ABROCITINIB RISK MANAGEMENT PLAN

RMP Version number: 5.0

Data lock point for this RMP: 05 September 2022 [Clinical Data] and 07 March 2023 [Post-Marketing Data inclusive of Clinical Trial and Non-Clinical Trial Data]

Date of final sign off: 16 July 2024

Rationale for submitting an updated RMP: RMP version 5.0 is being submitted to align with the final protocol for PASS B7451085 agreed with PRAC/CHMP in October 2023 via the PAM procedure EMEA/H/C/0005452/MEA/003.3, and the final protocol for PASS B7451084 agreed with PRAC/CHMP in June 2023 via the PAM procedure EMEA/H/C/005452/MEA/002.2.

Summary of significant changes in this RMP:

Part III Pharmacovigilance Plan (including post-authorisation safety studies [PASS]):

- Study B7451084: Updated *Study Population*.
- Study B7451085: Updated *Rationale and Study Objectives*; updated *Study Design*; updated *Study Population*; and updated *Milestones*.

Part VI Summary of the Risk Management Plan:

- Study B7451084: Updated *Purpose of the Study*.
- Study B7451085: Updated *Purpose of the Study*.

Annex 2 Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

- Study B7451084: Updated *Summary of Objectives*.
- Study B7451085: Updated *Summary of Objectives* and *Milestones*.

Annex 3 Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan:

- Removed protocol synopses for Study B7451084, Study B7451085, and Study B7451015. Hyperlinks to the protocols were added for these studies.

Annex 8 Summary of Changes to the Risk Management Plan over Time: Updates per changes in Version 5.0 and RMP approval dates with procedure numbers.

Other RMP versions under evaluation: None.
Details of the currently approved RMP:

Version number 4.4

Approved with procedure: EMEA/H/C/005452/II/0010

Date of approval (opinion date): 22 February 2024

QPPV name: Barbara De Bernardi, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

LIST OF ABBREVIATIONS

AD	Atopic Dermatitis
ADA	Anti-Drug Antibodies
ADAE	Analysis Dataset Adverse Event
ADAM	Analysis Data Model
ADHD	Attention-Deficit/Hyperactivity Disorder
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
aRMM	Additional Risk Minimisation Measures
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical (classification)
AUC	Area Under the Concentration-Time Curve
AUC_{inf}	Area Under the Curve from 0 to Infinity
AVDOS	Average Daily Dose
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
CBC	Complete Blood Count
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CK	Creatine Kinase
Cmax	Maximum Observed Concentration
CMQ	Customized MedDRA Query
COVID-19	Coronavirus Disease of 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DDI	Drug-Drug Interaction
DHPC	Direct Healthcare Professional Communication
DVT	Deep Vein Thrombosis
EASI	Eczema Area and Severity Index
EBV	Epstein Barr Virus
ECG	Electrocardiogram
EEA	European Economic Area
EFD	Embryo-Foetal Development
EMA/EMEA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FCP	Full Cumulative Pool
FLG	Filaggrin
GI	Gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor

HADS	Hospital Anxiety and Depression Scale
HCP	Health Care Professional
HCT	Haematocrit
HDL	High Density Lipoprotein
HGB	Haemoglobin
HIV	Human Immunodeficiency Virus
HLGT	High-Level Group Term
HLT	High-Level Term
HPA	Hypothalamic Pituitary Adrenal
HZ	Herpes Zoster
IBD	Inflammatory Bowel Disease
Ig	Immunoglobulin
IGA	Investigator Global Assessment
IL	Interleukin
INN	International Nonproprietary Name
IR	Incidence Rate
ISAAC	International Study of Asthma and Allergies in Childhood
JAK	Janus Kinase
JAKi	Janus Kinase Inhibitor
KLH	Keyhole Limpet Hemocyanin
KPNC	Kaiser Permanente Northern California
LDL	Low Density Lipoprotein
LTDCP	Long-Term Dose-Controlled Pool
LTE	Long-Term Extension
MACE	Major Adverse Cardiovascular Events
MAH	Marketing Authorisation Holder
MATE	Multidrug and Toxin Extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NA	Not Applicable or Not Available
NK	Natural Killer
NMN	N-methylnicotinamide
NMSC	Non-melanoma Skin Cancer
NOAEL	No Observed Adverse Effect Level
NSAID	Non-steroidal Anti-inflammatory Drug
OAT	Organic Anion Transporter
OI	Opportunistic Infection
OR	Odds Ratio
PAM	Post-Authorisation Measures
PASS	Post-Authorisation Safety Study
PE	Pulmonary Embolism
P-gp	P-glycoprotein
PHQ	Patient Health Questionnaire
PK	Pharmacokinetic

PL	Package Leaflet
PPND	Pre- and Postnatal Development
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PY	Person-year
QD	Once daily
QPPV	Qualified Person for Pharmacovigilance
QW	Once a Week
Q2W	Every 2 Weeks
RA	Rheumatoid Arthritis
RBC	Red Blood Cell
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
RSI	Request for Supplementary Information
SBQ-R	Suicidal Behaviors Questionnaire – Revised
SDS	Standard Deviation Score
SDTM	Study Data Tabulation Model
SIB	Self-injurious Behaviour
SIR	Standardised Incidence Ratio
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
STAT	Signal Transducer and Activator of Transcription
STS	Short-Term Studies
TB	Tuberculosis
TBD	To Be Determined
TK	Toxicokinetic
TOT	Total
TPO	Thrombopoietin
TYK	Tyrosine-Kinase
UGT	Uridine Diphospho-Glucuronosyltransferase
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VTE	Venous Thrombotic Event / Venous Thromboembolism
VZV	Varicella Zoster Virus
VZV IgG Ab	Varicella Zoster Virus Immunoglobulin G Antibody
Yrs	Years

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Abrocitinib
Pharmacotherapeutic group(s) (ATC Code)	D11AH08
Marketing Authorisation Holder (MAH)	Pfizer Europe MA EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Cibinqo
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class: Abrocitinib is a potent, Janus kinase 1 (JAK1) inhibitor.
	Summary of mode of action: Cibinqo is a JAK1 inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of haematopoiesis and immune cell function. JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Inhibition of JAK1 modulates the signalling pathways by preventing the phosphorylation and activation of STATs. In biochemical assays, abrocitinib has selectivity for JAK1 over the other 3 JAK isoforms JAK2 (28-fold), JAK3 (> 340-fold) and tyrosine kinase 2 (TYK2, 43-fold). In cellular settings, it preferentially inhibits cytokine-induced STAT phosphorylation by signalling pairs involving JAK1, and spares signalling by JAK2/JAK2, or JAK2/TYK2 pairs. The relevance of selective enzymatic inhibition of specific JAK enzymes to clinical effect is not currently known.
	Important information about its composition: Excipients with known effect: lactose monohydrate
Hyperlink to the Product Information:	Please refer to Module 1.3.1
Indication(s) in the EEA	Current: Cibinqo is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.
Dosage in the EEA	Current: The recommended starting dose is 100 mg or 200 mg once daily based on individual patient characteristics: • A starting dose of 100 mg once daily is recommended for patients at higher risk of venous thromboembolism (VTE),

	major adverse cardiovascular event (MACE) and malignancy. If the patient does not respond adequately to 100 mg once daily, the dose can be increased to 200 mg once daily. • A dose of 200 mg once daily may be appropriate for patients who are not at higher risk of VTE, MACE and malignancy with high disease burden or for patients with an inadequate response to 100 mg once daily. Upon disease control, dose should be decreased to 100 mg once daily. If disease control is not maintained after dose reduction, re-treatment with 200 mg once daily can be considered. The lowest effective dose for maintenance should be considered. Discontinuation of treatment should be considered in patients who show no evidence of therapeutic benefit after 24 weeks. Cibinqo can be used with or without medicated topical therapies for atopic dermatitis. *Elderly* For patients 65 years-of-age and older, the recommended dose is 100 mg once daily.
	Proposed: • In adolescents (12 years to 17 years of age), weighing 25 kg to < 59 kg, a starting dose of 100 mg once a day is recommended. If the patient does not respond adequately to 100 mg once daily, the dose can be increased to 200 mg once daily. In adolescents weighing at least 59 kg, a starting dose of 100 mg or 200 mg once daily may be appropriate.
Pharmaceutical form(s) and strengths	Current: Oral film-coated tablets containing 50 mg, 100 mg, or 200 mg of abrocitinib
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population(s)

Atopic dermatitis (AD), also known as *eczema* or *atopic eczema*, is a common, chronic, relapsing inflammatory skin condition affecting patients of all ages.[1,2]

Epidemiological Literature Search Strategy

The United States (US) National Library of Medicine PubMed database was searched for observational literature on AD among adults (18+ years-of-age) on 16 December 2019 using the following search string: "(atopic and [dermatitis or eczema]) AND (epidemiology OR epidemiologic OR risk OR rate OR incidence OR prevalence OR morbidity OR mortality). PubMed was then searched on 13 April 2020 for literature on AD among adolescents (≥ 12 to ≤ 18 years-of-age) using the following search string: ([atopic eczema or atopic dermatitis] and [adolescent or teenager or young adult] and [epidemiolog* or incidence or prevalence or risk or rate]). Finally, PubMed was searched on 12 May 2020 for literature on AD among children (0 to 12 years-of-age) using the following search string: (atopic AND [dermatitis OR eczema] AND [child OR children OR adolescent OR adolescent OR pediatric OR paediatric]) AND [epidemiolog OR epidemiologic OR risk OR rate OR incidence OR prevalence OR morbidity OR mortality]). Article titles were restricted to human populations, observational data, and the English language. Potentially relevant abstracts were reviewed by epidemiologists, and articles were excluded if they reported exclusively on clinical trial participants or were case reports. When available, disease severity data were extracted.

SI.1. Adults

Incidence and prevalence:

Estimates of incidence of AD among adults were not found.

The prevalence of AD varies throughout the world with an estimated global prevalence of 230 million.[3,4] Historically, AD prevalence was lower in Africa and the Middle East than in North America and Europe; however, recent trends suggest increasing AD prevalence in the developing world.[3] AD is much less common among adults than children and adolescents.[5,1,6] While some studies suggest that prevalence estimates of AD among adults range from 1 to 3%[7,8,9,10,11,12,13,14,15,16,5,17,18,19,20] others report higher estimates between 4.1 and 14%. [21,22,23,24,25,26,27,28,29,30,17,31,32,33,34] Specifically, point prevalence estimates range from 0.2% in Scotland[8] to 14% in Sweden.[33] Lifetime prevalence ranges from 1.2% in Ethiopia[10] to 19% among women in Norway.[35]

Severity: Among adults with AD, mild AD is more common than moderate or severe AD, with estimates ranging from 20.1%[28] to 85.3%.[36] Moderate AD ranges from 11.1%[36] to 57%,[17] and severe ranges from 2.6%[21] to 58.2%.[37]

Fewer studies stratified AD prevalence by severity. Two studies in Spain estimated a 0.02-0.08% prevalence of severe AD[38,39] and 0.008% of moderate AD.[39]

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age and age of onset: Between 9 and 26.1% of AD cases first appear during adulthood.[40,41,5,42] Peak onset occurs between 20 and 40 years-of-age,[5] with one study reporting the average age at onset to be around 35 years.[28]

The prevalence and onset of AD decrease with age.[23,24,26,43,44,17,33] One population-based study of 116,202 individuals in the United States reported that 18% developed AD between 18 and 29 years-of-age, 13% between 30 and 39, 10% between 40 and 49, 6% between 50 and 59, 4% between 60 and 69, and 2% 70 and older.[23]

Sex: Although several studies reported no significant difference of AD prevalence between men and women,[9,25] most reported a higher prevalence among women.[21,35,41,12,27,45,15,46,18,30,1,47,20,48,17,19,49,33,50,20] Five studies reported a higher prevalence of AD among men.[8,14,28,31,51]

Race and ethnicity: Atopic dermatitis presents similarly across racial and ethnic groups.[23,16] However, as darker skin may hide erythema, AD may be underdiagnosed among those with darker skin tones.[16] Two studies reported no significant difference in prevalence of AD between racial groups;[23,14] however, Hispanic ethnicity had a significantly lower prevalence of AD than non-Hispanic ethnic groups,[14] and two reported that Black and Asian patients were statistically significantly more likely to have AD compared with white patients.[31,19]

Risk factors: Risk factors for AD include family history of atopy,[27,52,6] female sex,[27] higher socioeconomic status,[1,6] loss of function mutations in the FLG gene,[52] current smoking,[27,1,53] past smoking,[27] exposure to heavy traffic and diesel exhaust,[27,29,1] lower temperature, indoor heating days,[1] and living in an urban area.[27,6] Several studies show that living on a farm, and higher humidity are negatively associated with AD (i.e., have a protective effect on the risk of AD).[27,1]

SI.2. Children and Adolescents

Incidence and Prevalence:

Children: Studies reporting estimates of AD incidence among children aged 0 to 12 years were limited. One study using prescription registry data from Norway reported the incidence rate (IR) in 2014 as 0.073 per person-year (PY) (95% confidence interval (CI), 0.071-0.075) among children <1 year and as 0.034 per PY (95% CI 0.033-0.035) among children <6 years.[54] From 4 available studies reporting incidence, cumulative incidence/incidence proportion ranged from 12.5-35.0%. The study from Norway, described above, reported an incidence proportion of 17.4% among children <6 years.[54] A German study based on cross-sectional data at three time points reported cumulative IRs in children aged 5-6 years ranging from 12.5-23.4% in the mid-1990s.[55] A serial cross-sectional questionnaire administered among 7-year old children in Denmark concluded that the age-and sex-adjusted cumulative incidence of physician-diagnosed AD did not change significantly from 18.9% to 19.6% between 1993 and 1998.[56] Finally, a US-based birth cohort study reported an early childhood (median age 3.3 years) cumulative incidence of 35.0%.[57]

The global 12-month prevalence of AD in children (aged 6-7 and 13-14 years) ranged from 0.7% (Neyveli, India) to 18.4% (Sweden) based on the ISAAC I survey (years of data collection: 1993-1997)[58,59,60] and from 0.9% to 22.5% based on the latest ISAAC III survey (years of data collection: 1999-2004).[61] Cumulative lifetime prevalence of AD ranges from 1.3-57.2% in the ISAAC I survey and 1.2-38.6% in the ISAAC III survey.[58,61] For ages 6-7, prevalence of AD varies greatly throughout the world, with an estimated global prevalence of up to 8.5% in the US, up to 29.3% (Sweden) in Europe, up to 16.9% (Japan) in Asia, and up to 17.1% (Australia) in the Oceania region across the ISAAC I-III worldwide surveys.[58,61]

Although most studies report 12-month period prevalence estimates fall within the range reported by the global ISAAC surveys above, more recent studies report estimates as high as 27-36% at age 1[62,63] and 25-35% between ages 2 and 9 years.[62]

Adolescents: There were limited estimates of incidence reported among adolescents. One study reported the incidence of AD among Danish and Swedish children, ages 10-15, as 79 per 10,000 person-years between 1997 and 2011.[64] Another study in Germany reported that the cumulative incidence among adolescents was 2.2 per 100 persons, per year and 1.7% during puberty.[65] Estimates of AD prevalence vary widely both within and between countries depending on the age of the study population, study design, AD definition, and geographic range.[66,67]

The prevalence of AD among adolescents was similar to that of children. It ranged from 0.2% in Tibet, China to 24.6% in Barranquilla, Colombia.[61] The highest prevalence estimates were observed in Africa and Latin America.[61] The worldwide ISAAC III survey reported that lifetime reported "eczema" ranges from 1.6% (Georgia) to 48.3% (Sweden), and 11.4% of boys and 14.1% of girls experience lifetime "eczema" globally.[61]

Severity: According to a recent review, 67% of children with AD have mild disease, while 33% have moderate-severe disease.[68]

In the current literature review, mild disease was the most common in children and adolescents, followed by moderate and severe disease. Among children and adolescents with AD, 47.6 to 82% had mild disease,[56, 69, 70, 71, 72, 73] 16-33.1% had moderate disease[71,56,70,72,69,73] and 0.9-12.8% had severe disease.[71,56,70,72,69,73]

The prevalence of severe AD ranges from 0 to 5.8%.[74,75,76,58,61,39,77] The global 12-month prevalence of severe AD among children and adolescents ranged from 0% to 5.1% based on the ISAAC I survey, and from 0% to 5.8% based on the latest ISAAC III survey.[58,61] A recent study in Japan reported that the prevalence of severe AD was 1.3%.[77] Another recent study published in Spain reported that the prevalence of moderate-to-severe AD was 0.01% (95% CI: 0.005%-0.02%).[39]

One Japanese study reported an 11% prevalence of mild/moderate AD.[77]

A study among 1420, 7 to 15-year-old school children in Korea, reported AD severity between 1996 and 2006. This study reported severity estimates falling outside the mild, moderate and severe ranges reported above: 17-25.6% had mild AD, 36.2-38.5% had moderate AD, and 38.2-44.5% had severe AD.[78]

Many studies using the ISAAC protocol reported prevalence estimates for AD-related sleep disturbance (i.e., a symptom of AD severity) during the past 12 months.[79,80,60,81,82,83,84] Prevalence estimates of sleep disturbance more than once per week due to AD symptoms ranged from 1.1%[79] to 13.5% among 13-14 year olds.[84] In general, sleep disturbance was more common among girls than boys.[84,79,60,81]

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Sex: The majority of the identified studies reported no significant difference of AD prevalence among children aged 0-12 between males and females.[73,85,57,61,86,55,87,88,89]

In the published observational literature among adolescents, the prevalence of AD is reported to be higher among females than males.[90,91,79,80,92,60,81,83,84,87,93,61,94,95,96] A couple of studies reported no difference between females and males.[97,88]

Race/ethnicity: Estimates of race and ethnic differences among children with AD were limited. A US-based birth cohort study reported that black children are at higher risk for AD compared with white children in early childhood (median age 3.3 years) (adjusted OR 2.67, 95% CI 1.86-3.83).[57] Another US-based study found that children with AD compared with no AD were more likely to have African American mothers.[98] An earlier UK-based study in the mid-1990s reported cumulative prevalence rates much lower in white children (8.7%) compared to black Caribbean children (16.3%), as well as reported prevalence eczema rates (white: 17.3%, black Caribbean: 33.9%).[99]

Risk factors: Most children with AD (more than 2/3)[68] have an immediate family member with atopic disease,[100,68,101] and the risk of AD is 3-5 times more likely with 2 atopic parents[102,68] and 2-3 times more likely with 1 atopic parent.[68] There is also a positive association between *FLG* mutations and AD.[68] Other risk factors include parental depression,[103] alcohol use during pregnancy,[104] higher BMI (adolescents),[100] being born premature,[100] pollution,[100] and self-reported allergies to drugs and food.[105] Early exposure to pathogens may be protective in the development of AD.[68] A study in Denmark found that persistent AD is associated with heritability, environmental exposures, asthma and allergic sensitization, and AD severity.[89] In a US-based study, persistent AD was associated with female sex, history of allergies, income <$50K and black race.[106] Another US-based study found that children with AD compared with no AD were more likely to have African American mothers and/or be on Medicaid.[98] A Swedish study found that sex did not influence disease persistence.[107]

Natural history of the indicated condition in the population (children and adolescents), including mortality and morbidity:

Atopic dermatitis is believed to be the most common childhood inflammatory skin condition in the world.[84]

Atopic dermatitis usually begins in infancy (50% of cases are within the first year of life), and up to 85% of children who will develop AD experienced onset by age 5.[1,42] The condition was believed to be a pediatric disease that dissipates throughout childhood and

adolescence,[1] and birth cohort studies indicate that up to 70% of AD pediatric cases greatly improve or resolve by late childhood.[108] However, recent prevalence estimates among adults suggest that AD persistence and adult-onset may be higher than previously assumed.[108,1] In fact, a recent systematic review and meta-analysis of AD across different countries found that approximately 1 in 4 adults with AD experienced adult-onset.[109]

A systematic review and meta-analysis of 45 studies from 15 countries reported that while most childhood AD remitted by adulthood, increased persistence was associated with already persistent disease, later onset, and/or more severe disease.[110] And a more recent longitudinal latent class analysis of 13,546 children from the UK and Netherlands showed that the most common pattern of AD between birth and 11-16 years-of-age was early-onset-early-resolving AD, which was also associated with male sex.[63]

AD can have a profound impact on quality of life due to pain, sleep disturbance, and negative mental health symptoms. The patient burden and high prevalence of AD make it the most burdensome skin disorder globally. AD skin is dry and itchy, which can lead to scratching at night and disturbed sleep. Sleep loss can lead to poor concentration at school, behavioral problems, and low self-esteem. Parents and siblings of children with AD can also lose sleep, leading to problems at schoolwork, and family dynamic challenges.[111]

One study found that 86% of children 2-13 years old and 83% of adolescents 14-17 years old with AD avoided everyday activities.[112] Another study found that adolescents with chronic and severe eczema experience poorer quality of life compared with adolescents with mild or moderate eczema.[113]

There is evidence that infants with moderate to severe AD can have poor weight gain and social and behavioral problems.[111] A study of preschool children found that 23% of those with severe AD had significant behavioral symptoms compared with 5% of matched healthy controls.[114,111] In addition, stress and alcohol can exacerbate clinical symptoms of AD in adults and children.[1]

SI.3. Main existing treatment options

Topical Therapies: Research has demonstrated that conventional treatments, including emollients and topical glucocorticoids, have limited efficacy for moderate-to-severe AD.[115,116] For patients with moderate-to-severe AD, current treatment paradigms for moderate-to-severe AD have specific limitations:

> **Topical Corticosteroids:** The mainstay of AD therapy, differ in formulation, concentration, and potency, which while providing patients with a myriad of options, simultaneously makes their reliability and adherence to effective regimens challenging.[117] Toxicity: both systemic (HPA axis suppression) and topical skin dystrophy, thinning and vascular changes additionally limit their continuous use, the need remains to continue to develop corticosteroid-sparing agents.
>
> **Topical Calcineurin Inhibitors:** Have limited efficacy in moderate-to-severe AD, are not approved for use in very young children (<2 years-of-age), have limitations on long-

term use and amount of affected area treated, and are associated with possible development of immunoproliferative disorders.

Systemic Corticosteroids: In clinical practice guidelines, the use of systemic corticosteroids is generally discouraged with use limited to special circumstances.[118] While systemic corticosteroids lead to rapid clearing of AD, their side-effect profile and the risk of severe rebound flares after discontinuation limit their use to short-course therapy only. Despite being discouraged by most international guidelines, and the inevitable systemic toxicities associated with their short[119] and long[120] term use, approximately 10% of patients with AD still use these agents upon flaring.[121]

In recent years, advanced systemic treatments belonging to 2 pharmacological classes have been approved for the treatment of patients with moderate-to-severe AD – A) biologics that inhibit IL-4 and/or IL-13, and B) oral JAK inhibitors.

A) Biologics that inhibit IL-4 and/or IL-13

Dupilumab:

Dupilumab is a monoclonal antibody that binds to the common receptor component IL-4Rα, thereby inhibiting the signaling of IL-4 and IL-13. While efficacy results from clinical studies of dupilumab are compelling,[122] a large proportion of subjects fail to achieve a favorable response of IGA 0-1/EASI 75% and continue to experience the burden of moderate-to-severe AD. Additionally, a slow onset of action (2 to 4 weeks), and an incomplete relief of pruritus highlights the need for faster-acting therapies that work in a larger percentage of patients, especially on pruritic symptoms. From the Phase 3 study in adolescents, dupilumab was reported to have significantly lower absolute response rates in monotherapy compared with adult subjects after 16 weeks of treatment.[123] Finally, it has been noted that response rates were significantly lower in subjects with severe disease at baseline (27% and 21%), compared to those with moderate disease (52% and 46%), in both dosing regimens.[124] Treatment with dupilumab is associated with the risk of injection site reactions, allergic reactions, conjunctivitis and facial dermatitis,[124] and herpes simplex infections. Additionally, dupilumab administration can lead to development of antidrug antibodies (13.6% and 7.2% of patients after 16 weeks with 300 mg QW and Q2W respectively developed anti-drug antibodies),[125] of which 18% (Q2W) and 13% (QW) are neutralizing antibodies that result in lower drug concentrations, potential loss of efficacy over time and safety concerns (e.g., serum sickness-like reactions). No conclusions have been made regarding the meaningfulness of ADAs on efficacy given the small number of subjects who developed ADA during the clinical development program of dupilumab.[125]

Delivery via subcutaneous injection is not a method of administration tolerated well by all patients. Research has found that both patients and dermatologists place significant value on the method of administration for immunologic skin diseases (i.e., psoriasis and psoriatic arthritis). For example, Alcusky et al. found that route-of-administration considerations were either the most important or second-most important attribution for patients with moderate-to-severe psoriasis and their dermatologists.[126] In all cases, an oral dosing regimen was preferred relative to all other regimens (either injection or infusions, each with various

frequencies of administration). A similar pattern was also found among psoriasis patients in the UK[127] and psoriatic arthritis patients in the US.[128]

Dupilumab is currently approved in the EU for the treatment of moderate-to-severe AD in adult and pediatric patients aged 6 months and older.

Tralokinumab:

Tralokinumab is a human monoclonal antibody that binds to IL-13 and inhibits its interaction with the IL-13 receptor.[129] Although it is more selective in its therapeutic target than dupilumab, across-study comparison suggests a similar safety profile but lower treatment effect compared with dupilumab.[129] A parenteral (subcutaneous) route of administration is also required.

Tralokinumab is currently approved in the EU for the treatment of moderate-to-severe AD in adult and adolescent patients 12 years and older.

B) Oral JAK inhibitors

Upadacitinib

Upadacitinib is a small molecule that selectively inhibits JAK1. Upadacitinib has been demonstrated to be superior to placebo when administered as monotherapy or in combination with background topical corticosteroids.[130, 131] In addition, in a head-to-head comparison, upadacitinib 30 mg QD has been shown to be more efficacious than dupilumab.[132]

Upadacitinib is currently approved in the EU for the treatment of moderate-to-severe AD in adults and adolescents 12 years and older.

Baricitinib

Baricitinib is a small molecule that selectively inhibits both JAK1 and JAK2. Baricitinib has been demonstrated to be superior to placebo when administered as monotherapy or in combination with background topical corticosteroids.[133, 134]

Baricitinib is currently approved in the EU for the treatment of moderate-to-severe AD in adult and paediatric patients 2 years of age and older who are candidates for systemic therapy.

Other Systemic Agents: Non-biologic systemic drugs used for adult AD include cyclosporine, azathioprine, mycophenolate mofetil, and methotrexate.[135] All these agents are used off label, except for cyclosporine, which is licensed and approved for short-term treatment of severe refractory AD in many European countries.[136]

Oral Antihistamines: Have been utilized in the management of pruritus in AD patients in an effort to improve their quality of life by inhibiting the vascular and neurologic effects of the "itch-scratch cycle," but there is insufficient evidence to recommend the general use of antihistamines as part of the treatment of AD.[137]

Phototherapy: Indicated for moderate[138] to severe AD, has limited efficacy, is inconvenient and impractical for most subjects to use effectively,[108,139] and as for other disease states for which phototherapy is used, the risk of NMSC and melanoma is a concern, especially in fair-skinned individuals.

SI.4. Important Co-morbidities Found in the Target Population

Information on comorbidities for AD were obtained from the studies identified from the literature search described above. Based on the literature search results, the most common comorbidities in patients with AD are shown below in Table 1.

Table 1. Comorbidities Among Persons with Atopic Dermatitis

Population	Comorbidities
Adults	Sleep disorders[52,140,141,142]
	Pruritus[143]
	Stress[144]
	Anxiety[140,31,141,33,50,34,20,42]
	Depression[145,52,38,140,144,103,141,33,20,50,34,42]
	Suicidal ideation[144,103,42]
	Obesity[20,42]
	Food allergies[52,142]
	Asthma[38,20,142,42]
	Hand eczema, allergic rhinitis/rhinoconjunctivitis[142,52,38,20,42]
	Nasal allergies/hay fever[140]
	Autoimmune disorders[146]
	Arterial hypertension[38]
	Diabetes[20,42]
	Dyslipidemia[38,20]
	Herpes simplex (eczema herpeticum) infections[147]
	Fracture[148,149,150]
Adolescents and children	Asthma, allergic rhinitis and food allergies (e.g., peanut allergy)[68]
	Sleep disruption[68,151,152]
	Obstructive sleep apnea (children)[153]
	Pruritus[68]
	Autoimmune disorders (adolescents)[146]
	Celiac disease (children and adolescents)[154]
	Rheumatoid arthritis[155]
	Inflammatory bowel disease (IBD)[155]
	Attention-deficit/hyperactivity disorder (ADHD), anxiety, conduct disorder[68]
	Depression[68,156,95]
	Mental disorder with impairment (children and adolescents)[157]
	Suicidal ideation (adolescents)[95,158]
	Suicidal planning and attempts (adolescents)[95,159]
	Fracture[160,161,162]

Module SII. Nonclinical Part of the Safety Specification

Abrocitinib has undergone a comprehensive toxicological evaluation in mice, rats, rabbits, and cynomolgus monkeys in studies up to 2 years in duration. Safety pharmacology studies

were conducted in vitro and in vivo (rats and monkeys) to assess potential effects on cardiovascular, pulmonary, and neurofunctional endpoints. In vitro and in vivo genetic toxicity studies were conducted to assess the genotoxic potential of abrocitinib. Chronic toxicity assessment was conducted in rats and monkeys. Fertility, embryo-fetal development, and pre- and postnatal development studies were conducted in rats and rabbits. Carcinogenicity was assessed in a 6-month rasH2 transgenic mouse study and a 104-week rat carcinogenicity study. The above comprehensive nonclinical data package supports using abrocitinib in subjects 12 years-of-age and above. In juvenile rats at various ages, abrocitinib-related effects on postnatal bone growth and development occurred only when abrocitinib dosing was initiated during an age window of sensitivity to bone effects (comparable to a human younger than 2 years-of-age). Administration of abrocitinib to juvenile rats beginning on postnatal Day 21 and older (comparable to a 2-year-old human and older) was not associated with microscopic or macroscopic bone findings.

Table 2 provides a summary of key safety findings from abrocitinib nonclinical studies.

Table 2. Key Nonclinical Safety Findings and Relevance to Human Usage

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
Repeat-Dose Findings	
• **Immune and Hematolymphopoietic Findings**	
The effects on the immune system that were observed in the rat and monkey toxicity studies were consistent with the intended pharmacologic activity of abrocitinib, inhibition of JAK1.	The level of the pharmacologic JAK inhibition effect may be dependent on dose and may result in immunosuppression (potential adverse effects) versus immunomodulation (potential efficacious effects).[163]
Expected pharmacologic decreases in circulating lymphocytes were observed at ≥25 mg/kg/day in rats and ≥15 mg/kg/day in monkeys. Decreases in NK cells were observed at ≥15 mg/kg/day in the 9-month monkey study. Decreases in T cells, T cells subsets (helper and cytotoxic), plasma cells, and B cells were observed at 150 mg/kg/day in the 1-month study in monkeys.	Lymphocyte decreases are thought to result from a complex set of interactions resulting from the inhibition of certain cytokines (IL-2, IL-7, IL-15) and since signaling of these is mediated by JAK1, lymphocyte decreases are expected to be observed with a JAK1 selective inhibitor.[163] In the placebo-controlled studies with abrocitinib, there was no change in lymphocyte count over time. Across all subjects treated with abrocitinib, a low proportion of subjects (0.1%) have required discontinuation related to a confirmed absolute lymphocyte count $<0.5 \times 10^3/mm^3$. There was no association between lower lymphocyte counts and the rate of serious infection or herpes zoster. The clinical data are sufficient to conclude that lymphopenia is an ADR, but not an important risk.
Lower neutrophil counts were observed at ≥30 mg/kg/day in the 6-month study in healthy rats.	Neutrophil decreases have been linked to inhibition of G- and/or GM-CSF signaling that are mediated through JAK2 homodimers and/or resolution of inflammation.[164] In the placebo-controlled studies with abrocitinib, no meaningful change in neutrophil count over time has

Table 2. Key Nonclinical Safety Findings and Relevance to Human Usage

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
	been seen. In all subjects treated with abrocitinib, no subjects have required discontinuation related to a confirmed absolute neutrophil count $<1.0 \times 10^3/mm^3$. Lower neutrophil counts were not associated with increased rates of herpes zoster or serious infections. The clinical data are sufficient to conclude that neutropenia is neither an ADR nor important risk.
Lower RBCs, HGB, HCT (at 200 mg/kg/day in the 1-month rat study and ≥45 mg/kg/day in the 6-month study), platelet count (at 300 mg/kg/day, ≥75 mg/kg/day, and ≥30 mg/kg/day in the 7-day, 1-month, and 6-month rat studies, respectively), and reticulocytes (at all doses in the 7-day, 1-month, and 6-month rat studies) were observed.	Changes in platelets after initiation of JAK inhibitors are likely the result of a balance between JAK2 mediated inhibition of thrombopoietin inhibition, decreasing platelet production; signaling and decreased IL6-driven thrombopoietin hepatic production.[165,166] In the placebo-controlled studies, decreased platelet counts have been observed in clinical studies with abrocitinib, with a nadir at Week 4 and returning toward baseline through Week 12. Most platelet values remained within the reference range. There were no meaningful events of bleeding in subjects with low platelet values. Haemoglobin changes with JAK inhibition have been thought to be due to inhibition of erythropoietin signaling through JAK2 homodimers. A JAK1 inhibitor that preserves selectivity in the clinic is not expected to produce significant haemoglobin decreases in a large percentage of patients.[167] In the placebo-controlled studies with abrocitinib, there was no change over time in median haemoglobin. Across all exposed subjects, 1 subject (<0.1%) met the discontinuation criteria of confirmed haemoglobin <8 gm/dL. The clinical data are sufficient to conclude that thrombocytopenia, but not anaemia, is an ADR. Neither is considered an important risk.
Adverse viral infection (consistent with polyomavirus) in the prostate was observed at 70 mg/kg/day in the 6-month study in rats at exposures 26x the unbound human AUC at a clinical dose of 200 mg QD and cytomegalovirus infection was observed in various organs at 150 mg/kg/day in the 1-month study in monkeys at exposures 31x the unbound human AUC at a clinical dose of 200 mg QD, which were likely secondary to over-immunosuppression at high systemic exposure and consistent with the expected pharmacology of abrocitinib. Decreased	Herpes zoster infections have been associated with the use of other JAK inhibitors.[168] As JAK1 inhibitors block signaling of type 1 and type 2 interferons and cytokines that signal using the gamma chain of the IL-2 receptor and are important in lymphocyte development herpes zoster is still expected to occur after abrocitinib administration.[163] There was a dose dependent increase in the proportion of subjects reporting herpes zoster and herpes simplex in the placebo-controlled studies with abrocitinib. Herpes zoster and herpes simplex have been identified

Table 2. Key Nonclinical Safety Findings and Relevance to Human Usage

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
serum IgA (at 75 mg/kg/day), and decreased T cell dependent antibody response (determined by anti-KLH-IgM and anti-KLH-IgG response to KLH challenge) at ≥15 mg/kg/day in the 9-month monkey study.	as ADRs but are not considered important (see Section SVII.1). Additionally, the clinical data are sufficient to conclude that serious and opportunistic infections is an important potential risk included in the list of safety concerns.
• **Bone**	
In toxicity studies of up to 1 month of abrocitinib dosing in rats at an age comparable to adolescent human age of ≥12 years, a microscopic bone dystrophy (metaphysis; growth plate was normal) finding, considered transient and reversible, was noted, and exposure margins at which no bone finding was noted were 6x to 6.4x the unbound human AUC at a clinical dose of 200 mg QD. No bone findings were observed in rats at any dose in the 6-month toxicity study (up to 26x the unbound human AUC at the clinical dose of 200 mg QD) or in any of the toxicity studies in cynomolgus monkeys (comparable to human age of ≥8 years; up to 31x the unbound human AUC at a clinical dose of 200 mg QD).	The microscopic finding of bone dystrophy noted with abrocitinib in rats comparable to humans ≥12 years is not expected to pose a risk in subjects ≥12 years-of-age at clinically relevant therapeutic doses because the finding is noted only at high exposure safety margins, is transient, and reversible with normal growth plate and the presence of exposure safety margins of at least 6x. Impaired bone growth and development if used off-label in paediatric patients <12 years is included as an important potential risk.
• **Alterations in Lipid Profile**	
Higher cholesterol was noted at 200 mg/kg/day and higher HDL was noted at ≥200 mg/kg/day in healthy rats. Decreased LDL was observed at 100 mg/kg/day in the 14-day study in healthy monkeys.	Dose dependent increases in total cholesterol, LDL-c, and HDL-c have been seen with other JAK and IL-6 antagonists in rheumatoid arthritis.[169,170] In the placebo-controlled studies with abrocitinib, increases in total cholesterol, LDL and HDL were noted at Week 4 in these studies. Levels remained elevated throughout the treatment period. There were no meaningful changes in the LDL/HDL ratio. The clinical data are sufficient to conclude that hyperlipidaemia is an ADR, but not an important risk.
• **Genotoxicity**	
Abrocitinib was not genotoxic in the bacterial mutation assay or the in vivo micronucleus assay but was positive in the 27-hour treatment without metabolic activation in the in vitro micronucleus assay in TK6 cells. Follow-up testing demonstrated that the positive in vitro micronucleus was related to an aneugenic mechanism. The in vivo micronucleus assay with abrocitinib in rats was negative.	In vitro aneugenicity with kinase inhibitors is a very common observation and is probably the consequence of off-target inhibition of kinases involved in cellular division at the high concentrations tested in the TK6 in vitro micronucleus assay. It is not expected that this effect will occur at lower systemic exposures in humans. The lack of human risk is further supported by the negative result in the in vivo micronucleus assay in rats even at high systemic concentrations up to the maximum tolerated dose (at high systemic concentrations up to the maximum tolerated dose (MTD) of 600 mg/kg and 33x and 121x the unbound human C_{max} and AUC_{24} at a clinical dose of 200 mg,

Table 2. Key Nonclinical Safety Findings and Relevance to Human Usage

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
	respectively). Given that a human exposure is significantly lower than the concentrations and doses tested for micronucleus formation both in vitro and in vivo, these data do not indicate a genotoxic risk for abrocitinib at the maximum clinical dose of 200 mg QD.
• **Reproductive and Developmental**	
Reproductive Abrocitinib did not cause malformations in pregnant rats or rabbits. In the definitive EFD study in rats, the average number of late resorptions per litter was increased at 60 mg/kg/day at exposures 17x the unbound human AUC at a clinical dose of 200 mg QD. The developmental NOAEL was established at 10 mg/kg/day and exposures were 2.4x the unbound human AUC at a clinical dose of 200 mg. No adverse effects were observed in the definitive rabbit EFD study at doses up to 75 mg/kg/day with exposures of 4x the unbound human AUC at a clinical dose of 200 mg QD. In a rat PPND study, effects on parturition (dystocia with prolonged parturition) and postnatal development (lower F1 postnatal survival and lower F1 body weights) were observed at ≥30 mg/kg/day and exposures were ≥11x the unbound human AUC at a clinical dose of 200 mg QD. No effects on parturition and postnatal development were noted at the NOAEL of 10 mg/kg/day with exposure multiples of 2.4x the unbound human AUC at a clinical dose of 200 mg QD.	Results from rat and rabbit EFD toxicology studies are potentially relevant to human usage. Embryofoetal toxicity following exposure in utero is an important potential risk.
Juvenile Rats Administration of abrocitinib to juvenile rats beginning on postnatal Day 21 and older (comparable to a 2-year-old human and older) was not associated with microscopic or macroscopic bone findings. Administration of abrocitinib to juvenile rats beginning on postnatal Day 10 (comparable to a 3-month-old human infant) resulted in adverse microscopic and macroscopic bone findings, including malrotated paws, fractures, and/or femoral head abnormalities.	Abrocitinib is not indicated in this paediatric younger age population. Relevance to adolescent human usage is not expected based on the presence of exposure multiples (6x to 6.4x) at which no bone effects occurred in the general toxicity studies relative to human exposure. Impaired bone growth and development is an important potential risk if abrocitinib is used off-label in paediatric patients <12 years.
Fertility Abrocitinib did not affect the male reproductive system, including fertility or spermatogenesis, but did result in reversible decreased female fertility.	Results from a female rat fertility toxicity study are potentially relevant to human usage.

Table 2. Key Nonclinical Safety Findings and Relevance to Human Usage

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
Effects on female fertility (decreased fertility index, corpora lutea, implantation sites) and increased post-implantation loss were observed in rats at 70 mg/kg/day and ≥30 mg/kg/day with exposures 29x and ≥11x, respectively, the unbound human AUC at a clinical dose of 200 mg QD. All the effects on female fertility were fully reversible following a 1-month cessation of abrocitinib administration. The NOAEL for female reproductive toxicity was 10 mg/kg/day, with exposure of 2x the unbound human AUC at a clinical dose of 200 mg. The NOAEL for male reproductive toxicity was 70 mg/kg/day, with exposures 26x the unbound human AUC at a clinical dose of 200 mg QD.	Based on the findings in female rats, oral administration of abrocitinib may result in temporary reduced fertility in females of reproductive potential. Effects on female rat fertility were reversible 1 month after cessation of abrocitinib oral administration. No effects on male fertility are anticipated based on nonclinical data. Also, the nonclinical data support that there is no need for male contraception because abrocitinib is not genotoxic and it did not affect male fertility or spermatogenesis. The amount of abrocitinib estimated to be available to a partner via drug in ejaculate is well below the developmental NOAELs in the definitive rat and rabbit EFD studies.
• **Carcinogenicity**	
In the 2-year rat carcinogenicity study abrocitinib-related neoplastic finding of benign thymomas (in thymus) for females administered ≥10 mg/kg/day was observed at corresponding exposures ≥2.8x the unbound human AUC at a clinical dose of 200 mg QD. No abrocitinib-related thymoma was noted in female rats at 3 mg/kg/day (exposures ~0.6x the unbound human AUC at a clinical dose of 200 mg QD). No thymomas were noted in males at doses up to 30 mg/kg/day (up to 17x exposures at a clinical dose of 200 mg QD). No abrocitinib-related neoplasms were noted in the 6-month mouse carcinogenicity study.	The mechanism by which abrocitinib leads to increased thymoma incidence in female Wistar Han rats is likely related to a non-genotoxic mechanism as abrocitinib is non-genotoxic. In addition, it is known that other immunosuppressive drugs, including other JAK inhibitors (tofacitinib) and other immunosuppressive drugs[171] also increase the incidence of thymoma in 2-year rat carcinogenicity studies.[172] Immunosuppression has not been linked to thymoma occurrence in humans. This is based on data from a large registry linkage study, thymoma risk was not elevated among 516,000 people with AIDS in the US (4 thymoma cases, SIR = 0.85). Similarly, thymoma risk does not seem to be elevated among immunosuppressed solid organ transplant recipients, as a literature search revealed no reported cases.[173] In humans, the mechanism for development of thymomas is unknown.[174]
• **Drug Interactions**	
Abrocitinib is metabolized predominantly by CYP2C19 and CYP2C9 enzymes, and its metabolites are renally excreted and are substrates of the OAT3. Therefore, exposures of abrocitinib and/or its active metabolites may be affected by medicinal products that strongly inhibit or induce CYP2C19 or enzymes CYP2C9 or inhibit the OAT3 transporter.	• Based on the fluconazole and fluvoxamine DDI study results, the dose of abrocitinib is recommended to be reduced by half when co-administered with one or more drugs that are strong CYP2C19 inhibitors. • Based on the rifampicin DDI study results, the co-administration of abrocitinib concomitantly with moderate or strong inducers of CYP2C19/CYP2C9 enzymes is not recommended. • Based on probenecid DDI study results, the inhibition of OAT3 transporter does not appear to have a clinically relevant effect on abrocitinib active moiety exposure, therefore, no change in standard dosing recommendation of abrocitinib is required when co-administered with OAT3 inhibitors.

Table 2. Key Nonclinical Safety Findings and Relevance to Human Usage

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
Abrocitinib or its metabolites are not inhibitors or inducers of CYP enzymes and are not inhibitors of UGTs in vitro. The overall risk of transporter interactions with abrocitinib and its metabolites is considered low.	• Co-administration of midazolam with abrocitinib 200 mg QD confirmed a lack of induction or inhibition effect on CYP3A4 and CYP3A5. • Abrocitinib 200 mg QD had no effect on the PK of oral contraceptives. • Co-administration with abrocitinib 200 mg QD did not affect the PK of rosuvastatin, a substrate for BCRP and OAT3. • Co-administration of abrocitinib 200 mg QD with metformin did not impact the exposures of metformin or NMN, an endogenous biomarker for MATE1/2K transporter. • Co-administration of a single dose of abrocitinib 200 mg increased the AUC_{inf} and C_{max} of dabigatran (substrate of P-gp) by approximately 53% and 40%, respectively, relative to a single dose of dabigatran 75 mg administered alone. The effect of abrocitinib on the pharmacokinetics of other P-gp substrates has not been evaluated. Caution should be exercised as the levels of P-gp substrates with a narrow therapeutic index, such as digoxin, may increase. The data are sufficient to make conclusions for clinical use. There is no missing information or important risks related to DDIs.
• **Safety Pharmacology**	
<u>Cardiovascular</u> Abrocitinib-related increases in heart rate and diastolic blood pressure were observed following a single dose in the pivotal cardiovascular safety pharmacology study in male monkeys at exposures 0.9x and 3.4x, respectively, the unbound human C_{max} at a clinical dose of 200 mg. The 4-hour postdose mean plasma abrocitinib concentrations in the monkey safety pharmacology study likely underestimates the true C_{max} at 150 mg/kg, which is based on the single dose monkey study C_{max} with exposures 16x the unbound human C_{max} at a clinical dose of 200 mg QD based on exposures achieved in the single-dose TK study in monkeys. All measurements returned to vehicle control values within 22 hours postdose, and no effects on the cardiovascular system and/or ECG parameters (including no primary QT signals or QTc prolongation) were observed in the repeat-dose toxicity studies in rats or monkeys.	Relevance to human usage is not expected based on the exposure multiples at which effects occurred in the safety pharmacology studies relative to human exposures. In addition, in a thorough QT study there was no clinically meaningful change in the QT/QTc interval in abrocitinib treated subjects. There is no related missing information or important risk.

Table 2. Key Nonclinical Safety Findings and Relevance to Human Usage

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
Nervous system No Abrocitinib-related effects on neurofunctional assessment were noted in rats at doses up to 600 mg/kg (exposures 34x the unbound human C_{max} at a clinical dose of 200 mg QD). **Respiratory** No Abrocitinib-related effects on respiratory rate, tidal volume, or minute volume were noted in rats at doses up to 600 mg/kg (exposures 34x the unbound human C_{max} at a clinical dose of 200 mg QD).	
• **Other Toxicity-Related Information or Data**	
Lactation Abrocitinib was secreted in milk of lactating rats.	There are no data on the presence of abrocitinib in human milk, the effects on the breast-fed infant, or the effects on milk production. A risk to newborns/infants cannot be excluded and abrocitinib is contraindicated during breast-feeding. This is not considered missing information as abrocitinib use is contraindicated while breast-feeding.

Module SIII. Clinical Trial Exposure

The abrocitinib AD clinical trial program includes 16 Phase 1 studies, 1 Phase 2 study, Phase 2a study, and 7 Phase 3 studies.

The clinical trial exposure data is provided for 2 safety pools, the Short-Term Studies Pool (Short-Term Pool) and the Long-Term Dose-Controlled Pool (LTDCP; 05 September 2022). The Short-Term Pool includes subjects treated with abrocitinib 100 mg QD, abrocitinib 200 mg QD and placebo in studies (B7451006, B7451012, B7451013, B7451029, B7451036) with a placebo comparator, of similar duration (12 - 16 weeks), same doses of abrocitinib, similar patient population, and comparable safety outcome assessment. The studies in this pool allow for comparison of monotherapy and combination therapy as Studies B7451006, B7451012, B7451013 were conducted as monotherapy and Study B7451029 and B7451036 were conducted in combination with background topical therapy. The pool also allows for comparison of adolescent and adult data as Studies B7451012 and B7451013 include both adolescents and adults, Studies B7451006 and B7451029 include adults, and Study B7451036 includes adolescents (12-<18 years). There were 1387 patients exposed to abrocitinib in the Short-Term Pool totaling 339.3 patient-years of exposure to abrocitinib.

The Long-Term Dose-Controlled Pool (05 September 2022) includes all subjects who received at least one dose of abrocitinib in the Phase 2b and 3 studies (B7451006, B7451012, B7451013, B7451014, B7451029, B7451036, B7451037, B7451050) of subjects with AD

from the relevant dosing groups (100 mg QD and 200 mg QD), including their experience in the long-term extension (LTE) study (B7451015) if they qualified and decided to participate. Cumulatively through 05 September 2022, there were 3050 patients exposed to abrocitinib in the LTDCP (05 September 2022) totaling 5166 patient-years of exposure to abrocitinib.

Exposure is presented for the Short-Term Safety Pool and the Long-Term Dose-Controlled Pool 2022 by treatment duration (Table 3 and Table 4), by age and gender (Table 5 and Table 6), by race (Table 7 and Table 8), and by ethnicity (Table 9 and Table 10).

Table 3. Drug Exposure by Treatment Duration - Short-Term Studies Pool

Duration of exposure[a]	Placebo		Abrocitinib 100 mg QD		Abrocitinib 200 mg QD		All Abrocitinib	
	N (%)	PY[b]	N (%)	PY[b]	N (%)	PY[b]	N (%)	PY[b]
< 1 week	4 (0.91)	0.0	8 (1.14)	0.1	5 (0.73)	0.0	13 (0.94)	0.1
≥1 week to <4 weeks	30 (6.85)	1.3	24 (3.41)	1.0	17 (2.49)	0.7	41 (2.96)	1.8
≥4 weeks to <8 weeks	34 (7.76)	3.6	23 (3.27)	2.5	17 (2.49)	1.9	40 (2.88)	4.4
≥8 weeks to <10 weeks	6 (1.37)	1.0	13 (1.85)	2.1	9 (1.32)	1.5	22 (1.59)	3.6
≥10 weeks to <14 weeks	240 (54.79)	56.2	408 (58.04)	95.3	424 (61.99)	99.2	832 (59.99)	194.5
≥14 weeks	124 (28.31)	38.2	227 (32.29)	69.8	212 (30.99)	65.2	439 (31.65)	135.0
Total	438	100.3	703	170.8	684	168.5	1387	339.3

a. Number of days from first to and including last day of study treatment (Last Dosing Date – date of First Dosing Date + 1).
b. PY: Person Time (years) calculated as Total duration (days)/365.25 in each category.
Includes studies: B7451006, B7451012, B7451013, B7451029, B7451036.
SDTM Creation: 11Mar2021, Table Generation: 11Mar2021
Source: Table RMP.STS.1

Table 4. Drug Exposure by Treatment Duration - Long-Term Dose-Controlled Pool 2022

Duration of Exposure[a]	Abrocitinib 100 mg QD (N = 1053)		Abrocitinib 200 mg QD (N = 1997)		All Abrocitinib (N = 3050)	
	N (%)	PY[b]	N (%)	PY[b]	N (%)	PY[b]
< 4 weeks	37 (3.5)	1.2	67 (3.4)	2.4	104 (3.4)	3.7
≥4 weeks to <12 weeks	71 (6.7)	10.5	160 (8.0)	24.9	231 (7.6)	35.4
≥12 weeks to <24 weeks	137 (13.0)	41.8	249 (12.5)	72.7	386 (12.7)	114.5
≥24 weeks to <36 weeks	55 (5.2)	30.9	121 (6.1)	67.8	176 (5.8)	98.7
≥36 weeks to <48 weeks	49 (4.7)	39.3	91 (4.6)	72.3	140 (4.6)	111.6
≥48 weeks to <60 weeks	41 (3.9)	41.7	66 (3.3)	67.5	107 (3.5)	109.2
≥60 weeks to <72 weeks	43 (4.1)	54.1	221 (11.1)	282.6	264 (8.7)	336.7
≥72 weeks to <84 weeks	36 (3.4)	53.1	103 (5.2)	150.0	139 (4.6)	203.1
≥84 weeks to <96 weeks	41 (3.9)	71.0	194 (9.7)	340.3	235 (7.7)	411.4
≥96 weeks to <108 weeks	31 (2.9)	60.4	134 (6.7)	258.9	165 (5.4)	319.3

Table 4. Drug Exposure by Treatment Duration - Long-Term Dose-Controlled Pool 2022

Duration of Exposure[a]	Abrocitinib 100 mg QD (N = 1053)		Abrocitinib 200 mg QD (N = 1997)		All Abrocitinib (N = 3050)	
	N (%)	PY[b]	N (%)	PY[b]	N (%)	PY[b]
≥108 weeks to <120 weeks	37 (3.5)	81.2	33 (1.7)	71.8	70 (2.3)	153.0
≥120 weeks to <132 weeks	29 (2.8)	70.4	35 (1.8)	85.6	64 (2.1)	156.0
≥132 weeks to <144 weeks	91 (8.6)	244.6	75 (3.8)	200.3	166 (5.4)	444.9
≥144 weeks to <168 weeks	176 (16.7)	524.3	200 (10.0)	601.9	376 (12.3)	1126.2
≥168 weeks to <192 weeks	112 (10.6)	384.8	164 (8.2)	560.2	276 (9.0)	945.0
≥192 weeks	67 (6.4)	263.8	84 (4.2)	333.3	151 (5.0)	597.2
Total	1053	1973.2	1997	3192.8	3050	5166.0

a. Number of days from first to and including last day of study treatment (Last Dosing Date – date of First Dosing Date + 1).
b. PY* Person Time (years) calculated as Total duration (days)/365.25 in each category
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050.
Source Data: adex Date of ADAM Dataset Creation: 17JAN2023 Output File: ./ad_scs/LTDCP2022/adex_s002_aep Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.1

Table 5. Study Treatment Exposure by Age and Gender - Short-Term Studies Pool

	Placebo (N=438)		Abrocitinib 100 mg QD (N=703)		Abrocitinib 200 mg QD (N=684)		All Abrocitinib (N=1387)	
Age Group (years)	Male N (%), PY[a]	Female N (%), PY[a]	Male N (%), PY[a]	Female N (%), PY[a]	Male N (%), PY[a]	Female N (%), PY[a]	Male N (%), PY[a]	Female N (%), PY[a]
<18	62 (26.05), 13.8	58 (29.00), 13.5	71 (18.68), 16.5	75 (23.22), 17.3	79 (22.13), 18.0	63 (19.27), 14.6	150 (20.35), 34.5	138 (21.23), 31.8
18 to <65	166 (69.75), 38.6	135 (67.50), 30.4	287 (75.53), 69.3	234 (72.45), 59.0	260 (72.83), 64.8	241 (73.70), 60.9	547 (74.22), 134.0	475 (73.08), 119.8
≥65	10 (4.20), 2.4	7 (3.50), 1.5	22 (5.79), 5.4	14 (4.33), 3.3	18 (5.04), 4.5	23 (7.03), 5.8	40 (5.43), 9.9	37 (5.69), 9.1
Total	238, 54.8	200, 45.4	380, 91.2	323, 79.6	357, 87.3	327, 81.3	737, 178.5	650, 160.8

a. PY: Person Time (years) calculated as Total duration (days)/365.25 in each category.
Duration of exposure is calculated as number of days from first to and including last day of study treatment (Last Dosing Date – date of First Dosing Date +1).
Includes studies: B7451006, B7451012, B7451013, B7451029, B7451036.
SDTM Creation 11Mar2021, Table Generation: 11Mar2021
Source: Table RMP.STS.2

Table 6. Study Treatment Exposure by Age and Gender - Long-Term Dose-Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)				Abrocitinib 200 mg QD (N = 1997)				All Abrocitinib (N = 3050)			
Age (yrs)	Male		Female		Male		Female		Male		Female	
	N (%)	PY[a]	N (%)	PY[a]	N (%)	PY[a]	N (%)	PY[a]	N (%)	PY[a]	N (%)	PY[a]
<18	105 (18.3)	206.4	96 (20.1)	198.1	152 (14.2)	303.6	137 (14.8)	255.9	257 (15.6)	510	233 (16.6)	454
18 to <65	441 (76.7)	838.7	354 (74.1)	633.7	871 (81.5)	1464.4	740 (79.7)	1039.5	1312 (79.8)	2303.1	1094 (77.8)	1673.2
≥65	29 (5.0)	55.8	28 (5.9)	40.6	46 (4.3)	66.5	51 (5.5)	62.8	75 (4.6)	122.3	79 (5.6)	103.4
Total	575	1100.8	478	872.4	1069	1834.5	928	1358.3	1644	2935.3	1406	2230.7

a. PY: Person Time (years) calculated as Total duration (days)/365.25 in each category.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
Duration of exposure is calculated as number of days from first to and including last day of study treatment (Last Dosing Date - date of First Dosing Date +1).
Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050.
Source Data: adex Date of ADAM Dataset Creation: 17JAN2023 Output File: ./ad_scs/LTDCP2022/adex_s02agesex Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.2

Table 7. Study Treatment Exposure by Race - Short-Term Studies Pool

Race	Placebo		Abrocitinib 100 mg QD		Abrocitinib 200 mg QD		All Abrocitinib	
	N (%)	PY[a]	N (%)	PY[a]	N (%)	PY[a]	N (%)	PY[a]
White	285 (65.07)	65.0	488 (69.42)	119.4	445 (65.06)	110.6	933 (67.27)	230.0
Black or African American	31 (7.08)	6.6	46 (6.54)	9.8	44 (6.43)	9.9	90 (6.49)	19.7
Asian	102 (23.29)	23.8	159 (22.62)	39.5	169 (24.71)	42.1	328 (23.65)	81.6
Other	20 (4.57)	4.8	10 (1.42)	2.1	26 (3.80)	5.9	36 (2.60)	8.0
Total	438	100.3	703	170.8	684	168.5	1387	339.3

a. PY: Person Time (years) calculated as Total duration (days)/365.25 in each category.
Duration of exposure is calculated as number of days from first to and including last day of study treatment (Last Dosing Date – date of First Dosing Date +1).
Includes studies: B7451006, B7451012, B7451013, B7451029, B7451036.
SDTM Creation 11Mar2021, Table Generation: 11Mar2021
Source: Table RMP.STS.3

Table 8. Study Treatment Exposure by Race - Long-Term Dose-Controlled Pool 2022

Race	Abrocitinib 100 mg QD (N = 1053)		Abrocitinib 200 mg QD (N = 1997)		All Abrocitinib (N = 3050)	
	N (%)	PY[a]	N (%)	PY[a]	N (%)	PY[a]
White	737 (70.0)	1325	1366 (68.4)	2150.3	2103 (69.0)	3475.3
Black or African American	65 (6.2)	109.1	140 (7.0)	150.1	205 (6.7)	259.1
Asian	231 (21.9)	504.9	429 (21.5)	790.3	660 (21.6)	1295.2
Other	20 (1.9)	34.2	62 (3.1)	102.1	82 (2.7)	136.3
Total	1053	1973.2	1997	3192.8	3050	5166.0

a. PY: Person Time (years) calculated as Total duration (days)/365.25 in each category.
PY* Person Time (years) calculated as Total duration (days)/365.25 in each category
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
Duration of exposure is calculated as number of days from first to and including last day of study treatment (Last Dosing Date - date of First Dosing Date +1).
Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050.
Source Data: adex Date of ADAM Dataset Creation: 17JAN2023 Output File: ./ad_scs/LTDCP2022/adex_s02dem Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.3

Table 9. Study Treatment Exposure by Ethnicity - Short-Term Studies Pool

Ethnicity	Placebo		Abrocitinib 100 mg QD		Abrocitinib 200 mg QD		All Abrocitinib	
	N (%)	PY[a]	N (%)	PY[a]	N (%)	PY[a]	N (%)	PY[a]
Hispanic or Latino	52 (11.87)	12.4	75 (10.67)	18.7	73 (10.67)	18.3	148 (10.67)	37.1
Not Hispanic or Latino	375 (85.62)	85.3	616 (87.62)	149.0	606 (88.60)	149.2	1222 (88.10)	298.2
Not reported	11 (2.51)	2.6	12 (1.71)	3.0	5 (0.73)	1.0	17 (1.23)	4.1
Total	438	100.3	703	170.8	684	168.5	1387	339.3

a. PY: Person Time (years) calculated as Total duration (days)/365.25 in each category.
Duration of exposure is calculated as number of days from first to and including last day of study treatment (Last Dosing Date – date of First Dosing Date +1).
Includes studies: B7451006, B7451012, B7451013, B7451029, B7451036.
SDTM Creation: 11Mar2021, Table Generation: 11Mar2021
Source: Table RMP.STS.4

Table 10. Study Treatment Exposure by Ethnicity - Long-Term Dose-Controlled Pool 2022

Ethnicity	Abrocitinib 100 mg QD (N = 1053)		Abrocitinib 200 mg QD (N = 1997)		All Abrocitinib (N = 3050)	
	N (%)	PY[a]	N (%)	PY[a]	N (%)	PY[a]
Hispanic or Latino	125 (11.9)	223.3	225 (11.3)	355.6	350 (11.5)	578.9
Not Hispanic or Latino	905 (85.9)	1703.9	1757 (88.0)	2818.5	2662 (87.3)	4522.4
Not reported	23 (2.2)	46.0	15 (0.8)	18.6	38 (1.2)	64.6
Total	1053	1973.2	1997	3192.8	3050	5166.0

a. PY: Person Time (years) calculated as Total duration (days)/365.25 in each category.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
Duration of exposure is calculated as number of days from first to and including last day of study treatment (Last Dosing Date - date of First Dosing Date +1).
Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050.
Source Data: adex Date of ADAM Dataset Creation: 17JAN2023 Output File: ./ad_scs/LTDCP2022/adex_s02dem2 Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.4

Module SIV. Populations Not Studied in Clinical Trials

Table 11. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
Exclusion criteria with respect to psychiatric conditions	Any psychiatric condition including recent or active suicidal ideation or behavior that meets any of the following criteria: • Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the Columbia suicide severity rating scale (C-SSRS); • Previous history of suicidal behaviors in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS; • Any lifetime history of serious or recurrent suicidal behavior; • Suicidal behaviors questionnaire – revised (SBQ-R) total score ≥8; • Clinically significant depression: patient health questionnaire – 8 items (PHQ-8) total score ≥15; • The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria.	Patients with AD have a higher incidence of SIB than the general population and, as such, it was important not to initiate patients with profound SIB in a trial that includes placebo and an experimental drug.[103]	Not considered missing information. JAK inhibition has not been associated with suicidal ideation and behaviour. Distribution of abrocitinib to the brain is limited (Brain:plasma AUC ratio <0.1). The screening criteria was applied only at baseline for the short-term parent studies. Given the high background rate and episodic nature of suicidal ideation and behaviours in this population, it is reasonable to conclude that the population was generalizable in this regard as the studies progressed.[103] Analysis of subjects with evidence of depression and anxiety at baseline (HADS scores ≥8) showed greater score improvement in patients treated with both the abrocitinib 100 and 200 mg QD compared to placebo in the depression and anxiety subscales. Across all patients treated with abrocitinib in the All Exposure Pool, there were 2 subjects (0.1%) with serious events of suicidal ideation, both adolescents, neither considered related to study drug by the investigator.
Exclusion criteria with respect to haematology parameters	Baseline values of • Absolute neutrophil count of <1.2 x 10^9/L (<1200/mm^3)	These criteria were included to mitigate the risk of the potential impact of JAK inhibition on hematologic parameters. Although decreases in haemoglobin or	Not considered missing information. The clinical data are sufficient to determine that lymphopenia and

Table 11. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
	• Haemoglobin <10.0 g/dL or hematocrit <30% • Platelet count of <150 x 10^9/L (<150,000/mm^3) • Absolute lymphocyte count of <0.50 x 10^9/L (<500/mm^3). A current or past medical history of conditions associated with thrombocytopenia, coagulopathy or platelet dysfunction. Receiving anti coagulants or medications known to cause thrombocytopenia, (unless considered safe to stop and washout for the duration of the study).	neutrophils were not predicted due to JAK1 specificity, this had not been proven in a large number of patients.	thrombocytopenia, but not anaemia or neutropenia, are ADRs. The SmPC will include those patients with a platelet count less than 0.5 × 10^3/mm^3 (<150 x 10^9/L), absolute lymphocyte count less than 0.5 × 10^3/mm^3 (<0.50 x 10^9 /L), absolute neutrophil count less than 1× 10^3/mm^3 (1.0 × 10^9/L) or haemoglobin less than 8 g/dL should not initiate abrocitinib.
Exclusion criteria with respect to other inflammatory skin diseases	Currently have active forms of other inflammatory skin diseases, i.e., not AD or have evidence of skin conditions (e.g., psoriasis, seborrheic dermatitis, Lupus) at the time of Day 1 that would interfere with evaluation of atopic dermatitis or response to treatment.	This criterion was adopted in order to allow proper evaluation of skin lesions, which could be confounded by other inflammatory skin diseases.	Not considered missing information. The safety profile is not anticipated to be different in these patients.
Exclusion criteria with respect to vaccinations	Vaccinated or exposed to a live or attenuated vaccine within the 6 weeks prior to the first dose of investigational product or is expected to be vaccinated or to have household exposure to these vaccines during treatment or during the 6 weeks following discontinuation of investigational product.	This exclusion criterion was included due to the risk of infection associated with the use of live vaccines in patients receiving drugs with immunosuppressive activity.	Use of live/attenuated vaccines is not considered missing information. The SmPC states that the use of live, attenuated vaccines during or immediately prior to abrocitinib therapy is not recommended. This information will be included under the important

Table 11. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
			potential risk of serious and opportunistic infection in the HCP brochure and the patient card.
	Adolescent subjects 12 to <18 years old without documented evidence of having received at least one dose of the varicella vaccine in countries where the vaccine is approved and standard of care or those who do not have evidence of prior exposure to varicella zoster virus (VZV) based on serological testing (i.e., varicella zoster virus immunoglobulin G antibody [VZV IgG Ab]) at screening.	Given the mechanism of action of JAK inhibitors, the known drug effects on lymphocyte function and the general effect on viral reactivation this was included to minimize the risk of subject's risk of infection.	This is not considered missing information as the proposed SmPC will recommend patients be up to date with vaccinations prior to initiating treatment. In addition, studies with other JAK inhibitors have demonstrated that for most vaccines (excluding pneumococcal polysaccharide vaccine) response to vaccination is comparable to that of healthy adults.[175,176]
Exclusion criteria with respect to infection history	• Have a history of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to Baseline. • Have active chronic or acute skin infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks prior to Baseline, or superficial skin infections within 1 week prior to Baseline. • A subject known to be infected with HIV, Hepatitis B or Hepatitis C. Have a history (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a	Subjects with a history of active or recurrent infection could have complicated interpretation of safety data. In addition, subjects with active tuberculosis (TB), serious infections such as sepsis, or opportunistic infections (OIs) may be at risk for prolonged or more complicated illness. Patients with recurrent or complicated HZ, active Hepatitis B or Hepatitis C may be at increased risk for reactivation.	Not considered missing information. Herpes zoster is an important identified risk and serious and opportunistic infection is an important potential risk. In addition, the SmPC will: • contraindicate use in patients with active serious systemic infections, including tuberculosis • recommend that patients be screened for TB and Hepatitis B and C prior to starting abrocitinib. • State that the risks and benefits of treatment with abrocitinib should be considered prior to initiating in patients: • with chronic or recurrent infection

Table 11. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
	recurrent (more than one episode of) localized, dermatomal herpes zoster.		• who have been exposed to TB • with a history of a serious or an opportunistic infection • who have resided or travelled in areas of endemic TB or endemic mycosis; or • with underlying conditions that may predispose them to infection.
Exclusion criteria with respect to renal function	Estimated Creatinine Clearance <40 mL/min based on the age-appropriate calculation, or serum creatinine >1.5 times the upper limit of normal (ULN).	These exclusion criteria were applied to clinical studies to protect subject safety while the effects of abrocitinib on renal parameters were further explored and understood.	Not considered missing information. Studies to evaluate PK in subjects with moderate and severe disease provide for dosing recommendations such that exposures can be maintained within a range comparable to that of patients with normal renal function and, as such, no difference in safety profile is anticipated.
Exclusion criteria with respect to hepatic impairment and transaminase increase	Severe, progressive, uncontrolled disease, including hepatic diseases. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2 times the ULN; Total bilirubin ≥1.5 times the ULN; subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ ULN.	These exclusion criteria were applied to clinical studies to protect subject safety while the effects of abrocitinib on hepatic parameters were further explored and understood.	Use in patients with mild, moderate and severe hepatic impairment or with transaminase increase is not considered missing information. Based on studies to evaluate PK in subjects with mild and moderate hepatic impairment, no dosing adjustment is required in patients with mild and moderate hepatic impairment. In addition, there are no adverse reactions or risks related to hepatic parameters. As such, no difference in safety profile is anticipated for patients with mild or

Table 11. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
			moderate hepatic impairment or in patients with transaminase elevation. Use in patients with severe hepatic impairment is not considered missing information as, in the SmPC, use in patients with severe hepatic impairment is contraindicated.
Exclusion with respect to other immunosuppressive agents	Have received any of the following treatment regimens specified in the timeframes outlined below: • Treatment with non-B cell-specific lymphocyte depleting agents, alkylating agents within 1 year of first dose. • Other biologic within 12 weeks of first dose of investigational product or 5 half-lives (if known), whichever is longer. • Use of oral immunosuppressive drugs within 4 weeks of first dose of investigational product or 5 half-lives (if known), whichever is longer. • Prior treatment with any JAK inhibitors. • Previous treatment with dupilumab in Study B7451029 only.	Concurrent use of these drugs may have compromised interpretation of efficacy endpoints and safety data.	Not considered missing information. Herpes zoster is an important identified risk and serious and opportunistic infection is considered an important potential risk.
Exclusion criteria with respect to history of malignancy and	• Have a history of any lymphoproliferative disorder such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, history	Drugs with immunosuppressive activity may have the potential to affect host defense against malignancies. Thus, exclusion of patients with known	Not considered missing information. Malignancy is an important potential risk.

Table 11. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
lymphoproliferative disorders	of lymphoma, leukemia, or signs or symptoms suggestive of current lymphatic or lymphoid disease. • Have any malignancies or have a history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ.	previous malignancy was prudent while data were generated on the incidence and type of malignancies observed in patients treated with abrocitinib.	
Exclusion due to known immunodeficiency disorder or with respect to family history of hereditary immunodeficiency	Have a known immunodeficiency disorder or a first-degree relative with a hereditary immunodeficiency.	Patients with an immunodeficiency disorder would confound interpretation of safety data.	Not considered missing information. This exclusion criteria addresses a rare condition. Prescribers will be able to assess risk without specific risk minimisation measures.

SIV.1. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development program, given its duration at the time of submission; the sample size, and the duration of follow-up will be limited in its ability to detect rare and long latency events such as malignancies or cardiovascular events. The long-terms safety data will continuously be collected via routine and additional pharmacovigilance activities.

SIV.2. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 12. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	There are no adequate and well-controlled studies on the use of abrocitinib in pregnant or breast-feeding women.
Breast-feeding women	
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Subjects were excluded with: • Severe, progressive, uncontrolled disease, including hepatic diseases. • Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2 times the ULN. • Total bilirubin ≥1.5 times the ULN; subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ ULN. Study B7451020 evaluated the pharmacokinetics, safety, and tolerability of abrocitinib in adult subjects with mild (N=8) and moderate (N=8) hepatic impairment relative to subjects with normal (N=8) hepatic function. No dose adjustment is required for patients with mild or moderate hepatic impairment. No difference in safety profile is anticipated for those with increased transaminase increase. Patients with severe hepatic impairment were not studied and, as such, the use of abrocitinib is contraindicated in these patients.
• Patients with renal impairment	Subjects with estimated Creatinine Clearance <40 mL/min based on the age-appropriate calculation, or serum creatinine >1.5 times the ULN were excluded from Phase 3 studies with abrocitinib. At baseline, in Phase 2 and 3 studies including the long-term extension, there were 877 patients with mild renal impairment (eGFR 60 - <90 mL/min) and 48 patients had an eGFR <60 mL/min.

Table 12. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
	Study B7451021 evaluated the pharmacokinetics, safety, and tolerability of abrocitinib in subjects with moderate (N=7) and severe (N=8) renal impairment relative to subjects with normal (N=8) renal function. No dose adjustment is proposed for patients with mild renal impairment. In patients with moderate (eGFR 30 to < 60 mL/min) renal impairment, the recommended dose of Cibinqo should be reduced by half to 100 mg or 50 mg once daily. In patients with severe (eGFR < 30 mL/min) renal impairment, 50 mg once daily is the recommended starting dose. The maximum daily dose is 100 mg.
• Patients with cardiovascular disease	There are no adequate and well-controlled studies on the use of abrocitinib in this patient population. Across all subjects exposed to abrocitinib (N = 3050), 1124 subjects (36.9%) had at least one cardiovascular risk factor (current smoker, diabetes mellitus, hypertension, baseline HDL <40 mg/dL, rheumatoid arthritis, coronary artery disease).
• Immunocompromised patients	Not included in the clinical development program.
• Patients with a disease severity different from inclusion criteria in clinical trials	The proposed indication will be for patients with moderate to severe AD. Clinical studies with abrocitinib were included this population. Subjects with mild AD were excluded from the clinical studies.
Population with relevant different ethnic origin	Across all subjects exposed to abrocitinib (N = 3050), there was more overall exposure in the White (2103 subjects, 3475.3 PY) and Asian (660 subjects, 1295.2 PY) subgroups relative to the Black or African American (205 subjects, 259.1 PY) and Other (82, 136.3 PY) subgroups. There were 350 subjects in the Hispanic/Latino subgroup (578.9 PY) and 2662 subjects in the Not Hispanic/Latino subgroup (4522.4 PY). No unique risks were identified by race or ethnicity.
Subpopulations carrying relevant genetic polymorphisms	Samples for the evaluation of genetic polymorphisms in the CYP2C9 and CYP2C19 genes were collected from participants in Phase 1 studies. There was no clinically meaningful effect of CYP2C19/2C9 metabolizer status on exposures of abrocitinib and active moiety. Based on these results, pharmacogenomic sampling in patients was not performed nor considered relevant.

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

The cumulative estimated patient-year exposure for abrocitinib is presented in Table 13.

Table 13. Cumulative Estimated Patient-Year Exposure for Abrocitinib (IBD - 07 March 2023)

	Units[a]	Patient Days	Patient Years
50 MG	13,080	13,080	36
100 MG	116,824	116,824	320
200 MG	106,554	106,554	292
Total	236,459	-	647

a. Units refers to the number of tablets
IBD = International Birth Date

The cumulative worldwide exposure to Abrocitinib since product approval is estimated to be 647 patient-years. The worldwide estimate is based on audited unit sales (SUs) of Abrocitinib from IQVIA Health's MIDAS Database. The data was extrapolated by taking the average of previous 4 quarters and pro-rated to the end of the current reporting period (07 March 2023). The average daily dose (AVDOS) was used to convert SUs into patient days (Days of therapy) and further divided by 365.25 (days in a year) to obtain patient years.

Cumulative exposure for region and age are presented in Table 14, Table 15, and Table 16. Information regarding gender was limited.

Table 14. Cumulative Estimated Exposure for Abrocitinib IBD Through 07 March 2023 for Indication and Region

Indication	Region		
	EU (5 EU/Mid-Level/Emerging Markets)	Japan	North America (US)
Atopic Dermatitis	25	616	2
Total Others	5	-	-

IBD = International Birth Date

Table 15. Cumulative Estimated Exposure for Abrocitinib IBD Through 07 March 2023 for Age (United States)

Indication	Age		
	16-20	21-65	>65
Atopic Dermatitis	2	98	7

IBD = International Birth Date

Table 16. Cumulative Estimated Exposure for Abrocitinib IBD Through 07 March 2023 for Age (Rest of World)

Indication	Age	
	17-65	>65
Atopic Dermatitis	533	2
Total Others	4	-

IBD = International Birth Date

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Given the mechanism of action of abrocitinib and the lack of reported pleasurable effects on the central nervous system, physiological or psychological dependency and resulting misuse for illegal purposes are not expected to occur with the medicinal product. Abrocitinib has no known attributes that make it attractive for intentional overdose or illegal use.

There is the potential for off-label use in paediatric patients <12 years-of-age, as atopic dermatitis often occurs in this younger population (see Section SI.2). There is an important potential risk of impaired bone growth and development in this population (see Section SVII.3.1.2.7).

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Table 17. Summary of the Safety Concerns

Important Identified Risks	Thrombotic events including pulmonary embolism
	Herpes zoster
Important Potential Risks	Serious and opportunistic infections
	Malignancy
	MACE
	Myopathies (including rhabdomyolysis)
	Gastrointestinal perforation
	Embryofoetal toxicity following exposure in utero
	Impaired bone growth and development if used off-label in paediatric patients < 18 years-of-age
Missing Information	Long-term safety

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

- Herpes simplex (except where serious and included as a serious infection)
- Thrombocytopaenia
- Lymphopaenia

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

These risks are described in the Summary of Product Characteristics (SmPC) and package leaflet (PL). It is anticipated that these risks can be adequately managed by routine pharmacovigilance with no need for additional risk minimisation activities. The outcomes of lymphopaenia, herpes zoster and serious and opportunistic infections, are included in list of safety concerns.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

The important potential risks are those events for which the level and/or the totality of the evidence, after thorough evaluation of the data as described above, was not judged sufficient to classify the risk as ‘identified’ but are still considered important and for which additional characterization is planned.

Table 18. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks and Missing Information	Risk-Benefit Impact
Important Identified Risks	
Venous thromboembolism	Venous thromboembolism events have the potential to impact the risk-benefit profile for abrocitinib as these events, though infrequent, may be serious or life-threatening. Additional pharmacovigilance and additional risk minimisation measures are planned (see Section SVII.3.1.1.1).

Table 18. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks and Missing Information	Risk-Benefit Impact
Herpes zoster	Herpes zoster has the potential to impact the risk-benefit profile for abrocitinib as these events, though infrequent, may be serious or life-threatening. Additional pharmacovigilance and additional risk minimisation measures are planned (see Section SVII.3.1.1.2).
Important Potential Risks	
Serious and opportunistic infections	Serious and opportunistic infections have the potential to impact the risk-benefit profile for abrocitinib as these events, though infrequent, may be serious or life-threatening. Additional pharmacovigilance and additional risk minimisation measures are planned (see Section SVII.3.1.2.1).
Malignancy	Malignancies have the potential to impact the risk-benefit profile for abrocitinib as these events, though infrequent, may be serious or life-threatening. Additional pharmacovigilance and additional risk minimisation measures are planned (see Section SVII.3.1.2.2).
MACE	Major cardiovascular events have the potential to impact the risk-benefit profile for abrocitinib as these events, though infrequent, may be serious or life threatening. Additional pharmacovigilance measures are planned (see Section SVII.3.1.2.3).
Myopathies (including rhabdomyolysis)	The impact on the risk-benefit profile ranges from asymptomatic elevations in serum muscle enzymes to life-threatening disease associated with electrolyte imbalances, and acute kidney injury. Additional pharmacovigilance measures are planned (see Section SVII.3.1.2.4).
Gastrointestinal perforation	GI perforations are life-threatening emergencies and warrant prompt medical/surgical intervention. Additional pharmacovigilance measures are planned (see Section SVII.3.1.2.5).
Embryofoetal toxicity following exposure in utero	If embryofoetal toxicity occurs, the effects could range from minor (no clinical effect) or major (having medical or social implications). While pregnancy is contraindicated, this risk may still exist given the patient population in AD which will include a significant number of women of childbearing potential. Additional pharmacovigilance and additional risk minimisation measures are planned (see Section SVII.3.1.2.6).
Impaired bone growth and development if used off-label in paediatric patients <18 years-of-age	The impact should be limited as abrocitinib is not indicated in this population. The nonclinical findings were observed when dosing was initiated in rats comparable to the human age of 3 months (see Section SVII.3.1.2.7)
Missing Information	
Long-term safety	There was limited long-term data in clinical studies.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

The important potential risk of Impaired bone growth and development if used off-label in paediatric patients <18 years-of-age was updated to Impaired bone growth and development if used off-label in paediatric patients <12 years-of-age. Bone safety of abrocitinib in adolescents is supported by the totality of the non-clinical bone safety data in monkeys and rats including the investigative age sensitivity window GLP toxicity study in juvenile rats, lack of bone safety findings in the interim analysis of the B7451015 MRI sub-study, and the

absence of safety issues from height SDS and fracture analyses in adolescents in the long-term treatment of abrocitinib. Current data supports favorable benefit-risk assessment for abrocitinib in adolescents, and resolves the remaining uncertainties related to safe use of abrocitinib in adolescents.

Further details on the safety concerns are provided in Section SVII.3.1.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

The important identified risks are venous thromboembolism and herpes zoster. The important potential risks discussed for abrocitinib include serious and opportunistic infections, malignancy (excluding NMSC), NMSC, major adverse cardiovascular events (MACE), myopathies (including rhabdomyolysis), gastrointestinal perforation, embryofoetal toxicity following exposure in utero, impaired bone growth and development if used off-label in paediatric patients <12 years-of-age, and fractures.

The presentation of data comes from 2 sets of pooled data from Phase 2 studies of abrocitinib (See Module SIII) through 05 September 2022.

The IR estimates and the corresponding number (%) of subjects with an event are calculated by inclusion of events occurring up to 28 days beyond the last dose (or to the data cut-off date for ongoing studies). Exposure (as PY) is defined as the total follow up time calculated up to the day of the first event within the event counting period for subjects with the event or the last dose day plus a risk period of 28 days beyond the last dose (or to the data cut-off date for ongoing studies) for subjects without events. These definitions were chosen because reporting to the company safety database may occur at any time regardless of the time elapsed from the last administration of study drug or since study completion. Inclusion of all events without regard to elapsed time may inflate IR estimations as the exposure time (denominator) is not similarly increased. IR estimates for adjudicated data is provided only for the Long-Term Dose-Controlled Pool 2022.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

SVII.3.1.1.1. Important Identified Risk: Venous Thromboembolism (VTE)

SVII.3.1.1.1.1. Potential Mechanisms

The potential mechanism is unknown.

SVII.3.1.1.1.2. Evidence Source and Strength of Evidence

Abrocitinib and other approved JAK inhibitors clinical trial data.

SVII.3.1.1.1.3. Characterisation of the Risk

Frequency

Potential cases of PE and DVT were adjudicated in Phase 3 studies with abrocitinib. The frequencies below include cases that were confirmed by adjudication. One case of PE occurred in the Phase 2 study with abrocitinib prior to adjudication processes being in place. Although that case occurred prior to the adjudication process, it is included in the IR calculation.

There were 10 subjects with adjudicated non-fatal adverse events (AEs) of VTE , in the Long-Term Dose-Controlled Pool 2022 (Table 19). There were 8 subjects with adjudicated events of PE (1 in the abrocitinib 100 mg QD group and 7 in the abrocitinib 200 mg QD group). There were 3 subjects with events of DVT (1 in the abrocitinib 100 mg QD group and 2 in the abrocitinib 200 mg QD group). There appeared to be a trend toward a dose-response for both VTE and PE; however, the 95% CIs overlapped.

Table 19. Proportion and Incidence Rates for Venous Thromboembolism – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)	Abrocitinib 200 mg QD (N = 1997)	All Abrocitinib (N = 3050)
Adjudicated Non-Fatal Venous Thromboembolism Events (CMQ)[a]			
Number of Subjects with Event, n (%)	1 (0.1)	9 (0.5)	10 (0.3)
Total Drug Exposure (PY)	2021.36	3271.41	5292.77
Incidence Rates (95% CI)	0.05 (0.0, 0.28)	0.28 (0.13, 0.52)	0.19 (0.09, 0.35)
Pulmonary Embolism[a]			
Number of Subjects with Event, n (%)	1 (0.1)	7 (0.4)	8 (0.3)
Total Drug Exposure (PY)	2021.36	3271.67	5293.02
Incidence Rates (95% CI)	0.05 (0.0, 0.28)	0.21 (0.09, 0.44)	0.15 (0.07, 0.30)
Deep vein thrombosis			
Number of Subjects with Event, n (%)	1 (0.1)	2 (0.1)	3 (0.1)
Total Drug Exposure (PY)	2021.36	3272.36	5293.72
Incidence Rates (95% CI)	0.05 (0.0, 0.28)	0.06 (0.01, 0.22)	0.06 (0.01, 0.17)

a. Pulmonary embolism event (not adjudicated) was included.
Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. IR (Incidence Rates): Number of subjects with events per 100 patient-years. CMQ: Customized MedDRA Query. CI: Confidence Interval
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.5

Seriousness/Outcomes

Interventional Clinical Trials:

There were 9 subjects with serious adjudicated non-fatal VTE events (1 in the abrocitinib 100 mg QD group and 8 in the abrocitinib 200 mg QD group) , in the Long-Term Dose-Controlled Pool 2022 (Table 20). There were 7 subjects with serious events of PE (1 in the abrocitinib 100 mg QD group and 6 in the abrocitinib 200 mg QD group). There were 3 subjects with serious events of DVT (1 in the abrocitinib 100 mg QD group and 2 in the abrocitinib 200 mg QD group). Most PE and DVT events were resolved at the time of reporting. (Table 20). No event was fatal (Table 21).

Table 20. Seriousness for Venous Thromboembolism – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)		Abrocitinib 200 mg QD (N = 1997)		All Abrocitinib (N = 3050)	
	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)
Adjudicated Non-Fatal Venous Thromboembolism Events (CMQ)[a]	1 (100.0)	0	8 (88.9)	1 (11.1)	9 (90.0)	1 (10.0)
Pulmonary Embolism[a]	1 (100.0)	0	6 (85.7)	1 (14.3)	7 (87.5)	1 (12.5)
Deep vein thrombosis	1 (100.0)	0	2 (100.0)	0	3 (100.0)	0

a. Pulmonary embolism event (not adjudicated) was included.
Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
For the same adverse event of interest, the most serious case was selected in this summary.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.5

Table 21. Latest Outcomes for Venous Thromboembolism – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)				Abrocitinib 200 mg QD (N = 1997)				All Abrocitinib (N = 3050)			
	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)
Adjudicated Non-Fatal Venous Thromboembolism Events (CMQ)[a]	0	1 (100.0)	0	0	3 (33.3)	6 (66.7)	0	0	3 (30.0)	7 (70.0)	0	0
Pulmonary Embolism[a]	0	1 (100.0)	0	0	2 (28.6)	5 (71.4)	0	0	2 (25.0)	6 (75.0)	0	0
Deep vein thrombosis	0	1 (100.0)	0	0	1 (50.0)	1 (50.0)	0	0	1 (33.3)	2 (66.7)	0	0

a. Pulmonary embolism event (not adjudicated) was included.
Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_out Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.7

Post-Marketing:

The global safety database was searched cumulatively through 07 March 2023 using MedDRA (version 25.1) search criteria: SMQ Embolic and thrombotic events, venous (Narrow).

Table 22. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases - Venous Thromboembolism

MedDRA PT	Number of Events	Serious Events	H	F	R	RS	NR	U
Cerebral venous thrombosis	1	1	1	0	1	0	0	0
Deep vein thrombosis	1	1	0	0	0	0	0	1
Embolism venous	1	1	0	0	0	0	0	1
Pulmonary embolism	1	1	1	0	0	0	1	0
Venous thrombosis	1	1	0	0	1	0	0	0
Total	5	5	2	0	2	0	1	2

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; H = Hospitalisation; F = Fatal; R = Resolved/Resolving; RS = Resolved with Sequelae; NR = Not Resolved; U = Unknown
MedDRA version 25.1
Cumulative through 07 March 2023
Post-Marketing Data inclusive of Clinical Trial and Non-Clinical Trial
Excludes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, and B7451050.

Severity and Nature of Risk

In the Long-Term Dose-Controlled Pool 2022, there were 1 subject with event classified as mild, 7 classified as moderate, and 17 events classified as severe (Table 23). Among the subjects with adjudicated VTE events, there was 1 subject with severe event in the abrocitinib 100 mg QD group and there was 1 mild, 3 moderate, and 5 severe in the abrocitinib 200 mg QD group. Among the subjects with PE events, there was 1 severe in the abrocitinib 100 mg QD group and there was 3 moderate and 4 severe in the abrocitinib 200 mg QD group. Among the subjects with DVT events, there was 1 severe in the abrocitinib 100 mg QD group and there was 1 with mild and 1 with severe event in the abrocitinib 200 mg QD group.

Table 23. Maximum Severity for Venous Thromboembolism – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)			Abrocitinib 200 mg QD (N = 1997)			All Abrocitinib (N = 3050)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Adjudicated Non-Fatal Venous Thromboembolism Events (CMQ)[a]	0	0	1 (100.0)	1 (11.1)	3 (33.3)	5 (55.6)	1 (10.0)	3 (30.0)	6 (60.0)
Pulmonary Embolism[a]	0	0	1 (100.0)	0	3 (42.9)	4 (57.1)	0	3 (37.5)	5 (62.5)
Deep vein thrombosis	0	0	1 (100.0)	1 (50.0)	0	1 (50.0)	1 (33.3)	0	2 (66.7)

a. Pulmonary embolism event (not adjudicated) was included.
Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050.
Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_sev Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.6

SVII.3.1.1.1.4. Risk Factors and Risk Groups

There was an insufficient number of events in the abrocitinib development program for formal risk factor or subgroup analysis. Risk factors that should be considered in prescribing include previous VTE, patients undergoing major surgery, immobilization, myocardial infarction (within the previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, and malignancy. Age, obesity (BMI ≥30), diabetes, hypertension, and smoking status should also be considered.

SVII.3.1.1.1.5. Preventability

In patients with cardiovascular or malignancy risk factors abrocitinib should only be used if no suitable treatment alternatives are available. In patients with known VTE risk factors other than cardiovascular or malignancy risk factors, abrocitinib should be used with caution. VTE risk factors other than cardiovascular and malignancy risk factors include previous VTE, patients undergoing major surgery, immobilization, heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder. Patients should be re-evaluated periodically during abrocitinib treatment to assess for changes in VTE risk. Patients ≥65 years-of-age should use the abrocitinib 100 mg dose. Patients with signs and symptoms of VTE should be promptly evaluated and treatment should be discontinued in patients with suspected VTE. See Section V.2 for the proposed additional risk minimisation measures for venous thromboembolism.

SVII.3.1.1.1.6. Impact on the Risk-Benefit Balance of the Product

Based on the established benefits of abrocitinib as described in the prescribing information and the routine and additional risk mitigation measures proposed to manage the risk of venous thromboembolism, the benefit:risk profile supports abrocitinib treatment in patients with moderate to severe AD.

SVII.3.1.1.1.7. Public Health Impact

Venous thromboembolism, comprised of DVT and PE, represents a global health concern. Up to 20% of patients with PE die from the event or shortly after. With approximately 10 million cases occurring every year globally, it is the third leading vascular disease after myocardial infarction and stroke.[177] In 2007 it was reported that there were approximately 500,000 DVTs and 300,000 PEs every year across 6 European countries with a combined population of more than 300 million inhabitants.[178] The incidence rates for PE and DVT in population-based cohort studies in subjects with moderate and severe AD are summarized below.

- In a study in the Kaiser Permanente Northern California (KPNC) database, the incidence rates for DVT and PE, in adult patients with moderate to severe AD, were 0.18/ 100 PY (95% CI: 0.14, 0.23), and 0.08/ 100 PY (95% CI: 0.05, 0.12), respectively.

- The incidence rate for DVT and PE in patients ≥12 years-of-age with moderate to severe AD in a Danish registry were 6.43/10,000 PY (95% CI: 5.23-7.91) and 6.46/10,000 PY (95% CI: 5.26-7.94).

SVII.3.1.1.2. Important Identified Risk: Herpes zoster

SVII.3.1.1.2.1. Potential Mechanisms

Of note, JAK1 inhibitors block signaling of Type 1 and Type 2 interferons and cytokines that signal using the gamma chain of the IL-2 receptor and are important in lymphocyte development.[163]

SVII.3.1.1.2.2. Evidence Source and Strength of Evidence

Clinical study data with abrocitinib and understanding of JAK mechanisms based on data from the JAK class of therapies.

SVII.3.1.1.2.3. Characterisation of the Risk

Frequency

The frequencies for both all herpes zoster and adjudicated opportunistic herpes zoster are provided in Table 24. Adjudicated opportunistic herpes zoster events are a subset of all herpes zoster.

Table 24. Proportion and Incidence Rates for Herpes Zoster

	Short-Term Pool[a]			Long-Term Dose-Controlled Pool 2022[b]	
	Placebo N = 438	**Abrocitinib 100 mg N = 703**	**Abrocitinib 200 mg N = 684**	**Abrocitinib 100 mg N = 1053**	**Abrocitinib 200 mg N = 1997**
All Herpes Zoster Infections[c]					
Number of Subjects with Event, n (%)	0 (0.0)	4 (0.6)	8 (1.2)	51 (4.8)	136 (6.8)
Total Drug Exposure (PY)	110.32	180.78	177.80	1955.84	3117.09
Incidence Rates (95% CI)	0.00 (0.00, 3.34)	2.21 (0.60, 5.67)	4.50 (1.94, 8.87)	2.61 (1.9, 3.43)	4.36 (3.66, 5.16)
Adjudicated Opportunistic Herpes Zoster[d]					
Number of Subjects with Event, n (%)	NA	NA	NA	14 (1.3)	31 (1.6)
Total Drug Exposure (PY)	NA	NA	NA	2008.82	3233.69
Incidence Rates (95% CI)	NA	NA	NA	0.70 (0.38, 1.17)	0.96 (0.65, 1.36)

a. Includes studies: B7451006, B7451012, B7451013, B7451029, B7451036. Includes data up to the end of risk period (the smallest of [last dose date + 28 days, death date]). SDTM Creation: 15Mar2021, Table Generation: 01Apr2021, Source: Table RMP.STS.5

b. Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.5

c. Includes herpes zoster and ophthalmic herpes zoster

d. Included in the events of All Herpes Zoster Infections

PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. IR (Incidence Rates): Number of subjects with events per 100 patient-years. CMQ: Customized MedDRA Query. CI: Confidence Interval

Seriousness/Outcome

Interventional Clinical Trials:

In the Long-Term Dose-Controlled Pool 2022, there were 15 subjects with serious events for all herpes zoster infections (4 in the abrocitinib 100 mg QD group and 11 in the abrocitinib 200 mg QD group) and there were 172 subjects with non-serious events for all herpes zoster infections (47 in the abrocitinib 100 mg QD group and 125 in the abrocitinib 200 mg QD group). Among these, there were 8 subjects with serious events of adjudicated opportunistic herpes zoster (2 in the abrocitinib 100 mg QD group and 6 in the abrocitinib 200 mg QD group) and there were 37 subjects with non-serious events of adjudicated opportunistic herpes zoster (12 in the abrocitinib 100 mg QD group and 25 in the abrocitinib 200 mg QD group).

Table 25. Seriousness for Herpes Zoster – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)		Abrocitinib 200 mg QD (N = 1997)		All Abrocitinib (N = 3050)	
	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)
All Herpes Zoster Infections (CMQ)	4 (7.84)	47 (92.16)	11 (8.09)	125 (91.91)	15 (8.02)	172 (91.98)
Adjudicated Opportunistic Herpes Zoster	2 (14.29)	12 (85.71)	6 (19.35)	25 (80.65)	8 (17.78)	37 (82.22)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
For the same adverse event of interest, the most serious case was selected in this summary.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.5

In the Long-Term Dose-Controlled Pool 2022, there were 12 subjects with events still present (6 in the abrocitinib 100 mg QD group and 6 in the abrocitinib 200 mg QD group) and 175 resolved (45 in the abrocitinib 100 mg QD group and 130 in the abrocitinib 200 mg QD group) for all herpes zoster infections. Among these, there were 3 subjects with events still present (1 in the abrocitinib 100 mg QD group and 2 in the abrocitinib 200 mg QD group) and 42 subjects with resolved (13 in the abrocitinib 100 mg QD group and 29 in the abrocitinib 200 mg QD group) events of adjudicated opportunistic herpes zoster. There were no fatal events (Table 26).

Table 26. Latest Outcomes for Herpes Zoster – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)				Abrocitinib 200 mg QD (N = 1997)				All Abrocitinib (N = 3050)			
	Still Present n (%)	**Resolved n (%)**	**Unknown n (%)**	**Death n (%)**	**Still Present n (%)**	**Resolved n (%)**	**Unknown n (%)**	**Death n (%)**	**Still Present n (%)**	**Resolved n (%)**	**Unknown n (%)**	**Death n (%)**
All Herpes Zoster Infections (CMQ)	6 (11.76)	45 (88.24)	0	0	6 (4.41)	130 (95.59)	0	0	12 (6.42)	175 (93.58)	0	0
Adjudicated Opportunistic Herpes Zoster	1 (7.14)	13 (92.86)	0	0	2 (6.45)	29 (93.55)	0	0	3 (6.67)	42 (93.33)	0	0

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_out Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.7

Post-Marketing:

The global safety database was searched cumulatively through 07 March 2023 using MedDRA (version 25.1) search criteria: HLT Herpes Viral Infections (Primary path). Excluding the following individual PTs: Congenital herpes simplex infection, Congenital varicella infection, Disseminated neonatal herpes simplex, Eczema herpeticum, and Herpes simplex virus conjunctivitis neonatal.

Table 27. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases - Herpes Zoster

MedDRA PT	Number of Events	Serious Events	H	F	R	RS	NR	U
Herpes zoster	21	3	1	0	11	0	1	9
Herpes simplex	5	0	0	0	3	0	0	2
Oral herpes	5	0	0	0	1	0	2	2
Herpes virus infection	3	0	0	0	0	0	0	3
Genital herpes	1	0	0	0	1	0	0	0
Ophthalmic herpes simplex	1	1	0	0	0	0	0	1
Ophthalmic herpes zoster	1	1	1	0	1	0	0	0
Varicella zoster virus infection	1	0	0	0	1	0	0	0
Total	38	5	2	0	18	0	3	17

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; H = Hospitalisation; F = Fatal; R = Resolved/Resolving; RS = Resolved with Sequelae; NR = Not Resolved; U = Unknown
MedDRA version 25.1
Cumulative through 07 March 2023
Post-Marketing Data inclusive of Clinical Trial and Non-Clinical Trial
Excludes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, and B7451050.

Severity and Nature of Risk

In the Long-Term Dose-Controlled Pool 2022 there were 64 subjects with events classified as mild (19 in the abrocitinib 100 mg QD group and 45 in the abrocitinib 200 mg QD group), there were 111 with events classified as moderate (28 in the abrocitinib 100 mg QD group and 83 in the abrocitinib 200 mg QD group), and there were 12 severe (4 in the abrocitinib 100 mg QD group and 8 in the abrocitinib 200 mg QD group) for all herpes zoster infections. Among these events, there were 11 subjects with events classified as mild (6 in the abrocitinib 100 mg QD group and 5 in the abrocitinib 200 mg QD group), there were 26 classified as moderate (6 in the abrocitinib 100 mg QD group and 20 in the abrocitinib 200 mg QD group), and there were 8 severe (2 in the abrocitinib 100 mg QD group and 6 in the abrocitinib 200 mg QD group) for events of adjudicated opportunistic herpes zoster.

Table 28. Maximum Severity for Herpes Zoster – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)			Abrocitinib 200 mg QD (N = 1997)			All Abrocitinib (N = 3050)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
All Herpes Zoster Infections (CMQ)	19 (37.25)	28 (54.90)	4 (7.84)	45 (33.09)	83 (61.03)	8 (5.88)	64 (34.22)	111 (59.36)	12 (6.42)
Adjudicated Opportunistic Herpes Zoster	6 (42.86)	6 (42.86)	2 (14.29)	5 (16.13)	20 (64.52)	6 (19.35)	11 (24.44)	26 (57.78)	8 (17.78)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_sev Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.6

SVII.3.1.1.2.4. Risk Factors and Risk Groups

For all herpes zoster events (regardless of adjudication as an opportunistic), age ≥65 years, a dose of 200 mg, a history of herpes zoster, severe AD at baseline, and an ALC $<0.5\times10^3/mm^3$ were identified as risk factors.

SVII.3.1.1.2.5. Preventability

Herpes zoster can have significant impact on individual patients. Therefore, routine and additional RMMs have been proposed to mitigate the risk.

Routine risk minimisation measures in the SmPC include a contraindication for patients with active serious systemic infections. The SmPC recommends that immunisation be up to date prior to initiating abrocitinib. In patients 65 years-of-age and older, abrocitinib should be initiated at the 100 mg once daily dose. In addition, special warnings and precautions for use include considering the risk and benefits of treatment in patients with chronic or recurrent infection.

Health care provider and patient educational materials will include the risk for infections, including herpes zoster (see Section III.2).

SVII.3.1.1.2.6. Impact on the Risk-Benefit Balance of the Product

Herpes zoster infections may be mild, moderate, or severe and sometimes life-threatening.

SVII.3.1.1.2.7. Public Health Impact

Severe types of herpes zoster infection (e.g., disseminated herpes zoster), can lead to morbidity and mortality. The impact of these infections on public health is significant both in terms of lost time at work and increased burden on medical care.

SVII.3.1.2. Important Potential Risks

SVII.3.1.2.1. Important Potential Risk: Serious and Opportunistic Infections

SVII.3.1.2.1.1. Potential Mechanisms

In subjects with rheumatologic diseases or inflammatory bowel disease, an increased incidence of serious infections has been observed during treatment with other JAK inhibitors.[168] These JAK inhibitors are prescribed for medical conditions where the background rates of infection are known to be higher than age and gender matched controls. Subjects with AD also have a higher incidence of cutaneous and extracutaneous infections and viral reactivation.[179] JAK1 inhibitors are expected to preserve signaling of IL-12 and IL-23. These cytokines are thought to be important in protection against mycobacterial infections, infections with other intracellular bacteria, and invasive fungal infections.[180,181,182] Infections for which incidence may be attenuated by preserving IL-12 and IL-23 signaling occur relatively infrequently in the countries where abrocitinib. Thus, JAK1 selective inhibitors still block signaling of important cytokines involved in mounting an immune response.

SVII.3.1.2.1.2. Evidence Source and Strength of Evidence

Abrocitinib and other approved JAK inhibitors clinical trial data.

SVII.3.1.2.1.3. Characterisation of the Risk

Frequency

Serious infections

The data from the abrocitinib studies do not suggest a meaningful increase in the incidence of serious infections overall compared to placebo nor exhibit a dose response.

Table 29. Proportion and Incidence Rates for Treatment-Emergent Serious Infections - Short-Term Studies Pool and the Long-Term Dose-Controlled Pool 2022

		Short-Term Studies Pool[a]		Long-Term Dose-Controlled Pool 2022[b]	
	Placebo (N = 438)	Abrocitinib 100 mg QD (N = 703)	Abrocitinib 200 mg QD (N = 684)	Abrocitinib 100 mg QD (N = 1053)	Abrocitinib 200 mg QD (N = 1997)
Serious Infections					
Number of Subjects with event, n (%)	2 (0.5)	6 (0.9)	2 (0.3)	44 (4.2)	80 (4.0)

Table 29. Proportion and Incidence Rates for Treatment-Emergent Serious Infections - Short-Term Studies Pool and the Long-Term Dose-Controlled Pool 2022

		Short-Term Studies Pool[a]		Long-Term Dose-Controlled Pool 2022[b]	
	Placebo (N = 438)	**Abrocitinib 100 mg QD (N = 703)**	**Abrocitinib 200 mg QD (N = 684)**	**Abrocitinib 100 mg QD (N = 1053)**	**Abrocitinib 200 mg QD (N = 1997)**
Serious Infections					
Total Drug Exposure (PY)	110.22	180.86	178.90	1997.32	3227.78
Incidence Rates (95% CI)	1.81 (0.22, 6.55)	3.32 (1.22, 7.22)	1.12 (0.14, 4.04)	2.20 (1.60, 2.96)	2.48 (1.97, 3.08)

a. Includes Studies: B7451006, B7451012, B7451013, B7451029, B7451036. Includes data up to the end of risk period (the smaller of [last dose + 28 days, death date]
SDTM Creation: 15Mar2021, Table Generation 01Apr2021
Source: Table RMP.STS.5

b. Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.5

PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. IR (Incidence Rates): Number of subjects with events per 100 patient-years. CMQ: Customized MedDRA Query. CI: Confidence Interval

Opportunistic infections

Most opportunistic infections were events of multidermatomal cutaneous herpes zoster (see Section SVII.3.1.1.2); there were 2 events of tuberculosis.

Seriousness/Outcomes

Interventional Clinical Trials:

By definition, all of the serious infections were serious.

The outcomes of each event type are provided in Table 30. There were 4 fatal events: 3 events of COVID-19 and 1 of septic shock.

Table 30. Latest Outcomes for Serious and Opportunistic Infections – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)				Abrocitinib 200 mg QD (N = 1997)				All Abrocitinib (N = 3050)			
	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)
Serious Infections	1 (2.27)	41 (93.18)	1 (2.27)	1 (2.27)	8 (10.00)	69 (86.25)	0	3 (3.75)	9 (7.26)	110 (88.71)	1 (0.81)	4 (3.23)
Adjudicated Opportunistic Infections (excluding Tuberculosis and Zoster)	0	0	0	0	2 (100.00)	0	0	0	2 (100.00)	0	0	0
Adjudicated Tuberculosis	0	0	0	0	2 (100.00)	0	0	0	2 (100.00)	0	0	0

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.

Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).

PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.

n: Number of subjects with the event. CMQ: Customized MedDRA Query.

Source Data: Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_out Date of Generation: 09MAR2023

Source: Table RMP.LTDCP2022.7

Post-Marketing:

The global safety database was searched cumulatively through 07 March 2023 using MedDRA (version 25.1) search criteria: SOC Infections and infestations (Primary Path) and PT Febrile neutropenia. Events that meet serious criteria only.

Table 31. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases - Serious and Opportunistic Infections

MedDRA PT	Number of Events	Serious Events	H	F	R	RS	NR	U
Eczema herpeticum	4	4	0	0	1	0	0	3
Herpes zoster	3	3	1	0	3	0	0	0
Pneumonia	3	3	1	0	1	0	0	2
COVID-19	2	2	1	0	0	0	1	1
Sepsis	2	2	1	0	1	0	0	1
Anal abscess	1	1	0	0	0	0	0	1
Atypical mycobacterial infection	1	1	0	0	0	0	0	1
COVID-19 pneumonia	1	1	1	1	0	0	0	0
Ear infection	1	1	0	0	0	0	0	1
Eye infection	1	1	0	0	0	0	0	1
Impetigo	1	1	0	0	1	0	0	0
Listeriosis	1	1	0	0	1	0	0	0
Localised infection	1	1	1	0	1	0	0	0
Lower respiratory tract infection	1	1	0	0	0	0	0	1
Ophthalmic herpes simplex	1	1	0	0	0	0	0	1
Ophthalmic herpes zoster	1	1	1	0	1	0	0	0
Pneumonia haemophilus	1	1	1	0	1	0	0	0
Renal abscess	1	1	1	0	1	0	0	0
Sinusitis	1	1	0	0	0	0	0	1
Skin bacterial infection	1	1	1	0	1	0	0	0
Tuberculosis	1	1	0	0	0	0	0	1
Upper respiratory tract infection	1	1	1	0	0	0	0	1
Urosepsis	1	1	1	0	1	0	0	0
Total	32	32	12	1	14	0	1	16

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; H = Hospitalisation; F = Fatal; R = Resolved/Resolving; RS = Resolved with Sequelae; NR = Not Resolved; U = Unknown
MedDRA version 25.1
Cumulative through 07 March 2023
Post-Marketing Data inclusive of Clinical Trial and Non-Clinical Trial
Excludes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, and B7451050.

Severity and Nature of Risk

The most frequent serious infections in the Long-Term Dose-Controlled Pool 2022 were those related to herpes zoster, herpes simplex, pneumonia, and COVID-19. Considering the recent global COVID-19 pandemic, cases of COVID- 19 are to be expected. However, there

was no meaningful dose response for all events of COVID-19; the CIs for the abrocitinib 100 mg dose (0.19/100 PY [95% CI: 0.05, 0.50]) and the 200 mg dose (0.30/100 PY [95% CI: 0.14, 0.55] were overlapping. There was 2 events of tuberculosis confirmed by adjudication.

Table 32. Maximum Severity for Serious and Opportunistic Infections – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)			Abrocitinib 200 mg QD (N = 1997)			All Abrocitinib (N = 3050)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Serious Infections	3 (6.82)	23 (52.27)	18 (40.91)	4 (5.00)	32 (40.00)	44 (55.00)	7 (5.65)	55 (44.35)	62 (50.00)
Adjudicated Opportunistic Infections (excluding Tuberculosis and Zoster)	0	0	0	1 (50.00)	0	1 (50.00)	1 (50.00)	0	1 (50.00)
Adjudicated Tuberculosis	0	0	0	0	0	2 (100.00)	0	0	2 (100.00)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050.
Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_sev Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.6

SVII.3.1.2.1.4. Risk Factors and Risk Groups

Elderly age and diabetes are general risk factors for serious infections.

SVII.3.1.2.1.5. Preventability

Serious infection can have significant impact on individual patients. Therefore, routine and additional RMMs have been proposed to mitigate the risk. As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. Patients ≥65 years-of-age should utilize abrocitinib 100 mg dose.

Routine risk minimisation measures include a contraindication for active serious systemic infections, including tuberculosis. The special warnings and precautions for use prior to initiating treatment the risk and benefits of treatment should be considered for patients:

- with chronic or recurrent infection
- who have been exposed to TB

- with a history of a serious or an opportunistic infection
- who have resided or travelled in areas of endemic TB or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

In addition, screening for TB and hepatis B and C and a recommendation for immunizations be up to date prior to initiating abrocitinib are included in SmPC Section 4.4.

Health care provider and patient educational materials will include the risk for serious and opportunistic infections (see Section III.2).

SVII.3.1.2.1.6. Impact on the Risk-Benefit Balance of the Product

Infections may be mild and self-limited or more severe and sometimes fatal. While routine risk minimisation measures, summarized above will mitigate much of the risk, some subjects may still have serious infections. Therefore, routine and non-routine risk minimisation measures are proposed (see Section III.1 and Section III.2).

Routine risk minimisation measures in prescribing information include instruction that patients should be monitored for infection, promptly evaluated and treated for infection and that therapy should be interrupted if the patient is not responding to standard therapy. Health care provider and patient educational materials include the risk for serious and opportunistic infections.

SVII.3.1.2.1.7. Public Health Impact

Serious infection is a common cause of morbidity and mortality. The impact of these infections on public health is significant both in terms of lost time at work and increased burden on medical care.

SVII.3.1.2.2. Important Potential Risk: Malignancy (excluding NMSC)

SVII.3.1.2.2.1. Potential Mechanisms

Malignancy events are of special interest for agents that have an immunomodulatory mechanism of action due to potential decreased immune surveillance. The immune system is thought to function as a tumor suppressor through the effect of cytokines or certain cell types (e.g., NK cells) that may be affected by JAK inhibitors and other immunomodulators.[168] When cancers developing in subjects with extreme immunosuppression (HIV infection or renal transplantation) are analysed, cancers related to infections with viruses and bacteria are over-represented whereas the incidence of epithelial cancers (for example ovary and prostate) are not increased relative to age-matched controls.[183]

SVII.3.1.2.2.2. Evidence Source and Strength of Evidence

Abrocitinib and other approved JAK inhibitors clinical trial data.

SVII.3.1.2.2.3. Characterisation of the Risk

Frequency

There were 14 subjects with events of malignancy (excluding NMSC) confirmed through adjudication (3 in the abrocitinib 100 mg QD group and 11 in the abrocitinib 200 mg QD group). Most commonly reported malignancies included breast cancer (4), prostate cancer (2) and lung cancer (2). There was a trend toward dose-response in the IR point estimates for malignancy (excluding NMSC); however, the 95% CIs overlapped. In addition, there was 1 event in the abrocitinib 200 mg group, gastric adenocarcinoma, which occurred early in the treatment period and symptoms were present prior to taking study treatment. The IR in the 200 mg group, excluding that subject, was 0.31/100 PY (95% CI: 0.15, 0.56).

Table 33. Proportion and Incidence Rates for Malignancy (Excluding Non-Melanoma Skin Cancer) – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)	Abrocitinib 200 mg QD (N = 1997)	All Abrocitinib (N = 3050)
Adjudicated Malignancies (excluding Non-Melanoma Skin Cancer)			
Number of Subjects with Event, n (%)	3 (0.3)	11 (0.6)	14 (0.5)
Total Drug Exposure (PY)	2020.90	3268.06	5288.96
Incidence Rates (95% CI)	0.15 (0.03, 0.43)	0.34 (0.17, 0.60)	0.26 (0.14, 0.44)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. IR (Incidence Rates): Number of subjects with events per 100 patient-years. CMQ: Customized MedDRA Query. CI: Confidence Interval
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.5

Seriousness/Outcomes

Interventional Clinical Trials:

Overall, there were 14 events of malignancy (excluding NMSC); all events were serious. Most commonly reported malignancies included breast cancer (4), prostate cancer (2) and lung cancer (2).

Table 34. Seriousness for Malignancy (Excluding Non-Melanoma Skin Cancer) – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)		Abrocitinib 200 mg QD (N = 1997)		All Abrocitinib (N = 3050)	
	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)
Adjudicated Malignancies (excluding Non-Melanoma Skin Cancer)	3 (100.00)	0	11 (100.00)	0	14 (100.00)	0

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
For the same adverse event of interest, the most serious case was selected in this summary.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.5

Table 35. Latest Outcomes for Malignancy (Excluding Non-Melanoma Skin Cancer) – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)				Abrocitinib 200 mg QD (N = 1997)				All Abrocitinib (N = 3050)			
	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)
Adjudicated Malignancies (excluding Non-Melanoma Skin Cancer)	3 (100.00)	0	0	0	7 (63.64)	2 (18.18)	1 (9.09)	1 (9.09)	10 (71.43)	2 (14.29)	1 (7.14)	1 (7.14)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_out Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.7

Post-Marketing:

The global safety database was searched cumulatively through 07 March 2023 using MedDRA (version 25.1) search criteria: SMQ Malignancy related conditions (Narrow), SMQ Malignancy related therapeutic and diagnostic procedures (Narrow), SMQ Malignant or unspecified tumours (Narrow), and SMQ Tumour markers (Narrow).

Table 36. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases - Malignancy (excluding NMSC)

MedDRA PT	Number of Events	Serious Events	H	F	R	RS	NR	U
Neoplasm malignant	2	2	0	0	0	0	0	2
Adenocarcinoma of colon	1	1	1	0	0	0	1	0
Brain neoplasm	1	1	0	0	1	0	0	
Cutaneous T-cell lymphoma	1	1	0	0	0	0	0	1
Hysterectomy	1	1	0	0	0	0	0	1
Lymphoma	1	1	0	0	0	0	0	1
Total	7	7	1	0	1	0	1	5

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; H = Hospitalisation; F = Fatal; R = Resolved/Resolving; RS = Resolved with Sequelae; NR = Not Resolved; U = Unknown
MedDRA version 25.1
Cumulative through 07 March 2023
Post-Marketing Data inclusive of Clinical Trial and Non-Clinical Trial
Excludes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, and B7451050.

Severity and Nature of Risk

Among the subjects with events of malignancy (excluding NMSC), 10 subjects with events were severe, 3 moderate and one event of pelvi ureteric obstruction was mild.

Table 37. Maximum Severity for Malignancy (Excluding Non-Melanoma Skin Cancer) – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)			Abrocitinib 200 mg QD (N = 1997)			All Abrocitinib (N = 3050)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Adjudicated Malignancies (excluding Non-Melanoma Skin Cancer)	1 (33.33)	1 (33.33)	1 (33.33)	0	2 (18.18)	9 (81.82)	1 (7.14)	3 (21.43)	10 (71.43)

Table 37. Maximum Severity for Malignancy (Excluding Non-Melanoma Skin Cancer) – Long-Term Dose Controlled Pool 2022

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_sev Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.6

SVII.3.1.2.2.4. Risk Factors and Risk Groups

There was an insufficient number of events in the abrocitinib development program for risk factor or subgroup analysis. Like other JAK inhibitors, age ≥65 years, current or past smoking history, and a history of malignancy (excluding basal cell carcinoma) are risk factors for malignancy.

SVII.3.1.2.2.5. Preventability

Like other JAK inhibitors, in patients 65 years-of-age and older, in patients who are current or past long-time smokers, or with other malignancy risk factors (e.g. current malignancy or history of malignancy) abrocitinib should be used if no suitable treatment alternatives are available. Patients ≥65 years-of-age should utilize the abrocitinib 100 mg dose.

SVII.3.1.2.2.6. Impact on the Risk-Benefit Balance of the Product

Malignancy can severely impact a patient's quality of life and can be fatal. Specific potential effects on an individual patient depend upon a variety of factors including site of malignancy and tolerance of therapy. As such, both routine and non-routine risk minimisation measures are proposed.

SVII.3.1.2.2.7. Public Health Impact

Malignancy is a major public health problem. It is among the leading causes of morbidity and mortality worldwide.[184]

SVII.3.1.2.3. Important Potential Risk: Non-Melanoma Skin Cancer (NMSC)

SVII.3.1.2.3.1. Potential Mechanisms

Malignancy events are of special interest for agents that have an immunomodulatory mechanism of action due to potential decreased immune surveillance. The immune system is thought to function as a tumor suppressor through the effect of cytokines or cell types (e.g., NK cells) that may be affected by JAK inhibitors and other immunomodulators.[168] Immunosuppression is a well-documented risk factor for skin cancer, as exemplified by the 65- to 250-fold higher squamous cell carcinoma risk, 10-fold higher basal cell carcinoma risk, in solid organ transplant recipients (SOTRs) receiving potent, prolonged courses of immunosuppressive therapies.[185]

SVII.3.1.2.3.2. Evidence Source and Strength of Evidence

Abrocitinib and other approved JAK inhibitors clinical trial data.

SVII.3.1.2.3.3. Characterisation of the Risk

Frequency

The IRs for adjudicated NMSC were assessed in the Long-Term Dose-Controlled Pool 2022. There were 7 subjects with an adjudicated event of NMSC (4 in the abrocitinib 100 mg QD group and 3 in the abrocitinib 200 mg QD group). Among the events of NMSC, there were 3 subjects with squamous cell carcinoma, 3 subjects with basal cell carcinoma and 1 subject with actinic keratosis.

Table 38. Proportion and Incidence Rates for Non-Melanoma Skin Cancer – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)	Abrocitinib 200 mg QD (N = 1997)	All Abrocitinib (N = 3050)
Adjudicated Non-Melanoma Skin Cancer			
Number of Subjects with Event, n (%)	4 (0.4)	3 (0.2)	7 (0.2)
Total Drug Exposure (PY)	2012.49	3266.98	5279.47
Incidence Rates (95% CI)	0.20 (0.05, 0.51)	0.09 (0.02, 0.27)	0.13 (0.05, 0.27)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. IR (Incidence Rates): Number of subjects with events per 100 patient-years. CMQ: Customized MedDRA Query. CI: Confidence Interval
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.5

Seriousness/Outcome

Interventional Clinical Trials:

Among the 7 subjects with an adjudicated event of NMSC, there were 2 serious events both in the 200 mg group and 5 non-serious events (4 in the abrocitinib 100 mg QD group and 1 in the 200 mg QD group. The 2 serious events were sebaceous carcinoma (adjudicated as both basal cell and squamous cell carcinoma), and squamous cell carcinoma.

Table 39. Seriousness for Non-Melanoma Skin Cancer – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)		Abrocitinib 200 mg QD (N = 1997)		All Abrocitinib (N = 3050)	
	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)
Adjudicated Non-Melanoma Skin Cancer	0	4 (100.00)	2 (66.67)	1 (33.33)	2 (28.57)	5 (71.43)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
For the same adverse event of interest, the most serious case was selected in this summary.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.5

Table 40. Latest Outcomes for Non-Melanoma Skin Cancer – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)				Abrocitinib 200 mg QD (N = 1997)				All Abrocitinib (N = 3050)			
	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)
Adjudicated Non-Melanoma Skin Cancer	0	4 (100.00)	0	0	1 (33.33)	2 (66.67)	0	0	1 (14.29)	6 (85.71)	0	0

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_out Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.7

Post-Marketing:

The global safety database was searched cumulatively through 07 March 2023 using MedDRA (version 25.1) search criteria: HLT Skin neoplasms malignant and unspecified (excl melanoma) (Primary path) and PT Squamous cell carcinoma.

No events have been identified in the global safety database for non-melanoma skin cancer.

Severity and Nature of Risk

In the Long-Term Dose Controlled Pool 2022 there was 1 subject with severe event of NMSC in the 200mg QD dose, 4 with moderate NMSC events: 3 in the 100 mg QD dose group and 1 in the 200mg dose group. Remaining 2 events were mild and 1 in each dose group.

Table 41. Maximum Severity for Non-Melanoma Skin Cancer – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)			**Abrocitinib 200 mg QD (N = 1997)**			**All Abrocitinib (N = 3050)**		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Adjudicated Non-Melanoma Skin Cancer	1 (25.00)	3 (75.00)	0	1 (33.33)	1 (33.33)	1 (33.33)	2 (28.57)	4 (57.14)	1 (14.29)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_sev Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.6

SVII.3.1.2.3.4. Risk Factors and Risk Groups

There was an insufficient number of events in the abrocitinib development program for risk factor or subgroup analysis. Like other JAK inhibitors, age ≥65 years, current or past smoking history, and a history of malignancy (excluding basal cell carcinoma) are risk factors for malignancy.

SVII.3.1.2.3.5. Preventability

Like other JAK inhibitors, in patients 65 years-of-age and older, in patients who are current or past long-time smokers, or with other malignancy risk factors (e.g. current malignancy or history of malignancy) abrocitinib should be used if no suitable treatment alternatives are

available. Periodic skin examination is recommended to assess for NMSC. Patients ≥65 years-of-age should utilize the abrocitinib 100 mg dose.

SVII.3.1.2.3.6. Impact on the Risk-Benefit Balance of the Product

Malignancy can severely impact a patient's quality of life and can be fatal. Specific potential effects on an individual patient depend upon a variety of factors including site of malignancy and tolerance of therapy. Skin cancer is the most common type of cancer in fair-skinned individuals around the world. Although NMSC is rarely fatal, it can cause significant morbidity. As such, both routine and non-routine risk minimisation measures are proposed.

SVII.3.1.2.3.7. Public Health Impact

Malignancy is a major public health problem. It is among the leading causes of morbidity and mortality worldwide.[184] Skin cancer is the most common type of cancer in fair-skinned individuals around the world. Although NMSC is rarely fatal, it can cause significant morbidity.

SVII.3.1.2.4. Important Potential Risk: MACE

SVII.3.1.2.4.1. Potential Mechanisms

Treatment with abrocitinib and other JAK inhibitors results in increases in total cholesterol, LDL and HDL. It is unknown if this contributes to an increased risk of MACE.

SVII.3.1.2.4.2. Evidence Source and Strength of Evidence

Clinical study data and data of other approved JAK inhibitors.

SVII.3.1.2.4.3. Characterisation of the Risk

Frequency

There were 15 subjects with adjudicated events of MACE in the Long-Term Dose-Controlled Pool 2022 (6 in the abrocitinib 100 mg QD group and 9 in the abrocitinib 200 mg QD group). No trend toward dose-response was observed.

Table 42. Proportion and Incidence Rates for MACE – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)	Abrocitinib 200 mg QD (N = 1997)	All Abrocitinib (N = 3050)
Adjudicated Major Adverse Cardiovascular Events			
Number of Subjects with Event, n (%)	6 (0.6)	9 (0.5)	15 (0.5)
Total Drug Exposure (PY)	2019.48	3271.28	5290.77
Incidence Rates (95% CI)	0.30 (0.11, 0.65)	0.28 (0.13, 0.52)	0.28 (0.16, 0.47)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. IR (Incidence Rates): Number of subjects with events per 100 patient-years. CMQ: Customized MedDRA Query. CI: Confidence Interval
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.5

Seriousness/Outcome

Interventional Clinical Trials:

There were 15 subjects with adjudicated MACE events. There were 10 subjects with serious (2 from the abrocitinib 100 mg QD group and 8 from the abrocitinib 200 mg QD group) and 5 with non-serious events (4 from the abrocitinib 100 mg QD group and 1 from the abrocitinib 200 mg QD group).

Table 43. Seriousness for MACE – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)		Abrocitinib 200 mg QD (N = 1997)		All Abrocitinib (N = 3050)	
	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)
Adjudicated Major Adverse Cardiovascular Events	2 (33.33)	4 (66.67)	8 (88.89)	1 (11.11)	10 (66.67)	5 (33.33)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
For the same adverse event of interest, the most serious case was selected in this summary.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.5

The adjudicated events of MACE were still present in 4 (all 4 in the abrocitinib 100 mg QD), resolved in 6 (1 in the abrocitinib 100 mg QD group and 5 in the abrocitinib 200 mg QD group), and was fatal in 5 (1 in the abrocitinib 100 mg QD group and 4 in the abrocitinib 200 mg QD group).

Table 44. Latest Outcomes for MACE – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)				Abrocitinib 200 mg QD (N = 1997)				All Abrocitinib (N = 3050)			
	Still Present n (%)	**Resolved n (%)**	**Unknown n (%)**	**Death n (%)**	**Still Present n (%)**	**Resolved n (%)**	**Unknown n (%)**	**Death n (%)**	**Still Present n (%)**	**Resolved n (%)**	**Unknown n (%)**	**Death n (%)**
Adjudicated Major Adverse Cardiovascular Events	4 (66.67)	1 (16.67)	0	1 (16.67)	0	5 (55.56)	0	4 (44.44)	4 (26.67)	6 (40.00)	0	5 (33.33)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_out Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.7

Post-Marketing:

The global safety database was searched cumulatively through 07 March 2023 using MedDRA (version 25.1) search criteria: SMQ Myocardial infarction (Narrow), SMQ Central nervous system vascular disorders (Narrow), SMQ Other ischaemic heart disease (Narrow), PT Cardiac death, PT Cardiac failure congestive, and PT Sudden cardiac death.

Table 45. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases - MACE

MedDRA PT	Number of Events	Serious Events	H	F	R	RS	NR	U
Cerebral venous thrombosis	1	1	1	0	1	0	0	0
Cerebrovascular accident	1	1	0	0	1	0	0	0
Myocardial infarction	1	1	0	0	0	0	0	1
Total	3	3	1	0	2	0	0	1

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; H = Hospitalisation; F = Fatal; R = Resolved/Resolving; RS = Resolved with Sequelae; NR = Not Resolved; U = Unknown
MedDRA version 25.1
Cumulative through 07 March 2023
Post-Marketing Data inclusive of Clinical Trial and Non-Clinical Trial
Excludes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, and B7451050.

Severity and Nature of Risk

The adjudicated event of MACE was mild in 3 (2 in the abrocitinib 100 mg QD group and 1 in the abrocitinib 200 mg QD group), moderate in 2 (abrocitinib 100 mg QD group) and severe in 10 (2 in the abrocitinib 100 mg QD group and 8 in the abrocitinib 200 mg QD group).

Table 46. Maximum Severity for MACE – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)			Abrocitinib 200 mg QD (N = 1997)			All Abrocitinib (N = 3050)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Adjudicated Major Adverse Cardiovascular Events	2 (33.33)	2 (33.33)	2 (33.33)	1 (11.11)	0	8 (88.89)	3 (20.00)	2 (13.33)	10 (66.67)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_sev Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.6

SVII.3.1.2.4.4. Risk Factors and Risk Groups

There was an insufficient number of events in the abrocitinib development program for formal risk factor or subgroup analysis. Like with other JAK inhibitors, age ≥65 years, current or past smoking history, and a history of atherosclerotic disease are risk factors for MACE.

SVII.3.1.2.4.5. Preventability

Like other JAK inhibitors, in patients over 65 years-of-age and older, patients who are current or past long-time smokers, and patients with other cardiovascular risk factors, abrocitinib should be used if no suitable treatment alternatives are available. Lipid assessment should be performed prior to initiation and at Week 4 and patients should be managed according to clinical guidelines. Patients ≥65 years-of-age should utilize the abrocitinib 100 mg dose.

Patients should be re-evaluated periodically during abrocitinib treatment to assess for changes in risk factors for MACE.

Lipid assessment should be performed prior to initiation and at Week 4 and patients should be managed according to clinical guidelines.

SVII.3.1.2.4.6. Impact on the Risk-Benefit Balance of the Product

Cardiovascular disease, although infrequent in this patient population, can have a significant impact on individual patients and may lead to significant morbidity and mortality.

SVII.3.1.2.4.7. Public Health Impact

Cardiovascular disease is a leading cause of death; however, the extent of the impact is sensitive to patient population. The incidence rate for MACE was examined in 2 cohorts of patients with atopic dermatitis.

- In a study in the Kaiser Permanente Northern California (KPNC) database, the incidence rates for MACE, in adult patients with moderate to severe AD, ≥18 years-of-age and ≥65 years-of-age with moderate to severe AD, were 0.31/ 100 PY (95% CI: 0.26, 0.38), and 1.41/ 100 PY (95% CI: 1.06, 1.86), respectively.

- The incidence rate for MACE in patients 18-<65 years-of-age and ≥65 years-of-age with AD in a Danish registry were 12.81 /10,000 PY (95% CI: 10.94, 15.00) and 229.51 /10,000 PY (95% CI: 200.67, 262.50).

SVII.3.1.2.5. Important Potential Risk: Myopathies (including Rhabdomyolysis)

SVII.3.1.2.5.1. Potential Mechanisms

The potential mechanism is unknown. Although increases in CK are seen in the JAK class, these elevations have generally not been associated with myopathy or rhabdomyolysis.

SVII.3.1.2.5.2. Evidence Source and Strength of Evidence

Clinical trial data and based on the data from the JAK class. Approved JAK inhibitors are being investigated for potential risk of myopathy (including rhabdomyolysis).

SVII.3.1.2.5.3. Characterisation of the Risk

Frequency

There were 5 subjects who experienced events of myopathy (including rhabdomyolysis) (1 from the abrocitinib 100 mg QD group and 4 from the abrocitinib 200 mg QD group).

Table 47. Proportion and Incidence Rates for Myopathies (including Rhabdomyolysis) – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)	Abrocitinib 200 mg QD (N = 1997)	All Abrocitinib (N = 3050)
Myopathies, including Rhabdomyolysis			
Number of Subjects with Event, n (%)	1 (0.1)	4 (0.2)	5 (0.2)
Total Drug Exposure (PY)	1577.99	2277.37	3855.36
Incidence Rates (95% CI)	0.06 (0.00, 0.35)	0.18 (0.05, 0.45)	0.13 (0.04, 0.30)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. IR (Incidence Rates): Number of subjects with events per 100 patient-years. CMQ: Customized MedDRA Query. CI: Confidence Interval
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.5

Seriousness/Outcome

Interventional Clinical Trials:

There were no subjects with serious events for myopathies.

Table 48. Seriousness for Myopathies (including Rhabdomyolysis) – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)		Abrocitinib 200 mg QD (N = 1997)		All Abrocitinib (N = 3050)	
	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)
Myopathies, including Rhabdomyolysis	0	1 (100.00)	0	4 (100.00)	0	5 (100.00)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
For the same adverse event of interest, the most serious case was selected in this summary.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.5

The events of myopathies were still present in 3 (in the abrocitinib 200 mg QD group) and resolved in 2 (1 in the abrocitinib 100 mg QD group and 1 in the abrocitinib 200 mg QD group).

Table 49. Latest Outcomes for Myopathies (including Rhabdomyolysis) – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)				Abrocitinib 200 mg QD (N = 1997)				All Abrocitinib (N = 3050)			
	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)
Myopathies, including Rhabdomyolysis	0	1 (100.00)	0	0	3 (75.00)	1 (25.00)	0	0	3 (60.00)	2 (40.00)	0	0

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_out Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.7

Post-Marketing:

The global safety database was searched cumulatively through 07 March 2023 using MedDRA (version 25.1) search criteria: SMQ Rhabdomyolysis/myopathy (Narrow).

Table 50. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases - Myopathies (Including Rhabdomyolysis)

MedDRA PT	Number of Events	Serious Events	H	F	R	RS	NR	U
Rhabdomyolysis	1	1	0	0	0	0	0	1
Total	1	1	0	0	0	0	0	1

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; H = Hospitalisation; F = Fatal; R = Resolved/Resolving; RS = Resolved with Sequelae; NR = Not Resolved; U = Unknown
MedDRA version 25.1
Cumulative through 07 March 2023
Post-Marketing Data inclusive of Clinical Trial and Non-Clinical Trial
Excludes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, and B7451050.

Severity and Nature of Risk

There were no severe events of myopathy.

Table 51. Maximum Severity for Myopathies (including Rhabdomyolysis) – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)			Abrocitinib 200 mg QD (N = 1997)			All Abrocitinib (N = 3050)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Myopathies, including Rhabdomyolysis	1 (100.00)	0	0	1 (25.00)	3 (75.00)	0	2 (40.00)	3 (60.00)	0

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_sev Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.6

SVII.3.1.2.5.4. Risk Factors and Risk Groups

There were insufficient events to establish risk factors.

SVII.3.1.2.5.5. Preventability

No risk minimisation measures are proposed. Screening for creatine phosphokinase would not be predictive of subjects with events of myopathy. Patients ≥65 years-of-age should start on the abrocitinib 100 mg dose.

SVII.3.1.2.5.6. Impact on the Risk-Benefit Balance of the Product

The impact on the risk-benefit profile ranges from asymptomatic elevations in serum muscle enzymes to life-threatening disease associated with electrolyte imbalances, and acute kidney injury.

SVII.3.1.2.5.7. Public Health Impact

Public health impact will be limited given that screening for increased creatine phosphokinase is not warranted and the incidence of myopathy is low.

SVII.3.1.2.6. Important Potential Risk: Gastrointestinal Perforation

SVII.3.1.2.6.1. Potential Mechanisms

The potential mechanism is unknown.

SVII.3.1.2.6.2. Evidence Source and Strength of Evidence

Approved JAK inhibitors are being investigated for potential risk of GI perforation.

SVII.3.1.2.6.3. Characterisation of the Risk

Frequency

There were 7 subjects reporting events in the gastrointestinal perforation CMQ (5 in the abrocitinib 100 mg QD group and 2 in the abrocitinib 200 mg QD group). There was only one subject in the 100 mg QD group with a perforation (diverticulitis intestinal perforated/ perforated sigmoid diverticulitis) of moderate severity and resolved with sequelae.

Table 52. Proportion and Incidence Rates for Gastrointestinal Perforation – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)	Abrocitinib 200 mg QD (N = 1997)	All Abrocitinib (N = 3050)
Gastrointestinal Perforation (CMQ)			
Number of Subjects with Event, n (%)	5 (0.5)	2 (0.1)	7 (0.2)
Total Drug Exposure (PY)	2020.25	3270.78	5291.03
Incidence Rates (95% CI)	0.25 (0.08, 0.58)	0.06 (0.01, 0.22)	0.13 (0.05, 0.27)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.

Table 52. Proportion and Incidence Rates for Gastrointestinal Perforation – Long-Term Dose Controlled Pool 2022

n: Number of subjects with the event. IR (Incidence Rates): Number of subjects with events per 100 patient-years. CMQ: Customized MedDRA Query. CI: Confidence Interval
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 18APR2023
Source: Table RMP.LTDCP2022.5

Seriousness/Outcome

Interventional Clinical Trials:

Of the 7 subjects gastrointestinal perforation CMQ events, 2 were serious from the abrocitinib 100 mg QD group and 5 were non-serious (3 from the abrocitinib 100 mg QD group and 2 from the abrocitinib 200 mg QD group).

Table 53. Seriousness for Gastrointestinal Perforation – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)		Abrocitinib 200 mg QD (N = 1997)		All Abrocitinib (N = 3050)	
	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)
Gastrointestinal Perforation (CMQ)	2 (40.00)	3 (60.00)	0	2 (100.00)	2 (28.57)	5 (71.43)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
For the same adverse event of interest, the most serious case was selected in this summary.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.5

The events of gastrointestinal perforation were still present in 4 (2 in the abrocitinib 100 mg QD group and 2 in the abrocitinib 200 mg QD group) and resolved in 3 (abrocitinib 100 mg QD group).

Table 54. Latest Outcomes for Gastrointestinal Perforation – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)				Abrocitinib 200 mg QD (N = 1997)				All Abrocitinib (N = 3050)			
	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)
Gastrointestinal Perforation (CMQ)	2 (40.00)	3 (60.00)	0	0	2 (100.00)	0	0	0	4 (57.14)	3 (42.86)	0	0

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_out Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.7

Post-Marketing:

The global safety database was searched cumulatively through 07 March 2023 using MedDRA (version 25.1) search criteria: SMQ Gastrointestinal perforation (Narrow), PT Abscess bacterial, PT Abscess rupture, PT Appendicectomy, PT Appendicitis, PT Biliary abscess, PT Colitis, PT Diverticulitis, PT Diverticulum, PT Gallbladder abscess, PT Liver abscess, PT Pancreatic abscess, PT Pelvic abscess, PT Perihepatic abscess, PT Postoperative abscess, PT Pyloric abscess, PT Rectovaginal septum abscess, PT Splenic abscess, and PT Subdiaphragmatic abscess.

Table 55. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases - Gastrointestinal Perforation

MedDRA PT	Number of Events	Serious Events	H	F	R	RS	NR	U
Anal abscess	1	1	0	0	0	0	0	1
Total	1	1	0	0	0	0	0	1

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; H = Hospitalisation; F = Fatal; R = Resolved/Resolving; RS = Resolved with Sequelae; NR = Not Resolved; U = Unknown
MedDRA version 25.1
Cumulative through 07 March 2023
Post-Marketing Data inclusive of Clinical Trial and Non-Clinical Trial
Excludes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, and B7451050.

Severity and Nature of Risk

Seven (7) subjects reported the following gastrointestinal perforation CMQ events: peptic ulcer, duodenal ulcer haemorrhage and gastritis erosive (both events reported in 1 subject), erosive duodenitis, diverticulitis intestinal perforated (1 subject each), and gastric ulcer (2 subjects).

Table 56. Maximum Severity for Gastrointestinal Perforation – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)			Abrocitinib 200 mg QD (N = 1997)			All Abrocitinib (N = 3050)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Gastrointestinal Perforation (CMQ)	2 (40.00)	2 (40.00)	1 (20.00)	0	2 (100.00)	0	2 (28.57)	4 (57.14)	1 (14.29)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_sev Date of Generation: 09MAR2023
Source: Table RMP.LTDCP2022.6

SVII.3.1.2.6.4. Risk Factors and Risk Groups

There was an insufficient number of events to establish risk factors. The subject with the serious event of duodenal ulcer haemorrhage and non-serious event of gastritis erosive was 83 years old.

SVII.3.1.2.6.5. Preventability

Patients ≥65 years-of-age should use on the abrocitinib 100 mg dose.

SVII.3.1.2.6.6. Impact on the Risk-Benefit Balance of the Product

Gastrointestinal perforation can be associated with significant morbidity and mortality.

SVII.3.1.2.6.7. Public Health Impact

Gastrointestinal perforation, occurring mostly in the lower GI tract, has rarely been associated with the use of other JAK inhibitors and IL-6 antagonists used in rheumatoid arthritis.[186] In RA patients, the risk is increased in those that are older, have underlying diverticulitis, using corticosteroids, and/or chronically using NSAIDs. These risk factors are less frequently present in AD populations.

SVII.3.1.2.7. Important Potential Risk: Embryofoetal Toxicity Following Exposure In Utero

SVII.3.1.2.7.1. Potential Mechanisms

The potential mechanism is unknown.

SVII.3.1.2.7.2. Evidence Source and Strength of Evidence

Abrocitinib did not cause malformations in pregnant rats or rabbits. Approved therapies in the JAK inhibitor class are being investigated for potential risk of foetal malformation following exposure in utero.

SVII.3.1.2.7.3. Characterisation of the Risk

Frequency

No events were reported.

Seriousness/Outcome

Interventional Clinical Trials:

Not applicable.

Post-Marketing:

The global safety database was searched cumulatively through 07 March 2023 using MedDRA (version 25.1) search criteria: SMQ Termination of pregnancy and risk of abortion (Narrow) and SMQ Foetal disorders (Broad and Narrow).

No events have been identified in the global safety database for embryofoetal toxicity following exposure in utero.

Severity and Nature of Risk

Not applicable.

SVII.3.1.2.7.4. Risk Factors and Risk Groups

Risk of foetal malformation pertains only to women of childbearing potential who become pregnant while receiving abrocitinib and/or for at least 4 weeks after treatment.

SVII.3.1.2.7.5. Preventability

The use of abrocitinib is contraindicated in pregnancy. Women of reproductive potential should be advised to use effective contraception during treatment and for 1 month following treatment with abrocitinib.

SVII.3.1.2.7.6. Impact on the Risk-Benefit Balance of the Product

If embryofoetal toxicity occurs, the effects could range from minor (minimal clinical implications) or major (having medical or social implications).

SVII.3.1.2.7.7. Public Health Impact

While pregnancy is contraindicated, this risk is included because the AD population includes a significant number of women of childbearing potential.

SVII.3.1.2.8. Important Potential Risk: Impaired Bone Growth and Development if used Off-label in Paediatric Patients <12 Years-of-Age

SVII.3.1.2.8.1. Potential Mechanisms

The potential mechanism is unknown.

SVII.3.1.2.8.2. Evidence Source and Strength of Evidence

In studies to support the use of abrocitinib in children <12 years old, administration of abrocitinib to juvenile rats (comparable to a 3-month-old human) resulted in macroscopic and microscopic bone findings.

SVII.3.1.2.8.3. Characterisation of the Risk

Frequency

No events were reported.

Seriousness/Outcome

Not Applicable.

Interventional Clinical Trials:

No events were reported.

Post-Marketing:

The global safety database was searched cumulatively through 07 March 2023 using MedDRA (version 25.1) search criteria:

Events contained in the Off Label Use Condition for Fractures (in patients <12 years of age):

HLGT Bone and joint injuries (Primary Path)

- Excluding all PTs within HLT Bone and joint injuries NEC.
- Excluding the following individual PTs from other HLTs: Bone fissure, Cuboid syndrome, Fracture delayed union, Fracture infection, Fracture nonunion, Joint dislocation, Joint dislocation pathological, Metaphyseal corner fracture, Pathological fracture, Pseudarthrosis, Pseudofracture, Anterior labroligamentous periosteal sleeve avulsion lesion, Bankart lesion, Fracture of clavicle due to birth trauma, Radial head dislocation, Scapulothoracic dissociation, Dislocation of vertebra, Intervertebral disc injury, Spinal fusion fracture, Costal cartilage fracture, Costochondral separation, Dislocation of sternum.

HLGT | Fractures (Primary Path)

- Excluding all PTs within HLT Fracture complications

Events contained in the Off Label Use Condition for impaired growth (in patients <12 years of age):

- PT Growth disorder, PT Growth failure, PT Growth retardation, PT Body height below normal, PT Body height abnormal, and PT Body height decreased.

No events have been identified in the global safety database for impaired bone growth and development if used off-label in paediatric patients <12 years-of-age.

Severity and Nature of Risk

Not Applicable.

SVII.3.1.2.8.4. Risk Factors and Risk Groups

There were findings in nonclinical studies apparent in rats comparable to a human age of 3 months.

SVII.3.1.2.8.5. Preventability

Abrocitinib is not indicated for patients <12 years-of-age.

SVII.3.1.2.8.6. Impact on the Risk-Benefit Balance of the Product

The impact is unknown.

SVII.3.1.2.8.7. Public Health Impact

The public health impact should be limited as abrocitinib is not indicated in this population. However, the risk is included here as the AD population contains patients <12 years-of-age.

SVII.3.1.2.9. Important Potential Risk: Fractures

SVII.3.1.2.9.1 Potential Mechanisms

The potential mechanism is unknown.

SVII.3.1.2.9.2. Evidence Source and Strength of Evidence

Nonclinical data and data from other JAK inhibitors.

SVII.3.1.2.9.3. Characterisation of the Risk

Frequency

There were 60 subjects reporting fractures (26 in the abrocitinib 100 mg QD group and 34 in the abrocitinib 200 mg QD group).

Table 57. Proportion and Incidence Rates for Fractures – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)	Abrocitinib 200 mg QD (N = 1997)	All Abrocitinib (N = 3050)
Fractures (CMQ)			
Number of Subjects with Event, n (%)	26 (2.5)	34 (1.7)	60 (2.0)
Total Drug Exposure (PY)	1987.73	3232.68	5220.41
Incidence Rates (95% CI)	1.31 (0.85, 1.92)	1.05 (0.73, 1.47)	1.15 (0.88, 1.48)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. IR (Incidence Rates): Number of subjects with events per 100 patient-years. CMQ: Customized MedDRA Query. CI: Confidence Interval
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser_1 Date of Generation: 1
4APR2023
Source: Table RMP.LTDCP2022.8

Seriousness/Outcome

Interventional Clinical Trials:

Of the 60 subjects reporting fractures, 13 were serious (6 in the abrocitinib 100 mg QD group and 7 in the abrocitinib 200 mg QD group) and 47 were non-serious (20 in the abrocitinib 100 mg QD group and 27 in the abrocitinib 200 mg QD group).

Table 58. Seriousness for Fractures – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)		Abrocitinib 200 mg QD (N = 1997)		All Abrocitinib (N = 3050)	
	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)
Fractures (CMQ)	6 (23.08)	20 (76.92)	7 (20.59)	27 (79.41)	13 (21.67)	47 (78.33)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
For the same adverse event of interest, the most serious case was selected in this summary.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_ser_1 Date of Generation: 14APR2023
Source: Table RMP.LTDCP2022.8

Of the 60 subjects reporting fractures, 9 were still present (3 in the abrocitinib 100 mg QD group and 6 in the abrocitinib 200 mg QD group) and 51 were resolved (23 in the abrocitinib 100 mg QD group and 28 in the abrocitinib 200 mg QD group).

Table 59. Latest Outcomes for Fractures – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)				Abrocitinib 200 mg QD (N = 1997)				All Abrocitinib (N = 3050)			
	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)	Still Present n (%)	Resolved n (%)	Unknown n (%)	Death n (%)
Fractures (CMQ)	3 (11.54)	23 (88.46)	0	0	6 (17.65)	28 (82.35)	0	0	9 (15.00)	51 (85.00)	0	0

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_out_1 Date of Generation: 18APR2023
Source: Table RMP.LTDCP2022.10

Post-Marketing:

The global safety database was searched cumulatively through 07 March 2023 using MedDRA (version 25.1) search criteria:

- HLGT Bone and joint injuries (Primary path). Excluding all PTs within HLT Bone and joint injuries NEC and Excluding the following individual PTs from other HLTs: Bone fissure, Cuboid syndrome, Fracture delayed union, Fracture infection, Fracture nonunion, Joint dislocation, Joint dislocation pathological, Metaphyseal corner fracture, Pathological fracture, Pseudarthrosis, Pseudofracture, Anterior labroligamentous periosteal sleeve avulsion lesion, Bankart lesion, Fracture of clavicle due to birth trauma, Radial head dislocation, Scapulothoracic dissociation, Dislocation of vertebra, Intervertebral disc injury, Spinal fusion fracture, Costal cartilage fracture, Costochondral separation, and Dislocation of sternum.
- HLGT | Fractures (Primary Path). Excluding all PTs within HLT Fracture complications.

Table 60. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases - Fractures

MedDRA PT	Number of Events	Serious Events	H	F	R	RS	NR	U
Radius fracture	1	1	1	0	1	0	0	0
Wrist fracture	1	1	0	0	0	0	0	1
Total	2	2	1	0	1	0	0	1

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; H = Hospitalisation; F = Fatal; R = Resolved/Resolving; RS = Resolved with Sequelae; NR = Not Resolved; U = Unknown
MedDRA version 25.1
Cumulative through 07 March 2023
Post-Marketing Data inclusive of Clinical Trial and Non-Clinical Trial
Excludes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, and B7451050.

Severity and Nature of Risk

Sixty subjects reported fracture events. In most subjects (73.3%) fractures were of moderate severity.

Table 61. Maximum Severity for Fractures – Long-Term Dose Controlled Pool 2022

	Abrocitinib 100 mg QD (N = 1053)			Abrocitinib 200 mg QD (N = 1997)			All Abrocitinib (N = 3050)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Fractures (CMQ)	4 (15.38)	18 (69.23)	4 (15.38)	3 (8.82)	26 (76.47)	5 (14.71)	7 (11.67)	44 (73.33)	9 (15.00)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029, B7451036, B7451037, B7451050. Data cutoff date for B7451015: 05Sep2022.
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date for B7451015]; except for subjects with last dose date in B7451050 beyond data cut date for B7451015: the smaller of [last dose date in B7451050 + 28 days] and [death date]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. CMQ: Customized MedDRA Query.
Source Data: adae Date of ADAM Dataset Creation: 01MAR2023 Output File: ./ad_scs/LTDCP2022/sum_ae_sev_1 Date of Generation:
18APR2023
Source: Table RMP.LTDCP2022.9

SVII.3.1.2.9.4. Risk Factors and Risk Groups

There were an insufficient number of events for formal risk factor analysis. Several studies suggest that the risk of fracture is increased in patients with AD compared to those without, with findings of an association seen for both any fracture as well as for specific sites in some cohorts.[148,149]

Further, fracture risk appears to increase with increasing AD disease severity.[148,149,187]

SVII.3.1.2.9.5. Preventability

No risk minimisation measures are proposed.

SVII.3.1.2.9.6. Impact on the Risk-Benefit Balance of the Product

The impact of fractures can range from self-limited injury to impaired physical functioning. Based on the established benefits of abrocitinib as described in the prescribing information, the benefit risk balance for abrocitinib in treating patients with AD at the recommended doses remains favourable.

SVII.3.1.2.9.7. Public Health Impact

The rates of fracture in the abrocitinib development program were consistent with those in external cohorts of patients with AD, so the potential for public health impact is limited.

- In the LTDCP2022, the IR for fractures in patient 18 - <65 years was 1.14/100 PY (95% CI: 0.84, 1.53) and in patients ≥65 years was 1.74/ 100 PY (95% CI: 0.47, 4.45).
- In a cohort of subjects with AD in the Danish National Registry, the IR for fractures in patient 18 - <65 years was 1.39/100 PY (95% CI: 1.32-1.46) and in patients ≥65 years was 3.42/100 PY (95% CI: 3.06-3.84).

SVII.3.2. Presentation of the Missing Information

Table 62. Missing Information: Long-Term Safety[a]

Evidence source and strength of evidence	There is limited long term safety in abrocitinib clinical studies.
Anticipated risk/consequence of the missing information	The incidence of longer latency events such as malignancy or cardiovascular disease may not be fully captured in the clinical development program.

a. For ≥18 years of age.

Table 63. Missing Information: Long-Term Safety in Adolescents[a]

Evidence source and strength of evidence	There is limited long term safety in abrocitinib clinical studies for adolescents.
Anticipated risk/consequence of the missing information	There is limited long term safety in abrocitinib clinical studies for adolescents.

a. Adolescent defined as ≥12 years of age and <18 years of age.

Module SVIII. Summary of the Safety Concerns

Table 64. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Venous thromboembolism
	Herpes zoster
Important potential risks	Serious and opportunistic infections
	Malignancy (excluding NMSC)
	Non-melanoma skin cancer (NMSC)
	MACE
	Myopathies (including rhabdomyolysis)
	Gastrointestinal perforation
	Embryofoetal toxicity following exposure in utero
	Impaired bone growth and development if used off-label in paediatric patients <12 years-of-age
	Fractures
Missing information	Long-term safety[a]
	Long-term safety in adolescents[b]

a. For ≥18 years of age.
b. Adolescent defined as ≥12 years of age and <18 years of age.

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns:**
- None.
- **Other forms of routine pharmacovigilance activities for safety concerns:**
- None.

III.2. Additional Pharmacovigilance Activities

Study Summary: B7451084

Study short name and title:

B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib Among Patients with Atopic Dermatitis in the EU (See RMP Part VII Annex 3 for protocol)

Rationale and study objectives:

Based on data from abrocitinib clinical program, it is of MAH's opinion that it is important to monitor the real-world safety of abrocitinib following its authorization in the EU. An active safety surveillance study will assess safety endpoints of interest associated with abrocitinib in the post-approval setting.

The objective of the study is to estimate the incidence rates of safety endpoints of interest among patients with AD receiving abrocitinib and patients with AD receiving biologic and/or non-biologic (non- Janus Kinase inhibitor [non-JAKi]) chronic systemic treatments for AD (comparator treatments) in a real-world setting.

The following are the safety endpoints of interest:

- VTE,
- Herpes zoster,
- Serious infections and opportunistic infections,
- Rhabdomyolysis,
- Gastrointestinal perforation,
- MACE,
- Fractures,
- Malignancy (excluding NMSC),
- NMSC,

- All-cause mortality, and
- Height as a measure of impaired bone growth in adolescents (Denmark only).

The endpoints of interest, listed above, are based on current understanding of the important identified and potential risks with abrocitinib. However, other endpoints may be added/updated as understanding of the safety profile of abrocitinib evolves and feasibility of their assessment permits.

Study design:

This will be a longitudinal, register-based, non-interventional post-authorisation safety cohort study using routinely collected (secondary) population-based data. The length of the study period will be 10 years from the record of first abrocitinib use in the data source. The proposed follow-up duration will allow sufficient time to assess long-term use of abrocitinib and endpoints of interest with long latency such as malignancy.

Study population:

The study population will comprise of patients with AD receiving abrocitinib following approval in the EU.

To contextualize the results, the study will also include patients with AD receiving other systemic treatments, identified as an appropriate comparator group, described in the study protocol.

Data source:

This study will utilize routinely collected electronic healthcare data from national or regional population-based electronic healthcare registers in Denmark and Sweden, and administrative healthcare database in France. A feasibility assessment was conducted to identify appropriate data source(s) collecting data from routine clinical practices in EU. The proposed data sources are selected based on the availability of required data elements and projected sample size/number of patients with abrocitinib exposure post-approval and comparator patients needed to address the study objectives. The large population size of these databases is expected to facilitate assessment of abrocitinib exposures and rare safety endpoints of interest in a real-world setting.

Data Analysis:

This will be a descriptive study. Summary baseline variables and incidence rates of safety endpoints of interest will be estimated for patients with AD exposed to abrocitinib and patients with AD exposed comparator treatments. Stratified analysis will be performed to estimate the incidence rates across various demographic attributes (e.g., age group, sex), clinical characteristics (e.g., comorbid conditions, prior systemic medications for AD) and dose of abrocitinib, depending on the availability of relevant data and sample size. Sub-group analysis will be conducted in patient populations such as adolescents. An exploratory analysis comparing IRs of the safety events of interest among patients treated with

abrocitinib compared with patients treated with comparator treatments will also be conducted, depending on study size. For the endpoint of serious and opportunistic infection, individual types of infections such as herpes simplex and eczema herpeticum, and pneumonia will be reported. Further, malignancy subtypes will be reported as available in the data sources.

Milestones:

Draft protocol submission: Within 6 months of abrocitinib approval in the EU (July 2022)

Start of data collection: 31 Dec 2024

End of data collection: 15 May 2034

Progress report 1: 15 November 2025

Progress report 2: 15 November 2027

Interim report 1: 15 November 2029

Interim report 2: 15 November 2031

Final study report: 15 November 2034

Proposed Study Summary: B7451085

Study short name and title:

B7451085: A Drug Utilization Study to Evaluate the Effectiveness of Risk Minimisation Measures for Abrocitinib in the EU using Electronic Healthcare Data (See RMP Part VII Annex 3 for protocol)

Rationale and study objectives:

To mitigate the risks associated with abrocitinib, required routine RMMs including the SmPC and package leaflet are being employed. In order to minimise important risks with the use of abrocitinib, the MAH has also implemented additional RMMs: an educational program intended to enhance the communication of the risk and risk minimisation practices to HCPs and patients. The program includes a Prescriber Brochure, one-time DHPC and a Patient Card.

The MAH will evaluate the effectiveness of both routine and additional RMM being implemented for abrocitinib. The study is designated as a Post-Authorisation Safety Study (PASS).

Does routinely collected data in the EU indicate adherence to the recommendations for the use of abrocitinib described in the SmPC, prescriber brochure, and DHPC?

The study objectives are to evaluate, to the extent measurable in the available routinely collected data, indicators of HCP's adherence to the risk minimisation measures in accordance with the abrocitinib SmPC, prescriber brochure, and DHPC specifically:

- Indicators of adherence to performing laboratory tests of complete blood count (CBC), lipid panel, hepatitis B/C and tuberculosis (TB) screening prior to initiation of abrocitinib treatment,
- Indicators of adherence to performing laboratory tests of CBC and lipid panel at Week 4 (± 2 weeks) from initiation of abrocitinib treatment,
- Indicators of adherence to consideration of risk factors for VTE, MACE, malignancy excluding NSMC, NMSC and serious infection prior to treatment with abrocitinib,
- Indicators of adherence to avoid live attenuated vaccine immediately prior to and during treatment with abrocitinib,
- Indicators of adherence to contraindications for use during pregnancy,
- Indicators of adherence to contraindications for use among patients with severe hepatic impairment,
- Indicators of adherence to no use in patients <12 years-of-age, and
- Indicators of adherence to recommended posology (estimated average daily dose).

Study design:

This will be a cross-sectional analysis of secondary data from healthcare databases in Denmark, France, Sweden, Spain and Hungary.

Study population:

The study population will comprise of all patients with a dispensing of abrocitinib as recorded in routinely collected electronic secondary population data.

Milestones:

Draft protocol submission: Within 6 months of abrocitinib approval in the EU (July 2022)

Feasibility assessment to evaluate changes in utilization patterns per aRMM was submitted to the EMA on 26 March 2023.

Start of data collection: 31 December 2024

Interim report 1: 15 November 2025

Interim report 2: 15 May 2027

End of data collection: 15 May 2028

Final study report: 15 November 2028

Proposed Study Summary: B7451015 Long-term Extension Study

Study B7451015 will continue through December 2024. The population will include currently enrolled subjects as well as subjects from ongoing abrocitinib studies. (See RMP Part VII Annex 3 for protocol)

Study Short Name and Title:

A Phase 3 Multi-Center, Long-Term Extension Study Investigating The Efficacy and Safety of Abrocitinib, With or Without Topical Medications, Administered to Subjects Aged 12 Years And Older With Moderate to Severe Atopic Dermatitis

Rationale and Study Objectives:

The objective of this study is to assess the long-term safety of 100 mg and 200 mg once daily of abrocitinib with or without topical treatments in adult and adolescent subjects who previously participated in qualifying abrocitinib AD trials.

Study Design:

This is a multi-center, long-term extension study to evaluate the long-term safety and efficacy of abrocitinib administered to subjects aged 12 years and older with moderate to severe AD. Subjects must have completed a qualifying Parent study and remain eligible to receive abrocitinib or have completed the full rescue treatment/open label run in period of B7451014 and failed to meet the protocol defined response criteria at Week 12. Based on treatment assignment, abrocitinib will be administered orally at doses of 200 mg or 100 mg QD.

Study Population:

In general, patients in this study must have completed a qualifying parent study and continued to meet safety related inclusion and exclusion criteria outlined in the parent study.

Data analysis:

Safety will be assessed by the spontaneous reporting of AEs, physical examinations and clinical laboratory results in all subjects who receive at least one dose of the investigational product. This study will continue to describe safety data to include:

- VTE,

- Serious and opportunistic infections,
- Herpes zoster,
- Malignancy (excluding NMSC),
- NMSC,
- Fractures, including in adolescent patients,
- Myopathy (including rhabdomyolysis),
- Gastrointestinal perforation,
- MACE,
- All-cause mortality,
- Height in adolescents,
- Development in adolescents, and
- Pregnancy outcomes.

Milestones:

End of data collection: December 2024 for the main study, subjects entering the study as adolescents will be followed until they reach age 18 or December 2024, whichever is later

Final report: July 2026

Study B7451015: Adolescent Imaging Substudy

Study Design:

This is a sub-study of the main B7451015 long-term extension study. The subject should then have the first MRI performed promptly following the screening/enrollment visit and approximately within 1 month following the visit. Subsequent MRI imaging will be performed annually.

Rationale and Substudy Objectives:

The objective of this substudy is to evaluate the potential effects of abrocitinib on bone via knee MRI in adolescent subjects 12 to <18 years-of-age who have received abrocitinib in the ongoing B7451015 long-term extension study. While there are no subjects <12 years-of-age in this study, the results will provide additional information pertinent to understanding of any potential effects on bone growth and development.

Study Population:

Subjects enrolled in the abrocitinib development program as adolescents (≥12 years) who are currently enrolled in the B7451015 study will have the option of enrolling in this sub-study.

Data Analysis:

Abnormal developmental bone findings related to study drug as adjudicated by the safety adjudication committee will be summarized by treatment group using frequency and proportions along with 95% confidence intervals for the proportions.

Milestones:

The first interim report was submitted with the Adolescent Type II Variation in Q2 2023. The final report will be submitted when all subjects have completed the substudy.

Proposed Study Summary: B7451120

Study short name and title:

B7451120: A Prospective Active Surveillance Study to Monitor Growth, Development, and Maturation Among Adolescents with Atopic Dermatitis Exposed to Abrocitinib (See RMP Part VII Annex 3 for protocol synopsis).

Rationale and study objectives:

As part of the abrocitinib pharmacovigilance plan, a long-term follow-up study is being proposed to actively monitor growth, development (including bone development) and maturation (including pubertal maturation) in adolescents aged 12-17 years in the post-approval setting.

The objectives are to:

- Describe growth, development (including bone development), and maturation (including pubertal maturation) metrics among adolescent patients with atopic dermatitis (AD) treated with abrocitinib and, separately, among adolescent patients with AD unexposed to abrocitinib and receiving systemic treatments;
- Describe the risk of fractures stratified by abrocitinib dose (100 mg and 200 mg).

Additionally, an exploratory objective is to compare adolescent patients treated with abrocitinib with adolescent patients unexposed to abrocitinib and treated with comparators for select outcomes, depending on the sample size.

Study design:

This will be a prospective observational cohort study of adolescent patients with AD exposed (and unexposed) to abrocitinib.

Study population:

The study population will comprise adolescent patients aged 12-17 who have been diagnosed with AD, and are receiving abrocitinib following approval in the EU. To contextualize the results, the study will also include adolescent patients with AD unexposed to abrocitinib and

receiving systemic treatments identified as an appropriate comparator group (i.e., comparable in terms of baseline risk).

The full protocol will describe the proposed data source (which will include patients from the EU), following an evaluation of existing and developing registries with respect to the availability of proposed study endpoints and the ability to provide the required adolescent sample size.

Data Analysis:

This will be a descriptive study, and baseline characteristics and measures assessing growth, development (including bone development), and maturation (including pubertal maturation) metrics will be descriptively presented for abrocitinib exposed and abrocitinib unexposed patients with AD receiving appropriate systemic treatment. A descriptive analysis of the risk of fractures stratified by abrocitinib dose (100 mg and 200 mg) will be conducted. Stratified analysis will be performed to assess study endpoints across various demographic attributes (e.g., age group, sex), and clinical characteristics (e.g., comorbid conditions, prior systemic medications for AD), depending on the availability of relevant data and sample size.

An exploratory analysis comparing adolescent patients treated with abrocitinib with adolescent patients unexposed to abrocitinib and treated with comparator therapies will also be conducted for select outcomes depending on the sample size.

Milestones:

The draft protocol will be submitted to the EMA within 6 months of abrocitinib adolescent indication approval in the EU. The final study report will be submitted to the EMA within 6 months from the end of data collection.

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

Table 65. On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				

Table 65. On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib Among Patients with Atopic Dermatitis in the EU Planned Category 3	The objective of the study is to estimate the incidence rates of safety events of interest among patients with AD receiving abrocitinib and patients with AD receiving biologic and/or non-biologic (non-JAKi) chronic systemic treatments for AD (herein referred to as "comparator treatments")in a real-world setting.	Safety concerns addressed include: • VTE • Herpes zoster, • Serious and opportunistic infection, • Myopathies (including rhabdomyolysis), • Gastrointestinal perforation, • Malignancy (excluding NMSC), • NMSC, • MACE, • Fractures, • Missing information: Long-term safety, and • Missing information: Long-term safety in adolescents	Draft protocol submission Start of data collection End of data collection Progress report 1 Progress report 2 Interim report 1 Interim report 2 Final report	Within 6 months of abrocitinib approval in the EU (July 2022) 31 Dec 2024 15 May 2034 15 November 2025 15 November 2027 15 November 2029 15 November 2031 15 November 2034
B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in the EU using Electronic Healthcare Data Planned Category 3	The study objectives are to evaluate to the extent measurable in the available routinely collected data, indicators of HCP's adherence to the risk minimisation measures in accordance with the abrocitinib SmPC, prescriber brochure, and DHPC specifically:	Safety concerns addressed include: • VTE • Herpes zoster, • Serious and opportunistic infections, • MACE, • Malignancy (excluding NMSC), • NMSC, • Impaired bone growth and development if used off-label in	Draft protocol submission Feasibility assessment to evaluate changes in utilization patterns	Within 6 months of abrocitinib approval in the EU (July 2022) Submitted to the EMA on 26 March 2023

Table 65. On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	• Indicators of adherence to performing laboratory tests of CBC, lipid panel, hepatitis B/C and TB screening prior to initiation of abrocitinib treatment, • Indicators of adherence to performing laboratory tests of CBC and lipid panel at Week 4 (± 2 weeks) from initiation of abrocitinib treatment, • Indicators of adherence to consideration of risk factors for VTE, MACE, malignancy excluding NSMC, NMSC and serious infection prior to treatment with abrocitinib, • Indicators of adherence to avoid live attenuated vaccine immediately prior to and during treatment with abrocitinib, • Indicators of adherence to contraindications for use during pregnancy, • Indicators of adherence to contraindications for use among	paediatric patients <12 years-of-age, and • Embryofoetal toxicity following exposure in utero.	per aRMM. Start of data collection End of data collection Interim Report 1 Interim Report 2 Final report	 31 December 2024 15 May 2028 15 November 2025 15 May 2027 15 November 2028

Table 65. On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	patients with severe hepatic impairment, • Indicators of adherence to no use in patients aged <12 years-of-age, and • Indicators of adherence to recommended posology (estimated average daily dose).			
B7451015: Long-term extension study Ongoing	• To assess the long-term safety and long- term safety in adolescents of 100 mg and 200 mg once daily of abrocitinib with or without topical treatments in adult and adolescent subjects who previously participated in qualifying abrocitinib AD trials.	This study will continue to describe safety data to include: • VTE, • Serious and opportunistic infections, • Herpes zoster, • Malignancy (excluding NMSC), • NMSC, • Fractures, • Myopathies (including rhabdomyolysis), • Gastrointestinal perforation, • MACE, and Embryofoetal toxicity following exposure in utero. • Missing information: Long-term safety, and • Missing information: Long-term safety in adolescents	Study Report	July 2026
B7451015: Adolescent Imaging Substudy	• To evaluate if abrocitinib has any clinically meaningful effects on bone	Safety concern addressed include: • Missing information: Long-term safety in adolescents	Draft protocol submission Interim Report	Within 6 months of abrocitinib approval in the EU (July 2022)

Table 65. On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Ongoing	growth and development • Primary endpoint • To detect the proportion of abnormal bone findings in knee MRI in adolescent subjects exposed to abrocitinib 100 mg and 200 mg		Final Report	December 2023 July 2026
B7451120: A Prospective Active Surveillance Study to Monitor Growth, Development, and Maturation Among Adolescents with Atopic Dermatitis Exposed to Abrocitinib Planned Category 3	The objectives are to: • Describe growth, development (including bone development), and maturation (including pubertal maturation) metrics among adolescent patients with atopic dermatitis (AD) treated with abrocitinib and, separately, among adolescent patients with AD unexposed to abrocitinib and receiving systemic treatments; and • Describe the risk of fractures stratified by abrocitinib dose (100 mg and 200 mg).	Safety concerns addressed include: • Fractures and • Missing Information: Long-term safety in adolescents	Draft protocol submission to EMA Interim report submission to EMA Final study report to EMA	Within 6 months of abrocitinib adolescent indication approval in the EU Year 4 of the study Within 6 months from the end of data collection

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Table 66. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Important Identified Risks	
Venous thromboembolism	**Routine risk communication** SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Package Leaflet (PL) Sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 supports use of the lowest effective dose. SmPC Section 4.4 recommends that abrocitinib should be used with caution in patients with known risk factors for VTE, regardless of dose. Patients should be re-evaluated periodically during abrocitinib treatment to assess for changes in VTE risk.
Herpes zoster	**Routine risk communication** SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 supports use of the lowest effective dose. SmPC Section 4.3 includes a contraindication for active serious systemic infections. SmPC Section 4.4 includes a list of considerations related to infection that should be considered prior to initiating abrocitinib. In addition, risk factors for herpes zoster infection are described. It also states that if a patient develops herpes zoster, temporary interruption of abrocitinib should be considered until the episode resolves. Prior to initiating abrocitinib, it is recommended that patients be brought up to date with all immunizations, including prophylactic herpes zoster vaccinations, in agreement with current immunization guidelines. ALC should be assessed prior to initiating and 4 weeks after initiating abrocitinib.
Important Potential Risks	
Serious and opportunistic infections	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects

Table 66. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	PL Sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 supports use of the lowest effective dose. SmPC Section 4.3 includes a contraindication for active serious systemic infections. SmPC Section 4.4 recommends that in patients 65 years-of-age and older abrocitinib should only be used if no suitable treatment alternatives are available and states that patients should be monitored for the development of infections and appropriate antimicrobial therapy should be initiated if a new infection develops. If the patient does not respond to standard therapy, treatment with abrocitinib should be interrupted. Patients should be screened for TB and viral hepatitis before starting therapy. Use of live, attenuated vaccines should be avoided during or immediately prior to abrocitinib therapy. Prior to initiating abrocitinib, it is recommended that patients be brought up to date with all immunizations, including prophylactic herpes zoster vaccinations, in agreement with current immunization guidelines.
Malignancy (excluding NMSC)	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 Posology and method of administration supports use of the lowest effective dose. SmPC Section 4.4 states that, like other JAK inhibitors, in patients 65 years-of-age and older, patients who are current or past long-time smokers, or with current malignancy or history of malignancy (except successfully treated basal cell carcinoma), abrocitinib should be used if no suitable treatment alternatives are available.
Non-melanoma skin cancer	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 Posology and method of administration supports use of the lowest effective dose. SmPC Section 4.4 states that, like other JAK inhibitors, in patients 65 years-of-age and older, patients who are current or past long-time smokers, or with current malignancy or history of malignancy (except successfully treated basal cell carcinoma), abrocitinib should be used if no suitable treatment alternatives are available.

Table 66. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
MACE	**Routine risk communication** SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use (lipid monitoring, including in the setting of a high burden of cardiovascular risk) SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 states that, like other JAK inhibitors, in patients 65 years-of-age and older, patients who are current or past long-time smokers, or with atherosclerotic cardiovascular disease abrocitinib should be used if no suitable treatment alternatives are available Patients should be re-evaluated periodically during abrocitinib treatment to assess for changes in risk factors for MACE.
Myopathies (including rhabdomyolysis)	**Routine risk communication** SmPC Section 4.2 Posology and method of administration SmPC Section 4.8 Undesirable effects (Blood creatine phosphokinase increase) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None
Gastrointestinal perforation	**Routine risk communication** SmPC Section 4.2 Posology and method of administration **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 recommends a dose of 100 mg once daily for patients ≥ 65 years-of-age.
Embryofoetal toxicity following exposure in utero	**Routine risk communication** SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, Pregnancy and Lactation **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.3 includes a contraindication for pregnancy. SmPC Section 4.6 states that abrocitinib is contraindicated during pregnancy.
Impaired bone growth and development if used off-label in paediatric patients <12 years-of-age	**Routine risk communication** SmPC Section 4.2 Posology and method of administration PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 states that the safety and efficacy of children under 12 years-of-age have not yet been established. No clinical data are available.

Table 66. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Fractures	**Routine risk communication** SmPC Section 5.3 Preclinical safety data SmPC Section 4.2 Posology and method of administration **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 Posology and method of administration (starting dose of 100 mg once a day is recommended in adolescents weighing <59 kg)
Missing Information	
Long-term safety	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None
Long-term safety in adolescents	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None

V.2. Additional Risk Minimisation Measures

Patient Card

Objectives:

The objective of the proposed aRMM is to provide an appropriate tool designed to enhance the awareness and knowledge of patients about the following safety concerns and to ensure the optimal use of abrocitinib.

- Venous thromboembolism
- Infections (including Herpes zoster and Serious and opportunistic infections)
- MACE
- Malignancy
- Embryofoetal toxicity following exposure in utero

Rationale for the additional risk minimisation activity:

Additional awareness and knowledge of patients about the risks will help to mitigate these risks.

Target audience and planned distribution path:

The target audience is patients via their prescribing physicians. The communication plan will vary according to local legal and regulatory requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:

A drug utilization study (B7451085) is planned to evaluate the effectiveness of RMMs for abrocitinib in EU using electronic healthcare data. The criteria for success will include indicators of adherence to the recommended risk minimisation measures in accordance with the abrocitinib SmPC, prescriber brochure, and DHPC. The relevant details will be included in the full PASS protocol.

Prescriber Brochure

Objectives:

The objective of the proposed aRMM is to provide an appropriate tool designed to enhance the awareness and knowledge of prescribers and patients about the following safety concerns and to ensure the optimal use of abrocitinib.

To accomplish the objective, a Prescriber Brochure was developed to inform prescribers about the risks and provide recommendations on how to mitigate the risk through appropriate monitoring and management.

- Venous thromboembolism
- Infections (including Herpes zoster and Serious and opportunistic infections)
- Malignancy (excluding NMSC)
- NMSC
- MACE
- Embryofoetal toxicity following exposure in utero

Rationale for the additional risk minimisation activity:

Additional awareness and knowledge of physicians about the risks help to mitigate these risks.

Target audience and planned distribution path:

The target audience is prescribing physicians. The communication plan will vary according to local legal and regulatory requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:

A drug utilization study (B7451085) is planned to evaluate the effectiveness of RMMs for abrocitinib in EU using electronic healthcare data. The criteria for success will include

indicators of adherence to the recommended risk minimisation measures in accordance with the abrocitinib SmPC, prescriber brochure, and DHPC. The relevant details will be included in the full PASS protocol.

Direct Healthcare Professional Communication

Objectives:

Communicate changes to the product information as a result of the Article 20 procedure

Provide rationale for the additional risk minimisation activity:

Increase awareness and knowledge of physicians about the risks and measures to mitigate these risks.

Target audience and planned distribution path:

The target audience is prescribing physicians. The communication plan will vary according to local legal and regulatory requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:

A drug utilization study (B7451085) is planned to evaluate the effectiveness of RMMs for abrocitinib in EU using electronic healthcare data. The criteria for success will include indicators of adherence to the recommended risk minimisation measures in accordance with the abrocitinib SmPC, prescriber brochure, and DHPC. The relevant details will be included in the full PASS protocol.

V.3. Summary of Risk Minimisation Measures

Table 67. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Venous thromboembolism	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: Prescriber Brochure Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for

Table 67. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Direct Healthcare Professional Communication	Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study
Herpes zoster	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: Prescriber Brochure Patient card Direct Healthcare Professional Communication	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study
Important Potential Risks		
Serious and opportunistic infections	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: Prescriber Brochure Patient Card Direct Healthcare Professional Communication	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study
Malignancy (excluding NMSC)	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Table 67. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 Additional risk minimisation measures: Prescriber Brochure Patient Card Direct Healthcare Professional Communication	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study
Non-melanoma skin cancer	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 Additional risk minimisation measures: Prescriber Brochure Patient Card Direct Healthcare Professional Communication	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study
MACE	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use (lipid monitoring, including in the setting of a high burden of cardiovascular risk) SmPC Section 4.8 Undesirable effects PL Sections: Section 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for

Table 67. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: Prescriber Brochure Patient Card Direct Healthcare Professional Communication	Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study
Myopathies (including rhabdomyolysis)	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.8 Undesirable effects (Blood creatine phosphokinase increase) Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study
Gastrointestinal perforation	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study
Embryofoetal toxicity following exposure in utero	Routine risk minimisation measures: SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, Pregnancy and Lactation Additional risk minimisation measures: Prescriber Brochure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data

Table 67. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Patient Card	B7451015: Long-term Extension Study
Impaired bone growth and development if used off-label in paediatric patients <12 years-of-age	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration PL Section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data
Fractures	Routine risk minimisation measures: SmPC Section 5.3 Preclinical safety data SmPC Section 4.2 Posology and method of administration (starting dose of 100 mg once a day is recommended in adolescents weighing <59 kg) Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study B7451120: A Prospective Active Surveillance Study to Monitor Growth, Development, and Maturation Among Adolescents with Atopic Dermatitis Exposed to Abrocitinib
Missing Information		
Long-term safety[a]	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU

Table 67. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		B7451015: Long-term Extension Study
Long-term safety in adolescents[b]	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study B7451015: Adolescent Imaging Study B7451120: A Prospective Active Surveillance Study to Monitor Growth, Development, and Maturation Among Adolescents with Atopic Dermatitis Exposed to Abrocitinib

a. For ≥18 years of age.
b. Adolescent defined as ≥12 years of age and <18 years of age.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Cibinqo (abrocitinib)

This is a summary of the risk management plan (RMP) for Cibinqo. The RMP details important risks of Cibinqo, how these risks can be minimised, and how more information will be obtained about Cibinqo's risks and uncertainties (missing information).

Cibinqo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Cibinqo should be used.

This summary of the RMP for Cibinqo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Cibinqo's RMP.

I. The Medicine and What It Is Used For

Cibinqo is indicated for the treatment of moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy (see SmPC for the full indication). It contains abrocitinib as the active substance and it is given by oral route of administration.

Further information about the evaluation of Cibinqo's benefits can be found in Cibinqo's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Cibinqo, together with measures to minimise such risks and the proposed studies for learning more about Cibinqo 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Cibinqo, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse events will be collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Cibinqo is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Cibinqo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Cibinqo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

Table 68. List of Important Risks and Missing Information

Important identified risks	Venous thromboembolism
	Herpes zoster
Important potential risks	Serious and opportunistic infections
	Malignancy (excluding NMSC)
	Non-melanoma skin cancer
	MACE
	Myopathies (including rhabdomyolysis)
	Gastrointestinal perforation
	Embryofoetal toxicity following exposure in utero
	Impaired bone growth and development if used off-label in paediatric patients <12 years-of-age
	Fractures
Missing information	Long-term safety[a]
	Long-term safety in adolescents[b]

a. For ≥18 years of age.
b. Adolescent defined as ≥12 years of age and <18 years of age.

II.B Summary of Important Risks

Table 69. Important Identified Risk - Venous Thromboembolism

Evidence for linking the risk to the medicine	Abrocitinib and other approved JAK inhibitors clinical trial data.
Risk factors and risk groups	There was an insufficient number of events in the abrocitinib development program for formal risk factor or subgroup analysis. Risk factors that should be considered in prescribing include previous VTE, patients undergoing major surgery, immobilization, myocardial infarction (within the previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, and malignancy. Age, obesity (BMI ≥30), diabetes, hypertension, and smoking status should also be considered.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: Prescriber Brochure Patient Card Direct Healthcare Professional Communication
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 70. Important Identified Risk - Herpes zoster

Evidence for linking the risk to the medicine	Clinical study data with abrocitinib and understanding of JAK mechanisms based on data from the JAK class of therapies.
Risk factors and risk groups	For all herpes zoster events (regardless of adjudication as an opportunistic), age ≥65 years, a dose of 200 mg, a history of herpes zoster, severe AD at baseline, and an ALC $<0.5\times10^3/mm^3$ were identified as risk factors.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: Prescriber Brochure Patient Card Direct Healthcare Professional Communication
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 71. Important Potential Risk – Serious and Opportunistic Infections

Evidence for linking the risk to the medicine	Abrocitinib and other approved JAK inhibitors clinical trial data.
Risk factors and risk groups	Elderly age and diabetes are general risk factors for serious infections.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: Prescriber Brochure Patient Card Direct Healthcare Professional Communication

Table 71. Important Potential Risk – Serious and Opportunistic Infections

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 72. Important Potential Risk – Malignancy (excluding NMSC)

Evidence for linking the risk to the medicine	Abrocitinib and other approved JAK inhibitors clinical trial data.
Risk factors and risk groups	There was an insufficient number of events in the abrocitinib development program for risk factor or subgroup analysis. Like with other JAK inhibitors, age ≥65 years, current or past smoking history, and a history of malignancy (excluding basal cell carcinoma) are risk factors for malignancy.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 Additional risk minimisation measures: Prescriber Brochure Patient Card Direct Healthcare Professional Communication
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 73. Important Potential Risk – Non-Melanoma Skin Cancer

Evidence for linking the risk to the medicine	Abrocitinib and other approved JAK inhibitors clinical trial data.
Risk factors and risk groups	There was an insufficient number of events in the abrocitinib development program for risk factor or subgroup analysis. Like with other JAK inhibitors, age ≥65 years, current or past smoking history, and a history of malignancy (excluding basal cell carcinoma) are risk factors for malignancy.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 Additional risk minimisation measures: Prescriber Brochure Patient Card Direct Healthcare Professional Communication
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 74. Important Potential Risk – MACE

Evidence for linking the risk to the medicine	Clinical study data and data other approved JAK inhibitors.
Risk factors and risk groups	There was an insufficient number of events in the abrocitinib development program for formal risk factor or subgroup analysis. Like with other JAK inhibitors, age ≥65 years, current or past smoking history, and a history of atherosclerotic disease are risk factors for MACE.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 and 4 Additional risk minimisation measures:

Table 74. Important Potential Risk – MACE

	Prescriber Brochure Patient Care Direct Healthcare Professional Communication
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 75. Important Potential Risk – Myopathies (including Rhabdomyolysis)

Evidence for linking the risk to the medicine	Clinical trial data and based on the data from the JAK class. Approved JAK inhibitors are being investigated for potential risk of myopathy (including rhabdomyolysis).
Risk factors and risk groups	There were insufficient events to establish risk factors.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.8 Undesirable effects (Blood creatine phosphokinase increase) Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 76. Important Potential Risk – Gastrointestinal Perforation

Evidence for linking the risk to the medicine	Approved JAK inhibitors are being investigated for potential risk of GI perforation.
Risk factors and risk groups	There was an insufficient number of events to establish risk factors. The subject with the serious event of duodenal ulcer haemorrhage and non-serious event of gastritis erosive was 83 years old.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 77. Important Potential Risk – Embryofoetal Toxicity Following Exposure in Utero

Evidence for linking the risk to the medicine	Abrocitinib did not cause skeletal malformations in pregnant rats or rabbits. Approved therapies in the JAK inhibitor class are being investigated for potential risk of foetal variations or malformation following exposure in utero.
Risk factors and risk groups	Risk of foetal malformation pertains only to women of childbearing potential who become pregnant while receiving abrocitinib or and for at least 4 weeks after treatment.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, Pregnancy and Lactation Additional risk minimisation measures: Prescriber Brochure Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 78. Important Potential Risk – Impaired Bone Growth and Development if Used Off-label in Paediatric Patients <12 Years-of-Age

Evidence for linking the risk to the medicine	Administration of abrocitinib to juvenile rats beginning on postnatal Day 21 and older (comparable to a 2-year-old human and older) was not associated with microscopic or macroscopic bone findings. Administration of abrocitinib to juvenile rats beginning on postnatal Day 10 (comparable to a 3-month-old human infant) resulted in adverse microscopic and macroscopic bone findings, including malrotated paws, fractures, and/or femoral head abnormalities.
Risk factors and risk groups	There is a potential risk for patients <12 years-of-age.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 79. Important Potential Risk – Fractures

Evidence for linking the risk to the medicine	Nonclinical data and data from other JAK inhibitors.
Risk factors and risk groups	There was an insufficient number of events to establish risk factors.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.3 Preclinical safety data SmPC Section 4.2 Posology and method of administration (starting dose of 100 mg once a day is recommended in adolescents weighing <59 kg) Additional risk minimisation measures: None

Table 79. Important Potential Risk – Fractures

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study B7451120: A Prospective Active Surveillance Study to Monitor Growth, Development, and Maturation Among Adolescents with Atopic Dermatitis Exposed to Abrocitinib See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 80. Missing Information – Long-Term Safety[a]

Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

a. For ≥18 years of age.

Table 81. Missing Information – Long-Term Safety in Adolescents[a]

Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study B7451015: Adolescent Imaging Substudy

Table 81. Missing Information – Long-Term Safety in Adolescents[a]

	B7451120: A Prospective Active Surveillance Study to Monitor Growth, Development, and Maturation Among Adolescents with Atopic Dermatitis Exposed to Abrocitinib See Section II.C of this summary for an overview of the post-authorisation development plan.

a. Adolescent defined as ≥12 years of age and <18 years of age.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies, which are conditions of the marketing authorisation or specific obligation of Abrocitinib-Pfizer Europe MA EEIG.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU

Purpose of the study:

Based on data from Cibinqo clinical program, it is of MAH's opinion that it is important to monitor the real-world safety of Cibinqo following its authorization in the EU. An active safety surveillance study will assess safety endpoints of interest with Cibinqo in the post-approval setting.

The study objective is to estimate incidence rates of safety events of interest among patients with AD receiving abrocitinib and patients with AD receiving biologic and/or non-biologic (non- Janus Kinase inhibitor [non-JAKi]) chronic systemic treatments for AD (comparator treatments) in the real-world setting.

The following are the primary safety endpoints of interest:

- VTE,
- Herpes zoster,
- Serious infections and opportunistic infections,
- Rhabdomyolysis,
- Gastrointestinal perforation,
- MACE,
- Fractures,
- Malignancy (excluding NMSC),

- NMSC,
- All-cause mortality, and
- Height as a measure for impaired bone growth in adolescents (Denmark only).

Study B7451085: A Drug Utilization Study to Evaluate the Effectiveness of Risk Minimisation Measures for Abrocitinib in the EU Using Electronic Healthcare Data

Purpose of the study:

To mitigate the risks associated with abrocitinib, required routine RMMs including the SmPC and package leaflet are being employed. In order to minimise important risks with the use of Cibinqo, the MAH has also implemented additional RMMs: an educational program intended to enhance the communication of the risk and risk minimisation practices to HCPs and patients. The program includes a Prescriber Brochure, a DHPC and a Patient Card.

The MAH plans to evaluate the effectiveness of RMMs being implemented for abrocitinib. The proposed study will be designated as a PASS.

Research question: Does routinely collected data in the EU indicate adherence to the recommendations for the use of abrocitinib described in the SmPC, prescriber brochure and DHPC?

The study objectives are to evaluate, to the extent measurable in the available routinely collected data, indicators of HCPs' adherence to the prescribing information in accordance with the abrocitinib SmPC, prescriber brochure, and DHPC specifically:

- Indicators of adherence to performing laboratory tests of complete blood count (CBC), lipid panel, hepatitis B/C and tuberculosis (TB) screening prior to initiation of abrocitinib treatment,
- Indicators of adherence to performing laboratory tests of CBC and lipid panel at Week 4 (± 2 weeks) from initiation of abrocitinib treatment,
- Indicators of adherence to consideration of risk factors for VTE, MACE, malignancy excluding NSMC, NMSC and serious infection prior to treatment with abrocitinib,
- Indicators of adherence to avoid live attenuated vaccine immediately prior to and during treatment with abrocitinib,
- Indicators of adherence to contraindications for use during pregnancy,
- Indicators of adherence to contraindications for use among patients with severe hepatic impairment,
- Indicators of adherence to not use in patients aged <12 years-of-age, and

- Indicators of adherence to recommended posology (estimated average daily dose).

Study B7451015: A Phase 3 Multi-Center, Long-Term Extension Study Investigating the Efficacy and Safety of Abrocitinib, With or Without Topical Medications, Administered to Subjects Aged 12 Years and Older with Moderate to Severe Atopic Dermatitis

Purpose of the Study:

The objective of this study is to assess the long-term safety of 100 mg and 200 mg once daily of abrocitinib with or without topical treatments in adult and adolescent subjects who previously participated in qualifying abrocitinib AD trials.

The study objectives will be to assess safety by the spontaneous reporting of AEs, physical examinations and clinical laboratory results in all subjects who receive at least one dose of the investigational product. This study will continue to describe safety data to include:

- VTE,
- Serious and opportunistic infections,
- Herpes zoster,
- Malignancy (excluding NMSC),
- NMSC,
- Fractures, including in adolescents,
- Myopathy (including rhabdomyolysis),
- Gastrointestinal perforation,
- MACE,
- Height in adolescents,
- Development in adolescents,
- Pregnancy outcomes, and
- All-cause mortality.

Study B7451015: Adolescent Imaging Substudy

Purpose of the Substudy:

The objective of this substudy is to evaluate the potential effects of abrocitinib in terms of abnormal bone findings in knee MRI in subjects enrolled as adolescents (12 to <18 years-of-age) in the abrocitinib development program. The substudy will evaluate the proportion of abnormal bone finding in knee MRI in adolescent subjects exposed to abrocitinib 100 mg and 200 mg QD.

Study B7451120: A Prospective Active Surveillance Study to Monitor Growth, Development and Maturation Among Adolescents with Atopic Dermatitis Exposed to Abrocitinib

Purpose and objectives: As part of the abrocitinib pharmacovigilance plan, a long-term follow-up study is being proposed to actively monitor growth, development (including bone development), and maturation (including pubertal development) in adolescents aged 12-17 years in the post-approval setting.

The objectives are to:

- Describe growth, development (including bone development), and maturation (including pubertal maturation) metrics among adolescent patients with atopic dermatitis (AD) treated with abrocitinib and, separately, among adolescent patients with AD unexposed to abrocitinib and receiving systemic treatments;

- Describe the risk of fractures stratified by abrocitinib dose (100 mg and 200 mg).

Additionally, an exploratory objective is to compare adolescent patients treated with abrocitinib with adolescent patients unexposed to abrocitinib and treated with comparators for select outcomes, depending on the sample size.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 – Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 – Protocols for proposed and on-going studies in RMP Part IV

Annex 6 – Details of Proposed Additional Risk Minimisation Activities

Annex 7 – Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

None

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES DRAFT KEY MESSAGES OF THE ADDITIONAL RISK MINIMISATION MEASURES

Prior to the launch of abrocitinib in each Member State MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness about the safety concerns of the product, including, infections (including herpes zoster and serious and opportunistic infections), venous thromboembolism (VTE), malignancy, major adverse cardiovascular event (MACE), and embryofoetal toxicity following exposure in utero.

The MAH shall ensure that in each Member State where abrocitinib is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use abrocitinib have access to/are provided with the following educational package:

The physician educational material should contain:

- The Summary of Product Characteristics
- Package leaflet
- Prescriber Brochure
- Patient card (PC)

The Prescriber Brochure shall contain the following key elements:

- Include a section about abrocitinib which describes the indication and posology.
- Language for Healthcare Professionals (HCPs) to inform patients of the importance of the PC.
- Use in patients aged 65 years and older
  - Language to reinforce risks in these patients and use of 100 mg dose
- *Infections (including herpes zoster and serious and opportunistic infections)*
  - Describe that Cibinqo must not be used in patients with active serious systemic infections.
  - Language on the risk of infections during treatment with Cibinqo.
  - Details on how to reduce the risk of infection with specific clinical measures (what laboratory parameters should be used to initiate Cibinqo, screening for TB, screening for hepatitis B and hepatitis C, getting patients immunised as per local guidelines, and temporary interruption of Cibinqo if an infection is not responding to standard therapy until the infection resolves).
  - Language stating the use of live, attenuated vaccines should be avoided during or immediately prior to treatment along with examples of live, attenuated vaccines.
  - Language recommending that risk factors for infections should be considered when prescribing abrocitinib, including elderly age and diabetes.
- *VTE*
  - Language describing the risk of VTE during treatment with Cibinqo.
  - Examples of risk factors which may put a patient at higher risk for VTE and in whom caution is needed when using abrocitinib.

- Language that patients should be periodically re-evaluated for changes in VTE risk.
- Language on the response if clinical features of VTE occur including prompt evaluation and the need for discontinuation of Cibinqo.

- *Malignancy*
  - Language describing that in patients at high risk for malignancy abrocitinib should only be used if no suitable treatment alternatives are available, with examples of who may be at high risk.
  - Reminder about the need for periodic skin examination for patients
- *MACE*
  - Language describing that in patients at high risk for MACE abrocitinib should only be used if no suitable treatment alternatives are available, with examples of who may be at high risk.
  - Language that lipids should be monitored prior to initiation, after 4 weeks of therapy and thereafter according to clinical guidelines. Lipids should be managed according to clinical guidelines.
- *Embryofoetal toxicity following exposure in utero*
  - Language describing that there are no or limited data on the use of Cibinqo in pregnant women.
  - Details on how to reduce the risk of exposure during pregnancy for women of childbearing potential based on the following: Cibinqo is contraindicated during pregnancy, women of childbearing potential should be advised to use effective contraception both during treatment and for 1 month after cessation of Cibinqo oral administration, and to advise patients to inform their HCP immediately if they think they could be pregnant or if pregnancy is confirmed.

The patient information pack should contain:

- Package leaflet
- Patient card

- **The patient card** shall contain the following key messages:
  - Contact details of the Cibinqo prescriber.
  - Language that the PC should be carried by the patient at any time and to share it with HCPs involved in their care (i.e. non-Cibinqo prescribers, emergency room HCPs, etc.).
  - Language describing Cibinqo (i.e. what it is and what it is used for).
  - Risk of infections:
    - Description of signs/symptoms of infections the patient needs to be aware of, so that they can seek attention from their HCP:
    - Language to advise patients and their HCPs about the risk of live vaccinations when given immediately before and during Cibinqo therapy with examples of live vaccines.
  - Risk of blood clots in veins or lungs:
    - Description of signs/symptoms of blood clots in veins (deep venous thrombosis) or lungs (pulmonary embolism) which the patient needs to be aware of, so that they can seek immediate attention from an HCP.
  - Risk of heart disease:
    - Describe signs/symptoms of heart disease that the patient needs to be aware of, so that they can seek attention from their HCP.
  - Reminder of the risk of cancer. Regarding skin cancer reminder to let their doctor know if they notice any new growth on the skin.

- Description of targeted risks for awareness by the patient and for HCPs involved in their care including:
  - The need for laboratory monitoring, including for high cholesterol.
  - A reminder to use contraception, that Cibinqo is contraindicated during pregnancy, and to notify their HCPs if they become pregnant while taking Cibinqo.