22 February 2024
EMA/104236/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cibinqo

International non-proprietary name: Abrocitinib

Procedure No. EMEA/H/C/005452/0010

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

Abbreviation/Acronym	Definition
Abro	abrocitinib
AC	adjudication committee
ACL	anterior cruciate ligament
AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
AUC	area under the curve
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CO	clinical overview
COMPARE	abrocitinib versus dupilumab comparison study (B7451029)
CSR	clinical study report
CYP	cytochrome P450
DARE	abrocitinib versus dupilumab comparison study (B7451050)
DVT	deep vein thrombosis
EASI	Eczema Area and Severity Index
EASI -75	Eczema Area and Severity Index ≥75 percent reduction in score
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EPAR	European Public Assessment Report
EU	European Union
EXTEND	long-term extension study (B7451015)
F	female
FOPE	Focal periphyseal edema zone
GLP	Good Laboratory Practices
IGA	Investigator's Global Assessment
IL	interleukin
IR	incidence rate
JAK	Janus kinase
LTDCP2022	long-term dose-controlled pool 2022
LTE	long-term extension
M	male
MAA	marketing authorization application
MACE	Major Adverse Cardiovascular Events
MAH	Marketing Authorization Holder
MONO (1,2)	monotherapy study (B7451012, B7451013)
MRHD	maximum recommended human dose
MRI	magnetic resonance imaging
MT	monotherapy
N	number of participants/subjects in each group
NA	not available or not applicable
NDA	New Drug Application
NMSC	non-melanoma skin cancer
NOAEL	no observed adverse effect level
NOEL	no observed effect level
PE	pulmonary embolism
PIP	Paediatric Investigational Plan (EU)
PK	pharmacokinetics
PND	postnatal day
POC	proof of concept
PP-NRS	Peak Pruritus Numerical Rating Scale
PP-NRS4	Peak Pruritus Numerical Rating Scale (4 points reduction on scale)
PRAC	Pharmacovigilance Risk Assessment Committee (European Medicines Agency)
PY	patient-year

Abbreviation/Acronym	Definition
Q (1,3)	quartile (1,3)
Q2W	every 2 weeks
QD	once daily
RDBPC	randomized, double-blinded, placebo-controlled
REGIMEN	randomized withdrawal study (B7451014)
RMM	risk management measure
RMP	Risk Management Plan
RRLTP2022	REGIMEN randomized long-term pool 2022
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	standard deviation
SDS	standard deviation score
SmPC	Summary of Product Characteristics
sNDA	Supplemental New Drug Application
TEAE	treatment-emergent adverse event
TEEN	combination therapy study in adolescents (B7451036)
US	United States of America
VTE	venous thromboembolism

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 22 May 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adolescents 12 to < 18 years of age with moderate to severe atopic dermatitis for CIBINQO based on final results from non-clinical study 00655292 [21GR211] and interim results from clinical study B7451015; this is a Phase III 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. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0023/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0023/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder

Timetable	Actual dates
Submission date	22 May 2023
Start of procedure:	17 June 2023
CHMP Rapporteur Assessment Report	1 August 2023
PRAC Rapporteur Assessment Report	18 August 2023
PRAC members comments	22 August 2023
Updated PRAC Rapporteur Assessment Report	24 August 2023
PRAC Outcome	31 August 2023
CHMP members comments	31 August 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 September 2023
Request for supplementary information (RSI)	14 September 2023
CHMP Rapporteur Assessment Report	13 November 2023
PRAC Rapporteur Assessment Report	17 November 2023
PRAC members comments	22 November 2023
Updated PRAC Rapporteur Assessment Report	22 November 2023
PRAC Outcome	30 November 2023
CHMP members comments	29 November 2023
Updated CHMP Rapporteur Assessment Report	7 December 2023
Second Request for supplementary information (RSI)	14 December 2023
CHMP Rapporteur Assessment Report	23 January 2024
PRAC Rapporteur Assessment Report	24 January 2024
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	1 February 2024
PRAC Outcome	8 February 2024
CHMP members comments	6 February 2024
Updated CHMP Rapporteur Assessment Report	15 February 2024
CHMP Opinion	22 February 2024

2. Scientific discussion

2.1. Introduction

Cibinqo (abrocitinib) was approved in the EU in December 2021 for the treatment of moderate-to-severe atopic dermatitis (AD) in adults who are candidates for systemic therapy (EMEA/H/C/005452/0000).

At the time of initial marketing authorisation, an indication for both adults and adolescents was proposed in section 4.1 of the SmPC. It was concluded that a statistically significant, and dose-dependent efficacy of abrocitinib 100 mg QD and 200 mg QD versus placebo was demonstrated in patients with moderate to

severe AD from 12 years of age and above. Efficacy data of abrocitinib in adolescents are thus described in the presently approved SmPC section 5.1. Nevertheless, because of bone findings noted in juvenile rats the CHMP concluded that there were remaining uncertainties on the safe use of abrocitinib in adolescents and the treatment indication was thus restricted to adults > 18 years of age only.

Additional long-term safety data in growing adolescents was requested to conclude that the benefits outweigh the risks. An MRI sub-study in adolescents from an ongoing long-term extension study was specified as a category 3 PASS in the RMP.

This type II variation is an application for an extension of the indication to adolescents with moderate-to-severe AD who are candidates for systemic therapy. Additional clinical safety data are based on the interim report of the MRI sub-study in adolescents and an update of the safety data up to 05 September 2022 (including the accrued data on height, weight and fractures in adolescents). Furthermore, non-clinical data of an additional investigative age sensitivity window GLP toxicity study in juvenile rats was submitted. In addition, a general updated safety data with a cut-off up to 05 September 2022, was included with corresponding changes of the SmPC section 4.8, as agreed as part of the Article 20 referral on Janus kinase inhibitor (JAKi).

2.1.1. Problem statement

Disease or condition

Atopic dermatitis is a chronic, relapsing inflammatory skin condition characterised by dry, pruritic skin, prevalent also among adolescents. Distribution and morphology are distinguishably different between paediatric and adult populations (Akdis et al, 2006; Weidinger & Novak, 2016; Guttman-Yassky et al, 2018). AD has 3 recognised clinical phases: infant (aged 3-6 months to <2 years), childhood (aged 2 to <12 years) and adult (aged 12 years and older) (Akdis et al, 2006). Adolescents and adults are grouped together in the adult phase based on the similarity of the clinical pattern and predominant areas of AD involvement. Adolescents and adults often present lichenified and excoriated plaques at flexures, wrists, ankles, and periorbital regions; in the head and neck type, the upper trunk, shoulders, and scalp are involved. For further information on the disease background, see EPAR, EMEA/H/C/005452/0000.

The therapeutic indication claimed by the MAH is as follows:

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.

Epidemiology and risk factors, screening tools/prevention

Atopic dermatitis is a chronic inflammatory skin condition that is prevalent among adolescents. In an international, cross-sectional, web-based survey conducted in 18 countries in 4 continents, mean 12-month prevalence of AD in adolescents 12 to <18 years of age was 14.8% (US 9.3%, United Kingdom 15.0%, Japan 9.1%, Germany 8.7%, France 14.3%) (Silverberg et al, 2021). In adolescents, disease burden due to AD has been reported to be higher than in adults (Urban et al, 2021), which could be partly because body image plays a more important role in this age group than in childhood and adulthood.

In addition to physical manifestations such as disruption of the skin barrier, affected adolescents often present behavioural problems, characterised by increased emotional dependency, anxiety and sleep disturbances. Itch, which is one of the main symptoms of the disease, affects mood and sleep quality of patients and consequently of their family (Ricci et al, 2012). The anxiety, depression and social

embarrassment associated with AD result in a significant psychosocial burden that contributes to school, work, financial and social struggles in the affected patients (Slattery et al, 2011). Adolescent patients with AD may also involve their caregivers and family members in the physical and psychosocial consequences of their condition. Family members are burdened with time-consuming treatment regimens, dietary and household changes, a heavy financial impact, and the emotional weight of seeing their children suffer (Ezzedine et al, 2020; Drucker et al, 2017). For these reasons, high disease severity was associated with low quality of life in patients and parents (Ezzedine et al, 2020).

Clinical presentation, diagnosis and stage/prognosis

The clinical presentation for AD, diagnosis and stage/prognosis have previously been presented in the initial MAA (see EPAR, EMEA/H/C/005452/0000).

Management

The general management of AD has previously been presented in the initial MAA (see EPAR, EMEA/H/C/005452/0000).

Up to now five agents from 2 pharmacological classes of advanced treatments have been approved for moderate-to-severe AD in adolescents in the EU. Dupilumab, a monoclonal antibody that targets IL-4 receptor and inhibits IL-4 and IL-13 signaling, as well as tralokinumab and lebrikizumab, IL-13 antagonists, have been demonstrated to be efficacious in adolescents in Phase 3 studies (Simpson et al, 2020; Paller et al, 2022; Bieber et al, 2022). These biologic agents are administered by injections, which are not well tolerated by all adolescents. Upadacitinib is an oral JAK1 inhibitor that is approved for treatment of moderate-to-severe AD in adolescents in the EU; and baricitinib is an oral JAK1/2 inhibitor that is approved for treatment of moderate-to-severe AD in adults and paediatric patients 2yo.

2.1.2. About the product

Abrocitinib is an orally bioavailable small molecule that reversibly and selectively inhibits Janus kinase (JAK) 1 by blocking the ATP binding site.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not seek Scientific advice at the CHMP for this variation application.

2.2. Non-clinical aspects

2.2.1. Introduction

During the initial MAA for abrocitinib (EMEA/H/C/005452/0000), the conclusion was reached that the B/R of abrocitinib was not positive for adolescents from the age of 12. The main underlying reason was that bone toxicities had been identified in the general toxicity studies (7-day and 1-month studies) in 6–9-week-old animals and in the juvenile toxicity studies. In the juvenile toxicity study where Wistar Han rats had been administered abrocitinib daily from the age of Postnatal Day (PND) 10 up to 53 days, in-life as well as macroscopic and microscopic bone findings with small or misshapen femur head were identified at all doses (5, 25 and 75 mg/kg).

To understand the effects of abrocitinib oral administration to juvenile rats at different ages, the MAH has conducted a bone growth and development investigative study. The objective of this study was to determine the age window of sensitivity of abrocitinib effects on postnatal bone development in juvenile rats and thereby address the uncertainty about using abrocitinib in paediatric patients.

2.2.2. Toxicology

Reproduction toxicity

Juvenile toxicity

The objective of this study was to determine the potential effects of abrocitinib on postnatal bone growth and development in juvenile male and female Wistar Han rats. Abrocitinib was administered by oral gavage at 25 mg/kg/day to 4 groups at different ages of dose initiation: from PND 10 through 63, PND 15 through 63, PND 21 through 63, or PND 30 through 63. The control group was administered vehicle control by oral gavage from PND 10 through 63. In addition, the toxicokinetic profile of abrocitinib was determined on PND 63 in all groups.

Study details	**No:Sex/ Group**	**Dose** mg/kg/day	**Exposure**		**Major findings & NOAEL**
			Cmax (ng/mL) PND63	$AUC_{0\text{-}24h}$ (ng×h/mL) PND63	
Juvenile toxicity study			**(NOAEL highlighted)**		
GLP 00655292 [21GR211] Rat (Wistar Han) Oral gavage, 10 mL/kg for 63 days Abrocitinib PF-04965842 Lot No: 19-AP-00235	Main: 10M/10F	0 vehicle	-	-	
		25 PND 10-63	M:4340 F: 6330	M:25500 F:37900	
		25 PND 15-63	M:4480 F: 6160	M:15700 F:30700	
		25 PND 21-63	M:3990 F: 6880	M:22600 F:32400	
		25 PND 30-63	M:4000 F: 6060	M:24300 F:33900	

Parameters collected: mortality, clinical signs, body weights, body weight gains, food consumption, toxicokinetic parameters (PND 63), and macroscopic and microscopic examinations.

Mortalities: There were no abrocitinib-related mortalities. One control female was found dead on PND15.

Clinical Observations: Malrotated left hindlimb was noted for 1 male and 1 female dosed from PND 10–63 at the weekly examinations during PND 44–64. This corresponded macroscopically to findings of small femoral head and/or bent femur, and microscopically to findings of abnormal morphology of the femoral head. No clinical findings in animals when dosing was initiated PND15, 21 or 30.

Body Weights: Reduced body weight gains in males and females (generally statistically significant) were noted in animals dosed from PND10 throughout the study (0.83-0.89x control).

Food consumption: Lower food consumption was only noted in animals dosed from PND10 throughout the dosing period which corresponded to lower weight gains. Differences were occasionally significant.

Macroscopic findings: Macroscopic findings (bone observations) were only evident in animals dosed from PND10. Small femoral head and misshapen femoral head were observed in the left and right femur of males and females which correlated with a microscopic finding of abnormal morphology of the left femoral head (right

femur was not examined microscopically as per protocol). A bent left femur was observed in 1 male but was without a microscopic correlate.

	Males					Females				
Start of dosing (PND)	10	10	15	21	30	10	10	15	21	30
Dose (mg/kg/day)	0	25				0	25			
Femur, Left [a]										
Femoral head, small	-	7	-	-	-	-	5	-	-	-
Femoral head, misshapen	-	2	-	-	-	-	1	-	-	-
Bent	-	1	-	-	-	-	-	-	-	-
Femur, Right [a]										
Femoral head, small	-	6	-	-	-	-	3	-	-	-
Femoral head, misshapen	-	2	-	-	-	-	1	-	-	-

- = No finding present.
[a] 10 examined per sex/group, except 9 for control group females.

Microscopic findings: Abrocitinib-related microscopic bone findings were evident in femur and tibia (only the left proximal femur and left femorotibial joint were examined).
In the proximal femur of animals dosed from PND10, abnormal morphology of the femoral head was observed (mild-severe) characterised by e.g., retention of cartilage, loss of normal microscopic morphology replaced by an irregular mass of acellular cartilage, with clefts in the cartilage, foci of fibroplasia, rare cysts and/or foci of fibroplasia, and a reduced size or absence of the neck of the femoral head.

In the distal femur and proximal tibia, decreased spongiosa (minimal) was observed characterised by decreased distance between the normal cartilage of the growth plate and the secondary spongiosa in the metaphysis and multifocal gaps between spicules of primary spongiosa. These findings were evident in animals dosed from PND10 and 2 animals dosed from PND 15.

	Males					Females				
Start of dosing (PND)	10	10	15	21	30	10	10	15	21	30
Dose (mg/kg/day)	0			25		0			25	
Femur, left[a]										
Abnormal morphology, femoral head	-	6	0	0	0	-	5	0	0	0
Mild	-	1	-	-	-	-	1	-	-	-
Moderate	-	1	-	-	-	-	1	-	-	-
Severe	-	4	-	-	-	-	3	-	-	-
Decreased primary spongiosa, metaphysis	-	6	0	0	0	-	7	0	0	0
Minimal	-	6	-	-	-	-	7	-	-	-
Tibia, left										
Decreased primary spongiosa, metaphysis	-	7	0	0	0	-	7	2	0	0
Minimal	-	7	-	-	-	-	7	2	-	-

- = No finding present.
[a] 10 examined per sex, except 9 for control group females.

2.2.3. Ecotoxicity/environmental risk assessment

No ERA was initially submitted by the MAH, and no discussion was undertaken regarding the increase in environmental exposure to abrocitinib and potential down-stream effects resulting from the increase in patient population. Upon CHMP's request, the MAH provided an updated ERA and clarified that the calculations in the original ERA submitted within the initial MAA were based on the default Fpen of 0.01, representing 1% of the total population, thereby including both adolescent and adult patients for the AD indication. The updated ERA also included a minor revision, where the PEC/PNEC for the wastewater micro-organisms had been recalculated using 10x PECsw given that a dilution with surface water is not applicable for wastewater treatment facility microorganisms. These revisions resulted in no change to the

overall outcome of the ERA. Abrocitinib at the proposed use is unlikely to represent a risk to the environment.

2.2.4. Discussion on non-clinical aspects

During the initial MAA for abrocitinib, the conclusion was reached that the benefit-risk balance of abrocitinib was negative for adolescents from the age of 12. The main underlying reason was that bone toxicities had been identified in the general toxicity studies (7-day and 1-month studies) in 6–9-week-old animals and in the juvenile toxicity studies. In the juvenile toxicity study where Wistar Han rats had been administered abrocitinib daily from the age of PND10 up to 53 days, in-life as well as macroscopic and microscopic bone findings with small or misshapen femur head were identified at all doses (5, 25 and 75 mg/kg).

To understand the effects of abrocitinib oral administration to juvenile rats at different ages, the MAH has conducted a bone growth and development investigative study. The objective of this study was to determine the age window of sensitivity of abrocitinib effects on postnatal bone development in juvenile rats and thereby address the uncertainty about using abrocitinib in paediatric patients. The study was designed with only one dose level but four groups with different time points for initiation of abrocitinib dosing to determine an age window of abrocitinib sensitivity and to identify an age with no toxicity effects on bone development in the rat.

Significantly reduced body weight gains (0.83-0.89x controls) were noted only in males and females dosed from PND10, and these findings correlated with lower food consumption. In addition, abrocitinib-induced effects were identified on bone development parameters in animals dosed from PND10 and non-adverse minor effects were also noted in two animals dosed from PND15.

The bone findings in the proximal femur consisted of small and misshapen femoral heads which correlated with an abnormal morphology characterised by e.g., a reduced size or absence of the neck of the femoral head, retention of cartilage, loss of normal microscopic morphology replaced by an irregular mass of acellular cartilage and (rare) cysts and/or foci of fibroplasia.

In the distal femur and proximal tibia, decreased spongiosa (minimal) was observed characterised by decreased distance between the normal cartilage of the growth plate and the secondary spongiosa in the metaphysis and multifocal gaps between spicules of primary spongiosa. In the two females dosed from PND15, a non-adverse microscopic finding of minimal decreased primary spongiosa in the metaphysis was identified.

Thus, the adverse bone toxicities identified only occur if the exposure is initiated on PND10 in the rat, which would correspond to a development phase corresponding roughly to a 3-month-old human infant. The effects identified are consistent with those observed in a previous GLP-compliant juvenile study in Wistar Han rats administered abrocitinib at ≥5 mg/kg/day, which also started dosing on PND10 (assessed during the initial MAA, see EPAR EMEA/H/C/005452/0000). While non-adverse developmental effects were identified in animals dosed from PND15 in the present study, no bone effects were identified in the animals dosed from PND21 which roughly corresponds to 2-year-old human. Overall, this study suggests that developmental exposure to abrocitinib in the rat at a bone age corresponding to 2-year-old human does not induce negative effects on bone development parameters. The above non-clinical findings, including the safety margins, were adequately added to SmPC section 5.3.

Upon CHMP's request, the MAH provided an updated ERA and clarified that the calculations in the original ERA were based on the default Fpen of 0.01 suggesting that the Fpen used includes the increased environmental exposure resulting from this type II variation. The updated ERA also included a minor revision, where the PEC/PNEC for the wastewater micro-organisms had been recalculated using 10x

PECsw given that a dilution with surface water is not applicable for wastewater treatment facility microorganisms. These revisions resulted in no change to the overall outcome of the ERA. The ERA studies consistently produced RQ-values below 1, therefore abrocitinib is not expected to pose a risk to the environment. According to the performed risk assessment, CHMP agreed that no specific requirements for disposal have to be included in the SmPC.

Assessment of paediatric data on non-clinical aspects

See discussion above.

2.2.5. Conclusion on the non-clinical aspects

The issues identified in the non-clinical programme have been properly addressed. This type II variation is therefore considered approvable from a non-clinical perspective.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of abrocitinib. Considering the above data, abrocitinib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1. Phase 2 and 3 Abrocitinib Clinical Studies in Atopic Dermatitis

Study	Description	Control	Treatment/Duration	Number of Subjects
Phase 3 Short-term Monotherapy Studies				
B7451012	Phase 3 randomised, monotherapy study in adults and adolescents	Placebo	Abrocitinib 100 mg QD Abrocitinib 200 mg QD Placebo Treatment duration = 12 weeks	Screened: 553 Randomised: 387 (randomised 2:2:1) 100 mg: 156 200 mg: 154 Placebo: 77
B7451013	Phase 3 randomised, monotherapy study in adults and adolescents	Placebo	Abrocitinib: 100 mg QD Abrocitinib: 200 mg QD Placebo Treatment duration = 12 weeks	Screened: 554 N = 391 (randomised 2:2:1) 100 mg: 158 200 mg: 155 Placebo: 78

Table 1. Phase 2 and 3 Abrocitinib Clinical Studies in Atopic Dermatitis

Study	Description	Control	Treatment/Duration	Number of Subjects
Phase 3 Short-term Combination Therapy Study				
B7451029	Phase 3 randomised combination study including a comparator and on background topical therapy in adult subjects	Placebo and dupilumab	Abrocitinib 100 mg QD Abrocitinib 200 mg QD Dupilumab: 300 mg SC every other week (loading dose of 600 mg at baseline) Matching placebo Total treatment duration = 20 weeks, including 16 weeks of randomized, placebo-controlled phase	N = 837 (randomised 2:2:2:1) 200 mg: 226 100 mg: 238 Dupilumab: 242 Placebo: 131
Phase 3 Dosing Regimen Study				
B7451014 (ongoing)	Phase 3 randomised withdrawal and retreatment study in adults and adolescents	Open-label run-in	200 mg QD for 12 weeks open label Responders, based on IGA and EASI-75, were randomised to 200 mg QD, 100 mg QD, or matching placebo up to 52 weeks. Subjects with loss of response enter a 12-week rescue treatment period of open-label 200 mg QD ± topical therapy Treatment duration is up to 64 weeks	Open label N = ~1370 N = ~600 (randomised 1:1:1) 100 mg ~200 200 mg ~200 Placebo ~200
Phase 3 Long-term Extension Study				
B7451015 (ongoing)	Phase 3 long-term extension study in adults and adolescents	Not Applicable	Subjects previously allocated to abrocitinib 200 mg or 100 mg QD in the qualifying parent study will be allocated to the same dose. Subjects previously randomised to active control drug or placebo only in a qualifying parent study were randomized to double blind treatment, either abrocitinib 200 mg or 100 mg QD when enrolled into B7451015.	N = ~3000
Phase 2 Studies				
B7451006	Phase 2b dose-ranging proof-of-concept randomised monotherapy study in adult subjects	Placebo	Abrocitinib 10 mg QD Abrocitinib 30 mg QD Abrocitinib 100 mg QD Abrocitinib 200 mg QD Placebo 12 weeks treatment, 4 weeks follow-up	N = 269 (randomised 1:1:1:1:1) 56 placebo QD 49 10 mg QD 51 30 mg QD 56 100 mg QD 55 200 mg QD
Ongoing Studies				
B7451036	Phase 3 randomised, combination therapy study with background topical therapy in adolescents only	Placebo	Abrocitinib 100 mg QD Abrocitinib 200 mg QD Placebo Treatment duration = 12 weeks Immunogenicity sub-study: Tdap vaccine at 8 weeks of treatment	N = ~225 (randomised 1:1:1) 100 mg ~75 200 mg ~75 Placebo ~75 Immunogenicity sub-study N = ~90 100 mg ~30 200 mg ~30 Placebo ~30
B7451037	Phase 2a randomised, double-blind, placebo-controlled, multicenter study investigating the mechanism of action of abrocitinib monotherapy in adult participants	Placebo	Abrocitinib 100 mg QD Abrocitinib 200 mg QD Placebo Treatment duration = 12 weeks	N = ~51 (randomised 1:1:1) 100 mg ~17 200 mg ~17 Placebo ~17

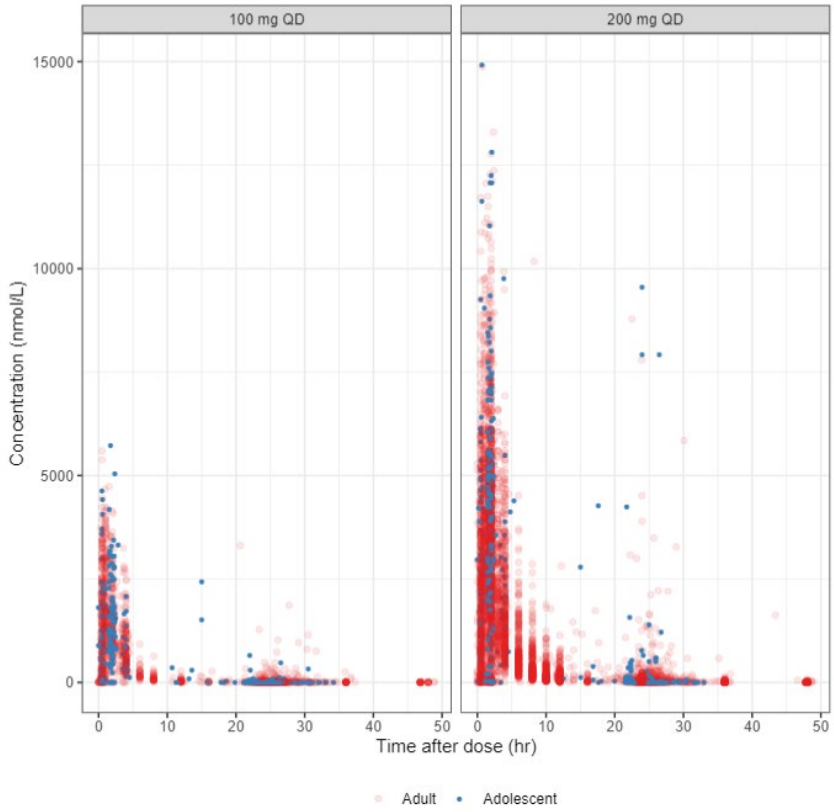
Abbreviations: EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; QD = once daily; SC = subcutaneous; Tdap = tetanus, diphtheria, and pertussis

2.3.2. Pharmacokinetics

The pharmacokinetics (PK) of abrocitinib has previously been assessed and agreed in the initial MAA.

At the time of initial MAA, there were some issues regarding the submitted popPK analysis with regards to adolescents. The MAH was therefore asked to submit figures of observed data (as shown below) in the initial MAA, which showed that exposures were largely overlapping between adults and adolescents and this information was added to the SmPC section 5.2.

Figure 1. Adolescent and adult Abrocitinib molar concentrations- figure from initial MAA

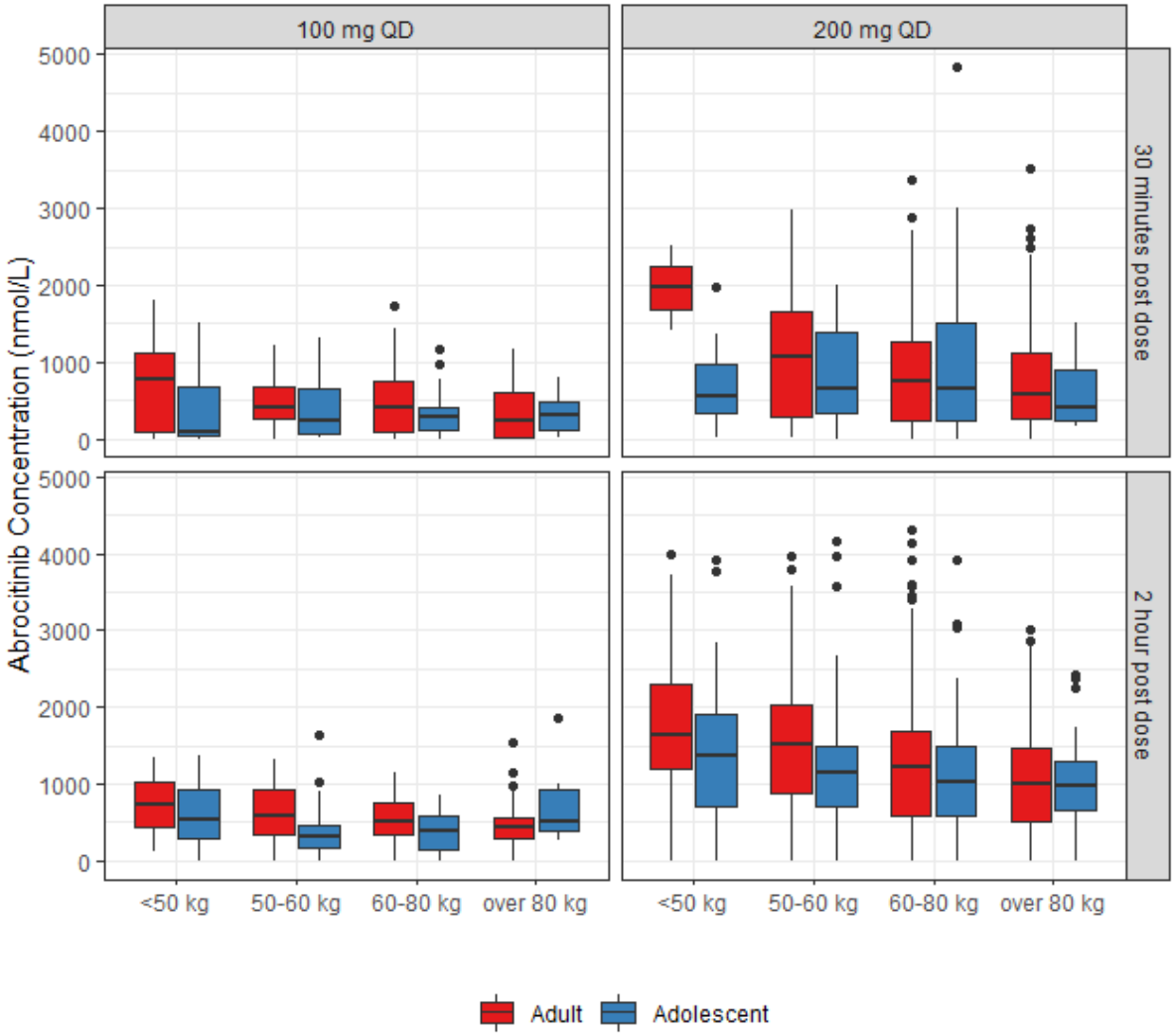


Repository artifact ID FI-16993349.
The observed abrocitinib sample PK concentrations for all AD patients are shown with the solid blue points are adolescent patients and the red points are adult concentrations.

The dose in adolescents was initially proposed to be the same as in adults. This is generally agreed however the adolescents with a low body weight (< 40 kg) below the adult weight range may be overexposed with the 200 mg dose compared to adults. The MAH was thus requested to discuss if the lowest body weight adolescents should start with the 100 mg dose.

In their responses, the MAH outlined that the Phase 3 clinical program enrolled participants with body weight ≥40 kg in studies B7451012, B7451013 and B7451014, and with body weight ≥25 kg in study B7451036. The median body weight of adolescent and adult participants in the clinical program was 59 and 77 kg, respectively. The observed abrocitinib plasma concentrations in adolescent and adult AD participants, in PK samples collected at 30 min and 2 hours post-dose at steady state during the Phase 3 trials, are shown in Figure 1. The comparison in Figure 1 demonstrates that abrocitinib exposures are similar between adolescent and adult participants within different body weight bands.

Figure 2. Observed Abrocitinib Plasma Concentrations in PK Samples Obtained from Adolescent and Adults Subjects in Phase 3 Clinical Studies



Based on the results of popPK simulations (Table 2), using the model included in the initial MAA dossier without a covariate effect on F and with a covariate effect included on CL, the exposures of abrocitinib active moiety in adolescent participants weighing 35 kg are estimated to be approximately 32.5% and 22.7% higher compared with adults when given 100 and 200 mg once daily (QD) doses. In participants weighing as low as 25 kg, the corresponding differences are estimated to be 64.5% and 62.6% higher, respectively.

Table 2. Estimated Steady-State AUC for Abrocitinib, M1, M2, and Active Moiety in AD Participants (Model without a Covariate Effect on F and with a Covariate Effect Included on CL)

Dose	Population	Body Weight	Active Moiety		Abrocitinib		M1	M2
			AUC	ΔAUC (%)	AUC	ΔAUC (%)		
100 mg QD	Adult	77	7382	0	9810	0	1259	3794
100 mg QD	Adolescent	25	12140	64.5	11173	13.9	4607	7647
100 mg QD	Adolescent	30	10740	45.5	10464	6.7	3726	6734
100 mg QD	Adolescent	35	9783	32.5	9944	1.4	2762	6104
100 mg QD	Adolescent	59	6728	-8.9	8344	-14.9	1384	3678
200 mg QD	Adult	77	18378	0	24148	0	2990	9695
200 mg QD	Adolescent	25	29884	62.6	26189	8.5	10777	19621

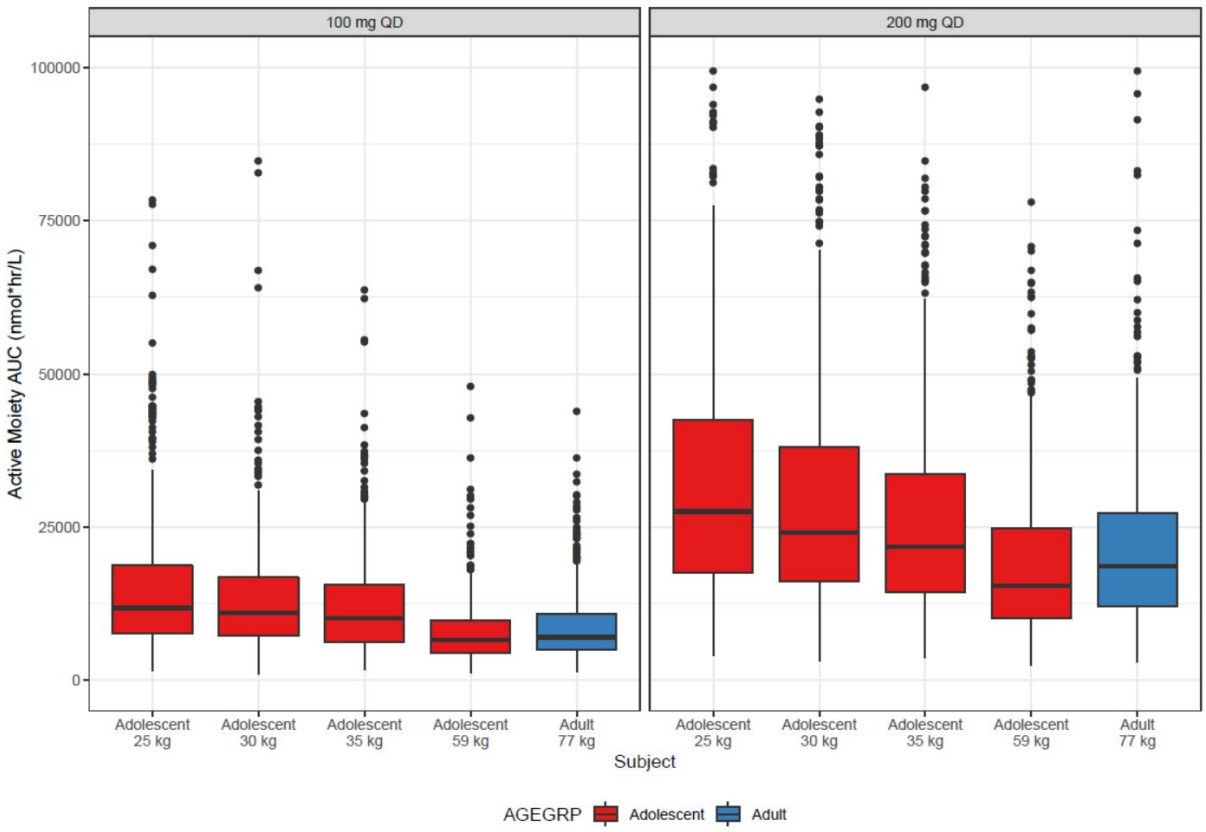
Table 2. Estimated Steady-State AUC for Abrocitinib, M1, M2, and Active Moiety in AD Participants (Model without a Covariate Effect on F and with a Covariate Effect Included on CL)

Dose	Population	Body Weight	Active Moiety		Abrocitinib		M1	M2
			AUC	ΔAUC (%)	AUC	ΔAUC (%)		
200 mg QD	Adolescent	30	24944	35.7	24217	0.3	8445	15768
200 mg QD	Adolescent	35	22551	22.7	22462	-7	6778	14285
200 mg QD	Adolescent	59	15781	-14.1	19428	-19.5	3183	8779

The abrocitinib and active moiety AUC (nmol*hr/L) were simulated out to steady state for a typical adult AD participant (white, male, 77 kg), a typical adolescent AD participant (white, male, 59 kg), a low weight adolescent (35 kg), 3rd percentile for 12-year-old adolescent (30 kg) and an extreme low weight adolescent (25 kg). Simulations were performed for 100 mg and 200 mg QD dosing.
AUC Area under the curve

The parameterisation of body weight using a power model means that extrapolations outside of the observed body weights of 34 kg in Phase 3 trials down to 25 kg have greater uncertainty. The simulations included intersubject variability to capture the distribution of active moiety area under the curve (AUC) at steady state. The distribution of the active moiety AUC at steady state in adolescents versus adults is shown in Figure 3. The distributions substantially overlap with a tendency for increasing active moiety AUC with decreasing body weight.

Figure 3. Comparison of Active Moiety AUC_{24} for Adult AD Participants Versus Adolescents (Model without a Covariate Effect on F and with a Covariate Effect Included on CL)



Repository artifact ID FI-45941712.
The abrocitinib and active moiety AUC (nmol*hr/L) were simulated out to steady state for a typical adult AD patient (white, male, 77 kg), a typical adolescent AD participant (white, male, 59 kg), a low weight adolescent (35 kg), and an extreme low weight adolescent (25 kg). Simulations were performed for 100 mg and 200 mg QD dosing.

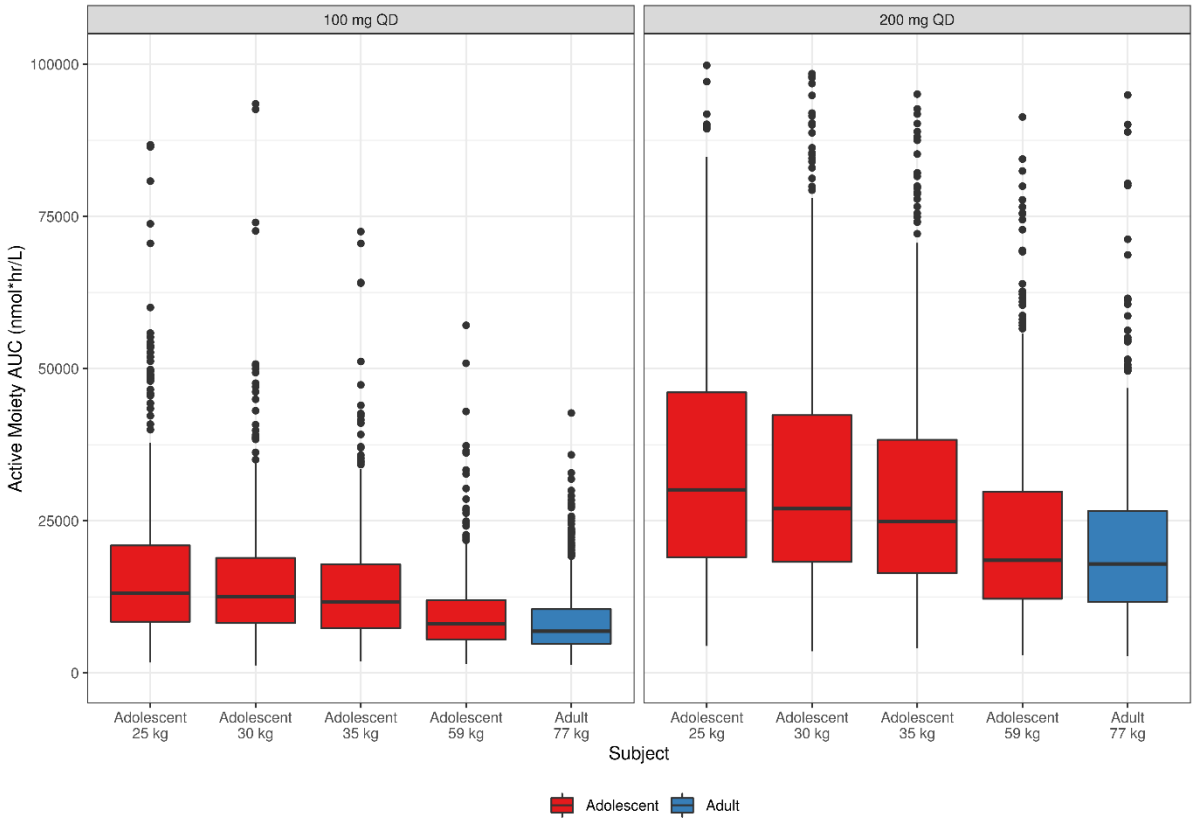
Additionally, to respond to the CHMP's request to simulate exposures in the low body weight adolescent participants using PopPK model without a covariate effect on F, simulations were also performed without a covariate effect on F or CL. The results are shown in Table 3 and Figure 4. This model, however, does not adequately describe the observed data compared with the model with covariate effect on CL. The latter is considered a significantly better model to describe the PopPK of abrocitinib and its metabolites in adults and adolescents, as evidenced by a reduction in the objective function value by over 30 points.

Table 3. Estimated Steady-State AUC for Abrocitinib, M1, M2, and Active Moiety in AD Participants (Model without a Covariate Effect on F or CL)

Dose	Population	Body Weight	Active Moiety		Abrocitinib		M1	M2
			AUC	ΔAUC (%)	AUC	ΔAUC (%)		
100 mg QD	Adult	77	7180	0	9336	0	1250	3767
100 mg QD	Adolescent	25	13485	87.8	12034	28.9	5203	8636
100 mg QD	Adolescent	30	12160	69.4	11500	23.2	4290	7754
100 mg QD	Adolescent	35	11257	56.8	11120	19.1	3234	7147
100 mg QD	Adolescent	59	8150	13.5	9875	5.8	1710	4544
200 mg QD	Adult	77	17702	0	22760	0	2939	9528
200 mg QD	Adolescent	25	32923	86	27955	22.8	12063	21962
200 mg QD	Adolescent	30	27991	58.1	26372	15.9	9639	17998
200 mg QD	Adolescent	35	25720	45.3	24877	9.3	7865	16576
200 mg QD	Adolescent	59	18924	6.9	22760	0	3892	10735

The abrocitinib and active moiety AUC (nmol*hr/L) were simulated out to steady state for a typical adult AD participant (white, male, 77 kg), a typical adolescent AD participant (white, male, 59 kg), a low weight adolescent (35 kg), 3rd percentile for 12-year-old adolescent (30 kg) and an extreme low weight adolescent (25 kg). Simulations were performed for 100 mg and 200 mg QD dosing.

Figure 4. Comparison of Active Moiety AUC_{24} for Adult AD Participants Versus Adolescents (Model without a Covariate Effect on F or CL)



Repository artifact ID FI-45941714.

The abrocitinib and active moiety AUC (nmol*hr/L) were simulated out to steady state for a typical adult AD participant (white, male, 77 kg), a typical adolescent AD participant (white, male, 59 kg), a low weight adolescent (35 kg), and an extreme low weight adolescent (25 kg). Simulations were performed for 100 mg and 200 mg QD dosing.

Overall, the exposures simulated based on the PopPK model without covariate effect on F and covariate included on CL (Table 3 and Figure 4), indicate that the differences in adolescent versus adults are within the limit of 70% increase in active moiety exposure; this limit has been previously established as not clinically significant at the time of initial MAA. Based on this assessment, a change in posology is not considered necessary for lower weight adolescent participants by the MAH.

2.3.3. Discussion and conclusion on clinical pharmacology

The clinical pharmacology has previously been assessed and agreed in the initial MAA (EMEA/H/C/005452/0000). The dose in adolescents was initially proposed to be the same as in adults. However, the adolescents with a low body weight below the adult weight range may be overexposed with the 200 mg dose compared to adults. The MAH was therefore asked to discuss if the lowest body weight (i.e. below 40 kg) adolescents should start with the lowest dose (i.e. 100 mg dose).

In their response, the MAH has simulated exposure for adolescent with lower body weight with and without a covariate effect on F. The MAH argues that there is uncertainty in the simulations outside of the studied body weight range and that the model without a covariate effect on F is significantly worse. The MAH also argues that the AUC distributions substantially overlap with a tendency for increasing active moiety AUC with decreasing body weight. This is agreed.

Further the MAH discusses that the 70% increase in abrocitinib active moiety exposure was established as the upper limit of the therapeutic window based on analysis of clinical data from AD participants with mild renal impairment. The acceptable safety profile in adolescent participants further leads to the conclusion that the 70% limit is also acceptable for this subpopulation of participants.

Thus, the exposure, as expected, is increased with lower body weight. The MAH argues that this is within the therapeutic window and that the safety data in adolescents also supports this conclusion. From a PK point of view, the MAH has satisfactory answered the question, however the suitability of the increased exposure is also dependent on the provided safety data (see Discussion on clinical safety).

2.3.4. Conclusion on clinical pharmacology

Overall, the pharmacokinetics of abrocitinib in the adolescent patients group has been appropriately characterised and relevant dose recommendations are proposed in the SmPC section 4.2 (see Discussion on clinical safety).

2.4. Clinical efficacy

At the time of initial MAA (EMEA/H/C/005452/0000), it was concluded that a statistically significant, and dose-dependent efficacy of abrocitinib 100 mg QD and 200 mg QD versus placebo was demonstrated in patients with moderate to severe AD from 12 years of age and above. As efficacy data of abrocitinib in adolescents have previously been assessed and agreed, these data are described in the presently approved SmPC section 5.1 and presented below.

The efficacy of abrocitinib as monotherapy was evaluated in 2 phase 3 randomised, double-blind, placebo-controlled studies B7451012 and B7451013 (MONO-1, MONO-2) which included 124 patients who were 12 to less than 18 years of age. The efficacy was also evaluated in an open-label induction, randomised withdrawal study B7451014 (REGIMEN), which included 246 patients who were 12 to less than 18 years of age. In these studies, the results in the adolescent subgroup were consistent with the results in the overall study population. The efficacy of abrocitinib in combination with background medicated topical therapy were evaluated in the phase 3 randomised, double-blind, placebo-controlled study B7451036 TEEN. The study included 287 patients who were 12 to less than 18 years of age with moderate-to-severe AD as defined by IGA score ≥ 3, EASI score ≥ 16, BSA involvement ≥ 10%, and PP-NRS ≥ 4 at the baseline visit prior to randomisation. Patients who had a prior inadequate response or who had received systemic therapy, were eligible for inclusion. In TEEN, across all treatment groups 49.1% were female, 56.1% were Caucasian, 33.0% were Asian and 6.0% were Black patients. The median age was 15 years and the proportion of patients with severe AD (IGA of 4) was 38.6%.

Table 4. Adolescent efficacy results in TEEN

	TEEN[d]		
	Abrocitinib		PBO
	200 mg QD N=96	100 mg QD N=95	N=96
IGA 0 or 1[a] % responders (95% CI)	46.2[e] (36.1, 56.4)	41.6[e] (31.3, 51.8)	24.5 (15.8, 33.2)
EASI-75[b] % responders (95% CI)	72.0[e] (62.9, 81.2)	68.5[e] (58.9, 78.2)	41.5 (31.5, 51.4)
PP-NRS4[c] % responders (95% CI)	55.4[e] (44.1, 66.7)	52.6 (41.4, 63.9)	29.8 (20.0, 39.5)

Abbreviations: CI=confidence interval; EASI=Eczema Area and Severity Index; IGA=Investigator Global Assessment; N=number of patients randomised; PBO=placebo; PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily.

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5point scale) and a reduction from baseline of ≥ 2 points.
b. EASI-75 responders were patients with ≥ 75% improvement in EASI from baseline.
c. PP-NRS4 responders were patients with ≥ 4-point improvement in PP-NRS from baseline.
d. Abrocitinib used in combination with medicated topical therapy.
e. Statistically significant with adjustment for multiplicity versus placebo.

Additional information on the efficacy evaluation in adolescents

To evaluate the efficacy of up to 48 weeks of cumulative abrocitinib treatment in adolescents, data were pooled from the parent studies and a long-term extension study B7451015. The Adolescent Long-term Therapy Pool was based on subjects who initially participated in the phase 3 studies B7451012, B7451013 or B7451036 and subsequently entered the phase 3 long-term extension study B7451015. A data cut-off date of 25 September 2021 was used for the efficacy evaluations in this data pool.

Table 5. Number of Adolescent Subjects Evaluated for Efficacy in This Type II Variation

Study	Treatment	Number of adolescents treated with abrocitinib or placebo	Number of adolescents treated with abrocitinib
B7451012	Placebo	17	
	Abrocitinib 100 mg QD	34	34
	Abrocitinib 200 mg QD	33	33
B7451013	Placebo	8	
	Abrocitinib 100 mg QD	17	17
	Abrocitinib 200 mg QD	15	15
B7451036	Placebo	96	
	Abrocitinib 100 mg QD	95	95
	Abrocitinib 200 mg QD	94	94
B7451014 open-label run-in period	Abrocitinib 200 mg QD	246	246
B7451014, randomised treatment	Placebo	49	
	Abrocitinib 100 mg QD	49	49
	Abrocitinib 200 mg QD	47	47
Overall number of unique adolescents treated		655	534
Overall number of unique adolescents in the monotherapy pool (B7451012, B7451013)		124	99
Overall number of unique adolescents in the Combined Adolescent Pool		409	288
Overall number of unique adolescents in the Adolescent Long-term Therapy Pool		357	357

Short-term

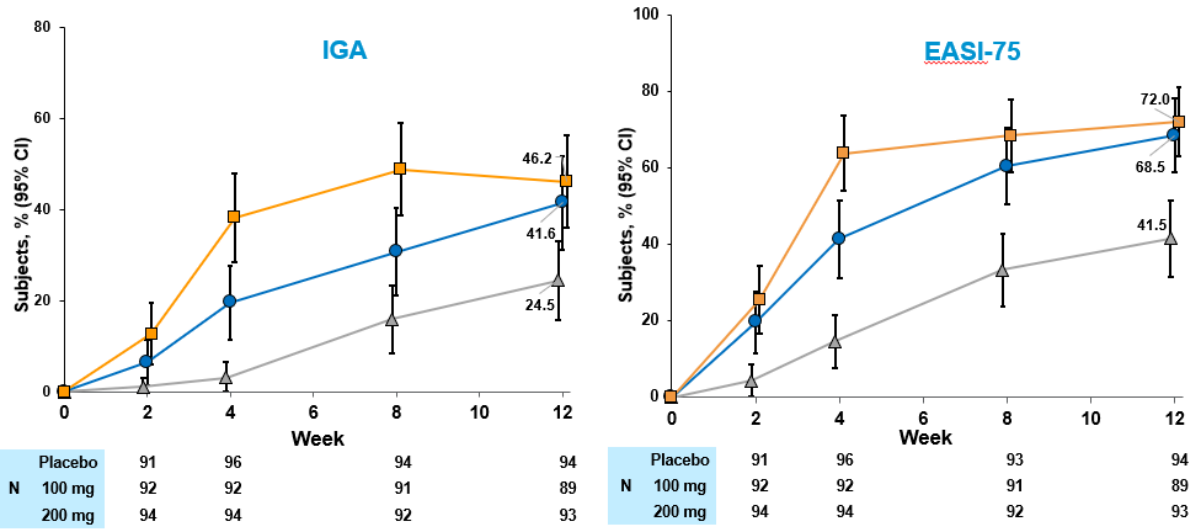
Among the 285 adolescents randomised and dosed in study B7451036, 96 received placebo, 95 received 100 mg QD, and 94 received 200 mg QD. With combination therapy in study B7451036, treatment with abrocitinib 100 mg QD and 200 mg QD resulted in a significantly greater proportion of subjects achieving IGA response and EASI-75 than placebo at Week 12 (Table 6).

Table 6. Proportions of Adolescents Who Achieved Response at Week 12 in the Short-term Adolescent Monotherapy Pool (Studies B7451012 and B7451013) and Study B7451036 (background medicated topical therapy)

	Short-term Adolescent Monotherapy Pool			Study B7451036		
	Placebo	Abrocitinib 100 mg QD	Abrocitinib 200 mg QD	Placebo	Abrocitinib 100 mg QD	Abrocitinib 200 mg QD
IGA response						
N	23	50	48	94	89	93
%	8.7	22.0	31.3	24.5	41.6	46.2
95% CI	(0.0, 20.2)	(10.5, 33.5)	(18.1, 44.4)	(15.8, 33.2)	(31.3, 51.8)	(36.1, 56.4)
EASI-75						
N	23	50	48	94	89	93
%	8.7	44.0	56.3	41.5	68.5	72.0
95% CI	(0.0, 20.2)	(30.2, 57.8)	(42.2, 70.3)	(31.5, 51.4)	(58.9, 78.2)	(62.9, 81.2)
PP-NRS4						
N	22	42	36	84	76	74
%	9.1	28.6	61.1	29.8	52.6	55.4
95% CI	(0.0, 21.1)	(14.9, 42.2)	(45.2, 77.0)	(20.0, 39.5)	(41.4, 63.9)	(44.1, 66.7)

IGA response is defined as IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points.
EASI-75 responders were patients with ≥75% improvement in EASI from baseline.
PP-NRS4 responders were subjects with ≥4-point improvement in PP-NRS from baseline.

Figure 5. Proportion of Adolescents Achieving IGA Response or EASI-75 in Study B7451036



Long-term Efficacy

Long-term efficacy in adolescents has been demonstrated for abrocitinib treatment.

- Among adolescent responders at Week 12, large proportions of adolescents maintained this response at Week 48, demonstrating durability of efficacy.

- o 73.7% and 81.0% of subjects maintained EASI-75 at Week 48 with 100 mg and 200 mg QD, respectively.
- o 58.3% and 65.4% of subjects maintained PP-NRS4 at Week 48 with 100 mg and 200 mg QD, respectively.

- Among adolescent non-responders at Week 12, a substantial proportion developed late onset response within a further 12 weeks of treatment, demonstrating the potential benefit of continued treatment with abrocitinib.
- O 37.0% and 50.0% of subjects achieved late-onset EASI-75 with a further 12 weeks of treatment (i.e., at Week 24) with 100 mg and 200 mg QD, respectively.
- O 23.6% and 33.3% of subjects achieved late-onset PP-NRS4 with a further 12 weeks of treatment (i.e., at Week 24) with 100 mg and 200 mg QD, respectively.

Comparison Between Adolescents and Adults

In short- and long-term studies, the efficacy of abrocitinib in adolescents was similar to that in adults for each dose. This supports the use of the same dosage in both age groups from an efficacy viewpoint (see discussion on clinical safety). Based on population pharmacokinetic analysis submitted within the initial MAA dossier (EMEA/H/C/005452/0000), there was no clinically relevant difference in mean abrocitinib steady-state exposures in adolescent patients compared to adults at their typical body weights.

Short-term

In the Monotherapy Pool, after controlling for other variables with multivariate analysis, there was no meaningful difference in Week 12 response rate between adolescents and adults less than 65 years of age.

Table 7. Proportion of Abrocitinib Monotherapy Responders in Adolescents and Adults at Week 12

	IGA (%)		EASI-75 (%)		PP-NRS4 (%)	
	Adolescents	Adults	Adolescents	Adults	Adolescents	Adults
Placebo	8.7	7.8	8.7	12.2	9.1	18.0
Abrocitinib 100 mg QD	22.0	26.6	44.0	41.9	32.3	44.3
Abrocitinib 200 mg QD	31.3	41.3	56.3	62.3	61.5	56.0

Considering all short-term abrocitinib clinical studies, regardless of the use of background topical medications or not, the response rates at Week 12 in adolescents were similar (within 11% for IGA response and EASI-75, and within 16% for PP-NRS4) to those in adults.

Table 8. Proportions of Adolescents and Adults who Achieved IGA, EASI-75, or PP-NRS4 Response at Week 12 in the Short-Term Pools

		Adolescents			Adults		
		Placebo	Abrocitinib 100 mg QD	Abrocitinib 200 mg QD	Placebo	Abrocitinib 100 mg QD	Abrocitinib 200 mg QD
IGA response							
Week 12	N	117	139	141	311	550	527
	Response (%)	21.4	34.5	41.1	10.3	31.3	45.2
	95% CI	(13.9, 28.8)	(26.6, 42.4)	(33.0, 49.3)	(6.9, 13.7)	(27.4, 35.1)	(40.9, 49.4)
EASI-75							
Week 12	N	117	139	141	311	550	526
	Response (%)	35.0	59.7	66.7	18.6	48.9	66.2
	95% CI	(26.4, 43.7)	(51.6, 67.9)	(58.9, 74.4)	(14.4, 23.1)	(44.7, 53.1)	(62.1, 70.2)
PP-NRS4							
Week 12	N	108	124	118	298	527	519
		Adolescents			Adults		
	Response (%)	9.3	29.7	59.7	17.4	44.9	56.9
	95% CI	(0.0, 21.6)	(16.2, 43.1)	(44.1, 75.3)	(11.7, 23.2)	(39.0, 50.8)	(51.1, 62.7)

IGA response is defined as IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points.
EASI-75 is defined as ≥75% improvement, respectively in EASI, from baseline.
PP-NRS4 is defined as ≥4-point improvement in PP-NRS from baseline.
Adolescents = short-term combined adolescent pool (studies B7451012, B7451013, B7451036)
Adults = short-term combined adult pool (studies B7451006, B7451012, B7451013, B7451029)

Adults in study B7451014 had higher point estimates for proportions of responders, when compared with adolescents, through Week 12 for IGA, EASI-75, and PP-NRS4. However, the overall trends of improvement from baseline were comparable for both groups, and confidence intervals often overlapped.

Long-term

Adolescents in the Adolescent Long-term Pool (357 adolescents) had similar IGA, EASI-75 and PP-NRS4 response rates at Week 48 (difference within 10%) compared with adults in the Adult Long-term Therapy Pool

Long term efficacy data from study B7451014, the phase 3 randomised withdrawal and retreatment study in adults and adolescents, are presented in Figure 6 and Figure 7 below.

Figure 6. Plot of Proportion of Subjects in Study B7451014 With IGA Response at Week 12, 16, 28, 40, and 52 (FAS-RA, Adults and Adolescents, NRI)

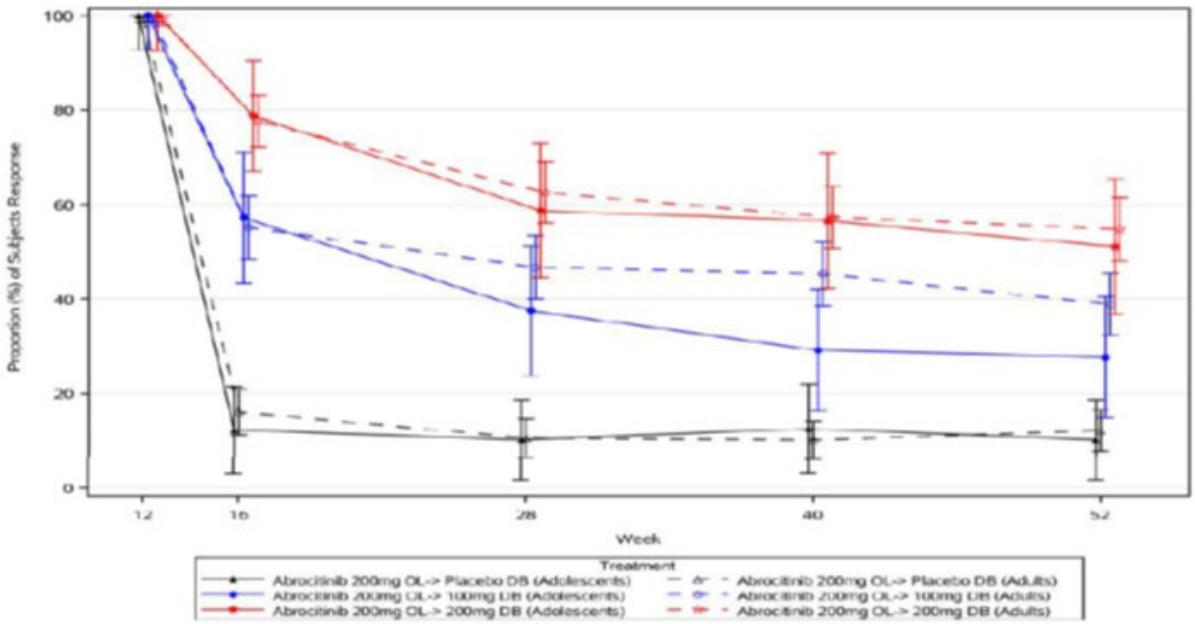
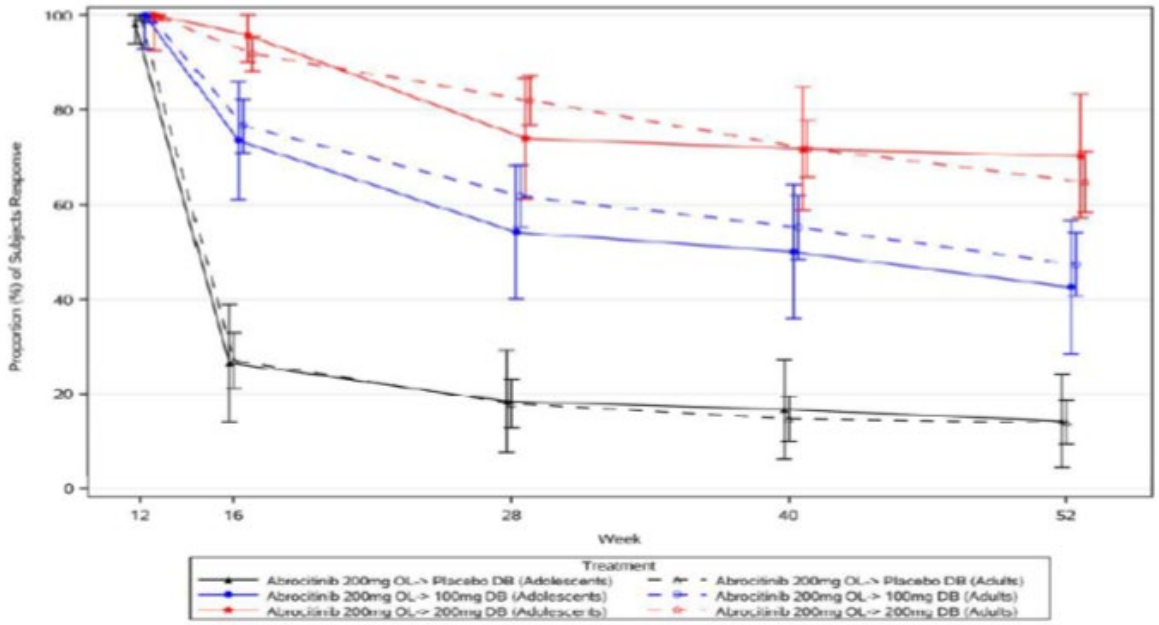


Figure 7. Plot of Proportion of Subjects in Study B7451014 Achieving EASI-75 Response at Week 12, 16, 28, 40, and 52 (FASA-RA Adults and Adolescents, NRI)



Although adults tended Week 12 to Week 52 to have higher point estimates for proportions of IGA, EASI-75, and PP-NRS4 responders in both abrocitinib treatment arms when compared to adolescents, the overall trends were comparable for both groups, and confidence intervals often overlapped. Responder proportions were greater for abrocitinib 200 mg QD than for abrocitinib 100 mg QD, but both abrocitinib doses had markedly higher responder proportions than placebo.

Upon CHMP's request, the MAH provided additional long-term efficacy data in adolescents up to week 96. The long-term efficacy data in adolescents was presented as observed data (instead of data based on

non-responder imputation [NRI]) in line with the data presented in the Long-term Efficacy sub-section in the currently approved Section 5.1 which are observed data.

The response rates from the long-term efficacy data presented as observed data are generally numerically greater than NRI data (Table 9, Table 10).

Table 9. Proportion of Adolescent Long-Term Pool Subjects Who Achieved Response at Week 12 on Abrocitinib and Maintained the Respective Response at Week 48 and Week 96 (NRI vs. Observed Data)

		Abrocitinib 100 mg QD ± Topical Medications		Abrocitinib 200 mg QD ± Topical Medication	
		NRI	Observed data	NRI	Observed data
IGA 0 or 1					
Week 48	N	45	40	51	45
	n (%)	25 (55.6)	25 (62.5)	35 (68.6)	35 (77.8)
	95% CI	(41.0, 70.1)	(47.5, 77.5)	(55.9, 81.4)	(65.6, 89.9)
Week 96	N	NA	34	NA	41
	n (%)	NA	21 (61.8)	NA	32 (78.0)
	95% CI	NA	(45.4, 78.1)	NA	(65.4, 90.7)
EASI-75					
Week 48	N	76	66	79	72
	n (%)	56 (73.7)	56 (84.8)	64 (81.0)	64 (88.9)
	95% CI	(63.8, 83.6)	(76.2, 93.5)	(72.4, 89.7)	(81.6, 96.1)
Week 96	N	NA	54	NA	67
	n (%)	NA	48 (88.9)	NA	62 (92.5)
	95% CI	NA	(80.5, 97.3)	NA	(86.2, 98.8)
PP-NRS4					
Week 48	N	48	41	52	47
	n (%)	28 (58.3)	28 (68.3)	34 (65.4)	34 (72.3)
	95% CI	(44.4, 72.3)	(54.0, 82.5)	(52.5, 78.3)	(59.6, 85.1)
Week 96	N	NA	30	NA	42
	n (%)	NA	23 (76.7)	NA	32 (76.2)

		Abrocitinib 100 mg QD ± Topical Medications		Abrocitinib 200 mg QD ± Topical Medication	
		NRI	Observed data	NRI	Observed data
	95% CI	NA	(61.5, 91.8)	NA	(63.3, 89.1)

CI = confidence interval; EASI-75 = ≥75% improvement from baseline in the Eczema Area and Severity Index total score; IGA = Investigator's Global Assessment; N = number of subjects who were evaluable at each time-point; NA = not available; NRI = non-responder imputation; n (%) = number of subjects who met criteria (percentage based on N); PP-NRS4 = ≥4 points increase in Peak Pruritus Numerical Rating Scale.

Data Cutoff Date: 05 September 2022

Included adolescents who had received abrocitinib or placebo in studies B7451012, B7451013, B7451036 and subsequently enrolled in study B7451015.

Table 10. Proportion of Adolescent Long-Term Pool Subjects Who Were Non - responders at Week 12 and Achieved the Respective Response at Week 24

		Abrocitinib 100 mg QD ± Topical Medications		Abrocitinib 200 mg QD ± Topical Medication	
		NRI	Observed Data	NRI	Observed Data
IGA 0 or 1 Week 24	N n (%) 95% CI	75 24 (32.0) (21.4, 42.6)	71 24 (33.8) (22.8, 44.8)	65 17 (26.2) (15.5, 36.8)	61 17 (27.9) (16.6, 39.1)
EASI-75 Week 24	N n (%) 95% CI	46 17 (37.0) (23.0, 50.9)	42 17 (40.5) (25.6, 55.3)	36 18 (50.0) (33.7, 66.3)	33 18 (54.5) (37.6, 71.5)
PP-NRS4 Week 24	N n (%) 95% CI	55 13 (23.6) (12.4, 34.9)	52 13 (25.0) (13.2, 36.8)	39 13 (33.3) (18.5, 48.1)	36 13 (36.1) (20.4, 51.8)

		Abrocitinib 100 mg QD ± Topical Medications		Abrocitinib 200 mg QD ± Topical Medication	
		NRI	Observed Data	NRI	Observed Data

CI = confidence interval; EASI-75 = ≥75% improvement from baseline in the Eczema Area and Severity Index total score; IGA = Investigator's Global Assessment; N = number of subjects who were evaluable at each time-point; NRI = non-responder imputation; n (%) = number of subjects who met criteria (percentage based on N); PP - NRS4 = ≥4 points increase in Peak Pruritus Numerical Rating Scale.

Data Cutoff Date: 05 September 2022.

Included adolescents who had received abrocitinib or placebo in studies B7451012, B7451013, B7451036 and subsequently enrolled in study B7451015.

2.4.1. Discussion on clinical efficacy

The published literature suggests that the severity of AD was either mild or moderate in a majority of infants and children, whereas a higher percentage of patients in their adulthood have severe AD. Although disease burden has been reported to be higher in adolescents than in adults there are also contradictory study results reporting the burden of AD appearing to increase in adult and elderly patients. Yet, it is agreed with the MAH that the prevalence and burden of AD in adolescents 12 to <18 years of age is significant in many countries worldwide including in the EU.

As stated in previous sections of this report, it was concluded at the time of initial MAA (EMEA/H/C/005452/0000) that a statistically significant, and dose-dependent efficacy of abrocitinib 100 mg QD and 200 mg QD versus placebo was demonstrated in patients with moderate to severe AD from 12 years of age and above. As efficacy data of abrocitinib in adolescents have previously been assessed data are also described in the present approved SmPC section 5.1. There are no new findings in the updated efficacy data that contradict the previous conclusions on efficacy in adolescents.

A type II variation (EMEA/H/C/005452/II/0007) has been approved in February 2023 with update of SmPC section 5.1 with long-term efficacy from the phase 3 studies B7451012, B7451013, and B7451029 and the long-term extension study B7451015 study. In this procedure, it was concluded that efficacy data from the overall study population through 96 weeks of cumulative treatment continue to support the long-term efficacy of both abrocitinib 100 mg QD and 200 mg QD in the treatment of moderate-to-severe AD.

The MAH argues that both abrocitinib 100 mg and 200 mg QD have been demonstrated to be efficacious and that a robust safety database of 635 adolescent subjects (1326.1 PY of exposure) supports a clinically manageable safety profile in adolescents. The MAH has proposed to include both doses for use in adolescents, similar to the posology for adults. With regards to efficacy, the same dose in adults and adolescents is endorsed by the CHMP. Nevertheless, from a safety viewpoint, 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, depending on the clinical characteristics of the patient (See discussion on clinical safety).

Upon CHMP's request, the MAH presented in SmPC section 5.1, the efficacy results in adolescents at week 12 from both monotherapy studies MONO-1 and MONO-2 in addition to the efficacy results in adolescents in the phase 3 study TEEN (study No. B7451036).

Long-term efficacy data (up to week 96) in adolescents has also been submitted and adequately represented in SmPC section 5.1, as requested by CHMP. The presentation of long-term efficacy data using observed data was considered to be more informative to the prescribers. Although the long-term efficacy through week 24 in non-responders at week 12 is not impressively higher compared to the outcome of the placebo group at week 12 of study TEEN, this is also valuable information to the prescriber. Therefore, the inclusion of the below additional wording in SmPC section 5.1 'Paediatric sub-section' is supported.

Among adolescent patients who achieved response after 12 weeks of treatment and entered long-term extension study EXTEND, the majority of patients maintained their response at Week 96 of cumulative treatment for both doses of abrocitinib [62% and 78% for IGA (0 or 1) response, 89% and 93% for EASI-75, and 77% and 76% for PP-NRS4 with 100 mg and 200 mg once daily, respectively].

Among adolescent patients who did not achieve response after 12 weeks of treatment and entered EXTEND, a proportion of patients achieved late-onset response by Week 24 (from baseline) of continued treatment with both doses of abrocitinib [34% and 28% for IGA (0 or 1) response, and 41% and 55% for EASI-75 with 100 mg and 200 mg once daily, respectively].

2.4.2. Conclusions on the clinical efficacy

Efficacy data of abrocitinib in adolescents have previously been assessed and agreed during the initial MAA. There are no new findings in the updated efficacy data submitted by the MAH in this application that contradict the previous conclusions on efficacy in adolescents. Upon CHMP's request, a brief summary on long-term efficacy in adolescents up to week 96 was added to section 5.1 of the SmPC.

Overall, abrocitinib is efficacious in adolescents from 12 and <18 years of age who have moderate to severe AD when administered as monotherapy or combination therapy.

2.5. Clinical safety

Introduction

Because of bone findings in juvenile rats, additional long-term data in growing adolescents was needed to conclude that the benefits of abrocitinib outweigh the risks in this population. The B7451015 MRI sub-study described below is part of the main B7451015 long-term extension study, in which subjects are administered abrocitinib 100 mg or 200 mg QD. The MRI sub-study is a post-authorisation study (category 3, see RMP) that addresses the uncertainties of abrocitinib related to bone safety in adolescents.

Safety data from B7451015 MRI sub-study

Methods

The B7451015 MRI sub-study was designed to detect and identify any potential bone safety findings in the knee in adolescents, including any adverse bone findings or adverse effects on cartilage mineralisation, abnormalities in the growth plate and whether epiphyseal plate closure occurs as expected in adolescents. The knee was considered a suitable body site to evaluate because there are 3 ossification centres. It was also considered that the spatial resolution for MRI provides the best opportunity to identify

morphologic changes that may be related to abrocitinib exposure and that MRI permits visualisation of the ossification centres and verification of epiphyseal plate closure.

To enhance the ability to detect bone safety findings, including (but not limited to) those that might be consistent with the macroscopic and microscopic bone abnormalities observed in rat studies, vigorous, standardised procedures in the performance of the knee MRI, review of the MRI by central radiologists and independent adjudication of potentially abnormal MRI findings were followed.

The sub-study was conducted at selected sites in Australia, China, Hungary, Japan, Poland, and the United States. Participants enrolled in this sub-study receive the same abrocitinib dose as in the main B7451015 study, and there was no randomisation at the time of the enrolment into the sub-study.

MRI

Subjects are to have MRI of the knee performed annually during participation until they reach 18 years of age. A key inclusion criterion was having at least one knee suitable for MRI based on the Investigator's judgment, without prior history of significant trauma or abnormality e.g., any knee condition requiring surgery, any knee condition that is a birth defect, or any condition which had resulted in long-term (>6 months) knee pain, reduction in knee function, or abnormal gait. The exclusion criteria were limited to those that would have any absolute or relative contraindication for an MRI scan e.g., implants, metallic foreign bodies, claustrophobia confounding the interpretation of MRI findings. All MRI units, imaging coils and imaging sequences are approved by a central imaging vendor prior to imaging study participants. In addition, the central radiologist review evaluates the image quality as part of the central review process.

After MRI scans are acquired by the site, they are uploaded for review by central readers. The central readers are blinded to the treatment allocation and all clinical information on a subject except for sex and age at the time of scanning. The central readers in the study are radiologists who are experienced in paediatric imaging and have significant experience evaluating paediatric bone and musculoskeletal abnormalities as part of their clinical practice. Through consultation with several experts in the field of paediatric bone development and paediatric radiography, the MAH developed comprehensive prespecified lists of potential findings on knee MRI that are categorised as 'Potential bone safety findings' or 'Other findings'. The 'Potential bone safety findings' are more likely to represent a potentially drug-related clinical manifestation of the non-clinical bone findings observed for abrocitinib and would be rare in a typical adolescent population. The 'Other findings' are more commonly observed in a typical adolescent population. Both types of findings are outlined on a structured electronic case report form that is completed by the central reader during the central review process of the knee MRI scans. Any potential bone safety findings or other findings that are identified by a central reader are forwarded to an independent Imaging AC for additional review. The AC is composed of 2 paediatric radiologists and 1 paediatric orthopaedist, all with extensive experience in bone imaging. The AC members are blinded to subject ID and treatment allocation.

Long-term data

Height

Height SDS benchmarks an individual's growth against standard growth curves (Johannsson et al, 2018). As such, it is the standard for assessing bone growth and elongation in clinical trials as it supports efficient use of data, allowing assessment in a population in which height needs to be assessed across ages and genders. Accordingly, height SDS over time was analysed in adolescents in the long-term safety data to evaluate the effect of abrocitinib on linear growth.

Weight

Weight SDS over time was also analysed in adolescents in the long-term safety data to evaluate the effect of abrocitinib on growth.

Fracture

Fracture is a relevant measure for assessing a clinically meaningful impact on bone. Fracture rates are high in adolescence because there is a lag in mineralisation relative to bone lengthening (Faulkner et al, 2006). As such, this is a sensitive period in which to assess fracture rates. In a population-based British cohort, approximately one-third of boys and girls sustained at least one fracture before 17 years of age (Cooper et al, 2004). To contextualise the data from the abrocitinib development program, fracture rates in adolescents were examined in 2 external cohorts, the Danish National Registry and The Health Improvement Network.

Results

A total of 58 adolescent subjects were enrolled and all 58 subjects had undergone the first knee MRI. The enrolled adolescents included 27 boys (46.6%) and 31 girls (53.4%). Among the 58 adolescents enrolled, 23 (39.7%) were <15 years of age at the screening visit of the qualifying parent study, including 13 of the 31 girls (41.9%) and 10 of the 27 boys (37.0%). Among the 58 adolescents enrolled, 23 (39.7%) were <15 years of age at first exposure to abrocitinib, including 12 of the 31 girls (38.7%) and 11 of the 27 boys (40.7%).

Demographics

Demographics and baseline characteristics of the MRI sub-study subjects are representative of the adolescent population enrolled in the abrocitinib program (Table 11).

The Long-term Safety Pool 2022 (LTDCP2022) included safety data in subjects on continuous dosing with either abrocitinib 100 mg or abrocitinib 200 mg.

The RRLTP2022 pool included subjects who participated in the randomised phase of study B7451014 as well as the data from B7451015. Therefore, the dosing regimens for these subjects were variable.

Table 11. Demographic and Baseline Characteristics of Adolescents in the MRI Sub-study, and the Long-term Safety Pools LTDCP2022 and RRLTP2022

	MRI Sub-study	**LTDCP2022 Adolescent Subgroup**	**RRLTP2022 Adolescent Subgroup**
	All Abrocitinib N=58	**All Abrocitinib N=490**	**All Abrocitinib N=145**
Gender, male, n (%)	27 (46.6)	257 (52.4)	80 (55.2)
Age, years, Median (Q1, Q3)	15.0 (13.0, 16.0)[a]	15.0 (13.0, 17.0)	15.0 (14.0, 17.0)
Race, n (%)			
White	37 (63.8)	313 (63.9)	109 (75.2)
Black or African American	2 (3.4)	40 (8.2)	7 (4.8)
Asian	19 (32.8)	111 (22.7)	27 (18.6)
Height, cm, Median (Q1, Q3)	164.2 (159.0, 170.3)	164.0 (157.5, 171.0)	165.0 (157.5, 170.2)
Weight, kg, Median (Q1, Q3)	60.6 (52.0, 69.0)	59.1 (50.4, 70.0)	59.4 (50.0, 69.0)
BMI, kg/m^2, Median (Q1, Q3)	22.0 (19.8, 24.5)	21.9 (19.5, 25.2)	21.5 (19.3, 24.5)

Table 11. Demographic and Baseline Characteristics of Adolescents in the MRI Sub-study, and the Long-term Safety Pools LTDCP2022 and RRLTP2022

	MRI Sub-study	LTDCP2022 Adolescent Subgroup	RRLTP2022 Adolescent Subgroup
	All Abrocitinib N=58	All Abrocitinib N=490	All Abrocitinib N=145
Investigator Global Assessment % Moderate/Severe	56.9/43.1	55.3/ 44.7	62.8/ 37.2

a. Age at screening visit of the qualifying parent study
The Long-term Safety Pool 2022 (LTDCP2022) included safety data in subjects on continuous dosing with either abrocitinib 100 mg or abrocitinib 200 mg. The pooling strategy is similar to the FCP2021 pooled data (data cut 16 April 2021) included in the current SmPC.

In addition, the sample size of 58 subjects, the proportion of subjects in the 12-14 years age range (39.7%), and the balance of boys and girls in the study population (male 46.6%) was previously agreed with the CHMP.

Patient Exposure to Abrocitinib in B7451015 study

The median (range) exposure to abrocitinib at the time of the MRI scans was 32.6 (27.7-53.6) months. The treatment duration of the subjects enrolled in the MRI sub-study is considered sufficient by the MAH for the evaluation of potential bone findings related to abrocitinib.

Adverse events

MRI sub-study subjects during the entire B7451015 study

Among the 58 subjects who enrolled in the MRI sub-study, during their participation in the entire main B7451015 long-term extension study, the majority of the AEs were mild or moderate and non-serious, and none resulted in study discontinuation (Table 12). The pattern of AEs in the MRI sub-study subjects was consistent with the known safety profile of abrocitinib.

Table 12. Treatment-emergent AEs (All Causalities) in Adolescents in the MRI Sub-study During Their Participation in the Main B7451015 Study

	Abrocitinib 100 mg QD n (%)	Abrocitinib 200 mg QD n (%)	Total n (%)
Subjects evaluable for adverse events	28	30	58
Number of adverse events	112	124	236
Subjects with adverse events	22 (78.6)	30 (100.0)	52 (89.7)
Subjects with serious adverse events	0	1 (3.3)	1 (1.7)
Subjects with severe adverse events	1 (3.6)	2 (6.7)	3 (5.2)
Subjects discontinued from study due to adverse events	0	0	0
Subjects discontinued study drug due to AE and continued study	0	0	0
Subjects with temporary discontinuation due to adverse events	3 (10.7)	5 (16.7)	8 (13.8)

MRI findings - interim results

Among the 58 subjects, there were no potential bone safety findings identified by central read. A summary of the central readers' findings for the knee MRI scans is shown in Table 13.

Table 13. Summary of Other Findings on Knee MRI by Central Read

	Abrocitinib 100 mg QD (N=28)	Abrocitinib 200 mg QD (N=30)	Total (N=58)
Number of subjects with Other findings in knee MRI	4	5	9
Meniscus tear	0	2 (6.7)	2 (3.4)
Bone marrow edema signal	1 (3.6)	1 (3.3)	2 (3.4)
Altered soft tissue fat signal	2 (7.1)	2 (6.7)	4 (6.9)
Joint effusion	1 (3.6)	2 (6.7)	3 (5.2)
Other discoid lateral meniscus	0	1 (3.3)	1 (1.7)
Other dorsal defect of the patella	1 (3.6)	0	1 (1.7)

Among the 58 subjects, there were no bone findings confirmed by adjudication. There were 'Other findings' in 9 subjects (Table 14). These 'Other findings' have been associated with sport participation or trauma (including overuse and microtrauma) in the radiology literature.

Table 14. Listing of MRI Adjudication Outcome for Other Findings

Subject Number	Abrocitinib dose	Sex	Age at MRI sub-study enrollment (years)	Other Findings	Adjudication Comments
10775001	100 mg QD	M	18	Focal cartilage defect	Dorsal patellar defect
14675002	100 mg QD	M	21	Altered soft tissue fat signal; Joint effusion	Small effusion Mild Hoffa's fat pad impingement
15395004	100 mg QD	M	18	Bone marrow edema signal	Bone contusion medial femoral condyle
17165003	100 mg QD	F	17	Altered soft tissue fat signal	Superolateral Hoffa fat pad edema
10505029	200 mg QD	M	17	Altered soft tissue fat signal	Hoffa's fat pad edema
10505030	200 mg QD	M	15	Bone marrow edema signal; Meniscus tear	There is a bone contusion extending through a closing physis, but it is believed to be traumatic and unlikely to result in any growth problem
10505046	200 mg QD	F	18	Other: Discoid lateral meniscus without signs of tear or instability	Discoid lateral meniscus without signs of tear or instability
11485016	200 mg QD	M	19	Meniscus tear	Bucket handle tear of a lateral discoid meniscus
15665001	200 mg QD	M	16	Joint effusion; Altered soft tissue fat signal	Effusion and fat signal are small. Interstitial ACL signal but ligament intact. No clinical implications of current findings

ACL= anterior cruciate ligament; F=female; M=male; QD=once daily.

Limitations and Mitigation Strategy

Limitations of the design of the B7451015 MRI sub-study and their mitigations are discussed in Table 15, as agreed by PRAC (EMEA/H/C/005452/MEA/004.1).

Table 15. Limitations of the design of the B7451015 MRI sub-study and mitigation strategy

Limitations	Mitigation Strategy
Lack of baseline or control	Although the B7451015 MRI sub-study does not include baseline knee MRI scans or a control group, the study design is appropriate for evaluating if there are any bone safety findings observed on the MRI scan. To support a broad approach to detect and identify any bone-related abnormalities, standardized procedures for performing the knee MRI, and vigorous, pre-specified processes of central read and independent adjudication are followed in the MRI sub-study. Any Potential bone findings and Other findings (non-bone or bone abnormalities commonly observed in a typical adolescent population) that are observed on the subject's knee MRI by the central reviewer are referred for review by an independent Imaging Adjudication Committee. In the absence of baseline MRI or a control group, the broad approach to identify any bone findings in the knee MRI scans could over-report bone safety findings if there are bone abnormalities unrelated to abrocitinib treatment. However, this approach is not expected to under-report bone safety findings. The absence of bone findings in the interim report of the B7451015 MRI sub-study thus effectively resolves the remaining uncertainties about the effect of abrocitinib on bone growth and development in adolescents.
Only 1 anatomical site (the knee) was imaged	The knee was chosen as the site for MRI for a number of reasons. MRI of the knee allows evaluation of 3 ossification centers (distal femur, proximal tibia and proximal fibula). The knee is the largest growth site; the knee accounts for 2/3 of growth in the lower limb (Dimeglio, 2001). In addition, the distal growth plates in the femur remain open longer than other proximal growth plates (Herring, 2022). Therefore, the knee provides a sensitive anatomic site for detecting possible abnormalities in bone growth with MRI. In addition, an atlas of knee MRI images across paediatric and adolescent years is available to provide historic controls such that disruptions in bone development can be readily detected. These factors support the choice of the knee as the optimal site for evaluating the potential effect of abrocitinib on bone growth and development by MRI in adolescents.
The specific bone abnormalities that indicate an adverse effect of abrocitinib on bone growth and development is not specified in the study protocol	It is not known if or how the microscopic effects on bones observed in rats would manifest on MRI scans in adolescent humans. The B7451015 MRI sub-study was therefore designed to broadly identify any potential bone safety findings observed on the MRI, rather than focusing on a narrow set of imaging findings or clinical signs and symptoms. Accordingly, any bone-related abnormalities identified by the central reader in the MRI sub-study were forwarded for review by the independent adjudication committee. Regardless of the specific adverse bone effects that could be attributable to abrocitinib, this approach is expected to detect and identify bone abnormalities in adolescents who underwent knee MRI in the B7451015 sub-study.
The sample size is limited	Sample size calculation for this study was complicated by the lack of information on the incidence of bone safety findings attributable to abrocitinib in adolescents, given no such bone safety findings have been observed in MRI scans in adolescents. Hence as discussed during the initial MAA, we used probabilities of detecting a signal based on what was understood of bone effects in the first juvenile rat study rather than the reported incidence as the basis of sample size calculation. In particular, the target sample size is based on being able to rule out incidence rates higher than a certain threshold based on the upper limit of the 95% confidence interval. For example, in the absence of any event in the study, the 95% confidence interval rules out rates > 7.13% with a very high probability, regardless of the true underlying incidence. Even if the true underlying incidence is as low as 5%, a sample size of 50 subjects gives >90% power to detect at least one event. In that respect, for the purpose of detecting a bone safety signal, the sample size is adequate.

Table 15. Limitations of the design of the B7451015 MRI sub-study and mitigation strategy

Limitations	Mitigation Strategy
The duration of exposure to abrocitinib may be insufficient	At the time of their enrollment in the MRI sub-study, the actual duration of treatment with abrocitinib for the adolescents ranged from 28 to 54 months, with a median treatment duration of 33 months. In other words, each individual adolescent had been exposed to abrocitinib for at least 28 months before enrolling in the MRI sub-study and undergoing the first MRI scan. The minimum actual exposure to abrocitinib (28 months) was thus >10-fold the onset time of any bone findings abnormalities noted in juvenile rats (observation of malrotation or impaired use of the limb or microscopic bone metaphysis dystrophy). Therefore, the duration of exposure to abrocitinib is considered sufficient for detecting if there were bone findings in adolescents participating in the MRI sub-study.
The adolescents enrolled in the MRI sub-study might be too old for growth plate abnormalities to be detected	While growth does slow by the end of puberty, it does not cease until later years. In a study of knee MRI in adolescents, the mean age of transition from Stage III to IV at the distal femur was 19.2 years for females (N=152) and 21.6 years for males (N=138) (Dedouit et al, 2012). Considering the median (Q1, Q3) age of 15.0 (13.0, 16.0) years among the adolescents in the MRI sub-study at the time of screening in the parent study, the age distribution of the enrolled adolescents was appropriate for detecting growth plate abnormalities.
There may be a selection bias among the subjects enrolled in the MRI sub-study because the subjects were not the first 50 adolescents enrolled in Study B7451015	Broad eligibility exclusion criteria for the MRI sub-study allowed most adolescents in Study B7451015 to be eligible to enroll in the MRI sub-study. Among the 58 MRI sub-study participants, their demographics (including age and gender distributions, and BMI) and baseline disease characteristics were similar to those of adolescents in the overall abrocitinib clinical program, indicating that the MRI sub-study participants are representative of the overall B7451015 adolescent study population. Any selection bias introduced is expected to be minimal, and not expected to confound the interpretation of the results.
There could be a survivor bias if a number of adolescent subjects had been discontinued from the main B7451015 study due to adverse events related to bone abnormalities (e.g., musculoskeletal symptoms)	No adolescent subjects have been discontinued in the main B7451015 study due to events related to bone safety in the abrocitinib clinical program. Among adolescents in the abrocitinib clinical program, there were no AEs of osteonecrosis or gait disorders, and only 1 event of "growth retardation" (Section 2.5.5.4.1) with the subject continuing abrocitinib treatment. Therefore, there is no evidence of a survivor bias that would confound the interpretation of the results.
A standardised method of growth plate analysis was not specified in the protocol	Because the B7451015 MRI sub-study is intended to broadly detect and identify any potential bone safety findings in the knee, including but not limited to abnormalities in the growth plate, a standardized approach to growth plate analysis was not incorporated. To enhance the ability to detect bone safety findings, including (but not limited to) those that might be consistent with the macroscopic and microscopic bone abnormalities observed in rat studies, standardized knee MRI procedures, vigorous review of the MRI by central radiologists, and independent adjudication of potential imaging findings were followed.

The MAH considers that the design of the MRI sub-study is appropriate for detecting if there are bone safety findings associated with abrocitinib treatment in adolescents. Considering each individual adolescent had been exposed to abrocitinib for at least 28 months before undergoing the first MRI scan, the minimum actual exposure to abrocitinib (28 months) was thus >10-fold the onset time of any bone findings abnormalities noted in juvenile rats (observation of malrotation or impaired use of the limb or microscopic bone metaphysis dystrophy) (see Table 15). Therefore, even at the time of the first MRI of each participating adolescent, the treatment duration of the subjects enrolled in the MRI sub-study is

considered sufficient for detecting potential bone findings related to abrocitinib. In addition, the target sample size of 50 subjects in the MRI sub-study was agreed before the protocol was finalised and is appropriate for the purpose of detecting if there is a signal of bone safety finding in adolescents. Even if the true underlying incidence is as low as 5%, a sample size of 50 subjects gives >90% power to detect at least one event. The actual number of adolescent subjects enrolled was 58. The observation of no bone safety findings in the interim analysis of the MRI sub-study is considered by the MAH to be consistent with the totality of the non-clinical data package, which suggests no bone safety risk to adolescents.

Adolescent subjects who continue in the MRI sub-study will have annual knee MRI performed until they reach 18 years of age. The results in the final B7451015 MRI sub-study report are expected to further confirm those from this interim analysis.

Based on the interim results from the B7451015 MRI sub-study, the MAH considers that:

- the number of enrolled subjects, age distribution, and male-to-female balance are consistent with those previously enrolled in the initial MAA pivotal studies/program;
- the demographics and baseline characteristics of the MRI sub-study subjects are representative of the adolescent population enrolled in the abrocitinib program;
- no bone-related safety findings were observed in the first knee MRI scans of the 58 subjects enrolled in the B7451015 MRI sub-study;
- there were no knee MRI finding suggestive of adverse effects of abrocitinib treatment on cartilage mineralisation, macroscopic bone effects, joint deformity, or abnormal epiphyseal plate closure; and
- the lack of bone-related safety findings in the knee MRI in adolescents administered abrocitinib is consistent with the totality of the nonclinical bone safety data package, including the data from the completed investigative age sensitivity window GLP toxicity study in juvenile rats.

Analyses of Height, Weight, and Fractures in Long-term data

Clinical safety data includes data from 2 longer-term safety pools with a data cut-off of 5 September 2022 in the LTE study. Within each of these pools there is a subgroup of adolescent subjects. These longer-term pools provided updated longer term safety data for adolescent subjects including updated fracture and height SDS data; and longer-term data in the full pooled datasets to provide context to the adolescent data.

There two long-term safety pools included in this Type II variation, both of which include adolescent subjects are presented below (Table 16; Figure 8).

Figure 8. Schematic for Long term Safety Pools

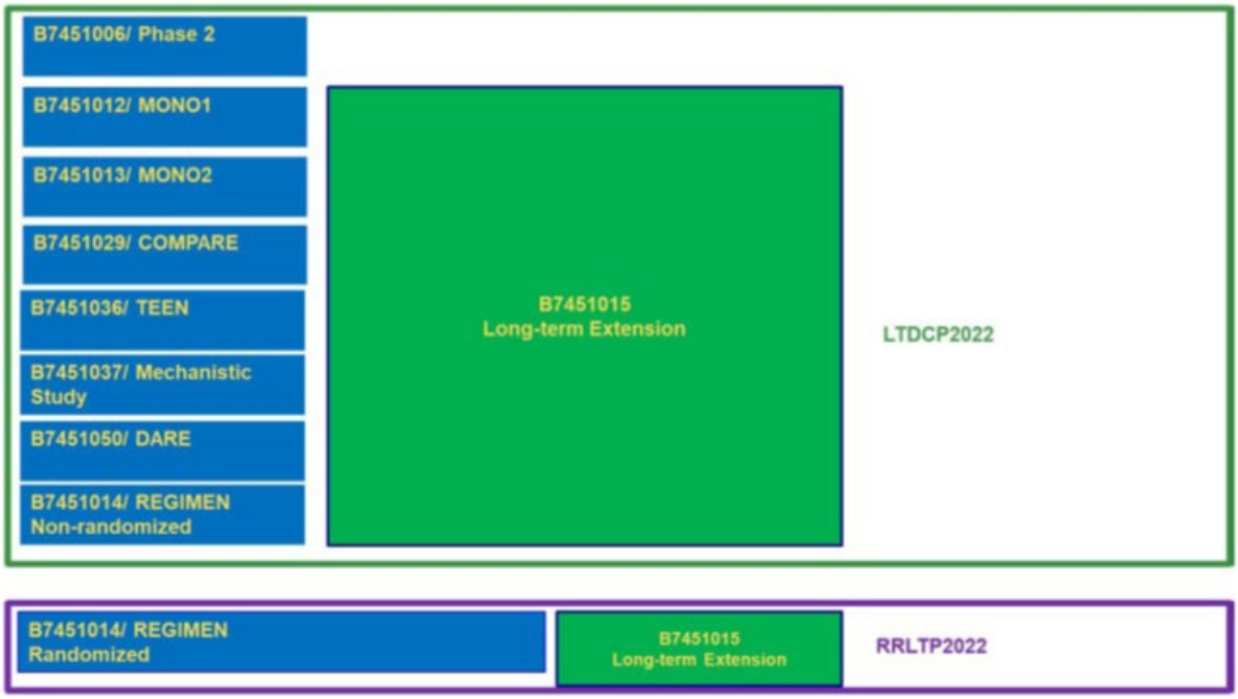


Table 16. Study Data in LTDCP2022, RRLTP2022, FCP2021 and RRLTP

Parent Study		Doses	LTDCP2022	RRLTP2022	FCP2021	RRLTP
B7451006	Phase 2	100/200 mg	X		X	
B7451012	MONO1	100/200 mg	X		X	
B7451013	MONO2	100/200 mg	X		X	
B7451014 Non-randomized/ Non-responders	REGIMEN	200 mg	X		X	
B7451014		Variable		X		X

Parent Study		Doses	LTDCP2022	RRLTP2022	FCP2021	RRLTP
Randomized responders						
B7451029		100/200 mg	X		X	
B7451036		100/200 mg	X		X	
B7451037	Phase 2a	100/200 mg	X			
B7451050 (LSLV 13 July 2021)	DARE	200 mg	X		X	
B7451015 (05 Sep 2022 datacut)	EXTEND	100/200 mg	X	X		
B7451015 (16 April 2021 datacut)		100/200 mg			X	X

The Long-term Safety Pool 2022 (LTDCP2022) included safety data in subjects on continuous dosing with either abrocitinib 100 mg or abrocitinib 200 mg. The pooling strategy is similar to the FCP2021 pooled data (data cut 16 April 2021) included in the current SmPC.

There are 2 additional sources of data:

- Data from the long-term safety study (B7451015) provided from a later data cut-off (05 September 2022 data cut-off).

- Data from the Phase 2a mechanism of action study (B7451037), as the study completed after the data cut-off for the previous pooling of safety data.

The RRLTP2022 included subjects who participated in the randomised phase of study B7451014 (Table 16; Figure 8). The pooling strategy is similar to the RRLTP pooled data (datacut 16 April 2021) included in the current SmPC.

Results

Exposure-long-term data of adolescents

Exposure in the Long-term Safety Pools: LTDCP2022 and RRLTP2022.

Across the two pools, there were 3848 subjects (7146.4 PY).

In the LTDCP2022 there were 490 adolescent subjects (964 PY). The median exposure was 868.5 days (Q1, Q3: 252.0, 1050.0).

In the RRLTP2022 there were 145 adolescent subjects (362.1 PY). The median exposure was 1135.0 days (Q1, Q3: 522.0, 1203.0).

Table 17. Study Treatment Exposure in Adolescents

	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib
N	201	289	145	201	289	145
Patient–Years	253.8	359.5	238.2	404.5	599.5	362.1
Median exposure (Q1, Q3)	492.0 (329.0, 563.0)	485.0 (199.0, 638.0)	641.0 (518.0, 714.0)	863.0 (329.0, 1035.0)	882.0 (199.0, 1068.0)	1135.0 (522.0, 1203.0)
Cumulative Exposure n (%)						
≥48 weeks	149 (74.1)	194 (67.1)	128 (88.3)	149 (74.1)	196 (67.8)	129 (89.0)
≥96 weeks	29 (14.4)	65 (22.5)	54 (37.2)	122 (60.7)	160 (55.4)	99 (68.3)

Demographics

Adolescents in the LTDCP2022: Baseline demographic and disease characteristics were balanced across treatment groups. The median age was 15.0 years (Q1,Q3: [13.0, 17.0]) and 52.4% were males. The majority of the subjects were White (63.9%) or Asian (22.7%). Median EASI was 26.9; 55.3% of subjects had moderate disease and 44.7% severe disease based on IGA. Approximately 33.9% used prior systemic therapy and 64.7% used prior topical agents only. Adolescents had a low prevalence of cardiovascular risk factors; no subjects had a history of CAD and 97.1% of adolescents had never smoked.

Adolescents in the RRLTP2022: Baseline demographic and disease characteristics were balanced across treatment groups. The median age was 15.0 years (Q1,Q3: [14.0, 17.0]) and 55.2% were males. The majority of the subjects were White (75.2%) or Asian (18.6%). Median EASI was 29.2; 62.8% of subjects had moderate disease and 37.2% severe disease based on IGA. Approximately 51% used prior systemic therapy and 49.0% used prior topical agents only.

Height

In adolescents, through approximately 2.5 years of treatment with abrocitinib (i.e., through Day 900), the median, Q1 and Q3 change in height SDS were ≥0 at each time point for each dose in the LTDCP2022 and for the All abrocitinib dose group in the RRLTP2022. Beyond Day 900, the number of evaluable subjects were more limited, but the median height SDS remained ≥0 at all-time points. The median, Q1 and Q3 change in height SDS were also ≥0 at each time point in participants who were 15 years of age or younger at baseline through Day 900. These findings indicate that adolescents treated with abrocitinib did not fall below their height growth curve established at baseline.

There was a single AE of growth retardation, however, the growth in this participant was within an expected range. Subject B7451036/ 11666003, abrocitinib 100 mg: This male participant in China, with a baseline age of 14 years, experienced a mild event of growth retardation (VT: height increase rate lowered [growth retardation] on Exposure Day 601 (12 June 2021). The event was recovering on Exposure Day 859 at the time of the data-cut. The subject had concurrent events of mild weight gain (Exposure Day 601 to >859) and hepatobiliary function abnormal (Exposure Day 601 to 675). There was no treatment or referral to specialist associated with the event. On 28 September 2019 (B7451036 Exposure Day 1), the subject's height was 168.00 cm. The subject's height increased by 3.5 cm, measuring 171.50 cm on 11 January 2020. The subject entered B7451015 on 11 January 2020 (B7451015 Study Day -1). During the B7451015 study, the subject's height increased by 0.5 cm, measuring 172.00 cm on 12 December 2020. The subject's height remained at 172.00 at subsequent study visits in the B7451015 study. The investigator noted that the participant's maternal height was 161 cm and paternal height was 174 cm. The investigator determined that the predicted height, based on

mid-parental height, should be 175 cm. This was the reason for the reported adverse event. The participant's height at baseline (14 years) was 168 cm. Based on the percentile curves of Beijing boys from age 0 through 18 years published by Li, 1999, the participant's height was tracking below this calculated mid-parental height prior to treatment.

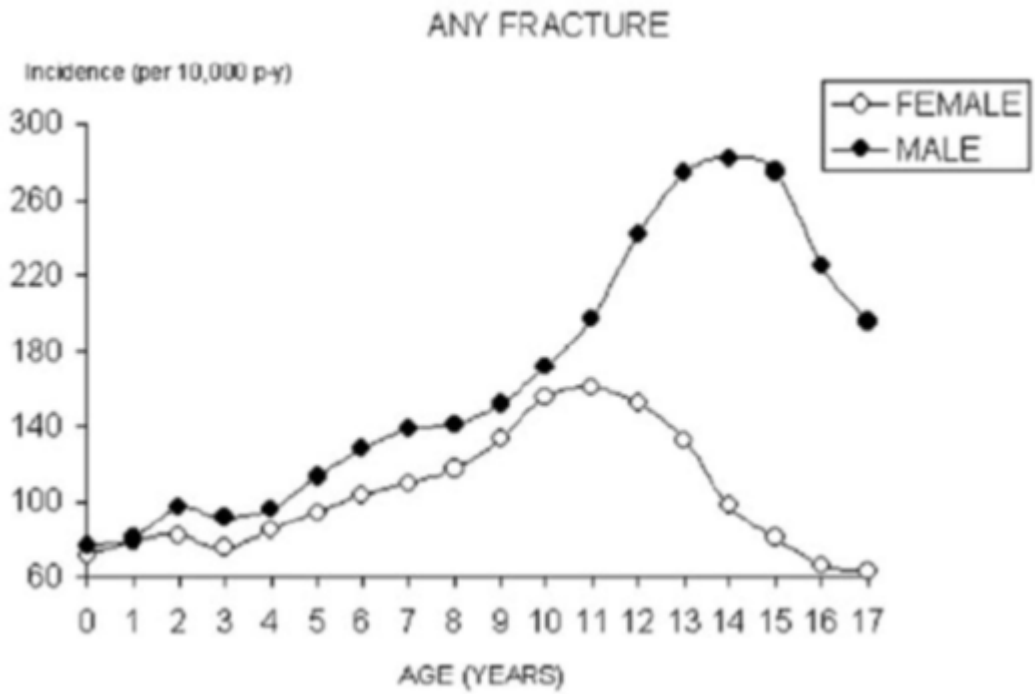
Weight

In adolescents, through approximately 2.5 years of treatment with abrocitinib (i.e., through Day 900), the median, Q1 and Q3 change in weight SDS were ≥0 at each time point for each dose in the LTDCP2022 and for the All abrocitinib dose group in the RRLTP2022. Beyond Day 900, the number of evaluable subjects were more limited, but the median weight SDS remained ≥0 at all-time points. The median, Q1 and Q3 change in weight SDS were also ≥0 at each time point in participants who were 15 years of age or younger at baseline through Day 900. These findings indicate that adolescents treated with abrocitinib did not fall below their weight growth curve established at baseline.

Fracture

Fracture is a relevant measure for assessment of a clinically meaningful impact on bone. Fracture rates are high in adolescence because there is a lag in mineralisation relative to bone lengthening (Faulkner, 2006). As such, this is a sensitive period in which to assess fracture rates. In a population-based British cohort approximately one-third of boys and girls sustained at least one fracture before 17 years of age (Cooper, 2004). At their childhood peak, the incidence of fractures (boys, 3%; girls, 1.5%) is only surpassed at 85 years of age among women and never among men (Cooper, 2004).

Figure 9. Incidence of Fractures in Adolescents



Age- and sex-specific incidence of fractures at any site among children (to age 17 years) registered in the General Practice Research Database, 1988 to 1998. The figure provides rates per 10,000 person-years.

The pattern of fracture events in adolescent subjects did not suggest bone toxicity or fragility fractures (i.e., atraumatic or low-impact trauma fractures). No subjects permanently discontinued treatment due to fracture, all events had recovered, and no subjects had a repeat fracture despite continuation of abrocitinib treatment. There were no clinically apparent vertebral fractures.

In addition, the rates for fracture in adolescents were consistent with relevant external cohort data. There were no increases in the IRs for fracture in adolescents presented as one homogenous group based on the updated database (05 September 2022 data cut) compared to the previously reported long-term safety data.

In the LTDCP2022 and RRLTP2022, there were no increases in the IRs for fracture in adolescents presented as one homogenous group compared to the previously reported long-term safety data in the FCP2021 and RRLTP (Table 18).

Table 18. Proportions and Incidence Rates for Treatment-Emergent Fractures (CMQ) in Adolescent Subjects

	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib
N	201	289	145	201	289	145
n (%)	1 (0.5)	6 (2.1)	2 (1.4)	3 (1.5)	7 (2.4)	3 (2.1)
IR/100 PY (95% CI)	0.39 (0.01, 2.15)	1.64 (0.60, 3.56)	0.83 (0.10, 2.99)	0.74 (0.15, 2.15)	1.24 (0.50, 2.56)	0.81 (0.17, 2.37)

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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.

The fracture rates in adults are described below for comparison. The IRs were similar for fractures in those 18-<65 years and those ≥65 years-of-age. Overall, there were no trends towards dose response (Table 19).

Table 19. Proportions and Incidence Rates for Fracture in Adults (Age 18 - <65 Years and ⩾65 Years

Event	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg N = 1023	Abrocitinib 200 mg N = 1761	All Abrocitinib N = 798	Abrocitinib 100 mg N = 1053	Abrocitinib 200 mg N =1997	All Abrocitinib N =798
Age 18-<65 years						
N	771	1380	623	795	1611	623
n (%)	11 (1.4)	11 (0.8)	9 (1.4)	21 (2.6)	25 (1.6)	15 (2.4)
IR/100 PY	1.11	0.82	0.88	1.42	0.99	0.96
(95% CI)	(0.56, 1.99)	(0.41, 1.47)	(0.40, 1.66)	(0.88, 2.17)	(0.64, 1.45)	(0.54, 1.58)
Age ≥ 65 years						
N	51	92	30	57	97	30
n (%)	1 (2.0)	2 (2.2)	1 (3.3)	2 (3.5)	2 (2.1)	2 (6.7)
IR/100 PY	1.52	2.59	1.97	2.04	1.51	2.62
(95% CI)	(0.04, 8.50)	(0.31, 9.35)	(0.05, 11.00)	(0.25, 7.36)	(0.18, 5.47)	(0.32, 9.47)

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]).
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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.

When combining data for fractures in adolescents overall, compared with adults, 18 to <65 years of age, the difference in IR is small IR 1.24 (0.50, 2.56) and 0.99 (0.64, 1.45) respectively. However, the IR of fractures was numerically higher when specifically studying the <59 kg subgroup compared to the ≥59 kg subgroup following exposure to 200 mg in the in LTDCP2022 pool. For adolescents weighing <59 kg (N=143) the number of fractures were 6, IR=2.17 (0.80, 4.73) compared with adolescents weighing >59 kg (N=146) where number of fractures was 1, IR=0.35 (0.01, 1.94). For the dose 100 mg the difference in number and IRs of fractures was reduced: fractures 2 (N=97) IR= 1.01 (0.12, 3.63) for the<59 kg subgroup and fractures 1 (N= 104), IR= 0.48 (0.01, 2.67) for the ≥59 kg subgroup. As a dose response relation concerning fractures in adolescents cannot be excluded; the MAH was requested to discuss the dose-response relationship of fractures in adolescents and its impact on the dose recommendation.

The MAH has performed a post-hoc analysis and provided estimates and confidence intervals for the incidence difference between groups as requested. No statistically significant differences were found in the IR of fractures between abrocitinib 100 mg and 200 mg in adolescents weighing <59 kg or between the <59 kg and ≥59 kg adolescent subgroups treated with 200 mg. The treatment comparison of difference of fracture incidence rates for subjects exposed to abrocitinib 200 mg QD in groups ≥59 kg vs. <59 kg, is -1.82 (-3.69, 0.04) [0.0554], i.e. including zero with a small margin. However, from a precautionary perspective, considering the numerically higher IR of fractures for adolescents weighing <59 kg treated with 200 mg compared with adolescents weighing ≥59 kg treated with 200 mg, the MAH proposed to limit the starting abrocitinib dose in adolescent patients weighing <59 kg to 100 mg QD. In adolescent patients weighing <59 kg who do not achieve adequate response to 100 mg QD, an increase in dose to 200 mg QD may be considered. See discussion on clinical safety.

Overall Safety in Adolescents

Patient exposure

Across the LTDCP2022 and the RRLTP2022, there were 635 adolescent subjects (1326.1 PY of exposure). A total of 381 adolescent participants had ≥ 96 weeks of exposure.

This represents a larger database of adolescents compared with the 16 April 2021 data cut submitted with the prior Type II variation (EMEA/H/C/005452/II/0001) (635 adolescents, 646.2 PY of exposure) or the initial MAA (364 adolescents, 230.3 PY of exposure).

Adverse events

Table 20. Incidence Rates of Treatment-emergent Aes and AESIs in Adolescents and All Subjects in the Long-term Safety Pools

IR/100 PY	LTDCP2022				RRLTP2022	
	Abrocitinib 100 mg QD		Abrocitinib 200 mg QD		All Abrocitinib	
	Adolescents	All subjects	Adolescents	All subjects	Adolescents	All subjects
N	201	1053	289	1997	145	798
Death	0.00	0.15	0.00	0.21	0.00	0.05
Serious Aes	3.45	6.07	5.47	6.96	3.84	4.20
TEAE Resulting in Permanent Discontinuation	5.39	7.42	6.78	10.13	5.42	5.60
Severe Aes	4.98	6.28	4.67	6.44	5.45	7.43
Serious Infections	0.97	2.20	1.76	2.48	1.08	1.78
All herpes zoster	1.47	2.61	2.17	4.36	2.52	3.17
Adjudicated opportunistic herpes zoster	0.24	0.70	0.53	0.96	0.54	0.59
Adjudicated Tuberculosis	0.00	0.00	0.17	0.06	0.00	0.00
Adjudicated opportunistic infections (excluding tuberculosis and herpes zoster)	0.00	0.00	0.00	0.06	0.00	0.00
Adjudicated MACE	0.24	0.30	0.00	0.28	0.00	0.10
Adjudicated non-fatal VTE	0.00	0.05	0.17	0.28	0.00	0.10
PE	0.00	0.05	0.17	0.21	0.00	0.10
DVT	0.00	0.05	0.00	0.06	0.00	0.00
NMSC	0.00	0.20	0.00	0.09	0.00	0.20
Malignancy (excl. NMSC)	0.00	0.15	0.00	0.34	0.00	0.20
Thrombocytopenia (confirmed platelet count $<50\times10^3/mm^3$)	0.00	0.00	0.00	0.15	0.00	0.00
Lymphopenia (confirmed ALC $<0.5\times10^3/mm^3$)	0.00	0.05	0.00	0.34	0.54	0.44
Fractures	0.74	1.31	1.24	1.05	0.81	0.99

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. Incidence Rates: Number of subjects with events per 100 patient-years.

There were no reported AEs of osteonecrosis or gait disorder. There was a single AE of 'growth retardation' but growth in this subject was within the expected range.

The overall safety profile in adolescents was consistent with that in all subjects in the long-term safety pools (Table 20). The risk of herpes zoster in adolescents was lower than that in adults (adolescents 1.88/100 PY versus adults 18-<65 years of age 4.00/100 PY). No malignancies or confirmed platelet count <50×103/mm3 were reported in adolescents.

Serious adverse event/deaths/other significant events in adolescents

Deaths

There were no deaths in adolescents.

Serious adverse events

Table 21. Proportions and Incidence Rates for Serious Adverse Events: Adolescents

	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib
N	201	289	145	201	289	145
n (%)	10 (5.0)	20 (6.9)	8 (5.5)	14 (7.0)	30 (10.4)	14 (9.7)
IR/100 PY	3.88	5.60	3.33	3.45	5.47	3.84
(95% CI)	(1.86, 7.13)	(3.42, 8.65)	(1.44, 6.56)	(1.89, 5.80)	(3.69, 7.80)	(2.10, 6.44)

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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.

The most frequent serious events in adolescents were infections in both the LTDCP2022 and RRLTP2022. Overall, the safety profile of adolescents related to infections was similar to that of the entire population. There were no unique safety concerns related to infections for adolescents.

Discontinuation due to adverse events

Data related to AEs leading to permanent discontinuation were similar to those that were previously reported.

Table 22. Proportions and Incidence Rates for AEs Leading to Discontinuation: Adolescents

	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib
N	201	289	145	201	289	145
n (%)	14 (7.0)	28 (9.7)	15 (10.3)	22 (10.9)	38 (13.1)	20 (13.8)
IR/100 PY	5.42	7.67	6.26	5.39	6.78	5.42
(95% CI)	(2.96, 9.09)	(5.09, 11.08)	(3.50, 10.32)	(3.38, 8.16)	(4.80, 9.31)	(3.31, 8.37)

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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.

Analysis of Selected Adverse Events by Selected Organ System or Syndrome

Infections

Among adolescents in the LTDCP2022, consistent with the entire population, the totality of the data suggests no meaningful dose relationship for serious infections. There was trend toward a dose-relationship for herpes zoster in adolescents. In the RRLTP2022, where subjects are exposed to variable doses, the IR was consistent with those in the LTDCP2022 (Table 23). The IR of serious infections for adolescents was lower than that of subjects ≥65 years and trended lower compared to those 18-<65 years (Table 23).

Table 23. Proportions and Incidence Rates for Infections in Adolescents

Event	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg N = 201	Abrocitinib 200 mg N = 289	All Abrocitinib N = 145	Abrocitinib 100 mg N = 201	Abrocitinib 200 mg N = 289	All Abrocitinib N = 145
Serious Infections						
n (%)	4 (2.0)	6 (2.1)	3 (2.1)	4 (2.0)	10 (3.5)	4 (2.8)
IR/100 PY	1.54	1.63	1.24	0.97	1.76	1.08
(95% CI)	(0.42, 3.94)	(0.60, 3.54)	(0.26, 3.62)	(0.26, 2.49)	(0.84, 3.23)	(0.29, 2.75)
All Herpes Zoster						
n (%)	5 (2.5)	8 (2.8)	5 (3.4)	6 (3.0)	12 (4.2)	9 (6.2)
IR/100 PY	1.95	2.21	2.12	1.47	2.17	2.52
(95% CI)	(0.63, 4.55)	(0.96, 4.36)	(0.69, 4.95)	(0.54, 3.21)	(1.12, 3.79)	(1.15, 4.78)
Adjudicated Opportunistic Herpes Zoster						
n (%)	1 (0.5)	2 (0.7)	1 (0.7)	1 (0.5)	3 (1.0)	2 (1.4)
IR/100 PY	0.38	0.55	0.41	0.24	0.53	0.54
(95% CI)	(0.01, 2.14)	(0.07, 1.97)	(0.01, 2.31)	(0.01, 1.35)	(0.11, 1.55)	(0.07, 1.95)
Adjudicated Tuberculosis						
n (%)	0	0	0	0	1 (0.3)	0
IR/100 PY	0.00	0.00	-	0.00	0.17	0.00
(95% CI)	(0.00, 1.42)	(0.00, 1.00)		(0.00, 0.89)	(0.00, 0.97)	(0.00, 0.99)
Adjudicated Opportunistic Infections (excluding Tuberculosis and Herpes Zoster)						
n (%)	0	0	0	0	0	0
IR/100 PY	-	-	-	0.00	0.00	0.00
(95% CI)				(0.00, 0.89)	(0.00, 0.65)	(0.00, 0.99)

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]).
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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.

Cardiovascular Safety

MACE

There was 1 event of adjudicated MACE reported in adolescents. Subject B7451036/11626004; abrocitinib 100 mg: Subject with ongoing AD, gout and hyperuricemia (treated with febuxostat) experienced an adverse event of right maxillary sinus submucosal cyst for which a skull MRI was obtained. An incidental finding of a little lacunar white matter degeneration on the right side of ventricle was adjudicated as an ischemic stroke based on the MRI report despite no report of clinical syndrome concerning stroke. The investigator stated that there is no suspicion of CVA, and this event was not considered as a serious event. Febuxostat is labeled with a warning for stroke.

VTE

There was 1 event of PE in an adolescent subject (Subject B7451012/10031004) with multiple risk factors (obesity, extensive family history of VTE including PE in a brother) that was previously described in the original submission (Initial MAA). There were no events of DVT in adolescent subjects.

Malignancy

NMSC: There were no events of NMSC in adolescents.

Malignancy (excluding NMSC): There were no events of malignancy (excluding NMSC) in adolescents.

Hematology events

There were no adolescent subjects with a platelet value meeting thresholds of concern. There were 2 events of lymphopenia in adolescent subjects.

Gastrointestinal Perforation

There were no new cases of gastrointestinal perforation in the LTDCP2022 or RRLTP2022.

Updated Safety in the Total Population

Patient exposure

Across the LTDCP2022 and the RRLTP2022, there were 3848 subjects (7146.4 PY of exposure).

This represents a larger database of subjects compared with the 16 Apr 2021 data cut submitted with the prior Type II variation (EMEA/H/C/005452/II/0001) (3582 subjects, 4313.4 PY of exposure).

Adverse events

TEAEs Long-Term Dose-Controlled Pool 2022-All subjects

Please refer to Table 20 above.

Serious adverse event/deaths/other significant events in adolescents

Serious Adverse Events -All subjects

Table 24. Proportions and Incidence Rates for Serious Adverse Events

	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib
N	1023	1761	798	1053	1997	798
n (%)	81 (7.9)	127 (7.2)	53 (6.6)	117 (11.1)	218 (10.9)	83 (10.4)
IR/100 PY	6.31	7.28	4.06	6.07	6.96	4.20
(95% CI)	(5.01, 7.84)	(6.07, 8.67)	(3.04, 5.31)	(5.02, 7.27)	(6.07, 7.95)	(3.35, 5.21)

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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.

Discontinuation due to adverse events

Data related to AEs leading to permanent discontinuation were similar to those that were previously reported (Table 25). Although there appeared to be a dose-response for AEs leading to discontinuation in the LTDCP2022, both IRs were consistent with those previously reported in the FCP2021.

Table 25. Proportion and Incidence Rates for AEs Leading to Discontinuation

	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib
N	1023	1761	798	1053	1997	798
n (%)	113 (11.0)	230 (13.1)	83 (10.4)	148 (14.1)	326 (16.3)	113 (14.2)
IR/100 PY	8.64	13.00	6.29	7.42	10.13	5.60
(95% CI)	(7.12, 10.38)	(11.37, 14.79)	(5.01, 7.80)	(6.27, 8.71)	(9.06, 11.29)	(4.61, 6.73)

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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.

Analysis of Selected Adverse Events by Selected Organ System or Syndrome

The safety profile for the total population of abrocitinib-treated subjects in the updated database (05 Septmber 2022 data cut-off) remains unchanged compared with that from the 16 Aprril 2021 data cut-off submitted in the prior Type II variation (EMEA/H/C/005452/II/0001).

Infections

Across the longer-term data, including the LTDCP2022 and RRLTP2022, the IRs for serious infection were consistent with that in the FCP2021 and RRLTP (Table 26). There remained no dose-response for serious infections.

Table 26. Proportions and Incidence Rates for Infections

	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg N = 1023	Abrocitinib 200 mg N = 1761	All Abrocitinib N = 798	Abrocitinib 100 mg N = 1053	Abrocitinib 200 mg N =1997	All Abrocitinib N =798
Serious Infections						
n (%)	32 (3.1)	44 (2.5)	28 (3.5)	44 (4.2)	80 (4.0)	36 (4.5)
IR/100 PY (95% CI)	2.43 (1.66, 3.44)	2.46 (1.79, 3.31)	2.11 (1.41, 3.06)	2.20 (1.60, 2.96)	2.48 (1.97, 3.08)	1.78 (1.25, 2.46)
All Herpes Zoster						
n (%)	31 (3.0)	84 (4.8)	41 (5.1)	51 (4.8)	136 (6.8)	62 (7.8)
IR/100 PY (95% CI)	2.39 (1.62, 3.39)	4.83 (3.85, 5.98)	3.17 (2.27, 4.29)	2.61 (1.94, 3.43)	4.36 (3.66, 5.16)	3.17 (2.43, 4.07)
Adjudicated Opportunistic Herpes Zoster						
n (%)	8 (0.8)	22 (1.2)	8 (1.0)	14 (1.3)	31 (1.6)	12 (1.5)

	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg N = 1023	Abrocitinib 200 mg N = 1761	All Abrocitinib N = 798	Abrocitinib 100 mg N = 1053	Abrocitinib 200 mg N =1997	All Abrocitinib N =798
IR/100 PY (95% CI)	0.61 (0.26, 1.20)	1.23 (0.77, 1.87)	0.60 (0.26, 1.19)	0.70 (0.38, 1.17)	0.96 (0.65, 1.36)	0.59 (0.31, 1.04)
Adjudicated Tuberculosis						
n (%)	0	1 (0.1)	0	0	2 (0.1)	0
IR/100 PY (95% CI)	0.00 (0.00, 0.28)	0.06 (0.00, 0.31)	-	0.00 (0.00, 0.18)	0.06 (0.01, 0.22)	0.00 (0.00, 0.18)
Adjudicated Opportunistic Infections (excluding Tuberculosis and Herpes Zoster)						
n (%)	0	0	0	0	2 (0.1)	0
IR/100 PY (95% CI)	-	-	-	0.00 (0.00, 0.18)	0.06 (0.01, 0.22)	0.00 (0.00, 0.18)

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]).
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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.

Cardiovascular Safety

MACE

The totality of the data did not suggest a dose-relationship for MACE. In the LTDCP2022, no trend toward dose-response was observed (Table 27). In the RRLTP2022, the point-estimate for the IR was lower than that in either dose group in the LTDCP2022 (Table 28).

Table 27. Proportions and Incidence Rates for MACE

	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib
N	1023	1761	798	1053	1997	798
n (%)	2 (0.2)	4 (0.2)	2 (0.3)	6 (0.6)	9 (0.5)	2 (0.3)
IR/100 PY	0.15	0.22	0.15	0.30	0.28	0.10
(95% CI)	(0.02, 0.55)	(0.06, 0.57)	(0.02, 0.54)	(0.11, 0.65)	(0.13, 0.52)	(0.01, 0.35)

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]).
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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.

There was an insufficient number of events to conduct a formal risk analysis. In review of subgroup data in the LTDCP2022, the rate of MACE was higher in subjects ≥65 years of age. The IR for MACE was higher

in the older subgroup (baseline age ≥65 years) relative to younger adults (baseline age 18 - <65 years) (1.72/100 PY versus 0.25/100 PY).

VTE

In the RRLLTP2022, the IR for VTE was comparable to the LTDCP2022 (Table 28).

Table 28. Proportions and Incidence Rates for VTE

	FCP2021		RRLTP	LTDCP20222		RRLTP2022
	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib
N	1023	1761	798	1053	1997	798
VTE [1]						
n (%)	1 (0.1)	5 (0.3)	2 (0.3)	1 (0.1)	9 (0.5)	2 (0.3)
IR/100 PY	0.08	0.28	0.15	0.05	0.28	0.10
(95% CI)	(0.00, 0.42)	(0.09, 0.65)	(0.02, 0.54)	(0.00, 0.28)	(0.13, 0.52)	(0.01, 0.35)
PE [1]						
n (%)	1 (0.1)	3 (0.2)	1 (0.1)	1 (0.1)	7 (0.4)	2 (0.3)
IR/100 PY	0.08	0.17	0.08	0.05	0.21	0.10
(95% CI)	(0.00, 0.42)	(0.03, 0.49)	(0.00, 0.42)	(0.00, 0.28)	(0.09, 0.44)	(0.01, 0.35)
DVT						
n (%)	0	2 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)	0
IR/100 PY	0.00	0.11	0.08	0.05	0.06	0.00
(95% CI)	(0.00, 0.28)	(0.01, 0.40)	(0.00, 0.42)	(0.00, 0.28)	(0.01, 0.22)	(0.00, 0.18)

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]).
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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.
[1] Pulmonary embolism event (not adjudicated) was included.

There were an insufficient number of events to conduct a formal risk analysis. In review of subgroup data in the LTDCP2022, there were trends towards a higher IR for VTE in subjects ≥65 years of age and current/former smokers.

Malignancy

NMSC

The IRs for NMSC in the LTDCP2022 excluding these events were 0.15/100 PY (95% CI: 0.03, 0.43) in the abrocitinib 100 mg group and 0.00/100 PY (95% CI: 0.00, 0.11) in the 200 mg group. In the RRLTP2022, where subjects were exposed to variable dosing regimens including both abrocitinib 100 mg and 200 mg, the point estimate and CI for NMSC was generally consistent with the data in the LTDCP2022 (Table 29). The point estimate for NMSC in the LTDCP2022 was lower in the abrocitinib 200 mg group compared to the 100 mg group; however, the 95% CIs overlapped.

Table 29. Proportions and Incidence Rates for NMSC

	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib
N	1023	1761	798	1053	1997	798
n (%)	5 (0.5)	3 (0.2)	4 (0.5)	4 (0.4)*	3 (0.2)	4 (0.5)
IR/100 PY	0.38	0.17	0.30	0.20	0.09	0.20
(95% CI)	(0.12, 0.89)	(0.03, 0.49)	(0.08, 0.77)	(0.05, 0.51)	(0.02, 0.27)	(0.05, 0.50)

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]).
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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.
*One event of NMSC in FCP2021 was reclassified as Malignancy excluding NMSC in LTDCP2022.

Malignancy other than NMSC

In the LTDCP2022, there was a trend toward dose-response in the IR point estimates for malignancy (excluding NMSC); however, the 95% CIs overlapped (Table 30).

Table 30. Proportions and Incidence Rates for Malignancy Excluding NMSC

	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib
N	1023	1761	798	1053	1997	798
n (%)	1 (0.1)	6 (0.3)	2 (0.3)	3 (0.3)	11 (0.6)	4 (0.5)
IR/100 PY	0.08	0.33	0.15	0.15	0.34	0.20
(95% CI)	(0.00, 0.42)	(0.12, 0.73)	(0.02, 0.54)	(0.03, 0.43)	(0.17, 0.60)	(0.05, 0.50)

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]).
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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.

Haematology events

Thrombocytopenia

The IRs for thrombocytopenia were higher in the older subgroup (baseline age ≥65 years) relative to younger adults (baseline age 18 - <65 years), as defined both by confirmed platelet count <75×103/mm3 (1.73/100 PY versus 0.20/100 PY, respectively) or defined by confirmed platelet count <50×103/mm3 (0.86/100 PY versus 0.07/100 PY, respectively). Most of these events occurred in the abrocitinib 200 mg group.

Table 31. Proportions and Incidence Rates for Thrombocytopenia (Confirmed Platelet Count <75 x $10^3/mm^3$ and <50 x $10^3/mm^3$)

	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib
N	1023	1761	798	1053	1997	798
Confirmed Platelet Count <75 × $10^3/mm^3$						
n (%)	0	8 (0.5)	4 (0.5)	1 (0.1)	11 (0.6)	4 (0.5)
IR/100 PY	0.00	0.45	0.30	0.05	0.34	0.20
(95% CI)	(0.00, 0.28)	(0.19, 0.88)	(0.08, 0.77)	(0.00, 0.28)	(0.17, 0.60)	(0.05, 0.50)
Confirmed Platelet Count <50 × $10^3/mm^3$						
n (%)	0	3 (0.2)	0	0	5 (0.3)	0
IR/100 PY	0.00	0.17	-	0.00	0.15	0.00
(95% CI)	(0.00, 0.28)	(0.03, 0.49)		(0.00, 0.18)	(0.05, 0.36)	(0.00, 0.18)

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]).
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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.

Lymphopenia

The IR for lymphopenia, defined as a confirmed ALC <0.5×103/mm3, was higher in the subjects ≥65 years of age subgroup compared to subjects 18-<65 years of age (3.01/100 PY versus 0.12/100 PY). Most of these events occurred in the abrocitinib 200 mg group (Table 32).

Table 32. Proportions and Incidence Rates for Lymphopenia (Confirmed Absolute Lymphocyte Count <0.5×$10^3/mm^3$

	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib
N	1023	1761	798	1053	1997	798
n (%)	0	10 (0.6)	5 (0.6)	1 (0.1)	11 (0.6)	9 (1.1)
IR/100 PY	0.00	0.56	0.38	0.05	0.34	0.44
(95% CI)	(0.00, 0.28)	(0.27, 1.02)	(0.12, 0.88)	(0.00, 0.28)	(0.17, 0.60)	(0.20, 0.84)

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]).
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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.

Gastrointestinal perforation

There was no dose response for gastrointestinal perforation (Table 33). There were 2 additional cases in the LTDCP2022/RRLTP2022 compared to the FCP2021/RRLTP.

Table 33. Proportions and Incidence Rates for Gastroinstestinal Perforation

	FCP2021		RRLTP	LTDCP2022		RRLTP2022
	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib	Abrocitinib 100 mg	Abrocitinib 200 mg	All Abrocitinib
N	1023	1761	798	1053	1997	798
n (%)	4 (0.4)	1 (0.1)	0	5 (0.5)	2 (0.1)	0
IR/100 PY	0.30	0.06	0	0.25	0.06	0.00
(95% CI)	(0.08, 0.77)	(0.00, 0.31)		(0.08, 0.58)	(0.01, 0.22)	(0.00, 0.18)

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]).
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. Incidence Rates: Number of subjects with events per 100 patient-years.
Confidence intervals (CI) were calculated for incidence rates based on the assumption that the actual count of cases arises from a Poisson distribution.

Post marketing experience

Post-marketing exposure data for abrocitinib are limited. A total of 525 adverse events have been reported to the MAH's safety database from 327 cases since the initial marketing of abrocitinib to the data cut-off of 07 September 2022. Of these 327 cases, 37 cases (49 adverse events) were reported in patients less than or equal to 17 years. Five of the 49 events were serious (Covid 19, eczema herpeticum, hematochezia, herpes zoster and skin lesion). The types of events reported from the post-marketing data were consistent with clinical trial data. No new safety signal was identified based on review of these data.

2.5.1. Discussion on clinical safety

Because of bone findings in juvenile rats, additional long-term data in growing adolescents was needed to conclude that the benefits of abrocitinib outweigh the risks in this population. The MRI sub-study was thus performed to address the uncertainties of abrocitinib related to bone safety in adolescents.

The MRI sub-study is a sub-study of the main long-term extension study B7451015 in which subjects, including adolescents, have been exposed to abrocitinib for a long period of time. Although the B7451015 MRI sub-study does not include baseline knee MRI scans or a control group, the study design was considered acceptable by the CHMP for evaluating bone safety findings. The advantage of results in a quick and timely fashion when performed as a sub-study of an already ongoing study of adults and adolescents was also seen. At the time of their enrollment in the MRI sub-study, the duration of treatment with abrocitinib for the adolescents ranged from 28 to 54 months, with a median treatment duration of 33 months i.e. each individual adolescent had been exposed to abrocitinib for at least 28 months before enrolling in the MRI sub-study and undergoing the first MRI scan. This is acceptable.

During the assessment of the protocol of this MRI study (EMEA/H/C/005452/MEA/004.1), several issues addressed by the MAH were discussed. The sample size is limited and information on the probability of detecting an event has been added to the protocol ('with a sample size of approximately 50 adolescents

and an event incidence of 20%, there is a >99% probability of observing at least 2 events and >80% probability of observing 8 or more events. Even if the true incidence were 5%, the probability of detecting at least 1 event is >92.3%'). The demographics of the 58 MRI sub-study participants (including age and gender distributions, weight, and BMI) and baseline disease characteristics were similar to those of adolescents enrolled in the completed Phase 3 study B7451036 and in the overall abrocitinib clinical program indicating that the MRI sub-study participants are representative of the overall B7451015 adolescent study population, addressing the raised concern of selection bias.

Adolescent subjects who continue in the MRI sub-study will have annual knee MRI performed until they reach 18 years of age. The results in the final B7451015 MRI sub-study report are expected to be submitted for additional follow-up of this interim analysis at agreed timelines for this category 3 PASS (see RMP). The MAH will also include a discussion on the limitations of the study methodology, as agreed by PRAC during the assessment of the study protocol.

The proportion of all subjects with TEAEs judged as treatment-related was higher in the abrocitinib 200 mg QD treatment group compared to the abrocitinib 100 mg QD treatment group already at the time of MA approval and a dose-response for AEs leading to discontinuation was also noted in the recent update, LTDCP2022, similar to previous update. In conclusion both adults and adolescents demonstrate similar dose-response for AEs leading to discontinuation.

In previous fracture data of adolescents discussed during the iMAA procedure, there was a concern of a dose relationship. It is agreed with the MAH that in the present LTDCP2022 and RRLTP2022 safety pools, there are no increases in the IRs for fracture in adolescents presented as one homogenous group compared to the previously reported long-term safety data in the FCP2021 and RRLT safety pools, but rather a numerically decreased gap between the two different dosages of abrocitinib. The 95% CIs are overlapping and do not suggest a dose-relationship for fractures. It is agreed that no bone-related safety findings were observed in the interim results of first knee MRI scans of the 58 subjects enrolled in the B7451015 MRI sub-study and that there were no knee MRI finding suggestive of adverse effects of abrocitinib treatment on cartilage mineralisation, macroscopic bone effects, joint deformity or abnormal epiphyseal plate closure. These clinical safety data together with the completed GLP preclinical age sensitivity window toxicity study in juvenile rats are reassuring concerning bone safety.

Following the JAKis Article 20 PhV referral, it was concluded that the lowest effective dose of abrocitinib for maintenance should be considered and that the recommended starting dose in adults is 100 mg or 200 mg once daily based on individual patient characteristics and the 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 (see section 4.4). If the patient does not respond adequately to 100 mg once daily, the dose can be increased to 200 mg once daily. The MAH argues that both abrocitinib 100 mg and 200 mg QD have been demonstrated to be efficacious and that a robust safety database of 635 adolescent subjects (1326.1 PY of exposure) supports a clinically manageable safety profile in adolescents and initially proposed to include both doses for use in adolescents, similar to the posology for adults.

While it is agreed that the safety profile as observed for the adult population seems similar to adolescents as presented in the submitted data with adolescents presented as one homogenous group; the exposure to abrocitinib, as expected, is increased with lower body weight.

To analyse the prevalence of AEs (including fractures) in adolescents with lower body weights, the following body weight thresholds were chose by the MAH: '<59 kg' (this threshold approximates the median of baseline body weight in adolescents who received abrocitinib in the Phase 3 program (59.1 kg in LTDCP2022; 59.4 kg in RRLTP2022) and with approximately equal number of adolescents in the <59 kg and ≥59 kg subgroups, this is considered the main analysis); '<50 kg' (this threshold approximates the first quartile of baseline body weight in adolescents who received abrocitinib (50.4 kg in LTDCP2022;

50.0 kg in RRLTP2022); however this subgroup includes fewer adolescents compared with the main analysis subgroup (<59 kg) and is included as a sensitivity analysis); and '<40 kg' (this threshold was chosen to explore the safety profile in adolescent subjects with the lowest body weights in the Phase 3 program, minimum weight 31.8 kg in LTDCP2022; 40.0 kg in RRLTP2022).

In the <59 kg subgroup of adolescents of the LTDCP2022 pool, following exposure to 200 mg, fractures were numerically higher compared to the ≥59 kg subgroup. This difference between the <59 kg subgroup group compared to the ≥59 kg subgroup was higher for the exposure to 200 mg compared to exposure to 100 mg; for the 200 mg dose IR=2.17 (0.80, 4.73) vs IR=0.35 (0.01, 1.94) and for the 100mg dose IR= 1.01 (0.12, 3.63) vs IR= 0.48 (0.01, 2.67) respectively. Therefore, from a safety viewpoint a dose response relation concerning fractures in adolescents could not be excluded. The MAH has performed post-hoc analysis and provided estimates and confidence intervals for the incidence difference between groups, as requested by CHMP. No statistically significant differences were found in the IR of fractures between abrocitinib 100 mg and 200 mg in adolescents weighing <59 kg or between the <59 kg and ≥59 kg adolescent subgroups treated with 200 mg. The treatment comparison of difference of fracture incidence rates for subjects exposed to abrocitinib 200 mg QD in groups ≥59 kg vs. <59 kg, is -1.82 (-3.69, 0.04) [0.0554], i.e. including zero with a small margin. However, from a precautionary perspective, considering the numerically higher IR of fractures for adolescents weighing <59 kg treated with 200 mg compared with adolescents weighing ≥59 kg treated with 200 mg, the MAH proposes to limit the starting abrocitinib dose in adolescent patients weighing <59 kg to 100 mg QD. In adolescent patients weighing <59 kg who do not achieve adequate response to 100 mg QD, an increase in dose to 200 mg QD may be considered. This information has been added to the text in section 4.2 of the SmPC. The MAH also agreed to maintain fractures as an important potential risk for abrocitinib (see RMP).

An updated safety data cut-off up to 05 September 2022 was also included as part of this submission as agreed as part of the Article 20 referral on JAKis. The Package Leaflet is updated in accordance. No new safety signals have emerged, and the safety profile, apart from the finding that fractures were numerically higher in the adolescents with lower body weight, is in line with previously reported data. The changes proposed to the SmPC section 4.8 on long-term safety representing a larger database of subjects compared with the 16 April 2021 data cut-off submitted with the prior Type II variation (EMEA/H/C/005452/II/0001) (3582 subjects, 4313.4 PY of exposure) are considered acceptable.

Post-marketing safety data will be continuously followed in future PSURs.

2.5.2. Conclusions on clinical safety

Due to the findings of detrimental effects on bone development in preclinical studies and the uncertainties of the relevance of these findings for growing adolescents, the therapeutic indication had been restricted to adults > 18 years of age at the time of iMAA. Non-clinical and clinical data submitted as part of this application suggest no risk to bone growth and development in adolescents.

The safety profile of the overall population of abrocitinib remains unchanged based on the updated safety data submitted by the MAH. The safety profile of adolescents presented as one homogenous group, is in line with the adult population. However, based on the precautionary principle, a recommended daily dose of 100 mg in adolescents <59 kg is proposed by the MAH and agreed by the CHMP.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The PRAC considered that the risk management plan version 4.4 is acceptable.

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
	Long-term safety in adolescents

Pharmacovigilance plan

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				
B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib Among Patients with Atopic Dermatitis in the EU Planned	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-JAKi) chronic	Safety concerns addressed include: • VTE • Herpes zoster, • Serious and opportunistic infection, • Myopathies (including rhabdomyolysis), • Gastrointestinal perforation,	Draft protocol submission Start of data collection	Within 6 months of abrocitinib approval in the EU (July 2022) 31 Dec 2024 15 May 2034

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3	systemic treatments for AD (herein referred to as "comparator treatments")in a real-world setting.	• Malignancy (excluding NMSC), • NMSC, • MACE, • Fractures, • Missing information: Long-term safety, and • Missing information: Long-term safety in adolescents	End of data collection Progress report 1 Progress report 2 Interim report 1 Interim report 2 Final report	 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: • 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,	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 paediatric patients <12 years-of-age, and • Embryofoetal toxicity following exposure in utero.	Draft protocol submission Feasibility assessment to evaluate changes in utilization patterns per aRMM. Start of data collection End of data collection Final report	Within 6 months of abrocitinib approval in the EU (July 2022) Submitted to the EMA on 26 March 2023 TBD TBD December 2028

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	and NMSC 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, and • Indicators of adherence to no use in patients aged <12 years-of-age.			
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 Ongoing	• To evaluate if abrocitinib has any clinically meaningful effects on bone growth and development • Primary endpoint • To detect the proportion of	Safety concern addressed include: • Long-term safety in adolescents	Draft protocol submission Interim Report	Within 6 months of abrocitinib approval in the EU (July 2022) December 2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	abnormal bone findings in knee MRI in adolescent subjects exposed to abrocitinib 100 mg and 200 mg		Final Report	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

Risk minimisation measures

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.

Safety Concern	Routine risk minimisation activities
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 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.

Safety Concern	Routine risk minimisation activities
	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.
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:**

Safety Concern	Routine risk minimisation activities
	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.
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

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template which accepted by the CHMP.

2.7.1. User consultation

No user consultation with target patient groups on the package leaflet has been submitted by the MAH, this is acceptable since the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication is treatment of moderate-to-severe atopic dermatitis (AD) in adolescents 12 years and <18 who are candidates for systemic therapy.

AD is a common disease affecting the skin that often starts in early childhood. The clinical picture differs depending on the affected subjects age, infants and toddlers have different locations on the body affected by the disease compared with adolescents and adults. In some cases, the disease disappears during puberty, however there are many individuals around the world with the more severe forms of AD that respond inadequately to standard treatment, most often emollients and topical corticosteroids of different potency. The prevalence and burden of AD in adolescents 12 to <18 years of age is considered to be significant in the EU.

3.1.2. Available therapies and unmet medical need

Available therapies include moisturizing creams (skin hydration and restoration of the skin barrier) and topical therapies (corticosteroids, calcineurin inhibitors and PDE4 inhibitor) and systemic therapies. Ciclosporin is approved for treatment of severe AD in most European countries, but it is not suitable for long term use due to toxicities. Five agents from 2 pharmacological classes of advanced treatments have been approved for moderate-to-severe AD in adolescents in the EU. Dupilumab, a monoclonal antibody that targets IL-4 receptor and inhibits IL-4 and IL-13 signaling, as well as tralokinumab and lebrikizumab, IL-13 antagonists, have been demonstrated to be efficacious in adolescents in Phase 3 studies. These biologic agents are administered by injections, which are not well tolerated by all adolescents. Upadacitinib is an oral JAK1 inhibitor that is approved for treatment of moderate-to-severe AD in adolescents in the EU; and baricitinib is an oral JAK1/2 inhibitor that is approved for treatment of moderate-to-severe AD in adults and paediatric patients 2yo.

There is no unmet medical need concerning systemic therapies for treatment of moderate to severe AD of adolescents. However, considering the heterogeneity of clinical manifestations and pathological pathways of AD, and varying PK and tolerance to side-effects among patients, additional treatment options are warranted in adolescents with moderate-to-severe AD.

3.1.3. Main clinical studies

The efficacy of abrocitinib as monotherapy was evaluated in 2 phase 3 randomised, double-blind, placebo-controlled studies B7451012 and B7451013 (MONO-1, MONO-2) which included 124 patients who were 12 to less than 18 years of age. The efficacy was also evaluated in an open-label induction, randomised withdrawal study B7451014 (REGIMEN), which included 246 patients who were 12 to less than 18 years of age. In these studies, the results in the adolescent subgroup were consistent with the results in the overall study population. The efficacy of abrocitinib in combination with background medicated topical therapy were evaluated in the phase 3 randomised, double-blind, placebo-controlled study B7451036 TEEN which included 287 patients who were 12 to less than 18 years of age with moderate-to-severe AD as defined by IGA score ≥ 3, EASI score ≥ 16, BSA involvement ≥ 10%, and PP-NRS ≥ 4 at the baseline visit prior to randomisation. See EPAR, EMEA/H/C/005452/0000.

3.2. Favourable effects

The main evidence of efficacy from performed studies has previously been submitted and evaluated during the initial MAA procedure for both adults and adolescents and considered positive (see EPAR, EMEA/H/C/005452/0000).

Superiority of abrocitinib 100 mg QD and 200 mg QD versus placebo was demonstrated in both co-primary efficacy endpoints (IGA and EASI-75) which are well established clinical endpoints used in AD studies. A dose-response relationship was shown, with the highest level of efficacy obtained for the dose 200 mg QD. The key secondary efficacy endpoints (PP-NRS-4 and PSAAD) that evaluated efficacy on itch supported the results obtained with the primary efficacy endpoints, that is a dose-dependent efficacy of abrocitinib that was superior to placebo. The results are considered of clinical relevance for the target population. With combination therapy in study B7451036, treatment with abrocitinib 100 mg QD and 200 mg QD resulted in a significantly greater proportion of subjects achieving IGA response and EASI-75 than placebo at Week 12.

In addition, the majority of adolescent responders at week 12 maintained response at week 96, demonstrating durability of response for both doses.

3.3. Uncertainties and limitations about favourable effects

Efficacy data of abrocitinib in adolescents were assessed during the initial MAA, (see EPAR, EMEA/H/C/005452/0000). There are no new finding in the updated efficacy data submitted as part of this application that contradict the previous conclusions on efficacy in adolescents.

3.4. Unfavourable effects

Non-clinical and clinical data submitted as part of this application suggest no risk to bone growth and development in adolescents. The safety profile of adolescents as presented in the submitted data, with adolescents presented as one homogenous group, is in line with the one observed for the adult population. However, the exposure to abrocitinib, as expected, is increased with lower body weight. In the <59 kg subgroup of adolescents of the LTDCP2022 pool, following exposure to 200 mg, fractures were numerically higher compared to the ≥59 kg subgroup. This difference between the <59 kg subgroup group compared to the ≥59 kg subgroup was higher for the exposure to 200 mg compared to exposure to 100 mg; for the 200 mg dose IR=2.17 (0.80, 4.73) vs IR=0.35 (0.01, 1.94) and for the 100mg dose IR= 1.01 (0.12, 3.63) vs IR= 0.48 (0.01, 2.67) respectively.

3.5. Uncertainties and limitations about unfavourable effects

Based on the fact that exposure to abrocitinib in adolescents with lower body weight is higher, and taking into account the notably numerically higher IR of fractures for adolescents weighing <59 kg treated with 200 mg QD compared with adolescents weighing ≥59 kg treated with 200 mg QD, the MAH proposed to limit the starting abrocitinib dose in adolescent patients weighing <59 kg to 100 mg QD. In adolescent patients weighing <59 kg who do not achieve adequate response to 100 mg QD, an increase in dose to 200 mg QD may be considered. This information has been adequately added to the section 4.2 of the SmPC. Fractures remain as an important potential risk for abrocitinib and will be further addressed post-marketing (see RMP).

3.6. Effects Table

Please refer to the initial MAA (see EPAR, EMEA/H/C/005452/0000).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The main evidence of efficacy from performed studies has previously been submitted and evaluated during the initial MAA procedure (EMEA/H/C/005452/0000) for both adults and adolescents; and considered positive. Efficacy data of abrocitinib in adolescents are described in the presently approved SmPC section 5.1. There are no new data in the updated efficacy finding that contradict the previous conclusions on efficacy in adolescents. Overall, studies show that abrocitinib is efficacious in adolescents with moderate to severe AD when administered as monotherapy or combination therapy from 12 and <18 years of age. The majority of adolescent responders at week 12 maintained response at week 96, demonstrating durability of response for both doses. Information on long term efficacy has been added to SmPC section 5.1.

The demonstrated safety profile of abrocitinib in adolescents including dose related common adverse events, show similarities with other JAK inhibitors and is consistent with the mechanism of action and the safety profile described in the approved SmPC. Overall, the exposure of adolescent patients to abrocitinib is considered sufficiently sized. Long-term data in growing adolescents, including the interim results of the B7451015 MRI sub-study aimed at addressing remaining uncertainties of abrocitinib related to bone safety in adolescents, are reassuring. The final results of the B7451015 MRI sub-study will be submitted for assessment by July 2026 (see RMP).

From a benefit/risk perspective, considering the increased exposure and numerically higher number of fractures set against the efficacy in adolescents with body weight <59 kg, a lower daily dose of 100 mg QD is recommended as starting dose in this population.

3.7.2. Balance of benefits and risks

A statistically significant and dose-dependent efficacy of clinical relevance of abrocitinib 100 mg QD and 200 mg QD has previously been concluded in the target population including adolescents of moderate to severe AD. The demonstrated safety profile of abrocitinib in adolescents including dose related common adverse events, show similarities with adults and with other JAK inhibitors and is consistent with the mechanism of action. The exposure of adolescent patients to abrocitinib is considered sufficiently sized.

Overall, the benefit-risk balance is considered positive with the recommended starting dose of 100 mg in adolescents (12 to 17 years of age) weighing 25 to <59 kg.

3.8. Conclusions

The overall B/R of Cibinqo for the treatment of adolescents 12-<18 years of age is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adolescents 12 to < 18 years of age with moderate to severe atopic dermatitis for CIBINQO based on final results from non-clinical study 00655292 [21GR211] and interim results from clinical study B7451015; this is a Phase III multi-center, long-term extension study investigating the efficacy and safety of abrocitinib, with or without topical medicines, administered to subjects aged 12 years and older with moderate to severe atopic dermatitis. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.3. The RMP (version 4.4) is acceptable.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0023/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Cibinqo-H-C-005452-II-Var.0010'

Attachments

1. Product Information of Cibinqo as adopted by the CHMP on 22 February 2024.