatory disease patients on $\omega^2_{Vc/F}$ (%)	2.39	(1.40, 3.38)	2.32	(1.44, 4.16)	
Effect of RA patients on CL/F (%)	-0.496	(-0.587, -0.405)	-0.494	(-0.592, -0.394)	
Effect of UC patients on CL/F (%)	-0.560	(-0.619, -0.501)	-0.556	(-0.643, -0.468)	
Effect of AA patients on CL/F (%)	-0.322	(-0.448, -0.196)	-0.325	(-0.411, -0.231)	
Effect of Vitiligo patients on CL/F (%)	-0.214	(-0.293, -0.135)	-0.214	(-0.269, -0.154)	
Effect of UC patients on F (%)	-0.224	(-0.305, -0.143)	-0.221	(-0.306, -0.141)	
Effect of MoHI on F (%)	0.255	(0.135, 0.375)	0.249	(0.00262, 0.496)	
Effect of high-fat meal on k_a (%)	-0.750	(-0.800, -0.700)	-0.754	(-0.908, -0.331)	
Effect of 800 mg dose on k_a (%)	-0.833	(-0.876, -0.790)	-0.833	(-0.904, -0.748)	
Effect of over-encapsulated capsules on loss from depot (%)	-0.134	(-0.163, -0.105)	-0.132	(-0.228, -0.027)	
Effect of capsules on k_a (%)	-0.598	(-0.701, -0.495)	-0.595	(-0.729, -0.420)	
Inter-Individual Variability					
$\omega^2_{CL/F}$ (%CV)	19.8	(13.0, 26.6)	19.7	(16.2, 23.8)	8.13
$\omega^2_{Vc/F}$ (%CV)	12.5	(5.40, 19.6)	12.8	(8.29, 16.9)	20.9
Random Unexplained Variability					
σ^2_{res} (SD)	1	Fixed	1.00	Fixed	5.61

Repository artifact ID FI-10438095.

Condition number = square root of the ratio of largest to smallest eigenvalues of correlation matrix, coefficient of variation (CV) = $\sqrt{\omega^2} \cdot 100$, asymptotic 95% CI are presented, 99.8% of bootstraps minimized successfully.

Source: Table 8, PMAR-EQDD-B798h-Proof of Concept-1091

Table 33: Parameter Estimates for Final Model (PMAR-EQDD-B798d-DP4-1157)

Parameter	Value	95% CI	SIR Median	SIR 95% CI	SHR (%)
Objective Function Value	31630.6				
Condition Number	7.5				
Population Parameter					
Apparent clearance (CL/F; L/hr)	107	(98.6, 116)	107	(99.4, 115)	
Apparent volume of the central compartment (Vc/F; L)	151	(147, 156)	151	(147, 156)	
Apparent inter-compartmental clearance (Q/F; L/hr)	0.297	(0.262, 0.332)	0.297	(0.264, 0.330)	
Apparent volume of the peripheral compartment (Vp/F; L)	4.87	(4.55, 5.20)	4.87	(4.54, 5.22)	
Maximum non-stationary effect on CL/F and F ($I_{max,P}$; %)	-0.452	(-0.485, -0.419)	-0.451	(-0.481, -0.421)	
Half-maximal concentration for non-stationary effect ($IC_{50,P}$, ng/mL)	16.5	(13.3, 19.7)	16.6	(13.1, 19.6)	
First-order absorption rate constant (k_a; hr^{-1})	7.91	(6.58, 9.25)	7.94	(6.85, 9.21)	
Proportional residual error (σ^2_{res}; SD)	0.356	(0.349, 0.363)	0.356	(0.349, 0.363)	
Effect of inflammatory disease patients on σ^2_{res} (%)	0.290	(0.255, 0.325)	0.290	(0.253, 0.325)	
Effect of inflammatory disease patients on $\omega^2_{CL/F}$ (%)	1.61	(1.29, 1.93)	1.61	(1.29, 1.92)	
Effect of inflammatory disease patients on $\omega^2_{Vc/F}$ (%)	1.43	(0.931, 1.94)	1.44	(0.897, 2.08)	
Effect of AA patients on CL/F (%)	-0.260	(-0.313, -0.207)	-0.260	(-0.302, -0.212)	
Effect of severe RI subjects on F (%)	0.353	(0.218, 0.488)	0.359	(0.214, 0.512)	
Inter-Individual Variability					
$\omega^2_{CL/F}$ (%CV)	18.8	(14.3, 23.2)	18.7	(16.8, 21.4)	11.4
$\omega^2_{Vc/F}$ (%CV)	11.5	(7.26, 15.7)	11.5	(9.49, 14.3)	33.1
Random Unexplained Variability					
σ^2_{res} (SD)	1	Fixed			12.2

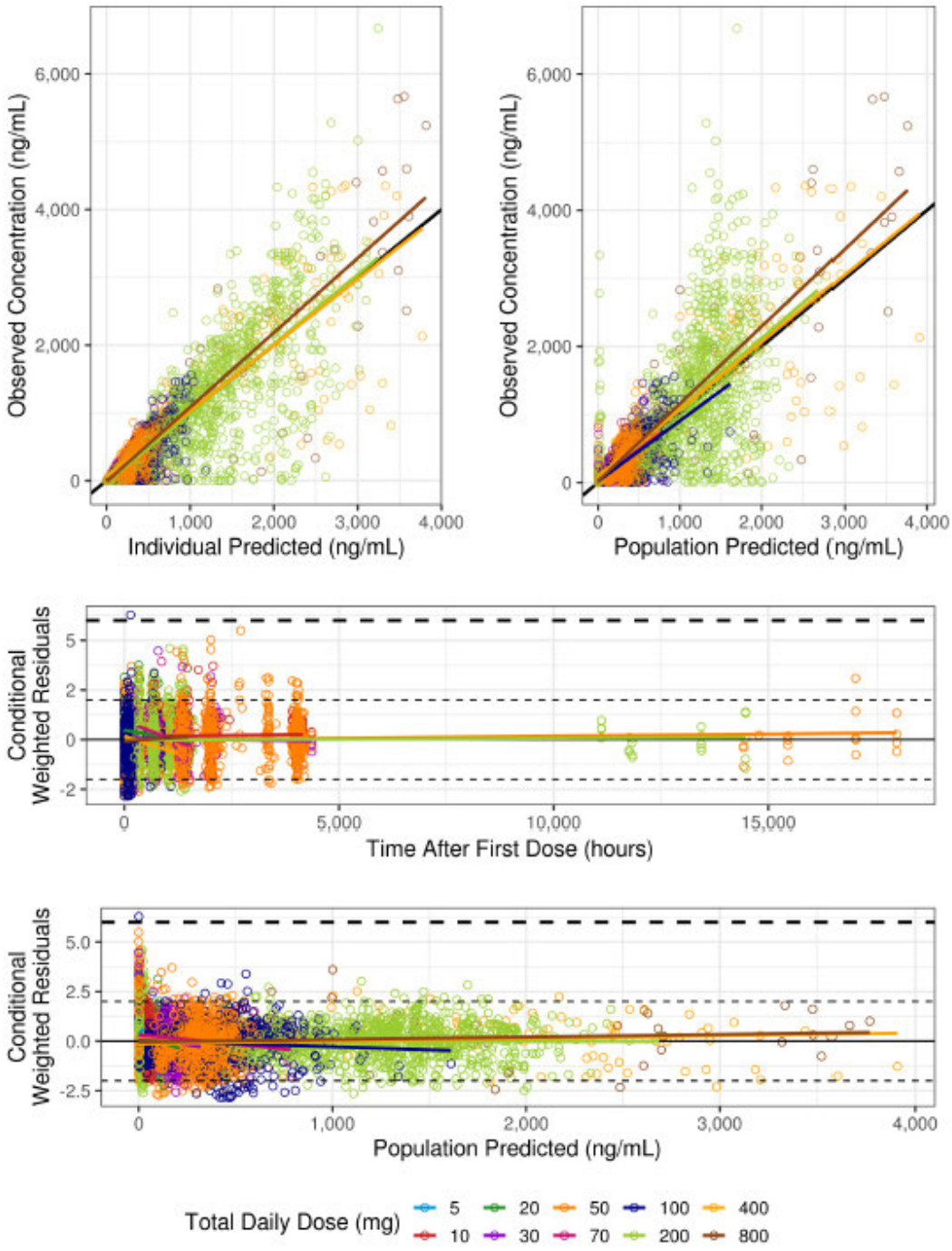
Repository artifact ID FI-20218492.

Condition number = square root of the ratio of largest to smallest eigenvalues of correlation matrix, coefficient of variation (CV) = $\sqrt{\omega^2} \cdot 100$.

SIR: Sampling importance resampling, SHR: Shrinkage, CI: Confidence interval

Source: Table 9, PMAR-EQDD-B798d-DP4-1157

Figure 8: Final Model Diagnostic Plots Stratified by Total Daily Dose (PMAR-EQDD-B798h-Proof of Concept-1091)

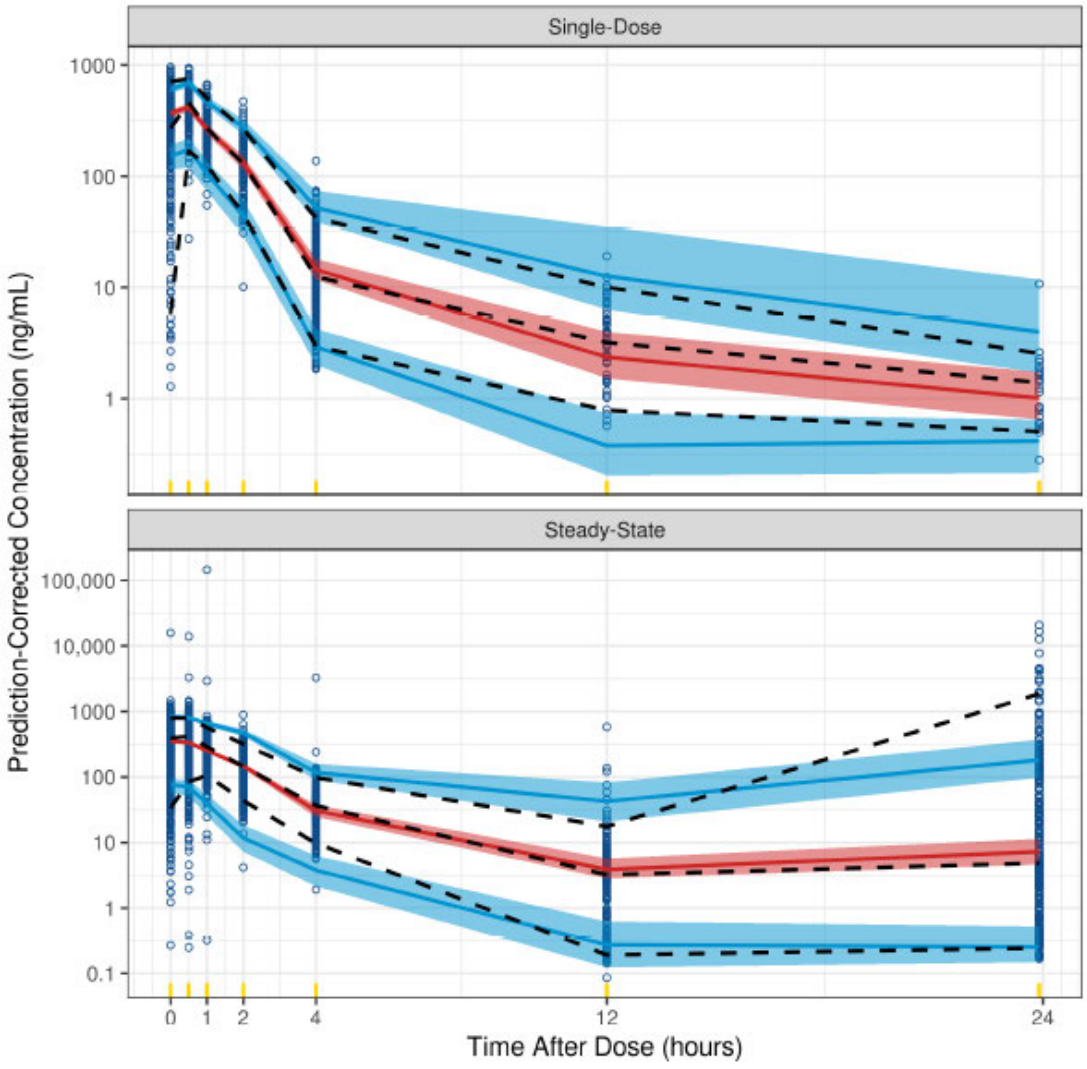


Repository artifact ID FI-18097006.

Top left: Observed versus individual predicted concentrations, *Top right:* Observed versus population predicted concentrations, *Middle:* CWRES versus TAFD, *Bottom:* CWRES versus population predicted concentrations. The black line is the line of identity, colored lines are the linear regression stratified by dose, black dashed lines represent CWRES ± 2 (fine) and ± 6 (bold) standard deviations from the mean.

Source: *Figure A5.1, PMAR-EQDD-B798h-Proof of Concept-1091*

Figure 9: Prediction-Corrected Visual Predictive Check (PMAR-EQDD-B798h-Proof of Concept-1091)

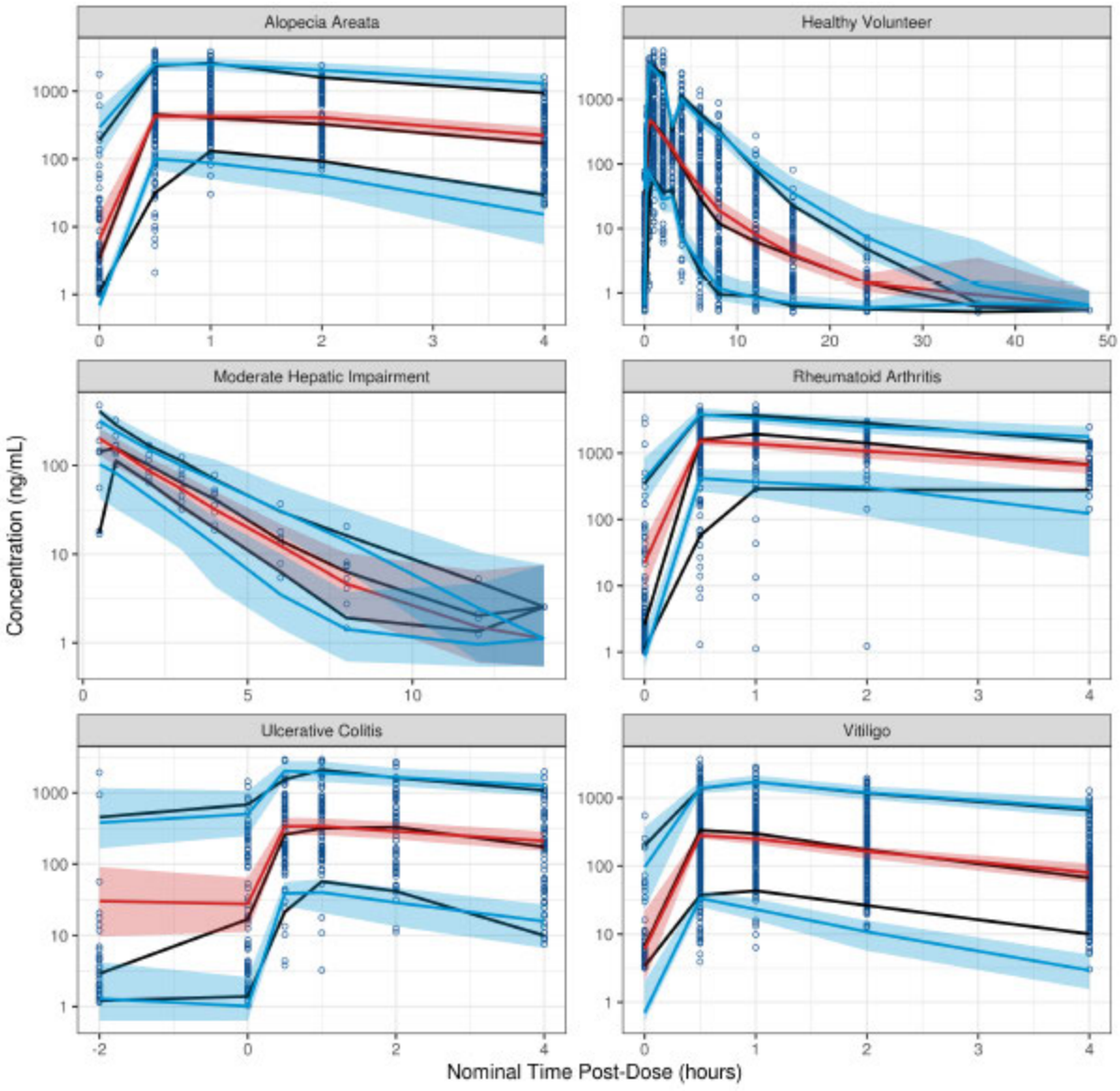


Repository artifact ID FI-8053766.

The prediction-corrected observed data are represented by blue circles and the dashed black lines (median, 5th and 95th percentiles). The simulated ritlecitinib concentrations based on the index population (n = 1000 simulations) are represented by the red line and red shaded ribbon (median and 95% prediction interval (PI) of the median, respectively) and the blue lines and blue shaded ribbons (median and 95% PIs of the 5th and 95th percentiles, respectively. Yellow indicators in the x-axis represent the time bins for summarizing the data (0, 1, 2, 4, 12, and 24 hours). Observed and simulated BLQ observations are excluded.

Source: *Figure 2, PMAR-EQDD-B798h-Proof of Concept-1091*

Figure 10: Visual Predictive Check Stratified by Patient Type (PMAR-EQDD-B798h-Proof of Concept-1091)

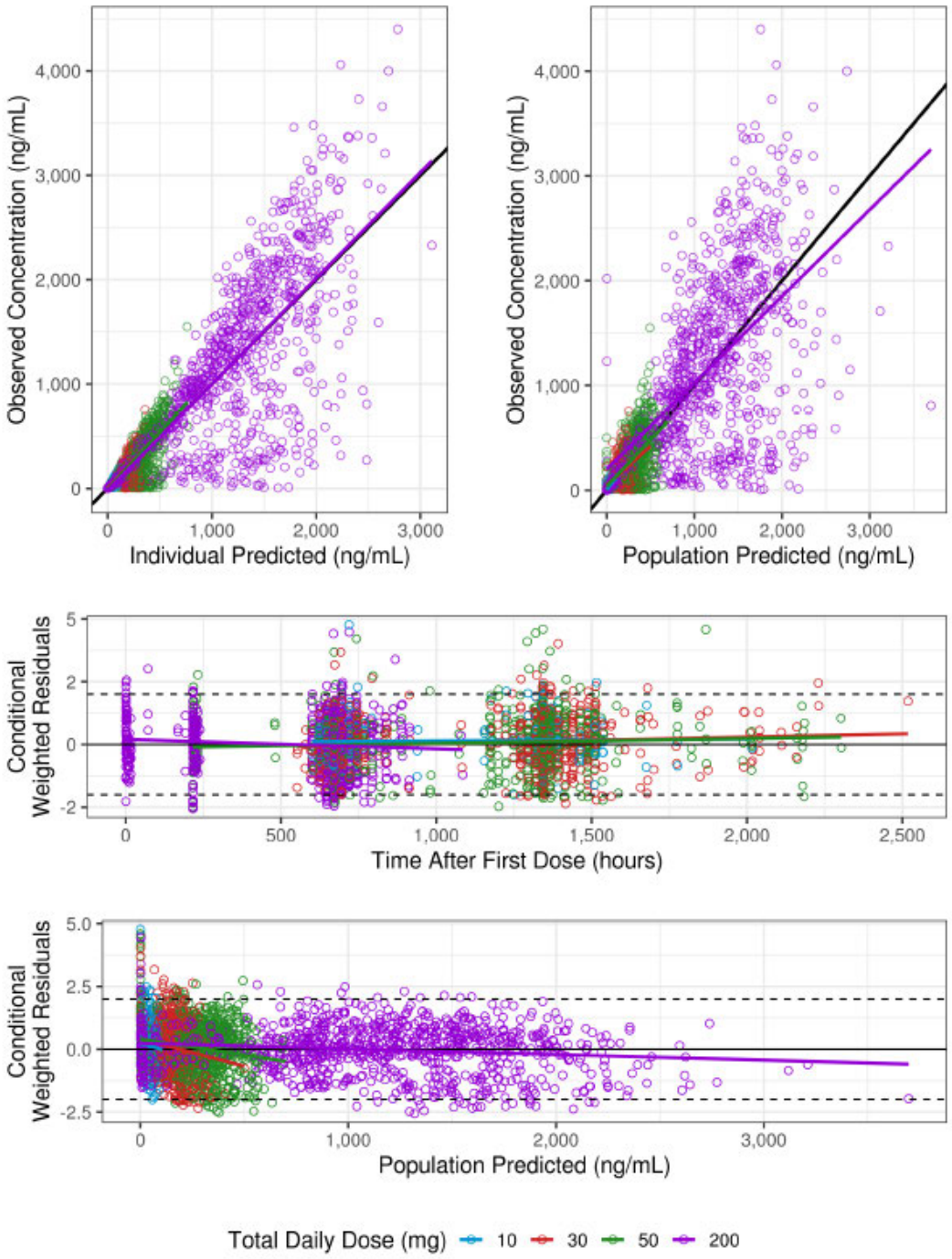


Repository artifact ID FI-8053797.

The observed data are represented by blue circles and the dashed black lines (median, 5th and 95th percentiles). The simulated ritlecitinib concentrations based on the index population (n = 1000 simulations) are represented by the red line and red shaded ribbon (median and 95% PI of the median, respectively) and the blue lines and blue shaded ribbons (median and 95% PIs of the 5th and 95th percentiles, respectively. Observed and simulated BLQ observations are excluded.

Source: Figure 3, PMAR-EQDD-B798h-Proof of Concept-1091

Figure 11: Final Model Diagnostic Plots Stratified by Total Daily Dose (PMAR-EQDD-B798d-DP4-1157)

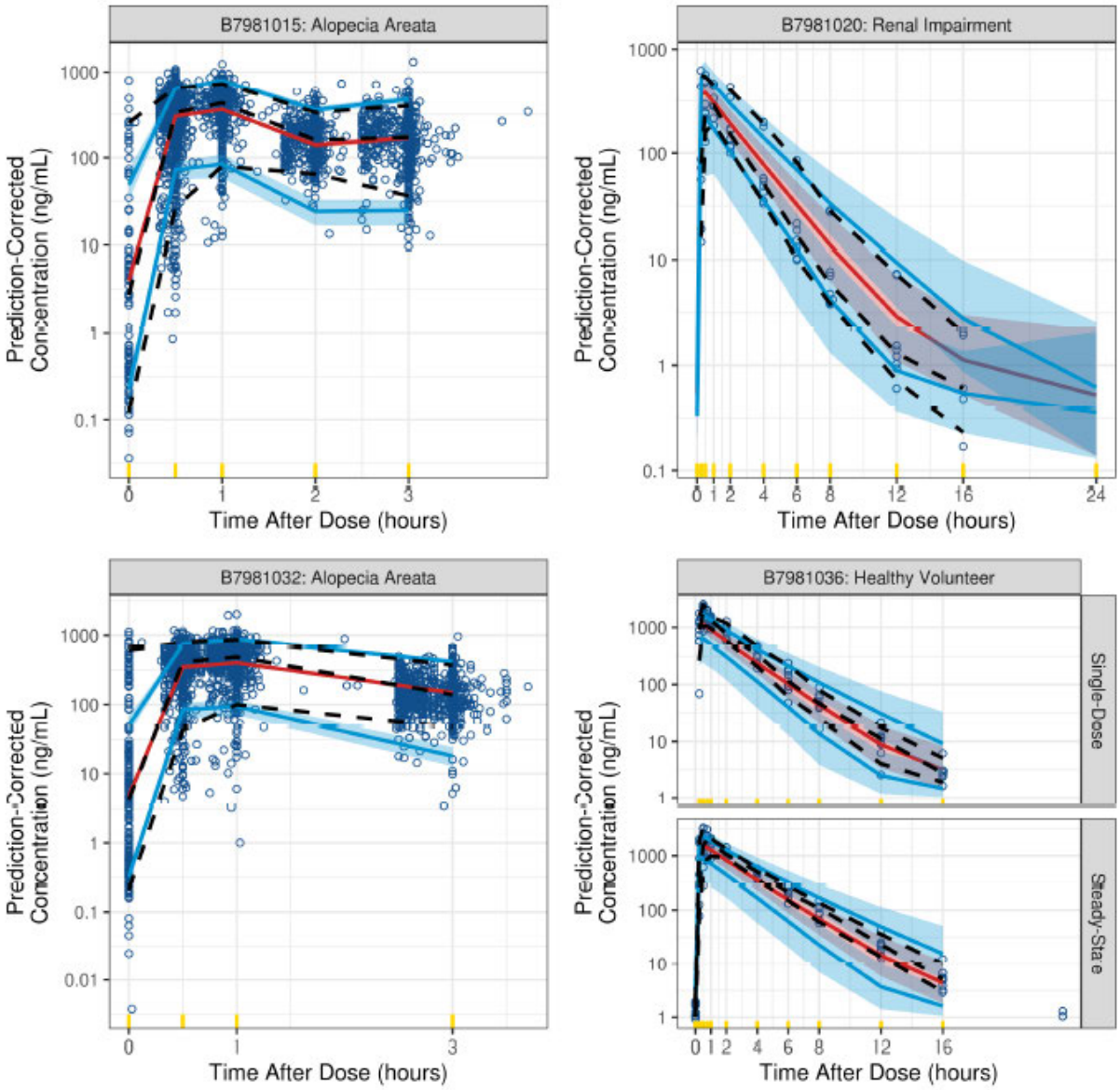


Repository artifact ID FI-20924323.

Top left: Observed versus individual predicted concentrations, *Top right:* Observed versus population predicted concentrations, *Middle:* CWRES versus TAFD, *Bottom:* CWRES versus population predicted concentrations. The black line is the line of identity, colored lines are the linear regression stratified by dose, black dashed lines represent CWRES ± 2 (fine) and ± 6 (bold) standard deviations from the mean.

Source: Figure A5.1, PMAR-EQDD-B798d-DP4-1157

Figure 12: Prediction-Corrected Visual Predictive Check (Final Model)



Repository artifact ID FI-21568546.

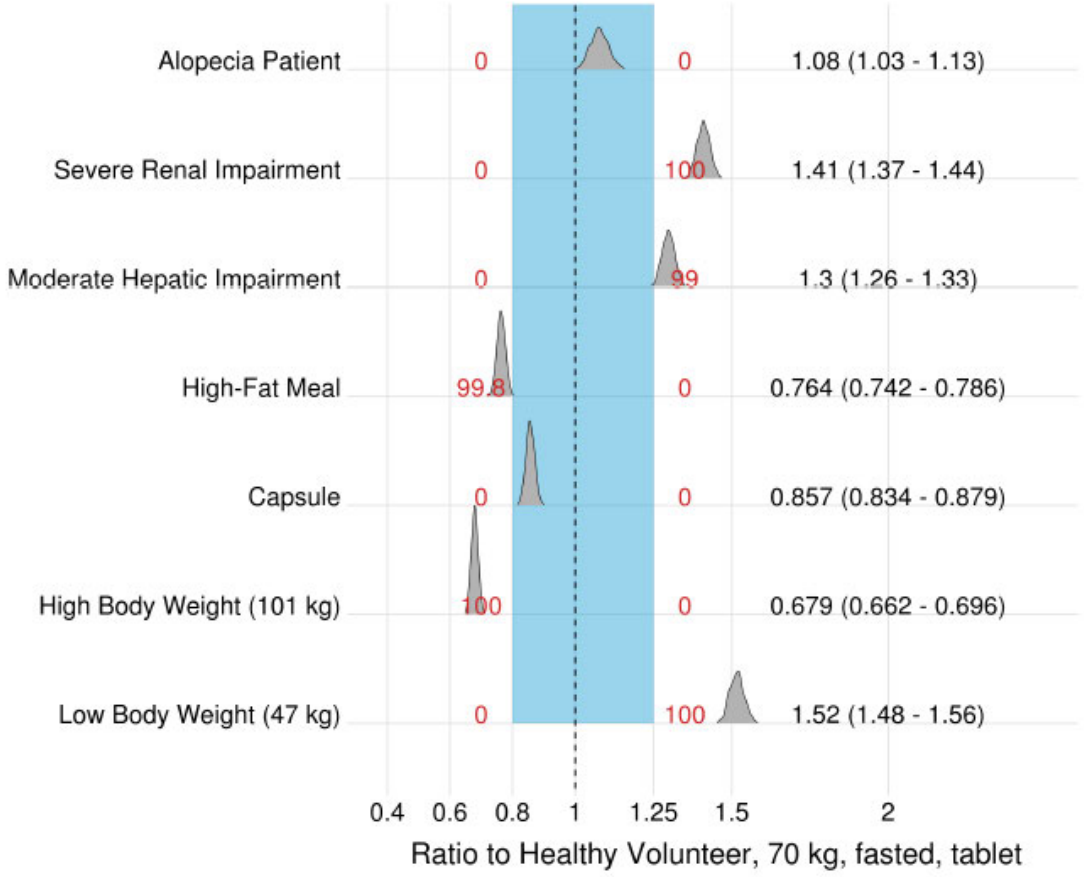
The prediction-corrected observed data are represented by blue circles and the dashed black lines (median, 5th and 95th percentiles). The prediction-corrected simulated ritlecitinib concentrations based on the index population (n = 1000 simulations) are represented by the red line and red shaded ribbon (median and 95% PI of the median, respectively) and the blue lines and blue shaded ribbons (median and 95% PIs of the 5th and 95th percentiles, respectively. Yellow indicators on the x-axis represent the time bins for summarizing the data. Observed and simulated BLQ observations are excluded. Prediction-corrected observations greater than 10,000 are excluded from the figure, but were not excluded from the observed summary.

Source: Figure 9, PMAR-EQDD-B798d-DP4-1157

Covariates Effects on Steady-State Exposure

The impact of intrinsic (patient type, severe renal impairment, hepatic impairment, and body weight) and extrinsic (fed status and formulation) on steady-state Cmax and AUCt are graphically depicted in Figure 13 and Figure 14, respectively. Covariates that did not establish statistical significance are not depicted in these figures.

Figure 13: Ratios of Steady-State Cmax Following 50 mg QD for Given Covariates Relative to Healthy Volunteers

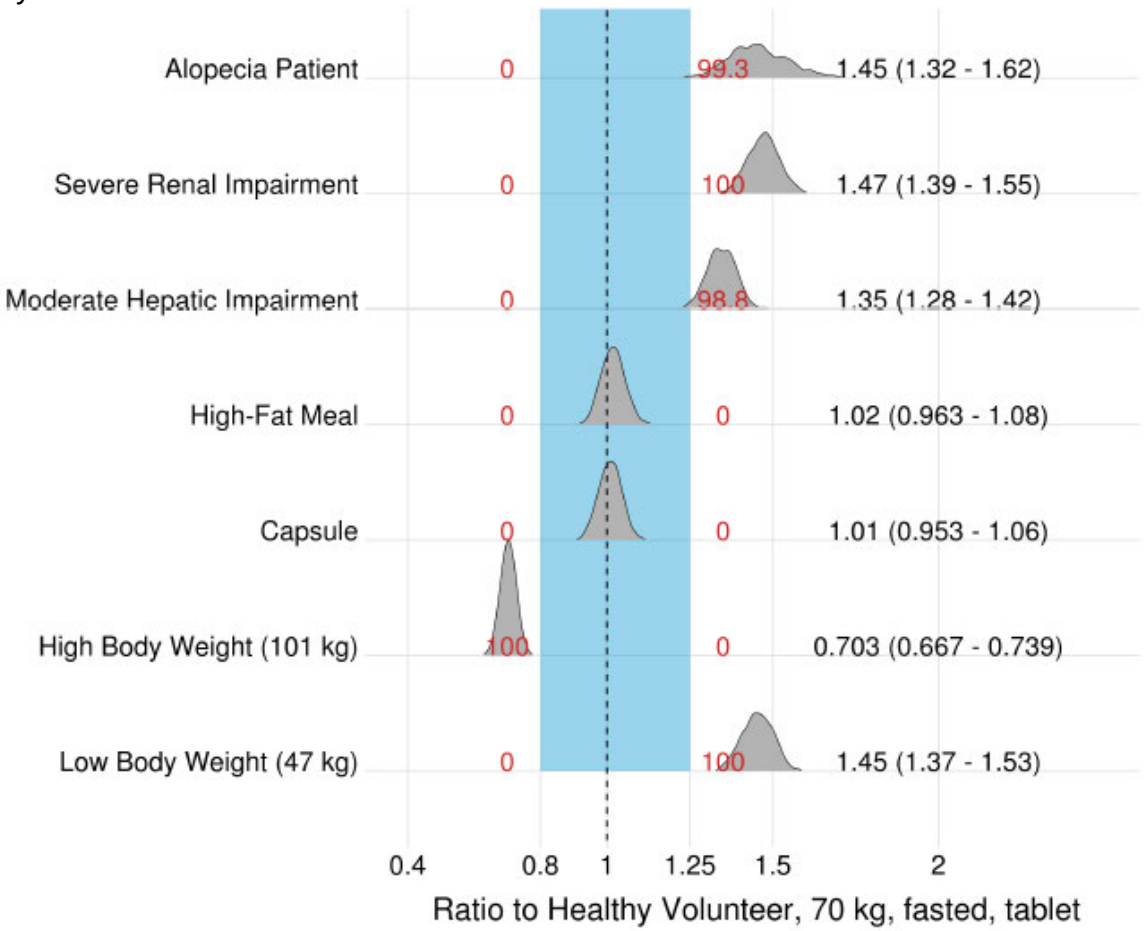


Repository artifact ID FI-20218884.

For each covariate scenario on the left y-axis, concentration-time profiles for 1000 trials of 118 randomly drawn individuals administered 50 mg QD for 14 days were simulated and summarized by C_{max}. The geometric mean ratio of C_{max} compared to the reference scenario (70 kg, fasted, HV) was calculated for each trial. The gray density distributions represent the geometric mean ratios across all trials, red numbers are the proportion of trials with ratios less than 0.8 (left) or greater than 1.25 (right). Black numbers on the right y-axis are the median (5^{th} and 95^{th} percentiles) of ratios for the covariate scenario. The blue shaded region is the range of geometric mean ratios from 0.8 to 1.25, and the black vertical dashed line is a geometric mean ratio of 1. Reference low and high body weights are the 5^{th} and 95^{th} percentiles of the analysis population. Scenarios for AA patients, severe RI, and high and low body were simulated using the final model presented in this analysis. Scenarios for moderate hepatic impairment, high-fat meal and the capsule formulation were simulated using the prior model.

Source: Figure 12, PMAR-EQDD-B798d-DP4-1157

Figure 14: Ratios of Steady-State AUCt Following 50 mg QD for Given Covariates Relative to Healthy Volunteers



Repository artifact ID FI-20218885.

For each covariate scenario on the left y-axis, concentration-time profiles for 1000 trials of 118 randomly drawn individuals administered 50 mg QD for 14 days were simulated using the final model and summarized by AUC_τ. The geometric mean ratio of AUC_τ compared to the reference scenario (70 kg, fasted, HV) was calculated for each trial. The gray density distributions represent the geometric mean ratios across all trials, red numbers are the proportion of trials with ratios less than 0.8 (left) or greater than 1.25 (right). Black numbers on the right y-axis are the median (5^{th} and 95^{th} percentiles) of ratios for the covariate scenario. The blue shaded region is the range of geometric mean ratios from 0.8 to 1.25, and the black vertical dashed line is a geometric mean ratio of 1. Reference low and high body weights are the 5^{th} and 95^{th} percentiles of the analysis population. Scenarios for AA patients, severe RI, and high and low body were simulated using the final model presented in this analysis. Scenarios for moderate hepatic impairment, high-fat meal and the capsule formulation were simulated using the prior model.

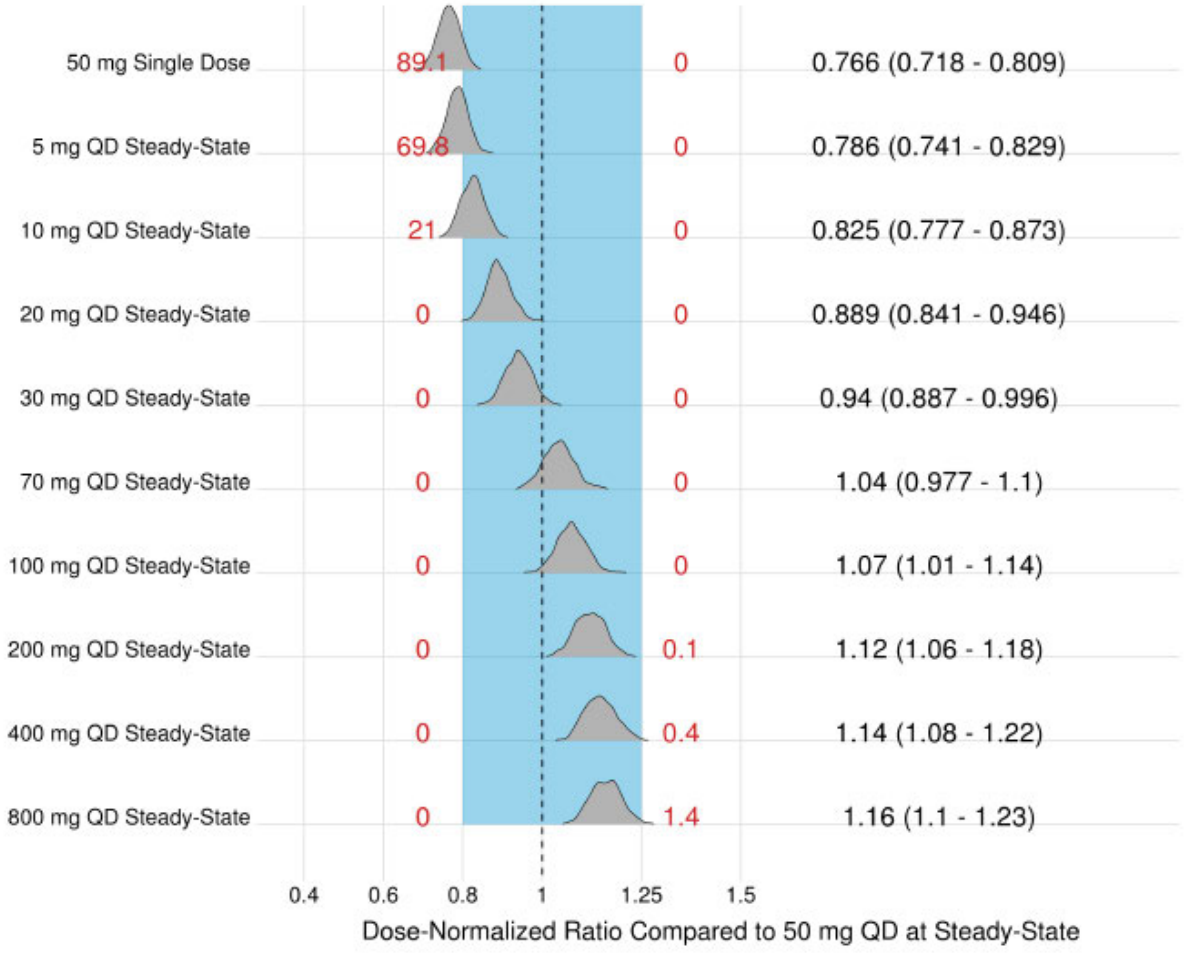
Source: Figure 13, PMAR-EQDD-B798d-DP4-1157

Reviewer's Comment: No clinically relevant differences in the pharmacokinetics of ritlecitinib were observed based on age (12-73 years), body weight, gender, and race. The effect of renal and hepatic impairment is in line with results observed in the dedicated clinical studies.

Dose Proportionality and Accumulation Assessments

The Applicant used final population PK model and simulated concentration-time profiles for 1000 trials of 118 randomly drawn individuals administered 50 mg QD for 14 days, for each dose scenario on the left y-axis and summarized by Cmax (Figure 15). The geometric mean ratio of Cmax compared to the reference scenario (AA patients, 70 kg, fasted) was calculated for each trial. The gray density distributions represent the geometric mean ratios across all trials, red numbers are the proportion of trials with ratios less than 0.8 (left) or greater than 1.25 (right). Black numbers on the right y-axis are the median (fifth and 95th percentiles) of ratios for the dose scenario. The blue shaded region is the range of geometric mean ratios from 0.8 to 1.25, and the black vertical dashed line is a geometric mean ratio of 1. Median dose normalized geometric mean ratios of Cmax 10 and 800 mg compared to 50 mg QD are within 0.8 to 1.25.

Figure 15: Dose Proportionality and Accumulation Assessment of Cmax

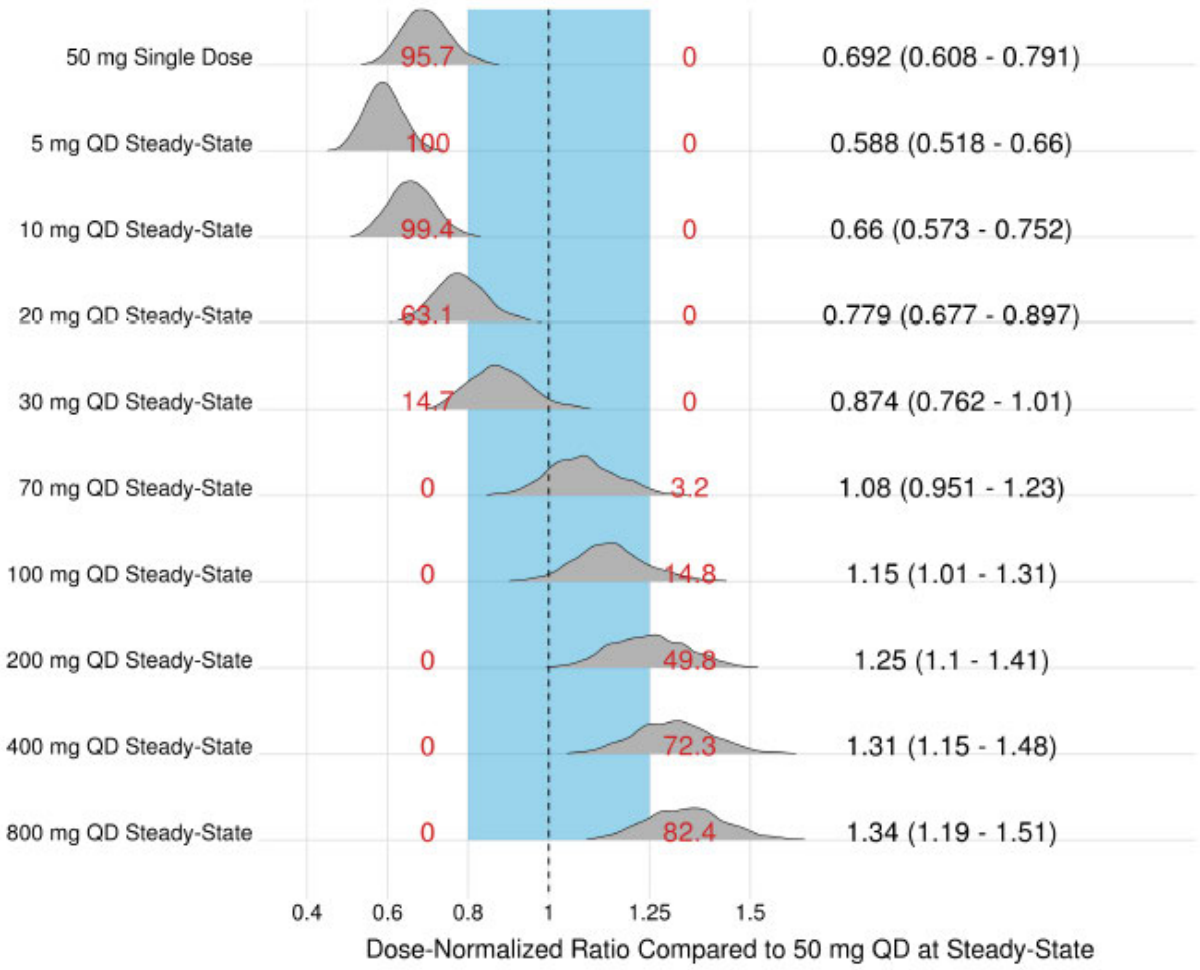


Source: Figure 10, PMAR-EQDD-B798d-DP4-1157

Similarly, the Applicant used final population PK model and simulated concentration-time profiles for 1000 trials of 118 randomly drawn individuals administered 50 mg QD for 14 days,

for each dose scenario on the left y-axis and summarized by 24 hours AUC (Figure 16). The geometric mean ratio of Cmax compared to the reference scenario (AA patients, 70 kg, fasted) was calculated for each trial. The gray density distributions represent the geometric mean ratios across all trials, red numbers are the proportion of trials with ratios less than 0.8 (left) or greater than 1.25 (right). Black numbers on the right y-axis are the median (fifth and 95th percentiles) of ratios for the dose scenario. The blue shaded region is the range of geometric mean ratios from 0.8 to 1.25, and the black vertical dashed line is a geometric mean ratio of 1. Median geometric mean ratios of AUCtau from 30 mg to 200 mg compared to 50 mg QD steady-state are within 0.8 to 1.25.

Figure 16: Dose Proportionality and Accumulation Assessment of of 24-Hour AUC



Source: Figure 11, PMAR-EQDD-B798d-DP4-1157

Reviewer's Comment: PopPK results showing median geometric mean ratios of AUCtau from 30 mg to 200 mg compared to 50 mg QD steady-state to be within 0.8 to 1.25 are supportive of the results shown in the study B7980001 showing approximate dose proportionality upto 200 mg.

19.4.17 Concentration Response Analyses (*PMAR-EQDD-B798d-sNDA-1158)*

Review Summary

The applicant's longitudinal exposure response relationship for ritlecitinib based on data from study B7931005, B7981015 and B7981032 (June 2021 data cut) is acceptable. The final model consisted of four major components: 1) Aranda-Ordaz link function to transform the skewed distribution of the data into the normal distribution to help fit the nonlinear mixed effects model; 2) indirect response model to describe the delay between PK exposure and response; 3) Emax-EC50 function to describe the ER relationship between Cavg and SALT score change; and 4) censoring approach to deal with the boundary values of 0 and 100%. The Cavg during the time interval between previous SALT score and the current SALT score were used as the PK exposure metric driving the efficacy in this analysis.

Model predictive performance was evaluated using a visual predictive check to determine if the final model was capable of simulating data that were consistent with the observed longitudinal SALT profiles. The observed median for AA population was generally similar to the simulated median and contained within the 95% prediction interval, indicating that the final model adequately describes the central tendency of the ritlecitinib longitudinal SALT score profiles for AA population. Most AT/AU participants did not reach the 30% change from baseline by Week 48, which limited the capability of ER characterization in AT/AU population.

The EC50 was estimated to be 53.6 ng/mL (Cavg), indicating that the top maintenance dose of 50 mg in the pivotal study is similar to the dose at half maximum effect (ED50) (Cavg for 30mg and 50mg QD are 27.0 and 52.0 ng/mL, respectively.

Data

A combined data set from completed studies (B7981005 and B7981015) and ongoing study B7981032 (data cutoff date of June 2021) was used for the analysis. The final analysis dataset included 13,101 observations of SALT score. Among these observations, 1244 (9.5%) data points were excluded because either they were collected in or before the screening period, or they have incorrect collection date (collection time is recorded as before the screening visit). A total of 11,857 observations from 1,268 participants were used in the analysis. Categorical and continuous covariates for study participants used in the covariate analysis are summarized in Table 34 and Table 35, respectively.

Table 34: Categorical Covariates Summary

Covariate	Level	Number of participants (%)
Total	Total	1268 (100)
Protocol	B7931005	95 (7.5)
	B7981015	715 (56.4)
	B7981032[a]	458 (36.1)
Sex	Female	805 (63.5)
	Male	463 (36.5)
Race	African American	46 (3.6)
	American Indian/Alaska native	8 (0.6)
	Asian	286 (22.6)
	Multiracial	15 (1.2)
	Native Hawaiian/Other Pacific islander	3 (0.2)
	Unknown	21 (1.7)
	White	889 (70.1)
Region	Asia	210 (16.6)
	Europe	271 (21.4)
	North America	595 (46.9)
	Rest of World	192 (15.1)
Disease severity	AA (non-AT/AU)	736 (58)
	AT/AU	532 (42)
Age group	Adolescent (≥ 12 and <18 years old)	170 (13.4)
	Adult	1098 (86.6)
Prior pharmacological treatment for AA	No	22 (1.7)
	Unknown	747 (58.9)
	Yes	499 (39.4)

Repository artifact ID FI-21568975. Line 1 substituted.
AA = alopecia areata; AT = alopecia totalis; AU = alopecia universalis.

Source: Table 5, *PMAR-EQDD-B798d-sNDA-1158*

Table 35: Continuous Covariates Summary

Covariate	Statistic	AA	AT/AU	Combined
Weight (kg)	Mean	70.2	71.4	70.7
	Median	67.8	69.3	68.4
	SD	18.2	16.8	17.6
	Min	29.6	35.0	29.6
	Max	200	131	200
Age (yrs)	Mean	33.3	34.3	33.8
	Median	31.0	33.0	32.0
	SD	14.3	14.0	14.2
	Min	12.0	12.0	12.0
	Max	72.0	72.0	72.0
Baseline SALT (%)	Mean	74.0	100	84.9
	Median	77.9	100	98.6
	SD	22.5	0	21.4
	Min	25.2	100	25.2
	Max	99.8	100	100
AA duration since first diagnosis (years)	Mean	10.0	10.0	10.0
	Median	6.84	6.43	6.67
	SD	10.3	10.8	10.5
	Min	0.0400	0.200	0.0400
	Max	58.2	60.1	60.1
Duration of current AA episode (years)	Mean	2.79	3.80	3.22
	Median	1.72	3.08	2.25
	SD	2.74	2.82	2.82
	Min	0.0200	0.0400	0.0200
	Max	29.5	10.7	29.5

Source: Table 6, *PMAR-EQDD-B798d-sNDA-1158*

Model

The SALT score data were analyzed using a nonlinear mixed effects modeling methodology in NONMEM Version 7.5.0. Exploratory analyses, diagnostic plots, and post-processing of NONMEM output were performed using R (Version 4.0.3). Perl-speaks-NONMEM (PsN) Version 5.2.6. was used for performing Sampling importance resampling (SIR). The NONMEM analyses were conducted using the Laplace estimation method with interaction and ADVAN13 with TOL=6. The SAEM with IMP was used for the estimation algorithm.

Non-boundary data were firstly scaled between 0 and 1, and then a transformation family was applied to help normalize the skewed distribution of bounded outcome score (BOS) data. For the transformation, Aranda-Ordaz flexible link function was used. Data on the boundaries, 0 or 100, were treated as censored data when constructing the likelihood. A general nonlinear

mixed-effects model was then constructed based on the transformed response. The equations for the selected base model are as follows:

$$f_{placebo}(t) = PBO(t) - 1,\ f_{drug}(t) = E(t) - 1$$
$$\frac{dPTR1(t)}{dt} = k_{out1} \cdot [1 + I_{PBO} \cdot P_{max}] - k_{out1} \cdot PTR1(t)$$
$$\frac{dPTR2(t)}{dt} = k_{out1} \cdot PTR1(t) - k_{out1} \cdot PTR2(t)$$
$$\frac{dPTR3(t)}{dt} = k_{out1} \cdot PTR2(t) - k_{out1} \cdot PTR3(t)$$
$$\frac{dPBO(t)}{dt} = k_{out1} \cdot PTR3(t) - k_{out1} \cdot PBO(t)$$
$$\frac{dDTR1(t)}{dt} = k_{out2} \cdot [1 + \frac{E_{max} \cdot C(t)}{EC_{50} + C(t)}] - k_{out2} \cdot DTR1(t)$$
$$\frac{dDTR2(t)}{dt} = k_{out2} \cdot DTR1(t) - k_{out2} \cdot DTR2(t)$$
$$\frac{dE(t)}{dt} = k_{out2} \cdot DTR2(t) - k_{out2} \cdot E(t)$$
$$PBO(t=0) = 1, E(t=0) = 1$$

The inter-individual variance (IIV) on BASE and Pmax was evaluated using an additive error model. The IIV on Emax (kin and kout if data permit) were evaluated with an exponential function assuming log-normal parameter distributions. The residual variability was modeled using an additive error model to the transformed response.

The final placebo model included three transit compartments in addition to the initial indirect response model to describe the delayed response. Separate kin1 and kout1 estimation was not supported from the data, hence kout1 was assumed to be the same as kin1. Since baseline SALT scores are different between AA vs AT/AU population, disease severity (AA vs AT/AU) was incorporated as a structural covariate on BASE. Due to the inclusion criteria of SALT score, SALT ≥ 50% for Study B7931005 and B7981015 and SALT ≥ 25% for Study B7981032, additive IIV could not properly handle the distribution of baseline values. The exponential function in Equation 7 was used instead to describe the IIV on BASE with subtraction of 1 to individual BASE parameter which allows negative values at baseline (SALT <50% values based on the original scale). Once the placebo model was selected, the model was expanded to include a drug effect. The kout1 for placebo effect onset was fixed to the estimate from the final placebo model to make the drug effect model stable. The Emax-EC50 model better described the observed data than the linear model. Two transit compartments were introduced to drug effect compartment to describe the delay between exposure and efficacy response. Separate kin2 and kout2 estimation was not supported from the data, hence kout2 was assumed to be the same

as kin2. Study B7981032 effect on BASE parameter was incorporated to address different eligibility criteria in baseline SALT score between Study B7981032 (SALT ≥ 25%), and Study B7931005 and B7981015 (SALT ≥ 50%). AT/AU effects on maximum placebo effect (Pmax) and kout2 were additionally included as the structural covariate to better describe AT/AU response.

Based on mechanistic plausibility, physiological relevance and clinical interest, a group of potential covariates listed in Table 36 were assessed for significance.

Table 36: Covariates Considered in the ER Analysis

Parameters	Covariates
BASE	gender, weight, age, race[b], region[c], disease severity[d], prior treatment[e].
E_{max}	gender, weight, age, race[b], region[c], disease severity[d], prior treatment[e], DURF, DURC, baseline SALT
k_{in2}^{a}	age, weight, region[c], disease severity[d], prior treatment[e], DURF, DURC
k_{out2}^{a}	age, weight, region[c], disease severity[d], prior treatment[e], DURF, DURC

[a] covariate on the onset and offset parameters will be evaluated only when the data supports inter-subject variability on those parameters; [b] race = African American vs Asian vs White vs Other (American Indian/Alaska native or Multiracial or Native Hawaiian/Other Pacific islander or Unknown); [c] region = North America vs Europe vs Asia vs Rest of World; [d] disease severity = AA (non-AT/AU) vs AT/AU; [e] prior treatment = prior exposure to any treatment for AA vs no prior treatment vs unknown; SALT = Severity of Alopecia Tool; AT = alopecia totalis; AU = alopecia universalis; DURF = duration of disease since first diagnosis; DURC = duration of disease for current episode.

Source: Table 3, *PMAR-EQDD-B798d-sNDA-1158*

Specific covariates included in the base model were Study B7981032 effect on baseline to account for the difference in eligibility criteria for B7981032 (SALT ≥ 25%), relative to Studies B7981015 and B7981005 (SALT ≥ 50%) and AT/AU effect on relevant parameters to describe the response in AT/AU patients. Other covariates tested such as gender, weight, race, region, disease status, prior treatment, duration since first diagnosis, duration of current episode and baseline SALT on relevant parameters were not identified as significant.

Baseline values were different based on the disease severity and study as expected, the population mean of 1.92 (87.4 % in original scale) for AA in Study B7931005 and B7981015, 0.68 (67.3% in original scale) for AA in Study B7981032, and 11.6 (100%) for AT/AU. Transformation factor was estimated to be 1.19, which adjusted the skewed distribution of the data to be normally distributed. The Pmax parameter was not precisely estimated for AA population and therefore it was fixed to zero, whereas a small positive placebo effect was estimated for AT/AU population. The Pmax estimate of 2.75 in transformed scale does not induce any changes in SALT score for AT/AU population due to their large baseline value. The Emax parameter estimate was 15.8 in transformed scale for both AA and AT/AU population, which is translated into almost 100% recovery in SALT score (SALT score of 0 for AA and 0.33 for AT/AU) for a typical individual. The kout2 estimate in half-life was smaller for AT/AU population (3.11 weeks vs 7.80 weeks; mean transit time of 13.5 weeks vs 33.8 weeks), but the quicker onset in AT/AU

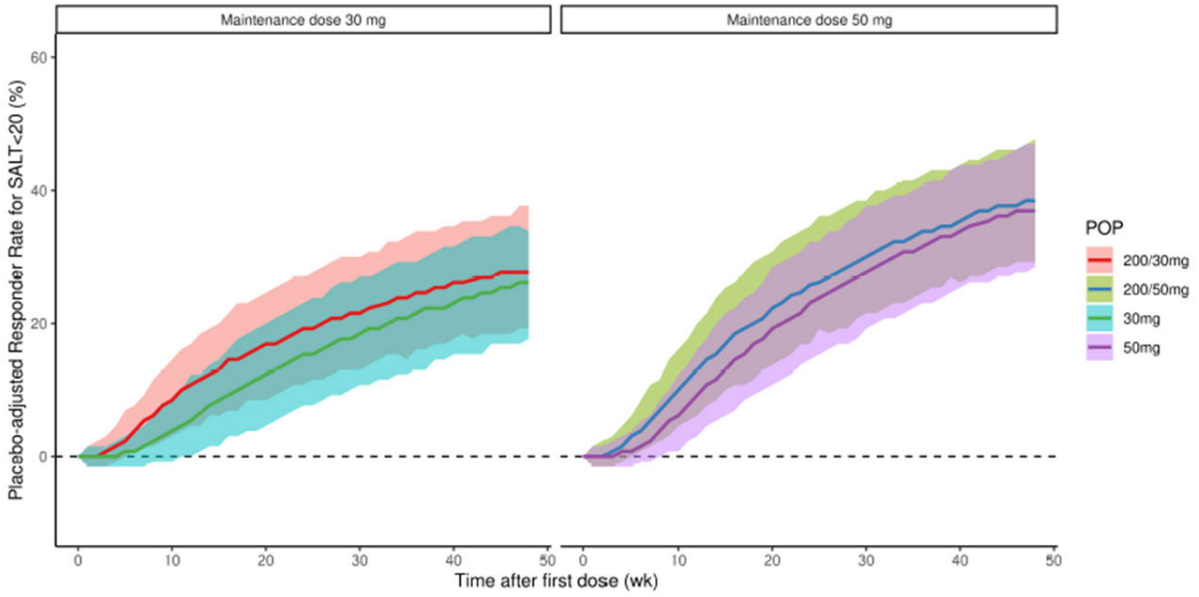
is offset by their higher baseline which requires large changes in SALT score to reach clinically meaningful response (SALT ≤ 20). The concentration at half maximum effect (EC50) estimate as in Cavg was 53.6 ng/mL, similar to the Cavg of 50 mg QD (52 ng/mL).

Plots of observed versus predicted (PRED or IPRED) showed random scatter around the identity line and plots of IWRES versus PRED and Time showed random scatter around the zero line, which demonstrated that the model appropriately described the observed SALT score data.

19.4.18 Clinical Trial Simulation for Assessing Loading Dose Effect

The final model was utilized to evaluate the loading dose effect. The model-based simulation results for the placebo-adjusted responder rate for SALT ≤ 20 are presented in Figure 17 for loading (200 mg QD for 4 weeks + 30 mg or 50 mg QD for 44 weeks) and non-loading (30 mg or 50 mg QD for 48 weeks) dose regimens. The tabulated summary of onset time and long-term efficacy (at Week 48) for each dose regimen is available in Table 37. The 200 mg loading dose accelerated the achievement of a SALT<20 response relative to the regimen without loading dose. However, the initial quicker response with loading dose regimen did not translate into long-term higher response rates relative to regimen without loading dose.

Figure 17: Evaluation of the Loading Dose Effect on the Clinical Onset of Efficacy



Red line with shaded region represents the simulated median for placebo-adjusted responder rate with 95% prediction interval for 200/30mg QD dosing regimen, blue line with shaded region represents the simulated median with 95% prediction interval for 30mg QD dosing regimen, green line with shaded region represents the simulated median with 95% prediction interval for 200/50mg QD dosing regimen, and purple line with shaded region represents the simulated median with 95% prediction interval for 30mg QD dosing regimen,.

Source: Figure 16, *PMAR-EQDD-B798d-sNDA-1158*

Table 37: Summary of the Loading Dose Effect on the Clinical Onset of Efficacy

Dosing Regimen	Onset Time[a] (wk)	Placebo-adjusted RR for SALT ≤20 at Onset Time (%)	Placebo-adjusted RR for SALT ≤20 at Week 48 (%)
200/30mg	6	3.85 (0.769,7.69)	27.7 (19.2,37.7)
30mg	13	6.54 (0.769,12.3)	26.2 (17.7,33.8)
200/50mg	6	3.85 (0.769,8.46)	38.5 (29.2,47.7)
50mg	9	5.38 (0.769,10.0)	36.9 (28.5,46.9)

Repository artifact ID FI-26259907. Line 1 substituted.
RR = responder rate. [a] Onset time is when the 95% CI of placebo-adjusted RR for SALT ≤20 becomes greater than 0.

Source: Table 9, *PMAR-EQDD-B798d-sNDA-1158*

19.4.19 Evaluation of Dose Interruption

The final model was used to evaluate the impact of dose interruption on the primary endpoint using a simulation approach for the 50 mg dose regimen. The simulation assumed uniform disruption in all study participants for each scenario and hence the results represent the worst case of each specific scenario. For the no dose interruption scenario, the responder rate for SALT ≤ 20 was 23.1 %. This is the expected value for the responder rate when no participant missed the study visit and no one skipped any ritlecitinib doses. The estimate was very similar to the observed value for 50 mg group in B7981015 study (23.39%), after exclusion of 6 missing participants due to COVID-19 and treating 5 missing participants due to reasons unrelated to COVID-19 as non-responders. The responder rate decreased for each of the various dose interruption scenarios, reflecting the impact of dose interruption on the primary endpoint. The impact of dose interruption was dependent upon both 1) dose interruption start time and 2) duration of interruption. The impact was generally larger when the duration of interruption was ≥6 weeks. Specifically, the result indicated that the responder rate can be reduced to less than a half of what is expected from no dose interruption case (10% vs 23.1%) if the duration of dose interruption was ≥6 weeks.

Table 38: Responder Rate of SALT ≤ 20 atWeek 24 for Various Dose Interruption Scenarios

Dose interruption start time (week)	RR for no dose interruption (%)	RR for 2 weeks of dose interruption (%)	RR for 4 weeks of dose interruption (%)	RR for 6 weeks of dose interruption (%)	RR for 8 weeks of dose interruption (%)
0	23.1	.	.	.	.
4	.	17.7	15.4	11.5	8.5
6	.	17.7	15.4	10	8.5
8	.	19.2	14.6	10.8	7.7
10	.	19.2	13.8	10	9.2
12	.	19.2	16.2	10	9.2
14	.	19.2	16.9	13.8	13.1
16	.	18.5	16.9	16.9	16.9
18	.	18.5	16.2	16.2	.
20	.	20	19.2	.	.
22	.	22.3	.	.	.

Source: Table 10, *PMAR-EQDD-B798d-sNDA-1158*

Effect of Dose Interruptions after Target Clinical Response (SALT <20) is Achieved

The final model was used to simulate responses up to 96 weeks to ensure a stable target clinical response. Dose was interrupted following 96 weeks and changes in SALT score were collected. The proportion of responders losing SALT ≤20 response was summarized according to the duration of treatment interruption in Table 39. Based on the model prediction, 12% of the responders were predicted to lose response when treatment was discontinued for ≥6 weeks, and almost half of the responders were predicted to lose response when treatment was discontinued for ≥16 weeks.

Table 39: Proportion of Responders Losing SALT ≤ 20 Response for Various Dose Interruption Durations

Treatment interuption duration (weeks)	Proportion of responders losing SALT ≤20 response (%)
4	5.2
6	12
8	21
10	29
12	36
14	43
16	47

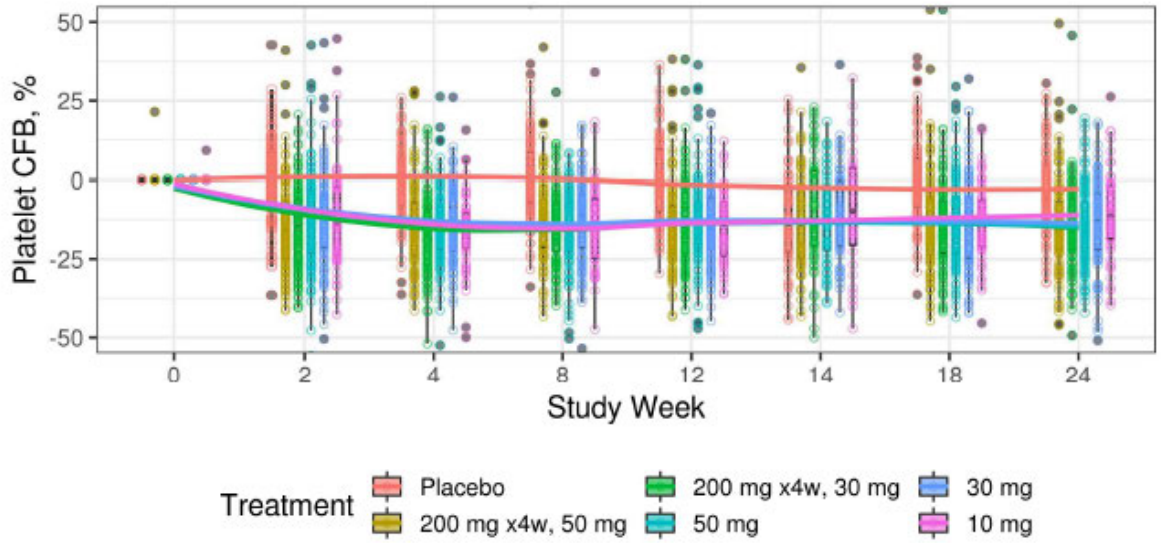
Source: Table 1, PMAR-EQDD-B798d-sNDA-1158-Addendum

19.4.20 Concentration Response Analyses for Platelets and Lymphocytes and Lymphocytes Subtypes

Effect of Riltecitinib on Platelets

A mean reduction from baseline counts of less than 25% was observed for all ritlecitinib doses with respect to placebo. However, the effect appears to be saturated as all doses demonstrated a similar response without a clear dose-response relationship. This level of change in platelet counts was not considered clinically significant in this population and is unlikely to result in increased risk of thrombocytopenia.

Figure 18: Observed Percent Change from Baseline for Platelets in B7981015



Source: PMAR-EQDD-B798d-Other-1163 Figure 1.

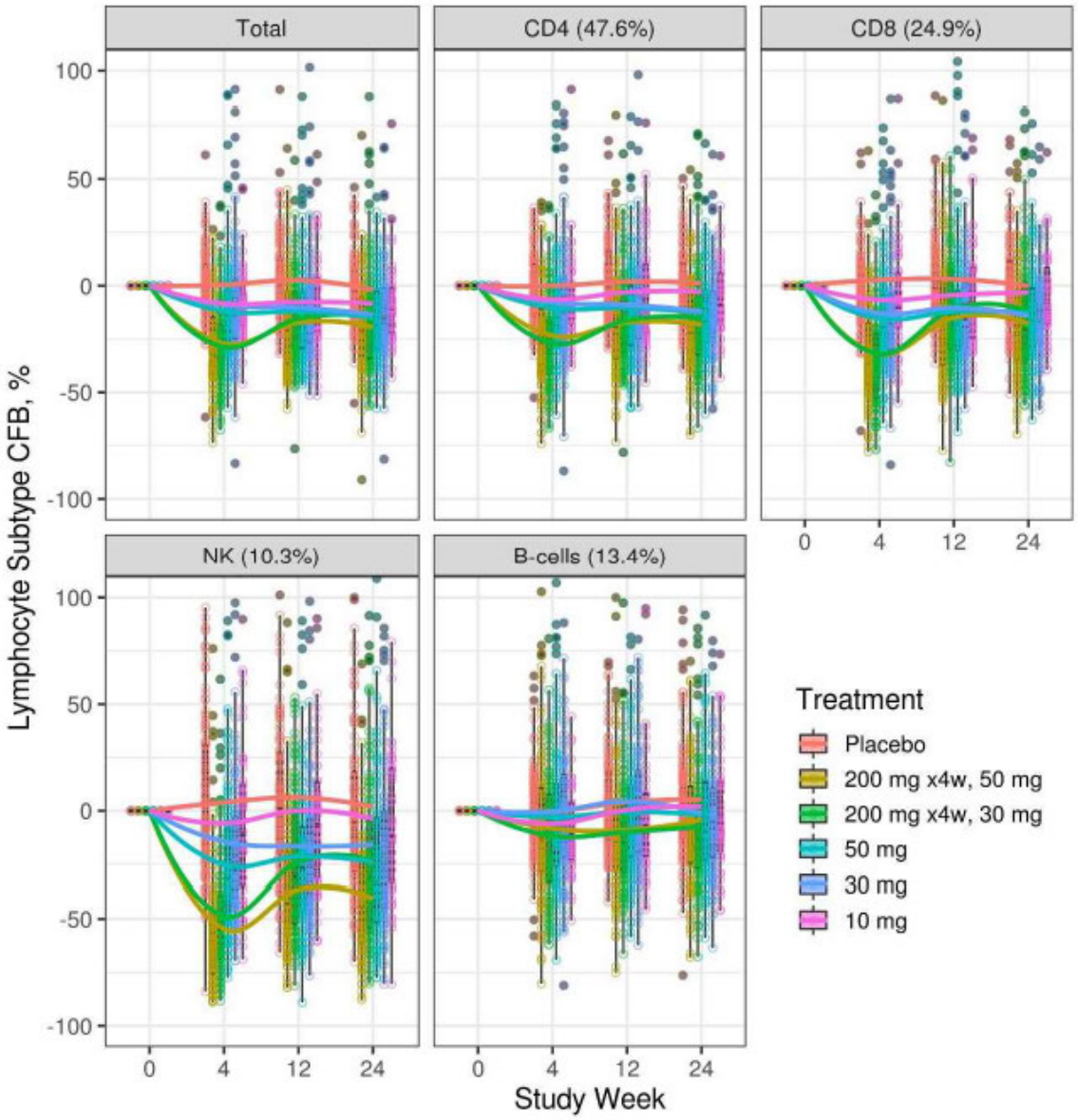
Plot is composed of individual points (circles) overlaying boxplots (boxed interquartile range, with whiskers to 1.5 times the interquartile range), summarized at nominal time points for the first 24 weeks. Time-courses are indicated by LOESS splines.

Source: Figure 9, Summary-Clin-Pharm

Effect of Ritlecitinib on Total Lymphocytes and Lymphocyte Subtypes

The lymphocyte subtypes CD4, CD8, and NK cells showed changes after ritlecitinib administration that were directionally similar and their dose-response relationship was adequately represented by the total lymphocytes. Hence, concentration response analysis of only the total lymphocytes was conducted. Ritlecitinib produced marginal changes on B lymphocytes which appear to trend towards baseline with continued exposure to ritlecitinib. Hence, additional concentration response analysis of B lymphocytes was not considered necessary.

Figure 19: Observed Percent Change from Baseline for Total Lymphocytes and Lymphocyte Subsets in B7981015



Source: PMAR-EQDD-B798d-Other-1163 Figure 2.

Each plot is composed of individual points (circles) overlaying boxplots (boxed interquartile range, with whiskers to 1.5 times the interquartile range), summarized at nominal time points where subtypes were assessed. Percentages indicate the fraction of each subtype of total lymphocytes at baseline. Time-courses are indicated by LOESS splines.

Source: Figure 10, Summary-Clin-Pharm

Concentration Response Analysis of Total Lymphocytes (PMAR-EQDD-B798d-Other-1163) Review Summary

The time-course of lymphocytes was adequately described by the semi-mechanistic model with a 2 parameter Emax relationship to characterize the magnitude of effect of ritlecitinib concentrations on lymphocyte proliferation. The model was adapted from the Friberg model.

Condition number (387) and shrinkage (RUV: 4%, η: 2.1%) were less than 400 and 25% respectively (predefined) and were acceptable. Predictive performance of the model was assessed by visual predictive check (VPC) and the predictive performance of the final model was also evaluated on three studies not used in the model building. These include the Phase 1 HV study B7981001, the Phase 2a AA study B7931005 and the Phase 3 long-term extension study B7981032 and were in general agreement with the model.

The final model included age and gender as covariates on baseline lymphocyte counts. Older age and male sex were associated with lower baseline lymphocyte count with a marginal higher risk of severe lymphopenia. Adolescents were not predicted to have an elevated risk of lymphopenia. The EC50 for ritlecitinib was estimated to be 25800 ng/ml which is several fold higher than the steady-state concentrations observed for 50 mg QD regimen. Simulations conducted with the final model demonstrated that the 200 mg loading dose regimen with 50 mg maintenance dosing was associated with a higher risk of lymphopenia than 50 flat dosing regimens.

Data

Summary of studies included for this analysis are listed in Table 40.

Table 40: Summary of included studies

Protocol	Phase	Protocol Design	Population	n	Dose Administration	Sampling
B7981001	1	Phase 1, randomized, double blind, third-party open, placebo-controlled, single and multiple dose escalation, parallel group study	HV	80	Doses ranging 5 to 800 mg were administered as single doses. 50 to 800 mg were administered daily, and 100 and 200 mg doses twice daily.	CBC at baseline, at 1, 3 and 7 days after single dose and every 3-4 days in multiple doses.
B7931005[b]	2a	Phase 2a, randomized, double-blind, placebo-controlled, multicenter study with a single-blind extension period and a cross-over open label extension period	AA	142	Initial 24-Week Treatment Period: 200 mg daily for 4 weeks, then 50 mg daily for 20 weeks or matching placebo.	CBC at baseline and every 1-4 weeks after.
B7981015	2b/3	Phase 2b/3 randomized, double blind, placebo controlled, dose ranging study in adult and adolescent subjects	AA	718	Placebo, or 10 - 200 mg daily for 4 weeks, followed by placebo or 10 -50 mg daily for 20 weeks, with a 24 week extension period of 20 - 50 mg daily (no placebo, and a 200 mg x4 weeks to 50 mg daily x20 weeks extension cohort).	CBC at baseline and every 1-4 weeks after, then at weeks 34, 40 and 48.
B7981032	3	Phase 3 long-term, open label extension study including new patients (de novo) and patients from B7931005 and B7981015	AA	960[a]	Continuation of 50 mg daily in returning subjects, or 200 mg daily for 4 weeks followed by 50 mg daily in de novo subjects, for 24 months.	CBC at baseline, 2 weeks, 1 month and every 2-3 months after.

Abbreviations: AA, alopecia areata; CBC: complete blood count; HV, healthy volunteer
[a]Ongoing study; planned recruitment
[b]B7931005 was an umbrella trial design with arms receiving various doses of brepocitinib (PF-06700841) or ritlecitinib.

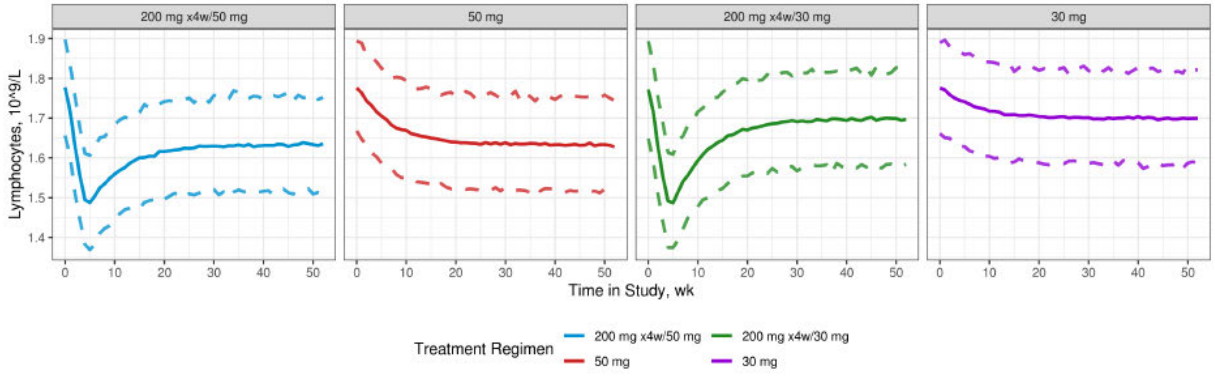
Source: Table 1, PMAR-EQDD-B798d-Other-1163

Model

Nonlinear mixed effects PK-PD (pharmacokinetic-pharmacodynamic) models were developed using NONMEM 7.5.0. First-order conditional estimation method with interaction (FOCEI) was used for model optimization and individual PK parameters were obtained from posthoc empirical Bayes estimates (EBE)s. The ADVAN13 subroutine was used to solve the ordinary differential equation (ODE) model. Perl-speaks-NONMEM (PsN) was used for batch model testing and sampling importance resampling (SIR) estimates of parameter uncertainty. R was used for statistical and graphical output, and in data or model manipulation.

The Friberg model was composed of a proliferation compartment, representing the progenitor cells upon which a drug may have a direct effect, feeding into three maturation (transit) compartments which end at the circulating pool of the lymphocytes. A feedback mechanism was built into the model which accelerates proliferation when lymphocyte counts are below baseline levels, and inhibits proliferation when counts rise above baseline.

Figure 20: Simulated Lymphocyte Counts by Ritlecitinib Dose Regimens with or without a 200 mg loading dose



Repository artifact ID FI-23597910.
Solid and dashed lines represent the median and 95% prediction intervals for the medians in the simulated trials.

Source: Figure 7, PMAR-EQDD-B798d-Other-1163

Table 41: Simulated Probability of Grades 1-4 Lymphopenia and Nadir

Treatment Regimen	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Nadir, 10^9/L	Nadir, wk	Steady-state, 10^9/L
200 mg x4w/50 mg	20.8 (14.2, 28.3)	7.5 (3.3, 11.7)	0.8 (0.0, 2.5)	0.0 (0.0, 0.0)	1.3 (1.2, 1.4)	4.0 (3.9, 4.0)	1.6 (1.5, 1.8)
50 mg	15.0 (9.2, 22.5)	2.9 (0.0, 6.7)	0.0 (0.0, 0.8)	0.0 (0.0, 0.0)	1.5 (1.4, 1.5)	13.6 (12.4, 14.9)	1.6 (1.5, 1.7)
200 mg x4w/30 mg	20.8 (14.2, 29.2)	7.5 (2.5, 12.5)	0.8 (0.0, 2.5)	0.0 (0.0, 0.0)	1.3 (1.2, 1.4)	3.9 (3.9, 4.0)	1.7 (1.6, 1.8)
30 mg	12.5 (6.7, 18.3)	1.7 (0.0, 5.0)	0.0 (0.0, 0.8)	0.0 (0.0, 0.0)	1.5 (1.4, 1.6)	9.3 (8.2, 10.7)	1.7 (1.6, 1.8)

Repository artifact ID FI-25059456.
Grades categorize the levels in patients at the time of nadir and represent the expected total incidence of lymphopenia (rather than the prevalence at steady state). Results are summarizing median and 95% prediction intervals of the proportions or the median.
Grades were based on CTCAE criteria: Grade 1: 1.1 - 0.8; Grade 2: 0.8 - 0.5; Grade 3: 0.5 - 0.2; Grade 4: < 0.2

Source: Table 10, PMAR-EQDD-B798d-Other-1163

Table 42: Lymphocyte Change from Baseline Stratified by Age for 50 mg Daily Dosing

Age	Baseline, 10^9/L	CFB, 10^9/L	CFB, %	Grade 1 or 2, %	Grade 3 or 4, %
12 - 17 yrs	2.0 (1.9, 2.1)	-0.3 (-0.4, -0.1)	-15.5 (-20.4, -7.2)	8.3 (3.3, 16.7)	0.0 (0.0, 0.8)
18 - 50 yrs	1.8 (1.7, 1.9)	-0.3 (-0.4, -0.1)	-14.7 (-20.3, -6.1)	16.7 (8.3, 26.7)	0.0 (0.0, 0.8)
51 - 72 yrs	1.6 (1.5, 1.7)	-0.3 (-0.4, -0.1)	-16.7 (-21.7, -8.9)	26.7 (15.8, 39.2)	0.0 (0.0, 1.7)

Repository artifact ID FI-23598307.
Results are summarizing median and 95% prediction intervals of the proportions or the median.
Grades were based on CTCAE criteria: Grade 1: 1.1 - 0.8; Grade 2: 0.8 - 0.5; Grade 3: 0.5 - 0.2; Grade 4: < 0.2

Source: Table 13, PMAR-EQDD-B798d-Other-1163

19.4.20 Concentration Response Analyses for Safety Outcomes (PMAR-EQDD-B798d-DP4-1306-Amendment-1)

Review Summary

Poisson regression was used to characterize the relationship between ritlecitinib exposure (characterized by time-weighted Cave metric) and treatment emergent safety outcomes e.g., infections, herpes zoster and rash. Population PK models from PMAR-EQDD-B798h-Proof of Concept-1091 and PMAR-EQDD-B798d-DP4-1157 were used to generate ritlecitinib exposure metrics for individuals (both have same structural model). Predicted ritlecitinib exposure, calculated as a time-weighted Cave metric, was used to evaluate the exposure-response relationship for incidence of AE. Time-weighted Cave was determined as the cumulative AUC divided by the time of the adverse event with respect to time of first dose.

Statistically significant exposure-response relationship was observed for infections and rash (95% confidence interval for the estimate of slope did not include zero). No statistically significant exposure-response relationship was observed for herpes zoster infections. Geographical location in Asia and female sex were identified as statistically significant covariates on the baseline incidence of infections. Patient type (HV vs. AA vs. vitiligo), geographical location in Asia, age (as a continuous relationship referenced to 35 years), and female sex were identified as statistically significant covariates on the baseline incidence of rash. Age (as a continuous relationship referenced to 34 years [median]) was identified as statistically significant covariate on the baseline incidence of herpes zoster infections.

Approximately 10-fold increase in ritlecitinib concentration (geometric mean Cav of 27 ng/mL [30 mg QD] vs. 257 ng/mL [200 mg QD]), was predicted to demonstrate an approximately 3-fold increase in the mean incidence of infections per 100 patient years (11.0 vs. 33.2,respectively) and approximately 4.4-fold increase in the mean incidence of rash per 100 patient years (18.3 vs. 80.1, respectively). An increase in chronic ritlecitinib dose from 30 mg to 50 mg QD was predicted to lead to marginal increase in mean (95% CI) incidence per 100 patient years for infections from 11.0 (9.61, 12.7) to 13.5 (11.9, 15.3), and from 18.3 (16.5, 20.4) to 24.1 (21.9, 26.6) for rashes. Looking at the efficacy/safety profile, the proposed dose of 50 mg QD seems acceptable.

Data

A summary of the studies and their overall designs and population type(s) included in the exposure-response analysis is provided in Table 43.

Table 43: Summary of Studies Included in the Modeling Analysis

Protocol	Phase	Protocol Design	Population	n	Dose Administration
B7981001	1	A Phase 1, Randomized, Double Blind, Third-Party Open, Placebo-Controlled, Single and Multiple Dose Escalation, Parallel Group Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PF-06651600 in Healthy Subjects	HV	80	SAD: Single doses of 5, 20, 50, 100, 200, 400, and 800 mg ritlecitinib or placebo. MAD: Repeated doses of 50, 200, or 400 mg QD or 100 or 200 mg BID for 14 days. Fasted.
B7981003	1	A Phase 1, Open Label, Single-Dose 3-Way Crossover study to Evaluate the Relative Bioavailability of a Solid Dose Formulation of PF-06651600 Under Fasting Conditions and the Effect of a High Fat Meal on the Bioavailability of the Solid Dosage Formulation on PF-06651600 in Healthy Subjects	HV	14	50 mg ritlecitinib tablet under fasted conditions, 50 mg ritlecitinib oral solution under fasted conditions, and 50 mg ritlecitinib tablet under fed conditions, each as a single-dose.
B7981008	1	A Phase 1, Randomized, Double-Blind, Third-Party Open, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics After Multiple Oral Doses of PF-06651600 in Healthy Japanese Subjects	HV	8	200 mg QD of ritlecitinib for 10 days. Fasted.
B7981015	2b/3	A Phase 2b/3 Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Investigate the Efficacy and Safety of PF-06651600 in Adult and Adolescent Alopecia Areata (AA) Subjects with 50% or Greater Scalp Hair Loss	AA	718	Period 1: 200 mg QD for 4 weeks then 50 mg QD for 20 weeks ritlecitinib, or 200 mg QD for 4 weeks then 30 mg QD for 20 weeks ritlecitinib, or 50 mg QD or 30 mg QD or 10 mg QD for 24 weeks ritlecitinib, or matching placebo. Period 2: 50 mg QD or 30 mg QD or 10 mg QD ritlecitinib for 24 weeks or 200 mg QD for 4 weeks then 50 mg QD for 20 weeks ritlecitinib. Regardless of food.
B7981019	2b	A Phase 2b Randomized, Double-Blind, Placebo-Controlled, Multicenter, Dose-Ranging Study to Evaluate the Efficacy and Safety Profile of PF-06651600 With a Partially Blinded Extension Period to Evaluate the Efficacy and Safety of PF-06651600 and PF-06700841 in Subjects with Active Non-Segmental Vitiligo	Vitiligo	366	Initial 24-Week Treatment Period: 200 mg QD ritlecitinib for 4 weeks then 50 mg QD for 20 weeks, or 100 mg QD ritlecitinib for 4 weeks then 50 mg QD for 20 weeks, or 50 mg or 30 mg or 10 mg QD ritlecitinib for 24 weeks, or matching placebo. Extension Period: 200 mg QD ritlecitinib for 4 weeks then 50 mg QD ± narrowband UVB, 30 mg QD ritlecitinib or 50 mg QD ritlecitinib, or 60 mg QD brepocitinib for 4 weeks then 30 mg QD. Regardless of food.
B7981022	1	A Phase 1, Randomized, Open-Label, Cross-Over, Single Dose Study to Estimate the Relative Bioavailability of Candidate Capsule Formulations of PF-06651600 Relative to Tablets in Healthy Participants	HV	12	100 mg ritlecitinib tablet, 100 mg ritlecitinib capsule, 100 mg ritlecitinib capsule, 100 mg ritlecitinib capsule, each as a single-dose under fasted conditions.
B7981032	3	A Phase 3 Open-Label, Multi-Center, Long-Term Study Investigating the Safety and Efficacy of PF-06651600 in Adult and Adolescent Participants with Alopecia Areata	AA	~960	Participants rolling over from B7931005 or B7981015: 50 mg QD ritlecitinib fasted. *de novo* participants: 200 mg QD for 4 weeks, then 50 mg QD ritlecitinib. Regardless of food.
B7981036	1	A Single Center, Open Label, Single Arm Study to Investigate the Repeated Dose (For 10 Days) Pharmacokinetics After Oral Administration of 200 mg PF-06651600 in Chinese Healthy Adult Participants	HV	9	200 mg QD for 10 days ritlecitinib. Fasted.

Protocol	Phase	Protocol Design	Population	n	Dose Administration
B7931005	2a	A Phase 2a Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety Profile of PF-06651600 and PF-06700841 in Subjects with Moderate to Severe Alopecia Areata With a Single-Blind Extension Period and a Cross-Over Open Label Extension Period	AA	142	Period 1: 200 mg QD ritlecitinib for 4 weeks, then 50 mg QD ritlecitinib for 20 weeks, or 60 mg QD brepocitinib for 4 weeks, then 30 mg QD brepocitinib for 20 weeks, or matching placebo. Period 2: 4-week drug holiday followed by re-treatment with ritlecitinib or brepocitinib (non-responders) or placebo until pre-defined efficacy criteria were met then re-treatment with ritlecitinib or brepocitinib (responders), for up to 24 weeks. Period 3 (non-responders): 4-week drug holiday followed by treatment with brepocitinib (for those receiving ritlecitinib in Periods 1 and 2) or ritlecitinib (for those receiving brepocitinib in Period 1 and 2), for up to 24 weeks. Regardless of food.

Source: Table 1, PMAR-EQDD-B798d-DP4-1306-Amendment-1

Infections: Exposure Response Analysis
The base model incorporated a square-root transformation for the effect of time-weighted Cave on slope. The 95% CI for the estimate of slope does not include zero, suggesting a statistically significant exposure-response relationship was observed.

The base model was used to generate the predicted incidence per 100 patient years of infection for doses of interest; 30 mg, 50 mg, 100 mg and 200 mg QD administered chronically (Table 44). A depiction of the exposure-response relationship for the effect of ritlecitinib on the incidence of infections per 100 patient years is presented in Figure 21. Geographical location in Asia and female sex were identified as statistically significant covariates on the baseline incidence of infections.

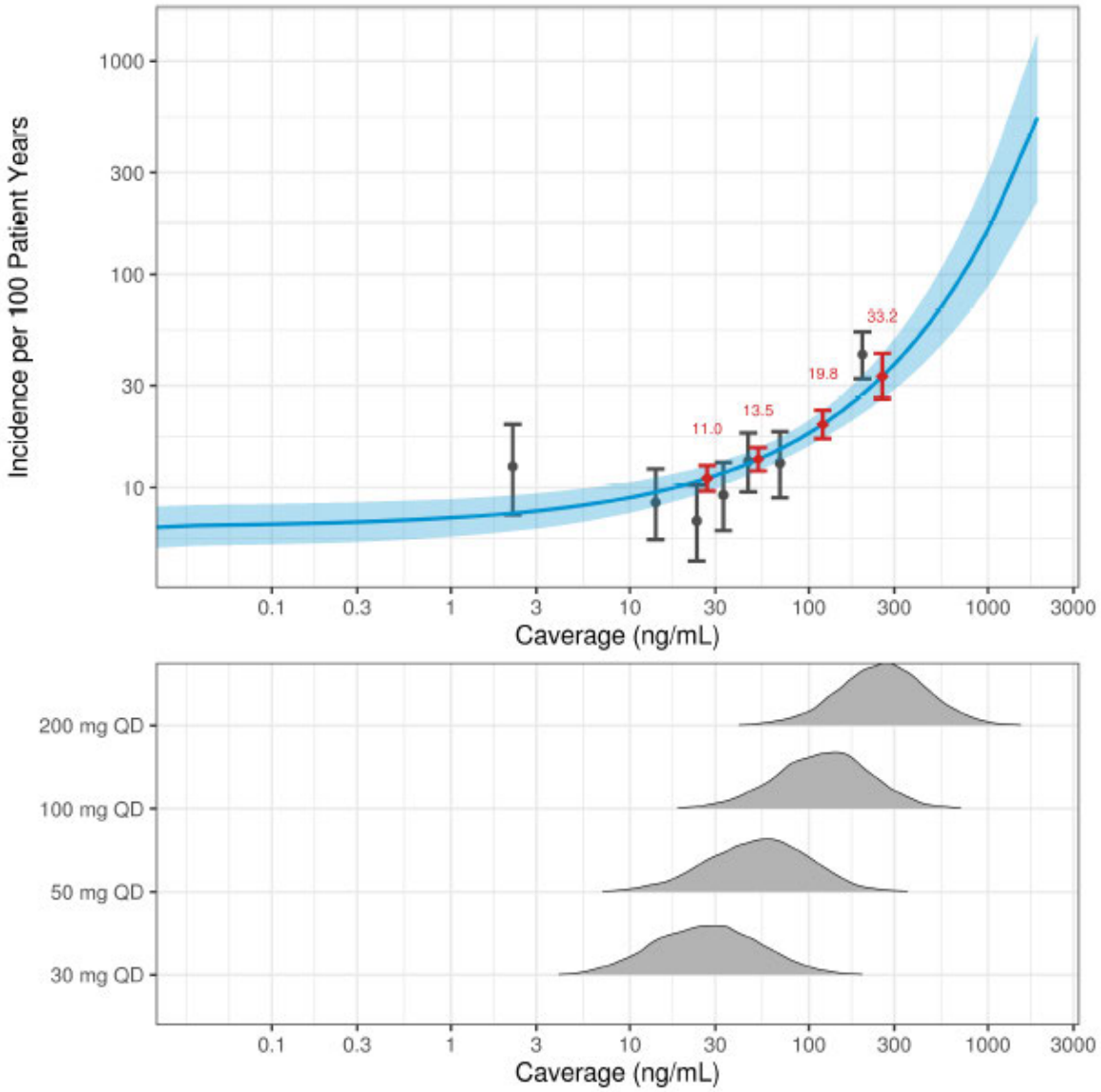
Table 44: Incidence of Infection per 100 Patient Years

Dose	Geometric Mean C_{ave} (ng/mL)[a]	Mean Incidence per 100 Patient Years (95% CI)
30 mg QD	27.0	11.0 (9.61, 12.7)
50 mg QD	52.0	13.5 (11.9, 15.4)
100 mg QD	119	19.8 (17.0, 23.0)
200 mg QD	257	33.2 (25.9, 42.6)

Repository artifact ID FI-29771748. Line 1 substituted.
[a]Predicted steady-state geometric mean C_{ave} values for each dose are derived from 10,000 simulated AA patients with randomly drawn random effect parameters for CL/F and Vc/F as described by the final population PK model [2] and body weights sampled from those observed in B7981015.

Source: Table 7, PMAR-EQDD-B798d-DP4-1306-Amendment-1

Figure 21: Incidence of Infections per 100 Patient Years Over the Range of Time-Weighted Observed Caverage



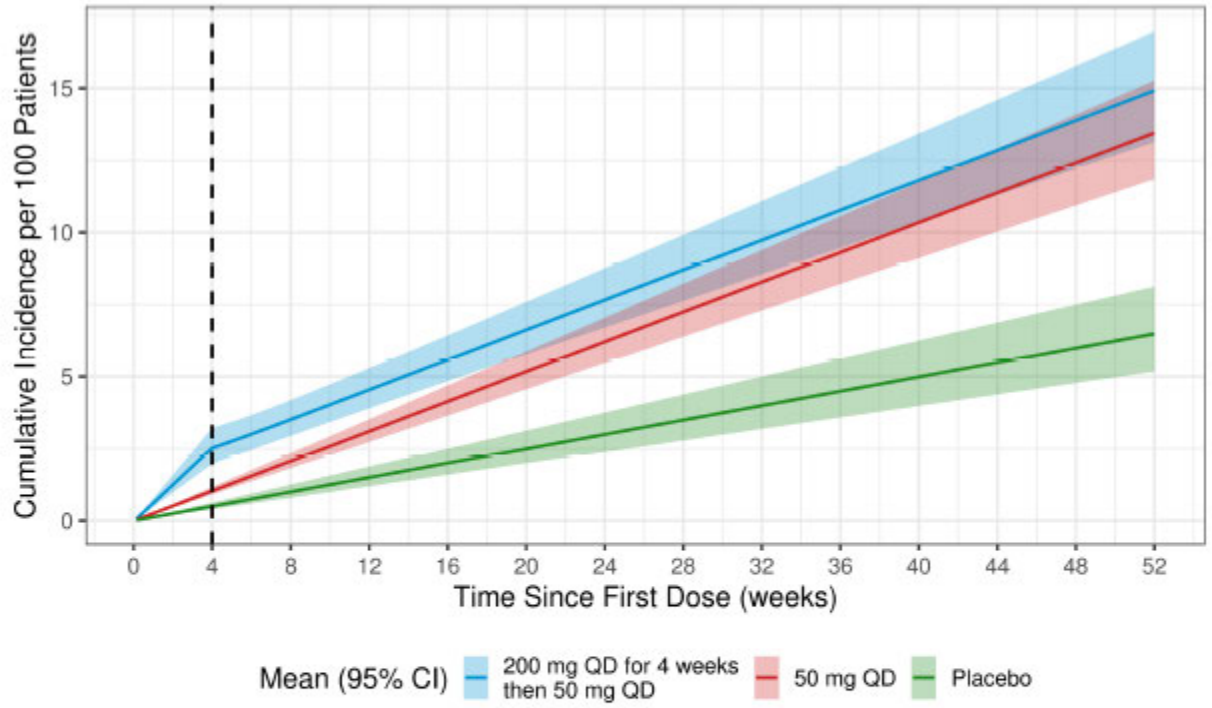
Repository artifact ID FI-29771746.

Top: Gray circles and error bars are the observed mean and 95% CI, respectively, of the incidence of infections (moderate, severe, leading to discontinuation) per 100 patient years for each bin of C_{ave} in the analysis population (n = 7). The blue line, (and blue shaded area) are the model-predicted mean (and 95% CI) incidence per 100 patient years for the range of observed C_{ave} in the analysis population. Red circles and error bars are the model-predicted mean and 95% CI, respectively, incidence of infection per 100 patients years at the geometric mean steady-state C_{ave} for 30 mg, 50 mg, 100 mg, and 200 mg QD in AA patients. *Bottom*: Gray distributions represent the predicted distribution of steady-state C_{ave} for 10,000 AA patients chronically administered 30 mg, 50 mg, 100 mg, and 200 mg QD with randomly drawn random effect parameters for CL/F and Vc/F as described by the final population PK model [2] and body weights sampled from those observed in B7981015.

Source: Figure 3, PMAR-EQDD-B798d-DP4-1306-Amendment-1

Predictions for incidence per 100 patient years assume that dose, and consequently Cave, are constant over the observation period. The cumulative incidence per 100 patients for infection over time was calculated using the base model to evaluate the difference between 200 mg QD for 4 weeks then 50 mg QD relative to a 50 mg QD continuous-dosing regimen over 1-year of ritlecitinib treatment (Figure 22).

Figure 22: Cumulative Incidence of Infection per 100 Patient Years Over Time



Repository artifact ID FI-29773621.

Solid lines and shaded areas are the model-predicted mean and 95% CI, respectively, cumulative incidence of infection occurring over time for the following dosing regimens; 200 mg QD for 4 weeks then 50 mg QD (blue) and 50 mg QD (red) for 52 weeks of continuous treatment. The vertical dashed line represents the conclusion of the 200 mg QD loading dose at Week 4. The cumulative incidence of infection is calculated as the incidence of events occurring at each time per 100 patients. Predicted time-weighted C_{ave} for each dosing regimen is based on the population-typical profile for an AA patient with body weight 70 kg using the final population PK model [2].

Source: Figure 4, PMAR-EQDD-B798d-DP4-1306-Amendment-1

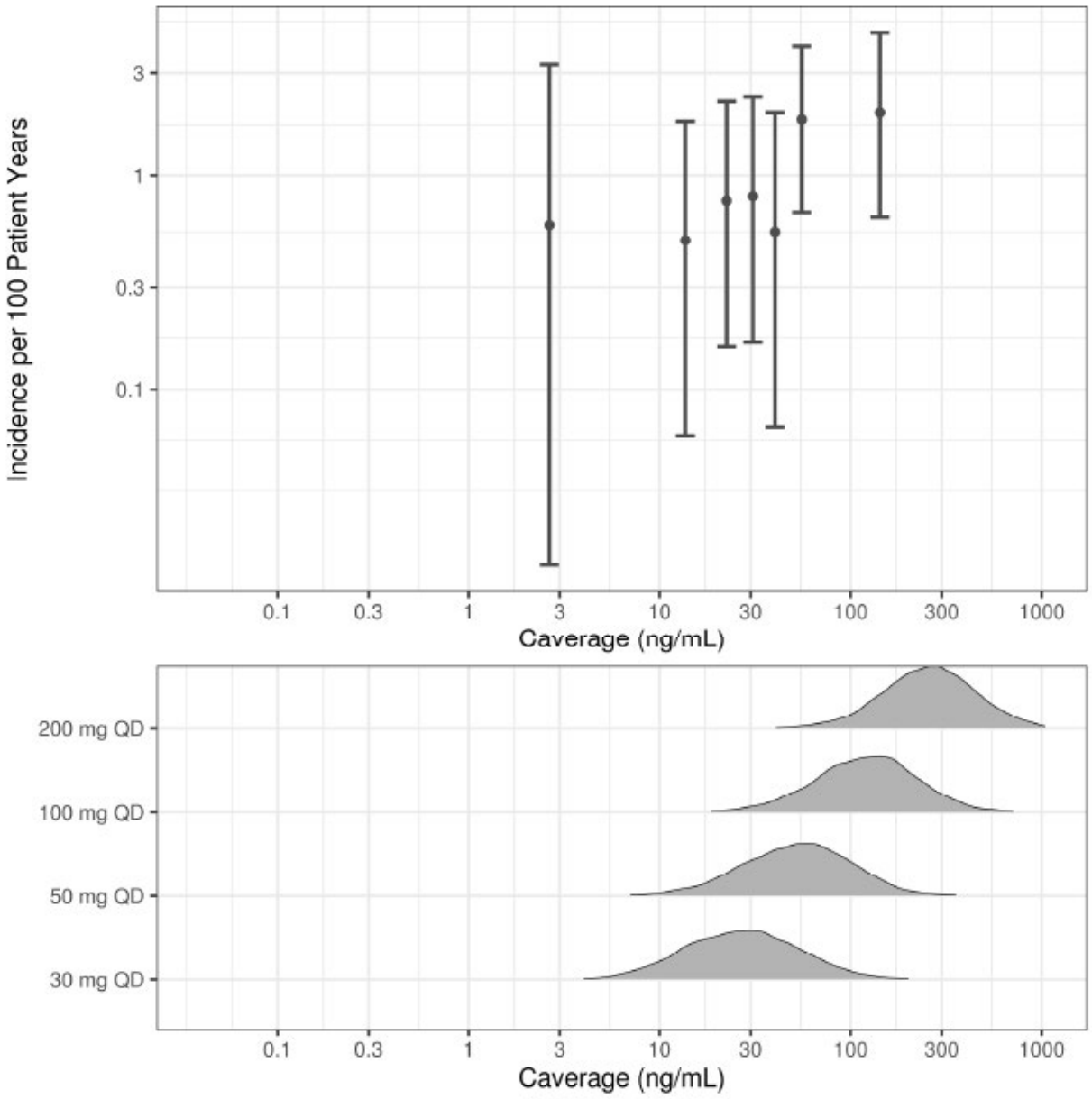
The greatest difference in the cumulative incidence per 100 patients for infection with the 200 mg QD for 4 weeks then 50 mg QD regimen occurred at the end of loading dose period (Week 4) compared to the 50 mg QD flag-dosing regimen (Figure 22). The higher cumulative incidence per 100 patients associated with the period of 200 mg QD exposure persists over time, however, the difference relative to the 50 mg QD regimen by Week 52 is negligible as depicted by overlapping of CI.

Covariates were evaluated on the intercept (baseline incidence) only. The effect of geographical location (Asia vs. North America/Europe/Rest of World) and sex (female) were the only covariates that established statistical significance.

Herpes Zoster: Exposure-Response Analysis

The base model quantifying the exposure-response relationship of the mean incidence for herpes zoster infections incorporated a square-root transformation for the effect of time-weighted Cave on slope. The 95% CI for the estimate of slope includes zero, suggesting that a statistically significant exposure-response relationship was not observed.

Figure 23: Incidence of Herpes Zoster Infections per 100 Patient Years Over the Range of Time-Weighted Observed Caverage



Repository artifact ID FI-29771752.

Top: Gray circles and error bars are the observed mean and 95% CI, respectively, of the incidence of herpes zoster infections per 100 patient years for each bin of C_{ave} in the analysis population (n = 7). *Bottom*: Gray distributions represent the predicted distribution of steady-state C_{ave} for 10,000 AA patients chronically administered 30 mg, 50 mg, 100 mg, and 200 mg QD with randomly drawn random effect parameters for CL/F and Vc/F as described by the final population PK model [2] and body weights sampled from those observed in B7981015.

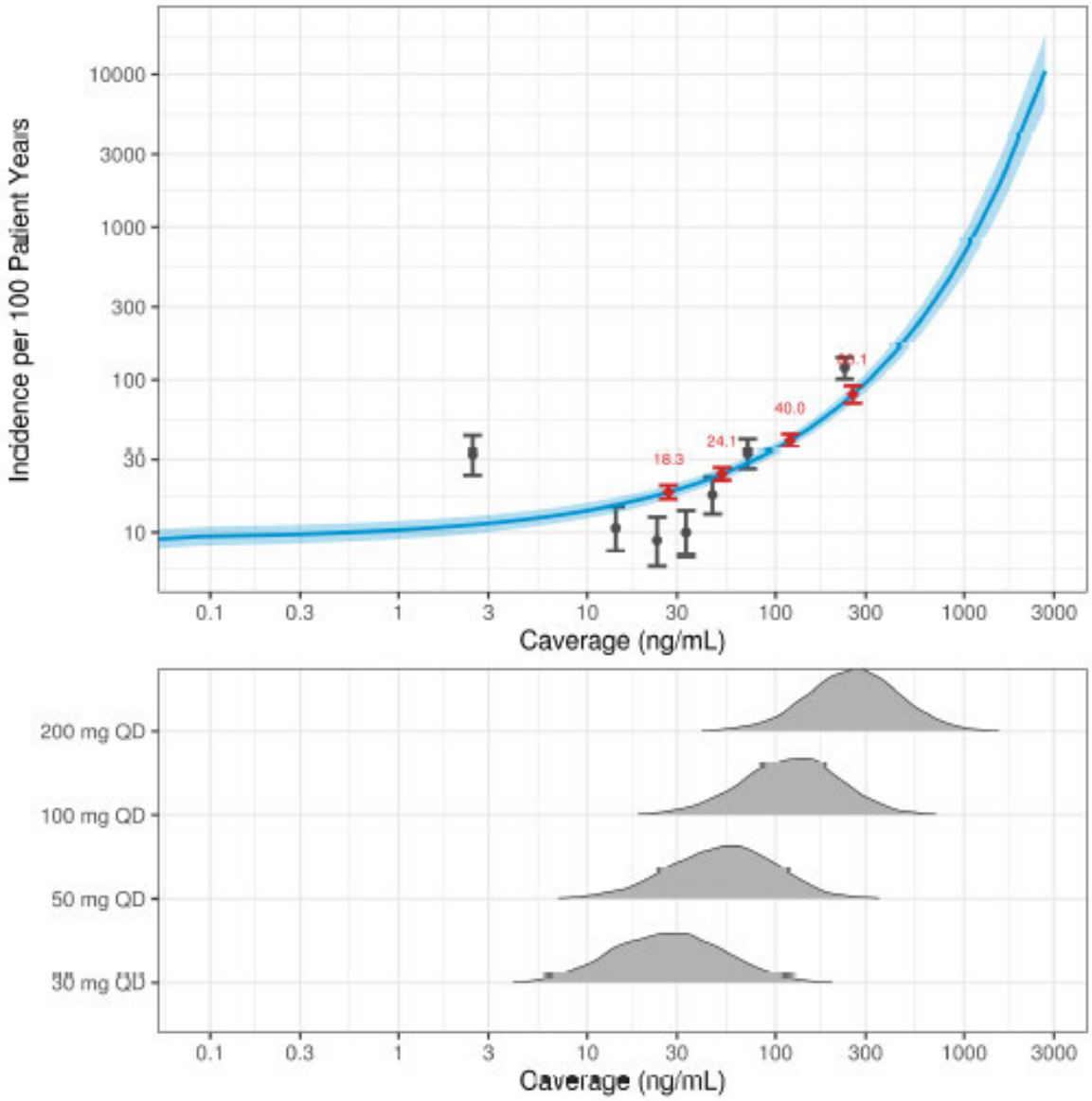
Source: Figure 5, PMAR-EQDD-B798d-DP4-1306-Amendment-1

Covariates were evaluated on the intercept (baseline incidence) only. The effect of age (as a continuous relationship) was the only covariate that established statistical significance.

Rash: Exposure-Response Analysis

The base model incorporated a square-root transformation for the effect of time-weighted Cave on slope. The 95% CI for the
estimate of slope does not include zero, suggesting a statistically significant exposure-response relationship was observed. Patient type (HV vs. AA vs. vitiligo), geographical location in Asia, age (as a continuous relationship referenced to 35 years), and female sex were identified as statistically significant covariates on the baseline incidence of rash.

Figure 24: Incidence of Rash per 100 Patient Years Over Range of Time-Weighted Observed Caverage

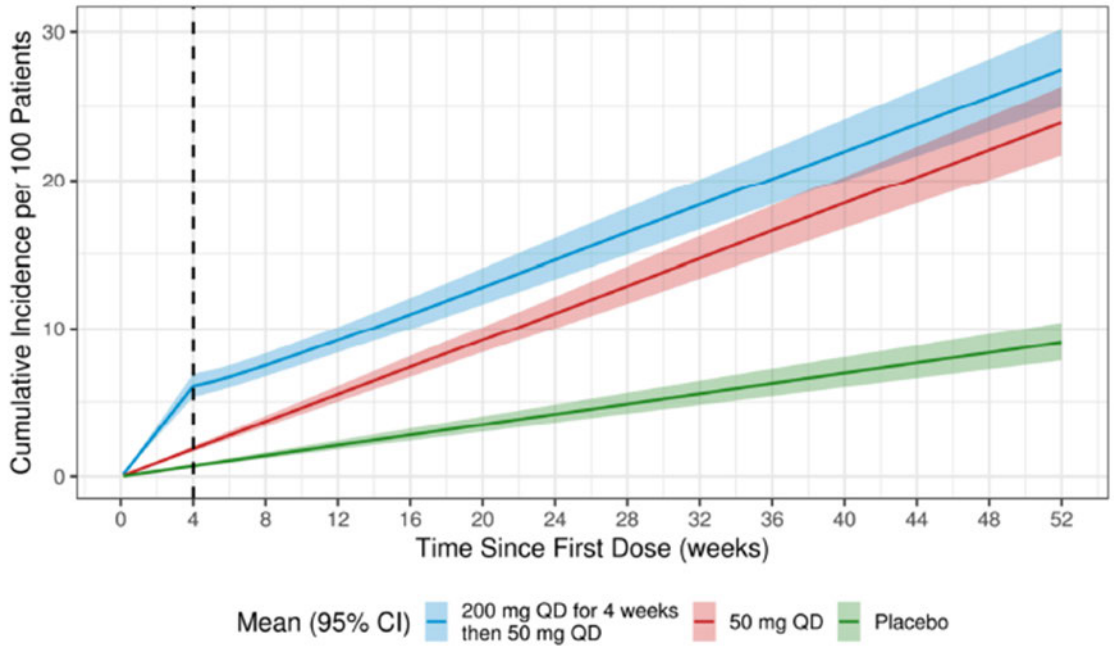


Repository artifact ID FI-29771758.

Top: Gray circles and error bars are the observed mean and 95% CI, respectively, of the incidence of rash (all types) per 100 patient years for each bin of C_{ave} in the analysis population (n = 7). The blue line, (and blue shaded area) are the model-predicted mean (and 95% CI) incidence per 100 patient years for the range of observed C_{ave} in the analysis population. Red circles and error bars are the model-predicted mean and 95% CI, respectively, incidence of rash per 100 patients years at the geometric mean steady-state C_{ave} for 30 mg, 50 mg, 100 mg, and 200 mg QD. *Bottom*: Gray distributions represent the predicted distribution of steady-state C_{ave} for 10,000 AA patients chronically administered 30 mg, 50 mg, 100 mg, and 200 mg QD with randomly drawn random effect parameters for CL/F and Vc/F as described by the final population PK model [2] and body weights sampled from those observed in B7981015.

Source: Figure 6, PMAR-EQDD-B798d-DP4-1306-Amendment-1

Figure 25: Predicted Cumulative Incidence of Rash per 100 Patients Over Time



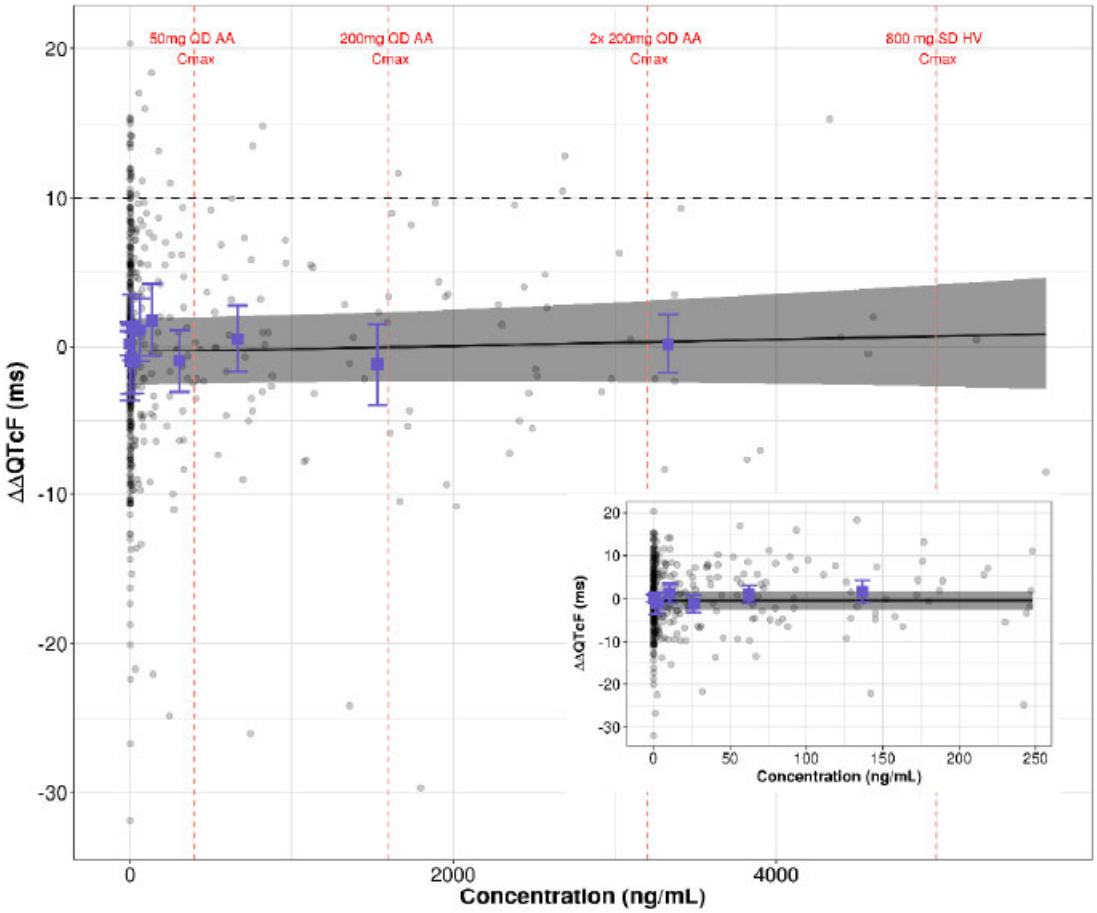
Solid lines and shaded areas are the model-predicted mean and 95% CI, respectively, cumulative incidence of rash occurring over time for the following dosing regimens; 200 mg QD for 4 weeks then 50 mg QD (blue) and 50 mg QD (red) for 52 weeks of continuous treatment. The vertical dashed line represents the conclusion of the 200 mg QD loading dose at Week 4. The cumulative incidence of rash is calculated as the incidence of events occurring at each time per 100 patients. Predicted time-weighted C_{ave} for each dosing regimen is based on the population-typical profile for an AA patient with body weight 70 kg using the final population PK model [2].

Source: Figure 7, PMAR-EQDD-B798d-DP4-1306-Amendment-1

The greatest difference in the cumulative incidence per 100 patients for rash with the 200 mg QD for 4 weeks then 50 mg QD regimen occurred at the end of loading dose period (Week 4) compared to the 50 mg QD flag-dosing regimen. The higher cumulative incidence per 100 patients associated with the period of 200 mg QD concentration persists over time.

19.4.21 Concentration QT/QTc Analysis and Prediction at Supratherapeutic Concentration
A prespecified linear mixed effect (LME) model was fitted to the SAD period data from Study B7981001. The model-predicted mean ΔΔQTcF values with their 90% CI across the entire studied concentration range are shown in Figure 26. The upper bounds of 90% CI for ΔΔQTcF estimates across the entire concentration range were all below 10 msec. The ΔΔQTcF estimates for specific concentrations of interest are summarized in Table 45. The upper bound of 90% CI for ΔΔQTcF estimate at the mean Cmax of the proposed dose of 50 mg QD was 1.98 msec. The upper bound of 90% CI for ΔΔQTcF estimate at supratherapeutic concentration (2-fold of 200 mg QD; 200 mg is highest dose studied in pivotal Phase 3 study) was 3.06 msec, and at the highest concentration after 800 mg SD (12.5-fold of mean Cmax at 50 mg QD) was 4.13 msec, which are all below 10 msec. Hence, it can be concluded that there are no clinically relevant effect for the proposed dose on the QTc interval.

Figure 26: QTcF Versus Concentration Plot



Source: PMAR-EQDD-B798d-Regulatory Response-1087 Figure S2.

Source:

Table 45: Model-Derived **ΔΔQTcF** Prediction at Specific Doses of Interest and Associated Cmax Values

Dose	Cmax (ng/mL)	Mean ΔΔQTcF (90% CI) (ms)
50mg QD AA	397.6	-0.27 (-2.51 - 1.98)
200mg QD AA	1601	-0.01 (-2.35 - 2.32)
2x 200mg QD AA	3202	0.33 (-2.4 - 3.06)
800 mg SD HV	4990	0.71 (-2.71 - 4.13)

Source: Table S1, PMAR-EQDD-B798d-Regulatory Response-1087
AA: Alopecia Areata, HV: Healthy volunteer

19.4.22 In Vitro Studies Using Human Biomaterials

Absorption

Ritlecitinib showed high apparent passive permeability and was a substrate for P-gp and BCRP (PF-06651600_15Jul19_063458, 18PFIZP1R1S1). Oral absorption of ritlecitinib was determined to be ~89% in humans and dose normalized Cmax was independent of dose within the range of 5 to 800 mg, collectively indicated insignificant impact of intestinal P-gp or BCRP efflux.

Distribution

The unbound fraction (fu) of ritlecitinib, and M2 are 0.86, and 0.95, respectively (PF-06651600_22May14_154304, and YDP/067/368). The partitioning of 1 μM of ritlecitinib, and M2 between red blood cells and plasma was investigated in human whole blood, with respective B/P ratios of 1.62, and 0.68 (YDP/067/018, and YDP/067/369).

Metabolism

CYP-Mediated Interactions

In vitro, ritlecitinib was not a significant competitive inhibitor of CYP enzymes. Ritlecitinib showed in vitro TDI versus CYP3A and CYP1A2. Ritlecitinib exhibited a potential to induce CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19. M2, a major inactive metabolite, was not a significant competitive inhibitor of CYP enzymes. M2 did not exhibit in vitro TDI versus CYP3A and CYP1A2 or other CYPs, and did not exhibit a potential to induce CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19. Clinical DDI studies were therefore conducted with midazolam, caffeine, efavirenz and tolbutamide as victim drugs. Both midazolam and caffeine showed increases in AUCinf and Cmax, indicating a net inhibition effect of ritlecitinib on CYP3A and CYP1A2. Ritlecitinib showed no effect on the exposure of efavirenz and tolbutamide indicating no clinically meaningful induction of CYP2B6 and CYP2C enzymes. Clinical DDI study results with ethinyl estradiol and levonorgestrel as victims indicated no significant net interaction with 50 mg QD ritlecitinib which is the proposed dose.

Table 46: Summary of Ritlecitinib and M2 In Vitro CYP Drug Interaction Studies

Studies	Concentration (μM)	Results	Study No.
Ritlecitinib CYP inhibition	0.1-100	1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5[a] reversible inhibition IC50 values >100 μM	XT135092
M2 CYP inhibition	0.01-100 or 0.00965-96.5	1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5 reversible inhibition IC50 values ≥96.5 μM	PF-07034562_18Feb21_111635
Ritlecitinib TDI of CYP3A4/5 (Midazolam)	3-200	k_{inact}/K_I = 0.871 mL/(min μmol)	PF-06651600_14Feb14_121415
Ritlecitinib TDI of CYP1A2 (Phenacetin)	30-600	K_I = 327 μM k_{inact} = 0.0917/min k_{inact}/K_I = 0.280 mL/(min μmol)	PF-06651600_04Feb20_123341
Ritlecitinib CYP induction	0.5-100	>2-fold induction of mRNA: 3A4 (≥5 μM), 2B6 (≥50 μM)	XT133107
Ritlecitinib CYP induction	0.3-100	>2-fold induction of mRNA: 3A4 (≥6 μM), 1A2 (≥3 μM), 2C8 (≥3 μM), 2C9 (≥10 μM), 2C19 (≥30 μM)	PF-06651600_28Aug20_022301
M2 CYP induction	0.3-250	No induction observed for 3A4, 2B6, or 1A2	PF-06651600_30Sep20_090107

a. IC50 = 90 μM for the CYP3A4/5 probe substrate testosterone.

Source: Table 6, Summary-Clin-Pharm

UGT-, GST-, and SULT-Mediated Interactions

In vitro, ritlecitinib and M2 were not significant inhibitors of the major UGT enzymes. Ritlecitinib did not significantly inhibit SULT or GST enzymes.

Table 47: Summary of Ritlecitinib and M2 in Vitro UGT, GST, and SULT Drug Interaction Studies

Studies	Concentration (μM)	Noteworthy Results	Study No.
Ritlecitinib UGT inhibition	1-100	(−2% BSA) reversible inhibition IC50: 1A1 (54 μM), 1A4 (81 μM), 1A6, 1A9, 2B7 (>100 μM) (+2% BSA) reversible inhibition unbound IC50: 1A4 (82 μM), 1A1, 1A6, 1A9, 2B7 (>100 μM)	PF-06651600_19Aug14_135124
M2 UGT inhibition	0.967-96.5	1A1, 1A4, 1A6, 1A9, 2B7, 2B15 reversible inhibition IC50 values >96.5 μM with and without 2% BSA	PF-07034562_09Mar21_034526
Preliminary ritlecitinib GST inhibition	300	Competitive inhibition <25% for all GSTs TDI of GSTs between 4 and 37%	PF-06651600_14Nov19_094951
Ritlecitinib SULT inhibition	0.1-100	1E1, 1A1, 2A1 reversible inhibition IC50 values >100 μM	PF-06651600_06May19_111809

Source: Table 7, Summary-Clin-Pharm

Transporter-Mediated Interactions

In vitro, ritlecitinib was not a substrate for OATP1B1 or OATP1B3. Ritlecitinib did not inhibit P-gp and BSEP, but inhibited BCRP, MATE1, MATE2K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2. M2 inhibited P-gp, BCRP, OATP1B1, OATP1B3, and OCT1. Clinical results showed ritlecitinib increased sumatriptan exposure (OCT1 probe substrate), but not that of rosuvastatin (BCRP, OAT3, OATP1B1/1B3 probe substrate).

Table 48: In Vitro Transporter Study Results of Ritlecitinib and M2

Substrate	Study No. and Transporter	Substrate (Yes / No)
Ritlecitinib	PF-06651600_15Jul19_063458 P-gp (0.3, 1, and 3 µM)	Yes
	18PFIZP1R1S1 BCRP (0.5 and 2 µM)	Yes
	PF-06651600_01Nov17_090524 OATP1B1 / 1B3 (0.1, 1, and 10 µM)	No
Inhibitor	**Study Number and Transporter**	**Inhibition IC_{50} (µM)**
Ritlecitinib	PF-06651600_27Jul15_103701	
	P-gp	>300
	OCT2	55.2
	MATE1	51.4
	MATE2K	48.3
	OATP1B1	>300
	OATP1B3	>300
	PF-06651600_28Nov17_101345	
	BCRP	27.0
	OAT1	156
	OAT3	41.3
	OATP1B1	312
	OATP1B3	934
	OCT1	3.74
	Pfizer-76-09Jan2018	
	BSEP	>200
M2	PF-07034562_16Feb21_073254	
	BCRP	5.6
	MDR1/P-gp	44.1
	OATP1B1	2.0
	OATP1B3	8.4
	OCT1	0.86
	OAT1	>300
	OAT3	>300
	OCT2	>300
	MATE1	>300
	MATE2K	>300

Source: Table 8, Summary-Clin-Pharm

19.4.22 Pharmcogenomics
In *GSTM1/GSTT1/GSTP1* Genotypes and Ritlecitinib PK

Ritlecitinib metabolism is mediated by multiple isoforms of Glutathione S-transferase (GST: cytosolic GST A1/3, M1/3/5, P1, S1, T2, Z1 and microsomal Membrane Associated Proteins involved in Eicosanoid and Glutathione metabolism [MAPEG]1/2/3) and CYP enzymes (CYP3A, CYP2C8, CYP1A2, and CYP2C9), with no single clearance route contributing more than 25%. In study B7981001, the sponsor conducted a study to evaluate the impact of *GSTP1*, *GSTM1*, and *GSTT1* genotypes on the pharmacokinetics of ritlecitinib from doses between 5 mg and 200 mg.

DNA was extracted from 59 whole blood samples. For *GSTP1*, genotyping was performed for two SNPs for *GSTP1* (rs1695 and rs1138272) using commercially available TaqMan® assays (Thermo Fisher Scientific). For *GSTM1* and *GSTT1*, the copy number was determined using commercially available CNV TaqMan® assays (Thermo Fisher) with RNaseP as the reference assay and analyzed on a QuantStudio 12K Flex Real-Time PCR System. For *GSTM1/GSTT1*, genotypes were called as either "0" for the absence of the gene or "One or more" for the presence of the gene. For *GSTP1*, the two common functional variants rs1695 (Ile105Val) and rs1138272 (Ala114Val) were genotyped and four haplotypes were inferred based on those two SNPs, including the wild-type GSTP1*A (Ile105 + Ala114), and three variant haplotype GSTP1*B (Val105 + Ala114), GSTP1*C (Val105 + Val114) and GSTP1*D (Ile105 +Val114) (Holley et al, 2007).

Compared with wild type, genotypic variation in *GSTM1*, *GSTT1* and *GSTP1* composite genotypes did not have a substantial impact on Cmax (Table 49) or AUC of ritilecitinib (Table 49: Summary Statistics of Dose Normalized C_{max} Values of Ritlecitinib by GST Composite Genotype.50). However, small sample size used in this analysis limited the study power to detect small differences in PK of ritlecitinib for those genetic variations. Analysis of differences across individual genotype groups for each gene also did not have a significant effect on either Cmax or AUC (not shown).

Table 49: Summary Statistics of Dose Normalized C_{max} Values of Ritlecitinib by GST Composite Genotype.

GST Genotype	C_{max} / Dose (ng/mL/mg) Mean	SD	N
P1 *A/*A; M1 √; T1 √ (Wild-type)	6.2	1.6	9
P1 *A/*A; M1 *0; T1 √	5.0	2.2	9
P1 *A/*A; M1 √; T1 *0	5.3	NC	1
P1 *A/*B; M1 √; T1 √	5.5	1.4	3
P1 *A/*B; M1 *0; T1 √	6.5	2.8	9
P1 *A/*B; M1 √; T1 *0	5.5	NC	2
P1 *B/*B; M1 *0; T1 √	8.5	2.3	3
P1 *B/*C; M1 √; T1 √	7.8	1.0	3
P1 *B/*C; M1 *0; T1 √	7.8	NC	2

Source: Table 1 in PF-06651600_16Oct19_073830. C_{max} = Maximum concentration; N = Number; NC = Not calculated; SD = Standard deviation. GST = Glutathione-S-transferase.

Table 50: Summary Statistics of Dose Normalized AUC Values of Ritlecitinib by GST Composite Genotype.

GST Genotype	AUC / Dose (ng*hr/mL/mg) Mean	SD	N
P1 *A/*A; M1 √; T1 √ (Wild-type)	12.4	5.4	9
P1 *A/*A; M1 *0; T1 √	9.7	4.3	9
P1 *A/*A; M1 √; T1 *0	12.0	NC	1
P1 *A/*B; M1 √; T1 √	8.8	2.6	3
P1 *A/*B; M1 *0; T1 √	12.1	4.9	9
P1 *A/*B; M1 √; T1 *0	12.2	NC	2
P1 *B/*B; M1 *0; T1 √	17.7	9.5	3
P1 *B/*C; M1 √; T1 √	11.3	1.8	3
P1 *B/*C; M1 *0; T1 √	16.1	NC	2

Source: Sponsor's Table 2 in PF-06651600_16Oct19_073830. AUC_{inf} and AUC 24 were measured. AUC= Area Under the Curve; N = Number; NC = Not calculated; SD = Standard deviation; AUC_{inf} = Area under the concentration-time curve from time 0 to infinite time; AUC_{24} = Area under the concentration-time curve from time 0-24 hours; GST = Glutathione-S-transferase.

Reference:
Holley SL, Fryer AA, Haycock JW, Grubb SE, Strange RC, Hoban PR. Differential effects of glutathione S-transferase pi (GSTP1) haplotypes on cell proliferation and apoptosis. Carcinogenesis. 2007 Nov;28(11):2268-73. doi: 10.1093/carcin/bgm135. Epub 2007 Jun 8. PMID: 17557902

19.4.23 Summary of Bioanalytical Methods

Bioanalytical methods using LC-MS/MS were developed and validated for the measurement of ritlecitinib concentrations in plasma and urine. LC-MS/MS methods for the determination of ritlecitinib concentrations in plasma (B7989001) and urine (B7989002) were developed and validated at (b) (4) These methods were used in the FIH study B7981001. The validated plasma method was transferred to (b) (4) (formerly (b) (4) (b) (4) with the LLOQ raised from 0.5 ng/mL to 1 ng/mL. The modified plasma method (B7989003) was fully validated at (b) (4) A cross validation was successfully completed confirming the equivalency of the two plasma methods (B7989001 and B7989003). An additional plasma method (B7989006) was fully validated at (b) (4) with quantitative range increased from 1 to 1000 ng/mL (B7989003) to 3 to 3000 ng/mL. A UPLC + AMS method (B7989007) to measure [14C]-ritlecitinib in plasma was qualified at TNO (Zeist, The Netherlands). A "fit for purpose" analytical method for the determination of M2 metabolite (PF-07034562) in plasma was qualified at (b) (4) and used to assess metabolite coverage.

All clinical samples were analyzed within the established stability period of the analytes, except for 3 samples in study B7981005. ISR assessments were conducted and met the acceptance criteria for all analytes in all studies listed in the above-mentioned tables. The performance and validation parameters of the analytical methods are summarized in Table 51-57.

Table 51. Summary of Method Performance B7989001

Bioanalytical method validation report name, amendments and hyperlinks	**B7989001 Validation Report for PF-06651600 in Human Plasma** **B7989001 Validation Report for PF-06651600 in Human Plasma Addendum 1**		
Method description	Protein precipitation followed by HPLC-MS/MS detection		
Materials used for standard calibration curve and concentration	PF-06651600 in solid form		
Validated assay range	0.5-1000 ng/mL for PF-06651600		
Material used for QCs and concentration	PF-06651600 in solid form		
Minimum required dilutions (MRDs)	NA		
Source and lot of reagents	Reference drug: PF-06651600-25 (malonate salt) Lot number: GR08117 Reference drug: PF-06651600-15 (tosylate salt) Lot number: E010016319 Internal standard: PF-06799324 (PF-06651600-d3) Lot number: CP1-2014-PF-FTE-023A3		
Regression model and weighting	Quadratic, weighted 1/x		
Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs[a]	Number of standard calibrators from LLOQ to ULOQ	8	B7989001 Validation Report Table 4 B7989001 Validation Report Addendum 1 Table 17
	Cumulative accuracy (%bias)[b] from LLOQ to ULOQ	-5.2% to 6.0% (malonate salt)	B7989001 Validation Report Table 4

		-3.4% to 5.2% (tosylate salt)	B7989001 Validation Report Addendum 1 Table 17

Table 51. Summary of Method Performance B7989001

Bioanalytical method validation report name, amendments and hyperlinks	**B7989001 Validation Report for PF-06651600 in Human Plasma** **B7989001 Validation Report for PF-06651600 in Human Plasma Addendum 1**		
	Cumulative precision (%CV) from LLOQ to ULOQ	≤8.7% (malonate salt) ≤10.5% (tosylate salt)	B7989001 Validation Report Table 4 B7989001 Validation Report Addendum 1 Table 17
Performance of QCs during accuracy and precision runs[a]	Cumulative accuracy (%bias)[b] in 5 QCs (LLOQ, QCL, QCM, QCH, and DilQC)	-4.8% to 0.9% (malonate salt; no DilQC) 3.0% (malonate salt; intra-run for DilQC) -6.8% to 1.3% (tosylate salt; QCL, QCM, QCH only)	B7989001 Validation Report Table 8 B7989001 Validation Report Table 10 B7989001 Validation Report Addendum 1 Table 19

Table 51. Summary of Method Performance B7989001

Bioanalytical method validation report name, amendments and hyperlinks	**B7989001 Validation Report for PF-06651600 in Human Plasma** **B7989001 Validation Report for PF-06651600 in Human Plasma Addendum 1**		
	Inter-batch %CV	≤13.6% (malonate salt; no DilQC) 1.7% (malonate salt; intra-run for DilQC) ≤10.8% (tosylate salt; QCL, QCM, QCH only)	B7989001 Validation Report Table 8 B7989001 Validation Report Table 10 B7989001 Validation Report Addendum 1 Table 19
	Total Error (TE)	NA	NA
Selectivity and matrix effect	Selectivity: interference (relative to LLOQ standard) with analyte and internal standard met acceptance criteria in 10 of 10 normal human plasma lots. Matrix Factor: 1.05 (QCL) and 0.99 (QCH), mean IS-normalized across 10 normal human plasma lots	B7989001 Validation Report Table 12 B7989001 Validation Report Table 11	

Table 51. Summary of Method Performance B7989001

Bioanalytical method validation report name, amendments and hyperlinks	**B7989001 Validation Report for PF-06651600 in Human Plasma** **B7989001 Validation Report for PF-06651600 in Human Plasma Addendum 1**	
Interference and specificity	No interference with analyte by IS Minimal (0.8%) interference with IS by analyte at ULOQ (1000 ng/mL) Evaluation of interference with PF-06651600 from rifampin and 25-desacetyl rifampin met acceptance criteria Evaluation of interference with PF-06651600 from caffeine and PF-07034562 (the M2 metabolite of PF-06651600) met acceptance criteria	B7989001 Validation Report Table 12 B7989001 Validation Report Table 13 B7981026 Bioanalytical Study Report Table 5 and Table 6 B7981054 Bioanalytical Study Report Table 9 and Table 10
Hemolysis effect	Matrix Factor: 1.00 and 1.01 (QCL), 1.03 and 1.03 (QCH), mean IS-normalized for 2 human plasma lots	B7989001 Validation Report Table 15
Lipemic effect	Matrix Factor: 1.02 and 1.05 (QCL), 1.00 and 1.01 (QCH), mean IS-normalized for 2 human plasma lots	B7989001 Validation Report Table 14
Dilution linearity and hook effect	NA	NA
Bench-top/process stability	Malonate salt: Bench-top plasma stability = 6 hours Refrigerated plasma stability = 24 hours Process (extract) stability = 36 hours at 4°C Tosylate salt: Bench-top plasma stability = 6 hours Refrigerated plasma stability = 24 hours Process (extract) stability = not assessed; considered equivalent to stability established for malonate salt	B7989001 Validation Report Table 18, Table 19, and Table 24 B7989001 Validation Report Addendum 1 Table 20 and Table 21

Freeze-thaw stability	5 cycles at -20°C and -80°C to +4°C (malonate and tosylate salts)	B7989001 Validation Report Table 21 and Table 22 (malonate salt) B7989001 Validation Report Addendum 1 Table 22 and Table 23 (tosylate salt)

Table 51. Summary of Method Performance B7989001

Bioanalytical method validation report name, amendments and hyperlinks	**B7989001 Validation Report for PF-06651600 in Human Plasma** **B7989001 Validation Report for PF-06651600 in Human Plasma Addendum 1**	
Long-term stability	184 days at -20°C and 392 days at -80°C (malonate salt) 222 days at -20°C and at -80°C (tosylate salt)	B7989001 Validation Report Addendum 1 Table 8 and Table 12 (malonate salt) B7989001 Validation Report Addendum 1 Table 29, Table 30, and Table 31 (tosylate salt)
Parallelism	NA	NA
Carryover	Carryover within acceptable limits for analyte (malonate salt) and for internal standard in 11 of 11 runs. Carryover within acceptable limits for analyte (malonate salt) in 2 of 4 runs and for internal standard in 4 of 4 runs. Carryover within acceptable limits for analyte (tosylate salt) in 5 of 6 runs and for internal standard in 6 of 6 runs.	B7989001 Validation Report Validation Summary--Selectivity (page 7) and Table 26 B7989001 Validation Report Addendum 1 Methodology Comments (page 7) and Table 13 B7989001 Validation Report Addendum 1 Methodology Comments (page 7) and Table 32
Method performance in Study B7981001, B7981001 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	100% (37 of 37) of runs passed	B7981001 Bioanalytical Study Report: Section 2. Report Summary (page 2), and Table 1
Standard curve performance	Cumulative bias[b] range: -3.8% to 6.2% Cumulative precision: ≤8.0% CV	B7981001 Bioanalytical Study Report Table 5
QC performance	Cumulative bias[b] range: -5.4% to -0.7% Cumulative precision: ≤8.7% CV TE: NA	B7981001 Bioanalytical Study Report Table 6
Method reproducibility	Incurred sample re-analysis was performed in ~9.2% (111/1207) of analyzed study samples, and 92.8% of the repeats met the pre-specified criteria. (Since >1000 samples were analyzed, 100 samples plus ≥5% of the excess number of analyzed samples over 1000 were selected for ISR.)	B7981001 Bioanalytical Study Report Section 2. Report Summary (page 2) and Table 7

Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -80°C. Study samples were analyzed within the 392 days (malonate salt) of established frozen plasma stability.	B7981001 Bioanalytical Study Report Section 6. Calibration Standard and Quality Control (QC) Preparation and Section 7. Study Samples Source and Storage

Table 51. Summary of Method Performance B7989001

Bioanalytical method validation report name, amendments and hyperlinks	**B7989001 Validation Report for PF-06651600 in Human Plasma** **B7989001 Validation Report for PF-06651600 in Human Plasma Addendum 1**	
Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981003, B7981003 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	100% (13 of 13) of runs passed	B7981003 Bioanalytical Study Report Section 2. Report Summary (page 2) and Table 1
Standard curve performance	Cumulative bias[b] range: -3.0% to 2.2% Cumulative precision: ≤9.6% CV	B7981003 Bioanalytical Study Report Table 5
QC performance	Cumulative bias[b] range: -2.8% to 7.0% Cumulative precision: ≤8.0% CV TE: NA	B7981003 Bioanalytical Study Report Table 6
Method reproducibility	Incurred sample re-analysis was performed in ~10.9% (52/477) of analyzed study samples, and 98.1% of the repeats met the pre-specified criteria.	B7981003 Bioanalytical Study Report Section 2. Report Summary (page 2) and Table 7
Study sample analysis/ stability	Calibration standards were prepared fresh on day of analysis. QCs and study samples were stored at -80°C. Study samples were analyzed within the 392 days (malonate salt) or 222 days (tosylate salt) of established frozen plasma stability.	B7981003 Bioanalytical Study Report Section 6. Calibration Standard and Quality Control (QC) Preparation and Section 7. Study Samples: Source and Storage
Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981011, B7981011 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	100% (4 of 4) of sample analysis runs passed	B7981011 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[b] range: -1.8% to 2.0% Cumulative precision: ≤6.4% CV	B7981011 Bioanalytical Study Report Table 3

QC performance	Cumulative bias[b] range: -2.0% to 1.5% Cumulative precision: ≤3.6% CV TE: NA	B7981011 Bioanalytical Study Report Table 5

Table 51. Summary of Method Performance B7989001

Bioanalytical method validation report name, amendments and hyperlinks	**B7989001 Validation Report for PF-06651600 in Human Plasma** **B7989001 Validation Report for PF-06651600 in Human Plasma Addendum 1**	
Method reproducibility	Incurred sample re-analysis was performed in ~11.3% (21/186) of analyzed study samples, and 100% of the repeats met the pre-specified criteria.	B7981011 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 7
Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -80°C. Study samples were analyzed within the 222 days (tosylate salt) of established frozen plasma stability.	B7981011 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.1 Calibration Standard Preparation, and Section 8.2 Quality Control Sample Preparation
Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981020, B7981020 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	66.7% (2 of 3) of sample analysis runs passed	B7981020 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[b] range: -1.8% to 2.2% Cumulative precision: ≤6.3% CV	B7981020 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[b] range: -2.0% to 4.3% Cumulative precision: ≤5.7% CV TE: NA	B7981020 Bioanalytical Study Report Table 5
Method reproducibility	Incurred sample re-analysis was performed in ~9.6% (10/104) of analyzed study samples, and 100% of the repeats met the pre-specified criteria.	B7981020 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 7
Study sample analysis/ stability	Calibration standards and QCs were stored at -20°C, and study samples were stored at -80°C. Study samples were analyzed within the 222 days (tosylate salt) of established frozen plasma stability.	B7981020 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.2 Calibration Standard Preparation, and Section 8.3 Quality Control Sample Preparation

Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981026, B7981026 Bioanalytical Study Report for PF-06651600 in Human Plasma		

Table 51. Summary of Method Performance B7989001

Bioanalytical method validation report name, amendments and hyperlinks	**B7989001 Validation Report for PF-06651600 in Human Plasma** **B7989001 Validation Report for PF-06651600 in Human Plasma Addendum 1**	
Assay passing rate	87.5% (7 of 8) of sample analysis runs passed	B7981026 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[b] range: -10.8% to 6.0% Cumulative precision: ≤6.7% CV	B7981026 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[b] range: 0.7% to 10.5% Cumulative precision: ≤3.7% CV TE: NA	B7981026 Bioanalytical Study Report Table 4
Method reproducibility	Incurred sample re-analysis was performed in ~10.4% (30/288) of analyzed study samples, and 100% of the repeats met the pre-specified criteria.	B7981026 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 7
Study sample analysis/ stability	Calibration standards and QCs were stored at -20°C, and study samples were stored at -80°C. Study samples were analyzed within the 222 days (tosylate salt) of established frozen plasma stability.	B7981026 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.2 Calibration Standard Preparation, and Section 8.3 Quality Control Sample Preparation
Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981030, B7981030 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	100% (13 of 13) of sample analysis runs passed	B7981030 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[b] range: -1.4% to 1.0% Cumulative precision: ≤4.6% CV	B7981030 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[b] range: -0.8% to 1.1% Cumulative precision: ≤3.1% CV TE: NA	B7981030 Bioanalytical Study Report Table 4
Method reproducibility	Incurred sample re-analysis was performed in ~10.3% (48/468) of analyzed study samples, and 97.9% of the repeats met the pre-specified criteria.	B7981030 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 5

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Table 51. Summary of Method Performance B7989001

Bioanalytical method validation report name, amendments and hyperlinks	**B7989001 Validation Report for PF-06651600 in Human Plasma** **B7989001 Validation Report for PF-06651600 in Human Plasma Addendum 1**	
Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -20°C. Study samples were analyzed within the 222 days (tosylate salt) of established frozen plasma stability.	B7981030 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.2 Calibration Standard Preparation, and Section 8.3 Quality Control Sample Preparation
Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981054, B7981054 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	100% (5 of 5) of sample analysis runs passed	B7981054 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[b] range: -1.0% to 1.8% Cumulative precision: ≤6.2% CV Includes sample analysis and selectivity runs	B7981054 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[b] range: -0.4% to 6.7% Cumulative precision: ≤5.0% CV TE: NA Includes sample analysis and selectivity runs	B7981054 Bioanalytical Study Report Table 5
Method reproducibility	Incurred sample re-analysis was performed in ~11.1% (24/216) of analyzed study samples, and 100% of the repeats met the pre-specified criteria.	B7981054 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 7
Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -80°C. Study samples were analyzed within the 222 days (tosylate salt) of established frozen plasma stability.	B7981054 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.2 Calibration Standard Preparation, and Section 8.3 Quality Control Sample Preparation

Standard calibration curve performance during accuracy and precision runs	NA	NA

Table 51. Summary of Method Performance B7989001

Bioanalytical method validation report name, amendments and hyperlinks	B7989001 Validation Report for PF-06651600 in Human Plasma B7989001 Validation Report for PF-06651600 in Human Plasma Addendum 1

a. Includes all validation runs.
b. %Bias is reported as %RE in the report.

Table 52. Summary of Method Performance B7989002

Bioanalytical method validation report name, amendments and hyperlinks	**B7989002 Validation Report for PF-06651600 in Human Urine**	
Method description	Sample dilution followed by HPLC-MS/MS detection	
Materials used for standard calibration curve and concentration	PF-06651600 in solid form	
Validated assay range	1-2000 ng/mL for PF-06651600	
Material used for QCs and concentration	PF-06651600 in solid form	
Minimum required dilutions (MRDs)	NA	
Source and lot of reagents	Reference drug: PF-06651600-25 (malonate salt) Lot number: GR08117 Internal standard: PF-06799324 (PF-06651600-d3) Lot number: CP1-2014-PF-FTE-023A3	
Regression model and weighting	Quadratic, weighted 1/x	
Validation parameters	Method validation summary	Source location

Standard calibration curve performance during accuracy and precision runs[a]	Number of standard calibrators from LLOQ to ULOQ	8	B7989002 Validation Report Table 5
	Cumulative accuracy (%bias)[b] from LLOQ to ULOQ	-2.0% to 2.0%	B7989002 Validation Report Table 5
	Cumulative precision (%CV) from LLOQ to ULOQ	≤7.9%	B7989002 Validation Report Table 5

Table 52. Summary of Method Performance B7989002

Bioanalytical method validation report name, amendments and hyperlinks	**B7989002 Validation Report for PF-06651600 in Human Urine**		
Performance of QCs during accuracy and precision runs[a]	Cumulative accuracy (%bias)[b] in 5 QCs (LLOQ, QCL, QCM, QCH, and DilQC)	-4.4% to 11.0% (no DilQC) -10.6% to -2.3% (intra-run for DilQC)	B7989002 Validation Report Table 9
	Inter-batch %CV	≤12.5% (no Dil QC) ≤2.9% (intra-run for DilQC)	B7989002 Validation Report Table 9
	Total Error (TE)	NA	NA
Selectivity and matrix effect	Selectivity: interference (relative to LLOQ standard) with analyte and internal standard met acceptance criteria in 10 of 10 normal human urine lots. Matrix Factor: 0.96 (QCL) and 1.01 (QCH), mean IS-normalized across 10 normal human urine lots		B7989002 Validation Report Table 13 B7989002 Validation Report Table 12
Interference and specificity	No interference with analyte by IS Minimal (0.4%) interference with IS by analyte at ULOQ (1000 ng/mL)		B7989002 Validation Report Table 13 B7989002 Validation Report Table 14

Hemolysis effect	NA	NA
Lipemic effect	NA	NA

Table 52. Summary of Method Performance B7989002

Bioanalytical method validation report name, amendments and hyperlinks	**B7989002 Validation Report for PF-06651600 in Human Urine**	
Dilution linearity and hook effect	NA	NA
Bench-top/process stability	Bench-top urine stability = 6 hours Refrigerated urine stability = 24 hours Process (extract) stability = 33 hours at +4°C	B7989002 Validation Report Table 16, Table 17, and Table 24
Freeze-thaw stability	5 cycles at -20°C and -80°C to +4°C	B7989002 Validation Report Table 22 and Table 23
Long-term stability	365 days at -20°C and at -80°C	B7989002 Validation Report Table 21
Parallelism	NA	NA
Carryover	Carryover within acceptable limits for analyte in 10 of 11 validation runs and for internal standard in 11 of 11 validation runs.	B7989002 Validation Report Validation Summary--Selectivity (page 7) and Table 26
Method performance in Study B7981001, B7981001 Bioanalytical Study Report for PF-06651600 in Human Urine and B7981001 Bioanalytical Study Report for PF-06651600 in Human Urine Amendment 1		
Assay passing rate	83.3% (10 of 12) of runs passed	B7981001 Bioanalytical Study Report Amendment 1 Section 2. Report Summary (page 2) and Table 1
Standard curve performance	Cumulative bias[b] range: -3.2% to 4.0% Cumulative precision: ≤8.2% CV	B7981001 Bioanalytical Study Report Amendment 1 Table 5
QC performance	Cumulative bias[b] range: -0.3% to 4.0% Cumulative precision: ≤12.7% CV TE: NA	B7981001 Bioanalytical Study Report Amendment 1 Table 6
Method reproducibility	Incurred sample re-analysis was performed in ~31.5% (23/73) of analyzed study samples, and 100% of the repeats met the pre-specified criteria	B7981001 Bioanalytical Study Report Amendment 1 Section 2. Report Summary (page 2) and Table 7
Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -80°C. Study samples were analyzed within the 365 days of established frozen urine stability.	B7981001 Bioanalytical Study Report Amendment 1 Section 6. Calibration Standard and Quality Control (QC) Preparation and Section 7. Study Samples: Source and Storage
Method performance in Study B7981011, B7981011 Bioanalytical Study Report for PF-06651600 in Human Urine		

Assay passing rate	100% (3 of 3) of sample analysis runs passed	B7981011 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[b] range: -1.1% to 2.0% Cumulative precision: ≤6.8% CV	B7981011 Bioanalytical Study Report Table 3

Table 52. Summary of Method Performance B7989002

Bioanalytical method validation report name, amendments and hyperlinks	**B7989002 Validation Report for PF-06651600 in Human Urine**	
QC performance	Cumulative bias[b] range: 0.0% to 7.0% Cumulative precision: ≤12.0% CV TE: NA	B7981011 Bioanalytical Study Report Table 5
Method reproducibility	Incurred sample re-analysis was performed in ~31.3% (15/48) of analyzed study samples, and 93.3% of the repeats met the pre-specified criteria.	B7981011 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 7
Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -80°C. Study samples were analyzed within the 365 days of established frozen urine stability.	B7981011 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.1 Calibration Standards, and Section 8.2 Quality Control Samples
Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981020, B7981020 Bioanalytical Study Report for PF-06651600 in Human Urine		
Assay passing rate	100% (3 of 3) sample analysis runs passed	B7981020 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[b] range: -2.0% to 4.0% Cumulative precision: ≤14.2% CV	B7981020 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[b] range: -3.6% to -1.3% Cumulative precision: ≤5.3% CV TE: NA	B7981020 Bioanalytical Study Report Table 5
Method reproducibility	Incurred sample re-analysis was performed in ~16.7% (4/24) of analyzed study samples, and 100% of the repeats met the pre-specified criteria.	B7981020 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 7
Study sample analysis/ stability	Calibration standards were stored at -20°C, and QCs and study samples were stored at -80°C. Study samples were analyzed within the 365 days of established frozen urine stability.	B7981020 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.2 Calibration Standard Preparation, and Section 8.3 Quality Control Sample Preparation

Standard calibration curve performance during accuracy and precision runs	NA	NA

Table 52. Summary of Method Performance B7989002

Bioanalytical method validation report name, amendments and hyperlinks	B7989002 Validation Report for PF-06651600 in Human Urine

a. Includes all validation runs.
b. %Bias is reported as %RE in the report.

Table 53. Summary of Method Performance B7989003

Bioanalytical method validation report name, amendments and hyperlinks	**B7989003 Validation Report for PF-06651600 in Human Plasma** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 1** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 2** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 3**	
Method description	Protein precipitation followed by HPLC-MS/MS detection	
Materials used for standard calibration curve and concentration	PF-06651600 in solid form	
Validated assay range	1-1000 ng/mL for PF-06651600	
Material used for QCs and concentration	PF-06651600 in solid form	
Minimum required dilutions (MRDs)	NA	
Source and lot of reagents	Reference drug: PF-06651600-15 (tosylate salt) Lot number: E010016319, E010018560, E010019066, 20-AP-00347 Internal standard: PF-06799324-00 (PF-06651600-d3) Lot number: PF-06799324-00-0001	
Regression model and weighting	Linear, weighted $1/x^2$	
Validation parameters	Method validation summary	Source location
	Number of standard calibrators from LLOQ to ULOQ: 8	B7989003 Validation Report Table 4

Table 53. Summary of Method Performance B7989003

Bioanalytical method validation report name, amendments and hyperlinks	**B7989003 Validation Report for PF-06651600 in Human Plasma** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 1** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 2** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 3**		
Standard calibration curve performance during accuracy and precision runs	Cumulative accuracy (%bias)[a] from LLOQ to ULOQ	-2.9% to 2.0% -2.2% to 3.5% (intra-run) -2.6% to 2.5% (intra-run)	B7989003 Validation Report Table 4 B7989003 Validation Report Addendum 1 Table 9 (single accuracy and precision run for method transfer) B7989003 Validation Report Addendum 2 Table 3 (single accuracy and precision run with new QCM)
	Cumulative precision (%CV) from LLOQ to ULOQ	≤5.0%	B7989003 Validation Report Table 4
Performance of QCs during accuracy and precision runs[b]	Cumulative accuracy (%bias) [a] in up to 6 QCs (LLOQ, QCL, QCLM, QCM, QCH, and DilQC)	-1.6% to 2.8% (no DilQC) -8.4% to -2.8% (intra-run for DilQC) -3.3% to 3.4% (intra-run) -3.0% to 2.2% (intra-run)	B7989003 Validation Report Table 6 B7989003 Validation Report Table 11 B7989003 Validation Report Addendum 1 Table 9 (single accuracy and precision run for method transfer) B7989003 Validation Report Addendum 2 Table 4 (single accuracy and precision run with new QCM)

Table 53. Summary of Method Performance B7989003

Bioanalytical method validation report name, amendments and hyperlinks	**B7989003 Validation Report for PF-06651600 in Human Plasma** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 1** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 2** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 3**		
	Inter-batch %CV	≤5.6% (no DilQC) ≤2.2% (intra-run for DilQC) ≤4.9% (intra-run) ≤6.1% (intra-run)	B7989003 Validation Report Table 6 B7989003 Validation Report Table 11 B7989003 Validation Report Addendum 1 Table 9 (single accuracy and precision run for method transfer) B7989003 Validation Report Addendum 2 Table 4 (single accuracy and precision run with new QCM)
	Total Error (TE)	NA	NA

Table 53. Summary of Method Performance B7989003

Bioanalytical method validation report name, amendments and hyperlinks	**B7989003 Validation Report for PF-06651600 in Human Plasma** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 1** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 2** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 3**	
Selectivity and matrix effect	Selectivity: interference (relative to LLOQ standard) with analyte and internal standard met acceptance criteria for 10 of 10 normal human plasma lots.	B7989003 Validation Report Validation Summary—Selectivity (page 6), Figure 8, and Figure 9
	Selectivity (Chinese plasma): interference (relative to LLOQ standard) with analyte and internal standard met acceptance criteria for 6 of 6 normal human plasma lots.	B7989003 Validation Report Addendum 3 Table 8 and Table 9
	Matrix Factor: 0.971-1.04 (QCL) and 0.995-1.02 (QCH), mean IS-normalized across 10 normal human plasma lots	B7989003 Validation Report Table 12 and Table 13
	Matrix Bridging (Chinese plasma QCs): 1 pooled plasma lot prepared from 6 individual normal human plasma lots: QCL: -1.0% bias, 3.0%CV QCH: -4.1% bias, 1.5%CV	B7989003 Validation Report Addendum 3 Table 10
Interference and specificity	No interference with analyte by IS	B7989003 Validation Report Figure 9
	Minimal (0.9%) interference with IS by analyte at ULOQ (1000 ng/mL)	B7989003 Validation Report Validation Summary—Selectivity (page 6), Figure 10
	Evaluation of interference with PF-06651600 from itraconazole and hydroxy itraconazole met acceptance criteria	B7981023 Bioanalytical Study Report Section 6.2 Assay Methodology Summary and Table 7

Hemolysis effect	Matrix Factor: 0.997 and 1.02 (QCL), 1.00 and 1.01 (QCH), mean IS-normalized for 2 human plasma lots	B7989003 Validation Report Table 12 and Table 13

Table 53. Summary of Method Performance B7989003

Bioanalytical method validation report name, amendments and hyperlinks	**B7989003 Validation Report for PF-06651600 in Human Plasma** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 1** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 2** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 3**	
Lipemic effect	Matrix Factor: 1.01 and 1.01 (QCL), 1.01 and 1.02 (QCH), mean IS-normalized for 2 human plasma lots	B7989003 Validation Report Table 12 and Table 13
Dilution linearity and hook effect	NA	NA
Bench-top/process stability	Bench-top plasma stability = 4 hours Refrigerated plasma stability = 6 hours Process (extract) stability = 190 hours at 2°C to 8°C Wet ice plasma stability = 17 hours	B7989003 Validation Report Table 21, Table 23, and Table 26 B7989003 Validation Report Addendum 1 Table 5
Freeze-thaw stability	5 cycles at -20°C and -70°C	B7989003 Validation Report Table 25
Long-term stability	58 days at -20°C 673 days at -70°C	B7989003 Validation Report Table 24 B7989003 Validation Report Addendum 1 Table 7
Parallelism	NA	NA
Carryover	Carryover within acceptable limits for analyte and internal standard.	B7989003 Validation Report Validation Summary--Selectivity (page 6)
Method performance in Study B7981005, B7981005 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	95.2% (20 of 21) of sample analysis runs passed	B7981005 Bioanalytical Study Report Section 4. Assay Performance Summary (page 9) and Table 1
Standard curve performance	Cumulative bias[a] range: -1.8% to 1.5% Cumulative precision: ≤5.2% CV	B7981005 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[a] range: -1.1% to 1.0% Cumulative precision: ≤3.8% CV TE: NA	B7981005 Bioanalytical Study Report Table 4

Table 53. Summary of Method Performance B7989003

Bioanalytical method validation report name, amendments and hyperlinks	**B7989003 Validation Report for PF-06651600 in Human Plasma** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 1** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 2** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 3**	
Method reproducibility	Incurred sample re-analysis was performed in ~7.9% (148/1882) of analyzed study samples, and 98.0% of the repeats met the pre-specified criteria. (Since >1000 samples were analyzed, 100 samples plus ≥5% of the excess number of analyzed samples over 1000 were selected for ISR.)	B7981005 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 5
Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -70°C. Three study samples were analyzed beyond the 673 days of established frozen plasma stability.	B7981005 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.2 Calibration Standard Preparation, and Section 8.3 Quality Control Sample Preparation
Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981006, B7981006 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	100% (8 of 8) of sample analysis runs passed	B7981006 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[a] range: -1.0% to 1.2% Cumulative precision: ≤6.1% CV	B7981006 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[a] range: -1.4% to 4.3% Cumulative precision: ≤5.7% CV TE: NA	B7981006 Bioanalytical Study Report Table 4
Method reproducibility	Incurred sample re-analysis was performed in ~10.0% (60/599) of analyzed study samples, and 90.0% of the repeats met the pre-specified criteria	B7981006 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 5

Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -70°C. Study samples were analyzed within the 364 days of established frozen plasma stability.	B7981006 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.1 Calibration Standards, and Section 8.2 Quality Control Samples

Table 53. Summary of Method Performance B7989003

Bioanalytical method validation report name, amendments and hyperlinks	**B7989003 Validation Report for PF-06651600 in Human Plasma** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 1** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 2** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 3**	
Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981008, B7981008 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	100% (3 of 3) of sample analysis runs passed	B7981008 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[a] range: -2.5% to 1.0% Cumulative precision: ≤6.3% CV	B7981008 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[a] range: -2.3% to 5.3% Cumulative precision: ≤4.6% CV TE: NA	B7981008 Bioanalytical Study Report Table 4
Method reproducibility	Incurred sample re-analysis was performed in ~21.9% (21/96) of analyzed study samples, and 100% of the repeats met the pre-specified criteria	B7981008 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 5
Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -70°C. Study samples were analyzed within the 224 days of established frozen plasma stability.	B7981008 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.1. Calibration Standards, and Section 8.2. Quality Control Samples
Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981016, B7981016 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	100% (3 of 3) of sample analysis runs passed	B7981016 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[a] range: -1.6% to 1.6% Cumulative precision: ≤5.0% CV	B7981016 Bioanalytical Study Report Table 3

QC performance	Cumulative bias[a] range: 0.3% to 1.0% Cumulative precision: ≤4.1% CV TE: NA	B7981016 Bioanalytical Study Report Table 4

Table 53. Summary of Method Performance B7989003

Bioanalytical method validation report name, amendments and hyperlinks	**B7989003 Validation Report for PF-06651600 in Human Plasma** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 1** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 2** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 3**	
Method reproducibility	Incurred sample re-analysis was performed in ~10.6% (24/226) of analyzed study samples, and 100% of the repeats met the pre-specified criteria	B7981016 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 5
Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -70°C. Study samples were analyzed within the 673 days of established frozen plasma stability.	B7981016 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.2. Calibration Standard Preparation, and Section 8.3. Quality Control Sample Preparation
Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981022, B7981022 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	100% (6 of 6) of sample analysis runs passed	B7981022 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[a] range: -1.5% to 1.0% Cumulative precision: ≤5.7% CV	B7981022 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[a] range: -2.5% to 1.4% Cumulative precision: ≤6.1% CV TE: NA	B7981022 Bioanalytical Study Report Table 4
Method reproducibility	Incurred sample re-analysis was performed in ~11.4% (60/528) of analyzed study samples, and 100% of the repeats met the pre-specified criteria	B7981022 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 5
Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -70°C. Study samples were analyzed within the 673 days of established frozen plasma stability.	B7981022 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.2. Calibration Standard Preparation, and Section 8.3. Quality Control Sample Preparation

Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981023, B7981023 Bioanalytical Study Report for PF-06651600 in Human Plasma		

Table 53. Summary of Method Performance B7989003

Bioanalytical method validation report name, amendments and hyperlinks	**B7989003 Validation Report for PF-06651600 in Human Plasma** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 1** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 2** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 3**	
Assay passing rate	100% (4 of 4) of runs passed	B7981023 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[a] range: -0.9% to 2.0% Cumulative precision: ≤11.1% CV	B7981023 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[a] range: -1.0% to 0.6% Cumulative precision: ≤6.6% CV TE: NA	B7981023 Bioanalytical Study Report Table 4
Method reproducibility	Incurred sample re-analysis was performed in ~10.2% (27/264) of analyzed study samples, and 100% of the repeats met the pre-specified criteria	B7981023 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 5
Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -70°C. Study samples were analyzed within the 673 days of established frozen plasma stability.	B7981023 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.2. Calibration Standards, and Section 8.3. Quality Control Samples
Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981029, B7981029 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	100% (23 of 23) of runs passed	B7981029 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[a] range: -1.6% to 2.0% Cumulative precision: ≤4.2% CV	B7981029 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[a] range: -3.3% to 1.7% Cumulative precision: ≤4.2% CV TE: NA	B7981029 Bioanalytical Study Report Table 4

Table 53. Summary of Method Performance B7989003

Bioanalytical method validation report name, amendments and hyperlinks	**B7989003 Validation Report for PF-06651600 in Human Plasma** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 1** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 2** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 3**	
Method reproducibility	Incurred sample re-analysis was performed in ~9.9% (276/2782) of analyzed study samples, and 100% of the repeats met the pre-specified criteria. (Since >1000 samples were analyzed, 100 samples plus ≥5% of the excess number of analyzed samples over 1000 were selected for ISR.)	B7981029 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 5
Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -70°C. Study samples were analyzed within the 673 days of established frozen plasma stability.	B7981029 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.2. Calibration Standard Preparation, and Section 8.3. Quality Control Sample Preparation
Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981036, B7981036 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	100% (4 of 4) of sample analysis runs passed	B7981036 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[a] range: -1.0% to 1.4% Cumulative precision: ≤6.0% CV	B7981036 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[a] range: 1.3% to 2.6% Cumulative precision: ≤3.6% CV TE: NA	B7981036 Bioanalytical Study Report Table 4
Method reproducibility	Incurred sample re-analysis was performed in ~14.8% (36/243) of analyzed study samples, and 97.2% of the repeats met the pre-specified criteria	B7981036 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 5

Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -70°C. Study samples were analyzed within the 673 days of established frozen plasma stability.	B7981036 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.2. Calibration Standard Preparation, and Section 8.3. Quality Control Sample Preparation

Table 53. Summary of Method Performance B7989003

Bioanalytical method validation report name, amendments and hyperlinks	**B7989003 Validation Report for PF-06651600 in Human Plasma** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 1** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 2** **B7989003 Validation Report for PF-06651600 in Human Plasma Addendum 3**	
Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7931005, B7931005 Bioanalytical Study Report for PF-06651600 in Human Plasma and B7931005 Bioanalytical Study Report for PF-06651600 in Human Plasma Addendum 1		
Assay passing rate	88.9% (16 of 18) of runs passed	B7931005 Bioanalytical Study Report Addendum 1 Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[a] range: -1.2% to 1.2% Cumulative precision: ≤4.4% CV	B7931005 Bioanalytical Study Report Addendum 1 Table 4
QC performance	Cumulative bias[a] range: 0.0% to 3.0% Cumulative precision: ≤6.1% CV TE: NA	B7931005 Bioanalytical Study Report Addendum 1 Table 5
Method reproducibility	Incurred sample re-analysis was performed in ~10.4% (104/1002) of analyzed study samples, and 98.1% of the repeats met the pre-specified criteria. (Since >1000 samples were analyzed, 100 samples plus ≥5% of the excess number of analyzed samples over 1000 were selected for ISR.)	B7931005 Bioanalytical Study Report Addendum 1 Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 6
Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -70°C. Study samples were analyzed within the 673 days of established frozen plasma stability.	B7931005 Bioanalytical Study Report Addendum 1 Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.1 Calibration Standards, and Section 8.2 Quality Control Samples
Standard calibration curve performance during accuracy and precision runs	NA	NA

a. %Bias is reported as %RE in the report.

b. Includes all validation runs.

Table 54. Summary of Method Performance B7989006

Bioanalytical method validation report name, amendments and hyperlinks	**B7989006 Validation Report for PF-06651600 in Human Plasma**		
Method description	Protein precipitation followed by HPLC-MS/MS detection		
Materials used for standard calibration curve and concentration	PF-06651600 in solid form		
Validated assay range	3-3000 ng/mL for PF-06651600		
Material used for QCs and concentration	PF-06651600 in solid form		
Minimum required dilutions (MRDs)	NA		
Source and lot of reagents	Reference drug: PF-06651600-15 (tosylate salt) Lot number: E010019066, 20-AP-00347 Internal standard: PF-06799324-00 (PF-06651600-d3) Lot number: PF-06799324-00-0001		
Regression model and weighting	Linear, weighted $1/x^2$		
Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs[a]	Number of standard calibrators from LLOQ to ULOQ	8	B7989006 Validation Report Table 3
	Cumulative accuracy (%bias)[b] from LLOQ to ULOQ	-2.6% to 3.0%	B7989006 Validation Report Table 3
	Cumulative precision (%CV) from LLOQ to ULOQ	≤6.0%	B7989006 Validation Report Table 3
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias)[b] in 6 QCs (LLOQ, QCL, QCLM, QCM, QCH, and DilQC)	-8.7% to –1.4% (no DilQC) -4.0% to -1.3% (intra-run for DilQC)	B7989006 Validation Report Table 4 B7989006 Validation Report Table 6
	Inter-batch %CV	≤6.3% (no DilQC)	B7989006 Validation Report Table 4

		≤2.1% (intra-run for DilQC)	B7989006 Validation Report Table 6

Table 54. Summary of Method Performance B7989006

Bioanalytical method validation report name, amendments and hyperlinks	**B7989006 Validation Report for PF-06651600 in Human Plasma**		
	Total Error (TE)	NA	NA
Selectivity and matrix effect	Selectivity: interference (relative to LLOQ standard) with analyte and internal standard met acceptance criteria for 10 of 10 normal human plasma lots. Matrix Factor: 0.999 (QCL) and 0.989 (QCH), mean IS-normalized across 10 normal human plasma lots Matrix Effect (QCs), 10 human normal plasma lots: QCL: -4.1% to 5.0% bias, ≤3.7%CV QCH: -4.6% to 2.5% bias, ≤2.6%CV	B7989006 Validation Report Table 12 and Table 13 B7989006 Validation Report Table 14 and Table 15 B7989006 Validation Report Table 20 and Table 21	
Interference and specificity	No interference with analyte by IS (200 ng/mL) Minimal (1.3%) interference with IS by analyte at ULOQ (3000 ng/mL)	B7989006 Validation Report Section 6. Summary Method Performance, Table 11, and Table 51	
Hemolysis effect	Matrix Factor: 0.978 (QCL) and 0.992 (QCH), mean IS-normalized for 2 human plasma lots Matrix Effect (QCs), 2 human plasma lots: QCL: -6.2% to 4.3% bias, ≤4.3%CV QCH: -2.1% to 0.0% bias, ≤0.7%CV	B7989006 Validation Report Table 16 and Table 17 B7989006 Validation Report Table 22 and Table 23	

Lipemic effect	Matrix Factor: 1.00 (QCL) and 0.988 (QCH), mean IS-normalized for 2 human plasma lots Matrix Effect (QCs), 2 human plasma lots: QCL: -0.9% to 1.4% bias, ≤1.2%CV QCH: -3.8% to 1.3% bias, ≤2.5%CV	B7989006 Validation Report Table 18 and Table 19 B7989006 Validation Report Table 24 and Table 25
Dilution linearity and hook effect	NA	NA

Table 54. Summary of Method Performance B7989006

Bioanalytical method validation report name, amendments and hyperlinks	**B7989006 Validation Report for PF-06651600 in Human Plasma**	
Bench-top/process stability	Bench-top plasma stability = 5 hours Wet ice plasma stability = 20 hours Refrigerated plasma stability = 20 hours Process (extract) stability = 164 hours at 2°C to 8°C	B7989006 Validation Report Table 40, Table 41, Table 42, and Table 48
Freeze-thaw stability	5 cycles at -20°C and -70°C	B7989006 Validation Report Table 44 and Table 45
Long-term stability	255 days at -20°C 713 days at -70°C	B7989006 Validation Report Table 46 and Table 47
Parallelism	NA	NA
Carryover	Carryover within acceptable limits for analyte and internal standard.	B7989006 Validation Report Table 11
Method performance in Study B7981015, B7981015 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	97.4% (38 of 39) of runs passed	B7981015 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[b] range: -1.7% to 1.5% Cumulative precision: ≤3.9% CV	B7981015 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[b] range: -1.3% to 1.6% Cumulative precision: ≤3.6% CV TE: NA	B7981015 Bioanalytical Study Report Table 4
Method reproducibility	Incurred sample re-analysis was performed in ~6.2% (280/4481) of analyzed study samples, and 98.6% of the repeats met the pre-specified criteria. (Since >1000 samples were analyzed, 100 samples plus ≥5% of the excess number of analyzed samples over 1000 were selected for ISR.)	B7981015 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 5

Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -70°C. Study samples were analyzed within the 713 days of established frozen plasma stability.	B7981015 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.2 Calibration Standard Preparation, and Section 8.3 Quality Control Sample Preparation

Table 54. Summary of Method Performance B7989006

Bioanalytical method validation report name, amendments and hyperlinks	**B7989006 Validation Report for PF-06651600 in Human Plasma**	
Standard calibration curve performance during accuracy and precision runs	NA	NA
Method performance in Study B7981019, B7981019 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	96.2% (51 of 53) of sample analysis runs passed	B7981019 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[b] range: -1.7% to 1.3% Cumulative precision: ≤4.4% CV	B7981019 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[b] range: -1.6% to 3.4%, -1.6% to 0.2% (excluding one statistical outlier) Cumulative precision: ≤31.1% CV, ≤5.1% CV (excluding one statistical outlier) TE: NA	B7981019 Bioanalytical Study Report Table 4
Method reproducibility	Incurred sample re-analysis was performed in ~5.9% (368/6273) of analyzed study samples, and 99.4% of the repeats met the pre-specified criteria. (Since >1000 samples were analyzed, 100 samples plus ≥5% of the excess number of analyzed samples over 1000 were selected for ISR.)	B7981019 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 5
Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -70°C. Study samples were analyzed within the 713 days of established frozen plasma stability.	B7981019 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.2 Calibration Standard Preparation, and Section 8.3 Quality Control Sample Preparation
Standard calibration curve performance during accuracy and precision runs	NA	NA

Method performance in Study B7981032, B7981032 Bioanalytical Study Report for PF-06651600 in Human Plasma		
Assay passing rate	88.9% (40 of 45) of runs passed	B7981032 Bioanalytical Study Report Section 4. Assay Performance Summary and Table 1

Table 54. Summary of Method Performance B7989006

Bioanalytical method validation report name, amendments and hyperlinks	B7989006 Validation Report for PF-06651600 in Human Plasma	
Standard curve performance	Cumulative bias[b] range: -1.0% to 1.3% Cumulative precision: ≤4.8% CV	B7981032 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[b] range: -1.2% to 0.4% Cumulative precision: ≤4.0% CV TE: NA	B7981032 Bioanalytical Study Report Table 4
Method reproducibility	Incurred sample re-analysis was performed in ~6.9% (334/4838) of analyzed study samples, and 98.2% of the repeats met the pre-specified criteria. (Since >1000 samples were analyzed, 100 samples plus ≥5% of the excess number of analyzed samples over 1000 were selected for ISR.)	B7981032 Bioanalytical Study Report Section 4. Assay Performance Summary, Section 5. Study Sample Information, and Table 5
Study sample analysis/ stability	Calibration standards, QCs, and study samples were stored at -70°C. Study samples were analyzed within the 713 days of established frozen plasma stability; one sample was reassayed beyond stability, but the reassay result confirmed the original.	B7981032 Bioanalytical Study Report Section 5. Study Sample Information, Section 6.2. Assay Methodology Summary, Section 8.2 Calibration Standard Preparation, and Section 8.3 Quality Control Sample Preparation
Standard calibration curve performance during accuracy and precision runs	NA	NA

a. Includes all validation runs.
b. %Bias is reported as %RE in the report.

Table 55. Summary of Method Performance B7989007

Bioanalytical method validation report name, amendments and hyperlinks	**B7989007 Qualification Report for 14C-PF-06651600 in Human Plasma** **B7989007 Qualification Report for 14C-PF-06651600 in Human Plasma Amendment 01**		
Method description	Protein precipitation followed by UPLC+AMS detection		
Materials used for standard calibration curve and concentration	[^{14}C]-PF-06651600 in solid form		
Validated assay range	2.32-232 mBq/mL for [^{14}C]-PF-06651600		
Material used for QCs and concentration	[^{14}C]PF-06651600 in solid form		
Minimum required dilutions (MRDs)	NA		
Source and lot of reagents	Reference drug: [^{14}C]-PF-06651600-15 Lot number: 20180823		
Regression model and weighting	Linear, weighted $1/x^2$		
Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	B7989007 Qualification Report Amendment 01 Table 3
	Cumulative accuracy (%bias)[a] from LLOQ to ULOQ	-2.39% to 1.66%	B7989007 Qualification Report Amendment 01 Table 3
	Cumulative precision (%CV) from LLOQ to ULOQ	≤6.7%	B7989007 Qualification Report Amendment 01 Table 3
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias)[a] in 5 QCs (LLOQ, QCL, QCM, QCH, and DilQC)	-17.4% to -10.3% (no DilQC) -3.9% (DilQC only; intra-run)	B7989007 Qualification Report Amendment 01 Table 4 B7989007 Qualification Report Amendment 01 Table 5

Table 55. Summary of Method Performance B7989007

Bioanalytical method validation report name, amendments and hyperlinks	**B7989007 Qualification Report for 14C-PF-06651600 in Human Plasma** **B7989007 Qualification Report for 14C-PF-06651600 in Human Plasma Amendment 01**		
	Inter-batch %CV (repeatability)	≤5.9% (no DilQC) ≤7.9% (DilQC only; intra-run)	B7989007 Qualification Report Amendment 01 Table 4 B7989007 Qualification Report Amendment 01 Table 5
	Total Error (TE)	NA	NA
Selectivity and matrix effect	Selectivity: interference (relative to LLOQ standard) with analyte met acceptance criteria for 6 of 6 individual and 1 of 1 pooled normal human plasma lots . Matrix effect: not assessed.		B7989007 Qualification Report Amendment 01: Table 6
Interference and specificity	NA		NA
Hemolysis effect	NA		NA
Lipemic effect	NA		NA
Dilution linearity and hook effect	NA		NA
Bench-top/process stability	Bench-top plasma stability: not assessed. [^{14}C]PF-06651600 considered to have equivalent matrix stability to unlabeled PF-06651600 = 4 hours bench-top plasma stability. Process (extract) stability = 62.5 hours at 15°C		B7989007 Qualification Report Amendment 01 Section 5. Qualification Performance Summary B7989003 Validation Report Table 21 B7989007 Qualification Report Amendment 01 Table 8
Freeze-thaw stability	Not assessed. [^{14}C]PF-06651600 considered to have equivalent matrix stability to unlabeled PF-06651600. 5 cycles at -20°C and -70°C		B7989007 Qualification Report Amendment 01 Section 5. Qualification Performance Summary B7989003 Validation Report Table 25

Long-term stability	Not assessed directly. [^{14}C]PF-06651600 considered to have equivalent matrix stability to unlabeled PF-06651600. 58 days at -20°C 673 days at -70°C	B7989007 Qualification Report Amendment 01 Section 5. Qualification Performance Summary B7989003 Validation Report Table 24 B7989003 Validation Report Addendum 1 Table 7

Table 55. Summary of Method Performance B7989007

Bioanalytical method validation report name, amendments and hyperlinks	**B7989007 Qualification Report for 14C-PF-06651600 in Human Plasma** **B7989007 Qualification Report for 14C-PF-06651600 in Human Plasma Amendment 01**	
Parallelism	NA	NA
Carryover	Carryover within acceptable limits for analyte.	B7989007 Qualification Report Amendment 01 Table 7
Method performance in Study B7981011, B7981011 Bioanalytical Study Report for [^{14}C]-PF-06651600 in Human Plasma		
Assay passing rate	75% (3 of 4) of runs passed	B7981011 Bioanalytical Study Report Section 5. Assay Performance Summary and Table 1
Standard curve performance	Cumulative bias[a] range: -2.1% to 4.3% Cumulative precision: ≤13.0% CV	B7981011 Bioanalytical Study Report Table 3
QC performance	Cumulative bias[a] range: -13.1% to -3.3% Cumulative precision: ≤6.6% CV (repeatability) TE: NA	B7981011 Bioanalytical Study Report Table 4
Method reproducibility	Incurred sample re-analysis was performed in ~19.4% (21/108) of analyzed study samples, and 95% of the repeats met the pre-specified criteria.	B7981011 Bioanalytical Study Report Section 5. Assay Performance Summary, Section 6. Study Sample Information, and Table 5
Study sample analysis/ stability	Calibration standards were prepared fresh on day of analysis. QCs and study samples were stored at -18°C for 2 and 30 days, respectively, then moved to -70°C. Study samples were analyzed within the 58 days of frozen plasma stability at -20°C and the 673 days of frozen plasma stability at -70°C established for unlabeled PF-06651600.	B7981011 Bioanalytical Study Report Section 6. Study Sample Information, Section 9.1. Calibration Standards, and Section 9.2. Quality Control Samples
Standard calibration curve performance during accuracy and precision runs	NA	NA

a. %Bias is reported as %RE in the report.

Table 56. Summary of Method Performance B7989009

Bioanalytical method validation report name, amendments and hyperlinks	**B7981054 Bioanalytical Study Report for PF-07034562 in Human Plasma**		
Method description	Protein precipitation (under yellow light, in an ice bath) followed by HPLC-MS/MS detection		
Materials used for standard calibration curve and concentration	PF-07034562 in solid form		
Validated assay range	0.5-200 ng/mL for PF-07034562		
Material used for QCs and concentration	PF-07034562 in solid form		
Minimum required dilutions (MRDs)	NA		
Source and lot of reagents	Reference drug: PF-07034562 Lot number: PF-07034562-00-0003		
Regression model and weighting	Linear, weighted $1/x^2$		
Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	7	B7981054 Bioanalytical Study Report Appendix B Table B-2
	Cumulative accuracy (%bias)[a] from LLOQ to ULOQ	-2.5% to 3.0%	B7981054 Bioanalytical Study Report Appendix B Table B-2
	Cumulative precision (%CV) from LLOQ to ULOQ	≤5.1%	B7981054 Bioanalytical Study Report Appendix B Table B-2

Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias)[a] in 6 QC levels (LLOQ, QCL, QCGM, QCM, QCH, and DilQC)	-8.7% to -2.0 (no QCGM) 5.0% (QCGM only; intra-run) (QCGM only; intra-run)	B7981054 Bioanalytical Study Report Appendix B Table B-4

Table 56. Summary of Method Performance B7989009

Bioanalytical method validation report name, amendments and hyperlinks	**B7981054 Bioanalytical Study Report for PF-07034562 in Human Plasma**		
	Inter-batch %CV	≤10.1% (no QCGM) 2.8% (QCGM only; intra-run)	B7981054 Bioanalytical Study Report Appendix B Table B-4
	Total Error (TE)	NA	NA
Selectivity and matrix effect	Selectivity: interference with analyte and internal standard met acceptance criteria for 6 of 6 normal human plasma lots Matrix Factor: 0.93-0.99 (QCL) and 0.98-1.01 (QCH), IS-normalized across 6 normal human plasma lots		B7981054 Bioanalytical Study Report Appendix B Table B-9 and B-10 B7981054 Bioanalytical Study Report Appendix B Table B-8
Interference and specificity	NA		NA
Hemolysis effect	Selectivity: interference with analyte and internal standard met acceptance criteria for 1 of 1 human plasma lot Matrix Factor: 0.99 (QCL), 0.99 (QCH), IS-normalized for 1 human plasma lot		B7981054 Bioanalytical Study Report Appendix B Table B-9 and Table B-10 B7981054 Bioanalytical Study Report Appendix B Table B-8
Lipemic effect	Selectivity: interference with analyte and internal standard met acceptance criteria for 1 of 1 human plasma lot Matrix Factor: 0.99 (QCL), 0.99 (QCH), IS-normalized for 1 human plasma lot		B7981054 Bioanalytical Study Report Appendix B Table B-9 and Table B-10 B7981054 Bioanalytical Study Report Appendix B Table B-8
Dilution linearity and hook effect	NA		NA

Bench-top/process stability	Bench-top plasma stability = 24 hours	B7981054 Bioanalytical Study Report Appendix B Table B-12
	Process (extract) stability (conducted as reinjection reproducibility) = 192 hours at 4°C	B7981054 Bioanalytical Study Report Appendix B Table B-11

Table 57. Summary and Reports of the Validated Bioanalytical Methods Used in Clinical DDI Studies

Pfizer /Vendor Validation No./link	Analyte(s)	Matrix	Assay Laboratory	Assay Range (ng/mL)	Inter-assay Precision %CV	Inter-assay Accuracy %RE	Pfizer Study Number
B7459006	Midazolam	Human Plasma	(b) (4)	0.05-50	≤6.46	-1.60 to 1.07	B7981017
B7459006 Addendum 1	Midazolam	Human Plasma		0.05-50	≤6.50	-3.20 to -1.33	B7981017
B7989005	Efavirenz	Human Plasma		20 - 4000	≤6.72	-1.45 to 5.46	B7981017
B7989005 Partial Validation Addendum1	Efavirenz	Human Plasma		20 - 4000	≤3.41	-1.33 to 0.5	B7981017
B7989004 Addendum 1	Levonorgestrel Ethinyl Estradiol	Human Plasma		Levonorgestrel: 0.05-10 Ethinyl Estradiol: 0.0025-0.5	Levonorgestrel: ≤4.3 Ethinyl Estradiol: ≤16.2	Levonorgestrel: 0.7 to 3.8 Ethinyl Estradiol: 0.3 to 3.6	B7981018 B7981035
B7459010	Rosuvastatin	Human Plasma		0.02-25	≤5.62	-5.20 to 10.86	B7981024
B7459010 Addendum 1	Rosuvastatin	Human Plasma		0.02 – 25	≤3.63	-8.93 to -2.31*	B7981024
B7459010 Addendum 2	Rosuvastatin	Human Plasma		0.02 – 25	2.56*	-10.72 to -2.13*	B7981024
B7459011 Revision 3	Rosuvastatin	Human Urine		5.0-2000	≤14.95	-0.73 to 5.28	B7981024
B7459011 Addendum 1	Rosuvastatin	Human Urine		5.0 – 2000	≤3.70*	-2.89 to 6.50*	B7981024
B7459011 Addendum 2	Rosuvastatin	Human Urine		5.0-2000	≤1.76*	(-4.22 to 0.89)*	B7981024
B7989008	Sumatriptan	Human Plasma		0.1-150	≤9.74	-6.15 to 9.12	B7981025

Table 57. Summary and Reports of the Validated Bioanalytical Methods Used in Clinical DDI Studies

Pfizer /Vendor Validation No./link	Analyte(s)	Matrix	Assay Laboratory	Assay Range (ng/mL)	Inter-assay Precision %CV	Inter-assay Accuracy %RE	Pfizer Study Number
C2548001	NMN	Human Plasma	(b) (4)	1-1000	≤7.15 (surrogate QCs), ≤4.12 (endogenous QCs)	-5.04 to 1.93 (surrogate QCs), -0.846 to 1.01 (endogenous QCs)	B7981025
C2548001 Addendum 1	NMN	Human Plasma		1-1000	Not available**	Not available**	B7981025
C2548001 Addendum 2	NMN	Human Plasma		1-1000	Not calculable***	0.268 to 14.3 (surrogate QCs), 1.87 to 3.40 (endogenous QCs)	B7981025
C2548001 Addendum 3	NMN	Human Plasma		1-1000	Not calculable***	2.70 to 4.82 (surrogate QCs), -0.496 to 6.26 (endogenous QCs)	B7981025
C2548001 Addendum 4	NMN	Human Plasma		1-1000	Not available**	Not available**	B7981025
C2548002	NMN	Human Urine		100-100000	≤7.61 (surrogate QCs), ≤3.44 (endogenous QCs)	-1.39 to 0.330 (surrogate QCs), -1.92 to -0.00421 (endogenous QCs)	B7981025

Table 57. Summary and Reports of the Validated Bioanalytical Methods Used in Clinical DDI Studies

Pfizer /Vendor Validation No./link	Analyte(s)	Matrix	Assay Laboratory	Assay Range (ng/mL)	Inter-assay Precision %CV	Inter-assay Accuracy %RE	Pfizer Study Number
C2548002 Addenda 1 and 2	NMN	Human Urine	(b) (4)	100-100000	Addendum 1: not available** Addendum 2: not calculable***	Addendum 1: not available** Addendum 2: -0.815 to 10.6 (surrogate QCs), -3.92 to -1.88 (endogenous QCs)	B7981025
C2548002 Addendum 3	NMN	Human Urine		100-100000	Not calculable***	2.37 to 3.41 (surrogate QCs), -7.15 to 1.94 (endogenous QCs)	B7981025
C2548002 Addendum 4	NMN	Human Urine		100-100000	NA**	NA**	B7981025
C2548002 Addendum 5	NMN	Human Urine		100-100000	Not available**	Not available**	B7981025
B7989011	Tolbutamide 4-Hydroxytolbutamide	Human Plasma		50-50000 50-5000	≤10.3 ≤6.7	-4.0 to 4.7 -3.5 to 3.2	B7981069
B7989010	Caffeine Paraxanthine	Human Plasma		50-5000 50-5000	≤9.0 ≤14.4	96.4 to 105 97.9 to 106	B7981054

* Only Intra-assay statistics available
** No run QCs to perform inter/intra run statistics.

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