NDA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	sNDA 213871/001
Priority or Standard	Priority
Submit Date(s)	May 9, 2022; August 23, 2022
Received Date(s)	May 9, 2022; August 23, 2022
PDUFA Goal Date	February 9, 2022
Division/Office	DDD/OII
Review Completion Date	February 7, 2023
Established/Proper Name	abrocitinib
Trade Name	CIBINQO
Pharmacologic Class	Janus Kinase Inhibitor
Code name	JAK
Applicant	Pfizer, Inc.
Doseage form	Tablets
Applicant proposed Dosing Regimen	100 mg orally once daily, if an adequate response is not achieved after 12-weeks, consider increasing dosage to 200 mg. Discontinue therapy if inadequate response is seen after dosage increase to 200 mg once daily.
Applicant Proposed Indication(s)/Population(s)	For the treatment of adults and pediatric patients 12 years of age and older with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	CIBINQO is a Janus kinase (JAK) inhibitor indicated for the treatment of adults and patients 12 years of age and older with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable.
Recommended Dosing Regimen	100 mg orally once daily, if an adequate response is not achieved after 12-weeks, consider increasing dosage to 200 mg. Discontinue therapy if inadequate response is seen after dosage increase to 200 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
DRISK=Division of Risk Management

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Glossary

AC	advisory committee
AD	atopic dermatitis
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
BSA	body surface areaCBER 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
CMH	Cochran-Mantel-Haenszel
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
EASI	Eczema Area and Severity Index
ETASU	elements to assure safe use
FAS	full analysis set
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
GLMM	Generalized Linear Mixed Model
GRMP	good review management practice
ICH	International Conference on Harmonisation
IGA	Investigator Global Assessment
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety

JTR	jump-to-reference
LOCF	last observation carried forward
LTE	long-term extension
MAR	missing at random
MCAR	missing completely at random
MCMC	Markov Chain Monte Carlo
MI	multiple imputation
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model with repeated measures
MTP	multiplicity testing procedure
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NRI	non-responder imputation
NRS	numeric rating scale
OC	observed cases
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
PPAS	per protocol analysis set
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSAAD	Pruritus and Symptoms Assessment for Atopic Dermatitis
PSUR	Periodic Safety Update report
Q2W	every two weeks
QD	once daily
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TCS	topical corticosteroids
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Abrocitinib is an orally bioavailable small molecule that reversibly and selectively inhibits Janus Kinase (JAK) by blocking the ATP binding site. Abrocitinib reversibly inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. In a cell-free isolated enzyme assay, abrocitinib was selective for JAK1 over JAK2 (28-fold), JAK3 (>340-fold), and tyrosine kinase (TYK) 2 (43-fold), as well as the broader kinome. The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known. Both the parent compound and the active metabolites inhibit JAK1 activity in vitro with similar levels of selectivity. The JAK-STAT signaling pathway is the common transduction pathway for Type 1 and Type 2 cytokine receptors in response to inflammatory and proliferative signals.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The original NDA application for CIBINQO (abrocitinib) tablets was approved on 14-January-2022. This approval was for the indication of treatment in adults with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. The approval included deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) and includes the following adolescent study:

4217-1 Clinical trial B7451036 (TEEN) in adolescents ages 12 years to 17 years 11 months was completed after submission of the original abrocitinib NDA for the treatment of moderate-to-severe atopic dermatitis. Submit the final study report as a supplement to the NDA.

Final Protocol Submission: complete
Study Completion: complete
Final Report Submission: 5/2022

The NDA supplement submitted, S-001, contains the data for clinical trial B7451036 (TEEN) completed on 08-April-2020. This is a phase 3, multinational, multi-center, randomized (1:1:1), double-blind, placebo-controlled, parallel-group study was to evaluate the efficacy and safety of abrocitinib in adolescent subjects 12 to <18 years of age with moderate-to-severe atopic dermatitis (AD). A total of 287 subjects were randomized globally from 99 sites to receive abrocitinib daily (QD) at 200 mg, 100 mg, or placebo for 12 weeks.

This trial included an immunogenicity sub-study integrated into the last 4 weeks of the main study treatment period. A total of 25 subjects who had completed 8 weeks of treatment with study intervention received a tetanus, diphtheria and acellular pertussis combination vaccine (Tdap), and had blood samples collected for the evaluation of immunogenicity at Weeks 8 and 12. Subjects of this sub-study completed all other protocol specified procedures in the main study.

At the end of the 12-week study treatment, qualified subjects completing the trial had the option to enter the long term extension (LTE) Study B7451015. Subjects discontinuing early from the trial underwent a 4-week follow-up period.

Clinical conclusions from the TEEN trial demonstrated that abrocitinib is effective for moderate-to-severe atopic dermatitis in adolescents 12 years to <18 years of age for 100 mg orally once daily (b) (4). In addition, the PP-NRS4 response was improvement in itch for its endpoint at week-12. Overall, the TEEN clinical trial demonstrated positive efficacy and based on the totality of the data, it is recommended that the indication is extended to include adolescents 12 years of age and older and keep the dose/indication in adolescents the same as the adults.

1.3. Benefit-Risk Assessment

[Do not insert text here. Use the table]

Benefit-Risk Summary and Assessment

Pfizer Inc. has submitted a supplement application for abrocitinib (CIBINQO), a Janus kinase (JAK) inhibitor proposed for the treatment of patients 12 years and older with moderate-to-severe atopic dermatitis, [redacted] (b) (4), who have had an inadequate response to systemic therapy, including biologics, or for whom these treatments are not advisable. Abrocitinib is proposed as an oral tablet (50 mg, 100 mg, 200 mg) that works by inhibiting JAK by blocking the ATP binding site, inhibiting cytokine induced STAT phosphorylation mediated by receptors utilizing JAK in response to inflammatory and proliferative signals in atopic dermatitis.

To establish the efficacy of oral abrocitinib, Pfizer conducted a single post-marketing, multinational, multi-center, randomized (1:1:1), double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of abrocitinib in adolescent subjects 12 to <18 years of age with moderate-to-severe atopic dermatitis (AD). A total of 287 subjects globally from 99 sites were randomized o receive abrocitinib QD at 200 mg (N=93), 100 mg (N=89), or placebo (N=94) for 12 weeks. The result showed a statistically significantly higher proportion of subjects achieved IGA responses (clear or almost clear and ≥ 2-point improvement from baseline at week-12) for abrocitinib with a difference from placebo of 16.7% (p = 0.0147) and 20.6% (p = 0.0030) for the 100 mg and 200 mg treatment groups, respectively.

Study B7451036 (TEEN) provides additional data on adolecents to inform the safety characterized within the original application. The most frequent treatment emergent adverse events included infections (nasopharyngitis and upper respiratory tract infections), gastrointestinal disorders (nausea), headaches, and worsening of atopic dermatitis. No pulmonary embolism, malignancies, or major adverse cardiac events were reported in this trial. No new safety signal was identified in this clinical study and there will not be a change in current safety labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• AD is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. In 60% of patients, the onset of disease is in	While AD is not a life-threatening condition, it may be serious. It may significantly impact the quality of life of the patient, as well as family members. The dysfunctional skin barrier, further compromised from scratching, may

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals. • The prevalence of AD in the United States in individuals 4-8 years of age has been reported as 10.63% and as 9.96% in those 9-12 years of age. For 10-30% of individuals, AD persists into the adult years. • AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In patients older than 2 years of age, the presentation is like that in adults. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, wrists, and volar aspects of the wrists. AD may be generalized. Common comorbidities include asthma, allergic rhinitis/rhinoconjunctivitis, and food allergies.	predispose patients to secondary infections. The primary and secondary disease-related skin changes may distort the appearance of the skin. Patients with AD often experience sleep disturbance, largely attributable to the associated extreme pruritus. During disease flares, approximately 80% of patients may experience disturbed sleep. The disruption in sleep could have carryover effects to impact behavior and neurocognitive functioning. Sleep disturbance in the affected individual may also disrupt the sleep of family members. Affected children may also experience depression, anxiety, social isolation, and impaired psychosocial functioning.
Current Treatment Options	• For the Applicant's target population, the only systemic biologic treatment that FDA approved for atopic dermatitis is DUPIXENT (dupilumab), approved on 28- MAR-2017. • Prior to this approval, the use of systemic steroids was used as systemic treatment. The American Academy of Dermatology recommends that systemic corticosteroids generally be avoided because of the potential for short- and long-term adverse reactions. Potential adverse effects include reversible hypothalamic-pituitary adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia and other endocrine effects. A particular concern with their use in children and adolescents is the risk of decreased linear growth during treatment.	The medical needs of adolescents 12 years of age and older with moderate-to-severe AD is not being adequately met by available therapies. DUPIXENT (dupilumab) was approved for use in patients 6 years and older with moderate-to-severe atopic dermatitis on May-2020 and contributes to the need for systemic therapies. The addition of an oral product, such as abrocitinib, to the armamentarium for the treatment of moderate-to-severe atopic dermatitis would represent an alternative to having injections or

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Phototherapy is considered safe and effective treatment for AD patients who are candidates for systemic therapy, including children. Its drawbacks include a potentially time intensive, in-office treatment schedule. Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburnlike reactions, skin cancer (nonmelanoma and melanoma), and cataracts. • Systemic products that are used off-label to treat moderate-to-severe AD include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. The reported effectiveness for the products varies from "efficacious" (cyclosporine) to "inconsistent" (mycophenolate mofetil). Similarly, the safety profiles vary, although each product carries the potential for significant adverse effects, and all of these product labels include boxed warnings. A small sampling of labeled risks includes nephrotoxicity (cyclosporine), cytopenias (azathioprine), hepatotoxicity (methotrexate), and embryofetal toxicity (mycophenolate mofetil).	systemic steroids.
Benefit	• To establish efficacy in adolescents, the clinical trial compared co-primary endpoints for abrocitinib to placebo: o IGA responder proportion of clear (0) or almost clear (1) and 2-point improvement from baseline with abrocitinib 100 mg QD 16.7% (*p = 0.0147*) and 200 mg QD 20.6% (*p = 0.0030*) treatment groups compared with placebo group. o EASI-75 responder proportion with abrocitinib 100 mg QD 26.5% (*p=0.0002*) and 200 mg QD 29.4% (*p=<0.001*) treatment groups compared to placebo group. • In addition, PP-NRS4 responders at Weeks 2, 4, and 12 were observed.	The Applicant has established abrocitnib 100 mg PO QD as safe and effective treatment for moderate-to-severe atopic in adolescent patients who needs alternative systemic therapy or cannot use those therapies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The applicant evaluated the safety and efficacy of oral abrocitinib for the treatment of moderate-to-severe atopic dermatitis in subjects 12 years and above. Common adverse events included nausea, vomiting, abdominal pain, increase blood creatinine phosphokinase, and headaches which showed dose dependency from 100 mg QD to 200 mg QD. • No significant serious adverse events occurred in the TEEN clinical trial that was observed in the adult clinical trials. • Serious Infections and opportunistic infections were not as prevalent in adolescents as they were in the adult clinical trials, especially with herpes zoster, herpes simplex, and eczema herpeticum. • Minor thrombocytopenia and lymphopenia were observed on laboratory evaluation for the TEEN trial, which had a nadir at 4 weeks and did not lead to any serious clinical outcome. • Serious adverse reactions which occurred in adult abrocitinib clinical trials as well as within the JAK inhibitor drug class (MACE and malignancy).Labeling for this drug product currently includes a boxed warning for both. • Labeling for this product (b) (4)	The risks for treatment with oral abrocitinib are significant considering the treatment options available currently. Although the TEEN trial did not reveal severe adverse events significant in the original clinical trials for approval (thrombocytopenia, pulmonary embolic events, deep venous thrombosis, MACE, severe infections, and opportunistic infections), the small size of the clinical trial limits the detection of these safety events. In conclusion, abrocitinib should be used as 3rd line therapy in adolescents with moderate-to-severe atopic dermatitis have failed or are intolerant to systemic treatment. The higher 200 mg QD dose may be used for those 12 years of age and older who have failed 100 mg QD and have no other options available.

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		8.2, 8.4
		X	Patient reported outcome (PRO)	8.2, 8.4
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	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):		
☐	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		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

Atopic dermatitis (AD) or commonly known as eczema, is a chronic, relapsing inflammatory skin condition characterized by dry, pruritic skin that occurs most frequently in children but also affects many adults. It is the leading non-fatal health burden attributable to skin disease, inflicts a substantial psychosocial burden on patients and their relatives, and increases the risk of food allergy, asthma, allergic rhinitis, other immune-mediated inflammatory diseases, and mental health disorders.[1] Clinical features of AD include skin dryness, erythema, oozing and crusting, and lichenification. Pruritis is a hallmark of the condition and responsible for much of the disease burden for patients and their families.

AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In patients older than 2 years of age, the presentation is like that in adults. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, wrists, and volar aspects of the wrists. AD may be generalized.

The pathogenesis involves a complex interplay of genetic, immunological, and environmental factors that result in abnormal skin barrier function and immune system dysfunction. Irregularities in the terminal differentiation of the epidermal epithelium lead to a faulty stratum corneum which permits the penetration of environmental allergens. The exposure to allergens may ultimately result in systemic sensitization and may predispose AD patients to other conditions, such as asthma and food allergies.

2.2. Analysis of Current Treatment Options

Food and Drug Administration (FDA)-approved or-licensed treatments for AD fall in the categories of corticosteroids (topical and systemic), calcineurin inhibitors (topical), phosphodiesterase-4 (PDE-4) inhibitors (topical), IL-4 receptor antagonist (dupilumab), and most recently JAK inhibitors (abrocitinib and upadacitinib). Prior to the licensure of dupilumab, corticosteroids were the only systemically-administered products that were FDA-approved for treatment of an AD indication in any age group. Corticosteroids are available for treatment of AD by various routes of administration, including topical, oral, and parenteral. Although their use may result in rapid improvement, the AD commonly recurs with worse severity on discontinuation of the systemic corticosteroids (rebound). For this reason and because of the

[1] Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016 Mar;387(10023):1109-22.

potential for adverse effects, the American Academy of Dermatology recommends that systemic steroids generally be avoided in the treatment of AD because potential risks generally outweigh the benefits.[2] Potential adverse effects include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia and other endocrine effects. A particular concern in children and adolescents is the risk of decreased linear growth during treatment. Labels for systemic corticosteroids do not specify any limitations on the age of indication.

Topical corticosteroids (TCS) represent the cornerstone of anti-inflammatory treatment of AD in all age groups.[3] Numerous TCS, in various dosage forms and potencies, are available for treatment of AD, and some are specifically indicated for pediatric use. For example, fluticasone propionate lotion, 0.05%, a medium potency TCS, is indicated for relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 3 months of age and older. According to product labels, TCS may be sufficiently absorbed to lead to systemic adverse effects. Additionally, pediatric patients may be more susceptible to systemic toxicity doses due to their larger skin surface to body mass ratios. Labeled potential local adverse effects include skin atrophy, striae, telangiectasias, and hypopigmentation.

The topical calcineurin inhibitors (TCI), tacrolimus ointment and pimecrolimus cream, are also indicated for treatment of AD in pediatric patients (2 years and older): tacrolimus for moderate-to-severe AD and pimecrolimus for mild-to-moderate AD. However, both are labeled for second-line, short-term use when other topical prescription treatments have failed or are inadvisable. The calcineurin inhibitors carry boxed warnings advising that the safety of their long-term use has not been established. More specifically, the boxed warnings describe that rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors; a causal relationship has not been established. Crisaborole ointment, 2%, a PDE-4 inhibitor, is approved for treatment of AD in pediatric patients (3 months of age and older). However, the product is indicated for a somewhat different AD population (mild-to-moderate AD) than the target population for dupilumab (moderate-to-severe AD).

Nonpharmacologic care is critical to AD management and includes attention to bathing practices and the regular use of moisturizers, which are available in several delivery systems, such as creams, ointments, oils, lotions. Moisturizers are directed at the xerosis and transepidermal water loss that are central elements of the disease. They may also relieve pruritus, lessen erythema and fissuring, and improve lichenification. Moisturizers themselves may be the principal treatment for mild disease. Although there are no standardized or

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[2] Sidbury et al. Guidelines of care for the management of atopic dermatitis. Section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014;71:327-49.
[3] Eichenfeld et al. Guidelines of care for the management of atopic dermatitis. Section 1. Management and treatment with topical therapies. J Am Acad Dermatol. 2014;71:116-32.

universal recommendations regarding the use of moisturizers, repeated application of generous amounts is thought to be important and required, irrespective of the severity of disease. The use of moisturizers during maintenance may stave off flares and may lessen the amounts of pharmacologic agents needed to control the disease

Dupilumab is currently indicated for use in patients > 6 years of age with moderate-to-severe atopic dermatitis (Supplement-17) who have failed topical therapies or when those therapies are inadvisable. Dupilumab is given by injection. New treatments, such as upadacitinib, are indicated in subjects as young as 12 years of age, but used as third line treatment due to safety issues with JAK inhibitors.

Phototherapy (UVA and UVB) is considered safe and effective treatment for AD patients who are candidates for systemic therapy, including children. However, phototherapy may require frequent in-office visits (e.g., several times a week) and time missed from school (and also, possibly from work for caregivers). Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn-like reactions (erythema, tenderness, pruritus), skin cancer (nonmelanoma and melanoma), and cataracts. However, long-term risks from phototherapy treatment of AD in children have not been evaluated. Narrowband UVB therapy may be considered first-line because of the safety profile relative to psoralen + UVA (PUVA).

Systemic immunomodulating agents are used off-label to treat AD, including in pediatric patients, include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. The reported effectiveness for the products varies from “efficacious” (cyclosporine) to “inconsistent” (mycophenolate mofetil).12 Similarly, the safety profiles vary, although each product carries the potential for significant adverse effects, and all of these product labels include boxed warnings. A small sampling of labeled risks includes nephrotoxicity (cyclosporine), cytopenias (azathioprine), hepatotoxicity (methotrexate), and embryofetal toxicity (mycophenolate mofetil).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

CIBINQO (abrocitinib) is an orally bioavailable Janus kinase 1 (JAK1) inhibitor that represents a potential anti-inflammatory therapy for atopic dermatitis (AD). Abrocitinib received first marketing authorization on 08-September 2021 in Great Britain for the indication of atopic dermatitis. CIBINQO (abrocitinib) tablets was approved on 14-January-2022 in the United States for the indication of treatment in adults with refractory, moderate-to-severe atopic dermatitis whosedisease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. Currently abrocitinib has received marketing authorisation in 39 countries and is marketed in 11 countries. Reviews of post-marketing safety was consistent with current labeling.

3.2. Summary of Presubmission/Submission Regulatory Activity

CIBINQO (abrocitinib) was approved on 14-January-2022 for the treatment of adults. The Applicant completed clinical trial B7451036 (TEEN) evaluating subjects 12 years to 17 years and 11 months prior to Agency approval of the adult indication. On approval, the Agency included a requirement to submit the TEEN trial as a PMR. Submission of these trial results is intended to fulfill the requirements of the PMR. In addition, a Pre-NDA meeting was held to discuss the details for this supplement-001. The meeting included agreement on the submission date and the format of the submission. The Agency commented that the submitted supplement should only include data to fulfill the requirements of the PMR and should not include additional data to support (b) (4) The Applicant submitted supplement-001 (b) (4) This supplement was rejected and a request for re-submission was made. The current supplement is the resubmission and the Agency took an extension on the priority review due to the delay.

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

4.1. Office of Scientific Investigations (OSI)

OSI was not tasked to review clinical trial sites for this supplement. The sites overlapped with the original adult clinical trials. Re-examination of these sites was unlikely to impact the overall outcome of the TEEN trial.

4.2. Product Quality

See product quality review.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new non-clinical data was submitted for this supplement.

6 Clinical Pharmacology

6.1. Executive Summary

This supplemental NDA was to fulfill post-marketing requirement (PMR) 4217-1 (shown below) supporting the approval of abrocitinib for the treatment of refractory, moderate-to-severe atopic dermatitis in adolescents.

4217-1 Clinical trial B7451036 (TEEN) in adolescents ages 12 years to 17 years 11 months was completed after submission of the original abrocitinib NDA for the treatment of moderate-to-severe atopic dermatitis. Submit the final study report as a supplement to the NDA.

PK data in adolescent subjects were submitted in the original NDA and the predicted exposure based on the population PK model in adolescents was found to be approximately 30% lower than that in weight-matched adults. Adolescent subject population was not approved in the original NDA as the clinical trial was ongoing at the time of original NDA submission. See original NDA Unireview dated 14-January-2020 in DARRTS.

In addition to the above, this prior approval supplement (PAS) also contains one clinical trial report in subjects from China (Study B7451028) and one pharmacometrics report (PMAR- 1110) for clinical pharmacology review.

Study B7451036 was a phase 3, randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of abrocitinib coadministered with background topical therapy in adolescent subjects 12-18 years of age with AD. Eligible subjects received abrocitinib 200 mg, abrocitinib 100 mg, or placebo once daily (QD) for 12 weeks. Both abrocitinib 100 mg and 200 mg were superior to the placebo in the treatment of moderate to severe active AD in adolescent patients in terms of co-primary efficacy endpoints, Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI) 75. The observed plasma abrocitinib conetrations in adolescent patients in study B7451036 were higher in 200 mg group compared to that in 100 mg group at both 2 hours pre- and 2 hours post- dose. The 100 mg and 200 mg doses had generally acceptable safety profile. See section 8 for further information on efficacy and safety.

Study B7451028 was a phase 1, open-label, single-arm, single dose and multiple doses trial to assess the PK, safety, and tolerability of abrocitinib in healthy adult subjects from China. Subjects received a single-dose followed by multiple-doses of abrocitinib 200 mg QD for 6 days. Following single dose and multiple doses of abrocitinib 200 mg, the geometric mean AUC was 5416 ng·hr/mL and 8249 ng·hr/mL, respectively. Abrocitinib 200 mg single- and multiple- dose were well-tolerated in healthy subjects from China.

In this PAS, an updated, integrated abrocitinib and its metabolites population PK model report (PMAR-EQDD-B745d-dp4-1110) was also submitted. The updated population PK model of abrocitinib was developed using additional PK results from three Phase 1 and two Phase 3 clinical trials that were not included in the previous population PK model analysis. Integrated population PK model for major metabolites of abrocitinib was developed using post hoc estimates of PK parameters from the abrocitinib parent model and available metabolites concentrations.

Both updated abrocitinib model and integrated metabolites model adequately predicted the concentrations of abrocitinib and its metabolites. Simulations were conducted with the updated abrocitinib PK model and the integrated metabolites model to calculate the combined exposure of unbound abrocitinib and its two active metabolites, M1 and M2. Simulation results agreed with current dosing recommendations for specific populations (patients with renal or hepatic impairment) and potential drug-drug interaction (DDI) cases.

6.1.1. Recommendations

The Division of Pharmacometrics and the Division of Inflammation and Immune Pharmacology have reviewed the clinical pharmacology information in the current application and determined that this supplemental NDA is acceptable from a clinical pharmacology perspective. Furthermore, post marketing requirement 4217-1 is considered as fulfilled from a clinical pharmacology perspective. No labeling change is warranted for the clinical pharmacology sections.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics
In Study B7451036, 189 adolescents received abrocitinib 100 mg QD or 200 mg QD and 183 completed 12 weeks treatment. PK samples were collected via sparse sampling in all randomized subjects. At 2 hours pre-dose, the observed median (range) abrocitinib concentration was 1.8 ng/mL (0.0 - 220 ng/mL) and 5.5 ng/mL (0.0 - 2570 ng/mL) after 100 mg and 200 mg administration, respectively. It was 391 ng/mL (0.0 - 1860 ng/mL) and 921 ng/mL (0.0 – 4150 ng/mL) at 2 hours post-dose after 100 mg and 200 mg dosing, respectively.

In Study B7451028, 13 healthy adult Chinese subjects were enrolled and 12 subjects completed the study. Subjects received a single-dose of abrocitinib 200 mg on Day 1 and multiple-doses of abrocitinib 200 mg QD from Day 3 to Day 8.
The geometric mean C_{max} was 1570 ng/mL and 1878 ng/mL where AUC was 5416 ng·hr/mL and 8249 ng·hr/mL, respectively for single- and multiple- dose of abrocitinib 200 mg. Estimated accumulation ratio was approximately 51% for AUC and 14% for C_{max}. Median time to reach

maximum abrocitinib plasma concentration was 1.5 and 2 hours following single and multiple doses, respectively.

Safety
Overall, abrocitinib 100 mg and 200 mg were tolerated in adolescent patient with AD. A higher incidence of adverse events (AEs) was reported in the abrocitinib groups, however, the percentage of subjects experiencing serious AEs (SAEs), severe AEs and AEs leading to study discontinuation were low and similar across treatment groups. No serious infections were reported in study B7451036. For further information, see Section 8.
Abrocitinib 200 mg single- and multiple- dose were well-tolerated in healthy adult Chinese subjects as well; however, concrete conclusions cannot be made due to small sample size. There were no deaths, SAE, or discontinuations due to AEs reported in this study. One subject had a severe AE of presyncope which was resolved and was considered as not related to the study treatments.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The efficacy results in Phase 3 trials overall support the acceptability of the proposed dosing regimen of abrocitinib 100 mg (b) (4) brocitinib dosing recommendation for adolescent patients with AD is 100 mg QD which is identical with the recommendation for adult AD patients. As in adult patients with AD, the 200 mg QD dose can be used in subjects with inadequate response to the 100 mg QD dose and in patients who have failed other systemic treatments and have tried abrocitinib 100 mg QD. See section 8 for the design of Phase 3 trials, their efficacy and safety results.

Therapeutic Individualization

A population PK model was previously developed for abrocitinib and was reported in PMAR-EQDD-B745d-DP4-962. A two compartment model with zero- and first-order absorption with dose-dependent and time-dependent clearance was found to describe the data well. No prior modeling of the metabolites has been conducted.
This submission presents an update to the abrocitinib population PK model with all available data, including PK samples from five additional studies that were not included in the previous population PK model: three Phase 1 studies (B7451021, B7451028, and B7451032) and two Phase 3 studies (B7451014 and B7451036). See Appendix for the description of these studies. Additionally, a model for the three metabolites (M1, M2, and M4) is developed and presented in the report.

The updated population PK analysis for abrocitinib and integrated metabolites model were verified by the reviewer, with no significant discordance identified. Both models have used to simulate the combined exposure of unbound abrocitinib and its two metabolites (M1 and M2) for each simulation scenario below.

Exposures of Abrocitinib in Adolescent and Asian Subjects: The difference in the abrocitinib exposures for a typical adult (a white male who is 30 years old with 77 kg body weight) AD patient was compared to the typical adolescent (a white male) AD patient for both the median observed bodyweight (59 kg) and the extreme low weight (25 kg) receiving 200 mg QD. The simulated abrocitinib AUC at steady state is lower by 17% in the typical adolescent AD patient and higher by 9% in the extreme low weight AD patient (25 kg) than that in the typical adult AD patient. The exposure of abrocitinib in typical Asian adult AD patient (66 kg) is slightly higher than that in typical non-Asian adult AD patient (77 kg). However, this difference is not considered clinically meaningful.

Renal Impairment: Simulation assumed steady state abrocitinib dosing in white male AD patients with 30 years of age and 70 kg of body weight rather than a single dose in healthy subjects as was the case in dedicated renal impairment (RI) study (B7451021). Simulated ratio of the combined exposure of unbound abrocitinib and its two active metabolites, M1 and M2, between moderate or severe RI and normal renal function was comparable to the observed ratio in the dedicated RI study despite of study design and population differences.

Hepatic Impairment: Simulation also assumed steady state abrocitinib dosing in white male AD patients with 30 years of age, 70 kg of body weight. Simulated ratio of the combined exposure of unbound abrocitinib and its two active metabolites between mild/moderate hepatic impairment (HI) and normal hepatic function was comparable to the observed ratio in the dedicated HI study (B7451020) despite of study design and population differences.

Drug Interaction: Combined exposure of unbound abrocitinib and its active metabolites (M1 and M2) was simulated with and without concomitant administration of following representative CYP enzyme inhibitor or inducer. Simulation assumed steady state abrocitinib 100 mg QD and 200 mg QD dosing in AD patients.

- Concomitant use of fluconazole (a strong CYP2C19, moderate CYP2C9, and moderate CYP3A4 inhibitor): Simulation results showed that the combined exposure was increased when abrocitinib was coadministered with fluconazole.
- Concomitant use of fluvoxamine (a strong CYP2C19 and moderate CYP3A4 inhibitor): Simulation results showed that the combined exposure was increased when abrocitinib was coadministered with fluvoxamine.
- Concomitant use of probenecid (a strong OAT3 transport inhibitor): Based on the simulation results, the combined exposure did not change when abrocitinib was coadministered with probenecid.

- Concomitant use of rifampin (a strong CYP2C19, CYP2C9, and CYP3A4 inducer): Simulation results showed that the combined exposure was significantly decreased when abrocitinib was coadministered with rifampin.

In conclusion, the no new labeling is needed for renal impairment, hepatic impairment and drug interactions in the adolescent population.

Outstanding Issues

There are no outstanding issues that would preclude the approval of the current efficacy supplement from the Clinical Pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Clinical formulation and the marketed formulation
The abrocitinib formulation used in the Studies B7451036 and B7451028 was phase 3 formulation. The comparability between the marketed formulation and the formulation used in phase 3 trials was demonstrated in the original application (Study B7451032, Part B). Therefore, bridging between tested formulation and marketed formulation is not needed.

Pharmacokinetics
In Study B7451036, 287 adolecents with AD were randomized, 189 subjects received either abrocitinib 100 mg QD or 200 mg QD, and 183 completed 12 weeks treatment.

PK samples were collected at 2 hours pre-dose on Day 57 and at 2 hours post-dose on Day 85. Table 6.3.1-1 presents the summary of plasma abrocitinib concentrations. The abrocitinib plasma concentration data from all subjects at Site 1173 (n=8) were excluded from the summary statistics because the concentrations in all samples except one were anomalously high (range 35,100-156,000 ng/mL) when the predicted C_{max} in adolescent patients after abrocitinib 200 mg QD dosing is 961 ng/mL based on the abrocitinib population PK model. Sponsor inspected measured concentrations in Site 1173 and confirmed that there was no analytical error. No other explanation was provided by the Sponsor for the potential reason of these high concentrations.

Table 6.3.1-1. Summary of Plasma Abrocitinib Concentrations (ng/mL) in Study B7451036

Abrocitinib dose	PK sampling time	N	Mean	Standard deviation	Median	Range
100 mg	2 hour predose	84	10.3	29.6	1.8	0, 220
	2 hour postdose	78	483	391	397.5	0, 1860
200 mg	2 hour predose	84	84.8	329.3	5.5	0, 2570
	2 hour postdose	80	1220	921	1265	0, 4150

Source: Reviewer's analysis using PK data (adpc.xpt) of Study B7451036

In Study B7451028, 13 healthy adult Chinese subjects were enrolled and 12 subjects completed the study. One subject withdrew the informed consent before the treatment was initiated. Subjects received a single-dose of abrocitinib 200 mg on Day 1 and multiple-doses of abrocitinib 200 mg once daily from Day 3 to Day 8. Intensive PK sampling was conducted up to 48 hours after dosing on Day 1 (single dose) and Day 8 (multiple doses). Samples were assayed using the identical bioanalytical method, HPLC-MS/MS, with the original NDA submission for all analytes: abrocitinib, active metabolite M1 and M2. Method validation was adequate in the review of original application. In-study analytical assay report supported that method performance was acceptable.

The exposure of abrocitinib following single and multiple doses of abrocitinib 200 mg in Chinese subjects was summarized in Table 6.3.1-2. The estimated accumulation ratio was 51% and 14% for AUC and C_{max}, respectively.

Table 6.3.1-2. Descriptive Summary of Plasma Abrocitinib Pharmacokinetic Metrics Following Single and Multiple Administration of Abrocitinib 200 mg Once Daily in the Study B7451028

PK metric (Units)[a]	Study B7451028 (Chinese Subjects)	
	Single Dose	Multiple Doses
N	12	12
C_{max} (ng/mL)	1570 (29)	1787 (25)
T_{max} (hr)	1.5 (0.5-3.0)	2.0 (0.5-3.0)
AUC_{inf} (ng·hr/mL)	5316 (37)	-
AUC_{last} (ng·hr/mL)	5409 (36)	-
$AUC_{tau,ss}$ (ng·hr/mL)	-	8249 (30)

Source: Study Report B7451028, Table 8;
a. Geometric mean (geometric % coefficient of variation) for all except: median (range) for T_{max}.

Safety of Aborocitinib

In adolescents, the proportion of subjects with all-causality TEAEs was higher for the abrocitinib 200 mg group (62.8%) compared to the abrocitinib 100 mg (56.8%) and placebo (52.1%) groups. However, the percentage of subjects experiencing SAEs, severe AEs and AEs leading to study discontinuation were similar across treatment groups. There were 3 SAEs that 2 were from the placebo group (angioedema and dermatitis atopic) and 1 was from the abrocitinib 200 mg group (anxiety). No SAEs were determined to be treatment-related. The most frequently reported system organ class was Infections and Infestations, with slightly higher proportion of subjects reported in the abrocitinib 200 mg (36.2%) and 100 mg (35.8%) groups compared with the placebo group (31.3%).

In healthy adult Chinese subject, a total of 24 all-causality TEAEs were reported by 9 subjects following oral administration of abrocitinib single and multiple doses of 200 mg, 19 of which were considered treatment related. The majority of TEAEs were mild in severity. There were no laboratory test abnormalities meeting the reporting criteria of clinically significant laboratory

test abnormalities. There was no subject whose platelet decreased over time throughout Study B7451028.

See Section 8 for further details on safety assessment.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The efficacy of abrocitinib for the treatment of moderate to severe AD adolescent patients was demonstrated in the Phase 3 trials B7451012, B7451013, and B7451036. Final study reports of B7451012 and B7451013 had submitted in the original application. In this PAS, the Sponsor has submitted the final report from the clinical trial B7451036 (TEEN) conducted to satisfy PMR to extend the indication down to 12 years of age. See Section 8 of this multidisciplinary review for details of study design and efficacy results of the Phase 3 trials.

Dose-Response

Abrocitinib treatments improved co-primary efficacy endpoints, IGA and EASI75, compared to the placebo group in the Phase 3 efficacy study in adolescent patients with moderate to severe AD. Study B7451036 was a phase 3, randomized, double-blind, placebo-controlled study designed to investigate the efficacy and safety of abrocitinib 100 and 200 mg QD compared to placebo. Table 6.3.2-1 presents the summary of the efficacy results following multiple doses of abrocitinib. Refer to Individual Study Review in OCP appendices 14.4.1 for more details and also see Section 8 for more information.

Table 6.3.2-1: Proportion of Subjects Achieving Co-Primary Efficacy Endpoints by Abrocitinib from Baseline at Week 12 (Study B7451036)

Efficacy Endpoints	Treatment		
	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg
IGA			
n/N	23/94	37/89	43/93
Proportion (%) (95% CI)	24.5 (15.8, 33.2)	41.6 (31.3, 51.8)	46.2 (36.1, 56.4)
Difference from Placebo (95% CI)		16.7[a] (3.5, 29.9)	20.6[a] (7.3, 33.9)
EASI75			
n/N	39/94	61/89	6793
Proportion (%) (95% CI)	41.5 (31.5, 51.4)	68.5 (58.9, 78.2)	72.0 (62.9, 81.2)
Difference from Placebo (95% CI)		26.5[a] (13.1, 39.8)	29.4[a] (16.3, 42.5)

Source: Study Report B7451036, Table 12 and Table 13

Full Analysis Set (FAS) was defined as all randomized subjects who received at least one dose of study medication.
Baseline was defined as the measurement collected on or prior to Day 1.
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
[a]=statistically significant with *p*-value <0.05
Abbreviation: n=number of subjects with response, N=number of subjects in the analysis set, IGA=Investigator's Global Assessment of Clear or Almost Clear and ≥2 Points Improvement, EASI75=Eczema Area and Severity Index Response ≥ 75% Improvement from Baseline at Week 12, CI=confidence interval

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

No. (b) (4)

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

Yes. Simulations were conducted for following scenarios for patient intrinsic factors.

Typical adolescent versus typical adult patient
The exposure of abrocitinib was simulated in the typical adult AD patient (white, male, 77 kg), the typical AD adolescent (white, male, 59 kg), low weight AD adolescent (white, male, 35 kg) and extreme low weight AD adolescent (white, male, 25 kg) patients. Abrocitinib exposure decreased by 14 % in a typical adolescent and increased 9% in the extreme low weight adolescent AD patients compared to a typical adult AD patient after 200 mg QD dose. Overall, the abrocitinib exposure increased as bodyweight decreased, and exposure is comparable between adolescents and adults .

Renal impairment (moderate and severe) versus normal renal function for a typical patient
Simulated ratio of the combined exposure ($AUC_{inf,u}$) of abrocitinib and its active metabolites was comparable to that observed in the dedicated RI Study (B7451021) despite of study design and population differences. Simulation assumed steady state abrocitinib dosing in white male AD patients with 30 years of age and 70 kg of body weight rather than single dose in healthy subjects as was the case in Study B7451021. In the simulation, the ratio was 152% and 338% for moderate RI and severe RI, respectively, when the combined exposure was compared to that in AD patients with normal renal function. In dedicated RI study, the observed combined exposure ($AUC_{inf,u}$) ratios were 210% for moderate RI and 291% for severe RI.

Hepatic impairment (mild or moderate) versus normal hepatic function for a typical patient
In dedicated HI study (B7451020), the observed combined exposure ($AUC_{inf,u}$) ratios were 96% for mild HI and 114% for moderate HI after 200 mg abrocitinib single dose in healthy subject. As in RI scenario, simulation assumed steady state abrocitinib dosing in a typical AD patient (white, male, 30 years old, and 70 kg). In the simulation, the ratio of combined exposure of abrocitinib and its active metabolites was 105% for mild/moderate HI compared to that in AD patients with normal hepatic function. Simulation result agrees with the observed ratio in the dedicated HI study despite of study design and population differences.

Typical Asian versus typical Non-Asian patients
In the updated abrocitinib PK model, Asian race had a significant effect on the bioavailability of abrocitinib. After multiple abrocitinib 200 mg QD dosing, the exposure of abrocitinib in Asian patients was approximately 40 % higher than that in white patients. Similarly, the combined exposure of abrocitinib and its active metabolites in Asian AD patients higher 34.7% and 33.6% compared to non-Asian AD patients for 100 mg and 200 mg, respectively. However, this difference is not considered clinically meaningful.

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

Yes. Simulations were conducted for following scenarios for potential DDI.

Strong inhibitors of CYP 2C19 and 2C9 versus monotherapy
A DDI simulation study evaluated the effect of fluconazole (a strong CYP2C19 inhibitor and a moderate CYP2C9 and CYP3A4 inhibitor) as well as fluvoxamine (a strong CYP2C19 inhibitor and moderate inhibitor of CYP3A4). Simulated exposure differences between scenarios were similar to the observed values in DDI study B7451017 despite of the different study design and population.

Strong inducer of CYP 2C19, 2C9, and 3A4 enzymes versus monotherapy
The effect of rifampin (a strong inducer of 2C19, 2C9, and 34A) on the combined exposure in simulation study was comparable to that observed results in DDI study B7451019.

Inhibitors of OAT transport versus monotherapy
Probenecid is a nonspecific chemical inhibitor of OAT transport; it blocks transport by OAT1, OAT3, and URAT1. The effects of probenecid on the combined exposure in simulation study was not significant as it was not in Study B7451043.

Refer to Individual Study Review in OCP appendices 14.4.1 for more details.

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

A single clinical trial is reviewed in this supplement.

Table 6.3.2-1: Clinical Trial B7451036 (TEEN)

Protocol	Study Design/Objecive/Endpoint	Treatment Groups	No. of Subjects (by Treatment Group, Optional)	Demographics (no. of Subjects)	Duration of treatment	Study Inititaion/Completion Date/Status
B7451036	A Phase 3, randomized, doubleblind, placebo-controlled, multicenter study investigating the efficacy and safety of abrocitinib co-administered with background medicated topical therapy in adolescent subjects 12 to <18 years of age with moderate-to-severe atopic dermatitis. Primary Objective To assess the efficacy of abrocitinib compared with placebo when co-administered with background medicated topical therapy in adolescent subjects 12 to < 18 years of age with moderate-to-severe AD. Primary Endpoints Proportion of subjects achieving IGA of clear (0)	Abrocitinib 100 mg QD Abrocitinib 200 mg QD Placebo	Screened: 408 Total randomized and treated: 285 Randomized but not treated: 2 subjects in 200 mg QD group (randomized 1:1:1) 100 mg QD; 95 200 mg QD: 94 Placebo: 96	Mean age: 14.9 years (Range: 11.0 to 18.0 years) 160 White 17 Black or African American 94 Asian 8 American Indian or Alaska Native 2 Native Hawaiian or Other Pacific Islander 2 Multiracial 2 Not reported	Treatment duration = 12 weeks Qualified subjects completing 12-week treatment had the option to enter LTE Study B7451015. Subjects discontinuing early from the study underwent a 4 week follow up.	18 Feb 2019/ 08 Apr 2020 Completed

	or almost clear (1) and a reduction from baseline of ≥2 points at Week 12. Proportion of subjects achieving EASI-75 at Week 12. <u>Key Secondary Endpoints</u> Proportion of subjects achieving at least 4 points improvements in the PP-NRS from baseline at Weeks 2, 4, and 12. Change from baseline in PSAAD total score at Week 12.					

Source: Table created by Clinical Reviewer based on the information from Supplement 1 NDA 213971

7.2. Review Strategy

A review of the single clinical trial, B7451036 (TEEN), is completed in this supplement. The evaluation of the safety and efficacy data will be included in supplement labeling.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial Design and Endpoints

The Applicant conducted a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial (B7451036) investigating the efficacy and safety of abrocitinib co-administered with background medicated topical therapy in adolescent subjects 12 to <18 years of age with moderate to severe atopic dermatitis (AD).

The key inclusion criteria for enrollment in the trial specified in the protocol are as follows:

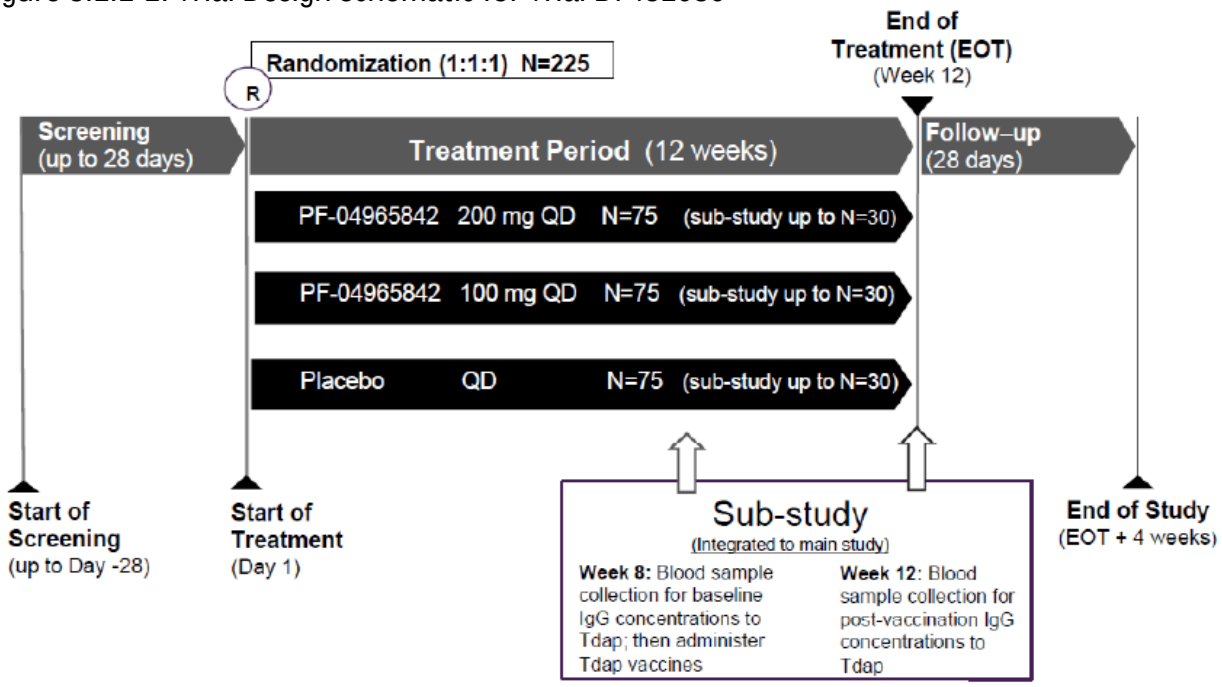
- Male or female 12 to <18 years of age
- Diagnosis of chronic AD at screening and baseline according to Hanafin and Rajka criteria
- Documentation of any of the following:
    - Inadequate response to treatment with medicated topical therapy for AD for at least 4 consecutive weeks, within 6 months before screening; or
    - Treatment with systemic therapy for AD within 6 months before screening; or
    - Subject was a candidate for systemic therapy for AD.
- Body weight ≥25 kg
- Have moderate to severe AD:
    - Affected body surface area (BSA) of ≥10% at baseline
    - Investigator Global Assessment (IGA) score of ≥3 at baseline; see Appendix 14.2 for details on the IGA scale
    - Eczema Area and Severity Index (EASI) score of ≥16 at baseline; see Appendix 14.2 for details on the calculation of EASI
    - Peak Pruritus numeric rating scale (PP-NRS) score of ≥4 at baseline
- During the last 7 days prior to Day 1 of treatment period, the subjects must have used only non-medicated topical therapy (i.e., emollient) at least twice daily, without other active ingredients indicated to treat AD, or other additives which could have affected AD with response to treatment remaining inadequate at baseline.

<u>Peak Pruritus numeric rating scale (PP-NRS):</u>
The pruritus NRS is a single-item patient-reported outcome (PRO) instrument designed to assess itch intensity at its worst. Subjects were asked to assess their worst itching due to atopic dermatitis over the past 24 hours on an NRS anchored by the terms “no itch” (0) and “worst itch imaginable” (10). Pruritus NRS was assessed using an eDiary, daily during the screening period and from Day 1 to 15. After Day 15, the Pruritus NRS was completed only on trial visit days.

The trial was designed to enroll and randomize approximately 225 subjects from approximately 120 global investigational sites. Subjects were randomized to one of the following treatment arms in a 1:1:1 ratio: abrocitinib 200 mg once daily (QD), abrocitinib 100 mg QD or matching placebo. The protocols specified stratifying randomization by baseline disease severity (moderate [IGA = 3] vs. severe [IGA = 4] AD) and age (<18 vs. ≥18).

The trial consisted of a screening period (28 days), a 12-week placebo-controlled, double-blind, treatment period and a 4-week follow-up period. The trial design schematic is presented in Figure 8.1.1-1. Qualified subjects completing the 12-week treatment period of the monotherapy trials had the option to enter the long-term extension (LTE) trial B7451015. Subjects discontinuing early from the trial, or who were otherwise ineligible for the LTE trial, underwent a 4-week follow-up period. Subjects had on-site visits at screening, baseline (Week 0) and Weeks 2, 4, 8, 12 and 16 (follow-up visit). Subjects were also contacted via phone calls at Weeks 1 and 6.

Figure 8.1.1-1: Trial Design Schematic for Trial B7451036



Source: Protocol Amendment 4 for Trial B7451036; page 16

Subjects were required to use non-medicated topical therapy (i.e., emollients) at least twice daily for the last 7 days prior to Day 1, and also be willing and able to use standardized background medicated topical therapy throughout the duration of the trial.

The protocol/SAP specified the following co-primary efficacy endpoints:

- IGA 0/1: Proportion of subjects with IGA score of 0 (clear) or 1 (almost clear) with a reduction of ≥2 points from baseline at Week 12
- EASI-75: Proportion of subjects with at least 75% reduction in EASI score from baseline to Week 12

The protocol/SAP also specified the following key secondary endpoints:

- PP-NRS4: At least 4 points reduction in the Peak Pruritis Numerical Rating Scale (PP-NRS) from baseline to Weeks 2, 4, and 12
- Change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at Week 12

Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD)
The PSAAD is an 11-item, patient-reported questionnaire using a 24-hour recall period, designed to assess the severity of key symptoms and signs of atopic dermatitis including itching, pain, dryness, flaking, cracking, bumps, redness, discoloration, bleeding, fluid, and swelling. Each item was assessed on an 11-point numeric rating scale. The PSAAD was assessed daily. According to the SAP, the PSAAD total score was calculated as the simple arithmetic mean of items 1-11. For analyses, simple weekly averages of all observed values of the PSAAD score were used.

The protocol/SAP also specified 'secondary endpoints' and 'other efficacy endpoints'; however, such endpoints were not included in the multiplicity testing strategy, and therefore, are not presented in this review.

8.1.2. Statistical Methodologies

Analysis Populations:
The primary analysis population specified in the protocol and SAP was the full analysis set (FAS), defined as all randomized subjects receiving at least one dose of study intervention.

The protocol/SAP also specified supportive analyses using the Per Protocol Analysis Set (PPAS), defined as a subset of FAS who had no major protocol violations. According to the SAP, this set included subjects who:

- Met inclusion criterion #1: be 12 to <18 years of age, inclusive, at the time of signing the informed consent.
- Were eligible for the study by way of meeting key inclusion criteria and none of the key exclusion criteria.
- Had valid and non-missing baseline efficacy data (IGA and EASI score).
- Met inclusion criterion #2 of documented prior qualifying treatment for AD.
- Did not permanently discontinue assigned study oral treatment prior to Week 12.
- Had actual, observed IGA and EASI scores at Week 12.
- Did not take a protocol-prohibited medication for the primary diagnosis (high potency TCS or systemic medication or phototherapy).
- Did not take a protocol-prohibited concomitant medication.
- Have an overall compliance of ≥80% but ≤120% with randomized oral treatment at Week 12.
- Adhered to standardized background topical therapy guidelines for ≥80% of treatment days and had used at least one medicated background topical therapy during treatment period.Had no other major protocol violations that is likely to affect materially the clinical observations, or the responses of the patient determined by the clinical team.

Estimand Framework
The protocol/SAP specified the primary estimand for the analysis of the efficacy endpoints to be the 'composite estimand' which estimates the effect of randomized treatment accounting for treatment adherence and response. It includes the following attributes:

- Population: Subjects with moderate-to-severe AD as defined by the inclusion criteria and exclusion criteria and are randomized;
- Variable: Response based on IGA and EASI-75 at Week 12 (co-primary endpoints), the binary key secondary endpoints of PP-NRS4 at Week 2, 4, and 12 and other binary endpoints. Subjects who discontinue from the study treatment for any reason are considered as treatment failures or non-responders after that point;
- Intercurrent event: The intercurrent event is captured through the variable definition;
- Population-level summary: Proportion of subjects who are responders in each treatment arm and differences in proportions of responders between each abrocitinib dose and placebo at Week 12.

The protocol/SAP also specified a secondary estimand to be the 'hypothetical estimand', which estimates the effect as if all subjects maintain their randomized treatment. It includes the following attributes:

- Population: Subjects with moderate-to-severe atopic dermatitis as defined by the inclusion criteria for the double-blind phase and are randomized;
- Variable: Change from baseline in PSAAD total score at Week 12 and other continuous secondary endpoints;
- Intercurrent event: All data after an intercurrent event (e.g., discontinuation of treatment), if collected, are censored;
- Population-level summary: Difference in least-square means between each abrocitinib dose and placebo.

The SAP specified an additional estimand (not specified in the protocol), the 'treatment policy estimand' for a supplemental analysis of the co-primary endpoints with the following attributes:

- Population: Subjects with moderate-to-severe AD as defined by the inclusion criteria to reflect the targeted subject population;
- Variable: Response based on IGA and EASI-75 at Week 12;
- Intercurrent event: All data collected are utilized;
- Population-level summary: Proportion of subjects who are responders in each treatment group and differences in proportions of responders between each abrocitinib dose and placebo.

Analysis methods for the primary and key secondary endpoints:
The SAP specified analyzing the co-primary endpoints (i.e., IGA 0/1 and EASI-75) and the binary key secondary endpoints (i.e., PP-NRS4) using the Cochran-Mantel-Haenszel (CMH) test adjusting for baseline disease severity (IGA = 3 or IGA = 4). The SAP specified summarizing the difference between two treatment groups by the weighted difference and its 95% confidence interval obtained by normal approximation. The SAP specified calculating the difference in proportions within each stratum. The final estimate of the difference in proportions was a weighted average of these stratum-specific estimates using CMH weights.

The SAP specified analyzing the change in PSAAD total score from baseline to Week 12 using a mixed-effect model with repeated measures (MMRM) including fixed effects for treatment group,

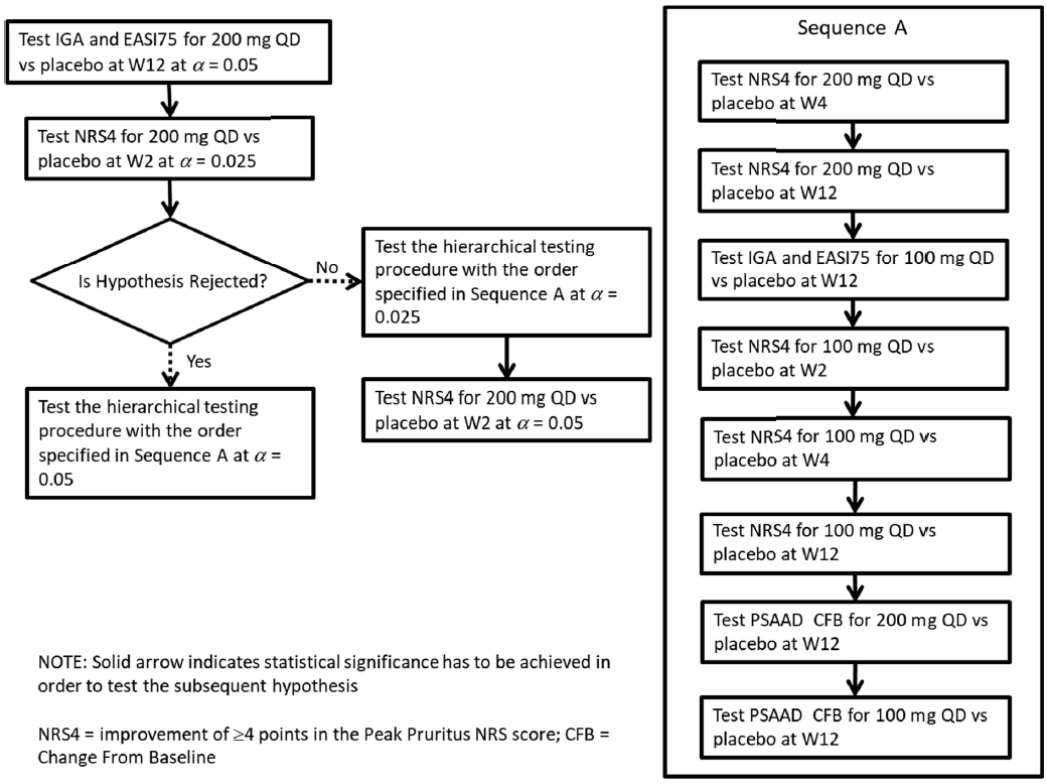
disease severity group, visit, treatment-by-visit interaction, and relevant baseline value. The SAP specified using an unstructured covariance matrix; however, the compound symmetry covariance matrix is used if the model with unstructured variance covariance doesn't converge.

Multiplicity Testing Procedure (MTP):

To control the overall Type I error rate at 5%, the SAP specified a sequential Bonferroni-based iterative multiple testing procedure of the two abrocitinib doses (200 mg QD and 100 mg QD) versus placebo on the primary and key secondary endpoints. The schematic illustrating the multiple testing procedure is provided in Figure 8.1.2-1. The procedure first assesses the co-primary endpoints (IGA and EASI-75 at Week 12) for 200 mg QD versus placebo at the 5% level. If this hypothesis is not rejected, then all subsequent hypotheses are not considered statistically significant. If this hypothesis is rejected, then the process continued as follows:

- The hypothesis for severity of pruritus (PP-NRS4) 200 mg QD versus placebo at Week 2 is assessed at the 2.5% level. If this hypothesis is rejected, then the unused alpha level of 2.5% is passed on to the assessment for the key secondary endpoints and the co-primary endpoints for 100 mg QD versus placebo, in the order specified in Sequence A of Figure 8.1.2-1 at a 5% significance level. All subsequent hypotheses from any point where a hypothesis wasn't rejected were not considered statistically significant.
- If the hypothesis for severity of pruritus (PP-NRS4) for 200 mg QD versus placebo at Week 2 is rejected at the 2.5% level, then the hypotheses for the key secondary endpoints and the co-primary endpoints for 100 mg QD versus placebo, in the order specified in Sequence A are assessed at a 2.5% significance level. If all hypotheses in this sequence are rejected, then the unused alpha level of 2.5% was passed on to the assessment of the hypothesis for severity of pruritus (200 mg QD versus placebo) at Week 2 at the 5% level. All subsequent hypotheses from any point where a hypothesis cannot be rejected are not considered statistically significant.

Figure 8.1.2-1: Schematic for Multiple Testing Procedure for Trial B7451036



Source: SAP for Trial B7451036; page 21

Methods for handling the missing data:

The SAP specified that for subjects who permanently discontinue trial for any reason, any data will be defined as "non-responsive" at all subsequent visits after the last observed value; for other subjects, any observations missing intermittently (including baseline values) will be considered missing completely at random (MCAR) and will remain missing in the analysis.

The SAP specified additional analyses based on the treatment policy estimand where missing data will be handled using a multiple imputation method with a tipping point (TP) approach as described below:

Missing observations for the active treatment groups (abrocitinib 200 mg and 100 mg) are imputed multiply using a tipping point analysis to estimate the treatment effect. The observed IGA/EASI-75 responses at Weeks 2, 4, 8, and 12 are used for the imputation model which is a logit Generalized Linear Mixed Model (GLMM) with treatment, visit and treatment-by-visit as fixed factors, and a subject-specific, zero-mean, normally-distributed random effect. Using the estimated posterior predictive distribution of the GLMM model parameters obtained using Markov Chain Monte Carlo (MCMC) methods, estimates of the posterior predictive probability of response will be calculated for each active treatment group. For each subject, missing responses are imputed using random Bernoulli draws based on the posterior probability of response. The posterior predictive response probability in each active group is re-defined as a weighted linear combination of the posterior predictive response probability from this group and the posterior predictive response probability from the placebo group, where the missing observations in placebo group are assumed to be missing at random (MAR). These weights are

fixed MNAR quantities for the active groups. A single imputation of the missing value was to be sampled from a Bernoulli distribution with this corresponding shifted/re-defined probability of response for the active groups. The SAP specified repeating this imputation multiple times with different MCMC samples to obtain multiple completed datasets. For each such completed dataset, the estimates of the proportions and CMH-weighted difference of proportions between each active group and placebo are obtained along with the associated standard errors. To combine the multiple estimates and standard errors across the imputed datasets and provide p-values, the Rubin's rule was used.

The SAP did not specify the number of imputations and the seed for the multiple imputations and the exact values of weights used for the tipping analysis process. However, the SAP specified two extreme scenarios: weights of 0 and 1 that correspond to analyses under Missing at Random (MAR) and Jump-to-Reference (JTR), respectively.

8.1.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial B7451036 enrolled and randomized a total of 287 subjects from 99 investigational sites. Two subjects in the abrocitinib 200 mg arm were not dosed, and therefore, were not included in the FAS. Table 8.1.3-1 presents the disposition of subjects for Trial B7451036. The discontinuation rate in the trial was generally low (4%) and slightly higher in the placebo arm compared to the abrocitinib arms.

Table 8.1.3-1: Disposition of Subjects – Trial B7451036

	Abrocitinib		
	200 mg	**100 mg**	**Placebo**
Randomized	94	95	96
Not dosed	2	0	0
FAS	96	95	96
Discontinued	3 (3%)	3 (3%)	6 (6%)
Adverse Event (AE)	2 (2%)	1 (1%)	2 (2%)
Lost to Follow-up	0 (0%)	1 (1%)	2 (2%)
Protocol Deviation	1 (1%)	0 (0%)	0 (0%)
Withdrawal by Parent/Guardian	0 (0%)	1 (1%)	0 (0%)
Other	0 (0%)	0 (0%)	1 (1%)

Source: Statistical Reviewer's Analysis (same as Applicant's analysis); ADSLxpt

Table 8.1.3-2 presents the demographics and baseline disease characteristics for Trial B7451036. The majority of the subjects in the trial were White (approximately 56%) followed by Asian (approximately 33%). Demographics were generally balanced across the treatment arms. A slightly higher proportion of males were randomized to the 100 mg and placebo arms compared to the 200 mg arm. It's noted that one subject in the placebo arm was over 18 years old when randomized in the trial.

Table 8.1.3-2: Demographics and Baseline Disease Characteristics- Trial B7451036 (FAS[1])

	Abrocitinib		
	200 mg (N=94)	100 mg (N=95)	Placebo (N=96)
Age (years)			
Mean (SD)	14.7 (1.8)	15.1 (1.8)	14.8 (1.7)
Median	15	16	14
Range	11 – 17	12 – 17	12 – 18[2]
Sex, n (%)			
Male	38 (40)	50 (53)	52 (54)
Female	56 (60)	45 (47)	44 (46)
Race, n (%)			
White	52 (55)	52 (55)	56 (58)
Black or African American	5 (5)	9 (9)	3 (3)
American Indian or Alaska Native	4 (4)	3 (3)	1 (1)
Native Hawaiian or Other Pacific Islander	1 (1)	0 (0)	1 (1)
Asian	31 (33)	31 (33)	32 (33)
Multiple	1 (1)	0 (0)	1 (1)
Missing	0 (0)	0 (0)	2 (2)
Region, n (%)			
Us/Canada	28 (30)	28 (29)	33 (34)
Asia	28 (30)	29 (31)	29 (30)
Europe	29 (31)	31 (33)	27 (28)
Latin America	9 (10)	7 (7)	7 (7)
Duration of AD (years)			
Mean (SD)	9.7 (5.3)	9.8 (5.4)	10.5 (4.8)
Median	12	11	12
Range	1 – 18	1 – 19	0 – 18
Prior Use to Systemic Therapy for AD			
Yes	22 (23)	27 (28)	24 (25)
No	72 (77)	68 (72)	72 (75)
IGA, n (%)			
3 – Moderate	61 (65)	57 (60)	57 (59)
4 – Severe	33 (35)	38 (40)	39 (41)
EASI			
Mean (SD)	29.5 (12.2)	31.0 (12.8)	29.2 (12.7)
Median	25.4	26.5	24.5
Range	16 – 67.8	16.6 – 72.0	8.7 – 63.6
Percent BSA			
Mean (SD)	48.7 (21.7)	51.2 (21.7)	45.8 (22.)
Median	47.0	48.0	38.2
Range	12 – 96	10 – 100	10.6 – 100
Pruritus NRS			
Mean (SD)	6.8 (2.0)	7.0 (1.8)	7.2 (1.7)
Median	7.0	7.0	7.0
Range	1.0 – 10.0	3.0 – 10.0	4.0 – 10.0
>=3	90 (96%)	95 (100%)	96 (100%)
>=4	90 (96%)	93 (98%)	96 (100%)

Source: Reviewer's Analysis (same as Applicant's analysis); ADSLxpt, ADAD.xpt, ADEA.xpt, ADNR.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention

[2] Subject [redacted] (b) (6) was over 18 years old when enrolled

8.1.4. Results for the Co-Primary Efficacy Endpoints

Table 8.1.4-1 presents the results for the co-primary endpoints at Week 12 for Trial B7451036 based on the primary estimand ('composite estimand'). Missing data are imputed using the non-responder imputation (NRI). It should be noted that such method for handling the missing data is slightly different from the one pre-specified in the protocols/SAPs, where only subjects who permanently discontinued the trial were defined as non-responders at all subsequent visits. Of note, there are a few subjects who did not permanently discontinue the trial and yet had missing outcomes at Week 12, either because they missed the visit or because they were out of the analysis window of time. Such subjects remained missing in Applicant's analysis (results not presented herein), while they were imputed as non-responders in the statistical reviewer's analysis (results in Table 8.1.4-1); conclusions remained the same in the two analyses. Both abrocitinib doses (200 mg and 100 mg) were statistically superior to placebo for the co-primary endpoints at Week 12. A higher treatment effect is observed in the higher dose 200 mg compared to the lower dose of 100 mg. The reviewer further conducted a sensitivity analysis based excluding the adult subject enrolled in the trial from FAS. Results are presented in Table 11.1.10-2 of Appendix 14.2 and are very similar to the results in Table 8.1.4-1.

Table 8.1.4-1: Results for the Co-Primary Endpoints at Week 12 - Trial B7451036 (FAS; NRI[1])

	Abrocitinib		
	200 mg (N=94)	**100 mg (N=95)**	**Placebo (N=96)**
IGA 0/1	43 (46%)	37 (39%)	23 (24%)
Difference from placebo (95% CI)[2]	21% (8%, 34%)	15% (2%, 28%)	-
P-Value[3]	0.0023	0.0248	-
EASI-75	67 (71%)	61 (64%)	39 (41%)
Difference from placebo (95% CI)[2]	30% (17%, 43%)	23% (10%, 37%)	
P-Value[3]	<0.001	<0.001	

Source: Statistical Reviewer's Analysis (slightly different from Applicant's Analysis); ADAD.xpt, ADEA.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention; Missing data are imputed using the non-responder imputation (NRI) method
[2] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.
[3] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by baseline disease severity.

Results for the per protocol analysis set (PPAS) as defined in Section 8.1.2 are presented in Table 8.1.4-2. The treatment effects for the co-primary endpoints were similar to the ITT population (see Table 8.1.4-1). It is noted that IGA results based on PPAS are not significant for the 100 mg dose which could be attributed to the smaller sample size.

Table 8.1.4-2: Results for the Co-Primary Endpoints at Week 12 - Trial B7451036 (PPAS; NRI[1])

	Abrocitinib		
	200 mg (N=78)	**100 mg (N=73)**	**Placebo (N=70)**
IGA 0/1	36 (46%)	32 (44%)	19 (27%)
Difference from placebo (95% CI)[2]	18% (3%, 33%)	15% (<0%, 31%)	-
P-Value[3]	0.0238	0.0586	-
EASI-75	59 (76%)	55 (75%)	30 (43%)

Difference from placebo (95% CI)[2]	31% (17%, 46%)	30% (15%, 45%)	-
P-Value[3]	<0.001	<0.001	-

Source: Statistical Reviewer's Analysis (slightly different from Applicant's Analysis); ADAD.xpt, ADEA.xpt
[1] Per Protocol Analysis Set (PPAS) as defined in Section 8.1.1.2.; Missing data are imputed using the non-responder imputation (NRI) method
[2] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.
[3] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by baseline disease severity

Table 8.1.4-3 presents the number of subjects with missing data for the co-primary efficacy endpoints by visit, treatment arm and trial through Week 12. The amount of missing data at Week 12 was in general low (approximately 6%) and comparable across treatment arms. Among subjects with missing data at Week 12, 9 subjects had missing measure due to COVID-19 impact.

Table 8.1.4-3: Missing Data for the Co-Primary Endpoints through Week 12 - Trial B7451036 (FAS[1])

	Abrocitinib		
	200 mg (N=94)	**100 mg (N=95)**	**Placebo (N=96)**
Week 2	2 (2%)	3 (3%)	5 (5%)
Week 4	3 (3%)	4 (4%)	0 (0%)
Week 8	5 (5%)	4 (4%)	5 (5%)
Week 12	4 (4%)	8 (8%)	6 (6%)
Due to COVID-19	1 (1%)	4 (4%)	4 (4%)

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADEA.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention

The primary method of handling missing data specified in the protocols was non-responder imputation (NRI). The statistical reviewer considered sensitivity analyses using the following methods for the handling of missing data:

- Last Observation Carried Forward (LOCF)
- Observed Cases (OC)
- Multiple Imputation (MI): The MI procedure used the Markov Chain Monte Carlo (MCMC) method stratifying on treatment arm to impute missing scores and generated 100 imputed datasets
- Worst Case Scenario (WCS): all subjects with missing data in the active arms are imputed as non-responders and all subjects with missing data in the placebo arm are imputed as responders.

The results for the co-primary endpoints were similar across the various methods of handling the missing data. Under the worst-case scenario analysis, the 200 mg remained superior to placebo (p-values<0.05) for both endpoints showing robust treatment effect for the 200 mg to the worst-case scenario. However, the worst-case scenario analysis led to placebo response rates that were comparable to the response rates on the 100 mg for the IGA 0/1 endpoint, while the 100 mg in this scenario remained superior to placebo (p-values<0.05) for the EASI-75 endpoint; see Table 8.1.4-4.

Table 8.1.4-4: Results for Co-Primary Efficacy Endpoints at Week 12 with Different Approaches for Handling Missing Data - Trial B7451036 (FAS[1])

Co-Primary Endpoint	Abrocitinib 200 mg (N=94)	Abrocitinib 100 mg (N=95)	Placebo (N=96)	200 mg - Placebo (P-Value)[2]	100 mg - Placebo (P-Value)[2]
IGA 0/1					
NRI (Primary)	46%	44%	27%	21% (0.002)	15% (0.025)
LOCF	47%	42%	27%	19% (0.007)	15% (0.028)
OC	48%	43%	26%	21% (0.003)	16% (0.020)
MI	48%	42%	27%	20% (0.005)	15% (0.026)
WCS	46%	39%	30%	15% (0.037)	9% (0.204)
EASI-75					
NRI (Primary)	71%	64%	41%	30% (<0.001)	23% (<0.001)
LOCF	72%	71%	45%	27% (<0.001)	26% (<0.001)
OC	74%	70%	43%	30% (<0.001)	26% (<0.001)
MI	74%	69%	44%	29% (<0.001)	25% (<0.001)
WCS	71%	64%	47%	23% (<0.001)	17% (0.0136)

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADEA.xpt
Abbreviations: NRI=Non-Responder Imputation; LOCF=Last Observation Carried Forward; OC=Observed Cases; MI=Multiple Imputation; WCS=Worst-Case Scenario
[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention.
[2] Difference and P-value were calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by baseline disease severity.

The Applicant conducted a tipping point (TP) analysis as a sensitivity analysis to assess the impact of missing data at Week 12 for the endpoints of IGA 0/1 and EASI-75. For this TP analysis, missing responses in the active treatment groups at Week 12 were imputed using multiple imputations using random Bernoulli based on the estimated posterior probability of response. For imputing missing responses in each of the active treatment groups, a weighted linear combination of the response probabilities from this group and the posterior predictive response probability from the placebo group was considered, using weight values of 0, 0.25, 0.5, 0.75 and 1. Values of 0 and 1 for this weight corresponded to analyses under Missing at Random (MAR) and Jump-to-Reference (JTR), respectively. For the imputation model and estimation method, the reader is referred to Section 8.1.2. For all weights considered for placebo response probability, abrocitinib 200 mg remained significant for IGA 0/1 and EASI-75 responses at Week 12. Abrocitinib 100 mg became insignificant for the IGA 0/1 endpoint when the weight was equal to 1 (i.e., Jump-to-Reference analysis) while it remained significant for the EASI endpoint.

The statistical reviewer conducted additional tipping point analysis for IGA 0/1 at Week 12 exploring smaller increments of response rates in the abrocitinib 100 mg and placebo arms: subjects with missing data were imputed as responders at rates 5% to 30%, with increments of 5% in the abrocitnib 100 mg arm, and 0% to 75%, with increments of 5%, in the placebo arm, using multiple imputation. Abrocitinib 100 mg was no longer significant on IGA 0/1 endpoint when the placebo response rate is 30% and abrocitinib response rate is 5% for the missing data; abrocitinib 200 mg did not become insignificant on EASI-75 endpoint in the range explored. When the missing values on the 100 mg arm were imputed as non-response, the results tipped into non-significance when more than 35% of subjects on the placebo arm and less that 10% in the active arm were imputed as responders; see. However, such assumptions do not appear plausible based on the observed response rates (43% for abrocitinib 100 mg and 26% for placebo). Thus, the IGA 0/1 endpoint results on the 100 mg dose also appear to be robust to the handling of missing data.

Table 8.1.4-5: Tipping Point Analysis for Abrocitinib 100 mg for IGA 0/1- Trial B7451036 (FAS[1])

100 mg		Placebo														
		0.2	**0.25**	**0.3**	**0.35**	**0.4**	**0.45**	**0.5**	**0.55**	**0.6**	**0.65**	**0.7**	**0.75**	**0.8**	**0.85**	**0.9**
0.3	Difference	16.2	16.0	15.8	15.5	15.2	14.8	14.8	14.7	14.4	14.2	13.7	18.6	13.4	12.7	12.4
	p-value	0.018	0.0197	0.022	0.0235	0.0275	0.0335	0.0335	0.035	0.039	0.042	0.049	0.008	0.054	0.066	0.074
0.25	Difference	15.5	15.3	15.1	14.9	14.6	14.2	14.2	14.1	13.8	13.6	13.0	12.7	12.1	11.8	11.4
	p-value	0.022	0.0245	0.027	0.030	0.035	0.041	0.041	0.0435	0.0485	0.053	0.059	0.066	0.078	0.089	0.0998
0.2	Difference	15.0	14.8	14.6	14.4	14.1	13.7	13.7	13.6	13.2	13.0	12.5	12.2	11.6	11.3	10.8
	p-value	0.0255	0.0278	0.031	0.033	0.039	0.046	0.046	0.049	0.054	0.058	0.067	0.074	0.0908	0.102	0.113
0.15	Diff	14.5	14.3	14.1	13.9	13.5	13.1	13.1	13.0	12.7	12.5	12.0	11.7	11	10.7	10.3
	p-value	0.032	0.034	0.038	0.040	0.047	0.055	0.055	0.0579	0.0635	0.0679	0.081	0.0873	0.108	0.119	0.1305
0.1	Difference	14	13.7	13.5	13.3	13.0	12.6	12.6	12.5	12.2	12	11.5	11.1	10.5	10.2	9.8
	p-value	0.0377	0.0402	0.044	0.047	0.055	0.0635	0.0635	0.066	0.074	0.0796	0.094	0.100	0.123	0.134	0.150
0.05	Difference	13.3	13.1	12.9	12.7	12.4	12.0	12.0	11.9	11.5	11.3	10.8	10.5	9.9	9.6	9.1
	p-value	0.046	0.0495	0.045	0.058	0.066	0.077	0.077	0.081	0.089	0.095	0.111	0.120	0.145	0.159	0.177

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADEA.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention.

Note: Difference and P-value were calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by baseline disease severity.

8.1.5. Results for the Key Secondary Efficacy Endpoints

The main key secondary endpoints are based on the Patient Reported Outcome (PRO) of Peak Pruritus numeric rating scale (PP-NRS). The reader is reminded that pruritus NRS was assessed daily from Day 1 to 15, while after Day 15, it was assessed only on trial visits (i.e., at Weeks 4, 8, and 12). Baseline was defined as the last observation collected on or prior to the first dose of the study drug. The Week 2 analysis value for PP-NRS was defined as the observation taken on the study day closest to Day 15 within a window starting from Day 2 and ending at Day 22. The COA reviewer assigned to the original submission of this NDA (approved on 1/14/2022 for adult patients), Dr. Mira Patel, noted that the single administration of the peak pruritus NRS at the clinic visits may not provide a complete presentation of the symptom as it may not reflect day-to-day variability in this condition.

Table 8.1.5-1 presents the number of subjects with missing PP-NRS data by visit and treatment arm from Week 2 through Week 12.

Table 8.1.5-1: Missing Data for PP-NRS by Visit - Trial B7451036 (FAS[1])

	Abrocitinib		
	200 mg (N=90)	**100 mg (N=93)**	**Placebo (N=96)**
Day 15	10 (11%)	10 (11%)	13 (14%)
Week 2	2 (2%)	1 (1%)	1 (1%)
Week 4	8 (9%)	5 (5%)	5 (5%)
Week 8	7 (8%)	8 (9%)	7 (7%)
Week 12	18 (20%)	19 (20%)	16 (17%)

Source: Statistical Reviewer's Analysis; ADNR.xpt,
[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention.
Note: The table excludes subjects with baseline PP-NRS score <4.

The results for the key secondary endpoint of at least 4 points reduction from baseline in the Peak Pruritus NRS score (PP-NRS4) at Weeks 2, 4 and 12 are presented in Table 8.1.5-2. Abrocitinib 200 mg was statistically superior to placebo for this endpoint at all timepoints; however, the 100 mg dose of abrocitinib was not statistically superior to placebo at Week 4. The reviewer further conducted a sensitivity analysis based excluding the adult subject enrolled in the trial from FAS. Results are presented in Table 11.1.10-3 of Appendix 14.2 and are very similar to the results in Table 8.1.5-2.

Table 8.1.5-2: Results for the Key Secondary Efficacy Endpoints - Trial B7451036 (FAS; NRI[1])

	Abrocitinib		
PP-NRS4[2]	**200 mg (N=90)**	**100 mg (N=93)**	**Placebo (N=96)**
Week 2	34 (38%)	25 (27%)	12 (13%)
Difference from placebo (95% CI)[3]	25% (13%, 37%)	15% (3%, 26%)	-
P-Value[4] (Significant per MTP[5])	<0.001	0.0124	-
Week 4	42 (47%)	28 (30%)	19 (20%)
Difference from placebo (95% CI)[3]	27% (14%, 40%)	10% (-2%, 23%)	-
P-Value[4] (Significant per MTP[5])	<.0001	0.1022 (No)	-
Week 12	41 (46%)	40 (43%)	25 (26%)
Difference from placebo (95% CI)[3]	19% (6%, 33%)	17% (4%, 30%)	-

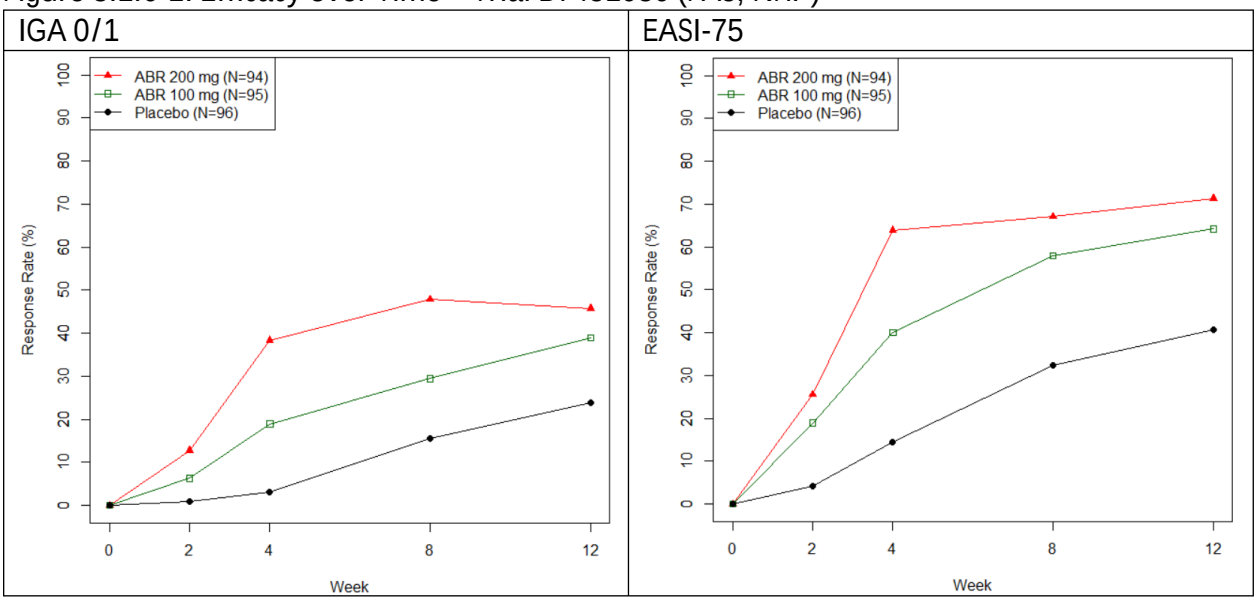
P-Value[4] (Significant per MTP[5])	0.0067 (Yes)	*	-

Source: Statistical Reviewer's Analysis (slightly different from Applicant's Analysis); ADNR.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention. N is the number with a baseline score ≥4. Missing data are imputed using the non-responder imputation (NRI) method
[2] Proportion of subjects achieving ≥4 points improvement from baseline in pruritus Numeric Rating Scale (NRS) among subjects with baseline score of ≥4
[3] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.
[4] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted baseline disease severity.
[5] Multiplicity Testing Procedure (MTP): the protocols specified a graphical approach to control the Type I error rate for testing multiple treatment groups and endpoints; see Figure 8.1.2-1
* Testing stops per MTP.

8.1.6. Efficacy Over Time

Figure 8.1.6-1 presents the results of IGA 0/1 and EASI-75 over time for Trial B7451036.

Figure 8.1.6-1: Efficacy over Time – Trial B7451036 (FAS; NRI[1])



Source: Statistical Reviewer's Analysis; ADAD.xpt, ADEA.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention; Missing data are imputed using the non-responder imputation (NRI) method
Abbreviations: ABR=abrocitinib.

8.1.7. Patient Reported Outcomes

In addition to PP-NRS4, the protocol Trials B7451036 specified the following key secondary efficacy endpoints based on the patient reported outcome (PRO) of Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD).

- Change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at Week 12 [100 mg vs. placebo and 200 mg vs. placebo]

As noted in Section 8.1.1 the PSAAD is an 11-item, patient-reported questionnaire using a 24- hour recall period, designed to assess the severity of key symptoms and signs of atopic dermatitis including itching, pain, dryness, flaking, cracking, bumps, redness, discoloration, bleeding, fluid, and swelling. Each item was assessed on an 11-point numeric rating scale. The PSAAD total score was calculated as the simple arithmetic mean of items 1-11.

Although the Agency did not provide comments on the protocol for Trial B7451036, the Agency commented on such endpoint (i.e., change from baseline in PSAAD total score) during the IND stage in the context of the phase 3 trials used to approve the product in adult patients. In particular, the Agency noted (advice letter dated 2/15/2018) that a mere change from baseline might not translate to a clinically relevant difference and the results from a mixed-effect model with repeated measures (MMRM) approach that incorporates information from each visit might not be clinically meaningful; yet the analysis might yield a statistically significant treatment effect due to the incorporation of all data. According to the pre-specified multiplicity testing plan (see Figure 8.1.2-1), as PP-NRS4 for comparison of abrocitinib 100 mg versus placebo at Week 4 was not statistically significant, formal testing cannot be done for the endpoints based on PSAAD listed above. The results for the absolute change from baseline in PSAAD total score to Week 12 are provided in Table 11.1.10-5 of Appendix 14.2.

The statistical reviewer also explored the proportion of subjects with PSAAD total score of 0 at Week 12. Weekly scores were average values of daily observations over 7 days for this analysis. Only a very small proportion of subjects treated with abrocitinib had PSAAD Total Score of 0 at Week 12 (are results in Table 11.1.10-6 of Appendix 14.2).

Of note, itching is one of the 11 items of PSAAD, where subjects responded to the question “how itchy was your skin over the past 24 hours” using a 0 to 10 numeric rating scale from “not itchy” to “extremely itch”. The statistical reviewer considered supportive analyses for itching based on a 4-point responder definition for PSAAD itching in subjects with a baseline PSAAD itching score of at least 4. For such analyses, weekly scores were average values of daily observations over 7 days; weekly scores were set to missing if there were less than 4 daily observations in the week. The results for the 4-point responder analyses are presented in Table 11.1.10-7 of Appendix 14.2. Response rates for Week 2 appear to be much lower compared to response rates based on the PP-NRS endpoint (using single-time assessments), while corresponding response rates at Weeks 4 and 12 appear comparable between analyses on pruritus NRS and PSAAD Itching Item 1.

8.1.8. Efficacy Results by Prior Use of Systemic Therapy

Table 8.1.8-1 presents the results for the co-primary efficacy endpoints at Week 12 by prior use of systemic therapy for AD in Trial B7451036. The treatment effect for abrocitinib 100 mg was lower in subjects with prior use of systemic therapy for AD compared to those without for both co-primary endpoints, while the treatment effect was more consistent across these two subgroups for the 200 mg dose. It should be noted though that a small proportion of subjects with prior use of systemic therapy for AD was enrolled in the trial (approximately 26%).

Table 8.1.8-2 presents the results of the co-primary efficacy endpoints at Week 12 in subjects who had treatment failure or who were intolerance to prior systemic therapy for AD. A very small proportion of subjects had treatment failure or intolerance to prior systemic therapy for AD to allow any meaningful conclusions regarding efficacy for such subgroup.

Table 8.1.8-1: IGA 0/1 and EASI-75 Response Rates at Week 12 in Subgroups by Prior Systemic Therapy for AD - Trial B7451036 (FAS; NRI[1])

	IGA 0/1			EASI-75		
	ABR 200 mg (N=94)	**ABR 100 mg (N=95)**	**Placebo (N=96)**	**ABR 200 mg (N=94)**	**ABR 100 mg (N=95)**	**Placebo (N=96)**
Prior Systemic: Yes						
N	22	27	24	22	27	24
Estimate, %	50%	26%	8%	68%	52%	29%
Active – Placebo (%)	42%	18%	-	39%	23%	
95% CI	(18%, 65%)	(-2%, 37%)	-	(12%, 66%)	(-4%, 49%)	
Prior Systemic: No						
N	72	68	72	72	68	72
Estimate, %	44%	44%	29%	72%	69%	44%
Active – Placebo (%)	15%	15%	-	28%	25%	-
95% CI	(<0%, 31%)	(-1%, 31%)	-	(12%, 43%)	(9%, 41%)	-

Source: Reviewer's Analysis; ADAD.xpt, ADEA.xpt, ADCM.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention; Missing data are imputed using the non-responder imputation (NRI) method.

Table 8.1.8-2: IGA 0/1 and EASI-75 Response Rates at Week 12 in Subgroup who had Treatment Failure or Intolerance to Prior Systemic Therapy for AD – Trial B7451036 (FAS; NRI[1])

	ABR 200 mg (N=94)	**ABR 100 mg (N=95)**	**Placebo (N=96)**
IGA 0/1 Response			
N	11	13	14
Estimate, %	45%	15%	7%
Active – Placebo (%)	38%	8%	-
95% CI	(6%, 71%)	(-16%, 32%)	-
EASI-75			
N	11	13	14
Estimate, %	64%	38%	21%
Active – Placebo (%)	42%	17%	-
95% CI	(7%, 78%)	(-17%, 51%)	-

Source: Reviewer's Analysis; ADAD.xpt, ADEA.xpt, ADCM.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention; Missing data are imputed using the non-responder imputation (NRI) method.

8.1.9. Additional Analyses for Itching at Week 2

As noted in Section 8.1.1, the peak pruritus NRS was assessed daily for the first two weeks in the pivotal trials, while after Day 15, it was assessed only on trial visit (i.e., at Weeks 4, 8, and 12). The reviewer in this section repeats the analysis for the PP-NRS4 endpoint (i.e., the proportion of subjects achieving ≥4 points improvement from baseline pruritus NRS among subjects with baseline score of ≥4) at Week 2 using the weekly average values of daily observations over 7 preceding days for the baseline and Week 2 scores. Results for such analyses are presented in Table 8.1.9-1

(Corresponding results excluding the adult subjects are presented in Table 11.1.10-4 of Appendix 14.2). Response rates in Table 8.1.9-1 are lower compared to response rates based on analyses using single timepoint assessment for baseline and Week 2 scores (see PP-NRS4 results at Week 2 in Table 8.1.5-2). Both doses did not show significant benefit over placebo.

Table 8.1.9-1: Results for Peak Pruritus NRS at Week 2 – Trial B7451036 (FAS; NRI[1])

	Abrocitinib		
PP-NRS4[2]	**200 mg (N=75)**	**100 mg (N=82)**	**Placebo (N=80)**
Week 2	14 (19%)	11 (13%)	7 (9%)
Difference from placebo (95% CI)[3]	10% (-1%, 21%)	5% (-5%, 15%)	
P-Value[4]	0.077	0.324	

Source: Statistical Reviewer's Analysis; ADNR.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention; Missing data are imputed using the non-responder imputation (NRI) method
[2] Proportion of subjects achieving ≥4 points improvement from baseline in Peak Pruritus Numeric Rating Scale (PP-NRS) among subjects with baseline score of ≥4
[3] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.
[4] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).
Note: Weekly scores were average values of daily observations over 7 days for this analysis; weekly scores were set to missing if less than 4 daily observations in the week.

8.1.10. Findings in Special/Subgroup Populations

Age, Sex, Race, Weight, and Baseline Disease Severity:
The results for IGA 0/1 and EASI-75 at Week 12 by age (<18, 18-64), sex, race, weight (<70, 70-100, >100 kg), and baseline IGA score are presented in Table 11.1.10-8 and Table 11.1.10-9 of Appendix 14.2, respectively.

Country:
Trial B7451036 was conducted in 13 countries (i.e., United States, Mexico, China, Japan, Taiwan, Australia, Hungary, Netherlands, Czech Republic, Poland, Latvia, Italy, and Spain). Table 11.1.10-10 of Appendix 14.2 presents efficacy results for IGA 0/1 and EASI-75 at Week 12 by country for Trial B7451036. The countries in the table are listed in descending order based on the total number of subjects enrolled. There was some variability in treatment effect across the countries; however, this may be due to the relatively small sample sizes in several of the countries.

8.2. Review of Safety

The submitted B7451036 (TEEN) clinical trial, evaluated the safety of abrocitinib 100 mg QD and 200 mg QD in adolescent subjects with moderate-to-severe atopic dermatitis. Abrocitinib was well tolerated in adolescents. A higher incidence of AEs was reported in abrocitinib dosed groups; however, the percentage of subjects experiencing SAEs, severe AEs, and AEs leading to study discontinuation were low and similar to the original clinial trials. No serious infections were reported and no deaths. There were no cases of MACE or VTE in the trial. No subjects discontinued the trial due to thrombocytopenia or lymphopenia. However, dose-dependent decrease in platelets in abrocitinib dosed subjects were seen with a nadir at Week 4, similar to the experience in adult trials. The safety in adolescents appears similar to the original approval clinical trials. Given the small sample size, the low numbers of AEs cannot be interpreted as having a better safety profile in this population. No unique safety signal was exposed in B7451036 (TEEN).

8.2.1. Safety Review Approach

The evaluation of safety based of clinical trial B7451036 (TEEN) focuses on the assessment of adverse events, comparison between the treatment arms and comparisons with the safety data characterized in the original NDA.

8.2.2. Review of the Safety Database

Overall Exposure

Both the median and mean duration of treatment were similar across the treatment groups. The median study treatment exposure time was similar across all treatment groups (85 days), and the mean study treatment exposure was also similar (84.0 days to 85.5 days).

Table 8.2.2-1: Duration of Treatment – Safety Analysis Set

Duration of Treatment (Days)	Placebo (n= 96)	Abrocitinib 100 mg QD (n= 95)	Abrocitinib 200 mg QD (n= 94)
n	96	95	94
Median (Min, Max)	84 (43, 105)	85 (28, 105)	84 (8, 113)
Mean (Std Dev.)	82.2 (8.3)	82.4 (10.7)	81.3 (13.7)

Source: Applicant Study Report B7451036.

Table 8.2.2-2: Study Treatment Exposure – Safety Analysis Set

Exposure Time (Days)	Placebo (n= 96)	Abrocitinib 100 mg QD (n= 95)	Abrocitinib 200 mg QD (n= 94)
n	96	95	94

Median (Min, Max)	85 (43, 113)	85 (28, 105)	85 (17, 113)
Mean (Std Dev.)	85.5 (8.0)	85.5 (8.4)	84.0 (11.8)

Source: Applicant Study Report B7451036.

Adequacy of the safety database:

The safety analysis set (safety database) for B7451036 (TEEN) study evaluated 285 subjects under the age of 18 years old with moderate-to-severe atopic dermatitis. The data provided was deemed adequate to evaluate high frequency events.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

All issues regarding data integrity was adequately addressed by the applicant during the review.

Categorization of Adverse Events

The categorization of adverse events are TEAE (treatment emergent adverse events), SAE (serious adverse events), and AE (common adverse events). Review of selected adverse events are evaluated for those at a 1% higher rate than placebo. The proportion of subjects with all-causality TEAEs was higher for the abrocitinib 200 mg group (62.8%) compared to the abrocitinib 100 mg (56.8%) and placebo (52.1%) groups.

8.2.4. Safety Results

Deaths

There were no reported death in trial B7451036.

Serious Adverse Events

The number of subjects reporting serious adverse events was limited. Only 3 subjects reported serious adverse events in TEEN trial and only 1 of the these 3 subjects was dosed with abrocitinib (200 mg dosing arm), while there were two subjects in the placebo group. These events were in the gastrointestinal disorders with severe nausea. No subjects reported serious infection TEAE and there were no deaths.

Table 8.2.4-1: Proportion and Incidence Rates for Serious TEAE (B7451036) – Short Term Safety Pool

		Placebo (n= 96)	Abrocitinib 100 mg QD (n= 95)	Abrocitinib 200 mg QD (n= 94)
Serious Adverse Events				
	Number of Subjects with Events, n (%)	2 (2.1)	0	1 (1.1)
	Total Drug Exposure (PY)	22.97	22.86	22.64
	Incidence Rates (95% CI)	8.71 (1..05, 31.46)	0.00 (0.00, 16.14)	4.42 (0.11, 24.61)
Treatment Comparison				
	Difference of Incidence Rates (95% CI): Abrocitinib vs Placebo		-8.71 (.22.88, 5.47)	-4.29 (-19.15, 10.56)
	Difference of Incidence Rates (95% CI): Abrocitinib (200mg vs 100mg)			4.42 (-7.28, 16.12)

Source: Supplement submission: 22-AUG-2022

The small sample size does not make incidence rates for SAEs accurate in this population.

Dropouts and/or Discontinuations Due to Adverse Effects

The incidence of permanent discontinuation due to TEAEs was low in the study and similar across all treatment groups. No specific pattern was identified.

Table 8.2.4-2: Summary of Subject Discontinuations from Study Drug Due to Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set

Number of Subjects Evaluable for AEs	Placebo (n= 96)	Abrocitinib 100 mg QD (n= 95)	Abrocitinib 200 mg QD (n= 94)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)
Any Adverse Event	2 (2.1)	1 (1.1)	2 (2.1)
Gastrointestinal Disorders	0	0	1 (1.1)
Gastroesophageal reflux disease	0	0	1 (1.1)
Nausea	0	0	1 (1.1)
Vomiting	0	0	1 (1.1)

Infection And Infestations	2 (2.1)	1 (1.1)	0
Gastrointestinal infection	0	1 (1.1)	0
Upper respiratory tract infection	1 (1.0)	0	0
Wound abscess	1 (1.0)	0	0
Nervous System Discorders	0	0	1 (1.1)
Headache	0	0	1 (1.1)

Source: B7451036 Report Body Table 24
Subjects were only counted once per treatment per event
Totals for the No. of Subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
MedDRA v23.0 coding dictionary applied.

Significant Adverse Events

This supplement review specifically evaluates adverse events of special interest that were notable in the adult clinical trials for the original NDA approval and across the JAK inhibitor class. For example, in this TEEN trial, a search forpulmonary embolism, malignancies, or MACE was conducted; no cases were found. The incidence of herpes infections are described in Table 8.2.4.3.

Table 8.2.4-3: Incidence of Herpes CMQ by System Organ Class and Preferred Term (B7451036) – Safety Analysis Set

	Placebo (n= 96) PY IR (95 CI)	Abrocitinib 100 mg QD (n= 95) PY IR (95 CI)	Abrocitinib 200 mg QD (n= 94) PY IR (95 CI)
TEAE of Special Interest (SOC and PT)	n (%)	n (%)	n (%)
Infection and Infestation	30 (31.6) 18.86 159.03 (107.3, 227.03)	34 (35.8) 17.84 190.58 (131.99, 266.32)	34 (36.2) 17.33 196.15 (135.84, 274.11)
Upper respiratory tract infection	10 (10.5) 21.88 45.71 (21.92, 84.07)	9 (9.5) 21.71 41.45 (18.96, 78.69)	10 (10.6) 21.4 46.73 (22.41, 85.93)
Herpez zoster	0 23.25 0.00 (0.00, 15.86)	1 (1.1) 22.69 4.41 (0.11, 24.55)	0 22.69 0.00 (0.00, 16.26)
Oral Herpes	0 23.25 0.00 (0.00, 15.86)	1 (1.1) 22.68 4.41 (0.11, 24.56)	2 (2.1) 22.38 8.93 (1.08, 32.28)
Herpes simplex	0 23.25 0.00 (0.00, 15.86)	0 22.86 0.00 (0.00, 16.104)	1 (1.1) 22.58 4.43 (0.11, 24.67)

Ophthalmic herpes simplex	0 23.25 0.00 (0.00, 15.86)	0 22.86 0.00 (0.00, 16.104)	1 (1.1) 22.62 4.42 (0.11, 24.81)
Kaposi's varicelliform eruption	0 23.25 0.00 (0.00, 15.86)	1 (1.1) 22.77 4.39 (0.11, 24.47)	0 22.69 0.00 (0.00, 16.26)

Source: Applicant Supplement 22-AUG-2022
MedDRA v23.0 coding dictionary applied

One subject from the abrocitinib 100 mg group had reported eczema herpeticum/Kaposi's varicellifrom and only 1 subject from the same group had reported herpes zoster. While these viral AEs were reported infrequently, herpes simplex AEs appear to be dose-dependent with 0 subjects, 1 subject, and 4 subjects reporting events.

The safety appears consistent with the adult clinical trials, with a trending signal for infections and viral reactivation..

Treatment Emergent Adverse Events and Adverse Reactions

Nausea, vomiting, and folliculitis were the most frequently reported all-causality TEAEs in the abrocitinib groups compared with the placebo group.

Table 8.2.4-4: Selected Treatment Emergent Adverse Events by Preferred Terms in ≥ 1% of Abrocitinib in Treated and at Higher Rate than Placebo for Trial B7451036 (Short Term), n(%)

Preferred Term (AEDECOD)	**Placebo N=95**	**100mg N=95**	**200mg N=94**
With Any Adverse Event	50 (52.6)	54 (56.8)	59 (62.8)
Nausea	1 (1.1)	7 (7.4)	17 (18.1)
Acne	1 (1.1)	3 (3.2)	5 (5.3)
Vomiting	0	4 (4.2)	5 (5.3)
Blood creatine phosphokinase increased	0	4 (4.2)	4 (4.3)
Pharyngitis	3 (3.2)	5 (5.3)	3 (3.2)
Blood lactate dehydrogenase increased	0	1 (1.1)	2 (2.1)
Folliculitis	1 (1.1)	7 (7.4)	2 (2.1)
Gastroenteritis	1 (1.1)	2 (2.1)	2 (2.1)
Influenza	1 (1.1)	4 (4.2)	2 (2.1)
Oral herpes	0	1 (1.1)	2 (2.1)
Alopecia	0	1 (1.1)	1 (1.1)
Aspartate aminotransferase increased	0	1 (1.1)	1 (1.1)
Diarrhoea	0	2 (2.1)	1 (1.1)
Hypercholesterolaemia	0	1 (1.1)	1 (1.1)
Hyperuricaemia	0	1 (1.1)	1 (1.1)
Monocyte count decreased	0	1 (1.1)	1 (1.1)
Nasal congestion	0	1 (1.1)	1 (1.1)
Rhinitis	0	1 (1.1)	1 (1.1)
Tonsillitis	0	1 (1.1)	1 (1.1)

Preferred Term (AEDECOD)	Placebo N=95	100mg N=95	200mg N=94
Viral infection	0	1 (1.1)	1 (1.1)

Source: Agency Biostatistical Reviewer's Analysis
- Population: TRTEMFL='Y' and SAFFL='Y' and FASFL='Y' for B7451036 short term and exlucded the adult subject
- Data source: dataset adae from /sasdata/users/ping.li/external/data_central/NDA/NDA213871/m5~b7451036~ADaM~DA/0008 in SARGE
- Counted per subject, per arm(TRT01A) and per Preferred Term(AEDECOD) [SAS: sort nodupkey by usubjid trt01a aedecod]
- Table is in descending order for the 200mg arm and generated by DAI

Laboratory Findings

There were 88 subjects (91.7%) in the placebo group, 90 subjects (94.7%) in the abrocitinib 100 mg group, and 85 subjects (91.4%) in the abrocitinib 200 mg group had laboratory abnormalities

- Overall, the most frequently occurring laboratory abnormalities across treatment groups (occurring in ≥ 25% of subjects in all treatment groups) were increased basophils/leukocytes (>1.2 × ULN; 36.5%, 25.3%, and 29.0% in the placebo, abrocitinib 100 mg, and 200 mg groups, respectively), increased eosinophils (>1.2 × ULN; 65.6%, 57.9%, and 41.9% in the placebo, abrocitinib 100 mg, and 200 mg groups, respectively), and increased eosinophils/leukocytes (>1.2 × ULN; 63.5%, 65.3%, and 50.5% in the placebo, abrocitinib 100 mg, and 200 mg groups, respectively).
- Four subjects had laboratory test values that met pre-specified monitoring criteria, with 2 subjects each from the abrocitinib 100 mg and 200 mg groups
- One subject from the abrocitinib 100 mg group had laboratory test value that met pre-specified discontinuation criteria: AST increased >5 × ULN

Two subjects (1 each from abrocitinib 100 mg and 200 mg groups) had increased AST >3 × ULN and 1 subject in the abrocitinib 100 mg group had increased ALT >3 × ULN that met the pre-specified monitoring criteria . There is 1 subject from the abrocitinib 100 mg group with AST >5 × ULN that met discontinuation criteria, this subject did not meet criteria for Hy's law. Although a few subjects showed concerning increase in liver functions during the clinical trial, one subject in the placebo group and 2 subjects in the abrocitinib 100 mg group met the criteria for Gilbert's sundrome (bilirubin >2 x ULN and ASL/AST <3 x ULN). The subject that presented with AST >5x ULN was in the 100 mg group and had a intestinal infection that may suggest the increase in LFTs was due to the medical condition rather than the drug relationship. The subject had the investigational drug discontinued and recovered.

There were no clinically significant hematologic parameters except for platelet which has a dose-dependent decrease in abrocitinib groups with nadir at Week 4; majority of subjects remained within the normal range. Events for thrombocytopenia and lymphopenia, based on adult data, are labeled.

An immunogenicity sub-study was used to evaluate the effect of abrocitinib on immunogenicity to Tdap vaccine in adolescent subjects 12 to <18 years of age with moderate-to-severe AD (see

clinical pharmacology review for details). In the immunogenicity sub-study analysis set, the proportion of subjects with all-causality TEAEs was higher for the abrocitinib 100 mg group (33.3%) compared to the abrocitinib 200 mg (16.7%) and placebo (10.0%) groups. TEAEs in this sub-study are included in the main study AE analysis. No subjects reported SAE, severe TEAE, or discontinued in this sub-study. There appears to be no regulatory utility for this study and thus there will be no labeling regarding the outcome. However, safety was evaluated both separately and within the context of the full study.

Vital Signs

There were no clinical significant changes or patterns associated with CIBINQO dosing.

Electrocardiograms (ECGs)

ECG readings were performed by a central reader (including observed data and changes from baseline) for PR interval single beat, QRS duration single beat, QT interval single beat, QTcF interval single beat, and ECG mean heart rate at each visit. No subject in any treatment group had post-baseline ECG data QTcF internal single beat value >500 msec or change from screening > 60 msec. In summary, the ECG did not show any clinical significant safety findings for this clinical trial.

8.2.5. Analysis of Submission-Specific Safety Issues

Specific safety issues identifiedin the original clinical trials for approval were not appearant in this adolescent clinical trial. There were no venous thrombosis, MACE, or pulmonary embolic events. In addition, limitedserious infections and viral reactivation were seen in this clinical trial. However, given the small sample size, it is expected that low frequency events would not be observed. Consistent with adult data, dose-dependent viral reactivation, decreases in platlet counts, and increases in creatine phosphokinase elevations were observed.

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

As described in the Agency biostatistical analysis, the main key secondary endpoints are based on the Patient Reported Outcome (PRO) of Peak Pruritus numeric rating scale (PP-NRS). The results for the key secondary endpoint of at least 4 points reduction from baseline in the Peak Pruritus NRS score (PP-NRS4) at Weeks 2, 4 and 12. Abrocitinib 200 mg was statistically superior to placebo for this endpoint at all timepoints; however, the 100 mg dose of abrocitinib was not statistically superior to placebo at Week 4.

In addition to PP-NRS4, the following key secondary efficacy endpoints based on the patient reported outcome (PRO) of Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD). The PSAAD is an 11-item, patient-reported questionnaire using a 24- hour recall period, designed to assess the severity of key symptoms and signs of atopic dermatitis including itching,

pain, dryness, flaking, cracking, bumps, redness, discoloration, bleeding, fluid, and swelling. Each item was assessed on an 11-point numeric rating scale. The PSAAD total score was calculated as the simple arithmetic mean of items 1-11.

8.2.7. Safety Analyses by Demographic Subgroups

There were no specific safety issues relating to subgroup analysis of age, sex, or race in clinical trial B7451036 (TEEN).

Table 8.2.7-1: Abreviated Table of Demographics of B7451036

	Abrocitinib		
	200 mg (N=94)	**100 mg (N=95)**	**Placebo (N=96)**
Age (years)			
Mean (SD)	14.7 (1.8)	15.1 (1.8)	14.8 (1.7)
Median	15	16	14
Range	11 – 17	12 – 17	12 – 18[2]
Sex, n (%)			
Male	38 (40)	50 (53)	52 (54)
Female	56 (60)	45 (47)	44 (46)
Race, n (%)			
White	52 (55)	52 (55)	56 (58)
Black or African American	5 (5)	9 (9)	3 (3)
American Indian or Alaska Native	4 (4)	3 (3)	1 (1)
Native Hawaiian or Other Pacific Islander	1 (1)	0 (0)	1 (1)
Asian	31 (33)	31 (33)	32 (33)
Multiple	1 (1)	0 (0)	1 (1)
Missing	0 (0)	0 (0)	2 (2)
Region, n (%)			
Us/Canada	28 (30)	28 (29)	33 (34)
Asia	28 (30)	29 (31)	29 (30)
Europe	29 (31)	31 (33)	27 (28)
Latin America	9 (10)	7 (7)	7 (7)
Duration of AD (years)			
Mean (SD)	9.7 (5.3)	9.8 (5.4)	10.5 (4.8)
Median	12	11	12
Range	1 – 18	1 – 19	0 – 18

Source: Reviewer's Analysis (same as Applicant's analysis); ADSLxpt, ADAD.xpt, ADEA.xpt, ADNR.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention
[2] Subject (b) (6) was over 18 years old when enrolled

The proportion of subjects experiencing AEs, SAEs, severe AEs, and AEs leading to discontinuation was similar in the adolescent (<18 years of age) population compared to the adult (18 to <65 years of age) groups in the originalclinical trials. There were no events of interest with meaningful difference in risk profile by sex or race subgroups in the adolescence trial.
As previously reviewed, it appears that the incidence rates for herpes zoster, malignancy events, cardiovascular events, and hematology events were higher in older subjects.

8.2.8. Additional Safety Explorations

This review assessed the safety dataof the subjects who completed the TEEN trial and then continued into the long-term, open-label, clinical trial, B7451015. This is considered the long-term, dose controlled safety pool for adolescents receiving CIBINQO 100 mg QD or 200 mg QD. The data cut off point of included in the submission was 24-September-2021. A comparison between the two abrocitinib doses was made for adverse events of special interest.

Table 8.2.8-1: CIBINQO Adolescent Clinical Safety for TEAE of Special Interest (Subjects B7451036 to Long-Term Dose-Controlled Pool)

		CIBINQO 100 mg QD (n= 137)	CIBINQO 200 mg QD (n= 134)
All infections	Number of Subjects with Event, n (%)	77 (56.2)	83 (61.9)
	Total Drug Exposure (PY)	119.74	95.44
	Incidence Rates (95% CI)	64.31 (50.75, 80.37)	86.96 (69.27, 107.81)
	Difference of IR (95% CI): CIBINQO (200 mg QD vs 100 mg QD)		22.66 (-0.93, 46.24)
Serious infections	Number of Subjects with Event, n (%)	2 (1.5)	4 (3.0)
	Total Drug Exposure (PY)	212.04	202.74
	Incidence Rates (95% CI)	0.94 (0.11, 3.41)	1.97 (0.54, 5.05)
	Difference of IR (95% CI): CIBINQO (200 mg QD vs 100 mg QD)		1.03 (-1.30, 3.36)
Herpes Zoster (CMQ)	Number of Subjects with Event, n (%)	4 (2.9)	2 (1.5)
	Total Drug Exposure (PY)	209.46	201.19
	Incidence Rates (95% CI)	1.91 (0.52, 4.89)	0.99 0.12, 3.59)
	Difference of IR (95% CI): CIBINQO (200 mg QD vs 100 mg QD)		-0.92 (-3.24, 1.41)
Herpes Simplex (CMQ)	Number of Subjects with Event, n (%)	6 (4.4)	9 (6.7)
	Total Drug Exposure (PY)	206.32	193.26
	Incidence Rates (95% CI)	2.91 (1.07, 6.33)	4.66 (2.13, 8.84)
	Difference of IR (95% CI): CIBINQO (200 mg QD vs 100 mg QD)		1.75 (-2.08, 5.58)
Gastrointestinal Perforation (CMQ)	Number of Subjects with Event, n (%)	1 (0.7)	0
	Total Drug Exposure (PY)	211.94	202.97
	Incidence Rates (95% CI)	0.47 (0.01, 2.63)	0.00 (0.00, 1.82)
	Difference of IR (95% CI):		-0.47 (-1.79, 0.84)

	CIBINQO (200 mg QD vs 100 mg QD)		
Creatine Kinase (U/L) >5x ULN	Number of Subjects with Event, n (%)	8 (5.8)	13 (9.7)
	Total Drug Exposure (PY)	202.09	187.82
	Incidence Rates (95% CI)	3.96 (1.71, 7.81)	6.92 (3.69, 11.84)
	Difference of IR (95% CI): CIBINQO (200 mg QD vs 100 mg QD)		2.96 (-1.69, 7.62)

Source: Applicants submission for Long-term Dose-Controlled Pool
Follow-up data in B7451015, cut off data date 24SEP2021
PY (Patient-year): Total follow-up time calculated up to the date of the first event for subject with events, and up to the end of risk period of subject without events
n: Number of subjects with the event, Incidence Rates: Number of subjects with event per 100 patient-years
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.
The confidence interval for the difference of incidence rates is calculated based on Wald's method.

The CMQ for herpes and herpes zoster are consistent with the adult trials. There was trend toward a dose-relationship for herpes zoster in adolescents. Age and dose were both significant in a Cox regression model assessing risk for herpes zoster. The risk of herpes zoster was age related in a Cox regression analysis;the IR for adolescents was lower than that of subjects ≥65 years of age and trended lower compared to those 18-<65 years of age. A dose-dependent response was observered for infections, serious infections, herpes reactivation, and an elevation in CPK. These AEs were observed in the adult trials, considered to be related to abrocitinib treatment and labeled.

A number of AEs seen in the adult clinical trials were not observed in the adolescent trial. There were no reported major cardiac events, venous or arterial thrombosis, (including pulmonary embolic events). This is not surprising as age is a likely a contributing factor for these occurences. There were no adolescent subjects in the long-term data reporting a malignancy. In laboratory events, thrombocytopenia <75,000 was not reported. There was a decreasing trend in platelet counts seen in the laboratory analysis of abrocitinib-treated subjects. Platelet counts appear to be at a higher baseline in the adolescents than the adult group..

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Abrocitinib is not approved for use in adolescents. There are no post-marketing data available in this population..

Expectations on Safety in the Postmarket Setting

Labeling is sufficient in conveying the safety issues associated with use of CIBINQO for moderate-to-severe atopic dermatitis as a treatment after failure with a systemic drug.

8.2.10. Integrated Assessment of Safety

CIBINQO (abrocitinib) is an orally bioavailable small molecule that inhibits janus kinase that has been approved for the treatment of moderate to severe AD. CIBINQO is currently indicated for the treatment of adults with moderate-to-severe AD who have failed or cannot tolerate another systemic therapy. This supplement provides data from the TEENtrial (B7451036) to address a PMR 4217-1 and supportthe safety and efficacy of treatment with CIBINQO 100 mg QD (b) (4) in adolescents 12 to <18 years of age with moderate-to-severe AD.. Higher incidence of AEs was reported in CIBINQO dosed groups. No deaths, serious infections, cases of MACE or VTE were reported in the trial. No subjects discontinued the trial due to thrombocytopenia or lymphopenia. However, dose-dependent decrease in platelets in abrocitinib dosed subjects were seen with a nadir at Week 4, similar to the experience in adult trials. Elevation of CPK was observed in abrocitinib-treated subjects. Generally, the safety in adolescents appears similar to the original approval clinical trials. Given the small sample size, the low numbers of AEs cannot be interpreted as having an improved safety profile in this population. The safety review of the short term and long-term adolescent subjects in clinical trial B7451036 (TEEN) showed no unique safety signals.

8.3. Summary and Conclusions

8.3.1. Statistical Issues

No significant statistical issues were identified regarding the analysis of the co-primary efficacy endpoints of IGA0/1 and EASI-75 at Week 12. Efficacy was demonstrated for both the 100 mg and 200 mg doses of abrocitinib for the co-primary endpoints, with higher treatment effect in the 200 mg dose compared to 100 mg.

For the key secondary endpoint of PP-NRS4 (i.e., at least 4-point reduction in pruritus NRS) at Week 12, pruritus was assessed daily for the first two weeks and then at the study visits (i.e., Weeks 4, 8, and 12). Abrocitinib 200 mg was statistically superior to placebo for this endpoint at all timepoints; however, the 100 mg dose of abrocitinib was not statistically superior to placebo at Week 4 (preceding testing at Week 12 per the MTP). Due to the single administration of the PP-NRS at the clinic visits (except for Week 2), it is difficult to obtain reliable treatment effect estimates for the PP-NRS4 endpoint.

The statistical reviewer repeated the analysis for the PP-NRS4 endpoint at Week 2 using the weekly average values of daily observations over 7 preceding days for the baseline and Week 2 scores. Results for such analyses showed non-significant benefit over placebo at Week 2 for both doses with much lower response rates compared to response rates based on analyses using single timepoint assessments. The statistical reviewer further conducted supportive analyses for itching at Week 12 using the PSAAD Itching item. Results from the supportive analyses indicated improvement in itch at Week 12.

Regarding improvement in AD signs and symptoms as measured by the PSAAD total score, the Agency previously noted (advice letter dated 2/15/2018) that a mere change from baseline might not translate to a clinically relevant difference. The statistical reviewer also explored the proportion of subjects with PSAAD total score of 0 at Week 12. Only a very small proportion of subjects treated with abrocitinib (2%-10% across the two doses) had PSAAD Total Score of 0 at Week 12, with 100 mg not having a benefit over placebo.

8.4. Conclusions and Recommendations

This supplemental NDA (001) is approvable. Efficacy was demonstrated for both the 100 mg and 200 mg doses of abrocitinib for the co-primary endpoints, with higher treatment effect in the 200 mg dose compared to 100 mg. Generally, the safety in adolescents appears similar to the safety in the original approval clinical trials. The benefit-risk calculus is favorable for approval in a restricted population of adolescents, 12 years of age and older, with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. Based on the totality of the evidence, 100 mg QD dosing regimen is recommended for approval for the treatment of AD in adolescent patients with the option of 200 mg QD for subjects who fail to respond to the 100 mg QD dose.

Labeling will reflect the change in indication to include patients down to 12 years of age. Post marketing requirement 4217-1 is considered as fulfilled.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not held for this supplement.

10 Pediatrics

An agree upon iPSP was provided by the Applicant for NDA 213871. This supplement was reviewed at PeRC as a PMR, there are no new safety issues.

34 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS in not required for this drug product.

13 Postmarketing Requirements and Commitment

This trial was conducted to address a PREA PMR. With this submission, post marketing requirement 4217-1 is considered as fulfilled.

14 Appendices

14.1. Financial Disclosure

In accordance with 21 CFR Part 54, Pfizer Inc., submitted financial disclosure information for clinical trial B7451036 (TEEN).

Covered Clinical Study (Name and/or Number): B7451036

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4091		
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): 44		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
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) 4047		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

14.2. Clinical/Biostatistics

Scales Used to Evaluate Efficacy

Table 11.1.10-1: Investigator's Global Assessment (IGA) Scale – Trial B7451036

Score	Category	Description*
0	Clear	Atopic dermatitis is cleared, except for any residual discoloration (post-inflammatory hyperpigmentation and/or hypopigmentation).
1	Almost Clear	Overall, the atopic dermatitis is not entirely cleared and remaining lesions are light pink (not including post inflammatory hyperpigmentation) and/or; have barely palpable hard thickened skin and/or papules and/or; have barely perceptible lichenification; excoriation and oozing/crusting are absent.
2	Mild	Overall, the atopic dermatitis consists of lesions that are light red; with slight, but definite hard thickened skin and/or papules; with slight, but definite linear or picked scratch marks or penetrating surface injury; with slight, but definite thickened skin, fine skin markings, and lichenoid scale; oozing/crusting is absent.
3	Moderate	Overall, the atopic dermatitis consists of lesions that are red; with easily palpable moderate hard thickened skin and/or papules; with moderate linear or picked scratch marks or penetrating surface injury; with moderate thickened skin, coarse skin markings, and coarse lichenoid scale; with slight oozing/crusting.
4	Severe	Overall, the atopic dermatitis consists of lesions that are deep, dark red; with severe hard thickened skin and/or papules; with severe linear or picked scratch marks or penetrating surface injury; with severe thickened skin with very coarse skin markings and lichenoid scale; with moderate to severe oozing/crusting.

Source: Protocol for Trial B7451012; page 79
* The IGA will exclude scalp, palms, and soles from the assessment/scoring.

Figure 11.1.10-1: Eczema Area and Severity Index (EASI) – Trial B7451036

The EASI quantifies the severity of a subject's atopic dermatitis based on both severity of lesion clinical signs and the percent of BSA affected. EASI is a composite scoring by the atopic dermatitis clinical evaluator of the degree of erythema, induration/papulation, excoriation, and lichenification (each scored separately) for each of four body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body.

Lesion Severity by Clinical Signs: The basic characteristics of atopic dermatitis lesions-erythema, induration/papulation, excoriation, and lichenification-provide a means for assessing the severity of lesions. Assessment of these four main clinical signs is performed separately for four body regions: head and neck, upper limbs, trunk (including axillae and groin) and lower limbs (including buttocks). Average erythema, induration/papulation, excoriation, and lichenification are scored for each body region according to a 4 point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. Morphologic descriptors for each clinical sign severity score are shown in the table below:

Score		Description*
Erythema (E)		
0	Absent	None; may have residual discoloration (post-inflammatory hyperpigmentation and/or hypopigmentation)
1	Mild	Light pink to light red
2	Moderate	Red
3	Severe	Deep, dark red
Induration/Papulation (I)		
0	Absent	None
1	Mild	Barely palpable to slight, but definite hard thickened skin and/or papules
2	Moderate	Easily palpable moderate hard thickened skin and/or papules
3	Severe	Severe hard thickened skin and/or papules
Excoriation (Ex)		
0	Absent	None
1	Mild	Slight, but definite linear or picked scratch marks or penetrating surface injury
2	Moderate	Moderate linear or picked scratch marks or penetrating surface injury
3	Severe	Severe linear or picked scratch marks or penetrating surface injury
Lichenification (L)		
0	Absent	None
1	Mild	Barely perceptible to slight, but definite thickened skin, fine skin markings, and lichenoid scale
2	Moderate	Moderate thickened skin, coarse skin markings, and coarse lichenoid scale
3	Severe	Severe thickened skin with very coarse skin markings and lichenoid scale

Percent BSA with Atopic Dermatitis: The number of handprints of skin affected with AD in a body region can be used to determine the extent (%) to which a body region is involved with atopic dermatitis:

Body Region	Total Number of Handprints in Body Region*	Surface Area of Body Region Equivalent of One Handprint*
Head and Neck	10	10%
Upper Limbs	20	5%
Trunk (including axillae and groin/genitals)	30	3.33%
Lower Limbs (including buttocks)	40	2.5%

Handprint refers to the hand size of each individual subject.

* The number of handprints will be for the entire body region; these values will not be adjusted for exclusion of scalp, palms, and soles from the BSA assessment.

The extent (%) to which each of the four body regions is involved with atopic dermatitis is categorized to a numerical Area Score using a non-linear scaling method according to the following BSA scoring criteria:

0 = no involvement
1 = >0 - <10% involvment
2 = 10 - <30% involvement
3 = 30 - <50% involvement
4 = 50 - <70% involvement
5 = 70 - <90% involvement
6 = 90 - <30% involvement

The EASI formula is:
EASI = 0.1Ah(Eh+Ih+Exh+Lh) + 0.2Au(Eu+Iu+ExU+Lu) + 0.3At(Et+It+Ext+Lt) + 0.4Al(El+Il+ExI+Ll)
where A = Area Score; E = erythema; I = induration/papulation; Ex = excoriation; L = lichenification; h = head and neck; u = upper limbs; t = trunk; l = lower limbs

Source: Protocol for Trial B7451036; pages 80-82

Sensitivity Analyses

Table 11.1.10-2: Results for the Co-Primary Endpoints at Week 12 Excluding Adult Subject - Trial B7451036 (FAS; NRI[1])

	Abrocitinib		
	200 mg (N=94)	**100 mg (N=95)**	**Placebo (N=95)**
IGA 0/1	43 (46%)	37 (39%)	23 (24%)
Difference from placebo (95% CI)[2]	21% (7%, 34%)	17% (4%, 30%)	-
P-Value[3]	0.0025	0.0270	-
EASI 75	67 (71%)	61 (64%)	39 (41%)
Difference from placebo (95% CI)[2]	29% (16%, 43%)	23% (10%, 36%)	-
P-Value[3]	<0.001	0.0010	-

Source: Statistical Reviewer's Analysis (slightly different from Applicant's Analysis); ADAD.xpt, ADEA.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention; Missing data are imputed using the non-responder imputation (NRI) method
[2] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.
[3] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by baseline disease severity.

Table 11.1.10-3: Results for the Key Secondary Efficacy Endpoints Excluding Adult Subject – Trial B7451036 (FAS; NRI[1])

	Abrocitinib		
PP-NRS4[2]	**200 mg (N=90)**	**100 mg (N=93)**	**Placebo (N=95)**
Week 2	34 (38%)	25 (27%)	12 (13%)
Difference from placebo (95% CI)[3]	25% (13%, 37%)	14% (3%, 26%)	-
P-Value[4] (Significant per MTP[5])	<0.001	0.00138	-
Week 4	42 (47%)	28 (30%)	19 (20%)
Difference from placebo (95% CI)[3]	27% (14%, 40%)	10% (-2%, 22%)	-
P-Value[4] (Significant per MTP[5])	<.0001	0.1109 (No)	-
Week 12	41 (46%)	40 (43%)	24 (25%)
Difference from placebo (95% CI)[3]	20% (7%, 33%)	18% (4%, 31%)	-
P-Value[4] (Significant per MTP[5])	0.0047 (Yes)	*	-

Source: Statistical Reviewer's Analysis (slightly different from Applicant's Analysis); ADNR.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention. N is the number with a baseline score ≥4. Missing data are imputed using the non-responder imputation (NRI) method
[2] Proportion of subjects achieving ≥4 points improvement from baseline in pruritus Numeric Rating Scale (NRS) among subjects with baseline score of ≥4
[3] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.
[4] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted baseline disease severity.
[5] Multiplicity Testing Procedure (MTP): the protocols specified a graphical approach to control the Type I error rate for testing multiple treatment groups and endpoints; see Figure 8.1.2-1.
* Testing stops per MTP.

Table 11.1.10-4: Results for Peak Pruritus NRS at Week 2 Excluding Adult Subject – Trial B7451036 (FAS; NRI[1])

PP-NRS4[2]	Abrocitinib 200 mg (N=75)	Abrocitinib 100 mg (N=82)	Placebo (N=79)
Week 2	14 (19%)	11 (13%)	7 (9%)
Difference from placebo (95% CI)[3]	10% (-1%, 20%)	5% (-5%, 14%)	
P-Value[4]	0.081	0.341	

Source: Statistical Reviewer's Analysis; ADNR.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention; Missing data are imputed using the non-responder imputation (NRI) method

[2] Proportion of subjects achieving ≥4 points improvement from baseline in Peak Pruritus Numeric Rating Scale (PP-NRS) among subjects with baseline score of ≥4

[3] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.

[4] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).

Note: Weekly scores were average values of daily observations over 7 days for this analysis; weekly scores were set to missing if less than 4 daily observations in the week.

Analyses for PSAAD

Table 11.1.10-5: Absolute Change from Baseline to Week 12 in PSAAD Total Score - Trials B7451036 (FAS[1])

	Abrocitinib 200 mg (N=94)	Abrocitinib 100 mg (N=95)	Placebo (N=95)
Baseline PSAAD total score			
N[2]	93	95	95
Mean (SD)	4.6 (2.31)	4.9 (2.11)	5.0 (2.4)
Median	4.8	5.0	4.5
Range	0.7 – 10.0	0.6 – 9.8	0.9 – 10.0
Change from baseline in PSAAD total score to Week 12			
Applicant's Analysis			
N[3]	85	93	87
LS Mean (repeated measures)[4]	-2.7	-2.5	-2.0
Difference from Placebo (95% CI)[4]	-0.7 (01.3, -0.1)	-0.5 (-1.1, 0.0)	-
P-Value[4]	*	*	-
Reviewer's Analysis			
N[5]	93	95	95
Mean	-7.4	-7.4	-6.9
LS Mean[6]	-7.5	-7.3	-6.7
Difference from Placebo (95% CI)[6]	-0.8 (-1.4, -0.3)	-0.6 (-1.1, -0.1)	-
P-Value[6]	*	*	-

Source: Statistical Reviewer's Analysis; ADPU.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention.

[2] Subjects with baseline PSSD total score

[3] Subjects with baseline PSSD total score; missing data were omitted (i.e., observed data)

[4] Least square (LS) means, difference (95% CI) and p-value are based on Mixed Model Repeated Measure (MMRM) with fixed factors of treatment, week, treatment by week interaction and randomization strata, baseline value as a covariate and an unstructured covariance matrix.

[5] Subjects with baseline PSSD total score; missing data was imputed using the last observation carried forward (LOCF).

[6] Least square (LS) means, difference (95% CI) and p-value are based on ANCOVA with factors of treatment group and randomization stratum, and baseline value as a covariate.

* Testing stops per Multiplicity Testing Procedure (MTP); see Figure 8.1.2-1.

Table 11.1.10-6: Proportion of Subjects with PSAAD Total Score of 0 at Week 12 – Trial B7451036 (FAS; NRI[1])

	Abrocitinib		
	200 mg (N=94)	100 mg (N=95)	Placebo (N=95)
N[1]	93	95	95
n (%)	9 (10%)	2 (2%)	8 (8%)

Source: Statistical Reviewer's Analysis; ADPU.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention. N is the number of subjects with a baseline PSAAD total score > 0. Missing data are imputed using the non-responder imputation (NRI) method.

Table 11.1.10-7: Responder Analysis for PSAAD Itching Item – Trial B7451036 (FAS; NRI[1])

	Abrocitinib		
	200 mg (N=75)	100 mg (N=81)	Placebo (N=80)
Week 2			
≥4-point reduction[2]	14 (19%)	14 (17%)	5 (6%)
Difference from Placebo[3]	12%	11%	-
Week 4			
≥4-point reduction[2]	28 (37%)	22 (27%)	10 (13%)
Difference from Placebo[3]	25%	15%	-
Week 12			
≥4-point reduction[2]	30 (40%)	28 (35%)	19 (24%)
Difference from Placebo[3]	16%	11%	-

Source: Statistical Reviewer's Analysis; ADPU.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention. N is the number with a baseline score ≥4. Missing data are imputed using the non-responder imputation (NRI) method

[2] Proportion of subjects achieving ≥4 points improvement from baseline among subjects with baseline score of ≥4

[3] The estimate for the difference was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by baseline disease severity.

Note: Weekly scores were average values of daily observations over 7 days for this analysis; weekly scores were set to missing if less than 4 daily observations in the week.

Findings in Special/Subgroup Populations

Table 11.1.10-8: IGA 0/1 Response at Week 12 by Age, Sex, Race, Weight and Baseline IGA Score – Trial B7451036 (FAS; NRI[1])

	Abrocitinib				
Subgroups (n[ABR200], n[ABR100], n[P])	**200 mg (N=94)**	**100 mg (N=95)**	**Placebo (N=96)**	**200 mg – Placebo (95% CI)**	**100 mg – Placebo (95% CI)**
Age (years)					
<18 (94, 95,95)	46%	39%	24%	22% (8%, 35%)	15% (2%. 28%)
18-64 (0, 0, 1)	-	-	0%	-	-
Sex					
Male (56, 45, 44)	50%	38%	20%	30% (12%, 47%)	17% (-1%, 36%)
Female (38, 50, 52)	39%	40%	27%	13% (-1%, 32%)	13% (-1%, 31%)
Race					
White (52, 52, 56)	52%	42%	23%	29% (11%, 46%)	19% (2%, 36%)
Black or African American (5, 9, 3)	60%	22%	0%	60% (17%, 100%)	22% (-5%, 49%)
Asian (31, 31, 32)	39%	42%	31%	7% (-16%, 31%)	11% (-13%, 34%)
Other (6, 3, 5)	17%	0%	0%	17% (-13%, 46%)	-
Weight					
<70 Kg (73, 73, 79)	52%	37%	27%	25% (10%, 41%)	10% (-4%, 25%)
70 – 100 Kg (20, 20, 15)	25%	50%	13%	12% (-14%, 37%)	37% (9%, 65%)
>100 Kg (1, 2, 2)	0%	0%	0%	-	-

Baseline IGA					
Moderate (61, 57, 57)	51%	46%	32%	19% (2%, 37%)	14% (-4%, 32%)
Severe (33, 38, 39)	36%	29%	13%	24% (4%, 43%)	16% (-2%, 34%)
Overall	**46%**	**39%**	**24%**	**22% (9%, 35%)**	**15% (2%, 28%)**

Source: Reviewer's Analysis (same as Applicant's analysis); ADAD.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention; Missing data are imputed using the non-responder imputation (NRI) method

Table 11.1.10-9: EASI-75 Response at Week 12 by Age, Sex, Race, Weight and Baseline IGA Score – Trial B7451036 (FAS; NRI[1])

	Abrocitinib				
Subgroups (n[ABR200], n[ABR100], n[P])	**200 mg (N=94)**	**100 mg (N=95)**	**Placebo (N=96)**	**200 mg – Placebo (95% CI)**	**100 mg – Placebo (95% CI)**
Age (years)					
<18 (94, 95,95	71%	64%	41%	30% (17%, 44%)	23% (9%, 37%)
18-64 (0, 0, 1)	-	-	0%	-	-
Sex					
Male (56, 45, 44)	71%	62%	32%	40% (21%, 58%)	30% (11%, 50%)
Female (38, 50, 52)	71%	66%	48%	23% (3%, 43%)	18% (-1%, 37%)
Race					
White (52, 52, 56)	69%	73%	39%	30% (12%, 48%)	64% (16%, 51%)
Black or African American (5, 9, 3)	80%	33%	67%	13% (-5%, 77%)	-33% (-95%, 28%)
Asian (31, 31, 32)	81%	65%	41%	40% (18%, 62%)	24% (<0%, 48%)
Other (6, 3, 5)	33%	0%	40%	-7% (-64%, 50%)	-40% (-83%, 3%)
Weight					
<70 Kg (73, 73, 79)	75%	66%	44%	31% (16%, 46%)	21% (6%, 67%)
70 – 100 Kg (20, 20, 15)	55%	65%	27%	28% (-3%, 60%)	68% 98%, 69%)
>100 Kg (1, 2, 2)	100%	0%	0%	-	-
Baseline IGA					
Moderate (61, 57, 57)	70%	72%	54%	16% (-1%, 33%)	18% (<1%, 35%)
Severe (33, 38, 39)	73%	53%	21%	52% (32%, 72%)	32% (12%, 52%)
Overall	**71%**	**64%**	**41%**	**31% (17%, 44%)**	**24% (10%, 37%)**

Source: Reviewer's Analysis (same as Applicant's analysis); ADEA.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention; Missing data are imputed using the non-responder imputation (NRI) method

Table 11.1.10-10: IGA 0/1 and EASI-75 Response at Week 12 by Country – Trial B7451036 (FAS; NRI[1])

	IGA 0/1			EASI-75		
	Abrocitinib			Abrocitinib		
Country (n[ABR200], n[ABR100], n[P])	**200 mg (N=94)**	**100 mg (N=95)**	**Placebo (N=96)**	**200 mg (N=94)**	**100 mg (N=95)**	**Placebo (N=96)**
United States (23, 27, 30)	39%	30%	37%	70%	70%	63%
China (14, 18, 20)	43%	39%	20%	64%	61%	25%
Poland (14, 12, 17)	86%	58%	6%	100%	67%	12%
Japan (9, 9, 8)	33%	56%	63%	100%	78%	75%
Mexico (9, 7, 7)	33%	14%	14%	33%	43%	43%
Hungary (5, 7, 5)	60%	86%	20%	40%	100%	40%
Spain (3, 8, 2)	33%	13%	0%	33%	25%	0%
Australia (5, 1, 3)	20%	0%	0%	80%	0%	33%
Taiwan (5, 2, 1)	40%	50%	0%	80%	100%	0%
Netherlands (2, 1, 3)	50%	0%	0%	100%	0%	33%
Czech Republic (2, 2, 0)	50%	50%	0%	50%	100%	0%
Italy (1, 1, 0)	100%	0%	0%	100%	0%	0%
Latvia (2, 0, 0)	0%	0%	0%	50%	0%	0%
Overall	46%	39%	24%	71%	64%	41%

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADAE.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study intervention; Missing data are imputed using the non-responder imputation (NRI) method

14.3. Nonclinical Pharmacology/Toxicology

[Insert carci data as needed. Limit to 2 pages]

14.4. OCP Appendices (Technical documents supporting OCP recommendations)

14.4.1. Clinical Pharmacology Study

In this submission, there were one phase 3 clinical trial report, one phase 1 PK study report, and one updated pharmacometrics report for clinical pharmacology review.

Study B7451036: A Phase 3 Efficacy and Safety Study in Adolescent Patients with Moderate to Severe Atopic Dermatitis

Clinical trial B7451036 was a phase 3, randomized, double-blind, placebo-controlled study designed to investigate the efficacy and safety of abrocitinib 100 and 200 mg QD dose compared to placebo. At the end of the 12-week study treatment, qualified subjects completing the study had the option to enter the long term extension study B7451015. Subjects discontinuing early from the study underwent a 4-week follow-up period. The co-primary endpoints of study B7451036 were IGA and EASI75 at week 12. Blood samples for PK analysis were collected at the following time points in all subjects: 22 hours post-dose (corresponding to 2 hours pre-dose) on Days 57 and 2 hours post-dose on Day 85.

A total of 285 adolescents with moderate to severe AD were randomized and treated: placebo (n=96), abrocitinib 100 mg (n=95), and abrocitinib 200 mg (n=94). The IGA and EASI75 response results are summarized in Table 19.5.1-1 and Table 19.5.1-2, respectively. Both 100 mg and 200 mg treatment groups were statistically significantly different from pacebo group.

The mean plasma abrocitinib concentrations observed at 2 hours prior to dosing (Week 8) and at 2 hours post-dose (Week 12) increased with an increase in dose. The summary of median and mean plasma abrocitinib concentrations (ng/mL) at nominal time points of 2 hours pre-dose (Week 8) and 2 hours post-dose (Week 12) are presented in Table 19.5.1-3. The abrocitinib plasma concentration data from all subjects at Site 1173 (8 patients in total; 3 patients in abrocitinib 100 mg QD group and 5 in abrocitinib 200 mg QD group) were excluded from the summary statistics, as the concentrations in all samples except one from abrocitinib-treated subjects were anomalously high (range 35,100-156,000 ng/mL) compared with the estimated C_{max} of 961 ng/mL from population PK model in adolescent patients after dosing with abrocitinib 200 mg QD.

Table 14.4.1-1. Proportion of Subjects Achieving Investigator's Global Assessment (IGA) Response of 'Clear' or 'Almost Clear' and >=2 Points Improvement from Baseline at Week 12 - CMH (FAS, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD
N	94	89	93
n (%)	23 (24.5)	37 (41.6)	43 (46.2)
95% CI	(15.8, 33.2)	(31.3, 51.8)	(36.1, 56.4)
Active - Placebo [1]			
Estimate (%)		16.7	20.6
95% CI		(3.5, 29.9)	(7.3, 33.9)
Two-sided P-value [2]		0.0147	0.0030
200 mg QD - 100 mg QD [1]			
Estimate (%)			3.9
95% CI			(-10.4, 18.2)

Source: Study Report B7451036, Table 12
Full Analysis Set (FAS) was defined as all randomized subjects who received at least one dose of study medication. Baseline was defined as the measurement collected on or prior to Day 1. If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
Abbreviation: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; N = number of subjects in the analysis set with NRI at the specified visit; n (%) = number of subjects with response (percentage based on N); NRI = non-responder imputation.

Table 14.4.1-2. Proportion of Subjects Achieving Eczema Area and Severity Index (EASI) Response >= 75% Improvement from Baseline at Week 12 - CMH (FAS, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD
N	94	89	93
n (%)	39 (41.5)	61 (68.5)	67 (72.0)
95% CI	(31.5, 51.4)	(58.9, 78.2)	(62.9, 81.2)
Active - Placebo [1]			
Estimate (%)		26.5	29.4
95% CI		(13.1, 39.8)	(16.3, 42.5)
Two-sided P-value [2]		0.0002	<.0001
200 mg QD - 100 mg QD [1]			
Estimate (%)			3.1
95% CI			(-9.9, 16.2)

Source: Study Report B7451036, Table 13

Full Analysis Set (FAS) was defined as all randomized subjects who received at least one dose of study medication. Baseline was defined as the measurement collected on or prior to Day 1. If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
Abbreviation: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; N = number of subjects in the analysis set with NRI at the specified visit; n (%) = number of subjects with response (percentage based on N); NRI = non-responder imputation.

Table 14.4.1-3. Summary of Plasma Abrocitinib Concentrations (ng/mL) in Study B7451036

Visit	Planned Time Post Dose	N	NALQ	Mean	Standard Deviation	Median	Range
100 mg							
WEEK 8	22H	72	46	7.9	26.4	1.825	0.0, 220
WEEK 12	2H	59	51	486.6	403.69	410.0	0.0, 1860
200 mg							
WEEK 8	22H	62	45	32.3	76.5	5.510	0.0, 516
WEEK 12	2H	50	44	1271	1000.4	1285	0.0, 4150

Source: Study Report B7451036, Table 14.4.4.1.1 and 14.4.4.1.2
Samples from site 1173 were excluded from the analysis. Summary statistics had been calculated by setting concentration values below the lower limit of quantification to zero.
Abbreviation: N=number of observations (non-missing concentrations), NALQ=Number of observations Above and equal to Lower limit of Quantification (1.0 ng/mL).

Study B7451028: A Single- and Multiple- Dose Study in Healthy Adult Chinese Subjects

A total of 13 subjects were enrolled and 12 subjects were received study treatments and 1 subject withdrew informed consent before the treatment. There were 9 males and 3 females, with a mean age of 31.6 years (range: 22 to 39 years). The mean body weight and BMI were 63.98 kg (range: 51.5 to 76.2 kg) and 23.05 kg/m^2 (range: 20.3 to 25.7 kg/m^2), respectively.
PK samples for blood abrocitinib concentrations were collected at 0 (within 15 minutes prior to dosing), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours after dosing on Day 1 and Day 8. Samples were analyzed for abrocitinib concentrations using a validated, sensitive and specific liquid chromatography tandem mass spectrometric method (LC-MS/MS).

In the single dose period of the study, subjects received single doses of 200 mg of abrocitinib. In the multiple dose period, the subjects received doses of abrocitinib 200 mg once daily (QD) for 6 consecutive days from Day 3 to Day 8. Following multiple dose administration QD for 6 days, geometric mean (geometric %CV) of the plasma abrocitinib accumulation was 1.521 (19%) on Day 8. Table 19.5.1-4 summarizes the abrocitinib PK parameter following single dose and multiple doses in the Study B7451028.

Table 14.4.1-4. Descriptive Summary of Plasma Abrocitinib PK Parameters in the Study B7451028.

Parameter, unit[a]	Period 1 PF-04965842 200 mg SD N=12	Period 2 PF-04965842 200 mg QD N=12
N1, N2, N3, N4, N5	12, 11, 12, NC, 11	12, NC, NC, 12, 12
AUC_{inf}, ng.hr/mL	5316 (37)	
AUC_{last}, ng.hr/mL	5409 (36)	
AUC_{tau}, ng.hr/mL	5416 (36)	8249 (30)
C_{av}, ng/mL		343.6 (30)
C_{max}, ng/mL	1570 (29)	1787 (25)
C_{min}, ng/mL		5.903 (113)
CL/F, L/hr	37.61 (37)	24.26 (30)
PTR		302.6 (95)
R_{ac}		1.521 (19)
$R_{ac,Cmax}$		1.138 (23)
$t_{1/2}$, hr	2.966±0.88382	3.529±1.0429
T_{max}, hr	1.50 (0.500-3.00)	2.00 (0.500-3.00)
V_Z/F, L	154.2 (46)	119.3 (36)

N = Total number of subjects in the treatment group in the indicated population
N1 = Number of subjects contributing to the summary statistics
N2 = Number of subjects contributing to the summary statistics for AUCinf
N3 = Number of subjects contributing to the summary statistics for AUClast
N4 = Number of subjects contributing to the summary statistics for PTR, Cmin, Cav, Rac and Rac,Cmax
N5 = Number of subjects contributing to the summary statistics for CL/F, VZ/F and t1/2
NC = Not calculated
a. Geometric mean (geometric %coefficient of variation) for all except median (range) for Tmax and arithmetic mean±standard deviation for $t_{1/2}$.
Source: Study Report B7451028, Table 8

14.4.2. Population PK and PK/PD Studies

Review Summary
The updated population PK analysis for abrocitinib were verified by the reviewer and no significant discordance identified. The updated abrocitinib population PK model adequately predicted the concentrations of abrocitinib. Empirical bayesian estimates of abrocitinib model parameter was included as they substantially improved the stability of the estimation for the metabolite model. The predictive ability of the metabolite model is considered to be good, as supported by the diagnostic plots.

There are major assumptions and limitations in the population PK analysis for abrocitinib metabolites. There were only 51 AD patients who had metabolite information available. All observations werefrom single sample collected roughly 2 hours post dose. Of these 51 patients, only 7 were adolescents. Consequently, model assumed that there were no differences in the metabolite levels between adults and adolescents. Additionally, the final model included 38 fixed effect parameters and 10 random effect parameters with a moderately high condition number. The scaling effect that was added to the parameterization of the abrocitinib clearance resulted in an overestimation of the abrocitinib AUC if simulated directly from the metabolite

model. Despite of these limitations, integrated PK model for abrocitinib metabolites adequately described the observations. The developed model is therefore acceptable to be used for simulating the combined exposure of abrocitinib and its metabolites for the specific population. The simulaitons for DDI scenarios should be considered as exploratory, but the simulations results are in general comparable to the observed results in the dedicated DDI studies.

Objectives

The primary objective of this analysis was to:

- To examine if the updated population PK model reasonably describe the abrocitinib and its metabolites observations.
- To valuate changes in the combined exposure of abrocitinib (PF-04965842), and its two active metabolites, M1 (PF-06471658) and M2 (PF-07055087), in subgroups, special populations, and DDIs

Data

Population PK Analysis for Abrocitinib

The population PK analyses for abrocitinib was updated with data from five additional trials. They were Studies B7451021 (renal impairment study), B7451028 (PK study in Chinese population), B7451032 (pivotal bioequivalence and food effect study), B7451014 (Phase 3 in AD patients), and B7451036 (Phase 3 in the adolescent AD patients). All subjects from Site 1173 from Study B7451036 were excluded from the analysis due to irregularities in the PK sample measurements. The study design, study population, dose, and timing of blood samples varied among the newly available studies as presented in Table 19.5.2-1.

Table 14.4.2-1. Summary of Studies with PK Sampling that Newly Included in the Updated Population PK Analysis of Abrocitinib

Protocol	Phase	Protocol Title	Population	n	Dose Administration	Plasma Sampling[a]	Analytes
B7451014	3	A Phase 3 Randomized Withdrawal, Double-Blind, Placebo-Controlled, Multi-Center Study Investigating the Efficacy and Safety of PF-04965842 in Subjects Aged 12 Years and Over, with Moderate to Severe Atopic Dermatitis with the Option of Rescue Treatment in Flaring Subjects	AD	1233 treated	200 mg QD[e] of abrocitinib for 12 weeks, then randomized to 100 or 200 mg QD[e] of abrocitinib or matching placebo for 40 weeks. Food not controlled.	2 hours post-dose on Day 85 (Week 12).	Abrocitinib, M1, M2, and M4
B7451021	1	A Phase 1, Non-Randomized, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of PF-04965842 in Subjects with Renal Impairment and in Healthy Subjects with Normal Renal Function	HV, MoRI, and SRI	23	Single dose of 200 mg[e] abrocitinib. Fasted.	0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48 and 72 hours post-dose.	Abrocitinib, M1, M2, and M4

Protocol	Phase	Protocol Title	Population	n	Dose Administration	Plasma Sampling[a]	Analytes
B7451028	1	A Phase 1, Open-Label, Single-Arm, Single Dose and Multiple Doses Study to Assess Pharmacokinetics, Safety and Tolerability of PF-04965842 in Chinese Healthy Participants	HV	13	Single-dose of 200 mg[e] abrocitinib (Period 1), then 200 mg QD[e] abrocitinib for 4 days (Period 2). Fasted.	0 (pre-dose) and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post-dose on Days 1 and 8. Predose samples collected on Days 6 and 7.	Abrocitinib, M1, M2, and M4
B7451032	1	A Phase 1, Open Label, Single-Dose, Crossover Study to Evaluate the Bioequivalence of a Commercial Tablet Formulation of PF-04965842 Relative to the Phase 3 Tablet Formulation Under Fasting Conditions and the Effect of Food on the Relative Bioavailability of the Commercial Tablet Formulation in Healthy Participants	HV	46	Part A: Single-dose of 200 mg abrocitinib as Phase 3 tablet[e], Commercial Tablet[f], and Variant Tablet[g] under fasted conditions, and Commercial Tablet[f] under fed conditions. Part B: Single, repeat-doses of 200 mg abrocitinib as Phase 3 tablet[e] and Commercial Tablet[f] under fasted conditions.	0 (pre-dose) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours post-dose. Fasted.	Abrocitinib
B7451036	3	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study Investigating the Efficacy and Safety of PF-04965842 Co-Administered With Background Medicated Topical Therapy in Adolescent Participants 12 to <18 Years of Age With Moderate-to-Severe Atopic Dermatitis	AD	287	100 or 200 mg QD[e] of abrocitinib or matching placebo for 12 weeks. Food not controlled.	Pre-dose on Day 57 (22 hours post previous dose) and 2 hours post-dose on Day 85.	Abrocitinib

[a]Only for plasma PK sampling times for abrocitinib and/or metabolite concentrations

(b) (4)

[e]Abrocitinib 100 mg (b) (4) Film Coated Tablet (DC) (D1700147) (Phase 3 100 mg Tablet).
[f]Abrocitinib 200 mg Tablet (D1800025).
[g]Abrocitinib 200 mg Tablet (b) (4) (DP-000459).

Source: Reposrt PMR-EQDD-B745d-dp4-1110, Table 1

The final NONMEM data file for analysis contained 11828 PK observations from 2302 subjects. Table 19.5.2-2 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 14.4.2-2. Summary of Baseline Patient Characteristics in the PK Dataset of Abrocitinib Population PK Model by Patient Type

Characteristics	Level	Healthy Subjects	Patients	Total
N (%)		262 (11)	2034 (89)	2296 (100)
Age (Years), Mean (SD)		40.5 (13.3)	31.9 (15.7)	32.9 (15.7)
Bodyweight (kg), Mean (SD)		79.5 (13.2)	74.0 (20.0)	74.6 (19.4)
SEX, n (%)	Male	223 (85)	1130 (56)	1353 (59)
	Female	39 (15)	904 (44)	943 (41)
RACE, n (%)	White	152 (58)	1440 (71)	1592 (69)
	Black	64 (24)	129 (6)	193 (8)

Characteristics	Level	Healthy Subjects	Patients	Total
	Asian	25 (10)	401 (20)	426 (19)
	Other	21 (8)	53 (3)	74 (3)
	Missing	0 (0)	11 (1)	11 (0)
Subject Type, n (%)	Healthy Volunteer	231 (88)	0 (0)	231 (10)
	AD Patient	0 (0)	1989 (98)	1989 (87)
	Mild Hepatic Impairment	8 (3)	0 (0)	8 (0)
	Moderate Hepatic Impairment	8 (3)	0 (0)	8 (0)
	Moderate Renal Impairment	7 (3)	0 (0)	7 (0)
	Severe Renal Impairment	8 (3)	0 (0)	8 (0)
AGE Group, n (%)	Adolescent	0 (0)	448 (22)	448 (20)
	Adult	262 (100)	1586 (78)	1848 (80)
Japanese; n(%)	Non-Japanese	250 (95)	1984 (98)	2234 (97)
	Japanese	12 (5)	50 (2)	62 (3)

Source: Reposrt PMR-EQDD-B745d-dp4-1110, Table 6

Population PK Analysis for Abrocitinib Metabolites (M1, M2, and M4)

The population PK analysis for metabolites was based on the data from seven clinical trials. They were Studies B7451017 (DDI study with fluvoxamine or fluconazole), B7451019 (DDI study with rifampin), B7451020 (hepatic impairment study), B7451021 (renal impairment study), B7451028 (PK study in Chinese population), B7451043 (DDI study with probenecid), and B7451014 (Phase 3 in AD patients). Table 19.5.2-3 presents the study design, study population, dose, and timing of blood samples in the studies that have the plasma concentrations of metabolites. The summary information of Studies B7451014, B7451021, B7451028 are included in Table 14.4.2-1.

Table 14.4.2-3. Summary of Studies with PK Sampling that Included in the Population PK Analysis of Abrocitinib Metabolites

Protocol	Phase	Protocol Title	Population	n	Dose Administration	Plasma Sampling[a]	Analytes
B7451017	1	A Phase 1, Open-Label, Randomized, Fixed-Sequence, Parallel-Cohort Study to Estimate the Effect of Fluvoxamine or Fluconazole on the Pharmacokinetics, Safety and Tolerability of a Single-Dose of PF-04965842 in Healthy Subjects	HV	24	Fluvoxamine: Single-dose 100 mg[e] abrocitinib (Period 1), and then 9 days of continuous fluvoxamine 50 mg QD dosing with a single-dose of 100 mg[e] abrocitinib on Day 8 (Period 2). Fluconazole: Single-dose 100 mg[e] abrocitinib (Period 1), and then 7 days of continuous fluconazole dosing (400 mg on Day 1 and then 200 mg QD on Days 2 to 7) with a single-dose of 100 mg[e] abrocitinib on Day 5 (Period 2). Fasted.	0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours (and 72 hours for the fluconazole cohort) post-abrocitinib dose in Period 1 and Period 2.	Abrocitinib, M1, M2, and M4
B7451019	1	A Phase 1, Open-Label, Fixed-Sequence Study to Estimate the Effect of Repeat-Dose Rifampin on the Pharmacokinetics of PF-04965842 in Healthy Subjects	HV	12	Single-dose 200 mg[e] abrocitinib (Period 1), and then 8 days of continuous rifampin 600 mg QD dosing with a single-dose of 200 mg[e] abrocitinib on Day 8 (Period 2). Fasted.	0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 48 hours post-abrocitinib dose in Period 1 and Period 2.	Abrocitinib, M1, M2, and M4

Protocol	Phase	Protocol Title	Population	n	Dose Administration	Plasma Sampling[a]	Analytes
B7451020	1	A Phase 1, Non-Randomized, Open-Label, Single-Dose Study to Compare the Pharmacokinetics, Safety and Tolerability of PF-04965842 in Adult Subjects with Mild and Moderate Hepatic Impairment Relative to Subjects with Normal Hepatic Function	HV, MiHI and MoHI	24	Single-dose of 200 mg[e] abrocitinib. Fasted.	0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 14, 24, 36, and 72 hours post-dose.	Abrocitinib, M1, M2, and M4
B7451043	1	A Phase 1, Open-Label, Fixed-Sequence Study to Assess Single-Dose and Multiple Dose Pharmacokinetics of PF-04965852 and its Metabolites, and the Effect of Repeat-Dose Probenecid on the Single-Dose Pharmacokinetics of Abrocitinib and its Metabolites in Healthy Participants	HV	12	Single-dose of 200 mg[e] abrocitinib (Period 1), then 200 mg QD[e] abrocitinib for 4 days (Period 2), and then single-dose of 200 mg[e] abrocitinib on Day 2 in the presence of probenecid (Period 3). Fasted.	0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours post-abrocitinib dose on Period 1 Day 1, Period 2 Day 4, and Period 3 Day 2.	Abrocitinib, M1, M2, and M4

[a]Only for plasma PK sampling times for abrocitinib and/or metabolite concentrations.

(b) (4)

[e]Abrocitinib 100 mg (b) (4) Film Coated Tablet (DC) (D1700147) (Phase 3 100 mg Tablet).
[f]Abrocitinib 200 mg Tablet (D1800025).
[g]Abrocitinib 200 mg Tablet (b) (4) (DP-000459).

Source: Reposrt PMR-EQDD-B745d-dp4-1110, Table 1

The final NONMEM data file for analysis contained 6549 PK observations from 107 subjects. Table 19.5.2-4 provides summary statistics of the baseline demographic covariates in the analysis dataset of abrocitinib metabolites.

Table 14.4.2-4. Summary of Baseline Patient Characteristics in the PK Dataset of Abrocitinib Metabolites Population PK Model by Study

Group	Study 1014	Study 1017	Study 1019	Study 1020	Study 1021	Study 1028	Study 1043	Total
Age (years)								
N (%)	51 (32)	24 (15)	12 (8)	24 (15)	23 (15)	12 (8)	12 (8)	158 (100)
Median	26	30	36	58	62	31	34	38
Mean (Std. Dev.)	32.1 (14.8)	33.3 (9.7)	37.6 (9.7)	58.3 (6.0)	62.0 (10.0)	30.6 (5.7)	37.9 (9.0)	41.4 (16.5)
Range (Min; Max)	(12; 64)	(22; 49)	(24; 54)	(48; 69)	(28; 74)	(21; 38)	(27; 55)	(12; 74)
Missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
N (%)	51 (32)	24 (15)	12 (8)	24 (15)	23 (15)	12 (8)	12 (8)	158 (100)
Median	70	79	73	85	84	64	79	78
Mean (Std. Dev.)	76.8 (24.5)	78.5 (11.7)	73.7 (8.2)	89.4 (17.0)	82.6 (12.0)	64.0 (7.9)	78.9 (10.0)	78.8 (18.2)
Range (Min; Max)	(40; 143)	(56; 98)	(62; 85)	(53; 126)	(54; 100)	(52; 76)	(64; 92)	(40; 143)
Missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sex; N(%)								
Male	29 (57)	22 (92)	10 (83)	15 (62)	16 (70)	9 (75)	7 (58)	108 (68)
Female	22 (43)	2 (8)	2 (17)	9 (38)	7 (30)	3 (25)	5 (42)	50 (32)

Group	Study 1014	Study 1017	Study 1019	Study 1020	Study 1021	Study 1028	Study 1043	Total
Race; N(%)								
White	43 (84)	20 (83)	8 (67)	18 (75)	19 (83)	0 (0)	6 (50)	114 (72)
Black	2 (4)	2 (8)	2 (17)	5 (21)	3 (13)	0 (0)	6 (50)	20 (13)
Asian	4 (8)	0 (0)	2 (17)	0 (0)	0 (0)	12 (100)	0 (0)	18 (11)
Other	2 (4)	2 (8)	0 (0)	1 (4)	1 (4)	0 (0)	0 (0)	6 (4)
Subject Type; N(%)								
Healthy Volunteer	0 (0)	24 (100)	12 (100)	8 (33)	8 (35)	12 (100)	12 (100)	76 (48)
AD Patient	51 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	51 (32)
Mild Hepatic Impairment	0 (0)	0 (0)	0 (0)	8 (33)	0 (0)	0 (0)	0 (0)	8 (5)
Moderate Hepatic Impairment	0 (0)	0 (0)	0 (0)	8 (33)	0 (0)	0 (0)	0 (0)	8 (5)
Moderate Renal Impairment	0 (0)	0 (0)	0 (0)	0 (0)	7 (30)	0 (0)	0 (0)	7 (4)
Severe Renal Impairment	0 (0)	0 (0)	0 (0)	0 (0)	8 (35)	0 (0)	0 (0)	8 (5)
Age Group; N(%)								
Adult	44 (86)	24 (100)	12 (100)	24 (100)	23 (100)	12 (100)	12 (100)	151 (96)
Adolescent	7 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (4)
Japanese; N(%)								
Non-Japanese	51 (100)	24 (100)	10 (83)	24 (100)	23 (100)	12 (100)	12 (100)	156 (99)
Japanese	0 (0)	0 (0)	2 (17)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)

Source: Reposrt PMR-EQDD-B745d-dp4-1110, Table 8

Methods

Population PK Analysis for Abrocitinib

The model parameters were re-estimated with additional dataset. The estimation method was stochastic approximation estimation-maximization (SAEM) with importance sampling (IMP).

All important intrinsic and extrinsic factors that accounted for variability in abrocitinib concentrations in the previously developed PK model were included in the base model. The prior model was re-estimated using a new dataset from five clinical trials: 3 phase 1 trials (B7451021, B7451028, and B7451032) and 2 phase 3 trials (B7451014 and B7451036). Studies B7451032 and B7451036 used a new formulation not studied in the previous model. Thus, formulation was re-evaluated as a covariate. The race parameter was adjusted to estimate an effect for Asian race and Other race separately rather than a combined effect. New dataset included subjects with impaired renal function (15 subjects; 7 moderate RI, and 8 severe RI) so that it was feasible to test renal function as a covariate. There was no additional covariate development to the abrocitinib model other than the aforementioned factors.

Population PK Analysis for Abrocitinib Metabolites (M1, M2, and M4)

During parent/metabolite model development, all analytes were converted to molar concentrations:

$$C_{nM} = 1000 \cdot \frac{C_{ng/mL}}{MW}$$

Where C_{nmol} is the molar concentration of an analyte (nmol), $C_{ng/mL}$ is the observed plasma concentration of the analyte (ng/mL), and MW is the analyte's molecular weight (g/mol). M4 is not an active metabolite, but is considered to be a major metabolite (>10%) and is therefore, included in this analysis.

Post hoc estimates for each individual PK pamameter from the abrocitinib parent model were used for the metabolite model development. The structural form of the selected base metabolite model used a formation rate and an elimination rate rather than estimates of both clearance and volume for each of the metabolites. A proportional residual error model was used to describe random unexplained variability.
Following covariates were evaluated for their individual significance in improving the fit of the model to the observed data: age, Asian race, bodyweight, sex, the effects of drug-drug interactions (DDIs) (fluconazole, fluvoxamine, rifampin, and probenecid), the effect of renal and hepatic impairment, and single versus multiple dosing. A stepwise covariate modeling approach was used in this analysis to develop the metabolite model.

Simulations
As in the original NDA, not only abrocitinib but its two major metabolites (M1 and M2) were considered in the assessment of pharmacological activity of abrocitinib because all of them exhibited JAK inhibitory activity. Exposures were simulated in two steps for 500 hypothetical individuals within each subpopulation. In the first step, the abrocitinib parent population PK model was used to simulate the AUC and post hoc estimates. In the second step, the post hoc estimates of abrocitinib model parameters were then used to simulate the concentrations of metabolites.
In simulations for each scenario, the unbound plasma PK metrics (i.e., $AUC_{inf,u}$, $AUC_{last,u}$ and $C_{max,u}$) for abrocitinib and active metabolites, M1 and M2, were calculated for each subject as the sum of the respective components using following equation.

$$AUC_{24,u}AM = AUC_{24,u}P + AUC_{24,u}M1 \bullet \left(\frac{IC_{50,u}P}{IC_{50,u}M1}\right) + AUC_{24,u}M2 \bullet \left(\frac{IC_{50,u}P}{IC_{50,u}M2}\right)$$

where $AUC_{24,u}$AM is the combined unbound exposure of abrocitinib and its two active metabolites at steady state; $AUC_{24,u}$P, $AUC_{24,u}$M1, and $AUC_{24,u}$M2 are the steady state unbound exposures of abrocitinib, M1, and M2, respectively; $IC_{50,u}$P / $IC_{50,u}$M1 and $IC_{50,u}$P / $IC_{50,u}$M2 are the relative potencies of abrocitinib to metabolite M1 and M2 respectively.

Smulations were conducted to evaluate the total pharmacological activity of abrocitinib and its metabolites for each scenario as below. In scenario 1, only abrocitinib exposure was simulated.

1. Exposures of Abrocitinib in Adolescent and Asian Subjects
2. Renal impairment (moderate or severe) vs normal renal function for a typical patient
3. Hepatic impairment (mild or moderate) vs normal hepatic function for a typical patient
4. Strong inhibitors of CYP 2C19 and 2C9 versus monotherapy
    - Fluvoxamine is a strong inhibitor of 2C19 and a moderate 3A4 inhibitor.
    - Fluconazole is a strong inhibitor of 2C19 and a moderate inhibitor of 2C9 and 3A4
5. Strong inducer of CYP 2C19, 2C9, and 3A4 enzymes versus monotherapy
    - Rifampin is a strong inducer of 2C19, 2C9, and 34A
6. Inhibitors of OAT transport versus monotherapy
    - Probenecid is a nonspecific chemical inhibitor of OAT transport; it blocks transport by OAT1, OAT3, and URAT1
7. Typical Asian versus typical non-Asian patient

Results

Population PK Analysis for Abrocitinib

The Applicant's updated population PK analysis is acceptable for the characterization of PK of abrocitinib. The final population PK parameters are presented in Table 19.5.2-5. The effect of renal impairment was evaluated on clearance and was not statistically significant. Renal impairment was not included in the final model.

The IIV for CL (57.7%), and Vc (35.8%) were moderate. The estimated shrinkages of eta and epsilon are greater compared to those estimated values in the previous model (<45% versus <30%). These estimated eta and epsilon values are the basis for EBE estimation used in population PK analyses of abrocitinib metabolites. Study B7451014 had the most subjects included in the model (n=1050 out of in total, 2296 subjects), but there was only a single PK sample collected in this study. The sparse sampling from large number of subjects is supposed to contribute the large shrinkage.

Table 14.4.2-5. Final Parameters Estimates of the Updated Population PK Model of Abrocitinib

	Value	95% CI	Shrinkage
Objective Function Value	130612		
Condition Number	14.6		
Population Parameter			
Clearance (CL; L/hr)	23.2	(21.3, 25.1)	
Volume of the central compartment (V_c; L)	80.6	(75.5, 85.7)	
Inter-compartmental clearance (Q; L/hr)	0.984	(0.506, 1.46)	
Volume of the peripheral compartment (V_p; L)	5.1	(3.81, 6.39)	
Zero-order absorption rate (k_0; mg/hr)	207	(196, 218)	
Amount absorbed by first-order processes (Ak_1; mg)	136	(128, 144)	
First-order absorption rate constant (k_a; hr^{-1})	3.06	(2.77, 3.35)	
Proportional residual error (*RUV PRO*; SD)	0.411	(0.406, 0.416)	
Additive residual error (*RUV ADD*; SD)	13.9	(13.7, 14.1)	
Effect of moderate variability studies on *RUV PRO*	0.452	(0.411, 0.493)	
Effect of high variability studies on *RUV PRO*	1.19	(1.07, 1.31)	
Effect of tablet formulations on *ALAG*1	0.159	(0.143, 0.175)	
Effect of rifampin on CL	0.299	(0.155, 0.443)	
Effect of rifampin on F	-2.12	(-1.96, -2.28)	
Effect of fluconazole on CL	-0.542	(-0.505, -0.579)	
Effect of fluvoxamine on CL	-0.315	(-0.267, -0.363)	
Effect of fluconazole or fluvoxamine on F	1.39	(0.913, 1.87)	
Effect of high-fat meal on Ak_1	-1	Fixed	
Effect of Phase 2 10 and 50 mg tablets on F	-0.711	(-0.475, -0.947)	
Effect of Phase 3 100 mg tablet on F	-0.438	(-0.342, -0.534)	
Effect of suspension on Ak_1	0.906	(0.696, 1.12)	

	Value	95% CI	Shrinkage
Effect of Phase 2 10 and 50 mg tablets on Ak_1	$0 \cdot 10^0$	Fixed	
Effect of multiple-dosing on F	-0.036	(0.144, -0.216)	
Maximum change in CL with respect to time (TAFO; %)	-0.306	(-0.272, -0.34)	
Rate of change in CL with respect to time (half-life; hr)	13.1	(9.15, 17.1)	
Effect of effective daily dose on CL	-0.223	(-0.184, -0.262)	
Effect of Asian subjects on F	0.66	(0.54, 0.78)	
Combined effect of PsO and AD patients on F	0.318	(0.115, 0.521)	
Combined effect of mild and moderate hepatic impairment on F	0.888	(0.303, 1.47)	
Effect of weight on CL and Q (referenced to 70 kg)	0.286	(0.151, 0.421)	
Effect of weight on V_c and V_p (referenced to 70 kg)	0.574	(0.462, 0.686)	
Effect of adolescent subjects on F	-0.387	(-0.228, -0.546)	
Effect of 800 mg dose on F	-0.828	(-0.723, -0.933)	
Effect of female subjects on F	0.484	(0.382, 0.586)	
Effect of Other subjects on F	0.23	(-0.0143, 0.474)	
Effect of Renal Impairment subjects on F	$0 \cdot 10^0$	Fixed	
Inter-Individual Variability			
ω_{CL} (% CV)	57.7	52.6, 62.8	29.1
ω_{V_c} (% CV)	35.8	30.6, 41	44.2
Correlation			
ρ_{CL-V_c}	0.256	0.163, 0.349	
Random Unexplained Variability			
ε_{res}	1	Fixed	11.9

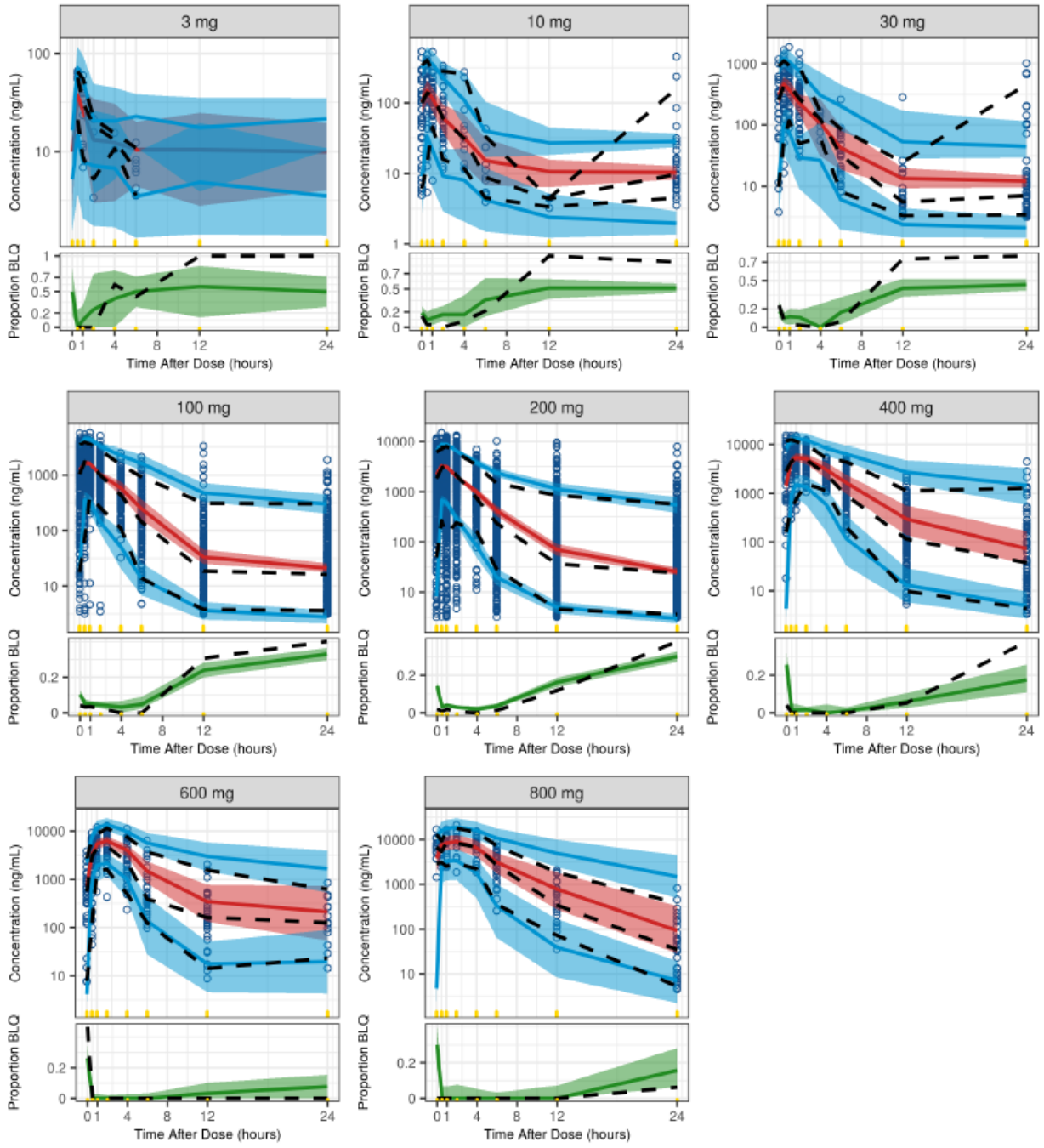
Repository artifact ID FI-16844382. Line 1 substituted.

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.

Source: Reposrt PMR-EQDD-B745d-dp4-1110, Table 10

To evaluate the predictive ability of the updated abrocitinib parent model, VPCs were created by simulating from the parent model 1000 times. The VPCs for each dose level are presented in Figure 19.5.2-1. Visual Predictive Check Stratified by Dose for Updated PK Model of Abrocitinib. Visual predictive checks indicate that the updated population PK model is reasonable in characterizing the PK profile of abrocitinib in all studied dose levels. Model predictions were generally within the 90% prediction intervals. No apparent bias was observed in the overall model fit for the data.

Figure 14.4.2-1. Visual Predictive Check Stratified by Dose for Updated PK Model of Abrocitinib



Source: Reposrt PMR-EQDD-B745d-dp4-1110, Figure 7

Population PK Analysis for Abrocitinib Metabolites (M1, M2, and M4)

A base model was developed to simultaneously model M1, M2, and M4. For each of the metabolites, a 1-compartment model adequately described PK character of each metabolite. The formation rates are modeled as population typical values without IIV where the elimination of the parent is assumed to be broken down as components formed into M1, M2, or M4, and everything else. A scaling effect on the abrocitinib clearance was added to the model as it helped improve the post hoc estimates of clearance.

The model building included an assessment on age, Asian race, bodyweight, and sex on either the formation rates, elimination rates or both. Bodyweight had a significant effect on elimination rate. Renal impairment on elimination rate and hepatic impairment on formulation rate met the significance criteria as well.

Parameter estimates and bootstrap results for the final model are presented in Table 19.5.2-6 Most of the fixed and random effect parameters were all estimated with good precision. The magnitude of the IIV was moderate for CLM1 (59.6 %CV) and CLP (69.5 %CV). Eta and epsilon shrinkages were minimal (<10%) for EBE estimation.
Model evaluations were based on successful model convergence, accuracy of parameter estimation (95% confidence interval and bootstrap, Table 19.5.2-6) and VPC (Figure 19.5.2-2. Visual Predictive Check Stratified by Dose in Each Metabolite for the Final Abrocitinib Metabolite Joint ModelFigure 19.5.2-2). The model described the observed data well and the model predictions were generally within the 90% prediction intervals. No apparent bias was observed in the overall model fit for the data.

Table 14.4.2-6. Parameters Estimates of the Final Abrocitinib Metabolite Joint Model

Parameter	Value	Standard Error	Bootstrap Median	Bootstrap 95% CI	SHR (%)
Objective Function Value	54043				
Condition Number	64.1				
Population Parameter					
Formation Rate of M1 (K_{24}; 1/hr)	0.103	0.0184	0.099	(0.0662, 0.143)	
Formation Rate of M2 (K_{25}; 1/hr)	0.0653	0.00947	0.0659	(0.0436, 0.108)	
Formation Rate of M4 (K_{26}; 1/hr)	0.0471	0.00659	0.0503	(0.0312, 0.0912)	
Elimination Rate of M1 ($k_{el,M1}$; 1/hr)	54.5	11.3	50.2	(33.5, 72.8)	
Elimination Rate of M2 ($k_{el,M2}$; 1/hr)	16.3	2.59	15.8	(10.5, 25.1)	
Elimination Rate of M4 ($k_{el,M4}$; 1/hr)	20.5	3.38	21.3	(13.1, 38.1)	
Proportional Err. of Parent	0	Fixed	0	Fixed	
Proportional Err. of M1	0.514	0.0162	0.488	(0.446, 0.53)	
Proportional Err. of M2	0.448	0.0156	0.427	(0.381, 0.46)	
Proportional Err. of M4	0.405	0.0128	0.427	(0.381, 0.46)	
Effect of Rifampin on $k_{el,M1}$	-0.863	0.00608	-0.863	(-0.897, -0.826)	
Effect of Rifampin on $k_{el,M2}$	-0.732	0.0153	-0.733	(-0.765, -0.69)	
Effect of Rifampin on $k_{el,M4}$	-0.857	0.00763	-0.858	(-0.872, -0.841)	
Effect of Probenecid on $k_{el,M1}$	-0.29	0.0612	-0.298	(-0.376, -0.193)	
Effect of Probenecid on $k_{el,M2}$	-0.522	0.027	-0.537	(-0.662, -0.437)	
Effect of Probenecid on $k_{el,M4}$	-0.523	0.0215	-0.54	(-0.648, -0.443)	
Effect of Fluconazole on K_{24}	1.26	0.125	1.24	(1.05, 1.49)	
Effect of Fluconazole on K_{25}	0.337	0.0281	0.341	(0.283, 0.423)	
Effect of Fluconazole on K_{26}	0.682	0.0445	0.698	(0.595, 0.871)	
Effect of Fluvoxamine on K_{24}	0.56	0.0594	0.553	(0.454, 0.679)	
Effect of Fluvoxamine on K_{25}	0.287	0.0261	0.29	(0.22, 0.376)	
Effect of Fluvoxamine on K_{26}	0.294	0.0303	0.301	(0.244, 0.394)	
Effect of Renal Impairment on $k_{el,M1}$	-0.0464	0.211	0.1	(-0.214, 0.569)	
Effect of Renal Impairment on $k_{el,M2}$	-0.521	0.088	-0.503	(-0.615, -0.361)	
Effect of Renal Impairment on $k_{el,M4}$	-0.543	0.0967	-0.5	(-0.619, -0.327)	
Effect of Hepatic Impairment on K_{24}	0.349	0.0886	0.362	(0.25, 0.479)	

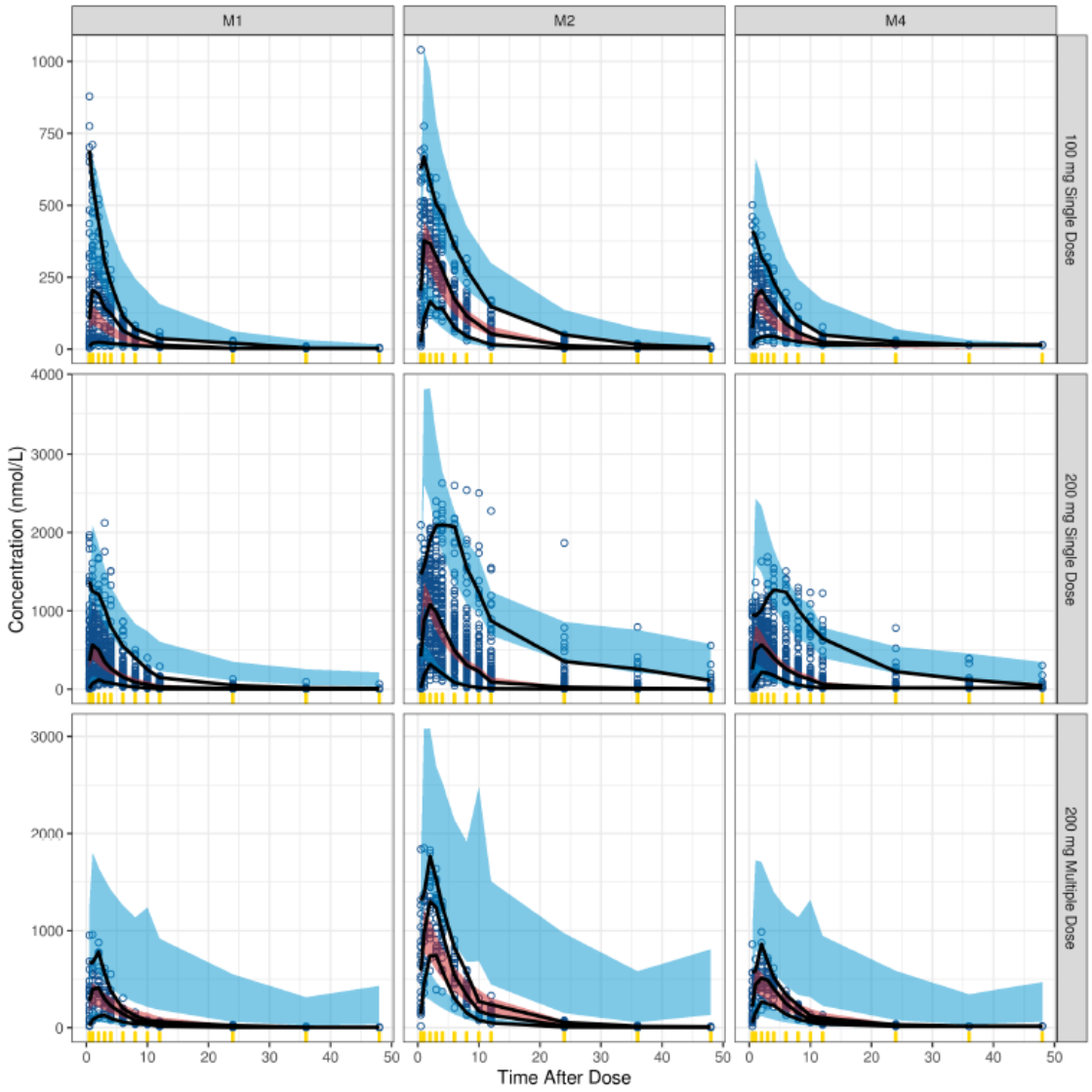
Parameter	Value	Standard Error	Bootstrap Median	Bootstrap 95% CI	SHR (%)
Effect of Hepatic Impairment on K_{25}	0	Fixed	0	Fixed	
Effect of Hepatic Impairment on K_{26}	0	Fixed	0	Fixed	
Scalar on post hoc parent CL_P	0.883	0.132	0.88	(0.734, 1.03)	
Effect of Multiple Dosing on the post hoc scalar	-0.595	0.491	-0.57	(-1.22, -0.0212)	
Effect of Renal Impairment on the post hoc scalar	-1.74	0.538	-1.69	(-2, -1.32)	
Effect of Multiple Dosing on $k_{el,M1}$	1.05	0.116	1.08	(0.747, 1.59)	
Effect of Multiple Dosing on K_{25}	0.131	0.0168	0.136	(0.0393, 0.26)	
Effect of Multiple Dosing on K_{26}	0.172	0.0174	0.175	(0.103, 0.268)	
Effect of Bodyweight on $k_{el,M1}$	1.63	0.458	1.49	(0.672, 2.47)	
Effect of Bodyweight on $k_{el,M2}$	1.09	0.332	1.21	(0.663, 1.94)	
Effect of Bodyweight on $k_{el,M4}$	1.35	0.31	1.37	(0.65, 2.2)	
Inter-Individual Variability					
ω_{CLM1} (% CV)	59.6	Fixed	58.1	Fixed	1.66
ω_{CLM2} (% CV)	41.8	Fixed	41.6	Fixed	3.26
ω_{CLM4} (% CV)	47.3	Fixed	47.4	Fixed	2.23
ω_{CLP} (% CV)	69.5	Fixed	69.3	Fixed	3.65
Correlation					
ρ_{M1-M2}	0.243	Fixed			
ρ_{M1-M4}	0.696	Fixed			
ρ_{M2-M4}	0.83	Fixed			
ρ_{M1-CLP}	0.33	Fixed			
ρ_{M2-CLP}	-0.104	Fixed			
ρ_{M4-CLP}	0.069	Fixed			
Random Unexplained Variability					
ε_{res}	1	Fixed			5.21

Repository artifact ID FI-17952734.

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. The OFV was estimated using importance sampling. All other parameter estimates were based on the SAEM estimation.

Source: Reposrt PMR-EQDD-B745d-dp4-1110, Figure 11

Figure 14.4.2-2. Visual Predictive Check Stratified by Dose in Each Metabolite for the Final Abrocitinib Metabolite Joint Model



Repository artifact ID FI-16768198.

The red band represents the 95% interval of the simulated median concentrations. The blue bands represent the 95% interval for the 5th and 95th percentiles. The dashed lines represent the percentiles in the observed data. The bins are based on the nominal sampling times.

Source: Reposrt PMR-EQDD-B745d-dp4-1110, Figure 8

Simulation Results

- *Exposure of Abrocitinib in Healthy Subjects and AD Patients*

Adolescent AD patients were found to have a statistically significant effect on bioavailability such that adolescent patients tended to have lower bioavailability than adult AD patients. The difference in the exposures for a typical adult (white, male, 77 kg) AD patient was compared to the typical adolescent (white, male) AD patient for both the median observed bodyweight (59 kg) and the extreme low weight (25 kg) receiving 200 mg QD as presented in Table 19.5.2-7.

Table 14.4.2-7. Simulated Abrocitinib Exposure for A Typical Adolescent Patient Versus A Typical Adult Patient Using the Updated PK Model for 200 mg Abrocitinib Once Daily

Subject	Age Group	Bodyweight (kg)	Race	C_{max} (ng/mL)	AUC (ng*hr/mL)
Healthy Volunteer	Adult	77	White	1047	6344
Atopic Dermatitis Patient	Adult	77	White	1201	7646
Atopic Dermatitis Patient	Adolescent	59	White	1164	6548
Atopic Dermatitis Patient	Adult	66	Asian	1598	10705
Atopic Dermatitis Patient	Adolescent	56	Asian	1557	9594
Atopic Dermatitis Patient	Adolescent	25	White	1805	8370
Atopic Dermatitis Patient	Adolescent	25	Asian	2343	12083

Repository artifact ID FI-16804810. Line 1 substituted.

The expected value is provided (ie simulation of a single subject without any variability) for each of the typical subjects. The median observed bodyweight was calculated for each combination of attributes. Unless otherwise noted, the subject was a white, male, AD patient at steady-state receiving 200 mg QD. The exposures have been converted from nmol/L back to ng/mL.

Source: Reposrt PMR-EQDD-B745d-dp4-1110, Table 12

- *Renal Impairment*

In Study B7451021, the observed AUC_{inf} ratios from the study were 210% for moderate renal impairment and 291% for severe renal impairment. Simulation assumed steady state abrocitinib dosing in white male AD patients with 70 kg of body weight rather than single dose in healthy subjects as was the case in Study B7451021.

Table 19.5.2-8 presents the comparison in the combined exposure of abrocitinib and its active metabolites, M1 and M2, between patients with AD (who were white male subjects with 70 kg of body weight) following 200 mg multiple once daily dose and observed combined exposure in healthy subjects after single 200 mg dose. Figure 19.5.2-3 presents further simulation of combined exposure of abrocitinib and its two active metabolites in adult and adolescent subject who received 100 mg or 200 mg multiple abrocitinib doses. The abrocitinib and active metabolites AUC (nM·hr) were simulated for the observed AD patients with at least 1 PK samples across the clinical trials. For patients without metabolite samples, the typical value was used to simulate the active metabolites. Since there was no adolescent patients with moderately impaired renal function, it was not feasible similating the abrocitinib exposure in them. The exposure difference was lesser in adolescents than in adults (Figure 19.5.2-3). However, conclusion was not made due to the small number of adolescent subjects (n=7) included in the simulation.

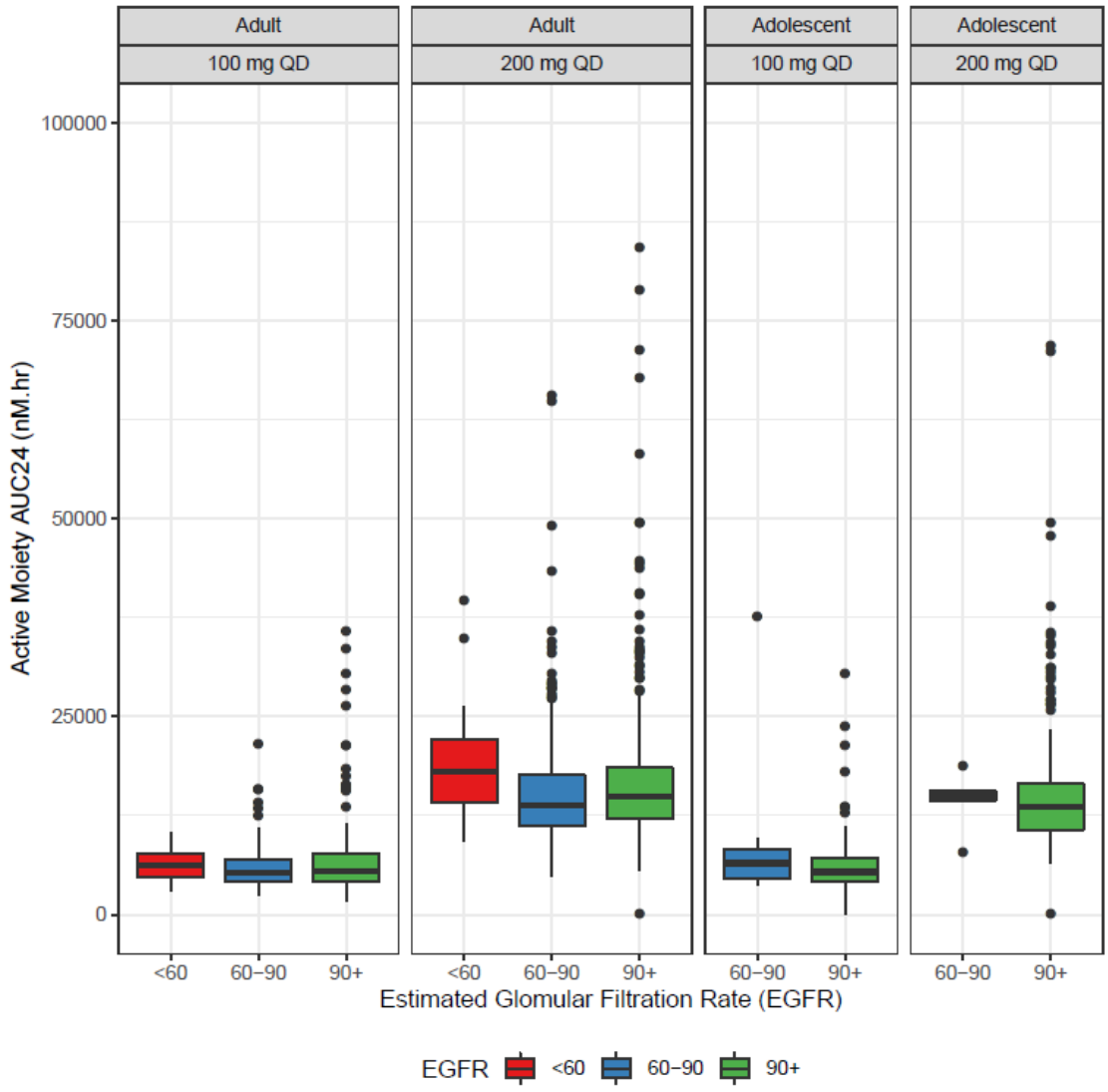
Table 14.4.2-8. Simulated Combined Exposure of Abrocitinib and its Two Active Metabolites (M1 and M2) Following 200 mg Once Daily in AD Patients with Renal Impairment Compared to the Observed Values in Healthy Subjects

Renal Function	Simulated AUC (nM·hr) of combined exposure	Simulated Ratio (%) of combined exposure[1] to normal renal function in typical patients[2] with AD	Observed Ratio (%) of combined exposure[1] to normal renal function in heathy subjects, Study B7451021

Normal	17981	-	-
Moderately Impaired	27406	152.4 %	210 %
Severe Impaired	60872	338.5 %	291 %

1: Combined $AUC_{inf,u}$ of abrocitinib, M1, and M2
2: white male patients with 30 years of age and 70 kg of body weight
Source: Reposrt PMR-EQDD-B745d-dp4-1110, Table 13; Study Report B7451021, Table 17

Figure 14.4.2-3. Effect of Renal Function on the Combined Exposure of Abrocitinib and Its Two Metabolites (M1 and M2) in Subejcts with AD

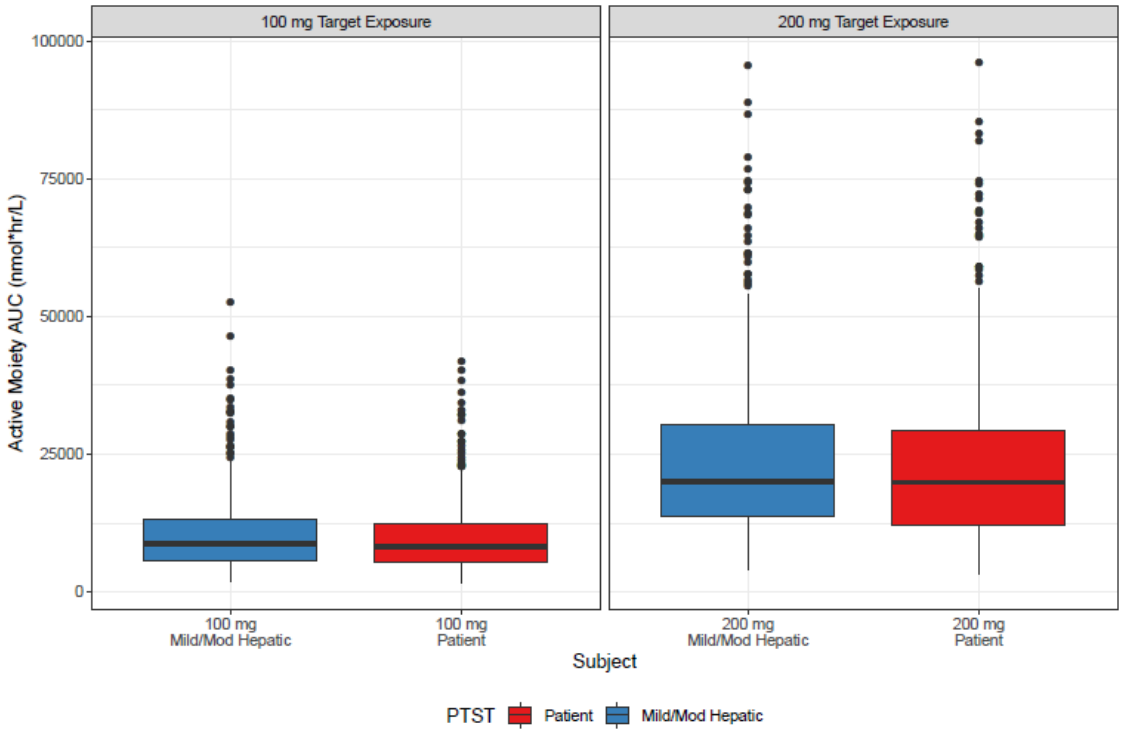


Repository artifact ID FI-17003552.
The abrocitinib and active moiety AUC (nmol*hr/L) were simulated for the observed AD patients with at least 1 PK samples across the clinical trials. For patients without metabolite samples, the typical value was used to simulate the active moiety.
Source: Reposrt PMR-EQDD-B745d-dp4-1110, Figure 10

- *Hepatic Impairment*

The total change in the combined exposure of abrocitinib and its active metabolites, M1 and M2, in AD patients with mild or moderate hepatic impairment was estimated to be a 6.3% and 4.7% increase for 100 mg and 200 mg QD. The distribution of the active moiety AUC are shown in Figure 19.5.2-4. These results are consistent with the observed change in the deidicated hepatic impairment study.

Figure 14.4.2-4. Effect of Hepatic Function on the Combined Exposure of Abrocitinib and Its Two Metabolites (M1 and M2) in AD Subejcts with Mild or Moderate Hepatic Impairment



Repository artifact ID FI-17003420.

The abrocitinib and active moiety AUC (nmol*hr/L) were simulated out to steady state for a typical AD patient (white, male, 70 kg, 30 years old) with no impairment, mild impairment, and moderate impairment.

Source: Reposrt PMR-EQDD-B745d-dp4-1110, Figure 11

- *DDI: Coadministration of Abrocitinib with Strong CYP2C19 Inhibitors*

A DDI study evaluated the effect of fluconazole (a strong CYP2C19 inhibitor and a moderate CYP2C9 and CYP3A4 inhibitor) as well as fluvoxamine (a strong CYP2C19 inhibitor and moderate inhibitor of CYP3A4). The combined exposure of abrocitinib and its active metabolites were simulated out to steady state for a typical AD patient (white, male, 70 kg, 30 years old) with receiving abrocitinib alone, abrocitinib with fluconazole, or abrocitinib with fluvoxamine at abrocitinib doses of 50 mg, 100 mg, and 200 mg. Table 19.5.2-9 presents the simulated combined exposure at 100 mg multiple dosing in AD patients in purpose of comparing the simulated values to the observed DDI results in healthy subjects (Study B7451017). Simulated

exposure differences between scenarios were similar to the observed values in Study B7451017 despite of the different study design and population.

Table 14.4.2-9. Simulated Combined Exposure of Abrocitinib and its Two Active Metabolites (M1 and M2) Following Abrocitinib 100 mg Once Daily in AD Patients With or Without Concomitant Administration of Fluvoxamine or Fluconazole

Scenario	Simulated $AUC_{24,ss}$ (nM·hr) of combined exposure	Simulated Ratio (%) of combined exposure[1] to abrocitinib alone in typical patients[2] with AD	Observed Ratio (%) of combined exposure[1] to abrocitinib alone in heathy subjects, Study B7451017
Abrocitinib Alone	7912	-	-
Abrocitinib +Fluvoxamine	13399	169.4 %	191 %
Abrocitinib + Fluconazole	18339	231.8 %	255 %

1: Combined $AUC_{inf,u}$ of abrocitinib, M1, and M2
2: white male patients with 30 years of age and 70 kg of body weight
Source: Reposrt PMR-EQDD-B745d-dp4-1110, Table 15; Study Report B7451017-metabolite-moiety-tables-2, Table 14.4.5.6.1 and Table 14.4.5.6.2

- *DDI: Coadministration of Abrocitinib with Strong CYP2C19, CYP2C9, and CYP3A4 Inducer*

The effects of rifampin as a strong inducer of CYP2C19, CYP2C9, and CYP3A4, on the combined exposure of abrocitinib and its two active metabolites, M1 and M2, are provided in Table 19.5.2-10. The effect of rifampin on the combined exposure in simulation study was comparable to that observed results in Study B7451019.

Table 14.4.2-10. Simulated Combined Exposure of Abrocitinib and its Two Active Metabolites (M1 and M2) Following Abrocitinib 200 mg Once Daily in AD Patients With or Without Concomitant Administration of Rifampin

Scenario	Simulated $AUC_{24,ss}$ (nM·hr) of combined exposure	Simulated Ratio (%) of combined exposure[1] to abrocitinib alone in typical patients[2] with AD	Observed Ratio (%) of combined exposure[1] to abrocitinib alone in heathy subjects, Study B7451019
Abrocitinib Alone	18451	-	-
Abrocitinib + Rifampin	6239	33.8 %	43.9 %

1: Combined $AUC_{inf,u}$ of abrocitinib, M1, and M2
2: white male patients with 30 years of age and 70 kg of body weight
Source: Reposrt PMR-EQDD-B745d-dp4-1110, Table 16; Study Report B7451019-metabolite-moiety-tables-2, Table 14.4.5.7.1

- *DDI: Coadministration of Abrocitinib with OAT Inhibitor*

The effects of probenecid as a OAT inhibitor on the combined exposure of abrocitinib and its two active metabolites, M1 and M2, are provided in Table 19.5.2-11. The effects of probenecid

on the combined exposure in simulation study was not significant as it was in Study B7451043.

Table 14.4.2-11. Simulated Combined Exposure of Abrocitinib and its Two Active Metabolites (M1 and M2) Following Abrocitinib 200 mg Once Daily in AD Patients With or Without Concomitant Administration of Probenecid

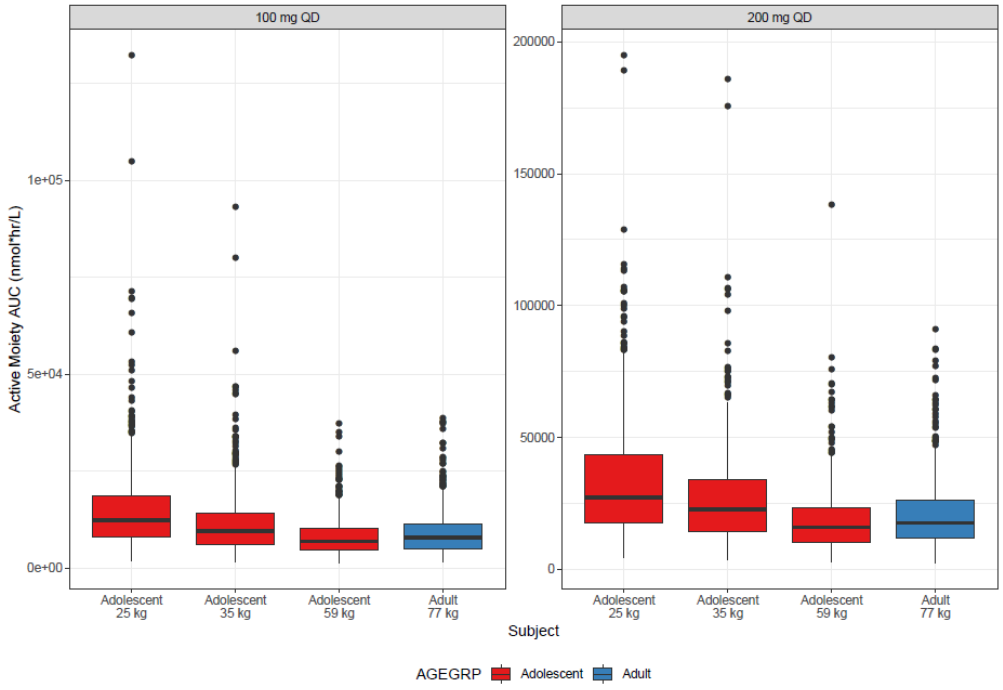
Scenario	Simulated $AUC_{24,ss}$ (nM·hr) of combined exposure[1]	Simulated Ratio (%) of combined exposure[1] to abrocitinib alone in typical patients[2] with AD	Observed Ratio (%) of combined exposure[1] to abrocitinib alone in heathy subjects, Study B7451043
Abrocitinib Alone	18451	-	-
Abrocitinib + Probenecid	28211	152.9 %	165.54%

1: Combined $AUC_{inf,u}$ of abrocitinib, M1, and M2
2: white male patients with 30 years of age and 70 kg of body weight
Source: Reposrt PMR-EQDD-B745d-dp4-1110, Table 17; Study Report B7451043, Table 18

- *Adolescents*

Figure 19.5.2-5 shows the simulated combined exposure of abrocitinib and its two active metabolites, M1 and M2, in the typical adult AD patient (white, male, 77 kg), the typical AD adolescent (white, male, 59 kg), low weight AD adolescent (white, male, 35 kg) and extreme low weight AD adolescent (white, male, 25 kg) patients. There was a tendency for increasing combined exposure of abrocitinib and its active metabolites with decreasing bodyweight, but it is in general comparable to adult exposure.

Figure 14.4.2-5. Comparison of Combined Exposure of Abrocitinib and Its Two Metabolites (M1 and M2) in Adut with AD versus Adolescent with AD

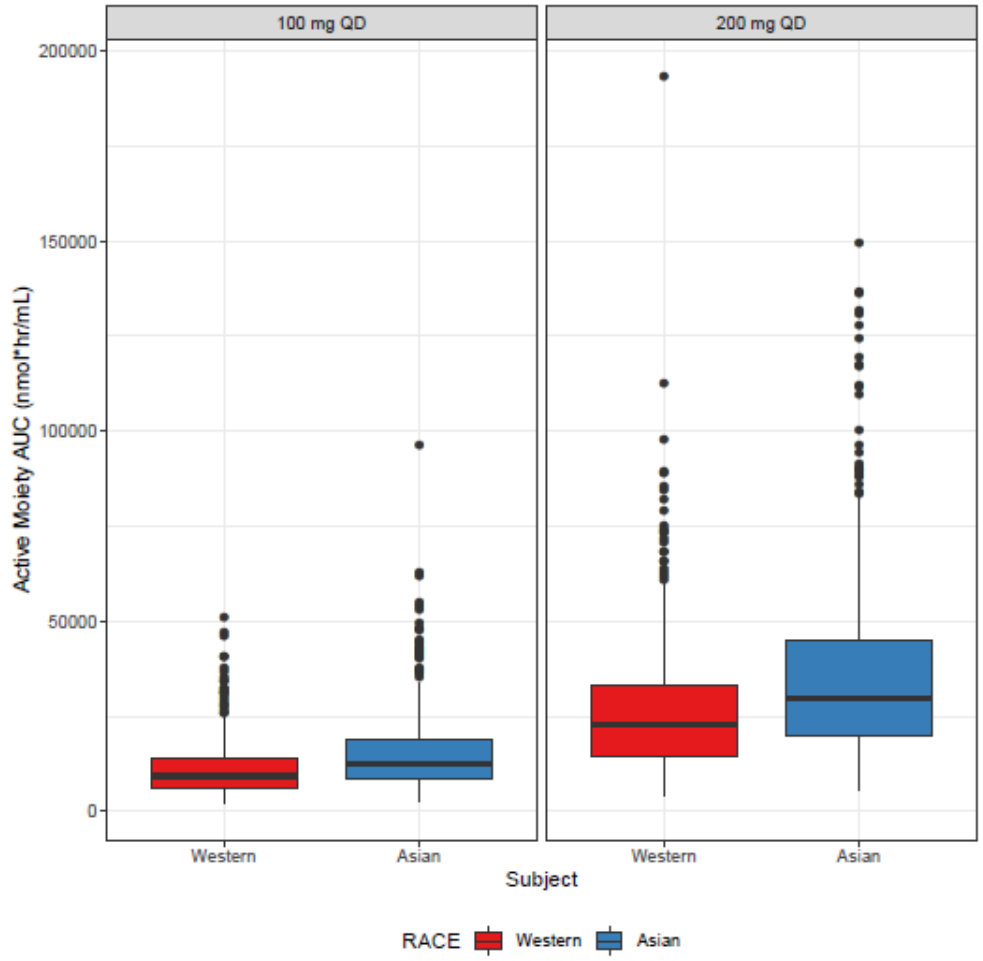


The abrocitinib and active moiety AUC (nmol*hr/L) were simulated out to steady state for a typical adult AD patient (white, male, 77 kg), a typical adolescent AD patient (white, male, 59 kg), a low weight adolescent (35 kg), and an extreme low weight adolescent (25 kg). Simulations were performed for 100 mg and 200 mg QD dosing.
Source: Reposrt PMR-EQDD-B745d-dp4-1110, Figure 15

- *Race*

Asian race had a significant effect on the bioavailability of abrocitinib. Differences related to race were simulated with the results shown in Figure 19.5.2-6. The typical body weight from subjects in the analysis dataset was used for the simulated patients. The difference was 34.7% and 33.6% increases for abrocitinib 100 mg QD and 200 mg QD, respectively, in the combined exposure of abrocitinib and its two active metabolites, M1 and M2, for Asian AD patients compared to non-Asian AD patients. This difference is not considered clinically meaningful.

Figure 14.4.2-6. Comparison of Combined Exposure of Abrocitinib and Its Two Metabolites (M1 and M2) in Western AD Patients versus Asian AD Patients



The abrocitinib and active moiety AUC (nmol*hr/L) were simulated out to steady state for a typical western AD patient (white or black, male, 77 kg) and a typical Asian AD patient (Asian, male, 66 kg). Simulations were performed for 100 mg and 200 mg QD dosing.

Source: Reposrt PMR-EQDD-B745d-dp4-1110, Figure 16

14.4.3. Summary of Bioanalytical Method Validation and Performance

Abrocitinib and Its Active Metabolites (M1, M2, and M4) Concentrations in Plasma

Plasma concentrations of abrocitinib and its metabolites i.e., M1, M2, and M4 were measured using validated bioanalytical methods with HPLC-MS/MS that were submitted and reviewed in the original application. The bioanalytical methods were adequate to analyze abrocitinib, M1, M2, M4. For the details, refer the Clinical Pharmacology review section in the Unireview of NDA 213871 original submission (SDN 001) available at https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8063c5ac.

Table 14.4.3-1. Summary of the Performance of the Bioanalytical Method to Measure Abrocitinib, M1, M2, and M4 in Human K2EDTA Plasma in Study B7451028

Method performance in study B7451028						
Analyte(s)		Abrocitinib	M1	M2	M4	Acceptability
Assay run performance: # of runs that met the acceptance criteria		10 out of 12 runs	7 out of 8 runs	7 out of 9 runs	7 out of 8 runs	Yes
Mean inter-assay performance	Precision (%CV)	≤ 5.79%	≤ 7.57%	≤ 9.8%	≤5.74%	Yes
	Accuracy (%RE)	-1.6-2.0%	-1.3-3.4%	-6.1-1.3%	0.1-3.7%	Yes
ISR assessment		100%	100%	100%	100%	Yes
Maximum days from collection to analysis		106 Days	98 Days	99 Days	98 Days	Yes
Maximum number of freeze/thaw cycles		5 Cycles	5 Cycles	5 Cycles	5 Cycles	Yes
Method performance in study B7451036						
Analyte(s)		Abrocitinib				Acceptability
Assay run performance: # of runs that met the acceptance criteria		11 out of 11 runs				Yes
Mean inter-assay performance	Precision (%CV)	≤ 6.6%				Yes
	Accuracy (%RE)	0.0-4.4%				Yes
ISR assessment		95.1%				Yes
Maximum days from collection to analysis		434 Days				Yes
Maximum number of freeze/thaw cycles		3 Cycles				Yes

Source: Bioanalytical Report of B7451028; Bioanalytical Report of B7451036
Abbreviations: CV=coefficient of variation; RE=relative error

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/s/

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I am signing for myself and on behalf of Marilena Flouri because she is no longer at the FDA

GORDANA DIGLISIC
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Signing on behalf of Dr. Tatiana Oussova