EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2021
EMA/647846/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cibinqo

International non-proprietary name: abrocitinib

Procedure No. EMEA/H/C/005452/0000

Note

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

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List of abbreviations

Abbreviation/Acronym	Definition
AD	Atopic dermatitis
ADA	Anti-drug antibodies
ADD/ADHD	Attention deficit disorder/attention deficit-hyperactivity disorder
AE	Adverse event
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration-time curve
AZA	Azathioprine
BA	Bioavailability
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics classification system
BR	Benefit risk
BSA	Body surface area
BSEP	Bile salt export pump
CDLQI	Children's dermatology life quality index
CI	Confidence interval
CMT	Continuous mixing technology
CNS	Central nervous system
CO	Clinical overview
COVID-19	Coronavirus 2019
CSR	Clinical study report
C-SSRS	Columbia suicide severity rating scale
CV	Cardiovascular
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLQI	Dermatology life quality index
DVT	Deep vein thrombosis
EASI	Eczema area and severity index
E. coli	Escherichia coli
eGFR	Estimated glomerular filtration rate
EQ-5D	Euroqol-5D
ESRD	End-stage renal disease
EU	European union
FDA	Food and drug administration
GCP	Good clinical practice
GWAS	Genome-wide association study
HADS	Hospital anxiety and depression scale
HDL	High-density lipoprotein
HDPE	High density polyethylene
HOME	Harmonising outcome measures for eczema
HPMC	Hydroxypropylmethyl cellulose
HPA	Hypothalamic pituitary adrenal
hsCRP	High sensitivity c-reactive protein
HS-GC	Head space gas chromatography
HZ	Herpes zoster
ICH	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
ICP-MS	Inductively coupled plasma mass spectrometry
IFN	Interferon
IGA	Investigator's global assessment
IgE	Immunoglobulin type e
IL	Interleukin
IPC	In-process control
IR	Incidence rate
IR	Infrared
JAK	Janus kinase

Abbreviation/Acronym	Definition
KPNC	Kaiser permanente northern california
LC	Liquid chromatography
LDL	Low-density lipoprotein
LSM	Least squares mean
LTE	Long-term efficacy
MAA	Marketing authorisation application
MACE	Major adverse cardiac events
MATE	Multidrug and toxin extrusion protein
MATE1/2K	Multidrug and toxic compound extrusion transporter 1 and 2k
MCID	Minimal clinically important difference
MMF	Mycophenolic acid
MTX	Methotrexate
NDA	New drug application
NIR	Near infrared spectroscopy
NMR	Nuclear magnetic resonance
NMSC	Non-melanoma skin cancer
NMT	Not more than
NOEL	No observable effect level
NTIS	Nighttime itch scale
OAT	Organic anion transporters
PACMP	Post approval change management protocol
PAT	Process analytical technology
PCMM	Portable, continuous, miniature and modular
PDE	Permitted daily exposure
PDE4	Phosphodiesterase type 4
PE	Pulmonary embolism
Ph. Eur.	European pharmacopoeia
PK	Pharmacokinetics
PMAR	Population modeling analysis report
POC	Proof of concept
POEM	Patient-orientated eczema measure
PP-NRS	Peak pruritus numerical rating scale
PRO	Patient-reported outcomes
PSAAD	Pruritus and symptoms assessment for ad
PVDC	Polyvinylidene chloride
PY	Patient-years
QD	One a day
QoL	Quality of life
QTc	Corrected qt interval
QW/Q2W	Once weekly/once every other week
RH	Relative humidity
RTD	Residence time distribution
SBP	Summary of biopharmaceutics
SCE	Summary of clinical efficacy
SCORAD	Scoring AD
SCP	Summary of clinical pharmacology
SCS	Summary of clinical safety
SmPC	Summary of product characteristics
SOC	System organ class
TAMC	Total aerobic microbial count
TARC	Thymus and activation regulated chemokine
TB	Tuberculosis
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroid
TEAE	Treatment-emergent adverse events
TH	T-helper cell
THIN	The health improvement network
TPMT	Thiopurine methyltransferase
TSLP	Thymic stromal lymphopoietin

Abbreviation/Acronym	Definition
TYK	Tyrosine kinase
TYMC	Total combined yeasts/moulds count
UGT	Uridine diphosphate-glucuronosyltransferase
UK	United Kingdom
ULN	Upper limit of normal
US	United states of America
USP	United states pharmacopoeia
USPI	Us prescribing information
UV/Vis	Ultraviolet/visible
VAS	Visual analog scale
VTE	Venous thromboembolism
WPAI-AD	Work productivity and activity questionnaire: ad

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 28 August 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Cibinqo, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 September 2019.

The applicant applied for the following indication:

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.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision 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.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

1.5. Applicant's request for consideration

1.5.1. New active Substance status

The applicant requested the active substance abrocitinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
14 December 2017	EMEA/H/SAH/085/2/2017/III	Ferran Torres, André Elferink

The Scientific Advice pertained to the following non-clinical and clinical aspects:

- Adequacy of the completed, on-going, and planned non-clinical studies to support future registration in adults, adolescents, and children with atopic dermatitis.
- Adequacy of the completed and proposed clinical pharmacology development plan to characterise the clinical pharmacology of PF-04965842 to support future registration.
- The selected dose(s) and dose regimen(s) to be evaluated in the Phase 3 clinical development programme.
- The design for the proposed pivotal Phase 3 Studies B7451012 and B7451013 including the inclusion criteria, the proposed co-primary endpoints and key secondary endpoint, duration of treatment and follow-up period, and statistical analysis.
- The design for the proposed pivotal Phase 3 Study B7451014 including the definition of responders, primary endpoint, rescue treatment, study duration for demonstrating the potential value of flexible dosing regimens, and statistical analysis.
- The 3-arm randomised, active comparator (dupilumab) and placebo-controlled double-blind design of the additional Phase 3 Study B7451029, including the primary/secondary endpoints, blinding, and statistical analysis.
- The 2-arm randomised, double blind design of the long-term extension Phase 3 Study B7451015.
- Adequacy of the projected safety database from the proposed Phase 3 programme to support registration.
- The proposed safety assessments and safety monitoring plans in the Phase 3 trials.
- Whether the Phase 3 programme could support the proposed posology.
- The inclusion of the "relief of pruritus" claim in the proposed indication statement and within the clinical data section of the label.
- Whether the Phase 3 programme would support inclusion of "use with or without topical therapies" as part of the proposed indication.
- Adequacy of the Phase 3 clinical data package to support the proposed indication statement "For the treatment of patients with moderate to severe atopic dermatitis, including the relief of pruritus, who have had an inadequate response to topical therapy or for whom these treatments are not appropriate. PF-04965842 can be used with or without topical therapies."
- Appropriateness of the proposed PRO instruments.
- Inclusion of adolescents in the Phase 3 studies to support the proposed indication.
- Use of the adolescent versions of the proposed PROs as secondary endpoints in the Phase 3 programme.
- The proposed strategy for paediatric development.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Andrea Laslop

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Nikica Mirošević Skvrce

The application was received by the EMA on	28 August 2020
The procedure started on	1 October 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 December 2020
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 December 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	4 January 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 January 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 April 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	31 May 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 June 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	24 June 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 August 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	01 September 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	14 September 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Cibinqo on	14 October 2021
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	14 October 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin condition characterised by dry, pruritic skin. The goals of treatment for AD include improving the skin's barrier function, suppressing inflammation, and relieving pruritus, one of the key diagnostic criteria for AD. Because of the chronic and recurrent nature of AD, patients often require long-term treatment to relieve symptoms and prevent flares. AD may have different endotypes, including race, ethnicity and age, and patients with and without filaggrin mutations (Czarnowicki et al, 2019). Lesions can affect any part of the body, but distribution and morphology are distinguishably different between pediatric and adult populations (Akdis et al, 2006; Weidinger & Novak, 2016; Guttman-Yassky et al, 2018).

Patients with moderate to severe AD disease are targeted for abrocitinib treatment. Disease severity (mild/moderate/severe) is determined in clinical practice by evaluating objective disease features such as erythema, edema/papulation, oozing/crusts, excoriations, lichenification and disease extent as well as by subjective patient assessment of pruritus and sleep disturbance.

2.1.2. Epidemiology and risk factors, screening tools/prevention

The observational literature suggests that AD affects up to 25% of children and up to 14% of adults worldwide (Sidbury, 2014; Theodosiou et al, 2019). Research suggests that approximately 17% of adolescents and up to 58% of adults with AD have moderate-to-severe disease (Johansson et al, 2015; Egeberg et al, 2017). AD has a global prevalence ranging from 1 to 20% (Daveiga, 2012); approximately 11% of US children and 0.5% of US adults report a diagnosis of AD (Shaw et al, 2011; Eckert et al, 2017).

Most observational studies report a higher prevalence among women than men (Egeberg et al, 2017; Thyssen et al, 2017); however, there is no universal consensus on this topic. AD has similar prevalence across racial and ethnic groups (Hanifin & Reed, 2007; Mei-Yen Yong & Tay, 2017), but because darker skin may hide erythema, AD may be underdiagnosed among those with darker skin tones (Mei-Yen Yong & Tay, 2017). There is growing appreciation that there are racial differences in the clinical presentation (Yew et al, 2018) and immunological polarisation of AD. For example, Asian AD patients show increased epidermal hyperplasia, greater TH17/TH22 and lower TH1 skewing, and similar TH2 activation compared with European or European American AD patients (Noda et al, 2015; Leung, 2015). Two risk factors appear to be consistently and strongly associated with the development of AD: (1) a family history of atopy and (2) the loss of function mutations in the FLG gene. The FLG gene encodes pro-filaggrin, which is degraded to filaggrin monomers, and these proteins play key roles in the terminal differentiation of the epidermis and formation of the skin barrier, including the stratum corneum.

2.1.3. Biologic features, aetiology and pathogenesis

Atopic dermatitis has a complex pathophysiology that is not completely understood. 2 major converging components have been described as the pillars of the disease: abnormalities of the epidermal structure and function; and cutaneous inflammation due to inappropriate immune responses to antigens in the skin (Weidinger & Novak, 2016), also referred as the "inside-out" and "outside-in"

theories (Guttman-Yassky et al, 2018). Epidermal barrier disruptions and skin inflammation are mutually reinforcing processes.

Perturbations of the epidermal barrier enhance the penetration of allergens to the skin and increases the risk of breaking the healthy interaction between the skin and its microbiome, and the likelihood of bacterial, viral and fungal skin infections (Werfel et al, 2016). In this context, antigens are presented to Langerhans cells and inflammatory epidermal dendritic cells with a high affinity receptor to IgE. This antigen presentation promotes the sensitisation of lymphocytes and a T-cell driven immune response.

Skin inflammation, the other component of the cyclic nature of AD, in the initial acute phase TH2 and TH22 responses are augmented with the help of TH17 cells. The mediators produced in this phase contribute to the skin barrier disruptions. The activated keratinocytes release chemokines that attract T-lymphocytes, and cytokines that mediate the innate immune response, and thus skin inflammation. Many of these cytokines signal through the JAK/STAT pathway, importantly those that signal through JAK1 homo and heterodimers are: IL-4, IL-13, IL-33, IL-31, IFN-γ, TSLP, and TARC (Schwartz et al, 2017; Cabanillas et al, 2017).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Atopic dermatitis is a chronic, relapsing inflammatory skin condition characterised by dry, pruritic skin. Lesions can affect any part of the body, but distribution and morphology are distinguishably different between pediatric 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. Adults may have only chronic hand eczema or present with prurigo-like lesions (Weidinger & Novak, 2016).

Diagnosis of AD

Diagnosis of AD is exclusively reliant on clinical features. No laboratory finding or histological feature is pathognomonic of the disease (D'Erme et al, 2017). The most used diagnostic criteria are the Hanifin and Rajka criteria (1980). Essential features include pruritus and eczematous lesions that can be acute, subacute, or chronic.

2.1.5. Management

Optimal control of all aspects of AD, including pruritus, is best achieved through skin hydration and restoration of the skin barrier with moisturizing creams, control of skin inflammation and allergen avoidance. Many published treatment guidelines recommend a stepwise approach to management.

The goals of treatment are to reduce symptoms (pruritus and dermatitis), prevent aggravation, and minimize therapeutic risks.

Topical therapies

1. **Topical corticosteroids,** the mainstay of AD therapy, differ in formulation, concentration, and potency, which while providing patients with a myriad of options, simultaneously makes their reliability and adherence to effective regimens challenging (Vangeli et al, 2015). Toxicity; both systemic (HPA axis suppression) and topical skin dystrophy, thinning and vascular changes

additionally limit their continuous use, the need remains to continue to develop corticosteroid-sparing agents (Del Rosso & Friedlander, 2005).

2. **Topical calcineurin inhibitors** have limited efficacy in moderate-to-severe AD, are not approved for use in very young children (<2 years of age) and have practical limitations on amount of affected area treated.

3. **Topical PDE4 inhibitors**: Crisaborole has been approved for the management of signs and symptoms of mild to moderate AD in major markets. Long-term safety and tolerability of 2% crisaborole ointment has been established with a small proportion of patients reporting early onset application site pain, and no effects associated with systemic exposure (Hoy, 2017).

4. **Phototherapy,** indicated for moderate to severe AD in some countries, has limited efficacy, is inconvenient and impractical for most subjects to use effectively (Weidinger & Novak, 2016; Sidbury et al, 2014), and as for other disease states for which phototherapy is used, the risk of NMSC and melanoma is a concern, especially in fair-skinned individuals.

Systemic therapies

Several drugs are used for the treatment of patients with AD who have failed to respond to topical agents and are in need for systemic therapy. Cyclosporine is approved for the treatment of severe AD in most European countries, but it is not suitable for long-term use due to toxicities. Dupilumab is approved for the treatment of moderate-to-severe AD in the EU.

1. **Systemic corticosteroids:** In clinical practice guidelines, the use of systemic corticosteroids is generally discouraged with use limited to special circumstances (Drucker et al, 2018a). While systemic corticosteroids lead to rapid clearing of AD, their side-effect profile and the risk of severe rebound flares after discontinuation limit their use to short-course therapy only. Despite being discouraged by most international guidelines, and the inevitable systemic toxicities associated with their short- (Waljee et al, 2017) and long- (Rice et al, 2017) term use, approximately 10% of patients with AD still use these agents upon flaring (Alexander et al, 2018).

2. **Dupilumab (Dupixent)** which is formulated for subcutaneous injection was originally approved for treatment of moderate to severe AD in adult patients, and subsequently received approval also for adolescents with moderate to severe AD who are candidates for systemic therapy. The product has recently received approval for treatment from 6 years of age in subjects with severe AD who are candidates for systemic therapy.

3. **Baricitinib (Olumiant)** has recently been approved by the CHMP (EMEA/H/C/004085/II/0016) for addition of the new indication "treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy". Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2. The recommended dose of Olumiant is 4 mg dosed once daily.

4. **Upadacitinib (Rinvoq)**, another JAK inhibitor, has also been recently approved by the CHMP (EMEA/H/C/004760/X/0006/G) for addition of the new indication 'treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy'.

5. **Tralokinumab (Adtralza)** is also approved by the CHMP (EMEA/H/C/005255/0000) for treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy.

6. **Other Systemic Agents (other than Corticosteroids)** are used in the treatment of AD. Non-biologic systemic drugs used for adult AD include cyclosporine, AZA, MMF, and MTX (Simon &

Bieber, 2014). All these agents are used off label, except for cyclosporine, which is licensed and approved for short-term treatment of severe refractory AD in many EU countries (Ring et al, 2012b).

7. **Oral antihistamines:** These have been used in the management of pruritus in AD patients in an effort to improve their quality of life by inhibiting the vascular and neurologic effects of the "itch-scratch cycle," but there is insufficient evidence to recommend the general use of antihistamines as part of the treatment of AD (Ring et al, 2012a).

2.2. 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.

The initially claimed indication was `*Moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy´.*

The posology is one film-coated tablet to be taken daily, preferably in the morning. The initially proposed dosage in the SmPC section 4.2 stated that `100 mg or 200 mg once daily, based on individual goal of therapy and potential risk for adverse reactions´.

2.3. Type of application and aspects on development

The application was submitted under the legal basis 8(3) of Directive 2001/83/EC which corresponds to a complete and independent application.

The applicant requested EMA scientific advices for abrocitinib for the treatment of AD. The questions concerned the clinical and non-clinical development (see in section 1.1. 'Scientific advice').

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as immediate release film-coated tablets containing 50 mg, 100 mg or 200 mg of abrocitinib as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose (E460i), anhydrous dibasic calcium phosphate (E341ii), sodium starch glycolate and magnesium stearate (E470b).

Film-coat: hypromellose (E464), titanium dioxide (E171), lactose monohydrate, macrogol (E1521), triacetin (E1518) and red iron oxide (E172).

The product is available in high-density polyethylene (HDPE) bottles with polypropylene closure or polyvinylidene chloride (PVDC) blisters with aluminium foil lidding film, as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of abrocitinib is *N*-((1*S*,3*S*)-3-(methyl(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide corresponding to the molecular formula $C_{14}H_{21}N_5O_2S$. It has a relative molecular mass of 323.42 Daltons and the following structure depicted in Figure 1:

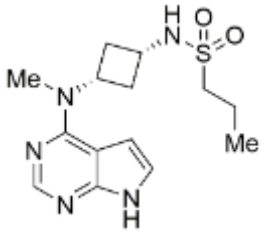


Figure 1 Active substance structure

The chemical structure of abrocitinib was elucidated by a combination of UV/VIS and IR spectroscopy, mass spectrometry, NMR spectroscopy and X-ray diffraction.

The active substance is a white to pale-purple or pale pink crystalline powder. It is non-hygroscopic and its solubility is pH dependent. Abrocitinib is classified as BCS Class II. The impact of particle size on finished product uniformity of dosage units and dissolution has been studied (see finished product section). Based on the abrocitinib finished product biopharmaceutics performance, stability, and manufacturing experience, the active substance particle size specification was established.

Abrocitinib is an achiral molecule, but with 2 stereocentres.

Only one crystalline anhydrous form (Form 1) of abrocitinib has been identified. This form has been the only form used in all toxicology and clinical studies. Extensive polymorph and hydrate screening have been conducted to investigate if additional solid forms of abrocitinib could be discovered. Abrocitinib, Form 1 was the only anhydrous crystalline form identified from these studies. No new anhydrous polymorphs, hydrates or amorphous solids of abrocitinib were isolated from these screens.

Experiments with 1,4 dioxane and dimethyl sulfoxide yielded solvated forms of abrocitinib. When these solvated structures were subjected to high temperature, these materials desolvated and converted to Form 1, free base anhydrous form of abrocitinib. However, these are not relevant since the commercial crystallisation step does not utilise either of these solvent systems.

It has been confirmed that the manufacturing process consistently yields polymorphic form I. This form is physically and chemically stable under normal manufacturing and storage conditions as well as under accelerated conditions. Hence the absence of control of form I is justified.

2.4.2.2. Manufacture, characterisation and process controls

The commercial active substance abrocitinib will be manufactured by Pfizer Ireland Pharmaceuticals, Ringaskiddy, Ireland. The development and clinical batch manufacture have been performed by Pfizer's site in Sandwich, Kent, UK.

The synthesis of abrocitinib consists of a five-step manufacturing process including three covalent bond forming manufacturing steps.

Materials used in the manufacture of the active substance (reagents, solvents and auxiliary materials) are listed including information where each material is used. Specifications for these materials are provided. No catalysts are used in the synthesis.

One of the starting materials proposed by the applicant (SM1) was not deemed acceptable by the CHMP, being a custom synthesised chemical and considered as an intermediate. The applicant was requested to redefine this starting material (Major Objection) so that the introduction of the stereocentres and the control of stereoisomeric impurities are performed under GMP. In order to address the CHMP concerns and increase the number of chemical transformation steps performed under GMP, to mitigate risks associated with contamination and future changes, the applicant redefined that starting materials an intermediate and proposed earlier as the new starting materials. This was accepted by the CHMP.

Other of the original proposed starting materials, SM2, is a commercially available chemical that is incorporated in abrocitinib. It is widely used in non-pharmaceutical commercial applications. However, it is included in the last step of the synthesis and the synthesis route of this material was not described in the original submission. The CHMP was concerned about the regulatory oversight of the control strategy for impurities and thus raised a MO asking the applicant to address this. In the response, the applicant discussed the route of synthesis and reagents used by all three suppliers of this starting material. Impurities that are structurally similar to SM2 can react to form impurities that may carry through into the active substance. Those impurities have been included on the specification for the starting material and detailed fate and purge studies performed demonstrating an extensive purge. Based on the additional information provided it is concluded that SM2 is adequately controlled and is an appropriate starting material for the synthesis of abrocitinib.

The isolation strategy was developed based on the physical properties of each intermediate and the knowledge of impurity generation and subsequent purge. Isolations provide multiple opportunities for the removal of reaction by-products and impurities. The control strategy and their specifications have been adequately justified.

Overall, the manufacturing process of the abrocitinib, the control of materials and intermediates and the control strategy has been described and justified by the applicant.

The current commercial batch size has been defined (typical final output range).

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Several impurities are associated with the manufacturing process. The origin and fate have been discussed for each of them.

The applicant proposes ICH M7 option 4 control strategy for some identified mutagenic impurities. These limits are considered acceptable.

Two synthetic pathways were employed for the manufacture of abrocitinib during clinical development. Changes introduced have been presented in sufficient detail and have been justified.

The active substance is packaged in and stored in double sealed low-density polyethylene (LDPE) bags stored in a high-density polyethylene (HDPE) drum or equivalent secondary container. A declaration of conformity of the primary packaging to Ph.Eur. 3.1.4 and EU regulation 10/2011 incl. amendments has been provided.

2.4.2.3. Specification

The active substance specification includes tests for appearance (visual), identity (LC, IR), particle size (laser diffraction), assay (HPLC), impurities (HPLC), residue on ignition (Ph. Eur.), and residual solvents (HS-GC).

The active substance specifications are based on the active substance critical quality attributes (CQA). The CQA identified are particle size, organic impurities, inorganic impurities and residual solvents.

Abrocitinib is classified as BCS Class II. The impact of particle size on finished product uniformity of dosage units, manufacturability, bioavailability, and dissolution has been studied (see finished product section). The particle size specification has been established based on the abrocitinib finished product biopharmaceutics performance, stability, and manufacturing experience.

The origin and fate of the specified impurities, which are classified as ICH M7 Class 5 impurities, have been discussed. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

Adequate justifications have been provided for the omission of tests.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and system suitability testing has been presented.

Batch analysis data from 35 batches of the active substance used for toxicology, development and stability studies and for the manufacture of finished product for clinical studies and registration stability have been presented. 17 batches were manufactured using the commercial process. These batches include 3 batches produced at the site of commercial manufacture, Pfizer Ireland Pharmaceuticals in Ringaskiddy, County Cork, Ireland, which were provided during the procedure to address a MO. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from 3 pilot scale batches of active substance manufactured at Pfizer, Sandwich, UK using the commercial process stored in the intended commercial package for up to 12 months under long term conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

Samples were evaluated for appearance, assay, degradation products, water content, solid form, particle size, and microbial quality (TAMC/TYMC). The analytical methods used in the primary stability programme are the same as the release methods. The additional methods have been described.

No changes in any of the studied attributes were noted. All tested parameters were within the specifications. No change was observed due to storage conditions.

In addition, photostability testing following the ICH guideline Q1B was performed on one batch. Samples were tested for appearance, assay and achiral purity.

The active substance did not show any instabilities due to light (ICH Q1B conditions). Therefore, it was concluded that abrocitinib is not light sensitive and does not require protection from light.

Samples of abrocitinib were subjected to forced degradation conditions (acid; base; light exposure; oxidation; and heat) to confirm the suitability of the assay and purity method and to identify potential primary degradation products. Samples were analysed for assay and purity. The results showed that abrocitinib is not sensitive to water, acidic, basic, metal ion, thermal thermal/humidity or light

degradation. Abrocitinib is shown to degrade under oxidative conditions. The results confirm that the HPLC assay and purity method for abrocitinib active substance is specific, selective, and stability-indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months stored at or below 30°C conditions in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is presented as immediate release film-coated tablets. The tablets are available in three strengths: 50, 100 and 200 mg. These are differentiated by their shape and/or debossing codes.

The 50 mg tablets are oval, pink film-coated tablets debossed with "PFE" on one side and "ABR 50" on the other side. The 100 mg tablets are round, pink film-coated tablets debossed with "PFE" on one side and "ABR 100" on the other side. The 200 mg tablets are oval, pink film-coated tablets debossed with "PFE" on one side and "ABR 200" on the other side.

The strengths are quantitatively proportional. The maximum dose of 200 mg does not fully dissolve in 250 mL of medium at equilibrium over the entire physiological pH range (1 to 7.5). Additionally, analysis of clinical study B7451008 showed total absorption of abrocitinib is greater than 85%. The active substance is classified as a BCS Class II compound (i.e., low solubility and high permeability). The impact of active substance particle size was an important consideration during finished product development.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The choice of the excipients has been justified. The list of excipients is included in section 6.1 of the SmPC.

The formulation is composed of microcrystalline cellulose and dibasic calcium phosphate, anhydrous (diluents), sodium starch glycolate (disintegrant), and magnesium stearate (lubricant). Tablet cores are subsequently film-coated with a non-functional HPMC/ lactose based Opadry II® formulation. The functionality-related characteristics of the excipients and their controls have been discussed and adequate specifications have been established. The amount of excipients used in the composition has been properly justified by different studies performed during the development. These included studies to optimise and evaluate the impact of formulation on finished product manufacturing and performance.

The applicant has described the pharmaceutical development in detail and has justified the proposed formulation and the manufacturing process.

The commercial manufacturing process for the abrocitinib tablet core uses a direct compression, continuous manufacturing (CM) platform developed by the applicant. The platform, named Pfizer's Portable, Continuous, Miniature and Modular (PCMM), has been approved previously in EU for the manufacture of other medicinal product from Pfizer, Daurismo.

The CM process involves three primary functions which are (1) continuous feeding and (2) continuous mixing to form a blend, followed by (3) tablet compression using a conventional rotary tablet press.

The final unit operation is a film-coating process, which is performed as a batch process using conventional equipment.

Studies have been performed to evaluate the impact of excipients on finished product manufacturing and performance including continuous feeding accuracy and variability, continuous mixing residence time distribution, blend uniformity, compression tablet hardness, disintegration, stability and dissolution.

A combination of risk-based assessments, laboratory studies, computational models, and manufacturing experience has resulted in a comprehensive understanding of the formulation and process conditions and their impact on the quality attributes (e.g., potency, purity, dissolution, uniformity of dosage units, and appearance) of the product.

An understanding of the relationships between formulation inputs and process parameters on the critical quality attributes and process dynamics of the commercial formulation and manufacturing process for abrocitinib film-coated tablets has been established. The process understanding developed for each integrated unit operation was used to define the manufacturing process.

A structured, quality risk management approach was employed to identify potentially critical material attributes and process parameters and assess their impact on critical quality attributes and process dynamics of the finished product. This risk assessment was performed based upon prior knowledge as well as the knowledge gained throughout the development of the manufacturing process.

For the formulation development, a material risk assessment has been provided. The impact of abrocitinib active substance and excipients on continuous feeding accuracy and variability, continuous mixing residence time distribution, blend uniformity, tablet hardness, disintegration, dissolution and stability was evaluated. Based on this risk assessment, the components with the highest potential to impact product quality attributes are the active substance (abrocitinib), the disintegrant (sodium starch glycolate) and the lubricant (magnesium stearate).

With regards to the manufacturing process development, summaries of multivariate studies performed on gravimetric feeders, continuous mixing and the continuous tablet press have been presented. These studies were designed to understand the impact of material properties and process parameters on dosage form quality attributes, such as potency, content uniformity, dissolution and tablet physical properties. Process parameters are controlled within operating ranges as defined in the manufacturing process description or through the use of in-process controls (IPCs). The abrocitinib film-coated tablet manufacturing process has been shown to be robust within the target and operating ranges.

Residence time distribution, process monitoring, traceability, segregation (blend uniformity), state of control and other elements of CM were also studied.

An integrated control strategy comprising material attributes and process parameters, finished product specifications, IPCs, as well as real time monitoring using PAT (near infrared - hybrid soft sensor method), steady state operation and diversion criteria for non-conforming product has been developed.

The in-line near-infrared (NIR) probe is inserted into the top of the feed frame immediately before tablet compression to continuously monitor the blend concentration and allow for potential diversion of tablet cores made from non-conforming blend. Sufficient information has been provided on the NIR method. Equivalence with the reference method (i.e. off-line testing with HPLC reference product) has been shown.

Information on the equipment design and configuration including the impact on the process performance has been provided by the applicant. Among these, a residence time distribution (RTD) model, referred to as the Mass Balance Model, is incorporated into the PCMM control and automation system to calculate the concentration of each formulation component in the exit stream of the continuous mixer (CMT), as a function of time to ensure robust control of the continuous mixing process.

The formulation used during clinical studies is the same as that intended for marketing, except for the film-coating which was white instead of pink. This change is considered acceptable. The phase 3 product was manufactured in the same way as the proposed 100 mg tablet with PCMM continuous manufacturing direct compression process and then film-coated.

Doses of 100 and 200 mg were administered with one or two 100 mg tablets, respectively during Phase 3 studies. A bioequivalence study has shown that two 100 mg phase tablets are equivalent to one 200 mg commercial tablet. The biowaiver to the two lower strengths, 50 and 100 mg tablets is considered acceptable from a pharmaceutical point of view based on:

- The three strengths are proportionally similar in their active and inactive ingredients (common blend).

- Data show similarity in dissolution profiles between 50, 100, and 200 mg abrocitinib film-coated tablets in three different pH media (pH 1.2, pH 4.5 and pH 6.8) and the proposed commercial dissolution method at pH 3.5. Overlapping dissolution profiles are presented as exemplified below.

- Dose proportional pharmacokinetics across the dose range from 30 mg to 400 mg (see pharmacokinetics section).

The development of the dissolution method used for quality control and comparison of batches has been described. The type of vessels, agitation rate and the media selection have been adequately investigated, optimised and hence are considered justified as they are needed to have a robust dissolution method that minimises sensitivity to hydrodynamics and maintain sink conditions.

Several parameters have been adjusted to achieve a discriminative method. The discriminatory power of the dissolution method has been demonstrated by testing variant tablet formulations

The primary packaging is a HDPE bottle with polypropylene closure, or unit dose PVDC blister with an aluminium foil lidding. The primary packaging materials comply with Commission Regulation (EU) No 10/2011. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The abrocitinib film-coated tablets are manufactured at Pfizer Manufacturing Deutschland GmbH, Mooswaldallee 1, 79090 Freiburg, Germany. This manufacturing site performs all stages in the manufacture including finished product manufacture, QC testing, primary and secondary packaging and EEA batch release.

As indicated above, the tablets are manufactured using Pfizer's PCMM manufacturing platform via direct compression from a common blend. The manufacturing process consist of three main steps: mixing, compression and film-coating. The mixing (including feeding) and compression steps are performed in a CM process whereas the film-coating and following packaging are performed as standard batch manufacturing.

The manufacturing process has been described in sufficient detail in the dossier based on the manufacturing process development studies. The batch size is determined by the amount of in-coming raw materials to manufacture a predetermined amount of tablet cores. The proposed commercial batch size has been defined.

The continuous feeders and continuous mixer are operated to deliver material to the tablet press at the defined total mass throughput rate.

Start up and shut down processes, as well as strategy for controlled process pause that may be required following process events that can occur during routine manufacture, and the strategy for material diversion have been described.

The product diversion duration has been defined.

Details on the IPCs, during primary mode and contingency mode have been provided. The methods have been sufficiently validated and shown to give similar results. The information provided on the NIR method proposed as an IPC test of blend potency of abrocitinib tablet cores is found to be in line with "Guideline on the use of near infrared spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations (EMEA/CHMP/CVMP/QWP/17760/2009 Rev2)". A post approval change management protocol (PACMP) has been presented for planned changes to the NIR IPC method and model maintenance. This is acceptable.

Although the manufacturer has experience from one previously approved product with the PCMM continuous manufacturing platform, the manufacturing process is still to be considered non-standard and process validation results has therefore been presented for three batches of each strength manufactured on commercial scale at the proposed manufacturing site, Freiburg, Germany.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

2.4.3.3. Product specification

The finished product release specifications, include appropriate tests for this kind of dosage form appearance (visual) identification (LC retention time and UV spectra), assay (HPLC), impurities (HPLC), dissolution (Ph. Eur.), uniformity of dosage units by weight variation (Ph. Eur.) and microbial limits: TAMC, TYMC, *E. coli* (Ph. Eur.)

The finished product specification includes relevant tests to ensure the quality of the film-coated tablets and the proposed limits are justified.

The limits proposed for related substances have been set in accordance with ICH guidelines and are considered acceptable.

The limit proposed for the dissolution method has been justified. The proposed limit is acceptable.

A justification for not controlling water content and elemental in the release specification has been presented and is acceptable.

The water content results showed some analytical variability and in general an increase is expected on storage with larger increases observed at higher humidity storage. A correlation analysis was performed water content did not have a strong correlation with assay, degradation products or dissolution.

An elemental impurities risk assessment ICH Q3D Guideline for Elemental Impurities (EI) was performed on the finished product. The risk assessment was conducted on the 200 mg tablets which represent the worst case among the 3 strengths. The in-going active substance, excipients, manufacturing equipment and utilities, and packaging components were evaluated as part of the risk-assessment. These assessments showed that the risk of the Class 1 and Class 2A EIs exceeding the

30% control threshold of the Option 2a concentration limits and associated oral PDEs were low to negligible.

To confirm the findings of the risk assessment, three batches of abrocitinib immediate release film coated 200 mg tablets manufactured according to the commercial process were screened for EIs identified during the risk assessments using a validated ICP-MS method. No individual Class 1 and Class 2A elemental impurities were observed at or above their Option 2a oral concentration limits in the finished product. The individual Class 1 and Class 2A elemental impurities were all below the 30% Control Threshold values, with respect to their individual oral PDEs and/or concentration limits.

Based on the risk assessment confirmatory data collected it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

To address two MOs raised during the procedure, the applicant has presented a risk assessment of the active substance and finished product for the potential presence of N-nitrosamines considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). A negligible amount of potential N-nitrosamines is estimated to be present in the active substance In the finished product one N-nitrosamine has the potential to be formed when combining nitrites from the excipients with a secondary amine degradation product. The amount of this N-nitrosamine potentially formed in the finished product over time is estimated to be <20 ppb using conservative, worst-case-scenario assumptions. This amount is well below the proposed acceptable intake and the approach to not test for this N-nitrosamine is considered acceptable. Overall, based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the abrocitinib reference standard has been presented.

Batch analysis data is presented for 3 batches of 200 mg tablets and 26 batches of 100 mg tablets and 7 batches of 50 mg tablets manufactured by the Pfizer site at Groton, USA. In addition, data for one 100 mg batch designated for clinical use and one technical batch of 200 mg tablets are presented from the proposed manufacturing site, Pfizer, Freiburg. All batch analysis data comply with the specification set at the time of analysis, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three batches of finished product from each strength manufactured in Groton CT, USA at greater than 10% commercial scale stored for up to 12 months (50 mg strength) or 18 months (100 mg and 200 mg strengths) under long term conditions (25ºC / 60% RH and 30ºC /75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of Cibinqo are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, degradation products and dissolution. Water content, water activity and microbiological quality were tested for information only. The analytical procedures used are stability indicating.

Tablets met the appearance acceptance criteria except the 12-month 100 mg and 200 mg 5-count HDPE bottle and blister samples stored at 30ºC /75% RH, where faint surface cracking was observed. However, investigation revealed no cracks on the tablets upon removal from the package and immediate inspection. Faint surface cracking did not occur in any of the samples that were stored at 25ºC /60% RH. The faint surface cracking is cosmetic and has been determined to not extend beyond the film-coat surface. All other attributes tested on stability meet the acceptance criteria and no meaningful trends were observed.

The water content and water activity results showed some analytical variability and in general an increase on storage with larger increases observed at higher humidity storage, but they did not adversely impact stability, quality or performance of the finished product as measured by assay, degradation products or dissolution.

Forced degradation experiments under heat; humidity; light exposure and oxidation conditions were performed on 100 mg abrocitinib film-coated tablets to establish the extent and nature of potential degradation pathways and to confirm the suitability of the assay and purity method. Samples were analysed for potency and degradation products. The liquid chromatographic assay and purity method for abrocitinib immediate release film-coated tablets was shown to be specific, selective and stability-indicating.

In addition, a photostability study was carried out according to the ICH Guideline Q1B on photostability testing of new drug substances and products, option 2. Samples were tested for appearance, assay, degradation products, water content (for information only) and water activity (for information only). The 50 mg samples were also tested for dissolution. No significant changes were observed in any of the parameters measured for the confirmatory photostability study for samples directly exposed to light with the exception of increases in water content which is expected in exposed unpackaged samples. Therefore, it is concluded that abrocitinib film-coated tablets are stable to light and no precautionary packaging or labelling is required.

Packaged samples were also exposed. Slight yellowing of the PVC/PVDC blister film was observed for exposed 50 mg supplies. The discoloration has no significant influence on the characteristic physical properties or functionality of the package, and it is not related to abrocitinib tablet quality or performance.

An in-use open bottle study was carried out on one batch of each strength (HDPE bottle, 30 count). The bottles were opened, and the cap and seal were removed. The bottles were stored open to the 30ºC /75% RH environment with a dust cover. The in-use study for the 50 mg strength was updated prior to the 12 months testing to include both long term storage conditions (25ºC / 60% RH and 30ºC /75% RH) and to better simulate actual patient use. The 50 mg bottles were opened and closed 30 times over the 45 days exposure to simulate a patient removing tablets.

Samples are tested for appearance, assay, degradation products, dissolution, water content and water activity. Results for the in-use samples were comparable to the 3 month or 12 month, unopened, 30ºC /75% RH sample of the same lot with the exceptions noted below, similar observations were made for 25ºC / 60% RH in-use samples tested at 12 months. As expected, water content and water activity increased with exposure to the 30ºC /75% RH storage environment. The increase in water did not adversely impact stability, quality or performance of the finished product as measured by assay, degradation products or dissolution. Assay, degradation products and dissolution results met the acceptance criteria. Faint surface cracking was observed in appearance testing of the 100 and 200 mg,

12 month in-use samples stored at 30ºC / 75% RH. However, similar to the finding in the long-term stability studies, the investigation revealed no cracks on the tablets upon removal from the package and immediate inspection. Faint surface cracking developed after tablets experienced a rapid change from high humidity in the package to low humidity in the laboratory condition. As mentioned above, the faint surface cracking is cosmetic and has been determined to not extend beyond the film-coat surface. All other attributes tested met the acceptance criteria.

As a result of the faint surface cracking observation, additional in-use studies were conducted on 100 mg and 200 mg samples stored at 25ºC / 60% RH and 30ºC /75% RH to simulate more realistic actual patient use. The results are consistent with the 12-month primary stability and 12-month in-use sample results except for the in-use appearance observations. No film-coat cracking was observed in any of the additional in-use study samples). The data confirm the finding of the investigation and hence it gives reassurance that crackling of the surface will not occur during use and it does not need to be reflected in the SmPC. As expected, water content and water activity increase with in-use storage but the increase does not impact the stability, quality or performance of the finished product. All testing met the acceptance criteria.

In addition, one lot of each strength stored in the 30-count HDPE bottle, were challenged to two separate storage condition studies, a thermal cycle study (two cycles of storage at 40ºC / 75% RH and -20ºC) and a short-term accelerated exposure study at 50ºC / 75% RH. Samples were tested for appearance, assay, degradation products, dissolution, water content and water activity. The appearance, assay, degradation products and dissolution performance of the abrocitinib film-coated tablet lots remained essentially unchanged through both the thermal cycle study and the 3-day 50ºC / 75% RH exposure. There were no reportable degradation products. These data are supportive of minor shipping excursions for the abrocitinib film-coated tablets.

Based on 18 months stability data for 100 and 200 mg batches and 12 months stability data for 50 mg batches from the primary stability programme, the proposed shelf-life is 30 months for 100 and 200 mg abrocitinib film-coated tablets and 2 years for 50 mg abrocitnib film-coated tablets when stored when stored in PVDC blister with aluminum foil lidding or HDPE bottles with polypropylene closure with induction seal liners as stated in the SmPC (section 6.3), is acceptable.

In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the EMA.

2.4.3.5. Adventitious agents

It is confirmed that the lactose monohydrate used in the manufacture of Opadry® II Pink is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

The film-coated tablets are manufactured using a continuous direct compression process comprising feeding, blending and compression, followed by a conventional film-coating batch process. The product is released based on end-product testing. Multiple layers of control and alarm (gravimetric feeder, CMT by the Mass Balance Model and NIR feed frame) have been established ensure adequate tablet

composition. Several MO were raised during the evaluation of this application. These pertained to the redefinition and justification of the proposed starting materials, the lack of batch analysis data from the proposed commercial active substance manufacturer, missing process validation on the finished product from the proposed commercial manufacturing site and the nitrosamines risk evaluation. All raised issues were satisfactorily addressed by the applicant. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

N/A.

2.5. Non-clinical aspects

2.5.1. Introduction

Abrocitinib (also referred to as PF-04965842) is an orally bioavailable Janus kinase (JAK) 1 inhibitor indicated for the treatment of patients with moderate-to-severe atopic dermatitis (AD). Three circulating metabolites (M1 [PF-06471658], M2 [PF-07055087], and M4 [PF-07054874]) were profiled in pharmacological, ADME, and *in vitro* safety pharmacology studies.

The pivotal toxicology and safety pharmacology studies were conducted in accordance with GLP regulations and ICH guidelines.

CHMP scientific advices have been given to the non-clinical development of abrocitinib (see Section 1). The given advices have been in general followed.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The primary pharmacology was assessed by evaluating the potency, and selectivity of abrocitinib in the *in vitro* assays using purified kinase domains from the JAK family of kinases (JAK1, JAK2, JAK3, and TYK2), and in assays against a broad kinome panel.

In Vitro biochemical assays

In vitro activity in the biochemical assay of abrocitinib was analysed against the four JAK family members (JAK1, JAK2, JAK3 and TYK2) using Caliper mobility shift assay. Fluorescent labelled synthetic peptides were used as substrates for recombinant enzymes and the enzymatic activity were analysed by Caliper Life Science Lab Chip 3000 (LC3000) instrument. The potency of the main metabolites was analysed against the JAK family members using the same method. Potency was

estimated in the presence of an ATP concentration of 1 mM, as well as the apparent Km for ATP for each enzyme where the ATP concentration of 1 mM is the more clinically relevant.

The IC50 of abrocitinib in the biochemical assay was 29.2 nM (JAK1), 803 nM (JAK2), >10000 nM (JAK3) and 1250 nM (TYK2), i.e. abrocitinib had a 28-fold higher selectivity for JAK1 compared to JAK2 in the biochemical assay and the corresponding figures for JAK3 and TYK2 were >342 and 43 nM, respectively, in the presence of 1 mM ATP. In the presence of the apparent Km for ATP in each enzymatic reaction, the selectivity was 9.3, 151 and 16.5-fold higher for JAK1 compared to JAK2, JAK3 and TYK2, respectively. According to the biochemical assay settings, abrocitinib appears to be rather selective against JAK1 compared to the other JAK family members. However, in a cellular setting, upon stimulation by divergent cytokine stimuli, the response will be dependent on JAK signalling pairs, meaning that inhibition of JAK1 will affect pathways mediated by other JAK family members as well. Hence, the relevance of selective enzymatic inhibition of specific JAK enzymes to clinical effect is currently not known.

The metabolites, M1, M2 and M3 had a similar potency on the JAK family members as abrocitinib and thus, may contribute to the overall pharmacology. The metabolite M4 was shown to be inactive on all JAK family members.

The rat and cynomolgus monkey were selected for investigation of the safety pharmacology and toxicity studies. Pharmacological efficacy has been proven in a study on AIA rat, symptomatically by dose dependent reduction of paw swelling and functionally by inhibition of STAT phosphorylation in ex vivo samples. *In vitro data* on the inhibition by abrocitinib regarding cytokine signalling in whole blood from cynomolgus monkey and rat for comparison to previously provided human data has been submitted. For this evaluation, the cytokines IL-15 (Jak1/Jak3), IL-12 (Jak2/Tyk2) and interferon-α (Jak1/Tyk2) were chosen for stimulation of whole blood. The results show the following inhibitory pattern using IC50 after stimulation by IL-15: 480/537; IL-12: 2660/9730; interferon-α: 362/183 for cynomolgus monkey and human, respectively. The corresponding figures for IC50 in rat are for stimulation by IL-15: 87.9; IL-12: 4090; interferon-α: 112. Thus, the activity by abrocitinib on the JAK family members is sufficient for the selected safety pharmacology/toxicity species.

In vitro human whole blood and other cellular assays

The inhibitory potency by abrocitinib was studied in various human cell types such as PMBC (cultured or analysed in whole blood), keratinocytes, CD34+ progenitor cells as well as cell lines (THP-1 and HT29). The cells where simulated with a number of different interleukins, IFNα, IFNγ, TSLP or EPO, all known to induce JAK mediated phosphorylation of STAT(s). The metabolites (M1-4) as well as other compounds, were compared to abrocitinib in the assays.

Inhibitory activity of abrocitinib in cultured human PMBCs and CD34+ progenitor cells showed highest affinity to signalling pairs involving JAK1 compared to those not involving JAK1 such as JAK2/TYK2 and JAK2/JAK2. Abrocitinib inhibited phosphorylation of STAT3 and STAT5 in lymphocytes mediated by signalling pairs involving JAK1 with an IC50 of 32.5-142 nM (stimulated by IFNα, IL-15, IL-10, IL-27). For JAK2/JAK2 signalling pairs stimulated by EPO on CD34+progenitor cells and JAK2/TYK2 signalling pairs stimulated by IL-23 on PMBC, the IC50 was 794 and 2130 nM, respectively.

In addition, the IC50 was estimated for abrocitinib using whole blood as a source of PMBC. The potency of abrocitinib was lower in whole blood PMBC (i.e. lymphocytes) compared to cultured PMBC. For the signalling pairs involving JAK1, abrocitinib inhibited phosphorylation of STAT3 and STAT5 with an IC50 of 174-576 nM (also stimulated by IFNα, IL-15, IL-10, IL-27 on lymphocytes). In the whole blood analyses, signalling pairs involving JAK1 were additionally stimulated by IFNγ (of lymphocytes and CD14+ cells), IL-6 (of CD3+ and CD14+ cells) and IL-21 (of lymphocytes) and abrocitinib inhibited STAT1 and STAT3 phosphorylation with an IC50 of 164-1690 nM. Abrocitinib had a

low/negligible potency on the JAK1 independent pathways. Induction of STAT3 and STAT4 phosphorylation by IL-12 and IL-23 stimulation of lymphocytes mediated by the signalling pairs JAK2/TYK2, showed an IC50 of 9730 and <16500 nM respectively, and EPO induced STAT5 phosphorylation mediated by JAK2/JAK2 signalling pair in whole blood, 7180 nM. STAT phosphorylation by the metabolites M1, M2 and M3 was tested in human whole blood and CD34+ cells (stimulated by IFNα, IFNγ, IL-6, IL-10, IL-12, IL-15, IL-21, IL-23, IL-27 and EPO). All metabolites were shown to be of pharmacological relevance without higher specificity of importance for other JAK members than abrocitinib. M3 had a lower potency than M1 and M2 in most cases. The IC50 for STAT phosphorylation mediated by JAK signalling pairs where JAK1 was involved, varied between 90.5-4840 nM and for the signalling pairs JAK2/JAK2 or JAK2/TYK2, between 5170-33400 nM.

Abrocitinib was compared to other inhibitors possessing high affinity to other members in the JAK family in whole blood and a variety of cell types. Abrocitinib exhibited a good inhibitory potency on various cell-types known to be implicated in the pathogenesis of dermal conditions such as AD. IL-4 induced STAT6 phosphorylation mediated by JAK1/(JAK3) in B-cells, T-cells and monocytes from human whole blood as well as primary keratinocytes and HT-29, and was inhibited by abrocitinib with an IC50 of 77-503 nM. Inhibition of IL-13 stimulated STAT6 phosphorylation in B-cells and monocytes from human whole blood had an IC50 of 285-351 nM while in HT-29 and keratinocytes the corresponding figures were 11 and 81.9 nM, respectively. IL-22 induced STAT3 phosphorylation (mediated by JAK1/TYK2) in primary epithelial cells and keratinocytes showed an IC50 of 1243 and 420 nM, respectively, and of IL-31 stimulated STAT3 phosphorylation in THP-1 cells, 40 nM.
The potency of metabolites M1 and M2 showed an equal pharmacological relevance after stimulation by IL-4, IL-13, IL, 22, IL-31 in the above-mentioned situations.

Thymic Stromal lymphopoetin (TSLP) is linked to multiple allergic diseases, such as the pathogenesis of AD. Inhibition by abrocitinib and the metabolites (M1 and M2) in TSLP-stimulated STAT5 phosphorylation in CD3+ T-(killer) cells from whole blood had an IC50 of 1021, 785 and 271 nM, respectively.

In vitro activity of JAK inhibition in functional settings in human cellular assays

Differentiation of human bone marrow CD34+ progenitor cells to platelet producing megakaryocytes is dependent on stimulation by many factors, including thrombopoietin (TPO) and IL-6. Abrocitinib exhibited a dose dependent inhibition of TPO induced STAT5 (IC50 = 1060nM) and IL-6 induced STAT3 phosphorylation (IC50 = 83.7 nM) in human bone marrow CD34+ progenitor cells. When further analysed with regard to development of CD34+ progenitor cells to CD41a cells (marker typically associated with megakaryocytic commitment), the inhibitory potency was shown to be dose dependent with an IC50 of 5670 nM. This pathway is assumed to be a TPO and IL-6 induced JAK2 dependent pathway. However, patients with a current or past medical history of conditions associated with thrombocytopenia, coagulopathy or platelet dysfunction as well as patients receiving anti-coagulants or medications known to cause thrombocytopenia have been excluded from the clinical trials as a precaution. The importance of these inhibitory effects by abrocitinib on TPO and IL-6 induced STAT phosphorylation in a clinical setting have not been discussed by the applicant and is therefore unknown. This lack of knowledge with regard to thrombopoiesis is accepted provided that it is clearly reflected in the SmPC.

TPO is also the primary regulator of platelet function and circulating levels are cleared after binding to the MPL receptor (cellular homologue of the myeloproliferative leukaemia virus oncogene) on the circulating platelets and megakaryocytes in bone marrow. This event is assumed to be partly mediated via JAK2. TPO clearance was further investigated and abrocitinib showed a weak dose dependent inhibition of internalisation of TPO in platelets with an IC50 of 10800 nM, and 4970 nM unbound (the IC50 of abrocitinib potency for JAK2 is 803 nM in biochemical assay). Baricitinib, a JAK2 inhibitor, was

also tested in this experiment, however, Baricitinib only inhibited 10% of the TPO clearance, nevertheless, with an IC50 of 22 nM. This suggests an alternatively mediated internalisation of TPO into platelets.

In vivo study on adjuvant induced arthritis (AIA) rat model

The anti-inflammatory effect of abrocitinib was investigated in the AIA rat model in two studies (experiment 1; 50, 15, and 5 mg/kg and experiment 2; 15, 5, 1, and 0.5 mg/kg) PO daily for seven days. Abrocitinib treatment resulted in a dose dependent inhibition of paw swelling (disease severity) in the rats after seven days of treatment which was significant for the dose levels between 5-50 mg/kg. In addition, *ex vivo* samples showed dose dependent inhibition of STAT phosphorylation in IL-6, IL-21, IFNγ and IFNα stimulated T-cells as well as GM-CSF stimulated monocytes (samples drawn at 15 minutes after dosing). The mean plasma concentrations in animals dosed with abrocitinib 15 minutes post-dosing (Cmax) were 1082, 4947, 26901 nM for 0.5, 5 and 15 mg/kg dose level and at 24 hours, 2.49, 7.24, and 139 nM, respectively.

2.5.2.2. Secondary pharmacodynamic studies

Secondary pharmacology was assessed by evaluating the binding potency of abrocitinib against a broad panel of receptors, transporters, enzymes, and ion channels *in vitro*. Follow-up KDR kinase (VEGFR2), MAO-A, and MAO-B functional assays were conducted.

Plasmacytoid dendritic cells (pDC) are suggested to be contributors in the pathogenesis of systemic lupus erythematosus (SLE), and pDC's are thought to become insensitive to the cell killing by glucocorticoids in an SLE setting. The applicant presented data, showing that purified pDC's are fairly easily killed in the presence of prednisolone in a dose dependent manner, however, in the presence of serum from SLE patients, pDC exhibits a reduced sensitivity to prednisolone. This insensitivity to steroid killing was reversed in the presence of 1 μM abrocitinib. Prednisolone concentration needed for 50% cell killing was 0.099 μM for control serum, 1.005 μM for SLE serum and 0.055 μM for SLE serum in the presence of 1 μM abrocitinib. However, the results from this pilot study are based on one donor of pDC only. In an additional study, abrocitinib inhibited type I interferon (IFN) induced gene expression in normal PMBC, stimulated with SLE immune complexes (IC). The expression of the three SLE-related genes, RSAD2, USP18 and GBP1, was inhibited with an IC50 (mean ± SD) of 82 ± 95, 114 ± 132 and 107 ± 120 nM, respectively, from five healthy PMBC donors.

Selectivity of abrocitinib was also tested against a panel comprising 40 kinases in the presence of the apparent Km for ATP for each enzyme. The highest selectivity of abrocitinib in the panel was against JAK3, showing an inhibition of 60.6%, which was equivalent to the inhibition of JAK3 in presence of apparent Km for ATP, revealing an IC50 of 493 nM. The apparent Km for ATP should result in a higher affinity of abrocitinib to other kinases compared with in the presence of 1 mM ATP. For testing the selectivity against other kinases, this approach is acceptable.

A broad ligand binding assay of abrocitinib in a concentration of 10 μM in all assays was performed. Abrocitinib inhibited VEGFR2 with 93.8% with an IC50 of 1.2 μM, and MAOA with 67% and IC50 of 6 μM. This corresponds to a marginal to human exposure of x 1 for VEGFR and x 4.8 for MAOA of the unbound clinical Cmax of 1.25 μM at a clinical dose of 200 mg. Further investigations were performed in order to assess the functional meaning of these results; VEGFR phosphorylation was assessed in KDR-transfected PAE cells and it was shown that abrocitinib had no effect on the VEGFR kinase activity up to the highest tested concentration, 30 μM. The applicant referred to a study by Ryan et al., 1999 where cynomolgus monkeys were administrated with a selective VEGF inhibitor and that events associated with VEGF inhibition, such as physeal dysplasia, did not occur in the 9-month toxicity study on cynomolgus monkey. However, according to the toxicological and juvenile study in particular,

skeletal variations where pointed out in rats. For the juvenile toxicity study these adverse events were evident at all dose levels, and a NOAEL could, thus, not be established. See further information in the toxicology section below.

Abrocitinib inhibits EGF at a concentration of 1 µM by 12.3% and at 10 µM, 33.2%. The inhibition of EGFR by abrocitinib is not large and in addition, the degree of inhibition is not increasing proportionally with increased concentration. The microscopic findings caused by abrocitinib inhibition was associated with a decrease in primary spongiosa without affecting the growth plate, which is unlike the effects by EGF inhibition. There were also differences in the nature of skin lesions in the abrocitinib-treated cynomolgus monkeys (alopecia and thinning hair coat) compared to those observed after EGFR inhibition (dry and flaky skin with haematoma, petechiae, and histologically disorganised hair follicles). The provided data does not point out a similar mechanistic effect by abrocitinib as those reported after EGFR or VEGFR inhibition. Thus, it is unlikely that the skeletal and skin findings observed in the juvenile and toxicity studies is caused by VEGFR or EGFR inhibition.

The inhibitory potency of abrocitinib was assessed on MAOA and MAOB. MAOB retained the activity by 98.8% at the highest concentration of abrocitinib, 100 µM. The retained MAOA activity was 67-55% in the 1-4 µM range, corresponding to the clinical exposure around Cmax, which for unbound is 1.25 µM and for total plasma concentration 3.47 µM, at the clinical dosage of 200 mg. From the subjects that had an ongoing psychiatric condition that required treatment, none were treated with MAO-A inhibitor antidepressants, indicating that the importance of MAOA inhibition by abrocitinib in the clinical trial has not been investigated together with MAOA inhibitors and an additional effect by aAbrocitinib has thus not been explored. According to the applicant, taking into account the low distribution of abrocitinib to brain (approximately 10%), the margin of 6.1x the unbound human C_{max} at the maximum clinical dose of 200 mg and the fact that the MAOA inhibition is reversible, the likelihood for serotonergic syndrome is unlikely to occur and it is thus not necessary to addressed the MAOA inhibitory effect in the SmPC.

2.5.2.3. Safety pharmacology programme

The safety pharmacology of abrocitinib was assessed by *in vitro* assays (hERG and Nav 1.5 inhibition) and *in vivo* in rats and cynomolgus monkeys.

The inhibition of Nav 1.5 was 6.0, 13.8, and 30.7% for the respective concentration of 30, 100 and 300 µM. The IC50 for Nav 1.5 current inhibition by abrocitinib was >300 µM, and for the positive control (propafenone), 0.58 µM. In the pivotal hERG study, the inhibition was 11.0, 21.9, 50.9, and 77.9%, for the respective concentration of 10, 30 100 and 300 µM. The IC50 for abrocitinib was 94.7 µM. The positive control (Terfenadine) showed an 88.8% inhibition at 60 nM.

In the functional observation battery (FOB) in rat, approximately one-hour post dosing, no apparent dose dependent deviations were observed. A decrease in forelimb grip strength was observed at 200 mg/kg but was not considered abrocitinib related or biologically relevant due to the lack of dose response. A decrease in body temperature of 0.6°C was observed at ≥ 200 mg/kg (and a decrease of 0.2°C at 100 mg/kg in the non-GLP study). Decreased locomotor activity was observed for all doses in the pivotal study. No effects were observed on the pulmonary parameters during the four-hour post-dosing period. The applicant states that LOEL of 75 mg/kg gave an unbound Cmax of abrocitinib of 12.6 µM (approximately 33 µM total drug). This reveals a x10 exposure margin to the human unbound drug plasma concentration at the recommended human dose of 200 mg revealing a Cmax of 1.25 µM of unbound drug. According to the study rationale, the exposure levels of 600 mg/kg were unknown in rat, and the exposure at 600 mg/kg was thus measured for this dose level only. Mean Cmax at 600 mg/kg in rat was 42 µM (unbound) and 111 µM (total) at 4.3 hours after administration (Tmax) and AUC24 was 810 µM (unbound) and 2130 µM (total)*h/L (i.e. 34x human unbound at Cmax). The Cmax

and AUC24 was approximately 2.5 to 3.5-fold higher at 600 mg/kg compared to an exploratory 7-day oral gavage toxicity study at 300 mg/kg in rat giving a Cmax of 45 µM and 17 µM for total drug and unbound, respectively. Corresponding values for AUC24 was 628 and 239 µM, respectively.

Oral gavage administration of abrocitinib to Cynomolgus monkey at ≥15 mg/kg (at 0.5-3.5 hours after administration) was associated with increased heart rate, decreased RR-interval and secondary decreases in PR- and QT-interval. Upon correction for the heart rate of the QT-interval (QTc), a small increase in QT interval over several time periods was observed for ≥40 mg/kg, however, according to test site, not dose dependent or of high magnitude and is thus not considered test item-related by the applicant. The clinical thorough QT study indicated a concentration dependent effect judged to have a lack of a clinically relevant effect on QTc interval. However, in clinical phase 3 studies increases in QTcF was observed in all subjects with measured ECG receiving abrocitinib (200 mg, QD. For the highest dose, 150 mg/kg, a test item-related increase in diastolic blood pressure was observed (range 4-8 mmHg in 4/8 animals), at 0.5-3.5 hours after administration. Emesis was found in 0 and 40 mg/kg for one animal in each group and a contributing effect from the vehicle may be anticipated. Test item related emesis started from 80 mg/kg in 3/8 animals, and for 150 mg/kg, in 6/8 animals. Plasma concentration was measured at 4 hours post dosing (HPD) and increased with increased dose level, however, not proportionally. The ±SD was large for all dose levels of unknown reason and individual plasma concentrations does not propose an effect due to emesis.

The Cmax (unbound) for LOEL at 15 mg/kg, was 1.18 µM (0.9 x human unbound exposure at Cmax) and Cmax of the total exposure was 3.18 µM at 2.2 hours (Tmax) and AUC(0-24) was 15.40 µM.

Overall, the pulmonary parameters were assessed in rat without any observed adverse effects during a four hours post dosing period. In the FOB studies in rat, a decrease in body temperature (at ≥200 mg/kg) and locomotor activity (≥LOEL, 75 mg/kg) was observed, revealing a margin of approximately x10 to the human dosage of 200 mg/day to LOEL. The *in vitro* studies of hERG and Nav 1.5 inhibition by abrocitinib does not suggest any potential effects in clinically relevant concentrations. The safety pharmacology studies does thus not indicate any particular concern from a non-clinical point of view.

2.5.2.4. Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interactions studies with abrocitinib have been conducted.

2.5.3. Pharmacokinetics

Studies have been performed to characterise the absorption, distribution, metabolism, and excretion (ADME) of abrocitinib, using the intended clinical route of administration (oral), and the species selected for non-clinical safety testing, i.e. rats and monkeys as the main non-clinical species but also mice and rabbits.

Methods of analysis

Abrocitinib was quantified by HPLC-MS/MS in plasma from mouse, rat, rabbit and monkey. Abrocitinib and metabolites in plasma, urine, bile, faeces, hepatocyte and liver microsomal incubations from mouse, rat and monkey ADME studies were identified and determined semi-quantitatively by HPLC-UV-MS. The analyses of M4 and M2 in rat plasma were performed by using the methods for human plasma which were validated in accordance with the guideline for bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 (2012) and bridged to the rat by QC-samples prepared in rat plasma. The analysis of M2 and M4 in rat plasma were confirmed to be performed with acceptable accuracy and precision and the methods used were adequately validated for rat plasma afterwards.

Absorption

Single dose pharmacokinetics of abrocitinib in plasma were determined in male rats and monkeys, the main toxicological species. Abrocitinib was rapidly absorbed following oral dose administration with a mean t_{max} of 0.50 h in both species. This was in line with the mean t_{max} of 0.77 in humans after a dose of 200 mg. Mean absolute oral bioavailability was high in rats (96%), low in monkeys (9.8%) and moderate in humans (60%).

Following intravenous administration, volume of distribution at steady state and plasma clearance in rats and monkeys were estimated to 1.04 L/kg and 0.814 L/kg, respectively, and to 26.6 ml/min/kg and 31.8 ml/min/kg, respectively, indicating wide distribution (beyond plasma and extracellular fluid), extensive metabolism and a short terminal half-life in both species. The terminal half-life was estimated to 0.82 h in rats and 0.52 h in monkeys. In humans, the terminal half-life was 2 to 5 h.

Multiple dose pharmacokinetics of abrocitinib in plasma are determined in the toxicokinetic parts of the oral repeat-dose toxicity studies in male and female mice, rats, monkeys and female rabbits. No consistent gender differences in plasma exposure to abrocitinib (C_{max} and AUC_{24h}) were observed in mice, rats and monkeys.

In all species mean C_{max} and AUC_{24h} of abrocitinib at steady state increased with increasing dose over the dose range studied. In rats, the increase in AUC_{24h} was somewhat higher than dose proportional (> 50%) from 3 to 30 mg/kg and then approximately dose proportional up to 200 mg/kg. No consistent accumulation was observed on days 29 and 182 in the repeated dose toxicity studies. In monkeys there was in general a higher than dose proportional increase (> 50%) in AUC_{24h} between the dose levels studied and no consistent accumulation, except at the 75 mg/kg dose in the 9 month study where an approximately 2-fold accumulation was observed from day 92 to day 273. In mice the increase in AUC_{24h} at steady state was approximately dose proportional up to 20/25 mg/kg and then higher (> 50% higher than dose proportional increase) at the 60/75 mg/kg dose level.

Distribution

Tissue distribution in pigmented (Long Evans) rats following oral administration of [^{14}C]-labelled abrocitinib was evaluated by quantitative whole-body autoradiography. The results showed that [^{14}C]-abrocitinib-derived radioactivity was widely and rapidly distributed with the highest levels occurring at 0.25 h post dose in most tissue and up to 4 h post dose for the eye. Highest concentrations of radioactivity, excluding the gastro-intestinal tract, were observed in the uveal tract, liver, kidney, adrenal glands and salivary glands.

Low levels of [^{14}C]-abrocitinib-derived radioactivity were detected in non-circumventricular CNS tissues at for at least 4 hours. The brain:plasma AUClast ratio was <0.1, indicating that the passage over blood-brain barrier was low. For most tissues the radioactivity was eliminated at 168 hours post-dose. In the thyroid, gland radioactivity was present up to 336 hours and the arterial walls, intervertebral ligament(s), uveal tract and whole eye(s) contained radioactivity at the last sampling 672 hours post-dose indicating affinity of [^{14}C]-abrocitinib-derived radioactivity to ocular and itegumentary melanin.

Plasma protein binding of abrocitinib was similar in rats, monkeys and humans (fu was 0.38, 0.37, and 0.36, respectively) and lower and higher in mice (fu: 0.55) and rabbits (fu: 0.19), respectively compared to humans. For rabbits, which has a lower unbound fraction than humans, an exposure margins calculated based on total plasma concentrations will be overestimated in terms of unbound concentrations. The use of unbound plasma PK parameters for calculation of exposure margins is thus considered relevant for the rabbit toxicity studies.

In humans the plasma protein binding of the major metabolites M2 (fu: 0.71) and M4 (fu: 0.83) were lower than for abrocitinib and lower than for the protein binding of M2 and M4 in rats (fu was 0.55 and

0.76, respectively). As the unbound fractions of M2 and M4 are higher in rats compared to humans, exposure margins calculated based on total plasma concentrations of these metabolites will not be overestimated in terms of unbound concentrations. According to the applicant, protein binding determined at a single concentration which is low relative the total plasma concentrations in the pivotal rabbit EFD study will result in conservative margins for the unbound plasma exposure and therefore sufficient. This is agreed by CHMP.

Abrocitinib showed no preferential partitioning into red blood cells in any of the species tested with, B/P ratios of 1.00, 0.92, 0.59, 1.01 and 1.07 in mouse, rat, rabbit, monkey and human, respectively.

In lactating rats the milk AUC_{inf}:plasma AUC_{inf} ratio was 5.24 suggesting exposure of pups to abrocitinib via milk from dams treated with oral doses from 10 mg/kg.

Metabolism

The metabolism of abrocitinib was investigated *in vitro* in liver microsomes and hepatocytes of mouse, rat, monkey and human and *in vivo* in mouse, rat, monkey and human.

In vitro

Unchanged drug and various metabolites mainly representing separate hydroxylation's of the aliphatic propyl group or the N-methyl-pyrrolo-pyrimidine (e.g. M1, M2, M3 and M4), oxidative demethylation (M5) and several minor metabolites involving secondary oxidations and hydrations as well as cysteine and glutathione conjugation were detected in liver microsomes and hepatocytes across species. All human metabolites detected except the glucuronide were observed in the animal liver preparations.

Based on *in vitro* CYP phenotyping, CYP2C19 (~ 50%) was indicated to be the primary clearance route for abrocitinib, followed by contributions from CYP2C9 (~ 30%), CYP3A4 (~ 10%) and CYP2B6 (~ 10%).

In vivo

Abrocitinib was extensively metabolised. Unchanged drug and various metabolites mainly representing separate hydroxylation's of the aliphatic propyl group or the N-methyl-pyrrolo-pyrimidine (e.g. M1, M2, M3 and M4), carboxylic acid (M7), hydroxylation/carboxylation (M6), tri-hydroxylation, hydroxylation/hydrolysis, oxidative demethylation (M5) and several minor metabolites involving secondary oxidations and hydrations, were detected in plasma, urine and faeces of humans and in plasma and/or urine of mice, rats and monkeys. All human metabolites detected were observed in plasma or urine of the animal species.

Two of the human metabolites, M2 and M4, were identified as major metabolites in accordance with ICH M3 (R2). Metabolites M2 and M4 were shown to be present in plasma of mice (M2 and M4), rats (M2 and M4) and monkeys (M4 only). For qualification of M2 and M4 a separate pharmacokinetic study was performed in rats. Steady state pharmacokinetics of abrocitinib, M2 and M4 were estimated following 5 days of daily repeated oral administration of NOAEL dosages from the 6-month chronic toxicity study (45 mg/kg for females and 70 g/kg for males) and compared to those in humans following daily oral dosing of 200 mg abrocitinib. The rat/human ratios for AUC_{24h} were above 0.5 indicating that the exposures for M2 and M4 in rats represent at least 50% of the exposure in humans. The applicant therefore considered these major metabolites to be toxicologically qualified in accordance with ICH M3 (R2). As there are no values available for the half-lives of metabolites M2 and M4 in rats it is not clear if steady state for these metabolites is reached following 5 days administration. In case steady state levels have not been reached the obtained rat/human exposure ratios for M2 and M4 are underestimated and thus still sufficient. It could be noted that [^{14}C]-abrocitinib-derived radioactivity was eliminated from plasma with a $t_{1/2}$ value of 8.95 h in Long Evans rats, which is markedly longer than the $t_{1/2}$ of 0.82 h obtained for abrocitinib in Spraque Dawley rats. This indicates that there are

metabolites with longer half-lives than abrocitinib and that 5 days should be sufficient to reach steady state.

As the strategy with qualification of major metabolites in a separate PK study is uncommon the applicant was requested to bridge the AUC_{24h} for abrocitinib in relevant toxicity studies to the corresponding results in the separate PK study in order to verify that the exposure to M2 and M4, especially M2 which is on the borderline, can be regarded as sufficient. Rat versus human ratios for M2 and M4 in various rat toxicity studies were extrapolated from the exposure ratios obtained in a PK bridging study and corresponding dose ratios assuming dose linear kinetics. As estimated exposure ratios above 0.5 were obtained for pivotal rat toxicity studies including the 6-month repeated toxicity study, the EFD study, the *in vivo* micronucleus study, and for all ratios except for M2 in females (0.28) in the carcinogenicity study, the major human metabolites M2 and M4 are considered toxicologically qualified.

Whereas the metabolism of abrocitinib was thoroughly investigated *in vitro* in liver microsomes and hepatocytes of mouse, rat, monkey and human and *in vivo* in mouse, rat, monkey and human, there were no metabolism data generated by the applicant in rabbit. The skeletal effects observed in the rabbit EFD study are described in SmPC section 5.3. Further, abrocitinib is contraindicated during pregnancy. Thus, the lack of information on the metabolism and exposure to metabolites in the rabbit is acceptable.

Excretion

In rats 7% of the dose was excreted as unchanged drug in urine and 0.1 % of the dose was excreted as unchanged drug in bile. This is in line with humans for which less than 1% was eliminated as unchanged drug in urine.

2.5.4. Toxicology

The applicant developed abrocitinib, an orally active small molecule that reversibly and selectively inhibits JAK1 by blocking the ATP binding site. The initially proposed use was in adult and adolescent patients from 12 years of age with moderate-to-severe AD as monotherapy or in combination with medicated topical therapy. The intended dosing is up to 200mg QD. Abrocitinib has been evaluated in a comprehensive set of non-clinical toxicity studies with the active substance administered by the oral route in mice, rats, rabbits and monkeys. According to the applicant, rats and monkeys were used for the general toxicology programme, as these species have previously been used in development programmes for other similar JAK inhibitors and they are sensitive to the pharmacological action of JAK inhibition. Further, all relevant human metabolites of abrocitinib have been identified in at least one of the species. Upon request from the CHMP, the activity of abrocitinib on the JAK family members in the selected safety pharmacology/toxicity species were made available.

The toxicology programme is comprised of general toxicology studies and studies of genotoxicity, carcinogenicity, reproductive toxicity including juvenile toxicity, phototoxicity and immunotoxicity. In addition, studies on metabolites and impurities have been performed to complete the programme. The oral route was chosen for the programme since it is the clinical route of administration. A suspension of abrocitinib was administered in the rat, mouse and rabbit studies. An SSD formulation was developed for the studies in cynomolgus monkey as it was identified by the applicant as the most appropriate formulation for the cynomolgus monkey studies based on tolerability and toxicokinetics. Despite these measures and the fact that the monkeys were dosed in the fed state to minimise emesis, reflux and emesis were quite frequent in the general toxicity studies in monkey.

The toxicity profile of abrocitinib was mostly reflective of the JAK inhibitory pharmacological action of the substance, with effects mainly on the immune and haematolymphopoietic systems. Adverse toxicities have been identified in the programme which are presented and discussed below.

2.5.4.1. Single dose toxicity

Two non-GLP single-dose toxicity studies have been submitted where one was performed in Sprague-Dawley (SD) rat and one in cynomolgus monkey. In the rat, oral gavage of 500mg/kg was identified as the highest non-lethal dose in the study. In the monkey study, where the objective was to identify an optimal oral formulation of abrocitinib for the future repeated dose toxicity studies, an SDD formulation was well tolerated at doses up to 150mg/kg/day when given as a single dose.

2.5.4.2. Repeat dose toxicity

Repeated-dose toxicity studies of abrocitinib have been performed in rats and cynomolgus monkey. In the rat studies, the SD strain was used for the non-GLP 7-day study, but 1-month and 6-month studies were undertaken in Wistar Han rats. The age of the rats in the studies varied. In the 7-day study, the ages were 6-8 weeks old when dosing was initiated, whereas the animals used in the 1-month study were 9 weeks and in the 6-month study dosing was initiated when the rats were 6-7 weeks old. The cynomolgus monkeys used were 2-4 years old.

Mortality

Mortalities were evident in the non-clinical study programme.

In the 6-month study in rat, three animals died or were euthanised in the study. Two high-dose deaths were related to the TK blood collection. The third animal was euthanised in a moribund condition on Day 101 of the dosing phase. Based on the data presented, the deaths were not likely related to the test substance.

In the 9-month cynomolgus monkey study, one female given 75 mg/kg/day was euthanised on SD 271 as she had self-mutilated her right foot. The animal had also injection-site lesions. Neuropathic pain or numbness secondary to sciatic nerve injection with ketamine was provided as explanations for the self-mutilation. While the explanation is plausible, the underlying reason is considered unknown.

In the 6-month carcinogenicity study in transgenic mice, 7/15 deaths in the abrocitinib dose-groups were considered related to obstructive nephropathy. Only 1 death was recorded in the control group. In the 2-year carcinogenicity study in rat, survival rate was overall low, especially in female controls with a survival rate of only 42% at study termination, suggesting that the study may have been terminated earlier.

Bodyweight and food consumption

Effects on bodyweight and food consumption were generally non-adverse. Overall, the effects noted were reductions in food consumption with transient effects on food consumption. However, in the 1-month study in rat, males receiving 200mg/kg/day had a 38% increase in bodyweight change over the study-period. The underlying reason for this is unclear. No correlating change in food consumption was evident.

Clinical signs

Reflux and emesis were reoccurring problems in the study programme in monkey. In the 14-day study, efflux and emesis were substantial problems in most animals during the dosing, but only in the 100mg/kg/day group post dosing. In the 1-month study, reflux was frequent during dosing, and it

occurred in 13/24 animals on the study. In the 9-month study, vomitus was frequently seen without clear treatment-relation during the study period. No vomitus was recorded in the recovery animals, which may suggest that the dosing phase was associated with nausea in the animals. In the 1-month study, these effects were most prominent around dosing. No such information is available in the 9-month study data.

Scabs and skin sores were prominent findings in the rat 6-month study with females more affected, and one female had scabs throughout the recovery period. These skin findings correlated with erosion/ulcer (mild-moderate) including dermal inflammation in three females receiving ≥45 mg/kg/day. According to the applicant, these findings are not adverse. While clearly treatment related, the findings were graded mild-moderate with a focal presentation and with no reported lack of impact on overall animal health. However, in the two females administered 70 mg/kg/day, granuloma formation was evident. It is generally held that this inflammatory response is particularly common whenever the immune system is unable to readily eliminate a pathogen. Thus, the inflammation is likely a representation of the immunosuppression. Given that the marked immunosuppression at 70 mg/kg/day also resulted in a prostate inflammation in two HD males (see below) it is clear that the dose-level is overly immunosuppressing to the point that opportunistic pathogen infections are allowed.

In the 9-month monkey study, females displayed alopecia and thinning hair coat (various locations) at 75mg/kg/day, but this was not considered adverse.

Effects on the lymphopoietic system and immune parameters

Abrocitinib-related changes in circulating total lymphocytes including specific lymphocyte subsets were consistently seen in the pivotal studies and is considered reflective of the JAK inhibitory effect of the substance. The reductions in lymphocyte counts generally correlated with lower mean lymphoid organ weights and decreased lymphoid cellularity in lymphoid organs.

In the rat 6-month study, decreases in lymphoid cellularity (graded up to severe) were evident in thymus, spleen, GALT and lymph nodes. For the spleen and thymus, they corresponded with reduced organ weights and for the spleen with macroscopic findings of small spleens at doses above 30 mg/kg/day. As these findings were not associated with clear organ damage (inflammation, fibrosis) the applicant did not consider them adverse. While no clear organ pathology was evident, it was clear from skin and prostate inflammations in the same study that the animals were severely immunosuppressed at the highest dose-level. Further, a male administered 45 mg/kg/day also presented with prostate inflammation, but without the epithelial atypia and inclusion material, thus the inflammation in this animal was considered unrelated to treatment and spontaneous. While it is considered unlikely that an unrelated spontaneous prostate inflammation would incidentally show up in an animal with clearly suppressed immune system, it is agreed that the causative agent was not likely the icosahedral virions found in the HD males. The inflammation could be treatment related, but as it only occurred in one animal, and moderate inflammation can be a spontaneous finding in the rat it was not further pursued by CHMP.

In the monkey studies, the effects on lymphocytes also correlated with reduced thymus weights and reduced lymphoid cellularity in thymus and spleen. In the 1-month study, these immunosuppressive effects resulted in cytomegalovirus infection in all males administered 150 mg/kg/day. As this infection is normally latent in immunocompetent macaques and is controlled by the cell-mediated immune response, this finding is suggestive of excessive immunosuppression and is considered adverse in males at 150 mg/kg/day. No findings of cytomegalovirus were noted in females. While exposure was slightly higher in males in the 150 mg/kg/day dose group which may signal a more severe immunosuppression, this does not explain the difference between the sexes at the individual level as the toxicokinetic data was very variable. According to the applicant, the reason for the occurrence of

CMV in only males in the study is less clear, as sex is not a known factor involved in CMV reactivation in monkey. However, immunocompetence in general is established as a sexually dimorphic trait in humans, thus a similar pattern in monkey is possible or even likely. As it is assumed that any obvious differences in environmental factors would have been identified by the applicant, the proposition of the finding as coincidental is also a possibility given that the group size in monkey studies is limited.

Decreased cellularity of the bone marrow was only noted in the 1-month study in monkey. It involved all cell lines (erythroid and myeloid precursors and megakaryocytes) and was observed from 40 mg/kg/day in males from 80 mg/kg/day in females. This finding correlated with decreases in RBCs, HGB, and HCT from 80 mg/kg/day and decreased reticulocytes from 40 mg/kg/day. However, given the relatively mild reductions in erythrocytes and platelets (minimal-mild) the finding was not considered adverse.

Immunophenotyping was performed in the monkey studies. In the 1-month study, there were test article-related decreases in T cells (T helper and T cytotoxic) and plasma cells at 150 mg/kg/day in both sexes and decreases in B cells only in males. Natural killer cells were consistently reduced at all dose levels in males and females. In the 9-month study, no test article-related changes were observed in the number of B, T, T helper, T cytotoxic, and T memory cell subsets. However, NK cells were decreased. Clear effects were noted on IgA (HD), IgG and IgM in serum (SD177 and SD274). Upon request from CHMP, the applicant provided mean values for IgA, IgG and IgM. Based on the mean data provided, the overarching conclusion remains from the initial assessment that abrocitinib-related effects are noted on IgM and IgA, whereas no meaningful effects are noted on IgG levels as a consequence of abrocitinib exposure.

A KLH study was performed in monkeys from the 9-month study. Abrocitinib exposure gave reduced IgG and IgM values (with dose relation) from 15mg/kg/day with partial recovery. While no signs of infection were noted in the study, the only partial recovery of the immune system after 2 months recovery is of concern.

Collectively, the effects on the lymphopoietic system and immune parameters reflect pharmacological effects of the JAK1-inhibition. While monitorable in the clinic, they ultimately lead to an increased susceptibility to infection and is a clear risk-factor for tumour development. No complete recovery of these effect was noted in the 9-month study in monkey, and thus should receive further attention in the clinical setting. See further discussion in clinical safety and risk management plan sections.

Bone

Effects on bone were noted in the 7-day and 1-month rat studies at an age comparable to adolescent human age of ≥ 12 years. Exposure margins at which no bone finding was noted were 5.7 to 6.1 times the human AUC at the maximum recommended human dose (MRHD) of 200 mg. In the 7-day study, reduced mineralised cartilage was noted in the physis of femur and tibia at the interface of the growth plate and the primary spongiosum (minimal-mild). In the longer 1 month-study, the same effects were noted graded minimal-mild at 75mg/kg/day and with up to the moderate grade at 200mg/kg/day. Importantly, no effects were identified in the 6-month study at doses up to 70 mg/kg/day (up to 25 times the human AUC at the MRHD of 200 mg). According to the applicant, this indicates high sensitivity to the bone dystrophy effect in rapidly growing rats. While this explanation is plausible, the rats in the 1-month study were 9 weeks at initiation of dosing, whereas the rats in the 6-month study were 6-7 weeks. Thus, the age parameter is not fitting to the explanation. The applicant was asked to elaborate on possible mechanisms why the bone-effect was apparent after 7 days or 1-month administration of 75 mg/kg/day and higher doses but not after 6 months administration of a similar dose of 70 mg/kg/day. Following the applicant's elaboration severe and partly irreversible bone findings in rats were only observed when the administration period covered the most vulnerable time

window of PND10 to 20. When administration started later in the life of rats, i.e. PND42-PND63, only microscopic bone findings (bone dystrophy at the interface of the growth plate and the primary spongiosum) were observed. No findings were reported when administration started at PND42-49 which was explained, according to the applicant, by resolution of a potential delay in ossification that occurred in the early phase of the study during maturation of the animals even during continuing administration of abrocitinib. The applicant added data generated with tofacitinib, a JAK1/3 inhibitor for which they hold a marketing authorisation, in order to broaden the view on potential bone effects provoked by JAK-inhibitors. No bone-findings were reported for tofacitinib when administered postnatally to rats and monkeys. Of note, tofacitinib was administered to rats only after PND 21 and, thus, when femoral bone neck formation was complete. From the information provided by the applicant it appears that microscopic evaluation, as done for abrocitinib, was not performed in juvenile rat studies with tofacitinib. Thus, based on the available information the lack of findings for tofacitinib might not be entirely translatable to abrocitinib due to differences in study design.

The applicant further outlined that the bone development in rats significantly differs from that in humans in that the femoral bone neck is fully developed before the start of ambulation which is not the case in rats. As a consequence, the translatability of rat findings to humans might be difficult. Therefore, probably more attention should be drawn to the second non-clinical species, the cynomolgus monkey. NHP studies conducted in support of the safety of abrocitinib covered the age range of 2 to 7 years corresponding to humans from 8 to 21 years. Thus, with regard to bone effects, children <8 years are not considered sufficiently covered by non-clinical studies. While it was clarified that microscopic evaluations that might have been able to capture analogies to rat findings (bone dystrophy at the interface of the growth plate and the primary spongiosum) have also been performed in monkeys, from a non-clinical point of view, the mechanism underlying inhibition of bone development is not clear, which poses a significant uncertainty to the use of abrocitinib in paediatric patients (including adolescents). Nevertheless, additional non-clinical studies would not significantly add to the elucidation of this uncertainty. See further discussion in clinical safety section.

Bone/skeletal effects in the DART programme

Skeletal observations including increased fetal incidences of short 13th ribs and increased fetal and/or litter incidences of thickened ribs, cervical arches with reduced ventral processes and unossified metatarsals were observed in the pivotal rat EFD study. In the pivotal EFD study in rabbits there were increased litter and fetal incidences of unossified forelimb phalanges as well as small increases in the litter and fetal incidences of unossified hind limb tarsals and phalanges and of unossified xiphoid.

No apparent effects on bone or skeleton were clinically evident in the PPND study. No skeletal examination was performed of any generation in the study, however, more discrete changes not evident from gross morphology are possible. This lack of apparent bone effects in the PPND study may support that while there is considerable transfer of abrocitinib to breast milk, lactational exposure to abrocitinib is insufficient to produce the bone effects evident in 6-9-week old rats or the effects noted in the juvenile toxicity study.

In the pivotal juvenile toxicity study, observations of malrotated and/or impaired forelimbs and hindlimbs were identified from PND 16 at all doses starting at PND10. No effects (clinical signs or otherwise) were reported from the DRF-study despite that the same dose-levels were used, and the pups were exposed to PND24. The reason for this is unclear. The findings in the pivotal study corresponded macroscopically to bent tibia and fracture, misshapen (or missing) femoral head and neck. Microscopic correlates included abnormal morphology of the femoral head in bones at all doses. No NOAEL could be identified in the study. Further, decreased mineralised cartilage in femur and physis dystrophy in stifle joint (decreased primary spongiosa) was present in all abrocitinib exposure

groups. This finding was also seen in the 7-day and 1-month (but not the 6-month) repeated dose toxicity studies as discussed above, but there they did not lead to apparent clinical signs. The similarity of these findings indicates that developmental exposure to abrocitinib (spanning from PND10 to week 9 at dose initiation) in the rat can induce dysmorphic effects in the bone.

A juvenile toxicity study in rats were used in the development of tofacitinib, a JAK1/3 inhibitor. No impact on bone development was evident in these studies, according to the applicant, this was because the studies were initiated at PND21, compared to PND 10 in the juvenile toxicity study in the present application. While this may partly explain the lack of effects in the tofacitinib studies, the decreased primary spongiosa noted at 6-9-week-old rats suggest that the abrocitinib induced effects on bone are occurring up to and including adolescence.

Overall, abrocitinib induced effects on bone development when administration occurs postnatally in the rat. Effects range from clearly adverse findings at early postnatal exposure where essentially no femoral head or neck is present to decreased mineralised cartilage in femur and physis dystrophy when exposure occurs around weeks 6-9. No effects on bone were noted in the 6-month study in rat, despite that these animals were 6-7 weeks old and had similar abrocitinib exposure. While the lack of effects on bone development in 2-4-year-old cynomolgus monkeys might be reassuring, the pharmacological relevance of the species for the human situation is currently unclear. No cross-reactivity studies have been shown, however, it is possible that the abrocitinib induced effects on bone development in rat (and likely human) are not inducible in the monkey.

Upon request from the CHMP, the applicant provided a comprehensive reflection and discussion regarding the abrocitinib-induced effects on bone development noted in the general toxicology studies in rat and in the DART programme. In the studies, abrocitinib-induced effects on bone development were evident during in utero and early postnatal life, and the effects were varied depending on when and to what extent the developing organism was exposed. In the EFD-studies in SD rat and NZW rabbit, the exposure resulted mainly in skeletal variations and developmental ossification delay. However, as no TK-data was made available, the extent of fetal exposure remains unclear. In the PPND study in rat, no obvious skeletal effects were noted in the F1-generation even if limited evaluation (i.e. macroscopic evaluation) was performed thus only gross malformations would likely be identified. In the juvenile toxicity study where abrocitinib was administered daily from PND10 to PND63, major skeletal malformations were evident with paw malrotation, bent bone (tibia), fractures and secondary joint inflammation. From 5 mg/kg/day, small or misshapen femoral heads were observed where there was essentially no femoral head or neck present at the highest severity level. Further, decreased mineralised cartilage in femur and physis dystrophy in stifle joint (decreased primary spongiosa) was present in all abrocitinib exposure groups. No NOAEL was set in the study, and the findings were considered adverse and not compatible with further juvenile development of the drug.

Interestingly, in the shorter general toxicity studies in 6-9-week-old rats, abrocitinib-induced microscopic bone metaphysis dystrophy (defined as decreased primary spongiosa) was also noted, but this finding was not seen in the 6-month study where 6-7-week-old rats were used.

According to the applicant, the underlying reasons for the differences in effects noted in the studies are related to a combination of developmental processes occurring at the time of exposure, bone structures at pre- and post-natal development, and changes in biomechanical loading associated with the onset of ambulatory activity.

In-house studies performed by the applicant have shown that at approximately PND 14 (the age at which rat pups become ambulatory), the proximal femoral growth plates are splitting into one plate for the formation of the femoral neck, and one for the formation of the greater trochanter. The hypothesis is that abrocitinib exposure leads to a delayed ossification of the femoral neck and other impacted long

bones such that the biomechanical loading associated with the starting ambulation leads to deformation of the cartilaginous femur head and neck which leads to fractures and other adversities of the bone. Accordingly, a major part of the effect is that ambulation is started before the bones have fully developed.

The applicant also considered that exposure to a JAK-1 inhibitor later in bone development, when the bones are more developed, does not induce bone morphogenic effects as a consequence of ambulation.

In the juvenile DRF-study with abrocitinib, rats were exposed to abrocitinib at doses up to 75 mg/kg/day from PND10 to PND24. In this study, no obvious bone effects were reported, whereas in the definitive study (exposure PND10-PND63), clinical observations of malrotated and impaired forelimbs and hindlimbs were noted at exposures at and above 25 mg/kg/day already from PND16, which led to termination of 5 severely affected juveniles. The clinical findings corresponded to various macroscopic and microscopic changes in the bone. Delays in ossification of long bones are not uncommon findings in DART and juvenile toxicity studies, but the severity of the effects (or consequences of the delay) are not as dramatic, despite change in mechanical loading postnatally as a consequence of ambulation. While the general explanation put forth by the applicant to explain the adverse bone effects in the juvenile toxicity study seems plausible there are remaining major uncertainties. Further, a potential mechanism behind the abrocitinib-induced delayed ossification and its dramatic effects on critical bones is currently lacking.

The bone metaphysis dystrophy noted in the shorter general toxicity studies (in Wistar and SD rats) and in the juvenile toxicity study were not seen in the pivotal 6-month study in the Wistar strain. According to the applicant, a possible explanation is that any delay in the ossification processes that occurred at younger ages resolved as the animals matured. While this is considered likely and is further supported by the recovery of this particular finding in the juvenile study animals after a 2-month recovery, it is unclear if these effects induced before attainment of peak bone mass may have effects on bone mineralisation and/or bone quality endpoints.

No bone effects were evident in the general toxicity study in monkey despite exposure to abrocitinib from an age comparable to approximately 8-10 years old in humans, up to 30 times the human AUC at the MRHD of 200 mg, in the 9-month toxicity study. While the underlying reason for the lack of effect in monkey is unknown, the applicant suggested that relative differences in bone development in relation to age is a possible reason. According to the applicant, in monkeys and humans major bone structures, including femoral neck, are fully developed prenatally and onset of ambulatory activity and associated biomechanical loading occur relatively later postnatally. Accordingly, in monkey (and human) a developmental delay in ossification of major bone structures (prenatally) would not be challenged by ambulation which could lead to bone deformation. While it is agreed that major bone structures in monkey and human are developed prenatally, postnatal development occurs and mechanical strain is required for postnatal, but not for prenatal skeletal development and maintenance. While no data support that abrocitinib induced bone effects in the 1- and 9-month studies in cynomolgus monkey, it is established that JAK signalling plays an important role in bone development and metabolism. However, the direct effects of inhibitors on bone development remain unclear but the relative inhibition of different JAKs seems to be an important factor. Thus, there is a remaining uncertainty regarding the developmental bone effects, which should receive further clinical attention.

Skin

Abrocitinib-related skin effects were noted across the non-clinical study programme. They were most prominent in the rat studies and included abrasions in the mouth, shoulder and cervical region which in some animals led to ulcers. Further, scabs and skin sores were noted from 45 mg/kg/day in the 6-

months study and perioral scab was found also after 2 months recovery at 70 mg/kg/day. Incidence alopecia and thinning hair coat was evident in the 9-month study in monkey at 75 mg/kg/day.

Kidney

The kidney was not identified as a target organ in the general toxicology programme. However, in the 1-month DRF studies Tg rasH2 (wt/wt) mice preceding the 6-month carcinogenicity study, adverse kidney findings were evident including nephropathy with renal tissue loss. In the mice (and in rats in the rat 6-month study administered abrocitinib at ≥45 mg/kg/day) urinary crystals were found. Pharmacokinetic excretion data showed that the crystals mainly contained the M4 metabolite. The applicant's position is that urinary crystals is a rodent phenomenon, related to the high rodent urine osmolality which favours crystal precipitation. As there were no renal findings reported in the general toxicology programme, and no urinary crystals identified in monkey urine, the clinical relevance of the renal findings in the rodents is considered limited.

2.5.4.3. Genotoxicity

A full programme of genotoxicity studies has been performed by the applicant. The Ames test performed in the Salmonella strains TA98, TA100, TA1535, TA1537 and the E. coli strain P2 uvrA pKM101 was negative up to 5000 µg abrocitinib per plate. In an *in vitro* micronucleus test in TK6-cells, a positive response was observed at 37.4 and 43.6 µg/mL. Based on further mechanistic investigations in a FISH-assay, the conclusion was reached that abrocitinib is aneugenic at concentrations from 37.4 µg/mL. An *in vivo* micronucleus assay in the rat where bone marrow smears were evaluated came out negative. Collectively, the genotoxicity studies presented do not indicate a genotoxic risk for abrocitinib at the proposed clinical dose of 200 mg QD.

2.5.4.4. Carcinogenicity

Carcinogenicity studies were conducted in mice (6-month study in Tg rasH2 mice) and rats (104-week study). In mice, no neoplasms were identified, but there was a dose-related increase in the incidence of thymic cell hyperplasia in females from 25 mg/kg/day. In rats, thymus hyperplasia was higher in females administered 30 mg/kg/day, and a higher incidence of thymoma was noted in females from 3 mg/kg/day. Immunosuppression is a clear risk-factor for tumour development, especially spontaneous tumours (like thymomas). However, thymomas were evident in females already from the lowest dose, with low margins of exposure to human exposure.

Further, only one case of malignant thymoma was noted in the study (in the 10 mg/kg dose group) which does not suggest a treatment-related increase. However, it is unclear to what extent there can be progression from a benign thymoma to a malignant thymoma and the tumour biology underlying such a shift.

The increase in thymoma incidence is noted in female rats and from exposures around clinical exposure whereas no apparent increase is not apparent in male rats up to 14x unbound human AUC. The reason for this sex difference is unclear, but the applicant referenced studies suggesting that thymuses of female Wistar Han rats exhibit a more delayed physiologic thymic involution than those of males or other rat strains and that a higher frequency of spontaneous thymoma formation in Wistar rats is related to higher numbers of thymocytes at baseline and higher proliferation rates of TECs. This then may lead to a higher sensitivity for thymoma formation in the female Wistar rat following administration of an immunosuppressive drug such as abrocitinib. Overall, this explanation regarding increase female sensitivity seems possible and it was agreed that abrocitinib treatment seems to accelerate the thymoma formation in the rat.

The human risk for abrocitinib-induced thymoma is currently unclear. Other immunosuppressive treatments (including the JAK inhibitor tofacitinib) have induced thymomas in cancer studies but there is according to the applicant currently no clinical evidence suggesting an increased risk for human thymoma development. Nevertheless, given the unclear human relevance of the thymoma findings, the applicant included data in section 5.3 of the SmPC.

2.5.4.5. Reproductive and developmental toxicity

In a fertility and early embryonic developmental study in male and female rats there were no treatment article-related findings on fertility in males (including copulation/fertility indices, sperm motility and sperm counts) following oral treatment with 30, 45 and 70 mg abrocitinib/kg/day. For the females an adverse lower female fertility index (56% vs 95% in controls) and mean number of corpora lutea (9.6 vs. 12.4 in the controls) were observed at the 70 mg/kg dose level. In addition, mean numbers per litter of viable embryos were decreased (4.2 at 70 mg/kg vs. 11.3 in controls) and mean percent per litter of post-implantation loss were increased (61% at 70 mg/kg/day vs. 5.3% in controls) in a dose-dependent manner at all dose levels of abrocitinib. Based on the lack of abrocitinib-related adverse effects, the NOAEL for male reproductive toxicity was set to 70 mg/kg/day. Due to adverse decreased numbers of corpora lutea at 70 mg/kg/day and higher post-implantation loss (embryo-lethal effects) from the lowest dose level of 30 mg/kg/day a NOAEL for female reproductive toxicity and early embryonic development could not be set.

In the follow-up study effects on female reproduction and early embryonic development following oral treatment with 3, 10 and 70 mg abrocitinib/kg/day with a 1 month-period of recovery for the 70 mg/kg dose level were investigated. In line with the other study, an adverse lower fertility index (50% vs 95% in controls) were observed in the 70 mg/kg/day dose group. Whereas no effects were noted for mean number of corpora lutea there was a decreased mean number of implantation sites (7.5 compared to 11.8 in control), an increased percentage of pre-implantation loss (31% compared to 4.7% in control) and a 100% post-implantation loss with 0 viable embryos at the 70 mg/kg dose level. No significant changes on fertility or embryonal development were observed in the 3 and 10 mg/kg dose group. All abrocitinib-induced effects on fertility and early embryonal development in the 70 mg/kg dose group was shown to be reversible, none of the effects was present in the recovery animals mated after 1-month recovery period. Due to the adverse lower fertility and higher embryonal lethality at 70 mg/kg/day the NOAEL for female reproductive toxicity and early embryonic development was set to 10 mg/kg/day, which represents a 1.9-fold exposure margin (total AUC) to the clinical exposure at 200 mg.

In the pivotal rat EFD study, there were increased average numbers of late resorptions (0.6 vs. 0.0 in controls) and dead fetuses (3 from 3 litters vs. 0 from 0 litter) at the highest dose level of 60 mg/kg which resulted in an increased post-implantation loss (mean% of 9.5 vs. 7.2 in controls). Skeletal observations considered as abrocitinib-related included increased fetal incidences of short 13th ribs in the 30 and 60 mg/kg dose groups and fetal and/or litter incidences of thickened ribs, cervical arches with reduced ventral processes and unossified metatarsals at the 60 mg/kg dose level. These skeletal findings were regarded by the applicant as common findings in this rodent species and strain representing reversible delays or accelerations in development not expected to adversely impact viability or health. As the skeletal findings observed at the 30 and 60 mg/kg dose levels are not confirmed as common findings at the study site or to resolve postnatally they should be considered adverse and the developmental NOAEL in rats should be set to 10 mg/kg/day. With respect to the adverse skeletal findings in the rat juvenile toxicity study, e.g. paw malrotation, bent bone and small or misshapen femoral head proposed to result from delayed ossification in combination with ambulation on underdeveloped bones, the delayed ossification observed in the rat EFD study should

however be regarded as adverse. Even if delayed ossification can be expected to resolve postnatally this has not been shown to occur before start of ambulation stated to occur approximately at PND 14, i.e. potential effects on postnatal bone development cannot be excluded. The margins of exposure at the NOAEL of 30 mg/kg/day for embryo-fetal lethality and at the NOAEL of 10 mg/kg/day for skeletal effects to the clinical exposure at 200 mg in terms of total AUC are presented in SmPC section 5.3 as 10 and 2.3-fold, respectively.

In the pivotal EFD study in rabbits two females in the 30 mg/kg dose group (mid dose) were euthanised due to abortion and total litter loss (including early and/or late resorptions) and one doe in the 10 mg/kg dose group (low dose) had total litter loss (100% late resorptions) at caesarean section on GD 29. Furthermore, in the 10 and 75 mg/kg (high dose) dose groups, increases in late resorptions and percentage post-implantation were observed. At 75 mg/kg, there was an abrocitinib-related increase in the litter and fetal incidences of unossified forelimb phalanges. Given the lack of other indications of skeletal dysmorphogenesis noted in this study, the applicant did not consider this skeletal observation to be indicative of an adverse effect on fetal development. The litter incidence of unossified forelimb phalanges was however increased also at 10 mg/kg. In addition, small increases in the litter and fetal incidences of unossified hind limb tarsals and phalanges and of unossified xiphoid were observed at all dose level. The skeletal findings observed from 10 mg/kg are not confirmed as common findings at the study site or to resolve postnatally and should therefore be considered adverse. Thus, it is not possible to set a NOAEL for embryofetal development. A developmental LOAEL of 10 mg/kg in rabbits is considered appropriate. The applicant did not consider the increased litter incidences of unossified forelimb phalanx at 10 mg/kg, unossified hindlimb phalanx at 75 mg/kg or of unossified hindlimb tarsal from 30 mg/kg, which are outside the historical control range, as adverse. The applicant considered that the adverse skeletal findings in the rat juvenile toxicity study result from delayed ossification in combination with ambulation on underdeveloped bones. Nevertheless, even if delayed ossification can be expected to resolve postnatally this has not been shown to occur before start of ambulation i.e. potential effects on postnatal bone development cannot be excluded. Whereas it is acknowledged that abrocitinib is contraindicated during pregnancy this does not have any impact on the developmental LOAEL of 10 mg/kg in the rabbit EFD study which has been adequately reflected with its exposure margin of 0.14 to the clinical exposure based on unbound AUC in SmPC section 5.3.

Adverse developmental toxicity was noted in the PPND study in offspring to dams administered abrocitinib at or above 30 mg/kg/day. The entire 60 mg/kg/day dose-group was electively euthanised in the study. 7 dams had total litter losses and the remaining 13 dams were euthanised due to low viability of the F1 pups. Complete resorptions were noted in two dams at 60 mg/kg/day. Further, 3 dams (2 at 60 mg/kg/day and 1 dam at 30 mg/kg/day) had dystocia. Bodyweight in the F1-generation was reduced at 30 mg/kg/day from PND1 and through weaning up until SD105. Thus, based on the dystocia noted in 1♀ and consistently reduced bodyweight in the F1-generation at 30mg/kg/day, the NOAEL for both maternal and developmental toxicity was set to 10mg/kg/day. Given that the margin to clinical exposure is very low, and that the LOAEL is associated with dystocia or reduced pup viability, abrocitinib should not be used during pregnancy. This is also reflected in SmPC sections 4.3 and 4.6. Further, the motor activity was reduced in rats (especially females) developmentally exposed to abrocitinib. While not statistically significant (due to large variation in the data), a similar effect on motor activity was noted in the safety pharmacology study. From a clinical perspective, no clear decrease in steps was noted in the pedometer evaluation included in the human phase I healthy-volunteer study. Thus, collectively the data available do not support an abrocitinib-induced effect on motor activity.

In the juvenile toxicity study, adverse findings from 25 mg/kg/day included paw malrotation, bent bone (tibia), fractures and secondary joint inflammation. From 5 mg/kg/day, small or misshapen femoral heads were observed where there was essentially no femoral head or neck present at the

highest severity level. Further, decreased mineralised cartilage in femur and physis dystrophy in stifle joint (decreased primary spongiosa) was present in all abrocitinib exposure groups. Thus, due to the functional, macroscopic and microscopic effects on bone (most notably misshapen femoral heads) noted at all dose levels no NOAEL could be identified in the present study.

In the DRF EFD study in rats, fetal external abnormalities in terms of e.g. medially rotated forelimbs were observed in 1 fetus from 1 litter in the 75 mg/kg/day group. This may indicate that skeletal abnormalities are induced *in utero* at high dose levels.

2.5.4.6. Other toxicity studies

Immunotoxicity

Based on an *in vitro* study in human PBMCs where abrocitinib and tofacitinib were compared in a panel of human *in vitro* assays, no unique activities on parameters of human cellular immune function or human cell-mediated host resistance were identified for abrocitinib.

Metabolites

Abrocitinib metabolites M1, M2 and M4 were evaluated for their effects on hERG and on the Nav1.5 (peak current) sodium and Cav1.2 calcium currents. Based on the IC-50 values in the studies, no activity of the metabolites is expected on hERG or the Nav1.5 or Cav1.2 ion channels.

Studies on impurities

Several impurities were tested in the Ames test for mutagenic potential. Three impurities were identified as Ames positive, suggesting that these should be limited to 1.5 µg per person per day unless otherwise justified. With a daily dose of 200 mg/day, this corresponds to an acceptable concentration limit in the drug product of 7.5 ppm. Impurity PF-07216658 was further evaluated in a Big Blue transgenic mouse assay. Statistically increased mutant frequency at the cII gene were seen in both the liver and duodenum of Big Blue mice at all doses (i.e. ≥100mgkg/day) supporting that PF-07216658 is a mutagenic substance. Based on benchmark modelling, a PDE which was established at 1.36 µg/kg/day corresponding to a concentration limit of 170 ppm.

Phototoxicity

A 7-day study in Long-Evans rats was been performed to evaluate the potential for phototoxic effects on the eyes and skin after abrocitinib exposure. No findings related to phototoxicity or dermal toxicity were evident. This suggests that the phototoxic potential of abrocitinib is low, thus no precautions to avoid UV exposure are considered warranted.

2.5.5. Ecotoxicity/environmental risk assessment

Based on study data, no PBT assessment was considered needed. Log Kow at pH7 was determined to 1.85 in an OECD 107 study. However, as the PECSW value was greater than the 0.01 µg/L action limit, a Phase II Tier A evaluation was performed.

Environmental fate

Based on the OECD 106 study, a geometric mean sludge Kd of 50 was evident. However, for Adsorption-Desorption (OECD 106) the use of three types of soils and two types of sludges is preferred. Upon request from the CHMP, the applicant provided a conclusive justification on the number and type of matrices selected for the OECD 106 test which was considered acceptable.

An estimated small fraction of 0.8 %, may be removed through sorption to sludge. Therefore, sludge application to land is not considered to be of concern.

The degradation rate of abrocitinib across 240d in a water-sediment system was studied in an OECD TG308 study. Aqueous dissipation half-life values of 7.5 and 20.9 days resulted under aerobic conditions, thus abrocitinib will likely dissipate to sediment, with approximately 25.1 to 28.4% becoming irreversibly bound.

Aquatic and sediment-dweller toxicity

Chronic aquatic effects of abrocitinib were assessed in green algae, daphnids and fish.
The green algeae was used for $PNEC_{surfacewater}$ as it was considered the most sensitive species with a NOEC of 0.88mg/L. The PNEC for chronic effects on *Chiromomus riparius* was 65.3 mg/kg why the $PNEC_{sed}$ (due to a single study) was 65.3/100 = 0.653.

Risk characterisation

The RQ for all measures were below 1, suggesting that abrocitinib at the proposed use is unlikely to represent a risk to the environment.

Table 1 Summary of main study results

Substance (INN/Invented Name): Abrocitinib					
CAS-number (if available): 1622902-68-4					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log Kow (pH7) =1.86			Potential PBT N
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	1.86			not B
	BCF				
Persistence	DT50 or ready biodegradability				
Toxicity	NOEC or CMR	N/A			
PBT-statement:	Log Kow for abrocitinib is below trigger value for PBT assessment.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC surfacewater (default)	1	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	N/A	N/A			
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	*Activated sludge* K_{oc} =148 Kd = 50 *Soil sorption* K_{oc} =26650 Kd = 517 *Sediment sorption* K_{oc} =8378 Kd = 110			Study with two soils, two sediments and two activated sludge solids
Ready Biodegradability Test	OECD 301	N/A			N/A
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ =7.5-20.9d $DT_{50,\ sediment}$ =77.9d $DT_{50,\ whole\ system}$ =79.5-249d (extrapolated beyond test duration) % shifting to sediment =42.6-73			DT50 sediment only measurable in Choptank river. Not possible to model in Brandywine creek due to unsuitable pattern of decline.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**

Algae, Growth Inhibition Test/*Species*	OECD 201	<u>Density</u> NOEC EC50 <u>Yield</u> NOEC EC50 <u>Growth rate</u> NOEC EC50	 0.88 >0.88 0.88 >0.88 0.88 >0.88	mg/L	Green alga (*Raphidocelis subcapitata)*
Daphnia sp. Reproduction Test	OECD 211	<u>Reproduction</u> NOEC LOEC <u>Length</u> NOEC LOEC <u>Mortality</u> NOEC LOEC	 0.971 >0.971 0.971 >0.971 0.971 >0.971	mg/L	Daphnids *(Daphnia magna)*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	Survival NOEC Hatching success NOEC	 0.922 0.922	mg/L	Fathead Minnow *(Pimephales promelas)*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC (EC15)	1000	mg/L	No inhibitory effect noted
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC LOEC	8.49 16.6	mg/kg	*Chironomus riparius*

2.5.6. Discussion on non-clinical aspects

<u>Pharmacology</u>

The primary pharmacology was assessed by evaluating the potency, and selectivity of abrocitinib in the *in vitro* assays using purified kinase domains from the JAK family of kinases (JAK1, JAK2, JAK3, and TYK2), and in assays against a broad kinome panel.

The rat and cynomolgus monkey were selected for investigation of the safety pharmacology and toxicity studies.

Abrocitinib appears to be rather selective against JAK1 compared to the other JAK family members. However, in a cellular setting, upon stimulation by divergent cytokine stimuli, the response is dependent on JAK signalling pairs, comprising at least two JAK family members. This means that inhibition of JAK1 will affect pathways mediated by other JAK family members as well. Hence, the relevance of selective enzymatic inhibition of specific JAK enzymes to clinical effect is currently not known (see SmPC 5.1).

Pharmacological activity has been proven in a study on adjuvant induced arthritis (AIA) rat, symptomatically by dose dependent reduction of paw swelling and functionally by inhibition of STAT phosphorylation in *ex vivo* samples.

In vitro data on the inhibition by abrocitinib regarding cytokine signalling in whole blood from cynomolgus monkey and rat for comparison to previously provided human data were submitted by the applicant upon request from the CHMP. The cytokines IL-15 (Jak1/Jak3), IL-12 (Jak2/Tyk2) and interferon-α (Jak1/Tyk2) were chosen for stimulation of whole blood. The results showed the following inhibitory pattern using IC50 after stimulation by IL-15: 480/537; IL-12: 2660/9730; interferon-α: 362/183 for cynomolgus monkey and human, respectively. The corresponding figures for IC50 in rat

are for stimulation by IL-15: 87.9; IL-12: 4090; interferon-α: 112. Thus, the activity of abrocitinib on the JAK family members is considered sufficient for the selected safety pharmacology/toxicity species for comparison to human whole blood.

Secondary pharmacology was assessed by evaluating the binding potency of abrocitinib against a broad panel of receptors, transporters, enzymes, and ion channels *in vitro*. Follow-up KDR kinase (VEGFR2), MAO-A, and MAO-B functional assays were conducted.

Abrocitinib inhibits EGF at a concentration of 1 µM by 12.3% and at 10 µM, 33.2%. It is agreed that the inhibition of EGFR by abrocitinib is not large and in addition, the degree of inhibition is not increasing proportionally with increased concentration. The microscopic findings caused by abrocitinib inhibition were associated with a decrease in primary spongiosa without affecting the growth plate, which is unlike the effects by EGF inhibition. Further, the applicant also highlighted that there are differences in the nature of skin lesions in the abrocitinib-treated cynomolgus monkeys (alopecia and thinning hair coat) compared to those observed after EGFR inhibition (dry and flaky skin with haematoma, petechiae, and histologically disorganised hair follicles). Therefore, it is agreed that the provided data does not point out a similar mechanistic effect by abrocitinib as those reported after EGFR or VEGFR inhibition. Thus, it is unlikely that the skeletal and skin findings observed in the juvenile and toxicity studies are caused by VEGFR or EGFR inhibition.

The inhibitory potency of abrocitinib was assessed on MAOA and MAOB. MAOB retained the activity by 98.8% at the highest concentration of abrocitinib, 100 µM. The retained MAOA activity was 67-55% in the 1-4 µM range, corresponding to the clinical exposure around C_{max}, which for unbound is 1.25 µM and for total plasma concentration 3.47 µM, at the clinical dosage of 200 mg. From the subjects that had an ongoing psychiatric condition that required treatment, none were treated with MAO-A inhibitor antidepressants, indicating that the importance of MAOA inhibition by abrocitinib in the clinical trial has not been investigated together with MAOA inhibitors and an additional effect by abrocitinib has thus not been explored. However, the low distribution of abrocitinib to brain (approximately 10%), the margin of 6.1x the unbound human C_{max} at the maximum clinical dose of 200 mg together with the fact that the MAOA inhibition is reversible, supports the applicant's position that the likelihood for serotonergic syndrome is unlikely to occur. Thus; CHMP considered that it was not necessary to address the MAOA inhibitory effect in the SmPC.

Overall, the pulmonary parameters were assessed in rat without any observed adverse effects during a four-hour post dosing period. In the FOB studies in rat, a decrease in body temperature (at ≥200 mg/kg) and locomotor activity (≥LOEL, 75 mg/kg) was observed, revealing a margin of approximately x10 to the human dosage of 200 mg/day to LOEL. The *in vitro* studies of hERG and Nav 1.5 inhibition by abrocitinib does not suggest any potential effects in clinically relevant concentrations. The safety pharmacology studies do thus not indicate any concern from a non-clinical point of view.

No non-clinical pharmacodynamic drug interaction studies were performed with abrocitinib. This is considered acceptable by CHMP.

Pharmacokinetics

Studies have been performed to characterize the absorption, distribution, metabolism, and excretion (ADME) of abrocitinib, using the intended clinical route of administration (oral), and the species selected for non-clinical safety testing, i.e. rats and monkeys as the main non-clinical species but also mice and rabbits.

Overall, the non-clinical pharmacokinetics of abrocitinib is considered adequately studied, including the chosen strategy and methods for qualification of major metabolites.

Toxicology

The non-clinical toxicity of abrocitinib has been evaluated in a full programme of toxicity studies. Expected effects on the immune- and lymphopoietic systems were noted which suggest that increased sensitivity to infection and likely tumour development will likely result from abrocitinib exposure in the clinical setting. Monkey was used as non-rodent species in the general toxicology programme. Nevertheless, the monkey should be, in principle, reserved for situations where no other species is considered relevant or useful. Thus, the applicant was requested by CHMP to justify this species choice. Further, the bone effects noted in the rat and the effects on neutrophils noted in rat (and human) are examples where no concordance was noted in the monkey studies. Indeed, the pharmacological relevance of the monkey was therefore questionable, as no cross-reactivity studies with abrocitinib had been presented. As part of its responses, the applicant acknowledged that the use of monkey is generally not desired but provided justification for the use of this specie in the development programme for abrocitinib. Monkey had previously been used in the development of tofacitinib, another JAKi owned by the applicant, and there was limited experience with other non-rodent non-clinical species for JAK pharmacology at the time of initiation of the development programme for abrocitinib. Overall, given the historical context and the possibility to build on previous experience and data from other JAK inhibitors, the use of monkey in the development programme was considered sufficiently justified by CHMP. Regarding cross-reactivity data, the activity of abrocitinib on the JAK family members in the selected safety pharmacology/toxicity species was presented by the applicant. The inhibitory activity and selectivity of abrocitinib on JAK-mediated cytokine signalling were evident in the rat and cynomolgus monkey, non-clinical species used in safety pharmacology and toxicity studies. This is accepted.

In the studies in cynomolgus monkey, lymphocyte reductions correlated with reduced thymus weights and reduced lymphoid cellularity in thymus and spleen. In the 1-month study, these immunosuppressive effects resulted in cytomegalus infection in all males administered 150mg/kg/day. No findings of cytomegalovirus were noted in females. While exposure was slightly higher in males in the 150mg/kg/day dose group which may signal a more severe immunosuppression, this does not explain the difference between the sexes at the individual level as the toxicokinetic data was very variable. Upon request from the CHMP, the applicant considered that the degree of immunomodulation induced by abrocitinib was likely dose-related, which may explain why only monkeys in the 150 mg/kg/day group had an overimmunosuppression. That said, other abrocitinib independent factors are also likely involved in CMV occurrence or reactivation. As a consequence, there is individual variability in susceptibility and reactivation of a prior CMS infection which is reflected in the 1-month study in monkey. The occurrence of CMV in only males in the study is however less clear, as sex is not a known factor involved in CMV reactivation in monkey. Immunocompetence in general is established as a sexually dimorphic trait in humans, thus a similar pattern in monkey is conceivable. Further, as it is assumed that any obvious differences in environmental factors would have been identified, the explanation as outlined by the applicant of the finding to be coincidental is accepted given that the group size in monkey studies is limited. Immunophenotyping was performed in the monkey studies.

In the 9-month study, clear effects were noted on IgA (HD), IgG and IgM in serum. However, only individual values have been provided for these measures (which seem to be low). Upon request from the CHMP, the applicant provided mean values for IgA, IgG and IgM to support the evaluation of these variables. Based on the mean data provided, the overarching conclusion remains from the initial assessment that abrocitinib-related effects are noted on IgM and IgA, whereas no meaningful effects are noted on IgG levels as a consequence of abrocitinib exposure.

A KLH study was performed in monkeys from the 9-month study. Abrocitinib exposure gave reduced IgG and IgM values (with dose relation) from 15mg/kg/day with partial recovery. While no signs of infection were noted in the study, the only partial recovery of the immune system after 2 months recovery is of concern.

Overall, the effects on the lymphopoietic system and immune parameters reflect pharmacological effects of the JAK1-inhibition of abrocitinib. This has been adequately reflected in SmPC section 5.3. However, while monitorable in the clinic, they ultimately lead to an increased susceptibility to infection and is a clear risk-factor for tumour development. Further, no complete recovery of these effect was noted in the 9-month study in monkey, and thus should receive further attention in the clinical setting. See further discussion in clinical safety and risk management plan sections.

Effects on bone development were evident in the repeated-dose toxicity studies in rats, and in the DART studies. These data support that the developing bones and skeleton are susceptible to abrocitinib-induced toxicities which currently limits the use of the product in developing children and adolescents. While the lack of effects on bone development in 2-4-year-old cynomolgus monkeys may be reassuring, the pharmacological relevance of the species for the human situation is currently unclear, thus the risks for the developing children and adolescents need to be further addressed. Therefore, the applicant was asked to discuss the abrocitinib-induced effects on bone development evident in the general toxicology studies in rat (but not in monkey) as well as in the DART programme with particular focus on developmental sensitivity, penetrance and toxicokinetics. Further, the risks associated with adolescent abrocitinib exposure was to be addressed as well. The applicant provided output from preliminary data, literature references and biological reasoning to explain the abrocitinib-induced effects on bone development evidenced in the non-clinical programme most notably fractures and changes associated with bone damage in juvenile rats exposed from postnatal day 10 to $\geq$ 0.8 times the AUC at the MRHD. While some of the data fit the applicant's explanation of an abrocitinib-induced developmental delay in combination with ambulation on underdeveloped bones, the dramatic bone effects after just a few days of administration could point to a potential direct effect of abrocitinib on developing bones. The lack of similar effects in cynomolgus monkeys, representative of children aged 8 years and above may be reassuring and aligned with the applicant's explanation that the most critical parts in bone development in primates (including humans) occurs earlier (prenatally) than in rodents. Nevertheless, given that postnatal development of long bones continues up into adolescence in both monkey and humans, an uncertainty regarding a possible effect on cartilage mineralisation in actively growing bones by abrocitinib remains, and thus should receive further clinical attention, in particular for a future broadening of indication to younger children. This is further discussed in the clinical safety section.

Dystocia and reduced viability in early postnatal life was noted in pups to mothers who had been exposed to abrocitinib throughout pregnancy. In combination with embryo-lethality and skeletal effects in the FEED and/or EFD studies with low exposure margins to clinical exposure this suggest that the product should not be used during pregnancy and lactation. Further, while the pregnancies disclosed in the clinical section are limited in number, they are not indicating a safe use of abrocitinib use during pregnancy. Other JAK-inhibitors in the class are contraindicated for use in pregnancy, and collectively the data presented support that the same labelling should be used also for abrocitinib. This was agreed by the applicant. Abrocitinib is therefore contraindicated in pregnancy and breast feeding as reflected in SmPC sections 4.3 and 4.6. Further, adequate risk minimisation measures and pharmacovigilance activities are included in the RMP to address the risk of foetal malformation following exposure in utero (see RMP Section).

Overall, the genotoxicity studies presented do not indicate a genotoxic risk for abrocitinib at the proposed clinical dose of 200mg QD. This information has been appropriately reflected in SmPC section 5.3.

Thymomas in the 104-week carcinogenicity study in rats were evident already at the lowest dose, with low margins of exposure to human exposure. The applicant was asked to further discuss the findings and the clinical relevance. In the response, the applicant argued that background incidence from literature suggest that incidence in Wistar rat may be as high as 18%, thus the thymoma findings in

the 3mg/kg group is not considered treatment related. This was not agreed by CHMP who was of the view that that the thymomas were treatment related. Further, only one case of malignant thymoma was noted in the study (in the 10mg/kg dose group) which does not suggest a treatment-related increase. However, it is unclear to what extent there can be progression from a benign thymoma to a malignant thymoma and the tumour biology underlying such a shift. While the applicant did not discuss this issue, it was agreed by CHMP that the single occurrence of malignant lymphoma may reflect a low progression.

Further, the increase in thymoma incidence was noted in female rats and from exposures around clinical exposure whereas no apparent increase was apparent in male rats up to 14x unbound human AUC. The reason for this sex difference is unclear, but the applicant referenced studies suggesting that thymuses of female Wistar Han rats exhibit a more delayed physiologic thymic involution than males or other rat strains and that a higher frequency of spontaneous thymoma formation in Wistar rats is related to higher numbers of thymocytes at baseline and higher proliferation rates of TECs. This then may lead to a higher sensitivity for thymoma formation in the female Wistar rat following administration of an immunosuppressive drug such as abrocitinib. Overall this explanation regarding increase female sensitivity is acceptable. Thus, it was agreed that abrocitinib treatment seems to accelerate the thymoma formation in the rat.

The human risk for abrocitinib-induced thymoma is currently unclear. Other immunosuppressive treatments have induced thymomas in cancer studies but there is according to the applicant currently no clinical evidence suggesting an increased risk for human thymoma development. Nevertheless, given the unclear human relevance of the thymoma findings, the applicant included data in section 5.3 of the SmPC.

ERA

Finally, 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.

2.5.7. Conclusion on the non-clinical aspects

In conclusion, the applicant provided a comprehensive evaluation of pharmacologic, pharmacokinetic and toxicologic properties of abrocitinib. The issues identified in the non-clinical programme have been properly addressed. Studies in animals have shown reproductive and skeletal toxicities. The impact on bone development is further discussed in the clinical sections. Abrocitinib is contraindicated in pregnancy and breast feeding. Women of reproductive potential should be advised to use effective contraception during treatment and for 1 month following the final dose of abrocitinib. Abrocitinib is therefore considered approvable from a non-clinical point.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The applicant 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 2 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
Phase 3 Short-term Combination Therapy Studies				
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 randomised, placebo-controlled phase	N = 837 (randomised 2:2:2:1) 200 mg: 226 100 mg: 238 Dupilumab: 242 Placebo: 131
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 = 287 (randomised 1:1:1) 100 mg: 95 200 mg: 96 Placebo: 96 Immunogenicity sub-study N = 25 100 mg: 9 200 mg: 6 Placebo: 10
Phase 3 Dosing Regimen Study				
B7451014	Phase 3 randomised withdrawal and retreatment study in adults and adolescents	Placebo control in randomised withdrawal period	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 with topical therapy Treatment duration was up to 64 weeks	Open label N treated = 1233 N = 798 (randomised 1:1:1) 100 mg: 265 200 mg: 266 Placebo: 267
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 randomised to double blind treatment, either abrocitinib 200 mg or 100 mg QD when enrolled into B7451015.	N = ~3000

Table 2 Phase 2 and 3 abrocitinib clinical studies in atopic dermatitis

Study	Description	Control	Treatment/Duration	Number of Subjects
Phase 2 Study				
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 Study				
B7451037	Phase 2a randomised, double-blind, placebo-controlled, multicentre 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

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Data from 15 clinical pharmacology studies in healthy subjects and 5 studies in subjects with atopic dermatitis (AD) provide an understanding of the key biopharmaceutic, pharmacokinetic (PK) and pharmacodynamic characteristics of abrocitinib and its main metabolites M1, M2 and M4, see Table 3 for an overview of the clinical pharmacology programme.

Table 3 Abrocitinib Clinical Pharmacology Studies

Study Number	Brief Description
B7451001	First-in-human single- and multiple-ascending dose
B7451004	Relative bioavailability and pilot food effect study
B7451008	ADME and absolute bioavailability
B7451016	Drug-drug interaction: abrocitinib effect on oral contraceptives pharmacokinetics
B7451017	Drug-drug interaction: fluconazole and fluvoxamine effect on abrocitinib and metabolite pharmacokinetics
B7451019	Drug-drug interaction: rifampin effect on abrocitinib and metabolite pharmacokinetics
B7451020	Hepatic impairment
B7451021	Renal impairment
B7451022	Drug-drug interaction: abrocitinib effect on midazolam pharmacokinetics
B7451026	Drug-drug interaction: abrocitinib effect on dabigatran pharmacokinetics
B7451027	Thorough QT
B7451032	Bioequivalence and food effect with commercial formulation
B7451033	Drug-drug interaction: abrocitinib effect on rosuvastatin pharmacokinetics
B7451034	Drug-drug interaction: abrocitinib effect on metformin pharmacokinetics
B7451043	Drug-drug interaction: probenecid effect on abrocitinib and metabolite pharmacokinetics

A full in vitro package characterising in vitro metabolism, transporters, protein binding as well as potential to inhibit or induce enzymes or transporters is also provided.

Methods

- ***Bioanalysis***

Plasma and urine concentrations of abrocitinib and plasma concentrations of its metabolites M1, M2 and M4 were determined with validated LC-MS/MS methods.

- ***Non-compartment data analysis***

Standard non-compartment analysis was performed in all studies where rich sampling was applied.

- ***Evaluation*** **and Qualification of Models**

Objectives of the population PK analysis

popPK analysis at time of initial submission:

1. Describe the PK of abrocitinib (PF-04965842) in healthy subjects, moderate to severe psoriasis (PsO) patients and moderate to severe AD patients.
2. Identify potential covariates in the study population(s) which account for variability in abrocitinib exposure.
3. Assess the relative bioavailability of abrocitinib doses and formulations administered during clinical development.
4. Provide individual-level estimates of PK parameters for subsequent exposure-response analyses

popPk analysis (updated) upon request from CHMP

1. Update the previous population PK model developed for abrocitinib (PMAR-EQDD-B745d-DP4-962) with PK samples from five additional studies
2. Develop a combined population PK model for abrocitinib and three of its metabolites (M1, M2, and M4)

Dataset (popPK analysis at time of initial submission):

All studies during the clinical development programme that sampled abrocitinib (PF-04965842) concentrations, which were available prior to conclusion of the population PK modelling analysis, were included. Therefore, studies B7451014, B7451021 and B7451032 were not included. Additionally, B7451008 (human absorption, metabolism and excretion (ADME) study using14C micro-tracer) was not included due its complex study design.

Included Studie(s):	Study Initiation and Completion Date(s):	Study Phase(s):
B7451001	13 MAY 2013 - 09 JUN 2014	Phase 1
B7451004	17 JUN 2014 - 05 AUG 2014	Phase 1
B7451005	25 NOV 2014 - 10 SEP 2015	Phase 2
B7451006	15 APR 2016 - 04 APR 2017	Phase 2b
B7451012	07 DEC 2017 - 26 MAR 2019	Phase 3
B7451013	29 JUN 2018 - 13 AUG 2019	Phase 3
B7451017	12 SEP 2018 - 13 DEC 2018	Phase 1
B7451019	13 SEP 2018 - 14 DEC 2018	Phase 1
B7451020	01 OCT 2018 - 30 APR 2019	Phase 1
B7451027	02 JUL 2018 - 01 OCT 2018	Phase 1
B7451043	21 MAY 2019 - 26 JUL 2019	Phase 1

Table 4 Summary of Observed Concentrations in Analysis Population by Dose

Summary	3 mg	10 mg	30 mg	100 mg	200 mg	400 mg	600 mg	800 mg	Total
Observations									
n	72	433	541	2275	3204	756	324	190	7795
%	0.9	5.6	6.9	29.2	41.1	9.7	4.2	2.4	100.0
Treatment Periods									
n	6	51	57	401	482	66	36	16	1115
%	0.5	4.6	5.1	36.0	43.2	5.9	3.2	1.4	100.0
ALQ									
n	32	188	267	1847	2811	610	284	167	6206
% in Dose Group	44.4	43.4	49.4	81.2	87.7	80.7	87.7	87.9	79.6
BLQ									
n	40	245	274	428	393	146	40	23	1589
% in Dose Group	55.6	56.6	50.6	18.8	12.3	19.3	12.3	12.1	20.4

Repository artifact ID RA16875248.

Data handling

Individuals that did not receive at least one dose of abrocitinib or did not have at least one measurable concentration (with correct dosing and time information) were excluded from this analysis. Missing values for covariates assumed the population median or mode value (for continuous or categorical variables, respectively) during covariate analysis.

Software

Model development used NONMEMR Version VII Level 4.3 (ICON Dev. Soln, Ellicott City,MD, USA).

Method model development

The structural model development was based on selecting models with regards to Akaike information criterion (AIC).

Structural covariates known to be highly influential a priori were built into the structural model:

Weight via allometric scaling on PK parameters. Known DDI effects on CL/F and bioavailability (F) on abrocitinib (rifampin, fluconazole, fluvoxamine, and probenecid). Dose, formulation and food effects on absorption parameters (F, ka, k0, duration of zero-order absorption process (Tk0), Ak1, ALAG1, ALAG2) were also included.

Stepwise covariate modelling approach:

1. Full model determined at the end of forward inclusion procedures to generate forest plots that summarize the impact of covariates on abrocitinib exposure metrics.
2. Final model determined by backwards elimination from the full model, to be used for the purpose of simulations.

Table 5 Covariate Relationships for Assessment

Population Parameter	Covariates
CL	Sex, age (continuous or adolescent vs. adult), race, patient type (HV, AD, PsO), hepatic impairment (normal, mild, moderate), concomitant medications
V_c	Sex, age (continuous or adolescent vs. adult), race, patient type (HV, AD, PsO)
Absorption[a]	Food (fasted or fed), formulation (oral suspension, tablets), dose
F	Food (fasted, high-fat meal, food not controlled), formulation (oral suspension, tablets), concomitant medications, dose

[a]Including k_a, k_0, Tk_0, Ak_1, and absorption lag parameters.

Final popPK model (at time of initial submission)

Following forward inclusion and backward elimination procedures, the full model was deemed to be the final model. Parameter estimates and bootstrap results for the final model are presented in Table 9. 85.4% of bootstraps minimised successfully. A pcVPC of the final model is presented in Figure 2 and a standard VPC stratified by dose is presented in Figure 3. The final model's predictions overlay the observed data with good agreement and adequately reproduces the proportion of observations BLQ.

Table 6 Parameter Estimates for Final Model

Parameter	Value	95% CI	Bootstrap Median	Bootstrap 95% CI	SHR (%)
Objective Function Value	65016.7				
Condition Number	10				
Population Parameter					
Clearance (CL; L/hr)	22	20.2, 23.8	21.7	17.9, 27.1	
Volume of the central compartment (V_c; L)	87.8	81.1, 94.5	86.3	73.7, 102	
Inter-compartmental clearance (Q; L/hr)	1.16	0.994, 1.33	1.13	0.718, 1.67	
Volume of the peripheral compartment (V_p; L)	8.25	7.6, 8.9	8.11	5.41, 11.5	
Zero-order absorption rate (k_0; mg/hr)	75.3	71.2, 79.4	73.1	55.1, 93.9	
Amount absorbed by first-order processes (Ak_1; mg)	121	109, 133	122	102, 146	
First-order absorption rate constant (k_a; hr^{-1})	4.01	3.48, 4.54	3.99	3.02, 5.41	
Proportional residual error (*RUVPRO*; SD)	0.437	0.429, 0.445	0.431	0.406, 0.46	
Additive residual error (*RUVADD*; SD)	0.509	0.48, 0.538	0.506	0.416, 0.599	
Effect of moderate variability studies on *RUVPRO*	0.495	0.434, 0.556	0.514	0.382, 0.636	
Effect of high variability studies on *RUVPRO*	1.16	1.05, 1.27	1.19	0.921, 1.54	
Effect of tablet formulations on *ALAG1*	0.183	0.167, 0.199	0.184	0.141, 0.212	
Effect of rifampin on CL	0.264	0.169, 0.359	0.24	-0.0167, 1.19	
Effect of rifampin on F	-2.08	-1.96, -2.2	-2.12	-2.48, -1.6	
Effect of fluconazole on CL	-0.541	-0.513, -0.569	-0.533	-0.61, -0.403	
Effect of fluvoxamine on CL	-0.234	-0.194, -0.274	-0.227	-0.336, -0.0594	
Effect of fluconazole or fluvoxamine on F	1.31	1.01, 1.61	1.3	0.795, 2.13	
Effect of high-fat meal on Ak_1	-1	Fixed	-1	Fixed	
Effect of Phase 2 10 and 50 mg tablets on F	-1.02	-0.744, -1.3	-1.07	-1.49, -0.627	
Effect of Phase 3 100 mg tablet on F	-0.766	-0.653, -0.879	-0.811	-1.12, -0.446	
Effect of suspension on Ak_1	1.17	0.858, 1.48	1.23	0.773, 2.34	
Effect of Phase 2 10 and 50 mg tablets on Ak_1	-0.68	-0.584, -0.776	-0.685	-0.787, -0.233	

Parameter	Value	95% CI	Bootstrap Median	Bootstrap 95% CI	SHR (%)
Effect of multiple-dosing on F	0.241	0.131, 0.351	0.253	-0.0216, 0.698	
Maximum change in CL with respect to time (TAFO; %)	-0.186	-0.167, -0.205	-0.192	-0.485, -0.106	
Rate of change in CL with respect to time (half-life; hr)	21.6	14.5, 28.7	23.1	8.31, 1189	
Effect of effective daily dose on CL	-0.169	-0.136, -0.202	-0.166	-0.227, -0.108	
Effect of Asian/Other subjects on F	0.815	0.692, 0.938	0.737	0.337, 1.92	
Combined effect of PsO and AD patients on F	0.489	0.256, 0.722	0.512	0.0678, 0.852	
Combined effect of mild and moderate hepatic impairment on F	1.3	0.783, 1.82	1.36	0.489, 2.3	
Effect of weight on CL and Q (referenced to 70 kg)	0.453	0.278, 0.628	0.472	0.238, 0.702	
Effect of weight on V_c and V_p (referenced to 70 kg)	0.52	0.379, 0.661	0.524	0.341, 0.705	
Effect of adolescent subjects on F	-0.589	-0.306, -0.872	-0.591	-0.916, -0.307	
Effect of 800 mg dose on F	-0.778	-0.666, -0.89	-0.776	-1.39, -0.508	
Effect of female subjects on F	0.353	0.24, 0.466	0.348	0.103, 0.666	
Inter-Individual Variability					
ω_{CL} (% CV)	57.7	51.8, 63.6	58	54, 63.2	9.71
ω_{V_c} (% CV)	41.4	34.8, 48	41.5	37.4, 46.3	27.3
Correlation					
ρ_{CL-V_c}	0.326	0.22, 0.432	0.337	0.211, 0.454	
Random Unexplained Variability					
ε_{res}	1	Fixed	1	Fixed	13.8

Repository artifact ID FI-1891215. Line 1 substituted.
Abbreviation(s): Shrinkage (SHR).
Condition number = square root of the ratio of largest to smallest eigenvalues of correlation matrix, CV = $\sqrt{\omega^2} \cdot 100$, asymptotic 95% CI are presented.

Figure 2 Prediction-Corrected Visual Predictive Check

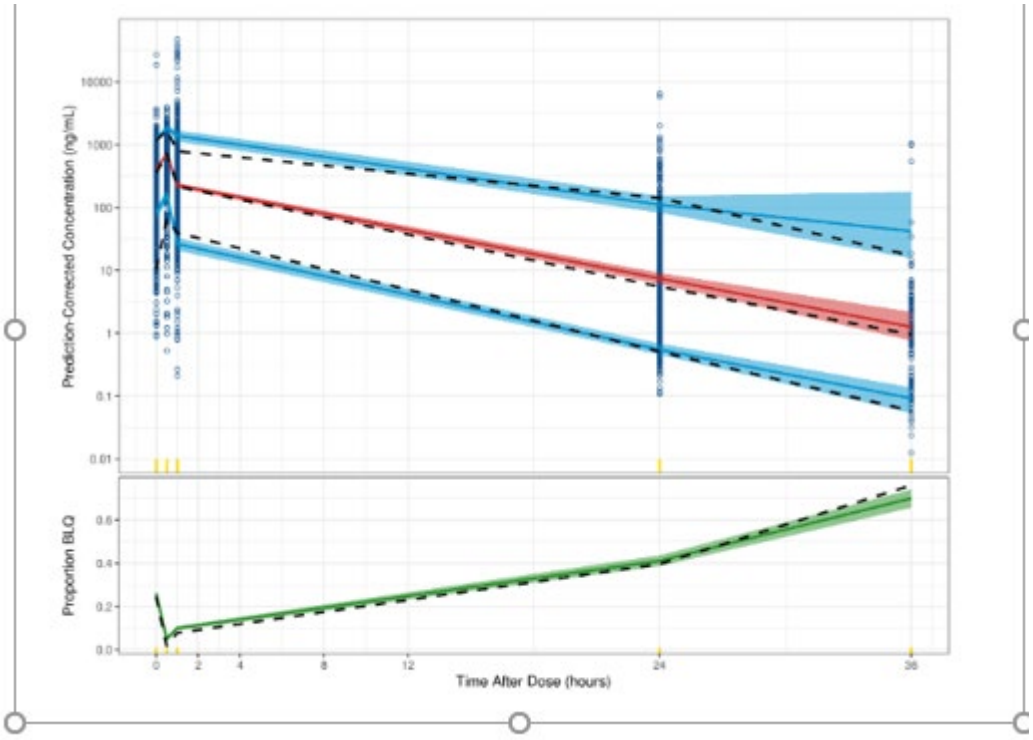
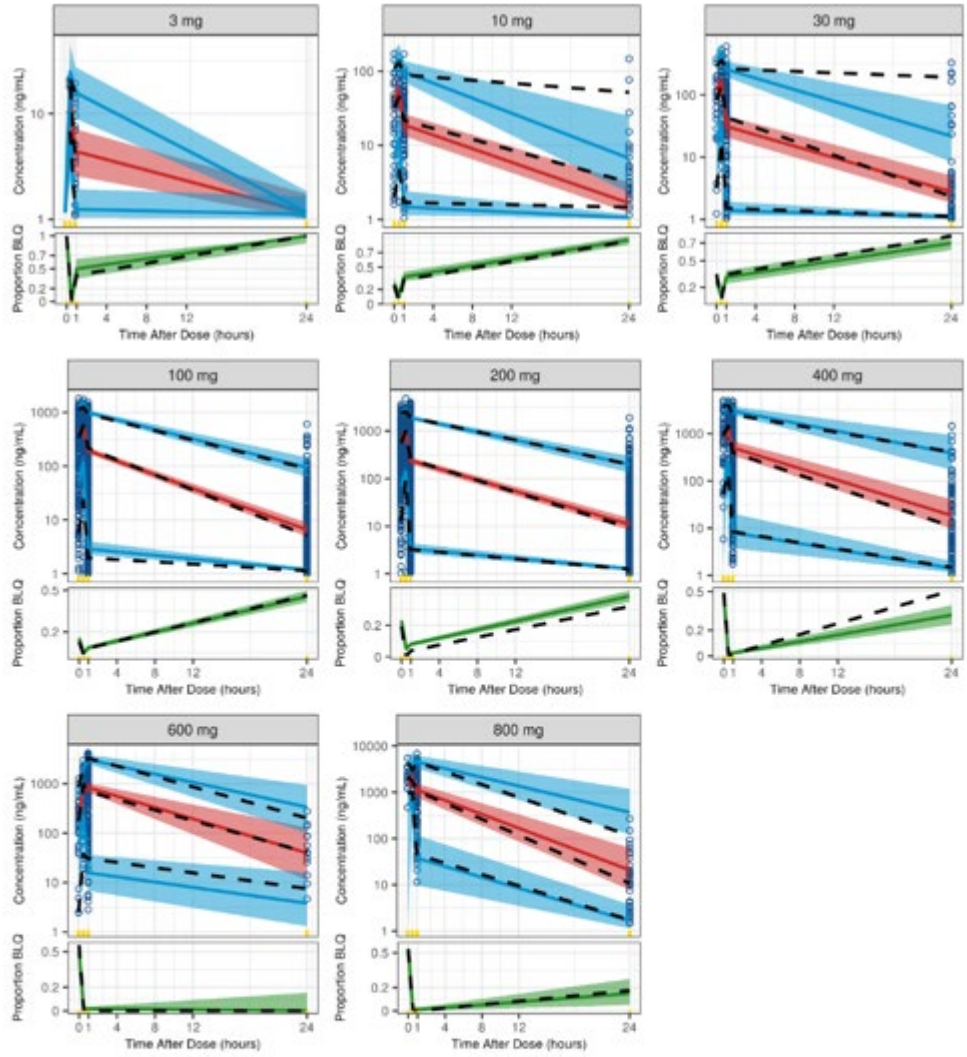


Figure 3 Visual Predictive Check Stratified by Dose



Repository artifact ID FI-1880214.

Top: The observed data are represented by blue circles and the dashed black lines (median, 5th and 95th percentiles). The simulated PF-04965842 concentrations based on the index population (n = 1000 simulations) are represented by the red line and red shaded ribbon (median and 95% PI of the median, respectively) and the blue lines and blue shaded ribbons (median and 95% prediction intervals of the 5th and 95th percentiles, respectively. *Bottom:* The black solid line represents the proportion of observed BLQ concentrations over time, and the green solid line and green shaded ribbons are the median and 90% predictions intervals, respectively, of simulated BLQ concentrations (n = 1000) based on the index population. Yellow indicators in the x-axis represent the time bins for summarizing the data (0, 0.5, 1, and 24 hours).

Updated Final popPK model

The population PK model was developed using non-linear mixed effects methods and NONMEMR 7.5.0.

A sequential approach was used where the parent abrocitinib model was updated followed by the development of the metabolite model.

Updated parent popPK model

The prior abrocitinib model was updated using a new analysis dataset that included the following studies: B7451014 (Phase 3 study in AD patients), B7451021 (renal impairment study), B7451028 (China PK Study), and B7451032 (pivotal bioequivalence (BE) and food effect study), and Study

B7451036 (Phase 3 study in adolescent AD patients). The abrocitinib dataset included 262 healthy volunteers and 2034 patients.

The final model for abrocitinib was re-estimated with an adjustment to the formulation and race parameters, using all available abrocitinib PK samples. Studies B7451032 and B7451036 used a new formulation not studied in the previous model. The race parameter was adjusted to estimate an effect for Asian race and Other race separately rather than a combined effect.

There was no additional covariate development to the abrocitinib model other than the changes to the formulation and race parameters as previously described. No additional model building with respect to covariate effects was conducted. Final model parameter estimates are shown in the table below. VPCs for adults and adolescents are shown in the figures below.

Table 7 Parameter estimates for final updated Model of the parent molecule

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

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

Repository artifact ID FI-16844382. Line 1 substituted.

Condition number = square root of the ratio of largest to smallest eigenvalues of correlation matrix, coefficient of variation (CV) = $\sqrt{\omega^2} \cdot 100$, asymptotic 95% CI are presented.

Figure 4 VPCs for adults and adolescents - parent drug - updated final model

Figure A5.8. VPC for Adults and Adolescents receiving 100 MG QD

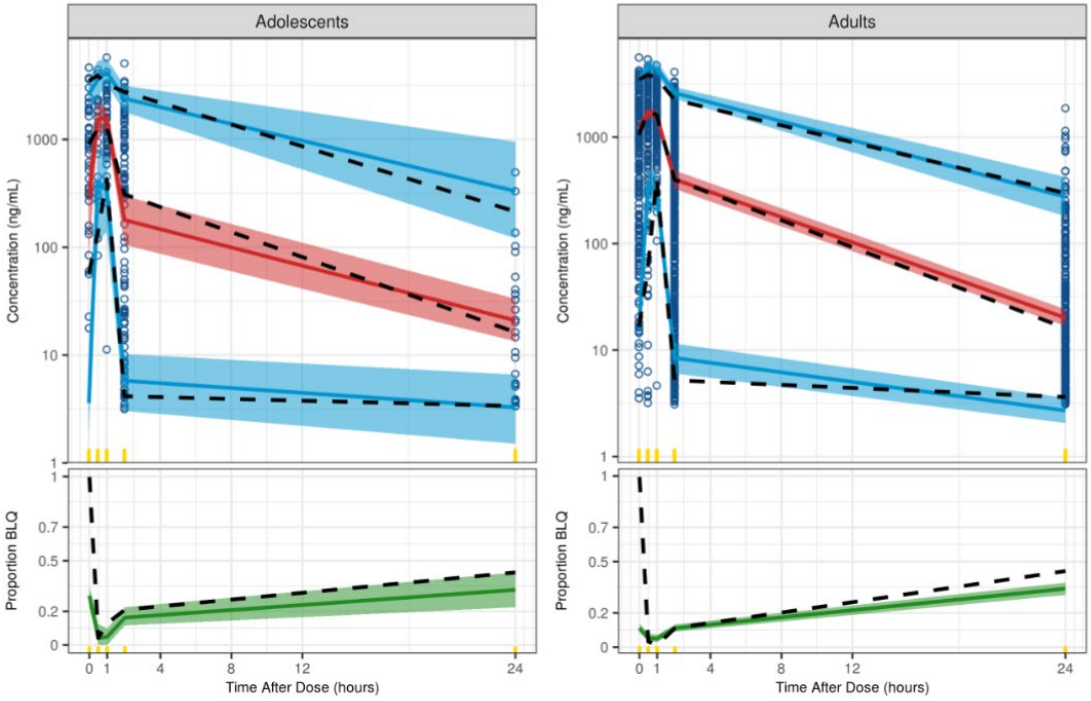
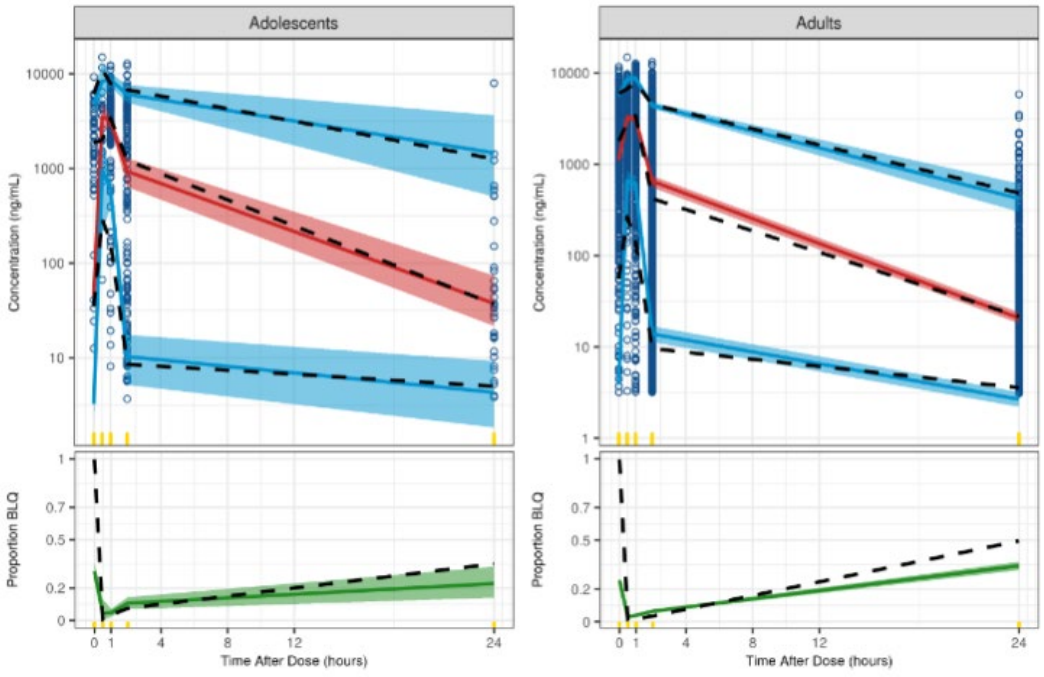


Figure A5.9. VPC for Adults and Adolescents receiving 200 MG QD



Repository artifact ID FI-17670180.

The estimates are from 1000 simulation from the model. The upper bands represent the 95th percentile and the lower bands represent the simulated 5th percentile. The dashed lines represent the 5th, 50th, and 95th percentiles of the observed data.

Metabolite model

Post hoc estimates for each individual from the parent model were used for the metabolite model. During parent/metabolite model development, all analytes were converted to molar. A stepwise covariate modelling approach was used in this analysis to develop the metabolite model. The applicant stated assumptions and limitations regarding the metabolite model:

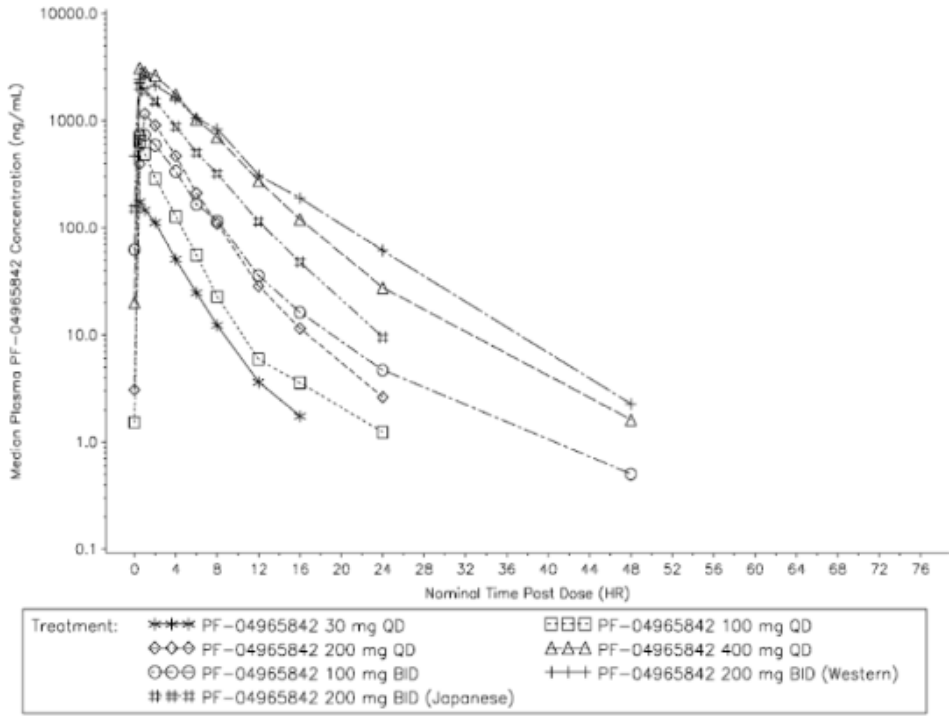
The patient metabolite information was available from only 51 AD patients and consisted of a single sample collected roughly 2 hours post dose. Of these 51 patients, only 7 were adolescents. Consequently, it was assumed that there were no differences in the metabolite PK beyond the differences incorporated in the abrocitinib model for both patient and adolescents. Additionally, the final model included 38 fixed effect parameters and 10 random effect parameters with a moderately high condition number. A scaling effect was added to the parameterisation of the abrocitinib clearance resulted in an overestimation of the abrocitinib AUC if simulated directly from the metabolite model.

Absorption

The absolute bioavailability of abrocitinib following a single 200 mg oral dose was 60% (90% CI of [46%, 78%]) and the fraction absorbed is high, 91%.

Single and multiple doses of 3mg up to 800mg have been studied. The absorption of abrocitinib is rapid with maximum plasma concentrations occurring generally between 0.5 and 1.5 hours after single and repeated doses, see Figure 5.

Figure 5 Median plasma PF-04965842 concentration-time profiles following multiple doses in healthy western and Japanese subject from study B7451001.



Abrocitinib is a substrate for both P-gp and BCRP *in vitro*. The fraction absorbed in human is close to 90% and inhibition of these transporters is unlikely to meaningfully increase the abrocitinib exposures at therapeutic doses.

The *in vitro* solubility of abrocitinib is pH dependent. At pH values >4.0, the compound demonstrates the characteristics of a low-solubility compound and thus dissolves more slowly.

- *Bioequivalence*

The bioequivalence of a single 200 mg dose of the commercial tablet formulation of abrocitinib relative to the phase-3 tablet formulation has been evaluated under fasting conditions using a replicate design. The standard BE criteria were met and the within subject variability was approximately 32%.
A biowaiver for the additional strengths 50 and 100 mg has been proposed.

- *Food interaction*

Abrocitinib AUC and Cmax was increased approximately 26 and 29% and there was a delay in the Tmax (by 2 hours) when a 200 mg dose of the commercial tablet formulation was administered with a high-fat breakfast as compared to administration in the fasted state. In the phase-3 studies abrocitinib was administered irrespective of food and no food restrictions are included in the SmPC.

Distribution

The volume of distribution at steady state (Vss) was 100.2 L (19%) after an IV microtracer dose [^{14}C]abrocitinib. The Vz/F was 235.3 L (31%) (geometric mean [CV%]), after the oral abrocitinib dose co-administered with the 14C-labeled IV tracer dose.

Plasma protein binding of 0.1-10 μM of abrocitinib and its metabolites was determined by equilibrium dialysis. The fu values for abrocitinib, M1, M2, and M4 were 0.36, 0.63, 0.71, and 0.83, respectively.

The mean blood-to-plasma ratio was 1.07, 1.13, 1.27, and 0.87 for abrocitinib, M1, M2, and M4 respectively.

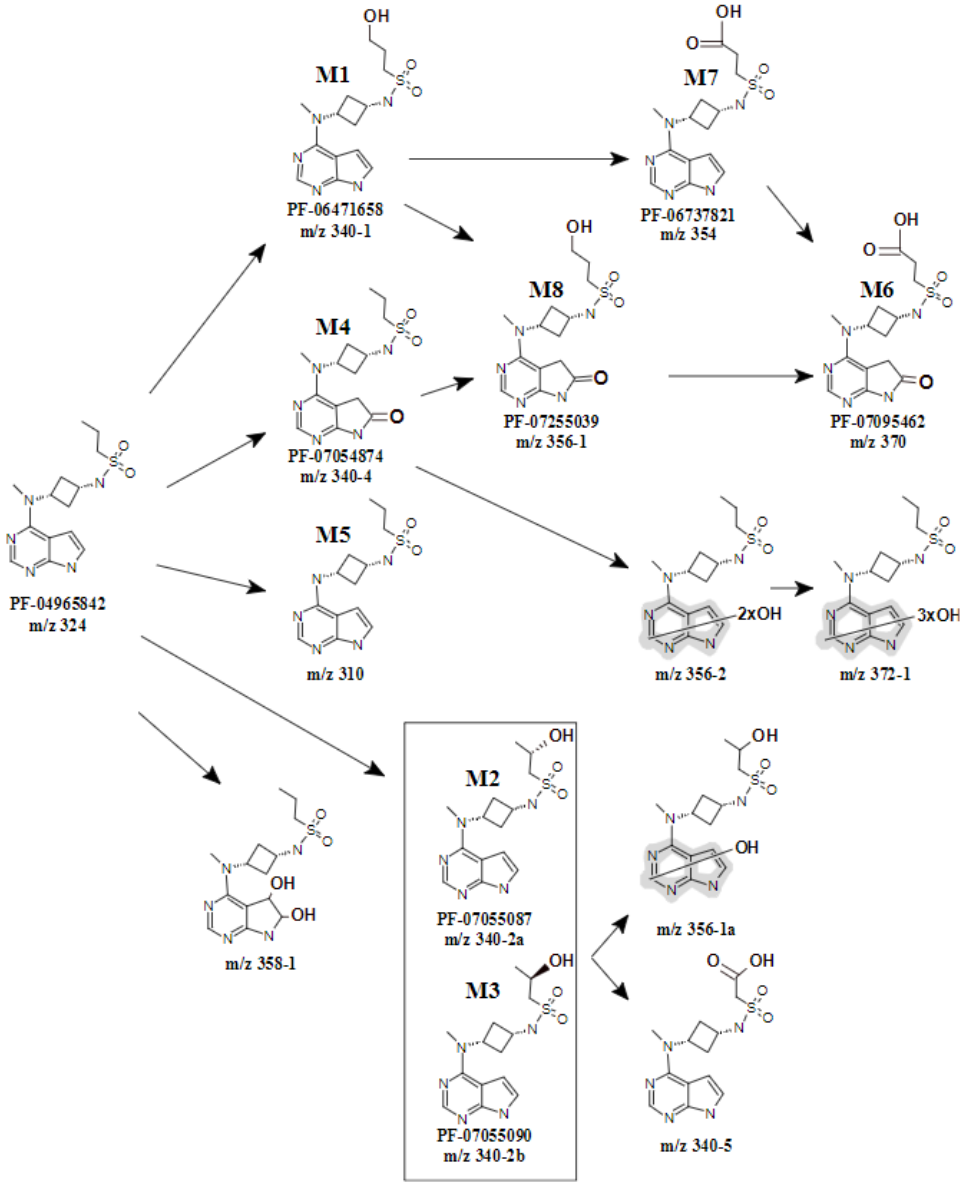
Elimination

The main route of elimination for abrocitinib is metabolism. In the mass balance study (IV tracer dose) total CL for abrocitinib was 1073 ml/min. The apparent clearance (CL/F) after the oral administration was 1794 ml/min. Renal CL of abrocitinib was calculated as 11 ml/min. Approximately 94.5% of the radioactivity was recovered of the total administered radioactive dose, 85% was recovered in urine and 9,5 % in faeces. Less than 1% (0.6%) of the dose was excreted as unchanged abrocitinib in urine and 0.3% in faeces. The terminal elimination half-life was generally estimated between 1,5-6 hours. Under steady state conditions, the elimination half-life was between 3-6 hours.

- *Metabolism*

Abrocitinib is extensively metabolised. *In vitro* results indicate that the metabolism of abrocitinib is mediated by multiple CYP enzymes, CYP2C19 (~53%), CYP2C9 (~30%), CYP3A4 (~11%) and CYP2B6 (~6%). Abrocitinib was the predominant component (approximately 26% of plasma radioactivity) in systemic circulation after oral administration. Single oxidative metabolites M1 (11.3%), M2 (12.4%) and M4 (13.8%) were also observed as major components of circulating profiled radioactivity. Several other minor metabolites were also identified. In urine the most abundant component was metabolites M1, M2, M3, M4 and M6. Of the 3 metabolites in circulation, M1 and M2 have similar JAK inhibitory profiles as abrocitinib, while M4 was pharmacologically inactive. M1 was estimated to contribute 11% and M2 47% to the *in vivo* activity. The sum of unbound exposures of abrocitinib, M1 and M2, each expressed in molar units and adjusted for relative potencies, is referred to as the abrocitinib active moiety.

Figure 6 Proposed biotransformation pathway of abrocitinib.

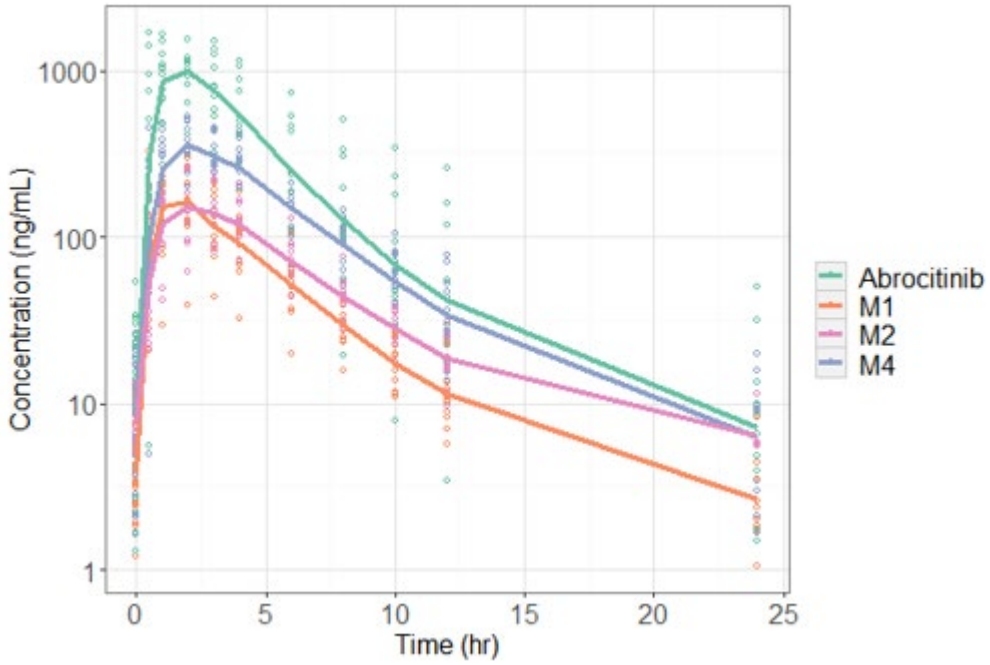


Abrocitinib, while chiral, contains two identical substituted stereo-centres and is therefore a meso compound. There is no indication that inter-conversion of abrocitinib occurs in vivo.

- *Pharmacokinetics of metabolites*

The plasma concentration-time profile of abrocitinib and metabolites at steady state can be seen in figure 7. The elimination phases of the metabolites are in parallel with that for the parent drug at steady state suggesting formation-rate limited PK of these 3 metabolites. In this study (1043) the half-life of abrocitinib after multiple doses was 6.0 h and of M1, M2 and M4 6.2 h, 4.6 h and 5.8 h respectively. Tmax was 1.5 hours for abrocitinib and M1 and 2 hours for M2 and M4.

Figure 7 The plasma concentration-time profile of abrocitinib and metabolites at steady state (B7471043).



The metabolites are predominantly renally excreted and substrates of the renal transporter protein OAT3. Multiple CYP-enzymes have been indicated in the metabolism pathways of the metabolites.

- *Consequence of pharmacogenetic polymorphisms*

Genotyping was performed for CYP2C19 (*1, *2, *3, *4 and *17) and CYP2C9 (*1, *2 and*3) in several of the phase-1 studies to evaluate the effect of poor and extensive metabolizers of either gene. A linear mixed effects model was used to evaluate the phenotypes effect on abrocitinib AUC and Cmax. Using an overall phenotype (a combination of both CYP2C19 and 2C9 phenotype) no relevant differences in abrocitinib exposure are found between different phenotypes (for AUC a 19.5% decrease for elevated phenotype and a 25.6% increase for reduced phenotype). No genotyping was performed in the phase-3 studies.

Dose proportionality and time dependency

Several different methods have been used to evaluate dose dependency of abrocitinib, all indicating a more than proportional increase in AUC with dose over the whole dose range (3-800 mg) but with some differences regarding the range showing dose proportionality. However, dose proportionality is expected within the clinically relevant dose range up to 400 mg once daily. Linear dose proportionality was observed for the active moiety for 100 mg QD and 200 mg single dose.

Rss values (AUCτ/AUCinf) were approximately 1.3-1.5, suggesting that there may be greater than linear increase in abrocitinib exposure with multiple-dose administration. Based on observed half-life of approximately 5 hours, the accumulation ratio after QD dosing is predicted to be approximately 1.04. Time- and dose-dependent changes in bioavailability and clearance were implemented in the popPK model to describe the observed higher than predicted accumulation in abrocitinib concentrations following repeated dosing and greater than proportional increases in area under the curve (AUC) at higher doses.

Intra- and inter-individual variability

The intra-subject %CV was low (<10%) for the AUCinf and 32% for Cmax at the highest clinical dose of 200 mg. Inter-individual variability for AUC and Cmax appears moderate to high (%CV for both AUC and Cmax varied 30-75%). In the final population PK model, the inter-individual variability was estimated to be 57.7% on CL and 41.4% on Vc.

Pharmacokinetics in target population

The final updated popPK model predicted population-typical value of steady-state Cmax and 24-hour AUC following 200 mg QD dosing, for parent drug. Infectious and inflammatory disease states have been shown to alter activities and expression of drug transporters and drug-metabolizing enzymes, such as CYP.

Table 8 Predicted 200 mg QD Steady-State Exposures for Atopic Dermatitis Patients by Age Group and Race and for Healthy Volunteers (updated final model)

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

Repository artifact ID FI-16804810. Line 1 substituted.

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

Special populations

Renal impairment

A renal impairment (RI) study investigating the effect of moderate (eGFR 30 to< 60 mL/min) and severe (eGFR < 30 mL/min) RI on abrocitinib PK has been performed. RI did affect the abrocitinib exposure. The overall exposure of abrocitinib as measured by geometric mean AUCinf increased by 83% and 21% in participants with moderate and severe RI, respectively, compared to that in participants with normal renal function (eGFR ≥ 90 mL/min). Increases in AUCinf for the moderate and severe RI groups were 54% and 187%, for M1, respectively and 170% and 471%, for M2 and 208% and 442% for M4. The Cmax of the active moiety increased with approximately 30% in both moderate and severe RI compared to subjects with normal renal function. The mean AUCinf,u values in participants with moderate and severe RI increased by 110% and 191%, respectively, compared to that in participants with normal renal function. Through extrapolation using the linear regression function a patient with an eGFR of 60 ml/min (mild renal impairment) is predicted to have an increase in active moiety exposure of about 70%. The use of abrocitinib has not been studied in patients with end-stage renal disease (ESRD) on renal replacement therapy.

Hepatic impairment

Mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment (HI) has been studied. Abrocitinib AUC increased 1.3 and 1.5-fold respectively while Cmax was unchanged. For the metabolites M1 and M2 the reduced exposure was observed while the exposure of M4 is not affected to any relevant extent by hepatic impairment. The metabolite-to-parent exposure ratios for all 3 metabolites decreased in participants with mild and moderate hepatic impairment compared to participants with normal hepatic function. The effect on the active moiety is low. AUCinf increases 4 and 15 % for mild and moderate HI respectively, while Cmax decreases 25 and 15% in the respective group. No dose-adjustments are proposed for mild or moderate HI. Severe (Child Pugh C) HI has not been studied and the use of abrocitinib is contraindicated in this population.

Table 9 Pharmacokinetic results of abrocitinib and its active moiety for intrinsic factors

Comparison	Abrocitinib Ratio, as Percent (90% CI)		Active Moiety Ratio, as Percent (90% CI)		Dosing Recommendation
	C_{max}	AUC_{inf}	C_{max}	AUC_{inf}	
Intrinsic Factors					
Moderate renal impairment vs normal function[a]	138.49 (93.74, 204.61)	182.91 (117.09, 285.71)	133.87 (102.45, 174.92)	210.20 (154.60, 285.80)	Reduce dose by half[c]
Severe renal impairment vs normal function[a]	99.1 (57.30, 171.43)	121.32 (68.32, 215.41)	129.49 (92.86, 180.57)	290.68 (217.39, 388.69)	Reduce dose by half[c]
Mild hepatic impairment vs normal function[a]	94.40 (62.96, 141.55)	133.33 (86.17, 206.28)	75.94 (57.39, 100.47)	95.74 (72.71, 126.08)	No adjustment
Moderate hepatic impairment vs normal function[a]	105.53 (70.38, 158.24)	153.99 (99.52, 238.25)	84.14 (63.59, 111.33)	114.82 (87.19, 151.20)	No adjustment

a. Abrocitinib 200 mg.
b. Abrocitinib 100 mg.
c. Recommended dose of abrocitinib is 50 or 100 mg QD when the indicated dose is 100 or 200 mg QD, respectively.

Elderly

Age is correlated to renal function and elderly are likely to have renal impairment and dose may need to be reduced according to renal function.

Gender

Gender was evaluated as covariate in the population PK modelling. Female participants had a greater F than male participants. However, simulations from the model showed no difference in overall exposure.

Race

Study 1001 evaluated abrocitinib exposure in Japanese subjects. At a single 800 mg dose, the geometric mean Cmax was similar in Western and Japanese subjects. However, geometric mean AUCinf was 26% higher in Western subjects than that observed in Japanese subjects. Geometric mean Cmax and AUCtau following multiple-dose administration of 200mg BID were 17% and 56% higher, respectively, in the Western subjects than in Japanese subjects. The popPK analysis also indicate a 50 % higher AUC in Asians/other compared to White, adult males of 70 kg.

Adolescents

No data is available for children below 12 years. Based on the updated popPK analysis the exposure is similar between adolescents and adults.

Special populations conclusions

It is agreed that body weight, gender, race and age did not have a clinically meaningful effect on abrocitinib exposure, and this is reflected in the SmPC.

Pharmacokinetic interaction studies

In vitro

Abrocitinib is metabolised by multiple CYP-enzymes, mainly 2C19 and 2C9 and to a lesser extent 3A4 and 2B6 and multiple CYPs have been indicated in the metabolism of each metabolite as well. Abrocitinib is a substrate for p-gp and BCRP while all metabolites are substrates of OAT3. Abocitinib has not been evaluated as a substrate for renal transporters due to its low renal excretion, conversely the metabolites have only been evaluated as substrates for renal transporters as this is their main elimination route.

Abrocitinib and all three main metabolites has been evaluated for their potential as inhibitors and inducers of all mandatory CYP enzymes. *In vitro* abrocitinib was a time-dependent inhibitor (TDI) of CYP3A4, 2D6 and 2C19 in the presence of NADPH. The metabolites showed TDI signals for CYP3A4 and 2D6 at concentrations above the cut-offs. Neither abrocitinib nor the metabolites were direct inhibitors of any CYP-enzyme investigated *in vitro*. Abrocitinib was an inducer of CYP3A4, 2C8, 2C19, 2B6 and 1A2 at the mRNA level. M1 and M2 were inducers of CYP3A4 and M2 also for 2B6. Further, abrocitinib was not an inhibitor of UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 or SULT1E1, 1A1 and 2A1.

Abrocitinib and all three main metabolites has been evaluated for their potential as inhibitors of all mandatory transporter proteins. *In vitro* abrocitinib was an inhibitor of p-gp, BCRP, OAT3, OCT1, MATE1 and MATE2k. Neither metabolite was an inhibitor of any transporter protein at relevant concentrations.

In vivo- abrocitinib as a victim

Fluconazole, a strong inhibitor of CYP2C19 and moderate inhibitor of 2C9 and 3A4 increased abrocitinib AUC 4.8-fold and Cmax 1.9-fold and the half-life was prolonged following fluconazole treatment, 3.1 vs 6.1 hours. Fluvoxamine, a strong CYP2C19 and moderate 3A4 inhibitor increased abrocitinib AUC 2.8-fold and Cmax 1.8-fold. The half-life was somewhat longer following fluvoxamine treatment, 5.2 vs 4.3 hours. This confirms the importance of these enzymes in abrocitinib metabolism. The exposure of active moiety increased by 1.9- and 1.3-fold (AUC and Cmax respectively) for fluvoxamine and 2.5- and 1.2-fold (AUC and Cmax respectively) for fluconazole.

Further, rifampin a strong inducer of several CYPs as well as p-gp decreased abrocitinib exposure with almost 90% and a shorter half-life of 2.1 hour with rifampin vs 4.3 hours without. The active moiety AUC decreased by 56% and the Cmax decreased by 31%.

Probenecid, an inhibitor of OAT3, increased abrocitinib exposure slightly (ca 30%) while as expected M1, M2 and M4 increased more, by 77%, 125% and 117% respectively. The unbound AUC and Cmax of the active moiety increased 1.7- and 1.3-fold respectively.

Table 10 Pharmacokinetic results of abrocitinib and its active moiety across DDI studies

Comparison	Abrocitinib Ratio, as Percent (90% CI)		Active Moiety Ratio, as Percent (90% CI)		Dosing Recommendation
	C_{max}	AUC_{inf}	C_{max}	AUC_{inf}	
Extrinsic Factors					
Effect of fluconazole[b]	192.10 (154.15, 0.39)	482.86 (383.94, 606)	123.46 (107.58, 141.70)	254.86 (241.75, 268.67)	Reduce dose by half[c]
Effect of fluvoxamine[b]	184.44 (133.27, 255.24)	275.22 (238.77, 317.24)	133.08 (99.58, 177.86)	191.24 (173.81, 210.43)	Reduce dose by half[c]
Effect of rifampin[a]	20.86 (14.31, 30.41)	12.45 (9.33, 16.60)	68.91 (50.28, 94.46)	43.86 (40.94, 46.98)	Not recommended
Effect of probenecid[a]	121.38 (92.93, 158.52)	127.60 (114.97, 141.61)	130.13 (104.10, 162.65)	165.54 (152.00, 180.29)	No Adjustment

a. Abrocitinib 200 mg.
b. Abrocitinib 100 mg.
c. Recommended dose of abrocitinib is 50 or 100 mg QD when the indicated dose is 100 or 200 mg QD, respectively.

In vivo- abrocitinib as a perpetrator

Given the *in vitro* signal of TDI and induction of CYP3A4 the applicant has investigated multiple doses of abrocitinib on midazolam exposure. At day 2 there was an approximately 16% decrease in midazolam AUC and Cmax. At day 7 there was an approximately 7% decrease in midazolam AUC and Cmax compared to midazolam being administrated alone.

In a study investigating the effect of multiple doses of abrocitinib on oral contraceptives, the AUCinf and Cmax values for ethinyl estradiol (EE) increased by approximately 19% and 7%, respectively, as compared to EE administration alone. No effect was seen on levonorgestrel AUC while Cmax decreased by 14%.

The exposure of dabigatran etexilate (p-gp substrate) increased approximately 1.5-fold after co-administration of a single 200 mg dose of abrocitinib.

No effect was seen on the exposure or on the renal clearance of either rosuvastatin (BCRP, OAT3, and OATP1s) or metformin (MATE1/2k) after co-administration with abrocitinib.

2.6.2.2. Pharmacodynamics

Mechanism of action

Abrocitinib is a Janus kinase (JAK)1 inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of haematopoiesis and immune cell function. JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Inhibition of JAK1 modulates the signalling pathways by preventing the phosphorylation and activation of STATs.

In biochemical assays, abrocitinib has selectivity for JAK1 over the other 3 JAK isoforms JAK2 (28-fold), JAK3 (> 340-fold) and tyrosine kinase 2 (TYK2, 43-fold). In cellular settings, it preferentially inhibits cytokine-induced STAT phosphorylation by signalling pairs involving JAK1, and spares signalling by JAK2/JAK2, or JAK2/TYK2 pairs. The relevance of selective enzymatic inhibition of specific JAK enzymes to clinical effect is not currently known.

Primary and Secondary pharmacology

The applicant has provided several PK/PD modelling reports:

PMAR-EQDD-B745d-913: Population Pharmacokinetic/Pharmacodynamic Modeling of the Effect of PF-04965842 on QT Intervals in Healthy Volunteers.

PMAR-EQDD-B745d-DP4-963 - Population Pharmacokinetic-Pharmacodynamic Modeling of Platelet Time-Courses Following Administration of PF-04965842.

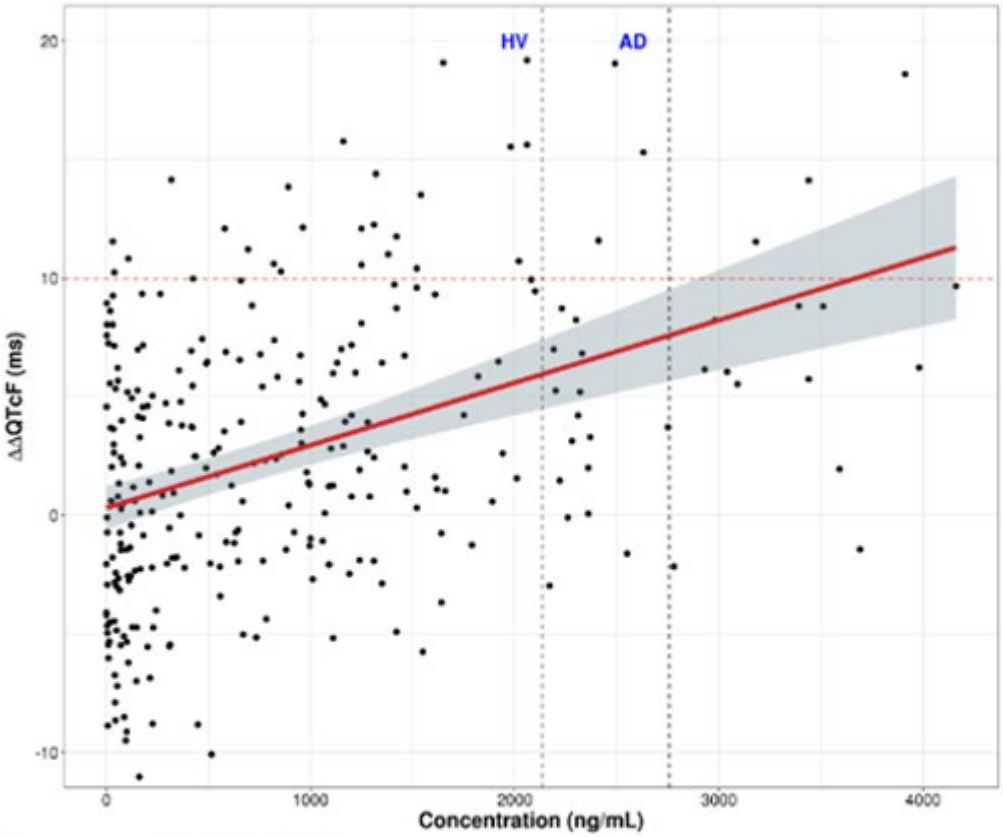
PMAR-EQDD-B745d-969: Population Pharmacokinetic/ Pharmacodynamic Modeling of the Effect of PF-04965842 on the Eczema Area and Severity Index and the Investigator's Global Assessment in Patients with Moderate to Severe Atopic Dermatitis.

The analyses are briefly described below.

Conc-QT modelling

A pre-specified linear mixed effects model was used in the concentration-QTc analysis. The model-predicted population-typical therapeutic Cmax at steady state after 200-mg QD dosing was 1123 ng/mL for adult patients with AD and the supratherapeutic concentrations in AD patients was set at 2757 ng/mL. The conc-QT modelling indicated the lack of a clinically relevant effect on QTc interval for the defined supratherapeutic concentrations, however at supratherapeutic concentration of around 3000 ng/mL (around 3-fold increase) the model predicts clinically relevant effect on QTc. QT-is further discussed in clinical safety section.

Figure 8 Model-predicted ΔΔQTcF across studied concentration range



Repository artifact ID RA15490354.

Red solid line corresponds to the predicted mean ΔΔQTcF across the studied concentration range and grey area corresponds to the associated 90% CIs. Concentrations of interest in healthy volunteers (HV) and patients with atopic dermatitis (AD) are highlighted with vertical dashed lines (see also Table 6). Black dots represent individual observations (corrected by population prediction of placebo effect). Horizontal dashed red lines highlight a change of 10 ms, a magnitude which can be considered clinically significant.

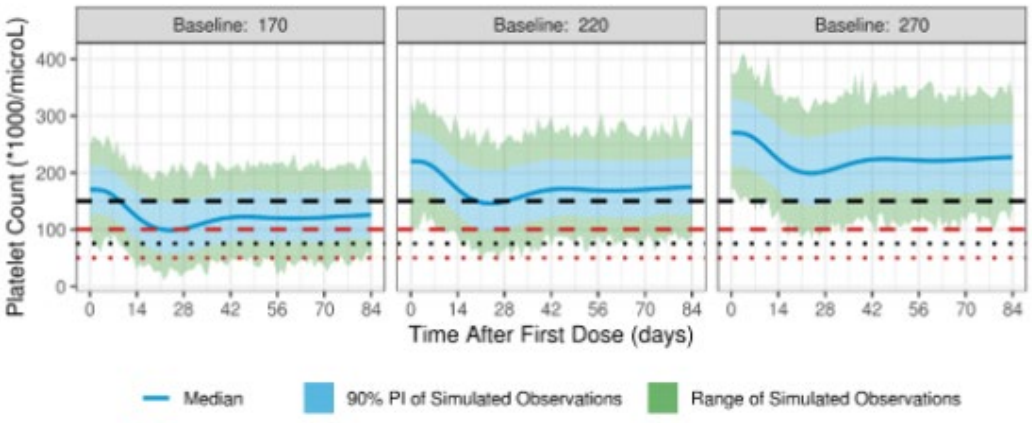
Exposure-safety, platelets

A semi-mechanistic model as the one proposed by Friberg et al has been used. The time course of platelets after the administration of abrocitinib was adequately described by the semi- mechanistic model. The probability of Grade ≥ 3 thrombocytopenia was <3%. Individuals with lower baseline platelet counts (170,000/μL and 220,000/μL) demonstrated higher net percentage decreases in platelet counts after 12 weeks.

Table 11 Probability of Thrombocytopenia Grades and Magnitude of Change at the Nadir and Week 12

	100 mg QD			200 mg QD		
Baseline platelets	170 × 10^3/μL	220 × 10^3/μL	270 × 10^3/μL	170 × 10^3/μL	220 × 10^3/μL	270 × 10^3/μL
Nadir[a]						
CFB (×10^3/μL)	−63.9 (−109.4, −12.0)	−65.4 (−117.5, −8.9)	−66.0 (−124.3, −2.1)	−70.1 (−114.0, −21.9)	−73.4 (−122.0, −13.8)	−71.5 (−129.9, −7.2)
CFB (%)	−37.6 (−64.3, −7.1)	−29.7 (−53.4, −4.1)	−24.4 (−46.0, −0.8)	−41.2 (−67.0, −12.9)	−33.4 (−55.5, −6.3)	−26.5 (−48.1, −2.7)
Grade 1 (%)	80.5	42.8	7.0	76.2	53.4	8.5
Grade 2 (%)	9.7	0.7	0	16.3	0.5	0.1
Grade ≥3 (%)	1.9	0	0	3.0	0	0

Figure 9 Simulated Platelet Counts for Baseline Values Administered 200 mg QD



Exposure-response

Two models were developed to evaluate the effect of abrocitinib on the main co-primary endpoints of the phase 3 studies (IGA and EASI). In general, the results are in line with the results presented in the efficacy section.

EASI

This model was able to adequately capture the profile of the EASI scores, including the rapid decrease for patients on treatment. In addition, the EASI-75 and EASI-90 rates across doses were accurately predicted. The 100-mg, 200-mg dose, and the 200-mg QD open-label QD dosing regimens showed meaningful efficacy in the expected percentage decrease in EASI scores from baseline, as well as high rates of patients achieving EASI-75 and EASI-90. With open-label dosing, responses were greater compared to double-blind dosing.

IGA

A longitudinal exposure-response model for the IGA score for each subject was developed. The Cavg (parent drug) was used as the measurement of exposure in the model. The responses compared to exposures shows that the Cavg is higher for responders versus non-responders at the end-of-study visit (Figure 10).
The 100 mg QD, 200 mg QD, and the 200 mg QD open-label dosing regimens both showed meaningful improvements in efficacy with higher average exposure. significantly associated with a higher probability of achieving an IGA response after 12 weeks of treatment. Both the 100 mg and 200 mg QD dosing regimens showed clinically meaningful improvements in the IGA response rate. When the patient knows they are taking the active treatment, the response to treatment was significantly higher. Patients with high baseline BGA has a lower predicted probability of response compared to reference.

Figure 10 C_{avg} Exposure at Last On-Treatment Visit for IGA Responders and Non-Responders at the Planned Week 12 Visit

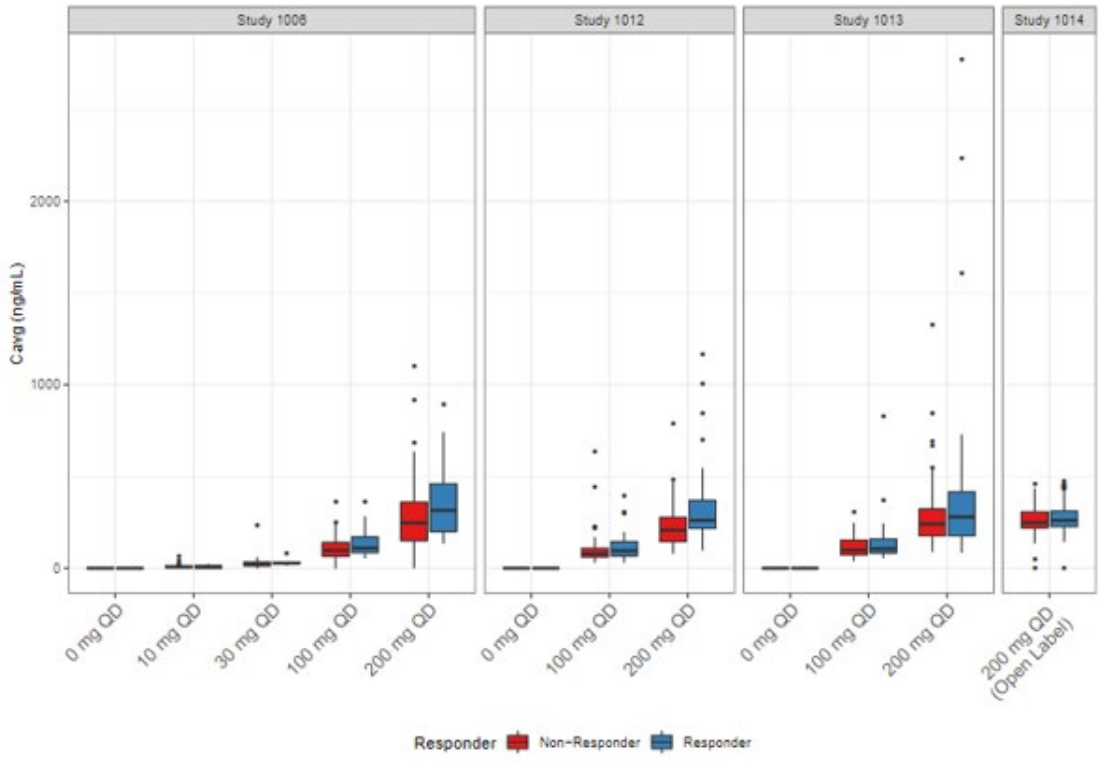


Table 12 Predicted Probability of an IGA Response at Week 12 by Subgroup

Patient	Placebo	100 mg QD	200 mg QD	200 mg QD - Open Label
Adolescent	14.1	30.6	44.5	69.2
Asian	14.2	37.0	53.3	76.3
Female.Asian	15.1	37.2	52.8	76.4
Female.White	14.7	35.4	50.8	74.5
High BIGA	7.4	16.9	30.6	49.0
Japanese	15.0	35.5	53.5	76.3
Low Weight	15.7	35.7	52.7	76.1
Reference	15.3	31.4	46.8	70.6

Repository artifact ID FI-4155805.
BIGA=baseline IGA score.
The probability of achieving an IGA response was estimated using the 1000 simulations and calculating the average probability of responding after 12 weeks of dosing. The reference is a White, male, 30 year old patient that weighs 70 kg with a baseline EASI score of 26. Adolescent represents a 12 year old, 40 kg, White, male, patient with moderate AD.

2.6.3. Discussion on clinical pharmacology

Abrocitinib is a small molecule kinase inhibitor of Janus kinase 1 (JAK1) available in 50, 100 and 200 mg film-coated tablets. The clinical effect is mediated by an active moiety which encompasses two identified pharmacologically active metabolites of abrocitinib. The applicant has justified that for the average AD patient 200 mg would be the starting dose. Based on the increased exposure of the active moiety, dose adjustments are proposed in patients with moderate and severe renal impairment (RI), patients ≥65 years of age and patients receiving concomitant use of strong CYP2C-inhibitors.

Abrocitinib is a weak base which exhibits pH-dependent solubility. At pH values >4.0, the compound demonstrates the characteristics of a low-solubility compound and thus dissolves more slowly. The effect of substances that increases the gastric pH on abrocitinib absorption has not been studied. Upon request from the CHMP, the applicant agreed to conduct a DDI-study of abrocitinib used concomitantly with a product that increase gastric pH. The results of this study will be submitted as a post-approval type II variation (Q1 2022). Information regarding concomitant use with substances that increases the gastric pH is included in the SmPC section 4.5, until the results of this study is available.

Abrocitinib is absorbed rapidly with a median Tmax around 1 hour. The fraction absorbed is high, 91%, while the absolute bioavailability is moderate, 60%. Over the dose range 30-800 mg different analyses indicate a more than proportional increase in AUC with dose, which in individual studies was obvious at 400 mg. However, in the clinically relevant interval between 50 and 200 mg, dose proportionality was shown. Time to steady state is 48 hours. A high-fat meal increased the bioavailability of the commercial formulation slightly (AUC and Cmax increased by approximately 26% and 29%, respectively, and Tmax was prolonged by 2 hours). This not considered clinically relevant. Further, in clinical studies, abrocitinib was administered without regard to food. The commercial formulation is bioequivalent to the formulation used in the phase-3 studies as well as in the majority of the clinical pharmacology studies.

After IV dosing, the steady-state Vss of abrocitinib was estimated to be 100.2 L, suggesting distribution into tissues. The fraction unbound was approximately 0.36, 0.63, 0.83 and 0.71 for abrocitinib, M1, M2 and M4 respectively in a clinically relevant concentration range.

Abrocitinib is extensively metabolised. Abrocitinib was the predominant component (approximately 26% of plasma radioactivity) in systemic circulation after oral administration. Single oxidative metabolites M1 (11.3%), M2 (12.4%) and M4 (13.8%) were also observed as major components of circulating profiled radioactivity. Several other minor metabolites were also identified. Of the 3 metabolites in circulation, M1 and M2 have similar JAK inhibitory profiles as abrocitinib, while M4 was pharmacologically inactive. M1 was estimated to contribute 11% and M2 47% to the *in vivo* activity. The sum of unbound exposures of abrocitinib, M1 and M2, each expressed in molar units and adjusted for relative potencies, is referred to as the abrocitinib active moiety. The PK profiles of the metabolites have been observed to be parallel to that of the parent drug in healthy individuals.

In vitro results indicate that the metabolism of abrocitinib is mediated by multiple CYP enzymes, CYP2C19 (~53%), CYP2C9 (~30%), CYP3A4 (~11%) and CYP2B6 (~6%). The importance of 2C19, 2C9 and 3A4 has been confirmed by *in vivo* studies. The consequences of genetic polymorphism have been evaluated using pooled data from the phase-1 studies. Using an overall phenotype (a combination of both CYP2C19 and 2C9 phenotype) no relevant differences in abrocitinib exposure are found between different phenotypes, indicating that other enzymatic pathways may overcome the loss of function in another pathway (or that the contribution of CYP2C19 and 2C9 is less *in vivo* than indicated by *in vitro* data). However, few individuals being classified as poor metaboliser of either enzyme were included in the analysis. As the DDI-studies with CYP inhibitors were performed using inhibitors (fluconazole and fluvoxamine) that are also moderate CYP3A4 inhibitors (in addition to inhibitors of CYP2C19 and CYP2C9) and these studies showed a much greater effect on abrocitinib exposure (4.8-fold increase for fluconazole) compared to the phenotype data exploring only the effect of CYP2C19 and CYP2C9 (30% increase), the *in vivo* contribution of the indicated CYPs to abrocitinib metabolism is not entirely clear. The fact that multiple enzymes are involved in the metabolism and may step in when one pathway is incapacitated is reassuring, thus no further studies are requested.

The exposure of abrocitinib is considerably affected by certain strong CYP-inhibitors and inducers, the effect is as expected less for the active moiety. In patients with renal impairment (RI) the effect is the opposite, abrocitinib exposure is not affected to such a large extent while the exposure of the

metabolites M1 and M2 indeed are, resulting in the exposure of the active moiety being increased more than that of abrocitinib. The applicant has discussed the therapeutic window and based the upper limit mainly on experience of the approximately 750 patients with mild renal impairment (defined as eGFR 60-90 ml/min) included in the phase-3 studies. The efficacy and safety for patients with mild renal impairment is considered acceptable. In a subgroup analysis of patients with mild RI, no obvious trend of more AEs in the group with lower eGFR was apparent. It can therefore be accepted that a 1.7-fold exposure is acceptable.

In vitro abrocitinib was a time-dependent inhibitor (TDI) and inducer of CYP2C19 the *in vivo* relevance of this will be evaluated in a planned DDI study. The results of this study will be submitted as a post approval type II variation (1H 2022). Information regarding the potential risk for interaction is included in the SmPC, until the results of this study are available.

The *in vitro* induction signals for CYP1A2 and 2B6 are now reflected in the SmPC and a clinical DDI study investigating the induction potential is planned. The results of this study will be submitted as a post approval type II variation (1H 2022).

In the mass balance study (IV tracer dose) total CL for abrocitinib was 1073 ml/min. Renal CL of abrocitinib was calculated as approximately 11 ml/min. The elimination half-life is around 5 hours. Abrocitinib is mainly (approximately 85%) excreted via urine, and to a low extend (9.5%) via faeces. Unchanged drug was less than 1% and 0.3% of the dose in urine and faeces, respectively.

Upon request from CHMP, the applicant provided an updated popPK analysis for both parent drug and metabolites. The popPK model has some issues, it is over parameterised and some of the pcVPC for the parent drug show model misspecification, mainly round 8-12 h after dose. The stratified pcVPCs for adolescent and adult for the relevant doses (100 mg and 200 mg) appear acceptable. While the data for the 200mg dose seem comparable, slightly lower concentrations are observed in adolescents compared to adults for the 100mg dose. No new covariate modelling was conducted for parent drug in the updated popPK analysis. Thus, adolescent as a covariate on F remains but the covariate effect is estimated to be lower than previously. Nevertheless, this issue was not further pursued by the CHMP as the product is currently not indicated in adolescents.

The joint metabolite model was not considered satisfactory. However, drawing conclusions on parent drug for adolescents based on parent drug for adults only is deemed adequate and despite some shortcomings of the updated parent popPK model, it is not expected for a flat dose, that adolescent patients would have much lower exposure than adults. Adolescent may have slightly higher clearance per kg but they also have lower body weight. The side by side VPCs for adults and adolescent for the relevant doses (100 and 200 mg) appear acceptable. Further, in the figure with observed PK data for adults and adolescents, the data were largely overlapping, providing some additional support that exposure is similar in adolescents and adults. The SmPC has been updated with an acceptable description of exposure in adolescents.

Please also see clinical efficacy section for further discussion on efficacy in adolescents.

In the dedicated renal impairment (RI) study the exposure of the active moiety increased approximately 3-fold in patients with severe (RI) and 2-fold in patients with moderate RI. For both groups the dose is proposed to be reduced by half. Subjects with mild renal impairment have not been studied. Through extrapolation using a linear regression function a patient with an eGFR of 60 ml/min is predicted to have an increase in active moiety of about 1.7-fold. This is reflected in the SmPC.

Treatment recommendations for patients with severe/moderate renal impairment are based on (full) extrapolation informed by modelling. For patients with moderate RI, the dose adjustment proposed by the applicant in SmPC section 4.2 is considered satisfactory with exposure similar to patients with normal renal function.

Comparison of active moiety exposure at the 100 mg QD dose in moderate or severe RI patients to the 200 mg QD dose in normal renal function patients demonstrates that there is a trend of higher exposures in patients with severe RI. Further, there is no clinical trial experience in patients with eGFR <30 mL/min and only very little in patients with eGFR ≤40 mL/min of whom a few were included in phase I studies (not in phase II or III). The PMAR-1110 model is however considered sufficiently robust to approach/predict exposure also in a population with eGFR ≤40 mL/min. Nevertheless, the applicant has proposed a more conservative wording in SmPC section 4.2 for patients with severe renal impairment to accommodate for uncertainties with the extrapolation approach which is acceptable.

Abrocitinib has not been studied in patients with end-stage renal disease (ESRD) on renal replacement therapy.

A dose-response Phase 2 b study (B7451006) with abrocitinib 10, 30, 100 and 200 mg and placebo dosed once daily was performed in adult subjects with AD. No statistical difference compared with placebo was observed for the two lowest doses 10 mg and 30 mg in either clinical endpoint (IGA or EASI-75) investigated. Both 100 mg and 200 mg of abrocitinib resulted in a statistically significant higher proportion of IGA responders and percent change from baseline in EASI score at week 12 compared with treatment with placebo and thus supports the doses chosen for the pivotal Phase 3 studies.

Similarly, the modelling of exposure-response for phase 2b and phase 3 data, indicate that both 100 mg and 200 mg have a relevant effect and that the 200 mg provide higher probability of IGA response than 100 mg. Patients with high baseline BGA had a lower predicted probability of response compared to reference. This indicate that these patients may warrant the higher 200 mg start dose.

In none of the presented studies the 50mg dose has been administered and only limited data is available for dose level below 100mg. The closest studied dose is 30mg for which only limited data from healthy volunteers is available. From the provided data it is currently doubted that relevant plasma concentrations might be reached with a dose of 50 mg in regular AD patients. However, dose reduction to 50 mg is only recommended for patients with increased exposure caused either by impairment or co-medication. In patients with normal renal function, the text in section 4.2 of the SmPC was updated to clarify the intended starting dose.

2.6.4. Conclusions on clinical pharmacology

Abrocitinib is a Janus kinase (JAK)1 inhibitor which reversibly and selectively inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. In a cell-free isolated enzyme assay, abrocitinib has biochemical selectivity for JAK1 over the other 3 JAK isoforms JAK2 (28-fold), JAK3 (> 340-fold) and TYK 2 (43-fold).

In the performed phase 2b dose-response study (B7451006) 10 mg and 30 mg of abrocitinib had no significant clinical efficacy in the target population, patients with moderate to severe AD. A dose-dependent statistically significant efficacy was observed for 100 mg and 200 mg of abrocitinib. Study (B7451006) supports doses chosen (100 mg and 200 mg) for the pivotal Phase 3 studies. Although the data is comprehensive for the intended dose level (100 and 200 mg), no data is available for the recommended reduced dose of 50 mg. However, dose reduction to 50 mg is only recommended for patients with increased exposure caused either by impairment or co-medication.

Treatment with abrocitinib should not be initiated in patients with a platelet count < 150 × 103/mm^3, an absolute lymphocyte count (ALC) < 0.5 × 103/mm^3, an absolute neutrophil count (ANC) < 1 × 103/mm^3 or who have a haemoglobin value < 8 g/dL. In addition, treatment should be interrupted if a

patient develops a serious infection until the infection is controlled. Abrocitinib is contraindicated in patients with severe renal impairment.

Overall, the pharmacokinetics of abrocitinib has been appropriately characterised and relevant dose adjustments and precautions are proposed in the SmPC.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

The phase 2b study B7451006 was a randomised, double-blind, placebo-controlled, parallel, multicentre, dose-ranging, study to evaluate the efficacy and safety profile of abrocitinib in participants with moderate to severe atopic dermatitis.

The primary objective of the study was to evaluate the efficacy of 4 QD dose levels (10, 30, 100, and 200 mg) of abrocitinib relative to placebo in adult participants with moderate to severe AD with Investigator's Global Assessment (IGA) as primary endpoint. The secondary objectives were to evaluate the effect of abrocitinib on additional efficacy endpoints and patient reported outcomes (PROs) over time. In addition, the safety and tolerability of abrocitinib were evaluated.

The results with the primary efficacy endpoint showed no statistical difference compared with placebo for the two lowest doses 10 mg and 30 mg. Both 100 mg and 200 mg resulted in a statistically significant higher proportion of IGA responders at week 12 compared with treatment with placebo, 21.5 (95% CI 5.5, 37.5) for 100 mg and 38.2 (CI 19.7, 56.6) for 200 mg. The key secondary efficacy endpoint was the percent change from baseline in the EASI total score at Week 12. Abrocitinib treatment, at both the 100 mg QD and 200 mg QD doses, resulted in a statistically significant higher percent change from baseline in EASI score at Week 12 compared to treatment with placebo, -23.82 (90% CI -38.76, -8.8) for 100 mg and -47.35 (90% CI -62.23, -32.47) for 200 mg.

To conclude, study B7451006 supports doses chosen for the pivotal Phase 3 studies (see below) where results with abrocitinib is further assessed.

2.6.5.2. Main studies

The efficacy of abrocitnib is supported by two pivotal phase 3 studies with identical design (studies B7451012 and B7451013). The methods and results of these studies are presented together in this report. Moreover, a phase 3 combination study including an active comparator (dupilumab, Dupixent) and background topical therapy (study B7451029) has been performed.

A phase 3 withdrawal and re-treatment study B7451014, and a combination therapy study B7451036 with background topical therapy in adolescents only have been completed. Study B7451015 is a long-term recurrence of efficacy and safety study. Study B7451037, a phase 2a study investigating the mechanism of action of abrocitinib monotherapy in adult participants, is ongoing.

This document focuses on the main studies i.e. the monotherapy studies B7451012 and B7451013 and the combination therapy study B7451029.

B7451012: a phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-center study to evaluate the efficacy and safety of abrocitinib monotherapy in subjects aged 12 years and older, with moderate to severe atopic dermatitis

B7451013: a Phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-center study to evaluate the efficacy and safety of abrocitinib monotherapy in subjects aged 12 years and older, with moderate to severe atopic dermatitis

Methods

- **Study Participants**

Main inclusion criteria

1. Male or female subjects of 12 years of age or older at the time of informed consent and body weight ≥40 kg.

2. Meet all the following atopic dermatitis (AD) criteria:

- Clinical diagnosis of chronic AD (also known as atopic eczema) for at least 1 year prior to Day 1 and has confirmed AD (Hanifin and Rajka criteria of AD);

- Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications for at least 4 weeks, or for whom topical treatments are otherwise medically inadvisable (e.g. because of important side effects or safety risks), or who have required systemic therapies for control of their disease;

- Moderate to severe AD (affected BSA ≥10%, IGA≥3, EASI≥16, and Pruritus NRS≥4 at the baseline visit).

3. If receiving concomitant medications for any reason other than AD, must be on a stable regimen, which is defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever is longer) prior to Day 1 and through the duration of the study.

Main exclusion criteria

1. Any psychiatric condition including recent or active suicidal ideation or behaviour that meets any of the following criteria:

    - Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the Columbia Suicide Severity Rating Scale (C-SSRS);
    - Previous history of suicidal behaviours in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behaviour items of the C-SSRS;
    - Any lifetime history of serious or recurrent suicidal behaviour;
    - Clinically significant depression: Patient Health Questionnaire –8 items (PHQ-8) total score ≥15;
    - The presence of any current major psychiatric disorder that was not explicitly permitted in the inclusion/exclusion criteria;
    - In the opinion of the investigator or Pfizer (or designee) exclusion was required.

2. A current or past medical history of conditions associated with thrombocytopenia, coagulopathy or platelet dysfunction.

3. Receiving anti-coagulants or medications known to cause thrombocytopenia, (unless considered safe to stop and washout for the duration of the study).

4. Have a history of any lymphoproliferative disorder such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, history of lymphoma, leukaemia, or signs or symptoms suggestive of current lymphatic or lymphoid disease.

5. Infection History:

a. Have a history of systemic infection requiring hospitalisation, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to Day 1.

b. Have active chronic or acute skin infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks prior to Day 1, or superficial skin infections within 1 week prior to Day 1.

c. A subject known to be infected with Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis

d. Have a history (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localised, dermatomal herpes zoster.

6. Have a known immunodeficiency disorder or a first-degree relative with a hereditary immunodeficiency.

7. Have any malignancies or have a history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ.

8. Have evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB).

- **Treatments**

Subjects took the investigational product orally once a day for 12 weeks. They took one tablet once daily, preferably in the morning, at approximately the same time of the day.

Since body weight did not appear to be a significant determinant of PK across the weight range evaluated in study B7451006, adolescents aged 12 years and older who weighed 40 kg or more were administered the same dose as the adults (i.e. 100 mg QD or 200 mg QD). The inclusion of adolescents in the clinical trials was agreed to in the CHMP scientific advice (EMEA/H/SAH/085/2/2017/III) also considered acceptable since the disease panorama of AD is similar in adults and adolescents.

The primary endpoint was evaluated 12 weeks post treatment, with a 4-week follow-up period.

- **Objectives**

The primary objective of studies B7451012 and B7451013 was to assess the efficacy of abrocitinib compared with placebo in subjects aged 12 years and older with moderate to severe AD. Secondary objectives were to evaluate the effect of abrocitinib on additional efficacy endpoints and patient reported outcomes over time, and to evaluate the safety and tolerability of abrocitinib in subjects aged 12 years and older with moderate to severe AD following 12 weeks of treatment.

The statistical hypothesis was superiority of abrocitinib 100 mg and 200 mg compared to placebo for the primary endpoints.

- **Outcomes/endpoints**

Co-primary efficacy endpoints

- Response based on the IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 12.
- Response based on EASI 75% or greater improvement from baseline (EASI-75) at Week 12.

Key secondary efficacy endpoints

- Response based on at least 4 points' improvement in the severity of pruritus numerical rating scale (PP-NRS4) from baseline at Weeks 2, 4, and 12.
- Change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at Week 12.

Furthermore, several other secondary efficacy endpoints and Patient-Reported Outcome (PRO) endpoint were investigated.

- **Sample size**

The sample size calculation for the two identically designed studies (Study B7451012 and B7451013) was based on the co-primary endpoints. With a total of 375 subjects; 150 randomised to each abrocitinib arm and 75 randomised to placebo, it was expected to have at least 95% power to detect a difference in IGA response rate of at least 20% between abrocitinib 200 mg QD (or 100 mg QD) and placebo, assuming a placebo response rate of 6% at Week 12. This sample size was also to provide at least 99% power to detect a difference in EASI-75 response rate of at least 30% between abrocitinib 200 mg QD (or 100 mg QD) and placebo, assuming the placebo response rate to be 15% at Week 12. The Type-I error for testing each individual co-primary endpoint was set at 5%. The study was to meet its primary objective only if both hypotheses, corresponding to each co-primary endpoint, could be rejected and, thereby was the type-I error rate controlled at 5% for testing the primary endpoints. The power to reject both hypotheses when a true difference exists was assumed to be at least 94% depending on the correlation between the endpoints.

- **Randomisation and Blinding (masking)**

Eligible subjects were randomised at Day 1/baseline in a 2:2:1 ratio (abrocitinib 200 mg QD, abrocitinib 100 mg QD, or placebo). Randomisation was stratified by baseline disease severity (moderate [IGA = 3] vs. severe [IGA = 4] AD), and age (<18 vs. ≥18 years of age). Allocation of subjects to treatment groups proceeded through an Interactive Response Technology (IRT) system. Investigators, subjects and the sponsor study team were blinded to treatment assignment. Abrocitinib and matching placebo, were provided as 100 mg tablets in separate bottles. Subjects were dispensed 2 bottles at each dispensing visit and were instructed to take one tablet from each bottle, once daily.

- **Statistical methods**

Study B7451012: All analyses were carried out as detailed in the final SAP (Version 4, 23 April 2019) but for several exceptions included and justified in the SAP.

Study B7451013: All analyses were carried out as detailed in the SAP Amendment 1, the final SAP (Version 2, dated 26 August 2019).

There was no interim analysis planned for any of the monotherapy studies and none was performed.

The primary analysis set was the Full Analysis Set (FAS) defined as all randomised subjects who received at least 1 dose of study treatment. Analyses for endpoints that were defined based on a threshold of change from baseline (e.g. NRS4) also required the baseline value to meet that threshold (e.g. for NRS4, the baseline value needed to be ≥4).

Analysis of co-primary endpoints

The co-primary endpoints were analysed using the Cochran-Mantel-Haenszel test adjusted by randomisation strata (baseline disease severity and age). The proportion of IGA/EASI75 responders in abrocitinib treatment groups versus placebo were summarised by the difference and corresponding 95% CI obtained by normal approximation. The difference in proportions were calculated within each randomisation stratum and the final estimate of the difference in proportions was a weighted average of these stratum-specific estimates using CMH weights. In case of study withdrawal or use of rescue, a subject was counted as non-responder (NR). Estimates of the difference in proportions between the two dosing regimens (100 mg and 200 mg) along with the two-sided 95% CI were also provided. No hypotheses were tested.

Sensitivity analyses of IGA/EASI-75 responses at Week 12 were performed using the CMH and normal approximation method, where missing responses were multiply imputed using a tipping point (TP) approach, which considered analyses under missing at random (MAR), as well as missing not at random (MNAR).

Table 13 Summary of the analyses of primary and key secondary efficacy endpoints

Efficacy Endpoints	Population	Analysis Method	Missing Data Imputation	Primary Analysis for Co-primary Endpoints
Week 12 IGA Response	FAS	CMH	NR	Yes
	PPAS	CMH	NR	No
	FAS	CMH	TP (MAR)	No
	FAS	CMH	TP (MNAR)	No
Week 12 EASI-75 Response	FAS	CMH	NR	Yes
	PPAS	CMH	NR	No
	FAS	CMH	TP (MAR)	No
	FAS	CMH	TP (MNAR)	No
Weeks 2, 4, 8 and 12 NRS4 for severity Response	FAS	CMH	NR+MI	
	PPAS	CMH	NR+MI	
	FAS	CMH	NR	
Week 12 CFBL in PSAAD	FAS	MMRM	OD	
	PPAS	MMRM	OD	

Response based on a ≥4-points improvement from baseline in pruritus NRS score for severity

Missing data imputation: Due to a technical error in the transmission and collection of electronic data, data on the pruritus NRS scale was not collected from several subjects at scheduled visits of Week 2 (Day 15) and after. This was foremost evident in study B7451012 but occurred also in study B7451013. To account for missing responses in the analyses (weeks 2, 4, 8, and 12), a hybrid approach (NR+MI) was used. The multiple imputation methodology was based on an assumption of missing at random (MAR). In addition, a sensitivity analysis was performed where all missing responses were defined as "non-response".

Change from baseline (CFB) in PSAAD score at Week 12

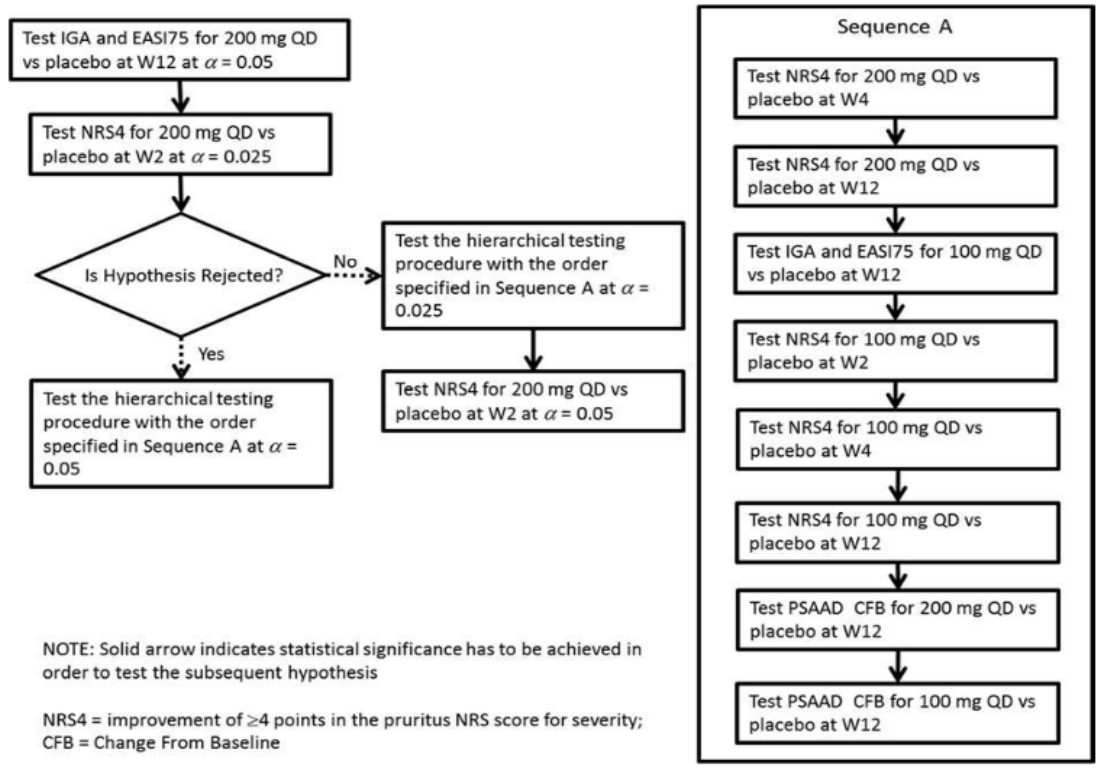
The PSAAD total score was calculated as the simple arithmetic mean of items 1-11. Change from baseline in the PSAAD score at week 12 was analysed using a mixed-effect, repeated measures (MMRM) model. The fixed effects of treatment, visit, treatment-by-visit interaction, and randomisation stratification factors were included. Visit was modelled as a categorical covariate. Unstructured covariance matrix was assumed for the model errors. Compound symmetry covariance matrix was

used if this model did not converge. Data was collected daily and were summarised using a simple average of the values recorded within a week. In the implementation of the MMRM models, data from all weekly visits were used. The preliminary PSAAD version is a 15-item questionnaire; four additional items (Items 12, 13, 14, and 15) were added for exploratory and psychometric validation purposes (Sleep & Usual Activities Questions and Patient Global Impression of Severity [PGIS] & Patient Global Impression of Change Questions [PGIC]).

Multiple testing procedure

To control the familywise Type 1 error at 5%, a sequential Bonferroni-based iterative multiple testing procedure was used for testing each of the two abrocitinib doses versus placebo on the primary and key secondary endpoints. See Figure 11.

Figure 11. Multiple testing procedure



Results

Participant flow

The subject evaluation groups and patient disposition in the clinical studies B7451012 and B7451013 can be seen in the figures below.

Figure 12 Subject Evaluation Groups and Disposition (B7451012)

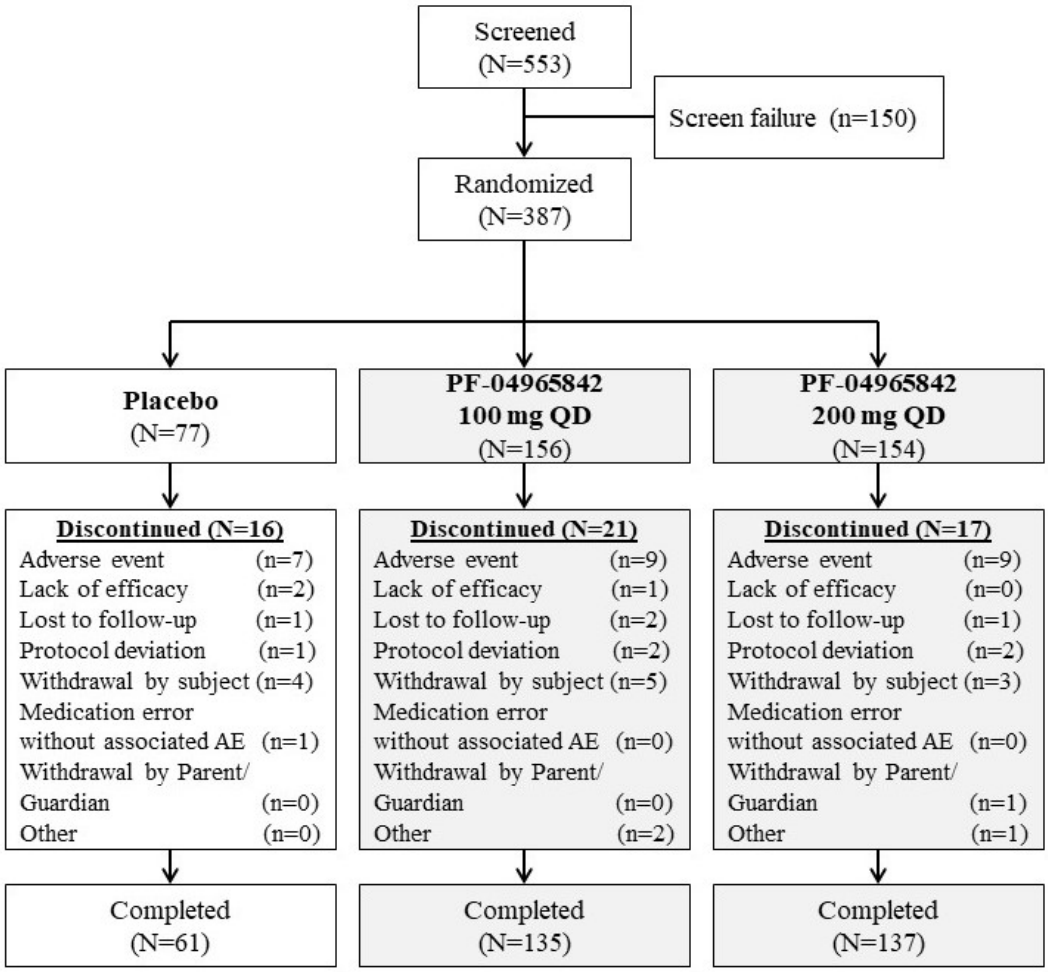
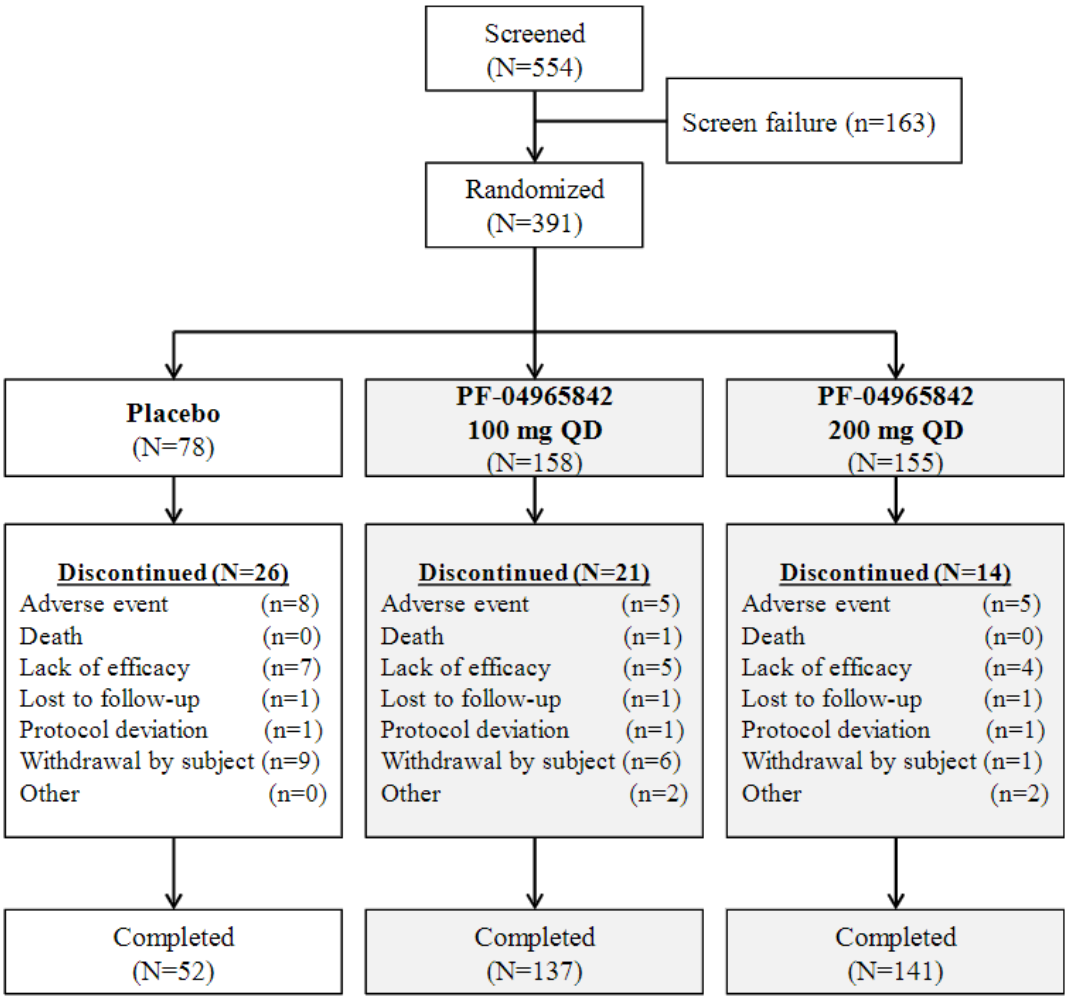


Figure 13 Subject Evaluation Groups and Disposition (B7451013)



Recruitment

Study B7451012

A total of 387 subjects were enrolled at 69 centres in 8 countries, including sites in the US (n=114), Canada (n=64), Germany (n=64), Australia (n=51), Poland (n=49), Czech Republic (n=19), United Kingdom (n=14), and Hungary (n=12). The study period was December 2017 to March 2019. The final study report was dated August 27, 2019.

Study B7451013

A total of 391 subjects were enrolled at 102 centres in 13 countries, including sites in the US (n=19), Poland (n=14), Republic of Korea (n=10), Japan (n=8), Australia (n=7), Bulgaria (n=7), Canada (n=7), Germany (n=7), United Kingdom (n=6), China (n=5), Latvia (n=5), Hungary (n=4), and Czech Republic (n=3). The study period was June 2018 to August 2019. The final study report was dated January 13, 2020.

Conduct of the study

Study B7451012

For efficacy analyses of co-primary and key secondary endpoints, subjects who had major protocol deviations were excluded from the PPAS.

Important protocol deviations were reported in 94% of subjects, most frequently in the category of procedures or tests, of which a missing NRS assessment at any study visit from day 15 forward

occurred most frequently. Other reasons were related to errors with laboratory results, inclusion/exclusion criteria, took prohibited concomitant medication, and dosing/administration errors of investigational product/study medication.

Treatment compliance was high, the mean dose compliance was 98%, 99% and 97% in the abrocitinib 200mg QD, abrocitinib 100mg QD, and placebo groups, respectively.

Study B7451013

For efficacy analyses of co-primary and key secondary endpoints, subjects who had major protocol deviations were excluded from the PPAS.

Important protocol deviations were reported in 86% of subjects, most frequently in the category of procedures or tests, of which a missing NRS assessment occurred most frequently. Other reasons were related to errors with laboratory results, inclusion/exclusion criteria, took prohibited concomitant medication, and dosing/administration errors of investigational product/study medication.

Treatment compliance was high, the mean (SD%) dose compliance was 97% across treatment groups.

Baseline data

The demographic and baseline disease characteristics of subjects in studies B7451012 and B7451013 can be seen in the tables below.

Table 14 Abrocitinib Summary of Clinical Efficacy (Atopic Dermatitis) Demographic Characteristics of Monotherapy Subjects

	B7451012 (N=387)	B7451013 (N=391)	B7451006 (N=164)	Monotherapy Pool (N=942)
Adolescent Age Distribution (Years), n (%)				
< 18	84 (21.7)	40 (10.2)	0	124 (13.2)
12 -< 15	39 (46.4)	10 (25.0)	0	49 (39.5)
15 -< 18	45 (53.6)	30 (75.0)	0	75 (60.5)
Age (Years), Median (Q1, Q3)	29.0 (19.0, 43.0)	31.0 (23.0, 45.0)	38.0 (27.0, 53.0)	31.0 (22.0, 46.0)
Female, n (%)	167 (43.2)	162 (41.4)	84 (51.2)	413 (43.8)
White, n (%)	279 (72.1)	232 (59.3)	114 (69.5)	625 (66.3)
Hispanic or Latino, n (%)	20 (5.2)	9 (2.3)	8 (4.9)	37 (3.9)
Height (cm), Median (Q1, Q3)	170.0 (162.6, 178.0)	170.0 (163.3, 176.4)	170.0 (162.6, 175.8)	170.0 (163.0, 177.0)
Weight (kg), Median (Q1, Q3)	74.3 (63.2, 88.5)	72.0 (61.0, 84.0)	77.1 (65.8, 91.0)	73.7 (62.3, 87.1)
BMI (kg/m^2), Median (Q1, Q3)	25.8 (22.3, 29.6)	24.5 (22.0, 28.1)	26.9 (23.2, 31.6)	25.3 (22.4, 29.3)

Pooled analysis included B7451006, B7451012 and B7451013.
BMI: Body Mass Index (kg/m^2) = weight (kg) / (0.01 × [height (cm)])^2.
N = total sample size; n (%) = number of subjects who met criteria (percentage based on N).
PFIZER CONFIDENTIAL Source Data: adsl Date of ADAM Dataset Creation: 28OCT2019 Output File: ./ad_sce/MT/adsl_s001_imm Date of Generation: 13JAN2020 (02:36)
Table MT.14.1.5 is for Pfizer internal use.

Table 15 Abrocitinib Summary of Clinical Efficacy (Atopic Dermatitis) Baseline Disease Characteristics of Monotherapy Subjects

	B7451012 (N=387)	B7451013 (N=391)	B7451006 (N=164)	Monotherapy Pool (N=942)
Disease Duration (Years), Median (Q1, Q3)	19.8 (12.8, 32.4)	19.6 (9.2, 29.2)	23.8 (12.1, 37.7)	20.2 (11.2, 32.0)
Investigator's Global Assessment (IGA), %Moderate/Severe	59.2/40.8	67.8/32.2	59.1/40.9	62.7/37.3

Table 15 Abrocitinib Summary of Clinical Efficacy (Atopic Dermatitis) Baseline Disease Characteristics of Monotherapy Subjects

	B7451012 (N=387)	B7451013 (N=391)	B7451006 (N=164)	Monotherapy Pool (N=942)
Eczema Area and Severity Index (EASI), Median (Q1, Q3)	25.6 (19.6, 39.8)	25.2 (19.7, 34.6)	22.5 (15.8, 32.7)	24.9 (19.2, 36.2)
Percent Body Surface Area (BSA) Affected by Atopic Dermatitis, Median (Q1, Q3)	45.0 (30.0, 68.0)	44.0 (32.0, 66.0)	35.5 (21.1, 54.5)	43.0 (29.5, 65.0)
Peak Pruritus Numeric Rating Scale (PP-NRS) (Severity), Median (Q1, Q3)	7.0 (6.0, 8.0)	7.0 (6.0, 8.0)	8.0 (6.0, 9.0)	7.0 (6.0, 8.0)
Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD), Median (Q1, Q3)	5.4 (3.6, 6.9)	5.3 (3.6, 6.8)	5.5 (4.1, 7.0)	5.3 (3.6, 6.9)
Scoring Atopic Dermatitis (SCORAD), Median (Q1, Q3)	64.0 (55.0, 74.6)	63.4 (55.2, 71.8)	63.1 (54.4, 72.3)	63.5 (55.0, 72.8)
Dermatology Life Quality Index (DLQI), Median (Q1, Q3)	14.0 (9.5, 19.0)	14.0 (10.0, 19.0)	14.0 (8.0, 20.0)	14.0 (10.0, 19.0)
Children's Dermatology Life Quality Index (CDLQI), Median (Q1, Q3)	13.0 (8.0, 17.0)	12.0 (8.0, 16.0)	NA	13.0 (8.0, 17.0)
Patient Oriented Eczema Measure (POEM), Median (Q1, Q3)	20.0 (16.0, 24.0)	20.0 (17.0, 25.0)	21.0 (17.0, 26.0)	21.0 (16.0, 25.0)
Hospital Anxiety Scale (HADS Anxiety), Median (Q1, Q3)	5.0 (3.0, 8.0)	5.0 (3.0, 9.0)	7.0 (4.0, 10.0)	5.0 (3.0, 9.0)
Hospital Anxiety Scale (HADS Depression), Median (Q1, Q3)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)	4.0 (2.0, 7.0)	3.0 (1.0, 6.0)
Patient Global Assessment (PtGA), %Moderate/Severe	47.3/45.5	45.0/49.1	32.3/55.5	43.7/48.7

Pooled analysis included B7451006, B7451012 and B7451013.
For PSAAD score, baseline was defined as the average of all values recorded between Day -6 and Day 1. For B7451012 (DLQI, CDLQI, POEM, PtGA and HADS) and B7451013 (DLQI, CDLQI, POEM, PtGA, HADS and PP-NRS), baseline was defined as the measurement collected on or prior to Day 1. For other variables, baseline was defined as the last measurement prior to first dosing (Day 1).
Subject handprints were used to determine the extent (%) of skin afflicted with atopic dermatitis. Body regions assessed did not include the scalp, palms and soles.
N = total sample size; NA = not applicable.
PFIZER CONFIDENTIAL Source Data: adad adcc adda adea adga adli adnr adpm adpu adsl Date of ADAM Dataset Creation: 28OCT2019 Output File: ./ad_sce/MT/adsl_s003_imm Date of Generation: 14JAN2020 (20:14)
Table MT.14.1.6 is for Pfizer internal use.

Numbers analysed

Study B7451012

	Placebo (N=77) n (%)	PF-04965842 100mg QD (N=156) n (%)	PF-04965842 200mg QD (N=154) n (%)
Screened: 553			
Screen Failure: 150			
Not Screen Failure but Not Randomized: 16			
Randomized	77 (100.0)	156 (100.0)	154 (100.0)
Treated	77 (100.0)	156 (100.0)	154 (100.0)
Not Treated	0	0	0
Analysis for Safety			
Safety Analysis Set	77 (100.0)	156 (100.0)	154 (100.0)
Analysis for Efficacy			
Full Analysis Set (FAS)	77 (100.0)	156 (100.0)	154 (100.0)
Per Protocol Analysis Set (PPAS)	57 (74.0)	132 (84.6)	132 (85.7)

Safety Analysis Set (SAS) was defined as those subjects who received at least one dose of study medication.
Full Analysis Set (FAS) was defined as all randomized subjects who received at least one dose of study medication.
Per Protocol Analysis Set (PPAS) was defined as a subset of FAS who had no major protocol violations.
PFIZER CONFIDENTIAL SDTM Creation: 01MAY2019 (05:56) Source Data: Table 16.2.1.1.2 Output File: ./nda1_cdisc/B7451012/adsl_s002 Date of Generation: 03MAY2019 (08:19)
Table 14.1.1.1 is for Pfizer internal use.

Study B7451013

	Placebo (N=78) n (%)	PF-04965842 100mg QD (N=158) n (%)	PF-04965842 200mg QD (N=155) n (%)
Screened: 554			
Screen Failure: 163			
Not Screen Failure but Not Randomized: 0			
Randomized	78 (100.0)	158 (100.0)	155 (100.0)
Treated	78 (100.0)	158 (100.0)	155 (100.0)
Not Treated	0	0	0
Analysis for Safety			
Safety Analysis Set	78 (100.0)	158 (100.0)	155 (100.0)
Analysis for Efficacy			
Full Analysis Set (FAS)	78 (100.0)	158 (100.0)	155 (100.0)
Per Protocol Analysis Set (PPAS)	52 (66.7)	128 (81.0)	130 (83.9)

Safety Analysis Set was defined as those subjects who received at least one dose of study medication.
Full Analysis Set (FAS) was defined as all randomized subjects who received at least one dose of study medication.
Per Protocol Analysis Set (PPAS) was defined as a subset of FAS who had no major protocol violations.
PFIZER CONFIDENTIAL SDTM Creation: 12SEP2019 (22:25) Source Data: adsl Output File: ./nda1_cdisc/B7451013/adsl_s002 Date of Generation: 17OCT2019 (23:55)
Table 14.1.1.1 is for Pfizer internal use.

Outcomes and estimation

The co-primary efficacy endpoints were:

- Response based on the IGA score of clear (0) or almost clear (1); and a reduction from baseline of ≥2 points at Week 12.
- Response based on the EASI ≥75% improvement from baseline (EASI-75) at Week 12.

Study B7451012
IGA response at week 12

Proportion of Monotherapy Subjects Achieving an IGA Score of 'Clear' or 'Almost Clear' and >=2 Points Improvement from Baseline at Week 12 (FAS, CMH) (Phase 3 Study)

	B7451012			B7451013			Phase 3 Monotherapy Pool		
	Placebo	Abrocitinib 100mg QD	Abrocitinib 200mg QD	Placebo	Abrocitinib 100mg QD	Abrocitinib 200mg QD	Placebo	Abrocitinib 100mg QD	Abrocitinib 200mg QD
N	76	156	153	77	155	155	153	311	308
n (%)	6 (7.9)	37 (23.7)	67 (43.8)	7 (9.1)	44 (28.4)	59 (38.1)	13 (8.5)	81 (26.0)	126 (40.9)
95% CI	(1.8, 14.0)	(17.0, 30.4)	(35.9, 51.7)	(2.7, 15.5)	(21.3, 35.5)	(30.4, 45.7)	(4.1, 12.9)	(21.2, 30.9)	(35.4, 46.4)
Active - Placebo									
Estimate (%)		15.8	36.0		19.3	28.7		17.5	32.3
95% CI		(6.8, 24.8)	(26.2, 45.7)		(9.6, 29.0)	(18.6, 38.8)		(10.9, 24.2)	(25.3, 39.3)
p-value		0.0037	<.0001		0.0008	<.0001			
200mg - 100mg									
Estimate (%)			20.0			9.7			14.8
95% CI			(9.9, 30.1)			(-0.7, 20.0)			(7.6, 22.1)

EASI ≥75% improvement from baseline (EASI-75) at Week 12

Proportion of Monotherapy Subjects Achieving Eczema Area and Severity Index (EASI) Response >=75% Improvement from Baseline at Week 12 (FAS, CMH) (Phase 3 Study)

	B7451012			B7451013			Phase 3 Monotherapy Pool		
	Placebo	Abrocitinib 100mg QD	Abrocitinib 200mg QD	Placebo	Abrocitinib 100mg QD	Abrocitinib 200mg QD	Placebo	Abrocitinib 100mg QD	Abrocitinib 200mg QD
N	76	156	153	77	155	154	153	311	307
n (%)	9 (11.8)	62 (39.7)	96 (62.7)	8 (10.4)	69 (44.5)	94 (61.0)	17 (11.1)	131 (42.1)	190 (61.9)
95% CI	(4.6, 19.1)	(32.1, 47.4)	(55.1, 70.4)	(3.6, 17.2)	(36.7, 52.3)	(53.3, 68.7)	(6.1, 16.1)	(36.6, 47.6)	(56.5, 67.3)
Active - Placebo									
Estimate (%)		27.9	51.0		33.9	50.5		30.9	50.7
95% CI		(17.4, 38.3)	(40.5, 61.5)		(23.3, 44.4)	(40.0, 60.9)		(23.5, 38.3)	(43.3, 58.1)
p-value		<.0001	<.0001		<.0001	<.0001			
200mg - 100mg									
Estimate (%)			23.0			16.5			19.8
95% CI			(12.3, 33.7)			(5.6, 27.4)			(12.1, 27.4)

Study B7451013

IGA response at Week 12

Table 16 Proportion of Subjects Achieving Investigator's Global Assessment (IGA) Response of 'Clear' or 'Almost Clear' and >=2 Points Improvement from Baseline at Week 12 - CMH (FAS, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD
N	77	155	155
n (%)	7 (9.1)	44 (28.4)	59 (38.1)
95% CI	(2.7, 15.5)	(21.3, 35.5)	(30.4, 45.7)
Active - Placebo [1]			
Estimate (%)		19.3	28.7
95% CI		(9.6, 29.0)	(18.6, 38.8)
Two-sided P-value [2]		0.0008	<.0001
200 mg QD - 100 mg QD [1]			

Table 16 Proportion of Subjects Achieving Investigator's Global Assessment (IGA) Response of 'Clear' or 'Almost Clear' and >=2 Points Improvement from Baseline at Week 12 - CMH (FAS, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD
Estimate (%)			9.7
95% CI			(-0.7, 20.0)

Full Analysis Set (FAS) was defined as all randomised subjects who received at least one dose of study medication.
Baseline was defined as the last measurement prior to first dosing (Day 1).
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; N = number of subjects in the analysis set with NRI at the specified visit; n (%) = number of subjects with response (percentage based on N); NRI = non-responder imputation.
[1] The estimate and confidence interval (CI) for difference were calculated based on the weighted average of difference for each randomisation stratum using the
normal approximation of binomial proportions. The confidence interval for the response rate was based on normal approximation (or the Clopper-Pearson exact method when there were no or if all were responders).
[2] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) method adjusted by randomisation strata (baseline disease severity and age category).

EASI ≥75% improvement from baseline (EASI-75) at Week 12

Table 17 Proportion of Subjects Achieving Eczema Area and Severity Index (EASI) Response >= 75% Improvement from Baseline at Week 12 - CMH (FAS, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD
N	77	155	154
n (%)	8 (10.4)	69 (44.5)	94 (61.0)
95% CI	(3.6, 17.2)	(36.7, 52.3)	(53.3, 68.7)
Active - Placebo [1]			
Estimate (%)		33.9	50.5
95% CI		(23.3, 44.4)	(40.0, 60.9)
Two-sided P-value [2]		<.0001	<.0001
200 mg QD - 100 mg QD [1]			
Estimate (%)			16.5
95% CI			(5.6, 27.4)

Full Analysis Set (FAS) was defined as all randomised subjects who received at least one dose of study medication.
Baseline was defined as the last measurement prior to first dosing (Day 1).
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; N = number of subjects in the analysis set with NRI at the specified visit; n (%) = number of subjects with response (percentage based on N); NRI = non-responder imputation.
[1] The estimate and confidence interval (CI) for difference were calculated based on the weighted average of difference for each randomisation stratum using the
normal approximation of binomial proportions. The confidence interval for the response rate was based on normal approximation (or the Clopper-Pearson exact method when there were no or if all were responders).
[2] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) method adjusted by randomisation strata (baseline disease severity and age category).

The key secondary efficacy endpoints were:

- Response based on ≥4 points improvement from baseline in the peak pruritus NRS (PP-NRS4) for severity at Weeks 2, 4, and 12. Pruritis is viewed as an important symptom of the disease and NRS-4 is viewed as a clinically meaningful response.
- Change from baseline in PSAAD at Week 12.

Study B7451012

Peak pruritus NRS4 response at Weeks 2,4 and 12

Table 18 PF-04965842 Protocol B7451012 Proportion of Subjects Achieving >=4 Points Improvement from Baseline in Numeric Rating Scale for Severity of Pruritus - CMH (FAS, NRI after Dropout + MI for Intermittent Missing)

		Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD
Week 2	N	74	147	147
	Estimate Response Rate (%)	2.7	20.4	45.6
	Difference from Placebo (Active - Placebo)			
	Estimate (%)		18.0	42.5
	95% Confidence Interval		(10.2, 25.8)	(33.6, 51.4)
	Two-sided p-value		0.0004	<.0001
	Difference between 200 mg QD - 100 mg QD			
	Estimate (%)			24.9
	95% Confidence Interval			(14.8, 35.0)
Week 4	Estimate Response Rate (%)	17.2	32.2	58.8
	Difference from Placebo (Active - Placebo)			
	Estimate (%)		15.0	41.1
	95% Confidence Interval		(1.9, 28.0)	(27.8, 54.4)
	Two-sided p-value		0.0251	<.0001
	Difference between 200 mg QD - 100 mg QD			
	Estimate (%)			26.5
	95% Confidence Interval			(13.7, 39.2)
Week 8	Estimate Response Rate (%)	14.4	34.3	59.9
	Difference from Placebo (Active - Placebo)			
	Estimate (%)		20.0	45.3
	95% Confidence Interval		(7.4, 32.7)	(32.7, 57.8)
	Two-sided p-value		0.0019	<.0001
	Difference between 200 mg QD - 100 mg QD			
	Estimate (%)			25.5
	95% Confidence Interval			(13.5, 37.6)
Week 12	Estimate Response Rate (%)	15.3	37.7	57.2
	Difference from Placebo (Active - Placebo)			
	Estimate (%)		22.5	41.7
	95% Confidence Interval		(10.3, 34.8)	(29.6, 53.9)
	Two-sided p-value		0.0003	<.0001
	Difference between 200 mg QD - 100 mg QD			
	Estimate (%)			19.3
	95% Confidence Interval			(7.3, 31.2)

Full Analysis Set (FAS) was defined as all randomised subjects who received at least one dose of study medication. Baseline was defined as the last measurement prior to first dosing (Day 1).
Each complete imputed data set was analyzed using the CMH risk difference method adjusting by randomisation strata, separately for each week. Results from multiply imputed data sets were combined using Rubin's rules to obtain treatment difference, 95% CI and p-value. Missing responses after permanent discontinuation were defined as non-responders. Any intermittent missing responses were imputed 500 times using random Bernoulli draws using a posterior probability of response at each visit. Posterior probabilities were estimated under a Bayesian framework from a logit-normal GLMM with treatment,
visit, treatment by visit interaction as fixed effects and a latent subject-level, zero mean, normally distributed random effect, with a logit link function.
At Week 2, there was no subject with intermittent missing data so no multiple imputations were performed.
CMH = Cochran-Mantel-Haenszel; N = Number of subjects available in the analysis set with baseline >= 4; NRI = Non-Responder Imputation; MI = Multiple Imputation; GLMM = Generalised Linear Mixed Model.

Change from baseline in PSAAD at Week 12

Table 19 PF-04965842 Protocol B7451012 Least Squares Mean of Change from Baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) at Week 12 - MMRM (FAS, OD)

		Placebo	PF-04965842 100MG QD	PF-04965842 200MG QD
Number of Subjects included in the Analysis Model:	N	68	137	138
Week 12	Least Squares Mean	-1.1	-2.2	-3.2
	95% Confidence Interval	(-1.7,-0.6)	(-2.6,-1.9)	(-3.6,-2.8)
	Difference from Placebo (Active - Placebo)			
	Least Squares Mean		-1.1	-2.1
	95% Confidence Interval		(-1.7,-0.4)	(-2.7,-1.4)
	Two-sided p-value		0.0010	<.0001
	Difference between 200 mg QD - 100 mg QD			
	Least Squares Mean			-1.0
	95% Confidence Interval			(-1.5,-0.5)

Full Analysis Set (FAS) was defined as all randomised subjects who received at least one dose of study medication.
Baseline was defined as the average of all values recorded between Day -6 and Day 1.
Weekly data were average values of daily observations over 7 days.
Mixed Model Repeated Measure (MMRM) contained fixed factors of treatment, week, treatment by week interaction, randomisation strata (baseline disease severity and age category), baseline value and an unstructured covariance matrix.
OD = Observed Data.

Study B7451013

Peak pruritus NRS4 response at Weeks 2,4 and 12

Table 20 Proportion of Subjects with >=4 Points at Baseline and Achieving >=4 Points Improvement from Baseline in Numeric Rating Scale for Severity of Pruritus - CMH (FAS, NRI after Dropout + MI for Intermittent Missing)

		Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD
Week 2	N	76	156	153
	Estimated Response Rate (%)	3.9	23.1	35.3
	95% CI	(0.0, 8.3)	(16.5, 29.7)	(27.7, 42.9)
	Active - Placebo			
	Estimate (%)		19.2	31.2
	95% CI		(11.0, 27.4)	(22.3, 40.2)
	Two-sided P-value		0.0002	<.0001
	200 mg QD - 100 mg QD			
	Estimate (%)			12.1
	95% CI			(2.2, 22.1)
Week 4	N	76	156	153
	Estimated Response Rate (%)	4.0	33.4	52.8
	95% CI	(0.0, 8.4)	(25.8, 41.0)	(44.7, 60.8)
	Active - Placebo			
	Estimate (%)		29.5	48.8
	95% CI		(20.5, 38.4)	(39.5, 58.2)
	Two-sided P-value		<.0001	<.0001
	200 mg QD - 100 mg QD			
	Estimate (%)			19.4
	95% CI			(8.4, 30.4)

Table 20 Proportion of Subjects with >=4 Points at Baseline and Achieving >=4 Points Improvement from Baseline in Numeric Rating Scale for Severity of Pruritus - CMH (FAS, NRI after Dropout + MI for Intermittent Missing)

		Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD
Week 8	N	76	156	153
	Estimated Response Rate (%)	12.0	40.4	54.4
	95% CI	(4.6, 19.4)	(32.6, 48.2)	(46.4, 62.4)
	Active - Placebo			
	Estimate (%)		28.5	42.4
	95% CI		(17.8, 39.3)	(31.4, 53.4)
	Two-sided P-value		<.0001	<.0001
	200 mg QD - 100 mg QD			
	Estimate (%)			14.0
	95% CI			(2.9, 25.1)
Week 12	N	76	156	153
	Estimated Response Rate (%)	11.5	45.2	55.3
	95% CI	(4.1, 19.0)	(37.1, 53.3)	(47.2, 63.5)
	Active - Placebo			
	Estimate (%)		33.7	43.9
	95% CI		(22.8, 44.7)	(32.9, 55.0)
	Two-sided P-value		<.0001	<.0001
	200 mg QD - 100 mg QD			
	Estimate (%)			10.2
	95% CI			(-1.1, 21.5)

Full Analysis Set (FAS) was defined as all randomised subjects who received at least one dose of study medication. Baseline was defined as the measurement collected on or prior to Day 1.
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal. Any other intermittent missing value was handled using multiple imputation.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; GLMM = generalised linear mixed model; MI = multiple imputation; N = number of subjects in the analysis set with NRI + MI at the
specified visit with baseline >= 4; NRI = non-responder imputation.
At Week 2, no multiple imputations were performed because there were <= 5 subjects with missing responses in all treatment groups.

Change from baseline in PSAAD at Week 12

Table 21 PF-04965842 Protocol B7451013 Least Squares Mean of Change from Baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) at Week 12 - MMRM (FAS, OD)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD
N	77	156	155
LSM	-0.8	-2.4	-3.0
95% CI	(-1.3, -0.3)	(-2.8, -2.1)	(-3.3, -2.7)
Active - Placebo			
LSM		-1.7	-2.2
95% CI		(-2.3, -1.1)	(-2.8, -1.6)
P-value		<.0001	<.0001
200 mg QD - 100 mg QD			
LSM			-0.6
95% CI			(-1.0, -0.1)

Full Analysis Set (FAS) was defined as all randomised subjects who received at least one dose of study medication.
Baseline was defined as the average of all values recorded between Day -6 and Day 1.
Weekly data were average values of daily observations over 7 days.
CI = confidence interval; LSM = least squares mean; N = number of subjects included in the analysis model; OD = observed data.
Mixed Model Repeated Measure (MMRM) contained fixed factors of treatment, visit, treatment by visit interaction, randomisation strata (baseline disease severity and age category), baseline value and an unstructured covariance matrix.

B7451029: A Phase 3 randomized, double-blind, double-dummy, placebo-controlled, parallel group, multi-centre study investigating the efficacy and safety of abrocitinib and dupilumab in comparison with placebo in adult subjects on background topical therapy, with moderate to severe atopic dermatitis.

Methods

Study Participants

Main inclusion criteria

1. Male or female subjects aged 18 years or older at the time of informed consent.
2. Met all the following AD criteria:

- Clinical diagnosis of chronic AD (also known as atopic eczema) for at least 1 year prior to Day 1 and had confirmed AD at the screening and baseline visits according to Hanifin and Rajka criteria for AD.
- Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with medicated topical therapy for AD for at least 4 weeks, or who had required systemic therapies for control of their disease.
- Moderate to severe AD (affected BSA ≥10%, IGA≥3, EASI≥16, and Pruritus NRS severity score≥4 on the day of the baseline visit).

3. During the last 7 days prior to Day 1, for the treatment of AD, the subject must have used only non-medicated topical therapy (i.e., emollient) without other active ingredients indicated to treat AD, or other additives which could affect AD (e.g., hyaluronic acid, urea, ceramide or filaggrin degradation products) at least twice daily, with response to treatment remaining inadequate at baseline. The subject also was willing and able to comply with standardised background topical therapy, as per protocol guidelines throughout the remainder of the study.
4. Must have agreed to avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources during the study.
5. If receiving concomitant medications for any reason other than AD, must have been on a stable regimen, defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever was longer) prior to Day 1 and through the duration of the study.

Main exclusion criteria

1. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behaviour or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
2. Any psychiatric condition including recent or active suicidal ideation or behaviour that met any of the following criteria:

    - Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the Columbia Suicide Severity Rating Scale (C-SSRS);

- Previous history of suicidal behaviours in the past 5years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behaviour items of the C-SSRS;
- Any lifetime history of serious or recurrent suicidal behaviour;
- Clinically significant depression: Patient Health Questionnaire –8 items (PHQ-8) total score ≥15;
- The presence of any current major psychiatric disorder that was not explicitly permitted in the inclusion/exclusion criteria;
- In the opinion of the investigator or Pfizer (or designee) exclusion was required.

3. A current or past medical history of conditions associated with thrombocytopenia, coagulopathy or platelet dysfunction.
4. Receiving anti-coagulants or medications known to cause thrombocytopenia, (unless considered safe to stop and washout for the duration of the study).
5. Had active forms of other inflammatory skin diseases, i.e., not AD or had evidence of skin conditions (e.g., psoriasis, seborrheic dermatitis, Lupus) at the time of Day 1 that would interfere with evaluation of AD or response to treatment.
6. Vaccinated or exposed to a live or attenuated vaccine within the 6 weeks prior to the first dose of investigational product or was expected to be vaccinated or to have household exposure to these vaccines during treatment or during the 6 weeks following discontinuation of investigational product.
7. Subjects who had received prior treatment with any systemic JAK inhibitors. Prior treatment with topical JAK inhibitors was not exclusionary.
8. Previous treatment with dupilumab and/or a history of hypersensitivity, intolerance, AE, or allergic reaction associated with prior exposure to dupilumab's excipients.

Treatments

The study design of the study B7451029 involved two doses of abrocitinib 100 mg and 200 mg dosed similarly as in the monotherapy studies B7451012 and B7451013. Moreover, one group received dupilumab dosed according to approved product information, and two placebo groups that received both a placebo injection and oral placebo. The two abrocitinib groups received placebo injections, and the dupilumab group got oral placebo.

Topical Corticosteroids (TCS) should be applied once daily to areas with active lesions, starting on baseline and throughout the study.

The treatment duration was 20 weeks. The primary efficacy assessment took place at week 12, and key secondary efficacy assessments at week 2 and week 16. At week 20, eligible subjects entered the B7451015 long-term extension study. Efficacy and safety endpoints were assessed throughout the entire study.

The study estimated the relative efficacy of both doses of abrocitinib and of dupilumab. The comparison of abrocitinib with dulilumab was based on their ability to reduce itch, measured by the severity of PNRS-4 from baseline at week 2. Moreover, the efficacy of abrocitnib combined with background topical treatment with moisturizer and medicated topical treatment was assessed.

Objectives

The primary objective of study B7451029 was to assess the efficacy of 100mg and 200mg once daily (QD) of abrocitinib versus placebo in adult subjects on background topical therapy with moderate to severe AD.

Secondary objectives were:

- To evaluate the efficacy of abrocitinib versus dupilumab in terms of attaining a clinically significant improvement in the severity of pruritus for adult subjects on background topical therapy with moderate to severe AD.
- To estimate the difference in efficacy measures between two doses of abrocitinib and dupilumab for adult subjects on background topical therapy with moderate to severe AD.
- To estimate the effect of abrocitinib on additional efficacy endpoints and patient-reported outcomes over time in adult subjects on background topical therapy with moderate to severe AD.
- To compare the safety and tolerability of 100 mg and 200mg QD of abrocitinib and dupilumab versus placebo in adult subjects on background topical therapy with moderate to severe AD.
- To estimate the safety and tolerability of the two doses of abrocitinib versus dupilumab, for adult subjects on background topical therapy with moderate to severe AD.

Outcomes/endpoints

The co-primary efficacy endpoints were:

- Response based on achieving the Investigator's Global Assessment (IGA) of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline (pre-dose Day1) of ≥2 points at week 12.
- Response based on achieving the Eczema Area and Severity Index (EASI)-75 (≥75% improvement from baseline) at week 12.

The key secondary efficacy endpoints were:

- Response based on achieving at least 4 points improvement in the severity of Pruritus Numerical Rating Scale (NRS) from baseline at week 2.
- Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16.
- Response based on achieving EASI-75 (≥75% improvement from baseline) at week 16.

Furthermore, several other secondary efficacy endpoints and Patient-Reported Outcome (PRO) endpoint were investigated.

Randomisation and blinding (masking)

Eligible subjects were randomised at baseline/Day 1 in a 4:4:4:1:1 ratio to 100 mg or 200 mg of abrocitinib, dupilumab, or one of two sequences of placebo for 16 weeks followed by either 100 mg or 200 mg of abrocitinib QD. For the purpose of the primary (final, week 16) analysis the two placebo sequences were combined. Treatment assignment was through a computer-generated randomisation schedule and Interactive Response Technology (IRT). Randomisation was administered using centre-based randomly permuted blocks with the centre-based randomisation chosen due to drug management considerations. This was a double-blind study with investigators, subjects, and the sponsor study team blinded as to treatment group. Using double-dummy technique, subjects were to receive both injectable and oral investigational product. Dupilumab, 300 mg/2mL and dupilumab placebo were provided as prefilled syringes for subcutaneous injection. Due to viscosity differences between dupilumab and the matched placebo, the administrator/trainer was to be treated as if unblind

and was kept from all other study activities. Blinded abrocitinib, 100 mg tablets, and its matched placebo tablets were provided in separate bottles. Subjects were dispensed two bottles of tablets and were to be given clear dosing instructions to take one tablet from each bottle, once daily.

Statistical methods

The final analysis for the co-primary and key secondary endpoints was performed after the last subject in the study had had the opportunity to complete the week 16 visit. At the time of week 16 analysis, access to the database containing individual treatment group assignments was to be restricted to the sponsor study team. Treatment duration was to be 20 weeks with the blinding hence maintained throughout; an end of study analysis was to be reported in a supplemental CSR. The study B7451029 CSR presents the results of the 16-week efficacy and safety data that include all primary and secondary efficacy analyses based on database release on 05 February 2020. The corresponding SAP (version) was dated 23 January 2020. No formal interim analysis was planned or has been performed.

The primary analysis population for efficacy data was the Full Analysis Set (FAS) defined as all randomised subjects who received at least one dose of investigational product.

Analysis of primary endpoints

The co-primary endpoints were analysed using the Cochran-Mantel-Haenszel test adjusted by baseline disease severity group (moderate and severe). The difference between each active group and the placebo group in the proportion of subjects achieving IGA response (similarly for EASI-75) along with its 95% confidence interval (using the normal approximation for the difference in binomial proportions) were reported. If a subject withdrew from the study, then this subject was counted as non-responder for endpoints after withdrawal.

Analysis of secondary endpoints

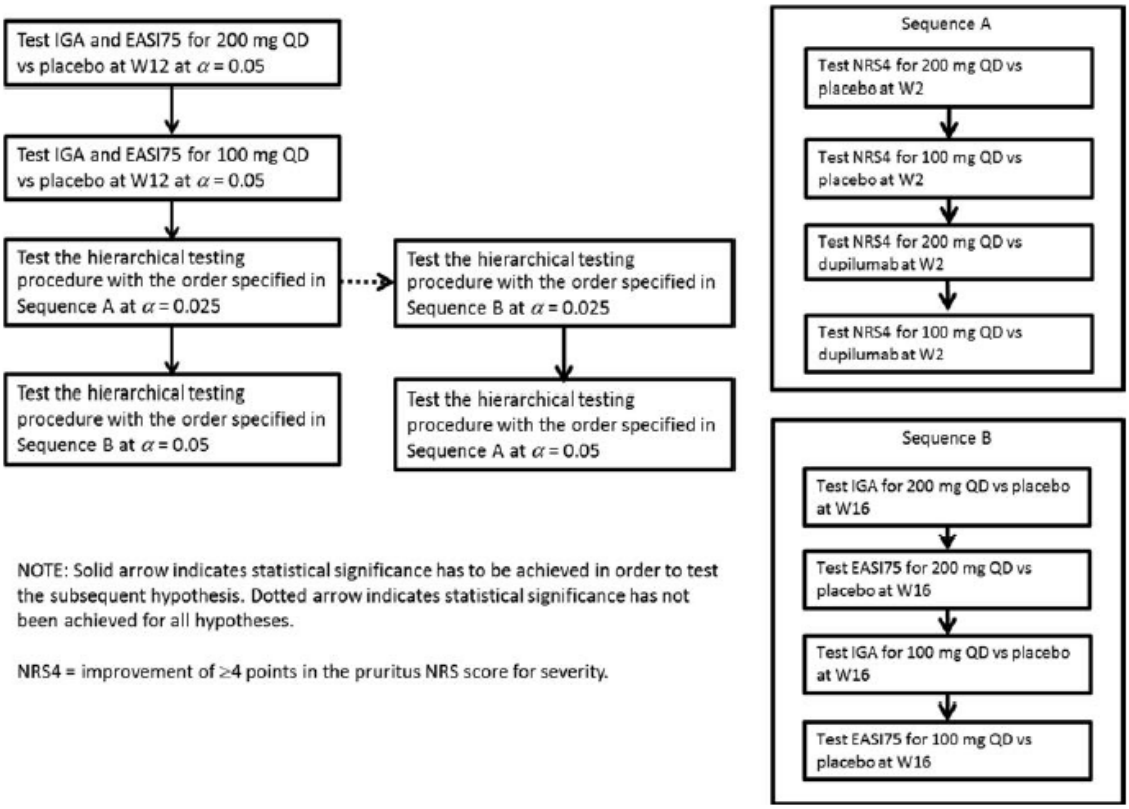
The key secondary endpoints were analysed using the same method as for the co-primary endpoints which also applied to any other binary endpoint.

For continuous endpoints, a mixed-effect model with repeated measures (MMRM) was used. The MMRM model included factors (fixed effects) for treatment group, disease severity group, visit, treatment-by-visit interaction, and relevant baseline value. Within the MMRM framework, the treatment difference was tested at the pre-specified primary time point, week 12, as well as at the other time points by time point-specific contrasts from the MMRM model. An unstructured covariance matrix was assumed for the model errors. Compound symmetry covariance matrix was to be used if the model with unstructured covariance did not converge. At each visit, estimates of least square mean (LSM) values and the LSM differences between treatment groups were derived from the model as was corresponding p-values and 95% confidence intervals. In the model all patients with baseline data were used for estimating baseline covariate effects and adjusting LS means.

Multiple testing procedure

To control the familywise Type 1 error at 5%, a sequential Bonferroni-based iterative multiple testing procedure was used for assessing each of the two abrocitinib doses versus placebo on the two primary and the three key secondary endpoints, see Figure 14 below.

Figure 14 Schematic for Multiple Testing Procedure



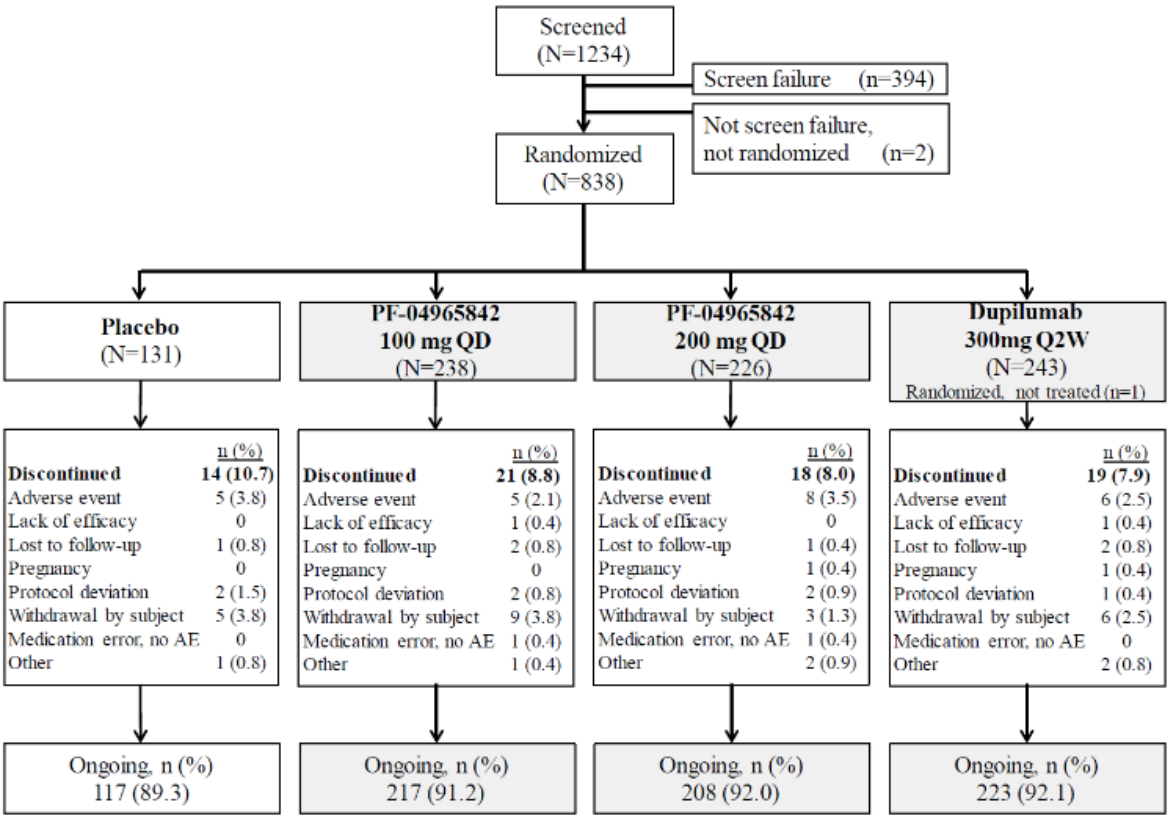
In order to be more rigorous regarding onset of relief of severity of pruritus, a step-down approach with the NRS4 endpoint from Week 2 *to earlier time points* was utilised as an additional family of hypothesis tests once statistical significance had been demonstrated at week 2 (rejection of each hypothesis of no difference in NRS4 at week 2 within Sequence A). Further hypotheses of no difference in NRS4 was then to be assessed along four sequences (abrocitinib 200 mg and 100 mg versus placebo and dupilumab, respectively). All hypotheses were to be assessed at a 5% significance level and concerned comparisons at Day 15, Day 14, Day, 13, Day 12, …, Day 2, in that order.

Results

Participant flow

The subject evaluation groups and patient disposition in the study B7451029 can be seen in the figure below.

Figure 15 Subject Evaluation Groups and Disposition (B7451029)



Baseline data

The demographic and baseline disease characteristics of subjects in study B7451029 can be seen in the tables below.

Table 22 Demographic characteristics – Safety Analysis Set

	Placebo (N=131)	PF-04965842 100mg QD (N=238)	PF-04965842 200mg QD (N=226)	Dupilumab 300mg Q2W (N=242)	Total (N=837)
18≤Age (Years)<65, n (%)	121 (92.4)	224 (94.1)	211 (93.4)	227 (93.8)	783 (93.5)
Age (Years)≥65, n (%)	10 (7.6)	14 (5.9)	15 (6.6)	15 (6.2)	54 (6.5)
Age (Years), Median (Q1, Q3)	34.0 (25.0, 46.0)	33.0 (25.0, 46.0)	36.0 (28.0, 48.0)	34.0 (25.0, 47.0)	34.0 (26.0, 47.0)
Male, n (%)	77 (58.8)	120 (50.4)	104 (46.0)	108 (44.6)	409 (48.9)
Female, n (%)	54 (41.2)	118 (49.6)	122 (54.0)	134 (55.4)	428 (51.1)
White, n (%)	87 (66.4)	182 (76.5)	161 (71.2)	176 (72.7)	606 (72.4)
Black or African American, n (%)	6 (4.6)	6 (2.5)	9 (4.0)	14 (5.8)	35 (4.2)
Asian, n (%)	31 (23.7)	48 (20.2)	53 (23.5)	46 (19.0)	178 (21.3)
American Indian or Alaska Native, n (%)	2 (1.5)	1 (0.4)	0	2 (0.8)	5 (0.6)
Native Hawaiian or Other Pacific Islander, n (%)	1 (0.8)	0	1 (0.4)	0	2 (0.2)
Multiracial, n (%)	1 (0.8)	1 (0.4)	1 (0.4)	2 (0.8)	5 (0.6)
Hispanic or Latino, n (%)	16 (12.2)	35 (14.7)	36 (15.9)	37 (15.3)	124 (14.8)
Not Hispanic or Latino, n (%)	113 (86.3)	200 (84.0)	187 (82.7)	201 (83.1)	701 (83.8)
Height (cm), Median (Q1, Q3)	170.2 (164.0, 177.9)	170.0 (162.9, 176.1)	168.0 (161.0, 176.0)	167.6 (162.2, 174.5)	168.6 (162.2, 176.0)
Weight (kg), Median (Q1, Q3)	74.9 (63.0, 84.3)	73.0 (64.0, 83.2)	72.3 (62.7, 84.0)	72.8 (61.1, 89.0)	73.0 (62.7, 84.7)
BMI (kg/m^2), Median (Q1, Q3)	25.3 (21.9, 29.1)	25.1 (22.5, 29.0)	25.6 (22.9, 29.1)	25.6 (22.2, 30.5)	25.4 (22.4, 29.3)

One subject (13599002) erroneously reported a height of 17701 cm and was excluded from summary calculations for height and BMI.
BMI: Body Mass Index (kg/m^2) = weight (kg) / (0.01 × [height (cm)])^2; N = total sample size; n (%) = number of subjects who met criteria (percentage based on N).
PFIZER CONFIDENTIAL SDTM Creation: 01FEB2020 (21:17) Source Data: adsl Output File: ./nda1_cdisc/B7451029_CSR/adsl_s001_imm Date of Generation: 17FEB2020 (07:44)
Table 14.1.2I is for Pfizer internal use.

Table 23 Disease characteristics – Safety Analysis Set

	Placebo (N=131)	PF-04965842 100mg QD (N=238)	PF-04965842 200mg QD (N=226)	Dupilumab 300mg Q2W (N=242)	Total (N=837)
Disease Duration (Years), Median (Q1, Q3)	21.3 (9.6, 30.4)	21.5 (8.6, 30.6)	23.3 (8.6, 34.5)	22.5 (9.6, 33.2)	21.8 (9.5, 32.5)
Investigator's Global Assessment (IGA), %Moderate/Severe	67.2/32.8	64.3/35.7	61.1/38.9	66.9/33.1	64.6/35.4
Eczema Area and Severity Index (EASI), Median (Q1, Q3)	26.0 (20.8, 41.4)	25.3 (19.2, 38.4)	29.8 (21.6, 39.4)	26.8 (20.3, 37.6)	27.2 (20.2, 38.8)
Body Surface Area (BSA) (%), Median (Q1, Q3)	42.9 (30.2, 69.0)	44.3 (28.3, 65.5)	48.1 (32.1, 67.1)	44.5 (28.0, 62.0)	45.6 (29.8, 65.9)
Pruritus Numeric Rating Scale (NRS) (Severity), Median (Q1, Q3)	7.0 (6.0, 8.0)	7.0 (6.0, 8.0)	8.0 (7.0, 9.0)	7.0 (6.0, 8.0)	7.0 (6.0, 8.0)
Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD), Median (Q1, Q3)	5.2 (3.4, 6.9)	5.2 (3.8, 6.8)	5.6 (4.2, 7.0)	5.2 (3.9, 6.6)	5.4 (3.8, 6.8)
Scoring Atopic Dermatitis (SCORAD), Median (Q1, Q3)	67.1 (58.7, 76.6)	66.2 (56.4, 77.2)	68.2 (60.6, 77.4)	67.8 (59.3, 74.7)	67.3 (58.8, 76.5)
Dermatology Life Quality Index (DLQI), Median (Q1, Q3)	15.0 (10.0, 20.0)	15.0 (10.0, 20.0)	16.0 (12.0, 21.0)	15.0 (11.0, 21.0)	15.0 (11.0, 21.0)
Patient Oriented Eczema Measure (POEM), Median (Q1, Q3)	21.0 (16.0, 26.0)	21.0 (18.0, 25.0)	22.0 (18.0, 26.0)	22.0 (18.0, 26.0)	22.0 (18.0, 26.0)
Patient Global Assessment (PtGA), %Moderate/Severe	51.9/44.3	47.5/47.1	42.5/54.4	48.3/48.3	47.1/49.0

For IGA, EASI, BSA, NRS and SCORAD, baseline was defined as the last measurement prior to first dosing (Day 1). For PSAAD score, baseline was defined as the average of all values recorded between Day -6 and Day 1. For other endpoints, baseline was defined as the measurement collected on or prior to Day 1.
Subject handprints were used to determine the extent (%) of skin afflicted with atopic dermatitis. Body regions assessed did not include the scalp, palms and soles.
N = total sample size
Source Data: admh, adad, adda, adea, adnr, adpu, adli, adpm and adga
PFIZER CONFIDENTIAL SDTM Creation: 01FEB2020 (21:17) Output File: ./nda1_cdisc/B7451029_CSR/oth_bas_imm Date of Generation: 06FEB2020 (01:19)
Table 14.1.3.3I is for Pfizer internal use.

Numbers analysed

Study B7451029

	Placebo (N=131)	PF-04965842 100mg QD (N=238)	PF-04965842 200mg QD (N=226)	Dupilumab 300mg Q2W (N=243)
	n (%)	n (%)	n (%)	n (%)
Screened: 1234				
Screen Failure: 394				
Not Screen Failure but Not Randomized: 2				
Randomized	131 (100.0)	238 (100.0)	226 (100.0)	243 (100.0)
Treated	131 (100.0)	238 (100.0)	226 (100.0)	242 (99.6)
Not Treated	0	0	0	1 (0.4)
Analysis for Safety				
Safety Analysis Set	131 (100.0)	238 (100.0)	226 (100.0)	242 (99.6)
Analysis for Efficacy				
Full Analysis Set (FAS)	131 (100.0)	238 (100.0)	226 (100.0)	242 (99.6)
Per Protocol Analysis Set (PPAS)	93 (71.0)	174 (73.1)	161 (71.2)	172 (70.8)

Safety Analysis Set was defined as those subjects who received at least one dose of study medication.
Full Analysis Set (FAS) was defined as all randomized subjects who received at least one dose of study medication.
Per Protocol Analysis Set (PPAS) was defined as a subset of FAS who had no major protocol violations.
PFIZER CONFIDENTIAL SDTM Creation: 01FEB2020 (21:17) Source Data: adsl Output File: ./nda1_cdisc/B7451029_CSR/adsl_s002 Date of Generation: 06FEB2020 (00:12)
Table 14.1.1.1 is for Pfizer internal use.

Outcomes and estimation

The co-primary efficacy endpoints were:

- Response based on the IGA score of clear (0) or almost clear (1); and a reduction from baseline of ≥2 points at week 12.
- Response based on the EASI ≥75% improvement from baseline (EASI-75) at week 12.

IGA response at Week 12

Table 24 PF-04965842 Protocol B7451029 Proportion of Subjects Achieving IGA Response of 'Clear' or 'Almost Clear' and >=2 Points Improvement from Baseline at Week 12 - CMH (FAS, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD	Dupilumab 300mg Q2W
N	129	235	219	241
n (%)	18 (14.0)	86 (36.6)	106 (48.4)	88 (36.5)
95% CI	(8.0, 19.9)	(30.4, 42.8)	(41.8, 55.0)	(30.4, 42.6)
Active - Placebo [1]				
Estimate (%)		23.1	34.8	22.5
95% CI		(14.7, 31.4)	(26.1, 43.5)	(14.2, 30.9)
Two-sided P-value [2]		<.0001	<.0001	
PF-04965842 - Dupilumab [1]				
Estimate (%)		0.5	12.4	
95% CI		(-8.0, 9.1)	(3.5, 21.3)	
200 mg QD - 100 mg QD [1]				
Estimate (%)			12.1	

Table 24 PF-04965842 Protocol B7451029 Proportion of Subjects Achieving IGA Response of 'Clear' or 'Almost Clear' and >=2 Points Improvement from Baseline at Week 12 - CMH (FAS, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD	Dupilumab 300mg Q2W
95% CI			(3.2, 21.1)	

Full Analysis Set (FAS) was defined as all randomised subjects who received at least one dose of study medication.
Baseline was defined as the last measurement prior to first dosing (Day 1).
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; IGA = investigator's global assessment; N = number of subjects in the analysis set with NRI at the specified visit; n (%) = number of subjects with response(percentage based on N); NRI = non-responder imputation.
[1] The estimate and confidence interval (CI) for difference were calculated based on the weighted average of difference by disease severity group using the normal approximation of binomial proportions. CI for the response rate was based on normal approximation (or the Clopper-Pearson exact method when there were 0 or 100% responders).
[2] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) method adjusted by baseline disease severity.

EASI ≥75% improvement from baseline (EASI-75) at Week 12

Table 25 PF-04965842 Protocol B7451029 Proportion of Subjects Achieving EASI Response >= 75% Improvement from Baseline at Week 12 - CMH (FAS, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD	Dupilumab 300mg Q2W
N	129	235	219	241
n (%)	35 (27.1)	138 (58.7)	154 (70.3)	140 (58.1)
95% CI	(19.5, 34.8)	(52.4, 65.0)	(64.3, 76.4)	(51.9, 64.3)
Active - Placebo [1]				
Estimate (%)		31.9	43.2	30.9
95% CI		(22.2, 41.6)	(33.7, 52.7)	(21.2, 40.6)
Two-sided P-value [2]		<.0001	<.0001	
PF-04965842 - Dupilumab [1]				
Estimate (%)		0.8	12.0	
95% CI		(-8.1, 9.6)	(3.3, 20.7)	
200 mg QD - 100 mg QD [1]				
Estimate (%)			11.5	
95% CI			(2.8, 20.2)	

Full Analysis Set (FAS) was defined as all randomised subjects who received at least one dose of study medication.
Baseline was defined as the last measurement prior to first dosing (Day 1).
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EASI = eczema area and severity index; N = number of subjects in the analysis set with NRI at the specified visit; n (%) = number of subjects with response (percentage based on N); NRI = non-responder imputation.
[1] The estimate and confidence interval (CI) for difference were calculated based on the weighted average of difference by disease severity group using the normal approximation of binomial proportions. CI for the response rate was based on normal approximation (or the Clopper-Pearson exact method when there were 0 or 100% responders).
[2] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) method adjusted by baseline disease severity.

The key secondary efficacy endpoints were:

- Response based on achieving at least 4 points improvement in the severity of Pruritus Numerical Rating Scale (NRS) from baseline at week 2.
- Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16.
- Response based on achieving EASI-75 (≥75% improvement from baseline) at week 16.

Peak pruritus NRS4 response at Week 2

Table 26 PF-04965842 Protocol B7451029 Proportion of Subjects Achieving Pruritus NRS Severity Response >=4 Points Improvement from Baseline at Week 2 - CMH (FAS with Baseline >=4, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD	Dupilumab 300mg Q2W
N	130	236	226	239
n (%)	18 (13.8)	75 (31.8)	111 (49.1)	63 (26.4)
95% CI	(7.9, 19.8)	(25.8, 37.7)	(42.6, 55.6)	(20.8, 31.9)
Active - Placebo [1]				
Estimate (%)		17.9	34.9	12.5
95% CI		(9.5, 26.3)	(26.0, 43.7)	(4.4, 20.7)
Two-sided P-value [2]		0.0002	<.0001	
PF-04965842 - Dupilumab [1]				
Estimate (%)		5.2	22.1	
95% CI		(-2.9, 13.4)	(13.5, 30.7)	
Two-sided P-value [2]		0.2084	<.0001	
200 mg QD - 100 mg QD [1]				
Estimate (%)			17.2	
95% CI			(8.4, 26.0)	

Full Analysis Set (FAS) was defined as all randomised subjects who received at least one dose of study medication.
Baseline was defined as the last measurement prior to first dosing (Day 1).
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; N = number of subjects in the analysis set with NRI at the specified visit; n (%) = number of subjects with response(percentage based on N); NRI = non-responder imputation; NRS = numeric rating scale.
[1] The estimate and confidence interval (CI) for difference were calculated based on the weighted average of difference by disease severity group using the normal approximation of binomial proportions. CI for the response rate was based on normal approximation (or the Clopper-Pearson exact method when there were 0 or 100% responders).
[2] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) method adjusted by baseline disease severity.

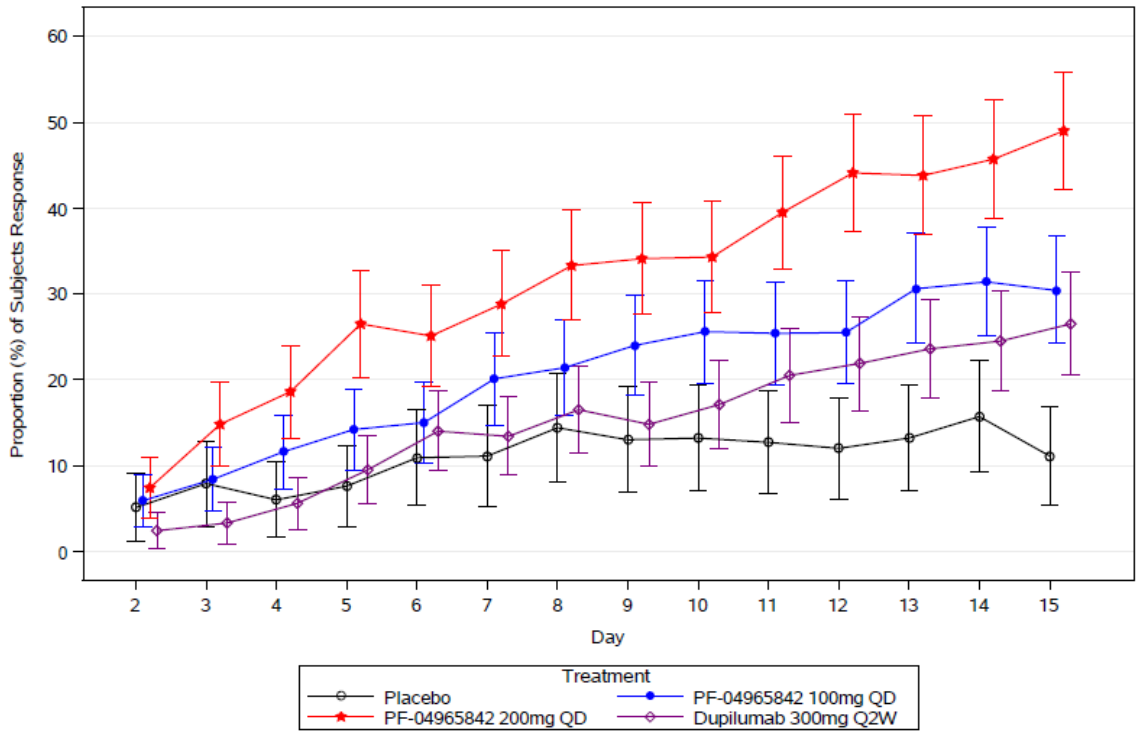
Peak pruritus NRS4 response at week 12 and week 16 are also presented below.

Table 27 Efficacy results of abrocitinib in combination with topical therapy at Week 12 and Week 16

	COMPARE[b]							
	Week 12				Week 16			
	Abrocitinib + topicals		PBO + topicals N=131	DUP + topicals N=243	Abrocitinib + topicals		PBO + topicals N=131	DUP + topicals N=243
	200 mg QD N=226	100 mg QD N=238			200 mg QD N=226	100 mg QD N=238		
	% Responders (95% CI)							
PP-NRS4[a]	63.1 (56.7, 69.6)	47.5 (40.9, 54.1)	28.9 (20.8, 37.0)	54.5 (47.9, 61.0)	62.8 (55.6, 70.0)	47.0 (39.5, 54.6)	28.7 (19.6, 37.9)	57.1 (50.1, 64.2)

Abbreviations: CI=confidence interval; DUP=Dupilumab; N=number of patients randomised; PBO=placebo; PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily.
a. PP-NRS4 responders were patients with ≥ 4-point improvement in PP-NRS from baseline.
b. Abrocitinib used in combination with topical therapy.

Figure 16 Proportion of Subjects Achieving ≥4 Points Improvement from Baseline in Pruritus NRS Severity at Days 2 – 15 – CMH (FAS with Baseline >=4, NRI) B7450129



Baseline was defined as the last measurement prior to first dosing (Day 1).
Full Analysis Set (FAS) was defined as all randomized subjects who received at least one dose of study medication.
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
Vertical line represented 95% confidence interval
NRI = non-responder imputation; NRS = numeric rating scale.
PFIZER CONFIDENTIAL SDTM Creation: 01FEB2020 (21:43) Source Data: adnr Output File: ./ndal_cdisc/B7451029_CSR/adnr_f201_3 Date of Generation: 06FEB2020 (00:39)

IGA response of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16

Table 28 PF-04965842 Protocol B7451029 Proportion of Subjects Achieving IGA Response of 'Clear' or 'Almost Clear' and >=2 Points Improvement from Baseline at Week 16 - CMH (FAS, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD	Dupilumab 300mg Q2W
N	124	230	221	232
n (%)	16 (12.9)	80 (34.8)	105 (47.5)	90 (38.8)
95% CI	(7.0, 18.8)	(28.6, 40.9)	(40.9, 54.1)	(32.5, 45.1)
Active - Placebo [1]				
Estimate (%)		22.1	35.0	25.6
95% CI		(13.7, 30.5)	(26.3, 43.7)	(17.1, 34.1)
Two-sided P-value [2]		<.0001	<.0001	
PF-04965842 - Dupilumab [1]				
Estimate (%)		-3.5	9.4	
95% CI		(-12.2, 5.2)	(0.4, 18.5)	
200 mg QD - 100 mg QD [1]				
Estimate (%)			13.1	
95% CI			(4.2, 22.1)	

Full Analysis Set (FAS) was defined as all randomised subjects who received at least one dose of study medication.
Baseline was defined as the last measurement prior to first dosing (Day 1).
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; IGA = investigator's global assessment; N = number of subjects in the analysis set with NRI at the specified visit; n (%) = number of subjects with response(percentage based on N); NRI = non-responder imputation.
[1] The estimate and confidence interval (CI) for difference were calculated based on the weighted average of difference by disease severity group using the normal approximation of binomial proportions. CI for the response rate was based on normal approximation (or the Clopper-Pearson exact method when there were 0 or 100% responders).
[2] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) method adjusted by baseline disease severity.

EASI-75 (≥75% improvement from baseline) response at Week 16.

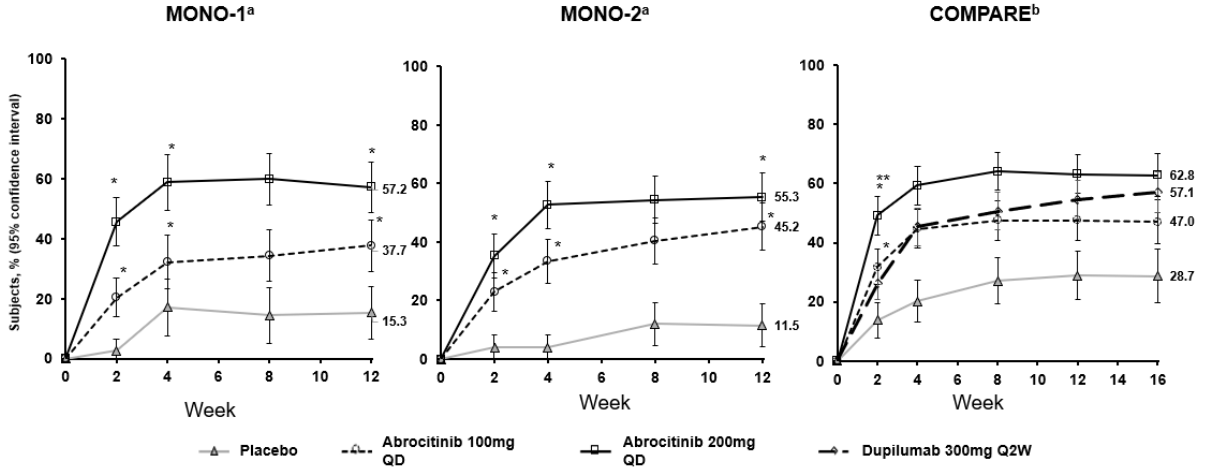
Table 29 PF-04965842 Protocol B7451029 Proportion of Subjects Achieving EASI Response >= 75% Improvement from Baseline at Week 16 - CMH (FAS, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD	Dupilumab 300mg Q2W
N	124	229	221	232
n (%)	38 (30.6)	138 (60.3)	157 (71.0)	152 (65.5)
95% CI	(22.5, 38.8)	(53.9, 66.6)	(65.1, 77.0)	(59.4, 71.6)
Active - Placebo [1]				
Estimate (%)		29.7	40.4	34.7
95% CI		(19.5, 39.9)	(30.4, 50.4)	(24.6, 44.8)
Two-sided P-value [2]		<.0001	<.0001	
PF-04965842 - Dupilumab [1]				
Estimate (%)		-5.1	5.5	
95% CI		(-13.9, 3.7)	(-3.1, 14.1)	
200 mg QD - 100 mg QD [1]				
Estimate (%)			10.7	
95% CI			(2.0, 19.4)	

Full Analysis Set (FAS) was defined as all randomised subjects who received at least one dose of study medication.
Baseline was defined as the last measurement prior to first dosing (Day 1).
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EASI = eczema area and severity index; N = number of subjects in the analysis set with NRI at the specified visit; n (%) = number of subjects with response (percentage based on N); NRI = non-responder imputation.
[1] The estimate and confidence interval (CI) for difference were calculated based on the weighted average of difference by disease severity group using the normal approximation of binomial proportions. CI for the response rate was based on normal approximation (or the Clopper-Pearson exact method when there were 0 or 100% responders).
[2] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) method adjusted by baseline disease severity.

The proportion of patients who achieved PP-NRS4 over time in studies MONO-1, MONO-2 and COMPARE are shown below.

Figure 17. Proportion of patients who achieved PP-NRS4 over time in MONO-1 (B7451012), MONO-2 (B7451013) and COMPARE (B7451029)



Abbreviations: PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily; Q2W=every 2 weeks.
PP-NRS4 responders were patients with ≥ 4-point improvement in PP-NRS from baseline.
a. Abrocitinib used as monotherapy.
b. Abrocitinib used in combination with medicated topical therapy.
* Statistically significant with adjustment for multiplicity versus placebo.
** Statistically significant with adjustment for multiplicity versus dupilumab.

Although not corrected for multiplicity, in all phase 3 pivotal studies, abrocitinib significantly improved patient-reported outcomes, including itch, sleep, AD symptoms and symptoms of anxiety and depression at week 12 compared to placebo, as shown below.

Table 30 Patient-reported outcomes results of abrocitinib monotherapy and in combination with topical therapy at Week 12

	Monotherapy						Combination therapy		
	MONO-1			MONO-2			COMPARE		
	200 mg QD	100 mg QD	PBO	200 mg QD	100 mg QD	PBO	200 mg QD + topicals	100 mg QD + topicals	PBO + topicals
N	**154**	**156**	**77**	**155**	**158**	**78**	**226**	**238**	**131**
SCORAD Sleep VAS, change from baseline (95% CI)	-3.7* (-4.2, -3.3)	-2.9* (-3.4, -2.5)	-1.6 (-2.2, -1.0)	-3.8* (-4.2, -3.4)	-3.0* (-3.4, -2.6)	-2.1 (-2.7, -1.5)	-4.6* (-4.9, -4.3)	-3.7* (-4.0, -3.4)	-2.4 (-2.8, -2.0)
DLQI ≥ 4-point improvement, % responders	72.6%*	67.2%*	43.6%	78.1%*	73.3%*	32.3%	86.4%*	74.7%*	56.5%
POEM, change from baseline (95% CI)	-10.6* (-11.8, -9.4)	-6.8* (-8.0, -5.6)	-3.7 (-5.5, -1.9)	-11.0* (-12.1, -9.8)	-8.7* (-9.9, -7.5)	-3.6 (-5.3, -1.9)	-12.6* (-13.6, -11.7)	-9.6* (-10.5, -8.6)	-5.1 (-6.3, -3.9)
HADS Anxiety, change from baseline (95% CI)	-2.1* (-2.5, -1.6)	-1.6 (-2.0, -1.1)	-1.0 (-1.7, -0.4)	-1.7* (-2.2, -1.2)	-1.6* (-2.1, -1.1)	-0.6 (-1.3, 0.2)	-1.6* (-2.0, -1.2)	-1.2* (-1.5, -0.8)	-0.4 (-0.9, 0.1)
HADS Depression, change from baseline (95% CI)	-1.8* (-2.2, -1.4)	-1.4* (-1.8, -0.9)	-0.2 (-0.8, 0.4)	-1.4* (-1.8, -1.0)	-1.0* (-1.5, -0.6)	0.3 (-0.3, 0.9)	-1.6* (-1.9, -1.2)	-1.3* (-1.6, -0.9)	-0.3 (-0.7, 0.2)

CI=confidence interval; DLQI=Dermatology Life Quality Index; HADS=Hospital Anxiety and Depression Scale; N=number of patients randomised; PBO=placebo; POEM=Patient-Oriented Eczema Measure; QD=once daily; SCORAD=SCORing for AD; VAS=visual analog scale.
*Statistically significant without adjusting for multiplicity

Clinical biomarkers

Treatment with abrocitinib was associated with dose-dependent reduction in serum biomarkers of inflammation in atopic dermatitis [interleukin-31 (IL-31), interleukin-22 (IL-22), eosinophil count, and thymus and activation-regulated chemokine (TARC)], JAK1 signalling [natural killer (NK) cell count and interferon gamma-induced protein 10 (IP-10)] or both [high sensitivity C-reactive protein (hsCRP)]. These changes were reversible after treatment discontinuation.

Mean absolute lymphocyte count increased by 2 weeks after starting treatment with abrocitinib and returned to baseline by Month 9 of treatment. Most patients maintained an ALC within the reference range. Treatment with abrocitinib was associated with a dose-related increase in B cell counts and a dose-related decrease in NK cell counts. The clinical significance of these changes in B cell and NK cell counts is unknown.

Ancillary analyses

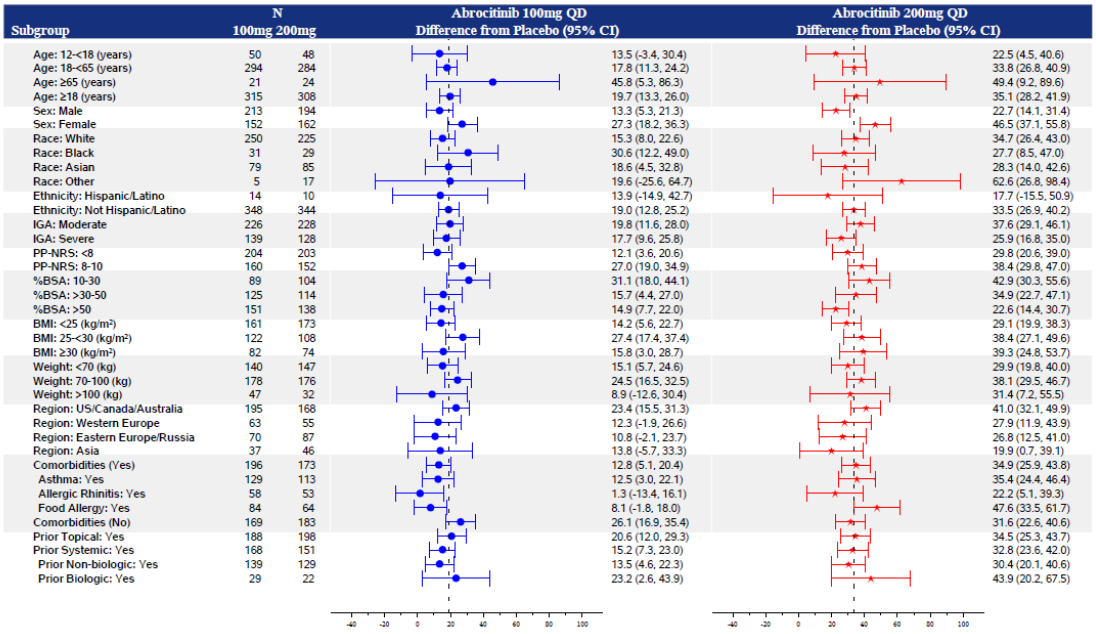
Subgroup analyses by intrinsic factors (age, sex, race ethnicity, weight and body mass index, disease severity by IGA and EASI, percent BSA affected by AD, and comorbidities) and extrinsic factors (geographic region and prior therapy for AD) were performed for the monotherapy studies (B7451012 and B7451013) and the combination therapy study B7451029.

The IGA response, and the EASI-75 response by subgroups is shown for studies B7451012, B7451013 and B7451029.

<u>IGA response by subgroups</u>

Monotherapy studies (B7451012 and B7451013)

Figure 18 Subgroup Analyses for Proportion of Monotherapy Subjects Achieving an Investigator's Global Assessment (IGA) Score of 'Clear' or 'Almost Clear' and ≥2 Points Improvement From Baseline at Week 12 (Placebo-Corrected) (FAS)

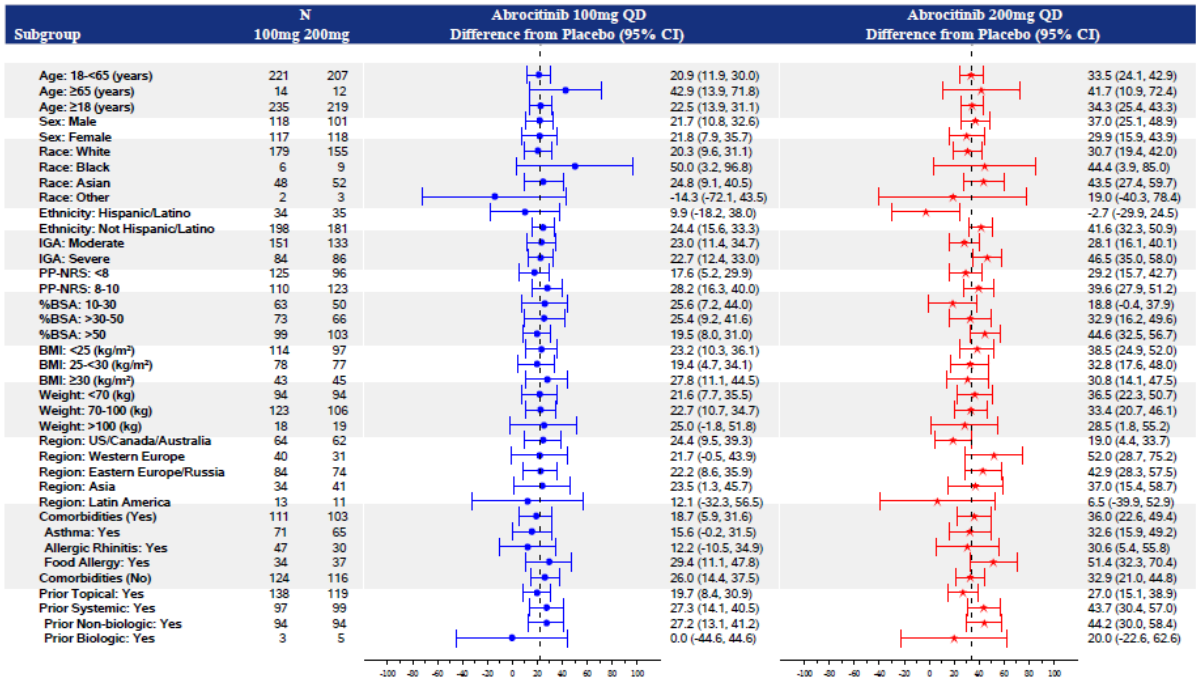


Pooled analysis included B7451006, B7451012 and B7451013.
Full Analysis Set (FAS) was defined as all randomized subjects who received at least one dose of study medication.
Baseline was defined as the last measurement prior to first dosing (Day 1).
The estimate and CI for difference were calculated based on the CMH-weighted average difference for each study using the normal approximation of binomial proportions.
Symbol (circle and star) represented the estimate of difference from placebo and bars represented 95% confidence interval of difference from placebo. Vertical reference line represented the estimate of difference from placebo for the overall FAS population.
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
Age was assessed at screening. Comorbidities included asthma, allergic rhinitis and food allergy only.
PFIZER CONFIDENTIAL Source Data: adad Date of ADAM Dataset Creation: 07NOV2019 Output File: ./ad_sce/MT_Final/adad_f103 Date of Generation: 15JAN2020 (01:55)

Difference from placebo represents the difference in responder proportion for each dose from placebo

Combination therapy study

Figure 19 Subgroup Analyses for Combination Therapy Subjects Achieving an Investigator's Global Assessment (IGA) Score of 'Clear' or 'Almost Clear' and ≥2 Points Improvement From Baseline at Week 12 (Placebo-Corrected) (FAS)



Subgroup	N 100mg	N 200mg	Abrocitinib 100mg QD Difference from Placebo (95% CI)	Abrocitinib 200mg QD Difference from Placebo (95% CI)
Age: 18-<65 (years)	221	207	20.9 (11.9, 30.0)	33.5 (24.1, 42.9)
Age: ≥65 (years)	14	12	42.9 (13.9, 71.8)	41.7 (10.9, 72.4)
Age: ≥18 (years)	235	219	22.5 (13.9, 31.1)	34.3 (25.4, 43.3)
Sex: Male	118	101	21.7 (10.8, 32.6)	37.0 (25.1, 48.9)
Sex: Female	117	118	21.8 (7.9, 35.7)	29.9 (15.9, 43.9)
Race: White	179	155	20.3 (9.6, 31.1)	30.7 (19.4, 42.0)
Race: Black	6	9	50.0 (3.2, 96.8)	44.4 (3.9, 85.0)
Race: Asian	48	52	24.8 (9.1, 40.5)	43.5 (27.4, 59.7)
Race: Other	2	3	-14.3 (-72.1, 43.5)	19.0 (-40.3, 78.4)
Ethnicity: Hispanic/Latino	34	35	9.9 (-18.2, 38.0)	-2.7 (-29.9, 24.5)
Ethnicity: Not Hispanic/Latino	198	181	24.4 (15.6, 33.3)	41.6 (32.3, 50.9)
IGA: Moderate	151	133	23.0 (11.4, 34.7)	28.1 (16.1, 40.1)
IGA: Severe	84	86	22.7 (12.4, 33.0)	46.5 (35.0, 58.0)
PP-NRS: <8	125	96	17.6 (5.2, 29.9)	29.2 (15.7, 42.7)
PP-NRS: 8-10	110	123	28.2 (16.3, 40.0)	39.6 (27.9, 51.2)
%BSA: 10-30	63	50	25.6 (7.2, 44.0)	18.8 (-0.4, 37.9)
%BSA: >30-50	73	66	25.4 (9.2, 41.6)	32.9 (16.2, 49.6)
%BSA: >50	99	103	19.5 (8.0, 31.0)	44.6 (32.5, 56.7)
BMI: <25 (kg/m²)	114	97	23.2 (10.3, 36.1)	38.5 (24.9, 52.0)
BMI: 25-<30 (kg/m²)	78	77	19.4 (4.7, 34.1)	32.8 (17.6, 48.0)
BMI: ≥30 (kg/m²)	43	45	27.8 (11.1, 44.5)	30.8 (14.1, 47.5)
Weight: <70 (kg)	94	94	21.6 (7.7, 35.5)	36.5 (22.3, 50.7)
Weight: 70-100 (kg)	123	106	22.7 (10.7, 34.7)	33.4 (20.7, 46.1)
Weight: >100 (kg)	18	19	25.0 (-1.8, 51.8)	28.5 (1.8, 55.2)
Region: US/Canada/Australia	64	62	24.4 (9.5, 39.3)	19.0 (4.4, 33.7)
Region: Western Europe	40	31	21.7 (-0.5, 43.9)	52.0 (28.7, 75.2)
Region: Eastern Europe/Russia	84	74	22.2 (8.6, 35.9)	42.9 (28.3, 57.5)
Region: Asia	34	41	23.5 (1.3, 45.7)	37.0 (15.4, 58.7)
Region: Latin America	13	11	12.1 (-32.3, 56.5)	6.5 (-39.9, 52.9)
Comorbidities (Yes)	111	103	18.7 (5.9, 31.6)	36.0 (22.6, 49.4)
Asthma: Yes	71	65	15.6 (-0.2, 31.5)	32.6 (15.9, 49.2)
Allergic Rhinitis: Yes	47	30	12.2 (-10.5, 34.9)	30.6 (5.4, 55.8)
Food Allergy: Yes	34	37	29.4 (11.1, 47.8)	51.4 (32.3, 70.4)
Comorbidities (No)	124	116	26.0 (14.4, 37.5)	32.9 (21.0, 44.8)
Prior Topical: Yes	138	119	19.7 (8.4, 30.9)	27.0 (15.1, 38.9)
Prior Systemic: Yes	97	99	27.3 (14.1, 40.5)	43.7 (30.4, 57.0)
Prior Non-biologic: Yes	94	94	27.2 (13.1, 41.2)	44.2 (30.0, 58.4)
Prior Biologic: Yes	3	5	0.0 (-44.6, 44.6)	20.0 (-22.6, 62.6)

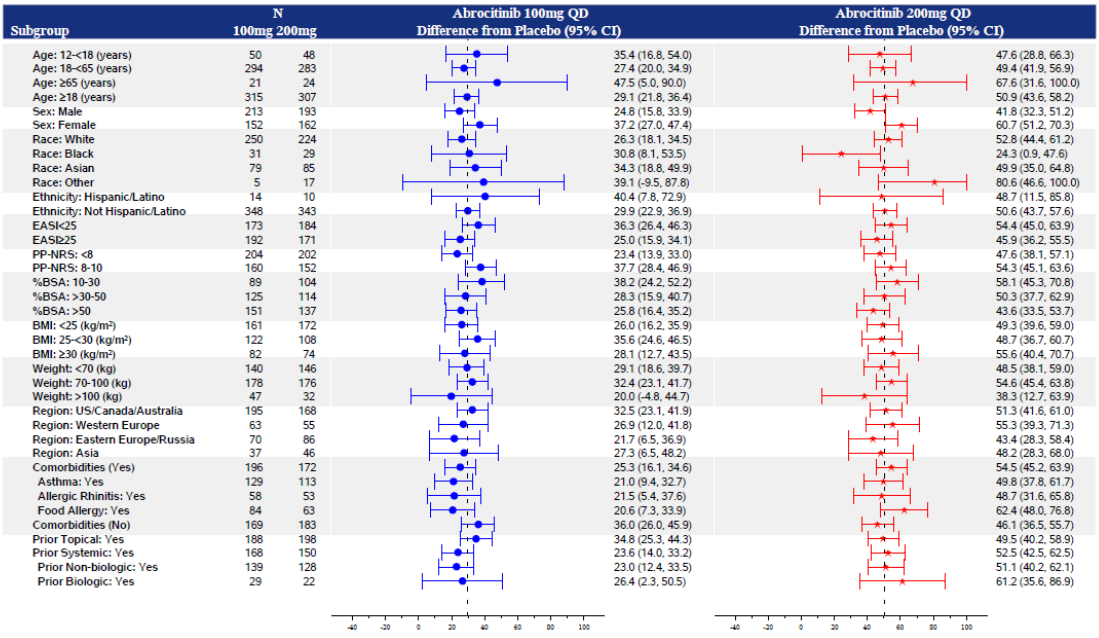
Full Analysis Set (FAS) was defined as all randomized subjects who received at least one dose of study medication.
Baseline was defined as the last measurement prior to first dosing (Day 1).
Comorbidities included asthma, allergic rhinitis and food allergy only.
The estimate and CI for difference were calculated using the normal approximation of binomial proportions.
Symbol (circle and star) represented the estimate of difference from placebo and bars represented 95% confidence interval of difference from placebo. Vertical reference line represented the from placebo for the overall FAS population.
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal. Age was assessed at screening.
IGA=Investigator's Global Assessment.
PFIZER CONFIDENTIAL Source Data: adad Date of ADAM Dataset Creation: 06MAR2020 Output File: ./ad_sce/BT/adad_f103 Date of Generation: 08MAR2020 (08:36)

Difference from placebo represents the difference in responder proportion for each dose from placebo.

EASI response by subgroups

Monotherapy studies (B7451012 and B7451013)

Figure 20 Subgroup Analyses for Proportion of Monotherapy Subjects with Eczema Area and Severity Index (EASI) Response ≥75% Improvement From Baseline at Week 12 (Placebo-Corrected) (FAS)

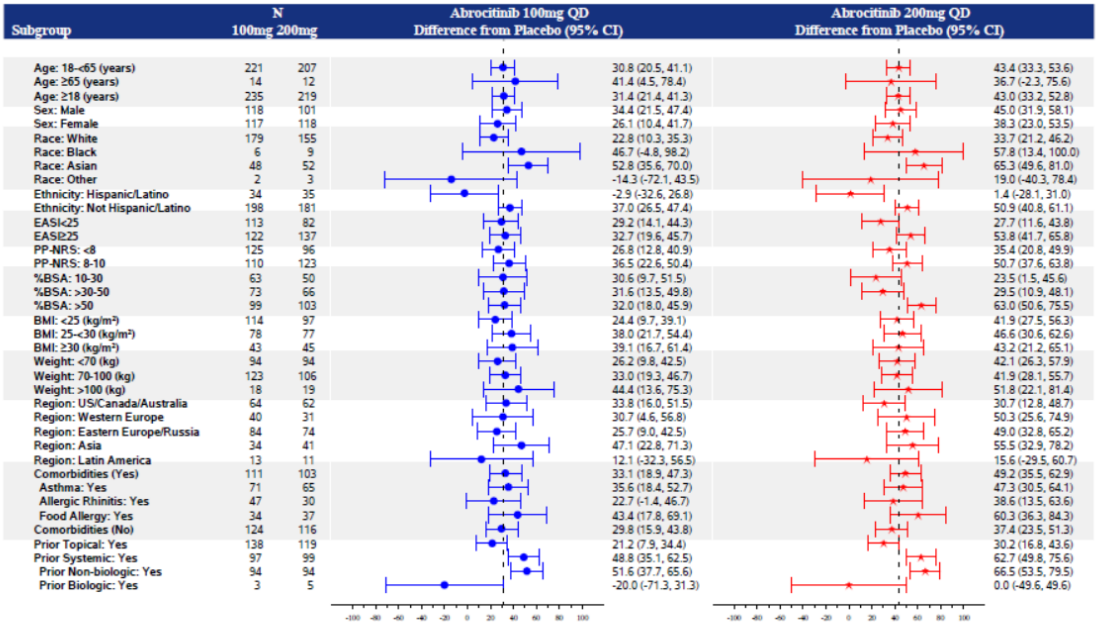


Pooled analysis included B7451006, B7451012 and B7451013.
Full Analysis Set (FAS) was defined as all randomized subjects who received at least one dose of study medication.
Baseline was defined as the last measurement prior to first dosing (Day 1).
The estimate and CI for difference were calculated based on the CMH-weighted average difference for each study using the normal approximation of binomial proportions.
Symbol (circle and star) represented the estimate of difference from placebo and bars represented 95% confidence interval of difference from placebo. Vertical reference line represented the estimate of difference from placebo for the overall FAS population.
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
Age was assessed at screening. Comorbidities included asthma, allergic rhinitis and food allergy only.
PFIZER CONFIDENTIAL Source Data: adea Date of ADAM Dataset Creation: 07NOV2019 Output File: /ad_sce/MT_Final/adea_f103 Date of Generation: 15JAN2020 (01:57)

Difference from placebo represents the difference in responder proportion for each dose from placebo.

Combination therapy study

Figure 21 Subgroup Analyses for Proportion of Combination Therapy Subjects with Eczema Area and Severity Index (EASI) Response ≥75% Improvement From Baseline at Week 12 (Placebo-Corrected) (FAS) B7451029



Full Analysis Set (FAS) was defined as all randomized subjects who received at least one dose of study medication.
Baseline was defined as the last measurement prior to first dosing (Day 1).
The estimate and CI for difference were calculated using the normal approximation of binomial proportions.
Symbol (circle and star) represented the estimate of difference from placebo and bars represented 95% confidence interval of difference from placebo. Vertical reference line represented the estimate of difference from placebo for the overall FAS population.
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
Age was assessed at screening. Comorbidities included asthma, allergic rhinitis and food allergy only.
PFIZER CONFIDENTIAL Source Data: adea Date of ADAM Dataset Creation: 09MAR2020 Output File: ./ad_sce/BT/adea_f103 Date of Generation: 09MAR2020 (01:38)

Difference from placebo represents the difference in responder proportion for each dose from placebo.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 31 Summary of efficacy for Study B7451012

Title: A phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-center study to evaluate the efficacy and safety of abrocitinib monotherapy in subjects aged 12 years and older, with moderate to severe AD		
Study identifier	Protocol Number: B7451012 EudraCT Number: 2017-003651-29	
Design	Randomised, double-blind, placebo-controlled, parallel group, multi-centre	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks not applicable not applicable
Hypothesis	Superiority	
Treatments groups	PBO	Placebo, 12 weeks, 77 randomised
	ABR 100	Abrocitinib 100 mg QD, 12 weeks, 156 randomised

	ABR 200		Abrocitinib 200 mg QD, 12 weeks, 154 randomised
Endpoints and definitions	Co-primary	IGA response at week 12	Investigator's Global Assessment (IGA) score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at week 12
	Co-primary	EASI-75 at week 12	Eczema Area and Severity Index 75% improvement from baseline (EASI-75) response at week 12
	Key secondary	PP-NRS4 at week 2	Response based on at least 4 points improvement in the severity of pruritus numerical rating scale (NRS) from baseline at week 2
	Key secondary	PP-NRS4 at week 4	Response based on at least 4 points improvement in the severity of pruritus numerical rating scale (NRS) from baseline at week 4
	Key secondary	PP-NRS4 at week 12	Response based on at least 4 points improvement in the severity of pruritus numerical rating scale (NRS) from baseline at week 12
	Key secondary	CFB PSAAD at week 12	Change from Baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at week 12
Database lock	01 May 2019		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set (FAS): The FAS was defined as all subjects who have been randomised and who have received at least one dose of treatment. Week 12			
Descriptive statistics and estimate variability	Treatment group	PBO	ABR 100	ABR 200
	Number of subjects randomised	77	156	154
	Number of subjects in analysis	76	156	153
	IGA response at Week 12, %	7.9	23.7	43.8
	95% confidence interval (CI)	(1.8, 14.0)	(17.0, 30.4)	(35.9, 51.7)
	Number of subjects in analysis	76	156	153

	EASI-75 at Week 12, %	11.8	39.7	62.7
	95% CI	(4.6, 19.1)	(32.1, 47.4)	(55.1, 70.4)

Effect estimate per comparison	Co-Primary endpoint: IGA response at Week 12	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	15.8
		95% CI	(6.8, 24.8)
		P-value by Cochran-Mantel-Haenszel (CMH) method	0.0037
		Comparison groups	PBO and ABR 200
		Difference from Placebo (Active - Placebo) (%)	36.0
		95% CI	(26.2, 45.7)
		P-value by CMH	<0.0001
	Co-Primary endpoint: EASI-75 at Week 12	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	27.9
		95% CI	(17.4, 38.3)
		P-value by CMH	<0.0001
		Comparison groups	PBO and ABR 200
		Difference from Placebo (Active - Placebo) (%)	51.0
		95% CI	(40.5, 61.5)
		P-value by CMH	<0.0001
Notes	The co-primary endpoints were analysed using non-responder imputation (NRI). If a subject withdrew from the study, this subject was counted as a non-responder after withdrawal. The number and percent, n (%), of subjects who discontinued from the study were as follows: - PBO, a total of 16 (20.8%) discontinued (7 [9.1%] due to Adverse Events, 2 [2.6%] due to Lack of Efficacy) - ABR 100, a total of 21 (13.5%) discontinued (9 [5.8%] due to Adverse Events, 1 [0.6%] due to Lack of Efficacy) - ABR 200, a total of 17 (11.0%) discontinued (9 [5.8%] due to Adverse Events, 0 due to Lack of Efficacy)		
Analysis description	**Key secondary analysis (pre-specified)**		
Analysis population and time point description	Full Analysis Set (FAS) week 2, 4 and 12		

Descriptive statistics and estimate variability	Treatment group	PBO	ABR 100	ABR 200
	Number of subjects randomised	77	156	154

	Number of subjects in analysis	74	147	147
	PP-NRS4 at week 2, %	2.7	20.4	45.6
	95% CI	(0.0, 6.4)	(13.9, 26.9)	(37.5, 53.6)
	Number of subjects in analysis	74	147	147
	PP-NRS4 at week 4, %	17.2	32.2	58.8
	95% CI	(7.7, 26.7)	(23.3, 41.1)	(49.5, 68.2)
	Number of subjects in analysis	74	147	147
	PP-NRS4 at week 12, %	15.3	37.7	57.2
	95% CI	(6.6, 24.0)	(29.2, 46.3)	(48.8, 65.6)
	Number of subjects in analysis	68	137	138
	CFB PSAAD at week 12, least squares mean (LSM)	-1.1	-2.2	-3.2
	95% CI	(-1.7, -0.6)	(-2.6, -1.9)	(-3.6, -2.8)

Effect estimate per comparison	Key secondary endpoint: PP-NRS4 at week 2	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	18.0
		95% CI	(10.2, 25.8)
		P-value by CMH	0.0004
		Comparison groups	PBO and ABR 200
		Difference from Placebo (Active - Placebo) (%)	42.5
		95% CI	(33.6, 51.4)
		P-value by CMH	<0.0001
	Key secondary endpoint: PP-NRS4 at week 4	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	15.0
		95% CI	(1.9, 28.0)
		P-value by CMH	0.0251
		Comparison groups	PBO and ABR 200
		Difference from Placebo (Active - Placebo) (%)	41.1

		95% CI	(27.8, 54.4)
		P-value by CMH	<0.0001
	Key secondary endpoint: PP-NRS4 at week 12	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	22.5
		95% CI	(10.3, 34.8)
		P-value by CMH	0.0003
		Comparison groups	PBO and ABR 200
		Difference from Placebo (Active - Placebo) (%)	41.7
		95% CI	(29.6, 53.9)
		P-value by CMH	<0.0001
	Key secondary endpoint: CFB PSAAD at Week 12, least squares mean	Comparison groups	PBO and ABR 100
		Active – Placebo, LSM	-1.1
		95% CI	(-1.7, -0.4)
		P-value by CMH	0.0010
		Comparison groups	PBO and ABR 200
		Active – Placebo, LSM	-2.1
		95% CI	(-2.7, -1.4)
		P-value by CMH	<0.0001

Table 32 Summary of efficacy for Study B7451013

Title: A phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-center study to evaluate the efficacy and safety of abrocitinib monotherapy in subjects aged 12 years and older, with moderate to severe AD		
Study identifier	Protocol Number: B7451013 EudraCT Number: 2018-001136-21	
Design	Randomised, double-blind, placebo-controlled, parallel group, multi-centre	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks not applicable not applicable
Hypothesis	Superiority	
Treatments groups	PBO	Placebo, 12 weeks, 78 randomised
	ABR 100	Abrocitinib 100 mg QD, 12 weeks, 158 randomised
	ABR 200	Abrocitinib 200 mg QD, 12 weeks, 155 randomised

Endpoints and definitions	Co-primary	IGA response at week 12	Investigator's Global Assessment (IGA) score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at week 12
	Co-primary	EASI-75 at week 12	Eczema Area and Severity Index 75% improvement from baseline (EASI-75) response at week 12
	Key secondary	PP-NRS4 at week 2	Response based on at least 4 points improvement in the severity of pruritus numerical rating scale (NRS) from baseline at weeks 2
	Key secondary	PP-NRS4 at week 4	Response based on at least 4 points improvement in the severity of pruritus numerical rating scale (NRS) from baseline at weeks 4
	Key secondary	PP-NRS4 at week 12	Response based on at least 4 points improvement in the severity of pruritus numerical rating scale (NRS) from baseline at weeks 2, 4, and 12
	Key secondary	CFB PSAAD at week 12	Change from Baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at week 12
Database lock	12 September 2019		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set (FAS): The FAS was defined as all subjects who have been randomised and who have received at least one dose of treatment. week 12			
Descriptive statistics and estimate variability	Treatment group	PBO	ABR 100	ABR 200
	Number of subjects randomised	78	158	155
	Number of subjects in analysis	77	155	155
	IGA response at week 12, %	9.1	28.4	38.1
	95% CI	(2.7, 15.5)	(21.3, 35.5)	(30.4, 45.7)

	Number of subjects in analysis	77	155	154
	EASI-75 at week 12, %	10.4	44.5	61.0
	95% CI	(3.6, 17.2)	(36.7, 52.3)	(53.3, 68.7)

Effect estimate per comparison	Co-Primary endpoint: IGA response at week 12	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	19.3
		95% CI	(9.6, 29.0)
		P-value by CMH	0.0008
		Comparison groups	PBO and ABR 200
		Difference from Placebo (Active - Placebo) (%)	28.7
		95% CI	(18.6, 38.8)
		P-value by CMH	<0.0001
	Co-Primary endpoint: EASI-75 at week 12	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	33.9
		95% CI	(23.3, 44.4)
		P-value by CMH	<0.0001
		Comparison groups	PBO and ABR 200
		Difference from Placebo (Active - Placebo) (%)	50.5
		95% CI	(40.0, 60.9)
		P-value by CMH	<0.0001

Notes	The co-primary endpoints were analysed using non-response imputation (NRI). If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal. The number and percent, n (%), of subjects who discontinued from the study were as follows: - PBO, a total of 26 (33.3%) discontinued (8 [10.3%] due to Adverse Events, 7 [9.0%] due to Lack of Efficacy) - ABR 100, a total of 21 (13.3%) discontinued (5 [3.2%] due to Adverse Events, 5 [3.2%] due to Lack of Efficacy) - ABR 200, a total of 14 (9.0%) discontinued (5 [3.2%] due to Adverse Events, 4 [2.6%] due to Lack of Efficacy])
Analysis description	**Key secondary analysis (pre-specified)**
Analysis population and time point description	Full Analysis Set (FAS) week 2, 4 and 12

Descriptive statistics and estimate variability	Treatment group	PBO	ABR 100	ABR 200
	Number of subjects randomised	78	158	155

	Number of subjects in analysis	76	156	153
	PP-NRS4 at week 2, %	3.9	23.1	35.3
	95% CI	(0.0, 8.3)	(16.5, 29.7)	(27.7, 42.9)
	Number of subjects in analysis	76	156	153
	PP-NRS4 at week 4, %	4.0	33.4	52.8
	95% CI	(0.0, 8.4)	(25.8, 41.0)	(44.7, 60.8)
	Number of subjects in analysis	76	156	153
	PP-NRS4 at week 12, %	11.5	45.2	55.3
	95% CI	(4.1, 19.0)	(37.1, 53.3)	(47.2, 63.5)
	Number of subjects in analysis	77	156	155
	CFB PSAAD at week 12, least squares mean (LSM)	-0.8	-2.4	-3.0
	95% CI	(-1.3, -0.3)	(-2.8, -2.1)	(-3.3, -2.7)

Effect estimate per comparison	Key secondary endpoint: PP-NRS4 at week 2	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	19.2
		95% CI	(11.0, 27.4)
		P-value by CMH	0.0002
		Comparison groups	PBO and ABR 200
		Difference from Placebo (Active - Placebo) (%)	31.2
		95% CI	(22.3, 40.2)
		P-value by CMH	<0.0001
	Key secondary endpoint: PP-NRS4 at week 4	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	29.5
		95% CI	(20.5, 38.4)
		P-value by CMH	<0.0001
		Comparison groups	PBO and ABR 200

		Difference from Placebo (Active - Placebo) (%)	48.8
		95% CI	(39.5, 58.2)
		P-value by CMH	<0.0001
	Key secondary endpoint: PP-NRS4 at week 12	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	33.7
		95% CI	(22.8, 44.7)
		P-value by CMH	<0.0001
		Comparison groups	PBO and ABR 200
		Difference from Placebo (Active - Placebo) (%)	43.9
		95% CI	(32.9, 55.0)
		P-value by CMH	<0.0001
	Key secondary endpoint: CFB PSAAD at Week 12, least squares mean	Comparison groups	PBO and ABR 100
		Active – Placebo, LSM	-1.7
		95% CI	(-2.3, -1.1)
		P-value by CMH	<0.0001
		Comparison groups	PBO and ABR 200
		Active – Placebo, LSM	-2.2
		95% CI	(-2.8, -1.6)
		P-value by CMH	<0.0001

Table 33 Summary of efficacy for Study B7451029

Title: A phase 3 randomized, double-blind, double-dummy, placebo-controlled, parallel group, multi-center study investigating the efficacy and safety of abrocitinib and dupilumab in comparison with placebo in adult subjects on background topical therapy, with moderate to severe AD		
Study identifier	Study number: B7451029 EudraCT number: 2018-002573-21	
Design	Randomised, double-blind, double-dummy, placebo-controlled, parallel group, multi-centre	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	16 weeks (double-blind, double-dummy), followed by 4 weeks when subjects only received oral investigational product Not applicable Not applicable
Hypothesis	Superiority	
Treatments groups	ABR 100	oral abrocitinib 100 mg + placebo injection, 16 weeks, 238 randomised
	ABR 200	oral abrocitinib 200 mg + placebo injection, 16 weeks, 226 randomised

	Dupi		Dupilumab as per label + oral placebo, 243 randomzied
	PBO		Placebo injection + oral placebo, 16 weeks, 131 randomised
Endpoints and definitions	Co-primary	IGA response at week 12	Investigator's Global Assessment (IGA) score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at week 12
	Co-primary	EASI-75 at week 12	Eczema Area and Severity Index 75% improvement from baseline (EASI-75) response at week 12
	Key secondary	IGA response at week 16	Investigator's Global Assessment (IGA) score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16
	Key secondary	EASI-75 at week 16	Eczema Area and Severity Index 75% improvement from baseline (EASI-75) response at week 16
	Key secondary	PP-NRS4 at week 2	Response based on at least 4 points improvement in the severity of pruritus numerical rating scale (NRS) from baseline at weeks 2
Database lock	01 February 2020		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set (FAS): The FAS was defined as all subjects who have been randomised and who have received at least one dose of treatment. Week 12			
Descriptive statistics and estimate variability	Treatment group	PBO	ABR 100	ABR 200
	Number of subjects randomised	131	238	226
	Number of subjects in analysis	129	235	219
	IGA response at week 12, %	14.0	36.6	48.4
	95% CI	(8.0, 19.9)	(30.4, 42.8)	(41.8, 55.0)
	Number of subjects in analysis	129	235	219

	EASI-75 at week 12, %	27.1	58.7	70.3
	95% CI	(19.6, 34.8)	(52.4, 65.0)	(64.3, 76.4)

Effect estimate per comparison	Co-Primary endpoint: IGA response at week 12	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	23.1
		95% CI	(14.7, 31.4)
		P-value by CMH	<0.0001
		Comparison groups	PBO and ABR 200
		Difference from Placebo (Active - Placebo) (%)	34.8
		95% CI	(26.1, 43.5)
		P-value by CMH	<0.0001
	Co-Primary endpoint: EASI-75 at week 12	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	31.9
		95% CI	(22.2, 41.6)
		P-value by CMH	<0.0001
		Comparison groups	PBO and ABR 200
		Difference from Placebo (Active - Placebo) (%)	43.2
		95% CI	(33.7, 52.7)
		P-value by CMH	<0.0001

Notes	The co-primary endpoints were analysed using non-response imputation (NRI). If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal. The number and percent, n (%), of subjects who discontinued from the study were as follows: - PBO, a total of 14 (10.7%) discontinued (5 [3.8%] due to Adverse Events, 0 due to Lack of Efficacy) - ABR 100, a total of 21 (8.8%) discontinued (5 [2.1%] due to Adverse Events, 1 [0.4%] due to Lack of Efficacy) - ABR 200, a total of 18 (8.0%) discontinued (8 [3.5%] due to Adverse Events, 0 due to Lack of Efficacy) - Dupi, a total of 19 (7.9%) discontinued (6 [2.5%] due to Adverse Events, 1 [0.4%] due to Lack of Efficacy)
Analysis description	**Key secondary analysis**
Analysis population and time point description	Full Analysis Set (FAS): The FAS was defined as all subjects who have been randomised and who have received at least one dose of treatment. Week 2 and Week 16

Descriptive statistics and estimate variability	Treatment group	PBO	ABR 100	ABR 200	Dupi
	Number of subjects randomised	131	238	226	243
	Number of subjects in analysis	124	230	221	232
	IGA response at week 16, %	12.9	34.8	47.5	38.8
	95% CI	(7.0, 18.8)	(28.6, 40.9)	(40.9, 54.1)	(32.5, 45.1)
	Number of subjects in analysis	124	229	221	232
	EASI-75 at week 16, %	30.6	60.3	71.0	65.5
	95% CI	(22.5, 38.8)	(53.9, 66.6)	(65.1, 77.0)	(59.4, 71.6)
	Number of subjects in analysis	130	236	226	239
	PP-NRS4 at week 2, %	13.8	31.8	49.1	26.4
	95% CI	(7.9, 19.8)	(25.8, 37.7)	(42.6, 55.6)	(20.8, 31.9)

Effect estimate per comparison	Key secondary endpoint: IGA response at week 16	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	22.1
		95% CI	(13.7, 30.5)
		P-value by CMH	<0.0001
		Comparison groups	PBO and ABR 200
		Difference from Placebo (Active - Placebo) (%)	35.0
		95% CI	(26.3, 43.7)
		P-value by CMH	<0.0001
	Key secondary endpoint: EASI-75 at week 16	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	29.7
		95% CI	(19.5, 39.9)

		P-value by CMH	<0.0001
		Comparison groups	PBO and ABR 200
		Difference from Placebo (Active - Placebo) (%)	40.4
		95% CI	(30.4, 50.4)
		P-value by CMH	<0.0001
	Key secondary endpoint: PP-NRS4 at week 2	Comparison groups	PBO and ABR 100
		Difference from Placebo (Active - Placebo) (%)	17.9
		95% CI	(9.5, 26.3)
		P-value by CMH	0.0002
		Comparison groups	PBO and ABR 200
		Difference from Placebo (Active - Placebo) (%)	34.9
		95% CI	(26.0, 43.7)
		P-value by CMH	<0.0001

2.6.5.3. Clinical studies in special populations

Adolescents were included in both monotherapy studies, 84 subjects in study B7451012 and 40 subjects in study B7451013. The combination therapy study B7451029 only included adults. The oldest individual in study B7451012 was 84 years, 83 years in study B7451013 and 84 years of age in study B7451029. The age distribution among subjects ≥ 65 years of age can be seen in the table below.

Table 34 Age distribution among subjects ≥65 years in Phase 3 studies of the abrocitinib clinical programme

	Age 65-74 years n/N, %	Age 75-84 years n/N, %	Age ≥85 years n/N, %
Controlled trials			
B7451012	14/387 (3.6%)	2/387 (0.5%)	0/387
B7451013	14/391 (3.6%)	5/391 (1.3%)	0/391
B7451014 randomised	27/798 (3.4%)	3/798 (0.4%)	0/798
B7451029	44/837 (5.3%)	10/837 (1.2%)	0/837
Uncontrolled trials			
B7451014 run-in	36/1233 (2.9%)	9/1233 (0.7%)	0/1233
B7451015	64/1590 (4.0%)	14/1590 (0.9%)	0/1590

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

A comparison of efficacy results across all pivotal studies (B7451012, B7451013 and B7451029) was made. In each individual phase 3 monotherapy or combination therapy studies, both doses of abrocitinib met each of the co-primary endpoints. Abrocitinib 200 mg QD consistently had a higher magnitude of effect than 100 mg QD. The differences from placebo were statistically significant and are assessed as clinically relevant.

The key secondary endpoints which evaluated itch supported the results obtained with the co-primary endpoints. The time-course of IGA, EASI-75 and PP-NRS4 responses of monotherapy and combination therapy showed that the effect on itch (PP-NRS4) is observed sooner than the effect on overall AD symptoms detected by IGA-75 and EASI.

2.6.5.5. Supportive studies

B7451014: A Phase 3 randomized withdrawal, double-blind, placebo-controlled, multi-centre study investigating the efficacy and safety of abrocitinib in subjects aged 12 years and over, with moderate to severe aAD with the option of rescue treatment in flaring subjects

Study B7451014 was designed to evaluate and compare the maintenance of effect of two doses of abrocitinib and placebo in subjects aged 12 and above with moderate to severe AD who respond to an initial open-label run-in treatment of 200 mg abrocitinib QD.

This was a randomised-withdrawal, responder-enriched, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy and safety of abrocitinib monotherapy in subjects aged 12 years and older with moderate-to-severe AD. The study consisted of an open-label induction treatment period with abrocitinib 200 mg QD for 12 weeks, from which responders were randomised after 12 weeks in a 1:1:1 ratio to receive abrocitinib 200 mg QD, abrocitinib 100 mg QD, or matching placebo in a double-blinded maintenance treatment period for 40 weeks. Subjects who met the protocol definition of flare during blinded treatment entered an open-label rescue treatment with abrocitinib 200 mg QD plus topicals for 12 weeks. During the open-label 12-week run-in period of the study, all subjects received abrocitinib 200 mg QD as monotherapy.

Main Inclusion Criteria

Adult and adolescent subjects aged 12 years and older with moderate-to-severe AD defined by the following at baseline: Investigator's Global Assessment (IGA) ≥3; Eczema Area and Severity Index (EASI) ≥16; pruritus severity score on the Peak Pruritus Numerical Rating Scale (PP-NRS) ≥4; Body

Surface Area (BSA) of involvement ≥10%. Subjects needed to have had a documented history of recent inadequate response to treatment with topical AD medications or had required systemic therapies for control of their disease.

Randomisation Criteria

Subjects who responded to induction treatment with abrocitinib 200 mg QD, defined as a) achieving an IGA of clear (0) or almost clear (1) (on a 5 point scale), b) a reduction from IGA baseline of ≥2 points, and c) obtaining a 75% reduction from their EASI from baseline (EASI-75) were randomised.

Primary Endpoint

- Loss of response or flare requiring rescue defined as a loss of at least 50% of the EASI response at Week 12 and an IGA score of 2 or higher.

Efficacy Results

12-week open-label run-in period

- At Week 12 of abrocitinib 200 mg QD treatment during the open label run-in period, 64.3% of subjects achieved IGA response, 74.4% of subjects achieved EASI-75, and 67.3% of subjects achieved PP-NRS4.

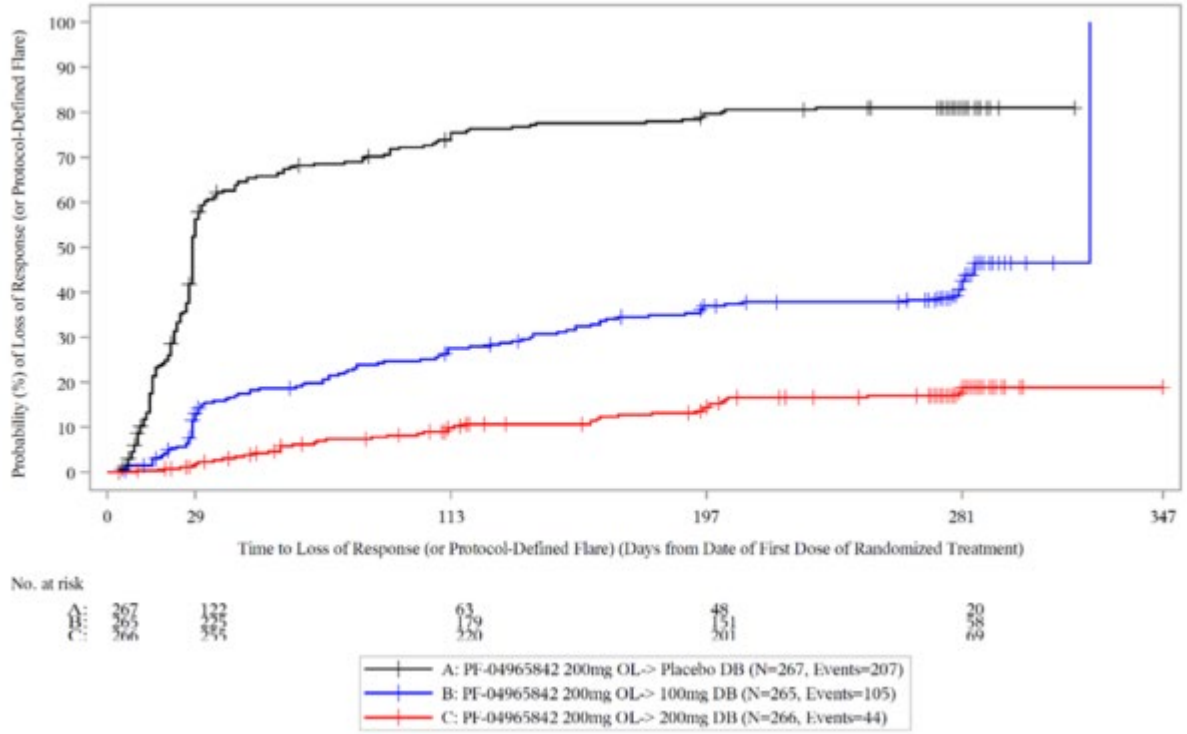
Disposition

- A total of 1233 subjects were treated in the run-in phase. Among these subjects, 798 subjects (64.7%) met responder criteria and were randomised to placebo (267 subjects), abrocitinib 100 mg QD (265 subjects), or abrocitinib 200 mg QD (266 subjects). Demographic and baseline disease characteristics were similar among randomised treatment arms.
- A slightly higher proportion of 200 mg subjects (13.2%) compared to 100 mg QD (8.3%) or placebo (6.0%) discontinued study during the randomised period. This was related to the lower proportion of subjects who experienced flares during the randomised period in the 200 mg arm compared to other arms.

Prevention of flares

- During the 40-week blinded, randomised treatment period, subjects in the placebo arm had a significantly higher probability of flaring compared to either dose of abrocitinib ($p<0.0001$ for both doses relative to placebo). Relative to the 100 mg QD group, the 200 mg QD group showed a significantly lower probability of flaring ($p<0.0001$) (Figure 21).
- The probability of not flaring (i.e., not experiencing protocol-defined flares) by week 52 was 19.1% for placebo, 57.4% for abrocitinib 100 mg, and 81.1% for abrocitinib 200 mg.
- The median time to flare was 28 days for the placebo group. In contrast, for both abrocitinib 100 mg QD and 200 mg QD groups, median time to flare could not be estimated as too few events were observed by week 40 of randomised treatment.

Figure 22 Kaplan-Meier Plot for Time to Loss of Response (or Protocol-Defined Flare)



Rescue treatment

- A total of 351 patients received developed protocol-defined flares and received rescue treatment of 200 mg QD abrocitinib. These included 76.4% of the placebo group (204 subjects), 39.2% of the abrocitinib 100 mg QD group (104 subjects), and 16.2% of the abrocitinib 200 QD mg group (43 subjects).
- Subjects responded to rescue treatment regardless of the treatment group. Overall, subjects who received rescue treatment achieved IGA clear or almost clear in 69.3% of subjects, and EASI-75 (relative to their rescue baseline) in 82.2% of subjects at rescue Week 12 (Table 36). The rate of recapture of response was highest for patients who were randomised to placebo and lowest for the patients who were randomised to abrocitinib 200 mg in the randomised withdrawal period of Study B7451014.

Table 35 Proportion of Subjects Achieving Investigator's Global Assessment (IGA) of 'Clear' or 'Almost Clear' or EASI-75 at Rescue Week 12 in Study B7451014

		Study Treatment in Randomized Withdrawal Phase of Study B7451014			
		Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg	All rescue subjects
IGA of clear or almost clear					
Rescue Week 12	N	196	102	41	339
	n (%)	160 (81.6)	60 (58.8)	15 (36.6)	235 (69.3)
	95% CI	(76.2, 87.1)	(49.3, 68.4)	(21.8, 51.3)	(64.4, 74.2)
EASI-75					

Rescue Week 12	N	196	102	40	338
	n (%)	180 (91.8)	76 (74.5)	22 (55.0)	278 (82.2)
	95% CI	(88.0, 95.7)	(66.1, 83.0)	(39.6, 70.4)	(78.2, 86.3)

EASI-75 = ≥75% Improvement in Eczema Area and Severity Index (EASI) from Rescue Baseline

Conclusions

- The study met its primary and key secondary endpoints. A significantly higher proportion of subjects were able to avoid protocol-defined flare on both active regimens relative to complete withdrawal (placebo), with a significantly higher proportion of subjects being able to do so while continuing 200 mg compared to a step-down to 100 mg.
- Despite this, the median time to flare in 100 mg QD of exceeding 40 weeks and the lower incidence of adverse events with 100 mg QD makes induction-maintenance (with a step-down in dose from induction to maintenance) a clinically viable strategy.
- The efficacy of abrocitinib in preventing AD flare relative to placebo during the 40-week randomised treatment period is consistent with the high degree of efficacy and dose-response demonstrated in the pivotal studies B7451012, B7451013, and B7450129.
- The majority of subjects who experienced flares achieved IGA response after receiving 12 weeks of rescue treatment.

B7451015: a phase 3 multi centre, 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 AD.

Study B7451015 was designed to estimate the long-term efficacy and safety of 100 mg and 200 mg QD abrocitinib with or without topical treatments in adult and adolescent subjects who previously participated in qualifying abrocitinib AD trials.

This is an ongoing, multi-centre, long-term extension study to evaluate the long-term safety and efficacy of abrocitinib administered to subjects aged 12 years and older with moderate-to-severe AD. The initial submission was based on a data cutoff date of 22 April 2020. To support the CHMP request for updated data from study B7451015, data cut was performed for efficacy with a cut-off date of 08 January 2021. A summary of the updated efficacy data is provided below.

Subjects must have completed a qualifying phase 3 study or have completed the open-label run-in period of study B7451014 and failed to meet the protocol defined response criteria at week 12. Study B7451015 enabled subjects to continue dosing at the same abrocitinib dose they were randomised to in the qualifying parent study or continue abrocitinib 200 mg QD if entering directly from the open-label run-in period of B7451014. If randomised to placebo or active comparator in the qualifying study, the subject was to be randomised to abrocitinib 100 mg QD or 200 mg QD upon entry into study B7451015. Following a 92-week Treatment Period 1, subjects remaining eligible are to progress to a variable-length open-label Treatment Period 2, in which subjects are to receive abrocitinib at the same dose as they received in Treatment Period 1 until commercial product is available in their country, until the applicant ends the study in that country, or until the subject requires discontinuation from the study.

Primary objective

To evaluate the long-term safety of abrocitinib 100 mg QD and 200 mg QD with or without topical treatments in adult and adolescent subjects who previously participated in abrocitinib AD phase 3 studies.

Blinding

Subjects previously randomised to abrocitinib 200 mg QD or 100 mg QD in the qualifying parent study were allocated to the same dose, and the blind was maintained throughout Treatment Period 1. In accordance with process specified in the protocol, once a qualifying study was completed, the treatment assignment for those subjects became known to the applicant study team and investigative site staff. With the exception of subjects entering from the open-label run-in period of study B7451014, subjects remained blinded to treatment group during the 92-week Treatment Period 1 of study B7451015. Blinding of the applicant study team, investigative site staff, and subjects remained intact for the interim analyses performed for the initial and updated submissions.

Data Pooling

To evaluate the efficacy of both doses of abrocitinib as up to 48 weeks of cumulative treatment, data were pooled from subjects who initially participated in study B7451012, B7451013, or B7451029 and subsequently entered the Phase 3 long-term extension study B7451015. In study B7451015, subjects continued the same dose of abrocitinib that they received in their qualifying parent study, except for those originally allocated to placebo or active comparator, who were re-randomised to abrocitinib 100 mg QD or 200 mg QD. This strategy allows appropriate evaluation and comparison of the 2 doses of abrocitinib, with or without topical therapy.

For the initial submission and this updated submission, efficacy data from the integrated long-term therapy pool were/are presented instead of study B7451015 as a stand-alone study. Efficacy data from the long-term therapy pool include data from both the qualifying phase 3 studies B7451012, B7451013, and B7451029 and the long-term extension study B7451015, and thus provide more meaningful analyses of efficacy over time.

Analytical Methods

The analytical methods for the efficacy evaluations included in this update are the same as those described for the initial submission. In both the initial submission and this updated submission, analyses of efficacy data from the integrated long-term therapy pool were/are based on as-observed data (i.e., only subjects with available data at a given time-point were included in the analysis).

Results

The long-term efficacy data is presented for the overall population, initial responders, and initial non-responders, because evaluation of maintenance of response in responders is not the only clinically relevant way to assess durability of response to a treatment. Maintenance of response only addresses the clinical question of a patient who has responded to initial treatment, continues that response long-term and does not account for early partial responders or non-responders who later become full responders with continued treatment (Bartos et al, 2016). A significant proportion of patients receiving long-term abrocitinib have demonstrated late-onset response. In addition, patients who are choosing to start a treatment may have a different clinical question - what are their chances of having a good response on long-term treatment.

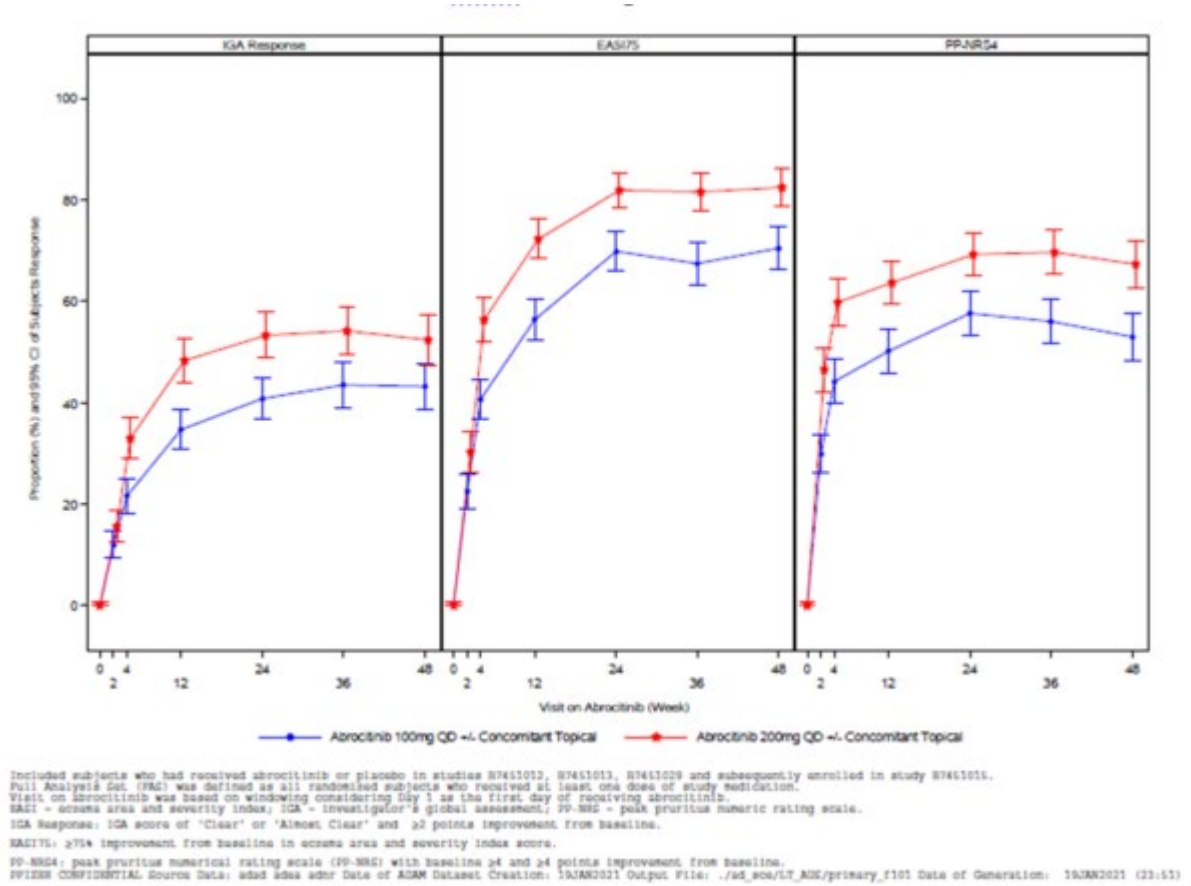
The overall population of the updated long-term therapy pool includes 1116 subjects: 595 subjects who received abrocitinib 100 mg QD continuously and 521 subjects who received abrocitinib 200 mg QD continuously (same as the original submission).

The response rates at Week 48 of cumulative abrocitinib treatment remained similar to or higher than those at week 12 for either dose of abrocitinib, thus demonstrating long-term efficacy (Figure 23). The response rates of 200 mg QD at week 48 were higher than those of 100 mg QD, indicating dose dependency of long-term efficacy.

At week 48, the updated response rates for abrocitinib 100 mg QD and 200 mg QD in the overall population were:

- IGA response: 43.2% and 52.4%, respectively
- EASI-50: 88.2% and 94.7%, respectively
- EASI-75: 70.5% and 82.5%, respectively
- PP-NRS4: 53.0% and 67.3%, respectively

Figure 23 Proportion of Long-term Therapy Pool Subjects Achieving IGA Response, EASI-75 or PP-NRS4 Over Time up to Week 48



Among responders to abrocitinib at Week 12, the majority of subjects maintained their response at Week 48 of cumulative abrocitinib treatment for both doses of abrocitinib, indicating durability of efficacy. The proportions of subjects with response at Week 48 were as follows:

- IGA response, responder proportion (95% CI):
  - 100 mg QD – 59.8% (49.1, 70.4)
  - 200 mg QD – 69.6% (61.1, 78.2)
- EASI-75, responder proportion (95% CI):
  - 100 mg QD – 79.1% (72.2, 86.0)
  - 200 mg QD – 87.0% (81.9, 92.1)
- PP-NRS4, responder proportion (95% CI):
  - 100 mg QD – 62.4% (52.9, 71.8)

- 200 mg QD – 82.9% (76.6, 89.1)

Among the Week 12 IGA non-responders, continuation of abrocitinib for an additional 12 weeks (through Week 24) resulted in IGA response rates of 24.7% and 28.5% with 100 mg QD and 200 mg QD, respectively. Among the Week 12 EASI-75 non-responders, the late-response rates were even higher, with 50.0% and 57.8% of the subjects continuing with abrocitinib 100 mg QD and 200 mg QD, respectively, achieving EASI-75 at Week 24.

Subjects who were partial responders (IGA=2, mild disease) at Week 12 had Week 24 IGA response rates of 39.8% and 35.5% for 100 mg QD and 200 mg QD, respectively, indicating a better response compared to initial non-responder.

Patients who received dupilumab in the COMPARE study and subsequently entered EXTEND were randomised to either 100 mg or 200 mg of abrocitinib once daily upon entering EXTEND. Among non-responders to dupilumab, a substantial proportion of patients achieved response 12 weeks after switching to abrocitinib [34% and 47% for IGA (0 or 1) response, and 68% and 80% for EASI-75 with 100 mg once daily or 200 mg once daily, respectively].

The numerical data presented in the SmPC for long-term efficacy are based on the data included in the initial submission. The applicant committed to submitting a post approval type II variation to further update SmPC section 5.1 by 31 December 2022.

B7451036: a phase 3, randomized, double-blind, placebo-controlled, multi-centre study investigating the efficacy and safety of abrocitinib coadministered with background medicated topical therapy in adolescent subjects 12 to <18 years of age with moderate-to-severe AD.

This was a randomised, double-blind, placebo-controlled, parallel-group, phase 3 study to evaluate the efficacy and safety of abrocitinib in adolescent participants 12 to <18 years of age with moderate-to-severe AD. A total of 287 participants were randomised globally in a 1:1:1 ratio to receive abrocitinib QD at 200 mg, 100 mg, or placebo for 12 weeks. All subjects were required to receive background medicated topical therapy.

Main inclusion criteria

Adolescent subjects 12 to <18 years of age with moderate-to-severe AD defined by the following at baseline: Investigator's Global Assessment (IGA) ≥3; Eczema Area and Severity Index (EASI) ≥16; pruritus severity score on the Peak Pruritus Numerical Rating Scale (PP-NRS) ≥4; Body Surface Area (BSA) of involvement ≥10%. Subjects needed to have had a documented history of recent inadequate response to treatment with topical AD medications or had received systemic therapies for AD or were candidates for systemic therapies for AD.

Co-primary endpoints

- IGA response: Response based on the IGA score of clear (0) or almost clear (1); and a reduction from baseline of 2 points at week 12.
- EASI-75 response: Response based on the EASI 75% improvement from baseline (EASI-75) at week 12.

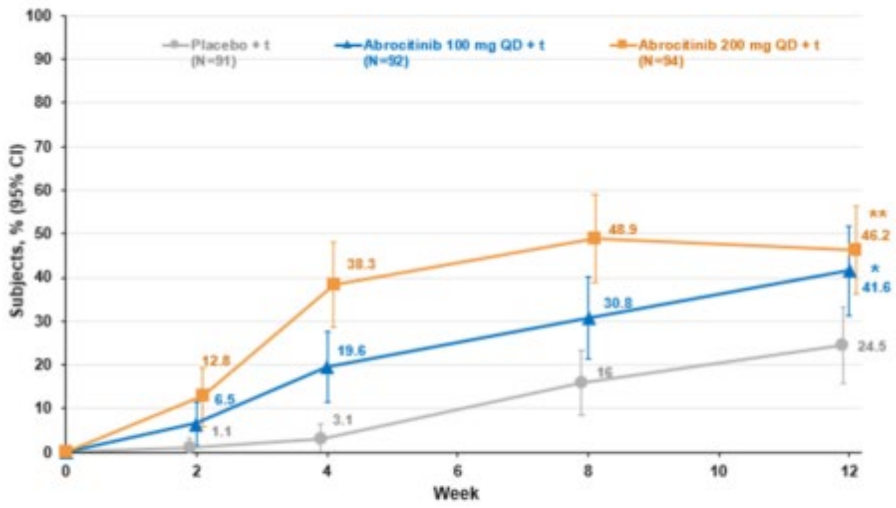
Efficacy Results

A total of 287 subjects were randomised. The discontinuation rate was 3.2-6.3% across treatment arm. Demographics and baseline characteristics were balanced among 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 atopic dermatitis (IGA of 4) was 38.6%.

Significantly higher proportion of subjects achieved IGA response at week 12 for abrocitinib 100 mg QD (p=0.0147) and 200 mg QD (p=0.0030) compared with placebo (Figure 24 and table 40). Similarly, significantly higher proportion of subjects achieved EASI-75 at week 12 for abrocitinib 100 mg QD (p=0.0002) and 200 mg QD (p<0.0001) compared with placebo. Significantly higher proportion of subjects achieved PP-NRS4 response at week 12 for both doses of abrocitinib compared with placebo (See below table). Dose response was demonstrated during the 12-week treatment period.

Figure 24 Proportion of Subjects Achieving IGA Response or EASI-75 Over Time in Study B7451036

Panel (a) IGA response



Panel (b) EASI-75

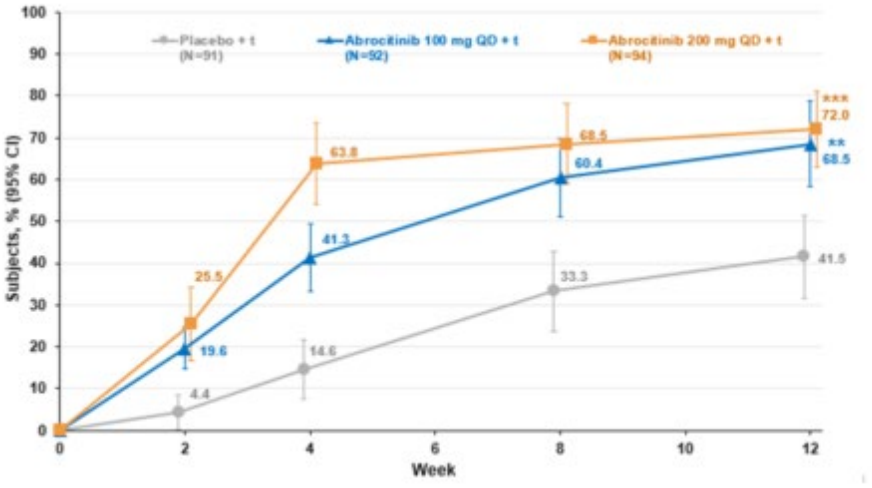


Table 36 Adolescent efficacy results in Study B7451036

	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[e] (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 5-point 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.

The study met both co-primary endpoints of IGA and EASI-75 responses at week 12 for both doses, demonstrating that both abrocitinib 100 mg QD and 200 mg QD arms were superior to placebo when administered in combination with medicated topical therapy in adolescents.

These results are consistent with the efficacy results of the pivotal monotherapy studies B7451012 and B7451013 (in adults and adolescents), and the combination therapy study B7451029 (in adults).

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The application for abrocitinib is supported by two Phase 3, randomised, double-blind, placebo-controlled, parallel-group studies with identical design; study B7451012 and study B7451013. Furthermore, a Phase 3, multi-centre active control study on background topical therapy study B7451029 has been performed.

The studies included men and women with moderate to severe atopic dermatitis (AD). Studies B7451012 and B7451013 also included adolescents (≥12 years of age), while study B7451029 was performed in adults only. The study participants were aged 12 to 84 and 12 to 83 years in studies B7451012 and B7451013, respectively, 18 to 84 years in study B7451029. In studies B7451012 and B7451013, the subjects should have a clinical diagnosis of chronic AD with inadequate response to treatment with topical medication. The AD should be of moderate to severe degree (affected BSA ≥10%, IGA≥3, EASI≥16, and Pruritus NRS≥4 at the baseline visit). The inclusion criteria of study B7451029 were overall similar with studies B7451012 and B7451013. The inclusion criteria are considered adequate to reflect the proposed therapeutic indication.

The exclusion criteria for studies B7451012, B7451013 and B7451029 reflected general warnings for use for JAK inhibitors, e.g. with respect to infection, haematological abnormalities, viral reactivation and the risks for venous thromboembolism. These exclusion criteria are all considered relevant. Subjects with recent or active suicidal ideation intent or behavior was excluded from the pivotal study protocols. However, several subjects (12.6%) participating in the pivotal studies B7451012, B7451013, and B7451029 had a medical history of psychiatric disorders related to depression, anxiety, or suicidal ideation.

Eligible subjects were treated with 100 mg or 200 mg abrocitinib mg or placebo for 12 weeks in studies B7451012 and B7451013, and for 20 weeks in study B7451029. The treatment was to be taken once daily, preferably in the morning, at approximately the same time of the day. The proposed dosing in the SmPC section 4.2 has been updated stating that for most patients 200 mg is the recommended starting dose. The general dosing recommendation is accepted by CHMP.

Furthermore, the applicant intends to market a 50mg tablet strength (for patients with mild or moderate renal impairment and for patients receiving strong inhibitors of cytochrome P450 (CYP) 2C19) and has included recommendations for the 50mg dose in the SmPC. As the 50mg tablet/dose was never used in clinical trials, it needed to be ensured that the provided model supported a full extrapolation of efficacy and safety from populations studied in the Phase 3 studies to these special populations with eGFR < 40 mL/min. Upon request from the CHMP, the applicant provided an updated popPK model (PMAR-1110) including the parent compound and the active metabolites and performed an additional analysis to evaluate the change in exposure based on renal impairment compared to normal AD patients. The analysis indicated that comparable exposure can be achieved in patients with moderate renal impairment with a lower dose. For patients with severe renal impairment (<30mL/min) 50mg is determined as the proposed starting dose (an up-titration to 100mg is possible) based on data extrapolation.

In study B7451029, dupilumab (Dupixent) was used as active comparator. Blinded dupilumab, 300 mg/ml, and its matching placebo were dosed according to the approved product information. At the time when the clinical programme of abrocitinib was designed and implemented, dupilumab was the only marketed product indicated for moderate to severe AD. The choice of comparator is therefore considered appropriate and of relevance in view of the EU approved treatment options. Recently, the JAK-inhibitors baricitinib (Olumiant) and upadacitinib (Rinvoq) received positive opinions for a new indication, treatment of moderate to severe AD (in adults only for Olumiant and in adults and in adolescents for Rinvoq). A comparison between abrocitinib and baricitinib or upadacitinib would have been of interest but was not optional at time of designing or submitting the present application. Tralokinumab (Adtralza) was also recently approved for the treatment of moderate to severe AD in adults.

In the combination therapy study B7451029, topical corticosteroids (TCS) were to be applied once daily to areas with active lesions, starting on Day 1 (baseline) and throughout the study according to a guidance. Topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus) or a PDE4 inhibitor (e.g., crisaborole) could be used instead of corticosteroids in body areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.) with active lesions or if continued treatment with TCS of any potency is not tolerated. In the CHMP scientific advice (EMEA/H/SAH/085/2/2017/III) it was stated that efficacy needed to be established also when combined with medicated topical therapy and was considered important since topical medicated therapy is the basis of AD treatment.

Subject e-diaries were given to the participating subjects and scores were collected at different intervals for the key secondary endpoints.

Treatment compliance was assessed using data from the subject diary across the entire study. Treatment compliance was verified through a combination of unused investigational product returned by the subject at the study visits, review of the dosing diary, and discussion with the subject.

The primary objective of studies B7451012 and B7451013 was to assess the efficacy of abrocitinib 100mg and 200mg once daily compared with placebo in subjects aged 12 years and older with moderate to severe AD. Secondary objectives were to evaluate the effect of abrocitinib on additional efficacy endpoints and patient reported outcomes over time, and to evaluate the safety and tolerability

of abrocitinib in subjects aged 12 years and older with moderate to severe AD following 12 weeks of treatment.

The primary objective of study B7451029 was to assess the efficacy of 100 mg and 200 mg once daily of abrocitinib versus placebo in adult subjects on background topical therapy with moderate to severe AD. Secondary objectives of were to evaluate the efficacy of abrocitinib versus dupilumab on pruritus and other efficacy measures among others.

The corresponding co-primary efficacy variables in all pivotal clinical trials were the response based on the IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at week 12., and the response based on EASI 75% or greater improvement from baseline (EASI-75) at week 12. These efficacy variables are well established, have been used in several AD studies over time and are considered to be of clinical relevance if met.

The key secondary endpoints in studies B7451012 and B7451013 were the response based on at least 4-points improvement in the severity of pruritus numerical rating scale (PP-NRS4) from baseline at weeks 2, 4, and 12, and change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at week 12.

The key secondary endpoints in study B7451029 were the response based on achieving at least 4-points improvement in the severity of pruritus numerical rating scale (PP-NRS4) from baseline at weeks 2, response based on achieving the IGA of clear (0) or almost clear (1) and a reduction from baseline of ≥2 points at week 16 and response based on achieving EASI-75 (≥75% improvement from baseline) at week 16.

All key secondary endpoints are considered important and of clinical relevance.

Several other secondary efficacy endpoints and patient-reported outcome endpoints were evaluated during the pivotal clinical studies.

The study objectives and outcomes are considered adequate for studies evaluating a new product with the proposed therapeutic indication. The number of subjects and the duration of treatment are in accordance with the requirements of EMA guidelines. The studies had a comparative design either to placebo or to the active comparator dupilumab (Dupixent). Hence, there was an objective related to superiority and randomisation and blinding were necessary. The study designs are overall accepted, there were however some issues requiring further clarification are discussed below.

The extent/maturity of the data package submitted (not all phase 3 studies were completed yet) is considered adequate to allow for informed decision on the benefits (and risks) of abrocitinib in the targeted indication. However, upcoming data from ongoing studies were reviewed to make sure that they are consistent with available results from the pivotal trials. By now study B7451014 and B7451036 have completed and updated efficacy data has been provided from study B7451015 with a new data cut-off of 08 January 2021 (the initial data cut-off for the initial submission was 22 April 2020). Study B7451015 is still ongoing, which is acknowledged, no final study report was expected. For Study B7451014 and B7451036 adequate study documentation has been submitted upon request from the CHMP. New/updated outcomes are discussed below.

Statistical aspects

Monotherapy studies B7451012 and B7451013

The samples size estimation is considered to be appropriate. Masking of randomised assignments was to be achieved using matching placebo and double-dummy technique which is appropriate for its purpose. There did not seem to have been any approach planned to assure that a minimum number of adolescents were randomised. Within the CHMP SA (EMEA/SAH/085/2/2017/IIII) the applicant was

cautioned that if specific claims for this age group were to be supported, a sufficient number of patients of this age range was needed. In this respect it should be acknowledged that efficacy among adolescents only was not a study objective in any of the studies. Also, as stated in the PIP compliance report (EMEA-C1-002312-PIP01-17-M01), the number of study participants by paediatric subset was to be at least 30 subjects evaluable for the primary analysis; a measure that was deemed PIP compliant for both study B7451012 and study B7451013. Further, abrocitinib performance in adolescents was evaluated specifically in study B7451036/TEEN and respective results have been provided upon request from the CHMP.

The monotherapy studies were identical in design and the SAP for each study was in all important aspects identical. Both SAPs were finalised before database lock (and unblinding) and the applicant confirmed that all analyses were carried out as detailed in the final SAP (study B7451012: version 4, 23 April 2019, study B7451013: version 2, dated 26 August 2019) but for a number of exceptions in the analysis of study B7451012 (described and justified; no major concerns are raised). Overall, the statistical analysis plan(s) were appropriate. The multiple testing procedure (MTP), the analysis of binary endpoints including the use of non-responder imputation (NRI) and the use of MMRM were commented in line with the CHMP SA (EMEA/SAH/085/2/2017/IIII) and largely also supported by the CHMP.

Study B7451012 was initiated in December 2017 and study B7451013 in June 2018. When a technical error in the process of transmission and collection of electronic data was found in study B7451012, mitigatory measures could be implemented in study B7451013. In study B7451012, this led to was missing data for several subjects at scheduled visits of week 2 (Day 15) and after for the pruritus NRS scale, a key secondary endpoint. According to the applicant, the main reason for this appeared to be that study sites had not been provided with adequately detailed instructions on how to operate the handheld devices used to record the PP-NRS. Eventually, a smaller proportion of subjects had missing PP-NRS data in study B7451013 than in study B7451012. Between 30% to 40% and 12% to 24% of randomised subjects seemed to have been impacted for studies B7451012 and B7451013, respectively. Upon request from the CHMP, the applicant presented number of subjects with missing data in total, imputed using NRI and imputed using MI and for each analysis time-point by randomised arms and study, respectively. More subjects in the placebo arm discontinued early and hence, the use of NRI was more common in the placebo arm. At week 8 and week 12, missing data was overall more common in the placebo arms with missing data due to technical issues fairly well balanced between randomised arms within each study. Most missing due to a technical error occurred in study B7451012 and at week 4 there was also an imbalance between placebo and active arms with the number of subjects concerned being 15/74 (20.3%), 49/157 (33.3%) and 57/147 (38.8%) in the placebo, the 100mg and the 200mg arm, respectively. This could in part be explained by the higher proportion in the placebo arm of subjects with missing data due to early discontinuation for which NRI was used. For especially the 200mg arm in study B7451012 and the week 4 analysis, there was a non-neglectable loss in number of actually observed responses. To further explore any impact on primary conclusions, analyses excluding those with missing data due to technical error was in addition requested by the CHMP and provided by the applicant (see further below).

All efficacy and PRO analyses were performed using the full analysis set defined as all randomised subjects who had received at least one dose and by the applicant is expected to be identical to a true ITT analysis set since the first dose was administered in-clinic. Overall, this was also shown to be true in both studies and thereby, the primary analysis population is endorsed. However, to be included in the PP-NRS analysis subjects were to have a baseline score ≥4. Although the approach could be comprehended, excluding subjects in the analysis with a baseline value <4 was not agreed thus new analyses were requested. As clear from re-analyses of PP-NRS data; also including those who did not meet the requirement of a baseline PP-NRS of at least 4 had overall only minor impact given the small

number of subjects excluded in the original analyses. However, in the week 4 analysis of 100mg vs placebo in study B7451012, the p-value for the difference was 0.1062. Considering the addition of only 9 and 3 subjects in the 100mg and placebo arm respectively, this could be considered to signal a lack of robustness in the original analysis. Nevertheless, this issue was not further pursued by the CHMP. Overall, the analyses requested by the CHMP supported the primary (original) analyses.

Although not optimally described in the figure provided as part of this application, the multiple testing procedure including re-cycling of alpha is considered acceptable. The co-primary and all but one of key secondary endpoints were binary/responder endpoints for which the same approach for test and estimation was applied. For testing of hypotheses and estimation of treatment differences, the Cochran-Mantel-Haenszel test adjusted by randomisation strata has been used which is supported. In case of study withdrawal or use of rescue, subjects were considered non-responders. This could in general be agreed but may not be sufficiently conservative depending on missing data pattern. Here it has been shown to be in favour of active treatments in that more subjects in the placebo arms than in abrocitinib arms, discontinued prematurely. For sensitivity purpose, Tipping point analyses (TP) based on both MAR and MNAR, have been performed. These are endorsed. In both studies they were shown to support a statistically significant difference between each abrocitinib dose and placebo respectively for both the IGA and the EASI-75 endpoints also under the scenario corresponding to Jump-to-reference and MNAR. There was no formal comparison planned nor performed between the two abrocitinib dose groups. The difference has however been estimated with corresponding 95% CI. This is endorsed.

However, methods specified to estimate confidence intervals for the effect sizes corresponding to primary and secondary endpoints included in the multiple testing procedure were not adjusted for multiplicity, such that the actual coverage probability of the simultaneous confidence region (covering the corresponding effect size estimate) may be substantially lower. This issue affects effect size estimates corresponding to primary and key-secondary endpoints. The applicant was requested to provide confidence intervals with simultaneous coverage probability of 95% two-sided (or 97.5% one-sided) that are compatible with the sequentially rejective multiple testing. In their response, the applicant claimed that no adjustment of CI was necessary for results from studies B7451012 and B7451013, because all null hypotheses considered in the sequentially rejective multiple test procedure are rejected. That is in line with simultaneous CIs proposed in *Strassburger & Bretz* (2008) and hence is accepted by CHMP.

Given the amount of missing PP-NRS data in study B7451012, the primary approach for handling missing in the analysis of this key secondary endpoint was changed (SAP version 4, 23 April 2019); from a failure/non-responder imputation (NRI) to a method that was to depend on whether intermittently or monotony missing. The applicant argues that those missing due to a technical error could be assumed to be missing at random and used a hybrid approach (NRI+MI) to replace data. In their argumentation it was pointed out that the error was not restricted to a particular site or country and was not indicative of being related to the missing value of pruritus endpoint or any other endpoints. Although unfortunate, the missing at random assumption appeared plausible. The amount of missing PP-NRS data was not as pronounced in study B7451013 but for comparison the same analyses were performed also for study B7451013 which is appreciated. A sensitivity analysis was performed (in both studies) in which all subjects with missing data was imputed as non-responders. Overall, primary PP-NRS4 outcomes were shown to be reasonably consistent across studies. The differences in study B7451012, each active dose versus placebo, was slightly smaller compared with study B7451013, which became more evident in the sensitivity analyses using NRI alone. In the requested analyses excluding subjects with missing data due to technical issues, there were no important differences in the proportion of subjects achieving PP-NRS ≥4-point improvement from baseline or the p-values for comparisons between arms at any of the analysis time-point compared

with the original analyses but for the week 4 analysis of 100mg vs placebo in study B7451012 where the p-value for the difference was 0.0718. This is considered to pertain to the limitations in group size and that the difference versus placebo was smaller for the 100 mg than the 200 mg arm.

Continuous secondary endpoints, among them the key secondary endpoint, change from baseline in 'Pruritus and Symptoms Assessment for Atopic Dermatitis' (PSAAD) score at week 12, were analysed using MMRM. Within the CHMP SA (EMEA/SAH/085/2/2017/IIII), the then planned sensitivity analysis was not endorsed and advice was given on options on how to handle missing data in an analysis for sensitivity purpose. With the only sensitivity analysis offered based on the PPS, additional analyses were requested. In their responses, the applicant provided a sensitivity analysis in which NRI was used in case of discontinuations while intermittent missing was imputed based on MNAR in active arms and MAR in the placebo arm. Using this approach, the outcomes were shown to be very similar compared with primary analyses outcomes, probably explained by the fact that more subjects in the placebo arm than in active arms discontinued early and were imputed as non-responders. NRI could generally be agreed in case of study/treatment discontinuation, albeit, depending on missing data pattern, may not be sufficiently conservative. Given what is considered convincing statistical evidence from the original as well the currently presented sensitivity analysis and based on the similarities in both estimates and p-values (both studies), this issue was not further pursued.

Furthermore, the need for and amount of rescue medication should also be considered as intercurrent event and be documented and analysed. In the analyses for binary endpoints, subjects who required a rescue medication were defined as "non-responders" at all subsequent visits. It was unknown which strategy (e.g. hypothetical strategy, treatment policy strategy) was used for these subjects in the sensitivity analyses for the binary endpoints using multiple imputation or for secondary analyses for continuous endpoints. The applicant explained that no rescue treatment was permitted in the studies and that the raised concern was likely due to a misleading formulation in the study protocol. This is accepted.

The PSAAD is a PRO developed by the applicant and contained in the application is a "EMA PRO Briefing book" describing development and validation exercises. An initial psychometric evaluation of the PSAAD was conducted using data from the phase 2b study (B7451006) while the confirmatory evaluation was based on data pooled across treatment arms from the phase 3 monotherapy studies. Validation exercises is considered to have been acceptable and is considered further supported by the outcomes in that a clear trend was shown across treatment arms within each study further supported by study B7451029 outcomes. However, the applicant used the notion "preliminary PSAAD" and described item 12-15 as included for further validation. No further mention regarding analysis or conclusions of any validation exercise based on item 12-15 were found. Upon request from the CHMP, the applicant clarified that items 12-15 were included for future (post-hoc) analyses and that no formal validation exercise based on these items has been conducted or planned. This is accepted. In addition, separate analyses of each of the 11 PSAAD items were requested to elucidate to what extent all items contributed to the PSAAD overall outcome (mean change from baseline) or whether foremost driven by a few items alone. Based on the results provided, it is agreed that there were improvements from baseline to week 12 across all items with what appears to have been similar patterns across both visits and treatment arms irrespective of item and confirmed comparing the studies.

Combination therapy study (B7451029)

Eligible subjects were randomised in a 4:4:4:1:1 ratio to receive 100 mg or 200 mg of abrocitinib or dupilumab or to one of two sequences of placebo for 16 weeks followed by either 100 mg or 200 mg of abrocitinib QD. For the purpose of the primary (final, week 16) analysis the two placebo sequences were combined which is acceptable. Randomisation was only stratified for study centre interpreted as being for administrative reasons only. In the study protocol it was explicitly stated that randomisation

was *not* to be stratified for disease severity or age. Regarding age this study enrolled adults only. While study centre was not considered in the analyses, analyses were performed adjusted by baseline disease severity. Despite not being a stratification factor, the proportion of subjects with moderate and severe disease were shown to be well balanced between treatments. Due to viscosity differences between dupilumab and the matched placebo, and a potential for functional unblinding of the administrator/trainer, the administrator/trainer was to be treated as if unblind and was to be isolated from all other study activities. The approach to achieve blinding of randomised treatment appears appropriate although the use of not identically matching dupilumab placebo is not ideal. Previous treatment with dupilumab was however an exclusion criterion and the risk that a subject could have guessed whether he/she had been randomised to the dupilumab arm should hence have been minor.

Study B7451029 shared a number of features with the two identical monotherapy studies; primary and a number of secondary endpoints, analysis sets and their definitions, the tests and models used in the analyses and missing data handling. Thereby, similar comments as for the monotherapy studies applied thus the applicant was requested to provide confidence intervals with simultaneous coverage probability of 95% two-sided (or 97.5% one-sided) that are compatible with the sequentially rejective multiple testing and to clarify which strategy (e.g. hypothetical strategy, treatment policy strategy) was used for subjects needing rescue in the sensitivity analyses for the binary endpoints using multiple imputation or for secondary analyses for continuous endpoints. This was adequately addressed. As for studies B7451012 and B745103, it was explained that no rescue treatment was permitted in the study and that the raised concern was likely due to a misleading formulation in the study protocol. This is accepted. Furthermore, the same alpha reallocation method as for B7451012/MONO 1 and B7451013/MONO 2 was used, but with different hypotheses and order of hypotheses due to the additional dupilumab comparisons. However, a step-down approach with the NRS4 endpoint from week 2 to earlier time points was used as an additional family of hypothesis tests separate from the described MTP once statistical significance was demonstrated at week 2 for each of the comparisons. The multiple type I error rate is however not protected when including this step-down procedure to test also earlier time-points. Therefore, the additional analyses of NRS4 at earlier time-points will only be considered exploratory and not part of the multiple testing procedure.

Compared to version 1, SAP version 2 (23 January 2020) foremost implemented changes concerning some secondary (non-key) endpoints and raise no concern. The primary completion date was 27 December 2019 and the primary (final, week 16) analysis now presented were based on a database release 05 February 2020. The primary efficacy assessment was at week 12 and used the same two co-primary endpoints as defined for the monotherapy studies. Key secondary efficacy assessments were at week 2 and week 16. Except for one subject, randomised to dupilumab but did not receive any treatment, all randomised subjects were included in the FAS.

Also, in this study, there were a number of subjects with missing PP-NRS data. Importantly they seem to have been similarly distributed between treatment arms; the proportion of subjects with missing data at any study visit from Day 15 forward ranged from 18% to 22%. It is however acknowledged that at time-points earlier than week 2, the proportion of subjects with one or more missing during the first 14 days of dosing ranged from 39% to 44%; one possible explanation being that during the first 14 days, subjects were to their pruritus severity on a daily basis. In study B7451029, PSAAD was among the PROs used and was included as a secondary endpoint but was not identified to be of key interest (compared with other PROs).

Overall, the pivotal studies have been designed in agreement with scientific advice provided by the CHMP and the NCA.

Concerning GCP aspects, no concerns have been identified based on the review of the studies.

Efficacy data and additional analyses

Monotherapy studies B7451012 and B7451013

Study **B7451012** was performed at 69 centres in 8 countries in the US, Canada and the EU. Study **B7451013** was performed at 102 centres in 13 countries in the US, Canada, EU and Asia. It is considered an advantage with inclusion of subjects from different regions of the world. In both studies, completion rates were high (≥ 86.7%) in all active treatment groups. The completion rate was however lower in the placebo groups, 79.2% in study B7451012 and 66.7% in study B7451013. Subjects in the placebo group discontinued due to lack of efficacy and withdrawal by subject/guardian. Groups treated with abrocitinib discontinued due to adverse events which peaked in the 200 mg QD dose group in study B7451012, lack of efficacy and withdrawal by subject/guardian in study B7451013.

In Study **B7451012**, important protocol deviations were reported in 94%, in the category of procedures or tests, of which a missing NRS assessment at any study visit from day 15 forward occurred most frequently. Other reasons were related to errors with laboratory results, inclusion/exclusion criteria, took prohibited concomitant medication, and dosing/administration errors of investigational product/study medication.

Treatment compliance was high, the mean dose compliance was 98%, 99% and 97% in the abrocitinib 200mg QD, abrocitinib 100mg QD, and placebo groups, respectively.

In Study **B7451013**, important protocol deviations were reported in 86%, in the category of procedures or tests, of which a missing NRS assessment occurred most frequently. Other reasons were related to errors with laboratory results, inclusion/exclusion criteria, took prohibited concomitant medication, and dosing/administration errors of investigational product/study medication.

Treatment compliance was high, the mean (SD%) dose compliance was 97% across treatment groups.

Overall, the impact of the protocol deviations in both monotherapy studies (B7451012 and B7451013) is considered to be minor on the efficacy and safety of abrocitinib.

In Study **B7451012**, the Full Analysis Set (FAS) population comprised 387 subjects and the Per Protocol Analysis (PPAS) population comprised 321 subjects. In Study **B7451013**, the FAS population comprised 391 subjects and the PPAS population comprised 310 subjects. Most subjects were males in both studies, females comprised approximately 40 % of the study populations. The median age was 29 and 31 years of age in studies B7451012 and B7451013, respectively. In study B7451012, 84 subjects (21.7%) were below 18 years of age. Of those, 39 subjects were between 12-≤15 of age, and 45 subjects between 15-≤18 years of age. The corresponding figure for study B7451013 was 40 subjects (10.2%) that were below 18 years of age. Of those, 10 subjects were between 12-≤15 of age and 30 subjects between 15-≤18 years of age. There is thus a slight asymmetry between the studies regarding participating number of adolescents, with higher percentage of adolescents in study B7451012. The discrepancy in the number of adolescents between the studies is acknowledged, although a more balanced inclusion of subjects would have been preferred. The number of adolescents in the pivotal monotherapy studies is not considered large, with most subjects being between 12-≤15 of age but accepted, since the clinical picture of moderate to severe AD and treatment options is overall similar between adolescents and adults.

Most subjects were white although subjects with Asian descent or Black/African American also were represented, which is viewed as an advantage. The number of subjects of Asian descent was slightly higher in study B7451013 compared with study B7451012, while the number of Black/African American were similar across the studies. The proportion of subjects from Western Europe and Eastern Europe/Russia were 41% and 45% in studies B7451012 and B7451013, respectively.

In Study **B7451012**, 59% had moderate AD and 41% severe AD according to established disease criteria, while the corresponding values for study **B7451013** were 68% with moderate AD and 32% with severe AD. The mean disease duration was 20 years for the monotherapy studies. Baseline disease characteristics of the abrocitinib clinical programme is considered consistent with those of patients with moderate-to-severe AD.

There were no remarkable findings with respect to medical history, or prior and concomitant medications in either of the monotherapy studies. Prior medication use was similar between treatment arms. Approximately half of subjects had prior exposure to topical agents only, while the other half of the subjects had prior exposure to systemic agents (the majority of which were non-biologics). In Study **B7451012** ~8% had been treated with dupilumab, the corresponding figure for study **B7451013** is ~4%.

For the subgroup analyses of **B7451012** and **B7451013** concerning continuous variables such as age, plots were requested by the CHMP to investigate how the estimated effect of treatment changes over the range of the factor separately for both treatments. It appears that there may be an association between age and treatment effect - especially for the lower dose - with younger subjects showing reduced response to treatment compared to older. It was clarified that this was merely a reflection of baseline difference (younger subjects had more severe disease at baseline, which was not accounted for in the analysis), which was considered comprehensible.

Combination therapy Study B7451029

Study B7451029 was performed at 194 centres in 18 countries including the US, Canada, South America, EU and Asia. It is, as stated above, considered an advantage with inclusion of subjects from different regions of the world including Asia and South America. Completion rates was high (≥ 89.3%) in all treatment groups and higher in study B7451029 compared with the monotherapy studies B7451012 and B7451013. The reasons for discontinuation were adverse events and withdrawal by subject in placebo groups which also was the most frequent reason for discontinuation in the abrocitinib 100 mg group, while adverse event was frequent reason for discontinuation in the abrocitinib 200 mg group. Withdrawal by subject / adverse event were equally frequent reasons for discontinuation in the dupilumab 300 mg Q2W group.

In study **B7451029**, important protocol deviations were reported in 85%, the most frequent in the category of procedures or tests, of which a missing NRS assessment occurred most frequently. Other reasons were related to errors concomitant medication, dosing/administration errors of investigational product/study medication and laboratory results. The impact of the protocol deviations is considered to be minor on the efficacy and safety of abrocitinib.

Treatment compliance was high, the mean (SD%) dose compliance was 100% across all treatment groups.

In study **B7451029**, the FAS population comprised 838 subjects and the PPAS population comprised 600 subjects. Most subjects were males as in the monotherapy studies. The median age was 34 years of age. A small proportion of subjects were older than 65 (n=54; 6.3%).

Most subjects were white (72.4%) although subjects with Asian (21.3%) of Black/African American (4.2%) descent were also represented, viewed as an advantage. The proportion of subjects from Western Europe and Eastern Europe/Russia were 51%.

The mean disease duration was 21.8 years. 64.6% had moderate AD and 35.4% severe according to established criteria. The pruritus numbering rating scale (NRS) showed that the subjects had moderate itch (7).

There were no remarkable findings with respect to medical history, or prior and concomitant medications in the study. Prior medication use was similar between treatment arms. Approximately half of subjects (56.5%) had prior exposure to topical agents only, the other half of the subjects had prior exposure to systemic agents (non-biologic or biologic, excluding dupilumab).

Efficacy results

In **study B7451012**, both co-primary efficacy endpoints were met when evaluated at week 12. The proportion of subjects who achieved an IGA response of clear or almost clear and a more than 2 points improvement from baseline at week 12, was statistically significant for both the 100 mg group 23.7 (17.0, 30.4) and the 200 mg group 43.8 (35.9, 51.7) compared with placebo group 7.9 (1.8, 14.0).

The proportion of subjects who achieved an EASI response of >= 75% improvement from baseline at week 12, was for the 100 mg group 39.7 (32.1, 47.4) and the 200 mg group 62.7 (55.1, 70.4) compared with placebo 11.8 (4.6, 19.1).

Superiority of abrocitinib versus placebo was demonstrated for both doses investigated, 100 mg QD and 200 mg QD. A dose-response relationship was demonstrated, with the highest level of efficacy obtained for the dose 200 mg QD. The results are assessed of clinical relevance in the investigated target population moderate to severe AD.

The key secondary efficacy endpoints were ≥4 points improvement from baseline in the peak pruritus NRS scale (PP-NRS4) at weeks 2, 4 and 12, and the change from baseline in Pruritus and Symptoms Assessment for AD (PSAAD).

In the PP-NRS4 analysis week 12, a dose-dependent efficacy was demonstrated for abrocitinib 100 mg, and for abrocitinib 200 mg versus the placebo group. A statistically significant efficacy on itch is obtained already at week 2. The maximum efficacy evaluated as PP-NRS-4 seems to be obtained in week 4.

Superiority of abrocitinib 100 mg QD ($p<0.001$) and 200 mg QD compared with vehicle ($p<0.001$) were demonstrated also for itch evaluated by PSAAD.

In **study B7451013**, both co-primary efficacy endpoints were met. The proportion of subjects who achieved an IGA response of clear or almost clear and a more than 2 points improvement from baseline at week 12, was statistically significant for both the 100 mg group 28.4 (21.3, 35.5) and the 200 mg group 38.1 (30.4, 45.7) compared with placebo 9.1 (2.7, 15.5).

The proportion of subjects who achieved an EASI response of >= 75% improvement from baseline at week 12, was for the 100 mg group 44.5 (36.7, 52.3) and the 200 mg group 61.0 (53.3, 68.7) compared with placebo 10.4 (3.6, 17.2).

Superiority of abrocitinib 100 mg QD and 200 mg QD versus placebo was thus demonstrated. A dose-response relationship was shown, with the highest level of efficacy obtained for the dose 200 mg QD.

The results are of clinical relevance in the investigated target population moderate to severe AD.

The key secondary efficacy endpoints were ≥4 points improvement from baseline in the peak pruritus NRS scale (PP-NRS4) at weeks 2, 4 and 12, and the change from baseline in Pruritus and Symptoms Assessment for AD (PSAAD).

In the PP-NRS4 analysis week 12, a dose-dependent efficacy was demonstrated for abrocitinib 100 mg, and for abrocitinib 200 mg compared with the placebo group. A statistically significant efficacy on itch is obtained already at week 2. The maximum efficacy evaluated as PP-NRS-4 seems to be obtained during week 4-8.

Superiority of abrocitinib 100 mg QD (p<0.0001) and 200 mg QD to vehicle (p<0.0001) were demonstrated also for itch evaluated by PSAAD.

In study **B7451029,** the proportion of subjects who achieved an IGA response of clear or almost clear and a more than 2 points improvement from baseline at week 12, was statistically significant for both the 100 mg group 36.6 (30.4, 42.8), the 200 mg group 48.4 (41.8, 55.0) and dupilumab 36.5 (30.4, 42.6) compared with the placebo group 14.0 (8.0, 19.9).

The proportion of subjects who achieved an EASI response of >= 75% improvement from baseline at week 12, was for the 100 mg group 58.7 (52.4, 65.0), the 200 mg group 70.3 (64.3, 76.4), dupilumab 58.1 (51.9, 64.3) and for placebo 27.1 (19.5, 34.8).

Superiority of abrocitinib 100 mg QD, 200 mg QD and dupilumab versus placebo was demonstrated.

The results with to co-primary endpoints IGA and EASI-75 demonstrated a similar level of efficacy for abrocitinib 100 mg QD and for dupilumab, while abrocitinib 200 mg QD was superior to dupilumab when dosed according to approved product information.

Additional supportive analyses were performed for the PPAS population, and for the FAS population using a TP analysis where all missing responses were multiply imputed, and with imputation using dropout reason. The results were consistent with the results of the FAS primary analyses.

Efficacy of abrocitinib 100 mg QD and 200 mg QD versus dupilumab

The key secondary efficacy endpoints were at least a 4 points improvement in the severity of Pruritus Numerical Rating Scale (NRS) from baseline at week 2, a response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16 and a response based on achieving EASI-75 (≥75% improvement from baseline) at week 16.

PP-NRS4 responder proportion at week 2 was statistically significantly higher for abrocitinib 100 mg and for 200 mg compared with placebo. Abrocitinib 200 mg QD had statistically significantly higher proportion of PP-NRS4 responders at week 2 compared with dupilumab, while the difference between abrocitinib 100 mg and dupilumab at week 2 did not reach statistical significance.

IGA responder proportion at week 16, was statistically significantly higher for abrocitinib 100 mg 34.8 (28.6, 40.9) and for abrocitinib 200 mg 47.5 (40.9, 54.1) compared with placebo 12.9 (7.0, 18.8). When compared with dupilumab, treatment effect (IGA responder proportion corrected for placebo) at week 16 was greater with abrocitinib 200 mg QD than dupilumab 38.8 (32.5, 45.1), and similar between abrocitinib 100 mg QD and dupilumab.

For the third key secondary efficacy endpoint, proportion of EASI-75 responders, a statistically significantly higher efficacy for abrocitinib 100 mg 60.3 (53.9, 66.6) and for abrocitinib 200 mg 71.0 (65.1, 77.0) compared with placebo 30.6 (22.5, 38.8) was noted. When compared with dupilumab, treatment effect (EASI-75 responder proportion corrected for placebo) at week 16 was greater with abrocitinib 200 mg QD than dupilumab, and similar between abrocitinib 100 mg QD and dupilumab.

Efficacy of medicated topical therapy when added to abrocitinib and dupilumab

In the combination therapy study B7451029, several treatment options were allowed (topical corticosteroids, calcineurin inhibitors (e.g., tacrolimus, pimecrolimus) or a PDE4 inhibitor (e.g., crisaborole) may be used instead of corticosteroids.

The applicant tried to calculate a net extra effect of abrocitinib plus topical corticosteroids. There was no evidence of clinically meaningful absolute or relative increase in treatment effect for EASI-75 or PP-NRS4 response. The applicant does not propose to add wording on an increase in treatment effect with the addition of medicated topical therapy to abrocitinib in the SmPC.

Effect of seasonal variations

There is no concern of seasonal variations on treatment with abrocitinib since the performed clinical trials were performed at different location all over the world which covers different seasonal variations.

Analysis performed across trials – magnitude of treatment effect

A comparison of efficacy results across all pivotal studies (**B7451012**, **B7451013** and **B7451029**) was made. In each individual phase 3 monotherapy or combination therapy study, both doses of abrocitinib met each of the co-primary endpoints. Abrocitinib 200 mg QD consistently had a higher magnitude of effect than 100 mg QD. The differences from placebo were statistically significant and are assessed as clinically relevant.

In the two phase 3 monotherapy studies, treatment effect for each abrocitinib dose was similar across studies for each of the key secondary endpoints. Abrocitinib 200 mg QD consistently had a higher magnitude of effect than 100 mg QD.

In the combination therapy study, treatment effect for each abrocitinib dose on the key secondary endpoint PP-NRS4 at week 2 was like that observed in the monotherapy pool, with evidence of dose-dependent increase in treatment effect.

The time-course of IGA, EASI-75 and PP-NRS4 responses of monotherapy and combination therapy showed that the effect on itch (PP-NRS4) is observed sooner than the effect on overall AD symptoms detected by IGA-75 and EASI.

Sub-group analyses

Subgroup analyses by intrinsic factors (age, sex, race ethnicity, weight and body mass index, disease severity by IGA and EASI, percent BSA affected by AD, and comorbidities) and extrinsic factors (geographic region and prior therapy for AD) demonstrated that effects of each dose of abrocitinib were similar across subgroups for the co-primary endpoints IGA and EASI-75. The effects of each dose of abrocitinib were similar across subgroups also for the key secondary efficacy endpoint PP-NRS4.

Both abrocitinib doses were efficacious regardless of the subject's baseline severity or extent of AD.

Clinical studies in special populations

Adolescents were included in both the monotherapy studies, 84 subjects in study B7451012 and 40 subjects in study B7451013. The combination therapy study B7451029 only included adults. The oldest individual in study B7451012 was 84 years, 83 years in study B7451013 and 84 years of age in study B7451029.

No special studies in children have been performed. The disease characteristics is similar in adults and adolescents with moderate to severe AD. Moreover, the treatment options are overall similar. The absence of adolescents in the combination therapy study could be considered a shortcoming of study B7451029, which has been extensively discussed by the applicant. The arguments (similar disease characteristics and treatment options as in adults) are overall accepted. Furthermore, a study with similar design as in study B7451029 with concomitant medicated topical therapy in adolescents is ongoing.

Duration of treatment effect – need for retreatment

The Phase 3 study **B7451014** was designed to evaluate and compare the maintenance of effect of two doses of abrocitinib and placebo in subjects aged 12 and above with moderate to severe AD who responded to an initial open-label run-in treatment of 200 mg abrocitinib QD. Data from week 12 were consistent with the short-term efficacy demonstrated for abrocitinib 200 mg QD in the individual Phase 2b and Phase 3 monotherapy studies.

Long-term efficacy

Phase 3 Study **B7451015** was designed to estimate the long-term efficacy and safety of 100 mg and 200 mg QD abrocitinib with or without topical treatments in adult and adolescent subjects who previously participated in qualifying abrocitinib AD trials.

Updated efficacy data submitted at D121 of the procedure indicate that after a quick onset the effect stabilises after about 24 weeks and tends to pertain or decrease a bit at 48 weeks. Upon request from the CHMP, the applicant discussed the slight decrease in response rate and found 'the fluctuating nature of the disease' or 'regression to the mean' potential causes of this observation. Data > 48 weeks supported the maintenance of the abrocitinib effect over time. The applicant committed to submitting a post-approval type II variation to further update SmPC section 5.1, if required, by 31 December 2022.

2.6.7. Conclusions on the clinical efficacy

Overall, the three pivotal studies had an adequate design. 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 atopic dermatitis from 12 years of age and above. The observed level of clinical efficacy is assessed to be of clinical relevance. Cibinqo can be administered together with medicated topical therapy (most often topical corticosteroids).

The current application includes a direct comparison with dupilumab. The efficacy of abrocitinib 100 mg QD is comparable to the efficacy of the active comparator dupilumab, while abrocitinib 200 mg QD is superior to dupilumab in overall AD endpoints, but most markedly on itch, the most troublesome symptom.

Nevertheless, from a safety perspective, the CHMP considered that the effect of abrocitinib on developing bone should be more thoroughly characterised including relevant long-term data before a potential use in adolescents can be further assessed (see Safety section). Therefore, the therapeutic indication was restricted to adults only.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Pooling strategy: There are 3 pre-specified safety pools, the Primary Safety Pool (Primary Pool), the All Exposure Safety Pool (All Exposure Pool) and the Phase 1 Safety Pool. In this document, the Primary Safety Pool will be referred to as the Primary Pool and the All Exposure Safety Pool will be referred to as the All Exposure Pool.

- The Primary Pool includes studies with a placebo comparator, of similar duration (12 16 weeks), same doses of abrocitinib, similar patient population, and comparable safety outcome assessment. The similarities in the study design, patient population, and assessment justify the pooling of these studies.

- The All Exposure Pool includes all subjects who received at least one dose of abrocitinib in all Phase 2b and 3 studies of subjects with AD from the relevant dosing groups (100 mg QD and 200 mg QD), including the LTE study. For ongoing studies, the cutoff date was 22 April 2020. Day 1 for all subjects is the first day of exposure to abrocitinib 100 or 200 mg QD.

In addition, there was a Phase 1 Safety Pool including 15 completed Phase 1 studies (please refer to the efficacy section for tables summarising these studies). The focus in this safety assessment will be on the Primary Safety and All Exposure pools.

A total of 2856 subjects with AD were exposed to abrocitinib during the development programme. Among these subjects 885 were exposed to 100 mg QD and 1971 to 200 mg QD.

Table 37 Overview of Exposure Duration in the Abrocitinib Studies Supporting the Summary of Clinical Safety

Phase	Study	Abrocitinib 100 mg QD n/PY	Abrocitinib 200 mg QD n/PY	All Abrocitinib n/PY
Phase 2	B7451006	56/ 10.9	55/ 12.0	111/ 23.0
Phase 3	B7451012 + B7451015	195/ 198.4	174/ 193.4	369/ 391.8
	B7451013 + B7451015	206/ 174.4	155/ 133.2	361/ 307.6
	B7451014 + B7451015	NA	1233/ 448.8	1233/ 448.8
	B7451029 + B7451015	428/ 237.1	354/ 205.4	782/ 442.5
Total	All Exposure Pool	885/ 620.8	1971/ 992.9	2856/ 1614

Abbreviations: NA = not applicable; PY = patient years; QD = once daily.

Table 38 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Study Treatment Exposure – Primary Safety Pool

	Placebo (N=342)	Abrocitinib 100mg QD (N=608)	Abrocitinib 200mg QD (N=590)	All Abrocitinib (N=1198)
Duration of Treatment (Days) [1]				
n	342	608	590	1198
Median (Q1, Q3)	85.0 (83.0, 112.0)	86.0 (84.0, 112.0)	86.0 (85.0, 112.0)	86.0 (85.0, 112.0)
Mean (Std. Dev.)	83.1 (31.6)	89.2 (25.2)	90.9 (21.9)	90.1 (23.7)
Range	(1 - 132)	(1 - 128)	(1 - 149)	(1 - 149)
Category n (%)				
< 1 Week	4 (1.2)	8 (1.3)	5 (0.8)	13 (1.1)
>= 1 Week to < 4 Weeks	30 (8.8)	24 (3.9)	15 (2.5)	39 (3.3)
>= 4 Weeks to < 8 Weeks	32 (9.4)	21 (3.5)	16 (2.7)	37 (3.1)
>= 8 Weeks to < 10 Weeks	5 (1.5)	13 (2.1)	9 (1.5)	22 (1.8)
>= 10 Weeks to < 14 Weeks	151 (44.2)	320 (52.6)	336 (56.9)	656 (54.8)
>= 14 Weeks	120 (35.1)	222 (36.5)	209 (35.4)	431 (36.0)
Total	342	608	590	1198

Includes Studies: B7451006, B7451012, B7451013, B7451029
[1] Number of days from first to and including last day of each study treatment (Last Dosing Date - First Dosing Date + 1).
PFIZER CONFIDENTIAL Source Data: adex Date of ADAM Dataset Creation: 03MAR2020 Output File: ./ad scs/PSP/adex s002 Date of Generation: 03MAR2020 (20:31)
Table PSP.14.4.1.1 is for Pfizer internal use.

Table 39 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Study Treatment Exposure – All Exposure Pool

	Abrocitinib 100mg QD (N=885)	Abrocitinib 200mg QD (N=1971)	All Abrocitinib (N=2856)
Duration of Treatment (Days) [1]			
n	885	1971	2856
Median (Q1, Q3)	244.0 (127.0, 373.0)	88.0 (85.0, 276.0)	133.0 (85.0, 309.0)
Mean (Std. Dev.)	256.2 (162.6)	184.0 (153.7)	206.4 (160.0)
Range	(1 - 756)	(1 - 741)	(1 - 756)
Category n (%)			
< 4 Weeks	36 (4.1)	50 (2.5)	86 (3.0)
>= 4 Week to < 12 Weeks	64 (7.2)	236 (12.0)	300 (10.5)
>= 12 Weeks to < 24 Weeks	232 (26.2)	990 (50.2)	1222 (42.8)
>= 24 Weeks to < 36 Weeks	139 (15.7)	114 (5.8)	253 (8.9)
>= 36 Weeks to < 48 Weeks	149 (16.8)	240 (12.2)	389 (13.6)
>= 48 Weeks to < 60 Weeks	112 (12.7)	140 (7.1)	252 (8.8)
>= 60 Weeks to < 72 Weeks	73 (8.2)	83 (4.2)	156 (5.5)
>= 72 Weeks to < 84 Weeks	44 (5.0)	71 (3.6)	115 (4.0)
>= 84 Weeks to < 96 Weeks	27 (3.1)	34 (1.7)	61 (2.1)
>= 96 Weeks	9 (1.0)	13 (0.7)	22 (0.8)
Total	885	1971	2856
Cumulative Exposure n (%)			
>= 24 Weeks	553 (62.5)	695 (35.3)	1248 (43.7)
>= 36 Weeks	414 (46.8)	581 (29.5)	995 (34.8)
>= 48 Weeks	265 (29.9)	341 (17.3)	606 (21.2)
>= 72 Weeks	80 (9.0)	118 (6.0)	198 (6.9)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029
[1] Number of days from first to and including last day of each abrocitinib treatment (Last Dosing Date - First Dosing Date + 1).
PFIZER CONFIDENTIAL Source Data: adex Date of ADAM Dataset Creation: 01JUN2020 Output File: ./ad scs/AEP/adex s002 Date of Generation: 01JUN2020 (04:39)
Table AEP.14.4.1.1 is for Pfizer internal use.

Subgroups

Adolescents: In the All Exposure Pool, 364 adolescent subjects were exposed representing 230.3 patient years.

Patients > 65: In the All Exposure Pool, 145 older subjects were exposed representing 79.4 patient years.

In the All Exposure group, a greater number of subjects were male (1553, 908.6 PY) compared to female (1303, 705.0 PY). There was more overall exposure in the White (2063, 1125 PY) and Asian (553, 350.3 PY) subgroups relative to the Black/African American (170, 97.0 PY) and Other (70, 41.4 PY) subgroups.

Reasons for Discontinuation

Table 40 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Discontinuation from Study – Primary Safety Pool

Number (%) of Subjects	Placebo (N=342) n (%)	Abrocitinib 100 mg QD (N=608) n (%)	Abrocitinib 200 mg QD (N=590) n (%)	All Abrocitinib (N=1198) n (%)
Discontinued	84 (24.6)	82 (13.5)	66 (11.2)	148 (12.4)
Adverse Event	29 (8.5)	31 (5.1)	30 (5.1)	61 (5.1)
Death	0	1 (0.2)	0	1 (0.1)
Lack of Efficacy	15 (4.4)	8 (1.3)	4 (0.7)	12 (1.0)
Lost to Follow-Up	5 (1.5)	5 (0.8)	3 (0.5)	8 (0.7)
Pregnancy	0	0	1 (0.2)	1 (0.1)
Protocol Deviation	9 (2.6)	6 (1.0)	7 (1.2)	13 (1.1)
Withdrawal By Subject or Parent/Guardian	24 (7.0)	23 (3.8)	12 (2.0)	35 (2.9)
Medication Error Without Associated Adverse Event	1 (0.3)	1 (0.2)	1 (0.2)	2 (0.2)
No Longer Meets Eligibility Criteria	0	1 (0.2)	1 (0.2)	2 (0.2)
Other	1 (0.3)	6 (1.0)	7 (1.2)	13 (1.1)
Completed the Study	141 (41.2)	309 (50.8)	316 (53.6)	625 (52.2)
Completed Evaluations for the Primary Safety Pool [1]	261 (76.3)	533 (87.7)	536 (90.8)	1069 (89.2)

2.6.8.2. Adverse events

Overall, in the Primary Pool there were more treatment emergent adverse events in the abrocitinib-treated groups compared to placebo (Table 42).

The proportion of subjects with treatment related TEAEs was similar between the abrocitinib 100 mg QD and placebo treatment groups and higher in the abrocitinib 200 mg QD treatment group. Of the all causality TEAEs, 29.1% to 41.2% were considered treatment-related by the Investigator.

Table 41 Abroticinib Summary of Clinical Safety (Atopic Dermatitis) Treatment-Emergent Adverse Events (All Causalities) – Primary Safety Pool

Number (%) of Subjects	Placebo n (%)	Abrocitinib 100mg QD n (%)	Abrocitinib 200mg QD n (%)	All Abrocitinib n (%)
Subjects evaluable for adverse events	342	608	590	1198
Number of adverse events	360	816	921	1737
Subjects with adverse events	188 (55.0)	371 (61.0)	403 (68.3)	774 (64.6)
Subjects with serious adverse events	11 (3.2)	19 (3.1)	11 (1.9)	30 (2.5)
Subjects with severe adverse events	20 (5.8)	29 (4.8)	19 (3.2)	48 (4.0)
Subjects discontinued from study due to adverse events [1]	31 (9.1)	33 (5.4)	32 (5.4)	65 (5.4)
Subjects discontinued study drug due to AE and continue study [2]	3 (0.9)	6 (1.0)	1 (0.2)	7 (0.6)
Subjects with dose reduced or temporary discontinuation due to adverse events	14 (4.1)	28 (4.6)	27 (4.6)	55 (4.6)

Includes Studies: B7451006, B7451012, B7451013, B7451029
Includes data up to 28 days after last dose of study.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
Two subjects (B7451029 1346 13469002, B7451029 1247 12479010) had an AE that started before Week 16 and discontinued due to that AE after Week 16. Those AEs were also included in this table.
[1] Subjects who had an AE record that indicated that the AE caused the subject to be discontinued from the study.
[2] Subjects who had an AE record that indicated that action taken with study treatment was drug withdrawn but AE did not cause the subject to be discontinued from study.
MedDRA v22.1 coding dictionary applied.

Table PSP.14.3.1.1.1.2 F
Abrocitinib Summary of Clinical Safety (Atopic Dermatitis)
Treatment-Emergent Adverse Events (Treatment Related) - Primary Safety Pool

Number (%) of Subjects	Placebo n (%)	Abrocitinib 100mg QD n (%)	Abrocitinib 200mg QD n (%)	All Abrocitinib n (%)
Subjects evaluable for adverse events	342	608	590	1198
Number of adverse events	107	238	380	618
Subjects with adverse events	63 (18.4)	142 (23.4)	201 (34.1)	343 (28.6)
Subjects with serious adverse events	3 (0.9)	7 (1.2)	2 (0.3)	9 (0.8)
Subjects with severe adverse events	9 (2.6)	9 (1.5)	6 (1.0)	15 (1.3)
Subjects discontinued from study due to adverse events [1]	15 (4.4)	15 (2.5)	17 (2.9)	32 (2.7)
Subjects discontinued study drug due to AE and continue study [2]	2 (0.6)	5 (0.8)	1 (0.2)	6 (0.5)
Subjects with dose reduced or temporary discontinuation due to adverse events	7 (2.0)	12 (2.0)	16 (2.7)	28 (2.3)

Table 42 Treatment-Emergent Adverse Events by System Organ Class (All Causalities) - Primary Safety Pool

Number of Subjects Evaluable for AEs	Placebo (N=342)	Abrocitinib 100mg QD (N=608)	Abrocitinib 200mg QD (N=590)	All Abrocitinib (N=1198)
Number (%) of Subjects: by SYSTEM ORGAN CLASS	n (%)	n (%)	n (%)	n (%)
With Any adverse event	188 (55.0)	371 (61.0)	403 (68.3)	774 (64.6)
Blood And Lymphatic System Disorders	1 (0.3)	10 (1.6)	16 (2.7)	26 (2.2)
Cardiac Disorders	5 (1.5)	9 (1.5)	12 (2.0)	21 (1.8)
Congenital, Familial And Genetic Disorders	0	0	1 (0.2)	1 (0.1)
Ear And Labyrinth Disorders	4 (1.2)	2 (0.3)	3 (0.5)	5 (0.4)
Endocrine Disorders	0	0	2 (0.3)	2 (0.2)
Eye Disorders	8 (2.3)	23 (3.8)	17 (2.9)	40 (3.3)
Gastrointestinal Disorders	27 (7.9)	78 (12.8)	135 (22.9)	213 (17.8)
General Disorders And Administration Site Conditions	12 (3.5)	32 (5.3)	30 (5.1)	62 (5.2)
Hepatobiliary Disorders	1 (0.3)	1 (0.2)	1 (0.2)	2 (0.2)
Immune System Disorders	1 (0.3)	3 (0.5)	5 (0.8)	8 (0.7)
Infections And Infestations	90 (26.3)	214 (35.2)	204 (34.6)	418 (34.9)
Injury, Poisoning And Procedural Complications	13 (3.8)	15 (2.5)	15 (2.5)	30 (2.5)
Investigations	13 (3.8)	33 (5.4)	50 (8.5)	83 (6.9)
Metabolism And Nutrition Disorders	5 (1.5)	8 (1.3)	13 (2.2)	21 (1.8)
Musculoskeletal And Connective Tissue Disorders	13 (3.8)	23 (3.8)	29 (4.9)	52 (4.3)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	1 (0.3)	4 (0.7)	1 (0.2)	5 (0.4)
Nervous System Disorders	21 (6.1)	62 (10.2)	67 (11.4)	129 (10.8)
Pregnancy, Puerperium And Perinatal Conditions	1 (0.3)	0	2 (0.3)	2 (0.2)
Psychiatric Disorders	10 (2.9)	14 (2.3)	9 (1.5)	23 (1.9)
Renal And Urinary Disorders	1 (0.3)	4 (0.7)	7 (1.2)	11 (0.9)
Reproductive System And Breast Disorders	2 (0.6)	7 (1.2)	9 (1.5)	16 (1.3)
Respiratory, Thoracic And Mediastinal Disorders	17 (5.0)	34 (5.6)	31 (5.3)	65 (5.4)
Skin And Subcutaneous Tissue Disorders	59 (17.3)	94 (15.5)	89 (15.1)	183 (15.3)
Social Circumstances	0	2 (0.3)	0	2 (0.2)
Surgical And Medical Procedures	0	3 (0.5)	1 (0.2)	4 (0.3)
Vascular Disorders	3 (0.9)	9 (1.5)	7 (1.2)	16 (1.3)

Table 43 Treatment-Emergent Adverse Events by System Organ Class (All Causalities) by Baseline Age Primary Safety Pool Baseline Age (years): < 18

Number of Subjects Evaluable for AEs	Placebo (N=25)	Abrocitinib 100mg QD (N=51)	Abrocitinib 200mg QD (N=48)	All Abrocitinib (N=99)
Number (%) of Subjects: by SYSTEM ORGAN CLASS	n (%)	n (%)	n (%)	n (%)
With Any adverse event	13 (52.0)	34 (66.7)	37 (77.1)	71 (71.7)
Blood And Lymphatic System Disorders	0	1 (2.0)	3 (6.3)	4 (4.0)
Cardiac Disorders	0	1 (2.0)	0	1 (1.0)
Ear And Labyrinth Disorders	0	1 (2.0)	0	1 (1.0)
Eye Disorders	0	2 (3.9)	0	2 (2.0)
Gastrointestinal Disorders	1 (4.0)	8 (15.7)	14 (29.2)	22 (22.2)
General Disorders And Administration Site Conditions	0	3 (5.9)	0	3 (3.0)
Immune System Disorders	0	0	1 (2.1)	1 (1.0)
Infections And Infestations	7 (28.0)	22 (43.1)	21 (43.8)	43 (43.4)
Injury, Poisoning And Procedural Complications	2 (8.0)	0	1 (2.1)	1 (1.0)
Investigations	1 (4.0)	0	3 (6.3)	3 (3.0)
Metabolism And Nutrition Disorders	2 (8.0)	2 (3.9)	0	2 (2.0)
Musculoskeletal And Connective Tissue Disorders	0	0	1 (2.1)	1 (1.0)
Nervous System Disorders	0	4 (7.8)	6 (12.5)	10 (10.1)
Psychiatric Disorders	1 (4.0)	0	0	0
Renal And Urinary Disorders	0	0	1 (2.1)	1 (1.0)
Reproductive System And Breast Disorders	0	0	1 (2.1)	1 (1.0)
Respiratory, Thoracic And Mediastinal Disorders	1 (4.0)	5 (9.8)	5 (10.4)	10 (10.1)
Skin And Subcutaneous Tissue Disorders	4 (16.0)	9 (17.6)	6 (12.5)	15 (15.2)

Table 44 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Incidence of Treatment-Emergent Adverse Events Occurring in >= 2% of Subjects in Any Treatment Group by System Organ Class and Preferred Term

Number of Subjects Evaluable for AEs	Placebo (N=342)	Abrocitinib 100mg QD (N=608)	Abrocitinib 200mg QD (N=590)	All Abrocitinib (N=1198)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)
Subjects with events	185 (54.1)	360 (59.2)	397 (67.3)	757 (63.2)
Blood And Lymphatic System Disorders	1 (0.3)	10 (1.6)	16 (2.7)	26 (2.2)
Cardiac Disorders	5 (1.5)	9 (1.5)	12 (2.0)	21 (1.8)
Eye Disorders	8 (2.3)	23 (3.8)	17 (2.9)	40 (3.3)
Gastrointestinal Disorders	27 (7.9)	78 (12.8)	135 (22.9)	213 (17.8)
Diarrhoea	10 (2.9)	10 (1.6)	16 (2.7)	26 (2.2)
Nausea	7 (2.0)	37 (6.1)	86 (14.6)	123 (10.3)
Vomiting	3 (0.9)	9 (1.5)	19 (3.2)	28 (2.3)
General Disorders And Administration Site Conditions	12 (3.5)	32 (5.3)	30 (5.1)	62 (5.2)
Infections And Infestations	90 (26.3)	214 (35.2)	204 (34.6)	418 (34.9)
Folliculitis	7 (2.0)	6 (1.0)	10 (1.7)	16 (1.3)
Herpes simplex	3 (0.9)	10 (1.6)	17 (2.9)	27 (2.3)
Nasopharyngitis	27 (7.9)	75 (12.3)	51 (8.6)	126 (10.5)
Upper respiratory tract infection	19 (5.6)	40 (6.6)	30 (5.1)	70 (5.8)
Urinary tract infection	4 (1.2)	10 (1.6)	13 (2.2)	23 (1.9)
Injury, Poisoning And Procedural Complications	13 (3.8)	15 (2.5)	15 (2.5)	30 (2.5)
Investigations	13 (3.8)	33 (5.4)	50 (8.5)	83 (6.9)
Blood creatine phosphokinase increased	5 (1.5)	14 (2.3)	17 (2.9)	31 (2.6)
Metabolism And Nutrition Disorders	5 (1.5)	8 (1.3)	13 (2.2)	21 (1.8)
Musculoskeletal And Connective Tissue Disorders	13 (3.8)	23 (3.8)	29 (4.9)	52 (4.3)
Nervous System Disorders	21 (6.1)	62 (10.2)	67 (11.4)	129 (10.8)
Dizziness	3 (0.9)	11 (1.8)	17 (2.9)	28 (2.3)
Headache	12 (3.5)	36 (5.9)	46 (7.8)	82 (6.8)
Psychiatric Disorders	10 (2.9)	14 (2.3)	9 (1.5)	23 (1.9)
Respiratory, Thoracic And Mediastinal Disorders	17 (5.0)	34 (5.6)	31 (5.3)	65 (5.4)
Skin And Subcutaneous Tissue Disorders	59 (17.3)	94 (15.5)	89 (15.1)	183 (15.3)
Acne	0	10 (1.6)	28 (4.7)	38 (3.2)
Dermatitis atopic	37 (10.8)	45 (7.4)	24 (4.1)	69 (5.8)

Table 45 Incidence of Treatment-Emergent Adverse Events Occurring in >= 2% of Subjects in Any Treatment Group by System Organ Class and Preferred Term by Baseline Age-Primary Safety Pool

Baseline Age (years): < 18

Number of Subjects Evaluable for AEs	Placebo (N=25)	Abrocitinib 100mg QD (N=51)	Abrocitinib 200mg QD (N=48)	All Abrocitinib (N=99)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)
Subjects with events	13 (52.0)	33 (64.7)	37 (77.1)	70 (70.7)
Blood And Lymphatic System Disorders	0	1 (2.0)	3 (6.3)	4 (4.0)
Cardiac Disorders	0	1 (2.0)	0	1 (1.0)
Eye Disorders	0	2 (3.9)	0	2 (2.0)
Gastrointestinal Disorders	1 (4.0)	8 (15.7)	14 (29.2)	22 (22.2)
Nausea	1 (4.0)	4 (7.8)	9 (18.8)	13 (13.1)
Vomiting	0	1 (2.0)	4 (8.3)	5 (5.1)
General Disorders And Administration Site Conditions	0	3 (5.9)	0	3 (3.0)
Infections And Infestations	7 (28.0)	22 (43.1)	21 (43.8)	43 (43.4)
Folliculitis	0	1 (2.0)	0	1 (1.0)
Herpes simplex	0	0	2 (4.2)	2 (2.0)
Nasopharyngitis	3 (12.0)	11 (21.6)	5 (10.4)	16 (16.2)
Upper respiratory tract infection	3 (12.0)	3 (5.9)	5 (10.4)	8 (8.1)
Urinary tract infection	0	0	1 (2.1)	1 (1.0)
Injury, Poisoning And Procedural Complications	2 (8.0)	0	1 (2.1)	1 (1.0)
Investigations	1 (4.0)	0	3 (6.3)	3 (3.0)
Blood creatine phosphokinase increased	0	0	1 (2.1)	1 (1.0)
Metabolism And Nutrition Disorders	2 (8.0)	2 (3.9)	0	2 (2.0)
Musculoskeletal And Connective Tissue Disorders	0	0	1 (2.1)	1 (1.0)
Nervous System Disorders	0	4 (7.8)	6 (12.5)	10 (10.1)
Dizziness	0	1 (2.0)	0	1 (1.0)
Headache	0	4 (7.8)	5 (10.4)	9 (9.1)
Psychiatric Disorders	1 (4.0)	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	1 (4.0)	5 (9.8)	5 (10.4)	10 (10.1)
Skin And Subcutaneous Tissue Disorders	4 (16.0)	9 (17.6)	6 (12.5)	15 (15.2)
Acne	0	0	1 (2.1)	1 (1.0)
Dermatitis atopic	2 (8.0)	8 (15.7)	1 (2.1)	9 (9.1)

The PT 'nausea' is the most commonly reported adverse reaction, together with 'vomiting' within the SOC gastrointestinal disorders demonstrating a dose relationship. According to the applicant, data indicates that the mechanism may be related to local gastric concentration of abrocitinib suggesting the risk of nausea which may be mitigated by taking abrocitinib with food for those that experience it. This is based on the findings in two Phase 1 studies (B7451004 and B7451032) examining abrocitinib exposure in the fed and fasted state.

The percentage of TEAEs are somewhat higher in adolescents compared to the total population within the Primary safety pool. The TEAEs within the placebo treated group on the other hand are not higher in adolescents, rather similar or slightly less. Based on the higher percentage of TEAEs in adolescents and the assumption of dose dependent TEAES, the applicant was requested by the CHMP to discuss this in relation to abrocitinib exposure in adolescents. According to the table of Treatment-Emergent Adverse Events by System Organ Class (All Causalities) by Baseline Age Primary Safety Pool- there is a clear discrepancy and increase of percentage of reported TEAEs within the SOC "Respiratory, Thoracic And Mediastinal Disorders" of abrocitinib treated subjects < 18 years of age compared to placebo and

compared to all subjects. Further, the applicant was requested to comment, present and discuss further data of these 11 (eleven) cases whereof 10 were reported from the abrocitinib treated groups.

All Exposure Pool

There was a similar proportion of subjects reporting AEs in the 2 treatment groups (Table 13). There were slightly more subjects with SAEs, severe AEs, and AEs leading to withdrawal in the 100 mg QD treatment group. The proportion of subjects with treatment-related TEAEs was higher in the abrocitinib 200 mg QD treatment group. Among all causality AEs, 38.6% were considered treatment-related by the Investigator

Table 46 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Treatment- Emergent Adverse Events (All Causalities)

Number (%) of Subjects	Abrocitinib 100mg QD n (%)	Abrocitinib 200mg QD n (%)	All Abrocitinib n (%)
Subjects evaluable for adverse events	885	1971	2856
Number of adverse events	1968	4315	6283
Subjects with adverse events	627 (70.8)	1420 (72.0)	2047 (71.7)
Subjects with serious adverse events	48 (5.4)	74 (3.8)	122 (4.3)
Subjects with severe adverse events	69 (7.8)	102 (5.2)	171 (6.0)
Subjects discontinued from study due to adverse events [1]	77 (8.7)	155 (7.9)	232 (8.1)
Subjects discontinued study drug due to AE and continue study [2]	11 (1.2)	14 (0.7)	25 (0.9)
Subjects with dose reduced or temporary discontinuation due to adverse events	83 (9.4)	206 (10.5)	289 (10.1)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029
Includes data up to 28 days after last dose of study.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
[1] Subjects who had an AE record that indicated that the AE caused the subject to be discontinued from the study.
[2] Subjects who had an AE record that indicated that action taken with abrocitinib treatment was drug withdrawn but AE did not cause the subject to be discontinued from study.
MedDRA v23.0 coding dictionary applied.

The SOCs with the highest proportion of events in abrocitinib treatment groups were Infections and infestations, Gastrointestinal disorders, Skin and subcutaneous tissue disorders, Nervous system disorders, and Investigations. The most frequent AEs by PT were similar to those in the Primary Pool. The only additional AE with a dose response was abdominal pain upper. Of treatment related TEAEs that occurred in ≥2% of subjects, nausea was most frequently reported. The majority of treatment related TEAEs were mild or moderate.

Table 47 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Incidence of Treatment-Emergent Adverse Events Occurring in >= 2% of Subjects in Any Treatment Group by System Organ Class and Preferred Term (All Causalities)

Number of Subjects Evaluable for AEs	Abrocitinib 100mg QD (N=885)	Abrocitinib 200mg QD (N=1971)	All Abrocitinib (N=2856)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)
Subjects with events	622 (70.3)	1408 (71.4)	2030 (71.1)
Blood And Lymphatic System Disorders	25 (2.8)	80 (4.1)	105 (3.7)
Cardiac Disorders	25 (2.8)	50 (2.5)	75 (2.6)
Eye Disorders	43 (4.9)	59 (3.0)	102 (3.6)
Gastrointestinal Disorders	136 (15.4)	524 (26.6)	660 (23.1)
Abdominal pain upper	9 (1.0)	51 (2.6)	60 (2.1)
Diarrhoea	25 (2.8)	61 (3.1)	86 (3.0)
Nausea	47 (5.3)	307 (15.6)	354 (12.4)
Vomiting	19 (2.1)	72 (3.7)	91 (3.2)
General Disorders And Administration Site Conditions	62 (7.0)	125 (6.3)	187 (6.5)
Infections And Infestations	416 (47.0)	823 (41.8)	1239 (43.4)
Conjunctivitis	19 (2.1)	26 (1.3)	45 (1.6)
Folliculitis	14 (1.6)	52 (2.6)	66 (2.3)
Herpes simplex	23 (2.6)	54 (2.7)	77 (2.7)
Herpes zoster	12 (1.4)	40 (2.0)	52 (1.8)
Influenza	20 (2.3)	46 (2.3)	66 (2.3)
Nasopharyngitis	144 (16.3)	203 (10.3)	347 (12.1)
Oral herpes	27 (3.1)	52 (2.6)	79 (2.8)
Pharyngitis	19 (2.1)	30 (1.5)	49 (1.7)
Upper respiratory tract infection	77 (8.7)	156 (7.9)	233 (8.2)
Urinary tract infection	31 (3.5)	48 (2.4)	79 (2.8)
Injury, Poisoning And Procedural Complications	46 (5.2)	80 (4.1)	126 (4.4)
Investigations	82 (9.3)	262 (13.3)	344 (12.0)
Blood creatine phosphokinase increased	33 (3.7)	74 (3.8)	107 (3.7)
Metabolism And Nutrition Disorders	21 (2.4)	58 (2.9)	79 (2.8)
Musculoskeletal And Connective Tissue Disorders	51 (5.8)	98 (5.0)	149 (5.2)
Nervous System Disorders	92 (10.4)	273 (13.9)	365 (12.8)
Dizziness	18 (2.0)	56 (2.8)	74 (2.6)
Headache	48 (5.4)	185 (9.4)	233 (8.2)
Psychiatric Disorders	31 (3.5)	40 (2.0)	71 (2.5)
Renal And Urinary Disorders	17 (1.9)	40 (2.0)	57 (2.0)
Reproductive System And Breast Disorders	21 (2.4)	33 (1.7)	54 (1.9)
Respiratory, Thoracic And Mediastinal Disorders	82 (9.3)	156 (7.9)	238 (8.3)
Asthma	22 (2.5)	21 (1.1)	43 (1.5)
Cough	21 (2.4)	33 (1.7)	54 (1.9)
Skin And Subcutaneous Tissue Disorders	221 (25.0)	420 (21.3)	641 (22.4)
Acne	24 (2.7)	124 (6.3)	148 (5.2)
Dermatitis atopic	123 (13.9)	164 (8.3)	287 (10.0)
Vascular Disorders	26 (2.9)	45 (2.3)	71 (2.5)
Hypertension	19 (2.1)	31 (1.6)	50 (1.8)

To conclude, there are similar findings of the all exposure pool as in the primary safety pool concerning the most frequent TEAEs by PT and a demonstrated dose relationship. In addition, a dose relationship is indicated also for the PT upper abdominal pain.

Dupilumab comparator study

Separate study B7451029 contained both a placebo and dupilumab comparator arm.

Table 48 PF-04965842 Protocol B7451029 Treatment-Emergent Adverse Events (All Causalities) – Safety Analysis Set

Number (%) of Subjects	Placebo n (%)	PF-04965842 100mg QD n (%)	PF-04965842 200mg QD n (%)	Dupilumab 300mg Q2W n (%)
Subjects evaluable for adverse events	131	238	226	242
Number of adverse events	150	269	308	223
Subjects with adverse events	70 (53.4)	121 (50.8)	140 (61.9)	121 (50.0)
Subjects with serious adverse events	5 (3.8)	6 (2.5)	2 (0.9)	2 (0.8)
Subjects with severe adverse events	3 (2.3)	5 (2.1)	4 (1.8)	2 (0.8)
Subjects discontinued from study due to adverse events [1]	5 (3.8)	6 (2.5)	10 (4.4)	8 (3.3)
Subjects discontinued study drug due to AE and continued Study [2]	2 (1.5)	2 (0.8)	1 (0.4)	0
Subjects with temporary discontinuation due to adverse events	9 (6.9)	15 (6.3)	12 (5.3)	9 (3.7)

Included data up to 28 days after last dose of study.
Except for the number of adverse events subjects were counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment
[1] Subjects who had an AE record that indicated that the AE caused the subject to be discontinued from the study. Three subjects (13089008, 13469002, 12479010) had an AE that started before Week 16 and discontinued due to that AE after Week 16. Those AEs were also included in this table.
[2] Subjects who had an AE record that indicated that action taken with study treatment was drug withdrawn but AE did not cause the subject to be discontinued from study
MedDRA v22.1 coding dictionary applied.

Safety in study B7451029 and Dupilumab Non-responders

- The incidence of subjects reporting adverse events was higher in the abrocitinib 200 mg QD group compared to the abrocitinib 100 mg QD, dupilumab, and placebo treatment groups.
- The percentages of subjects reporting SAEs, severe adverse events, and adverse events leading to study discontinuation were low and similar across the abrocitinib, placebo, and dupilumab treatment groups.
- Abrocitinib treated subjects were more likely to experience nausea, herpes simplex, acne, and herpes zoster. Dupilumab treated subjects were more likely to experience conjunctivitis.
- There was no unique safety signal in the dupilumab non-responder subgroup.

Subjects in the combination topical subgroup (combination therapy study (B7451029))

There were no significant differences between the safety profile of abrocitinib as monotherapy or in combination with topical medicated therapy in terms of frequent events, serious and severe events, or AEs leading to discontinuation.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

There were 3 deaths as of a cut-off date of 22 April 2020. One during the treatment period and 1 during the follow-up period. Another death was reported 8 months after discontinuation from study. All 3 deaths were in abrocitinib-treated subjects.

- The first case concerned a 73-year-old female with an SAE of sudden death on study Day 107, occurring 22 days after discontinuation of study drug abrocitinib 100 mg QD. The subject had a history of aortic sclerosis and calcification as observed in a chest X-ray performed during screening and a history of untreated hypertension. No autopsy was performed, and the sudden death event was adjudicated as a CV death. The event was assessed as not related to study drug per the investigator.

- The second case was a 69-year-old female. She received abrocitinib 200 mg QD. The subject tested positive for COVID-19 infection on study Day 84 and was hospitalised. The subject died on study Day 107. The investigator considered the event to be unrelated to study drug.

- The third case concerned a 78 -year old female that experienced an SAE of Adenocarcinoma Gastric on study Day 22, she received abrocitinib 200 mg QD. Prior to enrolment, the subject experienced pain and discomfort under the ribs. On study Day 43, the subject had unclear dyspeptic problems and excessive bloating. On the same day (study Day 43), a CT scan showed carcinomatosis with multifocal hepatic metastases. This subject SAE was assessed as not related to treatment as per PI judgment. The action taken in response to the event for the study drug was withdrawn permanently. A follow-up SAE report was received on 09 March 2020 that stated that the subject died approximately 7 months after discontinuation from study participation due to gastric adenocarcinoma (14 August 2019).

The three described fatal cases of different diagnoses are considered unlikely to be related to the study drug.

Other Serious Adverse Events

The incidence of SAEs was similar across the abrocitinib and placebo groups.

Short-term treatment

Primary Safety Pool

Table 49 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Incidence of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number of Subjects Evaluable for AEs	Placebo (N=342)	Abrocitinib 100mg QD (N=608)	Abrocitinib 200mg QD (N=590)	All Abrocitinib (N=1198)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)
Subjects with events	11 (3.2)	19 (3.1)	11 (1.9)	30 (2.5)
Blood And Lymphatic System Disorders	0	1 (0.2)	0	1 (0.1)
Pancytopenia	0	1 (0.2)	0	1 (0.1)
Eye Disorders	0	1 (0.2)	0	1 (0.1)
Retinal detachment	0	1 (0.2)	0	1 (0.1)
Gastrointestinal Disorders	1 (0.3)	1 (0.2)	1 (0.2)	2 (0.2)
Abdominal pain	1 (0.3)	0	0	0

Inflammatory bowel disease	0	0	1 (0.2)	1 (0.1)
Pancreatitis acute	0	1 (0.2)	0	1 (0.1)
General Disorders And Administration Site Conditions	1 (0.3)	1 (0.2)	0	1 (0.1)
Chills	1 (0.3)	0	0	0
Pyrexia	1 (0.3)	0	0	0
Sudden death	0	1 (0.2)	0	1 (0.1)
Hepatobiliary Disorders	0	1 (0.2)	0	1 (0.1)
Drug-induced liver injury	0	1 (0.2)	0	1 (0.1)
Immune System Disorders	1 (0.3)	0	1 (0.2)	1 (0.1)
Anaphylactic reaction	1 (0.3)	0	0	0
Anaphylactic shock	0	0	1 (0.2)	1 (0.1)
Infections And Infestations	2 (0.6)	7 (1.2)	2 (0.3)	9 (0.8)
Appendicitis	1 (0.3)	1 (0.2)	0	1 (0.1)
Diarrhoea infectious	0	1 (0.2)	0	1 (0.1)
Eczema herpeticum	1 (0.3)	1 (0.2)	0	1 (0.1)
Herpangina	0	1 (0.2)	0	1 (0.1)
Oral herpes	0	1 (0.2)	0	1 (0.1)
Osteomyelitis bacterial	0	1 (0.2)	0	1 (0.1)
Peritonsillitis	0	0	1 (0.2)	1 (0.1)
Pneumonia	0	2 (0.3)	1 (0.2)	3 (0.3)
Staphylococcal infection	0	1 (0.2)	0	1 (0.1)
Staphylococcal skin infection	1 (0.3)	0	0	0
Injury, Poisoning And Procedural Complications	0	2 (0.3)	1 (0.2)	3 (0.3)
Ankle fracture	0	1 (0.2)	0	1 (0.1)
Femoral neck fracture	0	0	1 (0.2)	1 (0.1)
Muscle injury	0	1 (0.2)	0	1 (0.1)
Tendon injury	0	1 (0.2)	0	1 (0.1)
Investigations	1 (0.3)	0	0	0
Aspartate aminotransferase increased	1 (0.3)	0	0	0
Metabolism And Nutrition Disorders	0	0	1 (0.2)	1 (0.1)
Dehydration	0	0	1 (0.2)	1 (0.1)
Musculoskeletal And Connective Tissue Disorders	1 (0.3)	0	1 (0.2)	1 (0.1)
Intervertebral disc protrusion	0	0	1 (0.2)	1 (0.1)
Meniscal degeneration	1 (0.3)	0	0	0
Nervous System Disorders	0	2 (0.3)	0	2 (0.2)
Dizziness	0	1 (0.2)	0	1 (0.1)
Seizure	0	1 (0.2)	0	1 (0.1)
Reproductive System And Breast Disorders	1 (0.3)	0	1 (0.2)	1 (0.1)
Breast mass	1 (0.3)	0	0	0
Uterine haemorrhage	0	0	1 (0.2)	1 (0.1)
Respiratory, Thoracic And Mediastinal Disorders	1 (0.3)	2 (0.3)	3 (0.5)	5 (0.4)
Asthma	0	1 (0.2)	2 (0.3)	3 (0.3)
Dyspnoea	1 (0.3)	0	0	0
Interstitial lung disease	0	1 (0.2)	0	1 (0.1)
Pulmonary embolism	0	0	1 (0.2)	1 (0.1)
Skin And Subcutaneous Tissue Disorders	5 (1.5)	2 (0.3)	0	2 (0.2)
Dermatitis atopic	3 (0.9)	2 (0.3)	0	2 (0.2)
Dermatitis exfoliative	1 (0.3)	0	0	0
Night sweats	1 (0.3)	0	0	0

Includes Studies: B7451006, B7451012, B7451013, B7451029
Subjects are only counted once per treatment per event.
Totals for the Number of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
Includes data up to 28 days after last dose of study.
MedDRA v22.1 coding dictionary applied.

The Infections and infestations SOC had the highest incidence of SAEs. SAEs of pneumonia (3 subjects, 0.3%), asthma (3 subjects, 0.3%), and dermatitis atopic (2 subjects, 0.2%) occurred in more than 1 abrocitinib treated subject; all other SAEs occurred in 1 subject. All subjects with asthma were considered not related by investigators as all subjects had a history of asthma. One led to study discontinuation. There seems to be no dose related increase of SAEs. It is noted though that all three serious cases of pneumonia were only reported for subjects in the abrocitinib treated group.

Long-term treatment

All Exposure Pool

There was no dose response for SAEs in the All Exposure Pool. SAEs accumulated in a linear fashion over time.

Table 50 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Incidence of Treatment-Emergent Serious Adverse Events Occurring in >= 2 Subjects in All Abrocitinib Treatment Group by System Organ Class and Preferred Term (All Causalities)

Number of Subjects Evaluable for AEs	Abrocitinib 100mg QD (N=885)	Abrocitinib 200mg QD (N=1971)	All Abrocitinib (N=2856)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)
Subjects with events	47 (5.3)	71 (3.6)	118 (4.1)
Blood And Lymphatic System Disorders	1 (0.1)	2 (0.1)	3 (0.1)
Cardiac Disorders	0	2 (0.1)	2 (0.1)
Myocardial infarction	0	2 (0.1)	2 (0.1)
Eye Disorders	1 (0.1)	2 (0.1)	3 (0.1)
Retinal detachment	1 (0.1)	1 (0.1)	2 (0.1)
Gastrointestinal Disorders	4 (0.5)	3 (0.2)	7 (0.2)
General Disorders And Administration Site Conditions	1 (0.1)	1 (0.1)	2 (0.1)
Hepatobiliary Disorders	2 (0.2)	2 (0.1)	4 (0.1)
Drug-induced liver injury	1 (0.1)	1 (0.1)	2 (0.1)
Immune System Disorders	3 (0.3)	1 (0.1)	4 (0.1)
Anaphylactic reaction	2 (0.2)	0	2 (0.1)
Infections And Infestations	17 (1.9)	24 (1.2)	41 (1.4)

Appendicitis	1 (0.1)	1 (0.1)	2 (0.1)
Cellulitis	0	3 (0.2)	3 (0.1)
Eczema herpeticum	4 (0.5)	0	4 (0.1)
Herpes simplex	0	2 (0.1)	2 (0.1)
Herpes zoster	0	3 (0.2)	3 (0.1)
Osteomyelitis	1 (0.1)	1 (0.1)	2 (0.1)
Pneumonia	2 (0.2)	2 (0.1)	4 (0.1)
Skin infection	1 (0.1)	1 (0.1)	2 (0.1)
Injury, Poisoning And Procedural Complications	5 (0.6)	3 (0.2)	8 (0.3)
Ankle fracture	2 (0.2)	0	2 (0.1)
Ligament rupture	1 (0.1)	1 (0.1)	2 (0.1)
Investigations	0	2 (0.1)	2 (0.1)
Metabolism And Nutrition Disorders	0	2 (0.1)	2 (0.1)
Musculoskeletal And Connective Tissue Disorders	3 (0.3)	5 (0.3)	8 (0.3)
Intervertebral disc protrusion	2 (0.2)	2 (0.1)	4 (0.1)
Myositis	0	2 (0.1)	2 (0.1)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	2 (0.2)	4 (0.2)	6 (0.2)
Ovarian neoplasm	0	2 (0.1)	2 (0.1)
Prostate cancer	1 (0.1)	1 (0.1)	2 (0.1)
Nervous System Disorders	3 (0.3)	2 (0.1)	5 (0.2)
Psychiatric Disorders	2 (0.2)	2 (0.1)	4 (0.1)
Suicidal ideation	0	2 (0.1)	2 (0.1)
Renal And Urinary Disorders	2 (0.2)	2 (0.1)	4 (0.1)
Reproductive System And Breast Disorders	0	3 (0.2)	3 (0.1)
Respiratory, Thoracic And Mediastinal Disorders	3 (0.3)	7 (0.4)	10 (0.4)
Asthma	2 (0.2)	4 (0.2)	6 (0.2)
Pulmonary embolism	0	3 (0.2)	3 (0.1)
Skin And Subcutaneous Tissue Disorders	7 (0.8)	8 (0.4)	15 (0.5)
Dermatitis atopic	5 (0.6)	7 (0.4)	12 (0.4)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029
Subjects are only counted once per treatment per event.
Totals for the Number of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
Includes data up to 28 days after last dose of study.
MedDRA v23.0 coding dictionary applied.

Specific SAEs

There were 6 subjects with an SAE of asthma and 1 with an SAE of status asthmaticus. All SAEs of asthma were resolved (all but 1 without sequelae), drug withdrawn in 2 subjects and interrupted in 1 subject. Asthma was a common comorbidity in the population, being reported as ongoing in more than 30% of subjects according to the applicant. Atopic dermatitis (AD) is associated with a significantly higher risk of asthma as well as other conditions of allergic atopy e.g. allergic rhinoconjunctivitis. Case histories of five asthma events whereof one case of Status Asthmaticus have been presented.

Table 51 Adverse events of special interest.

Cumulative Incidence Rates (Events/100 Subject Years) for Selected Safety Events of Interest in Subjects Treated with Abrocitinib 200 and 100 mg QD in the Phase 3 Development Program

Safety Event	Abrocitinib 100 mg QD N= 885			Abrocitinib 200 mg QD N= 1971			All Abrocitinib Doses N= 2856		
	n	%	IR (95% CI)	n	%	IR (95% CI)	n	%	IR (95% CI)
Serious infections	17	1.9	2.65 (1.55, 4.25)	24	1.2	2.33 (1.49, 3.47)	41	1.4	2.46 (1.76, 3.33)
All Herpes zoster[a]	13	1.5	2.04 (1.09, 3.49)	44	2.2	4.34 (3.15, 5.82)	57	2.0	3.45 (2.61, 4.47)
Eczema herpeticum	15	1.7	2.34 (1.31, 3.86)	8	0.4	0.78 (0.34, 1.53)	23	0.8	1.38 (0.87, 2.06)
Malignancies excl NMSC	1	0.1	0.15 (0.00, 0.869)	3	0.2	0.29 (0.06, 0.85)	4	0.1	0.24 (0.07, 0.61)
NMSC*	3	0.3	0.47 (0.10, 1.36)	4	0.2	0.39 (0.11, 0.99)	7	0.2	0.42 (0.17, 0.86)
MACE*	1	0.1	0.15 (0.00, 0.86)	2	0.1	0.19 (0.02, 0.70)	3	0.1	0.18 (0.04, 0.52)
PE*	0	0.0	0.00 (0.00, 0.57)	3	0.2	0.29 (0.06, 0.85)	3	0.1	0.18 (0.04, 0.52)
DVT*	0	0.0	0.00 (0.00, 0.57)	2	0.1	0.19 (0.02, 0.70)	2	0.1	0.12 (0.01, 0.43)

Abbreviations: DVT = deep vein thrombosis; N = number of subjects; n = number of subjects with event; IR = Incidence Rates; CI = confidence interval; excl = excluding; NMSC = non-melanoma skin cancer; MACE = major adverse cardiovascular event; PE = pulmonary embolism.
*Adjudicated events.
IR was a naïve estimate without adjusting for study.
a. Includes opportunistic herpes zoster (multi-dermatonal)

Risk Contextualisation

The applicant followed a method of risk contextualisation that relies on rates of adverse events observed in external real-world observational databases. A uniform protocol was executed in which 2 external databases were used to assess the rates of safety events of interest for abrocitinib in patients with moderate to severe AD. Analyses were conducted in the following external clinical practice databases: KPNC (US) and THIN (UK) and a population based cohort study using data from the Danish registries to evaluate IRs of VTE (DK).

Serious Infections including opportunistic infections

Infections have been associated with other JAK inhibitors.

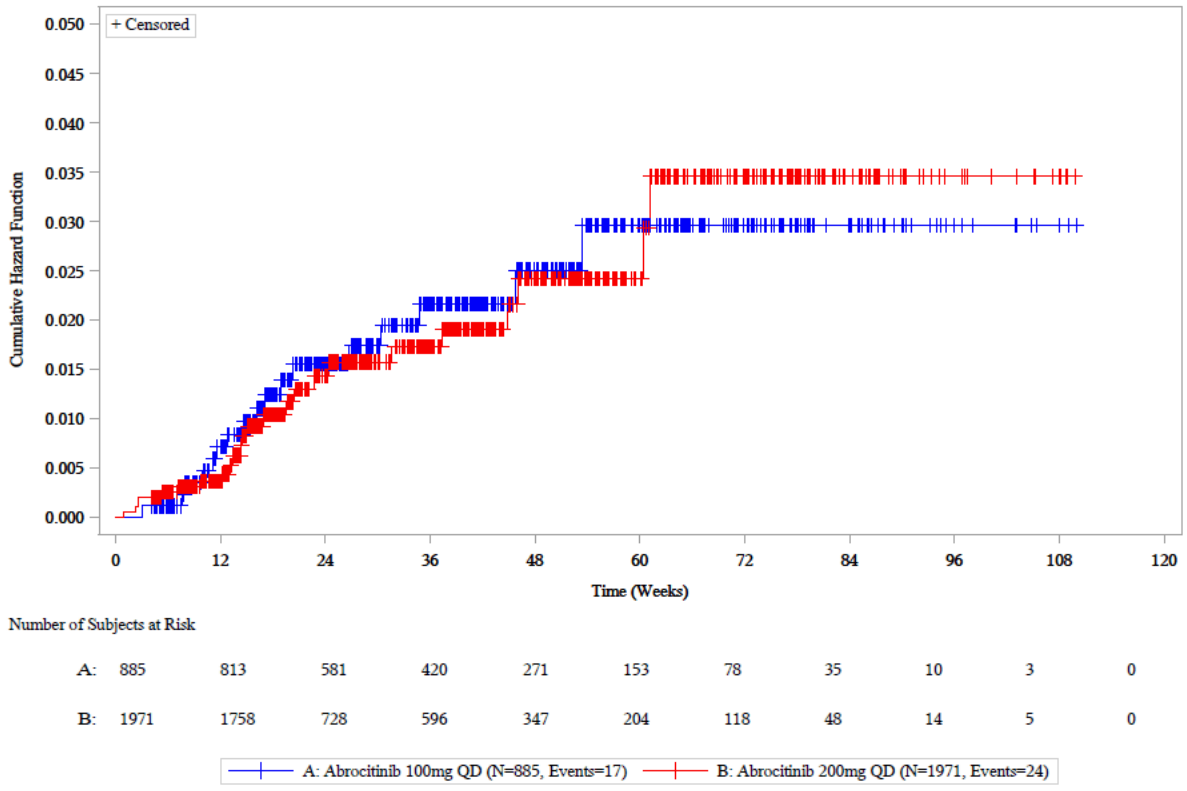
The proportion of subjects reporting serious infections was low (<2%) in each treatment arm (including placebo) and there was no dose response. Pneumonia, herpes zoster, and herpes simplex were the most frequent serious infections across all abrocitinib-exposed subjects.

In the placebo-controlled studies with abrocitinib, the IR for serious infection was lower in the abrocitinib 200 mg QD treatment group (2 subjects, 1.28/100 PY [95% CI: 0.16, 4.62]) compared to the placebo (2 subjects, 2.31/100 PY [95% CI: 0.28, 8.33]) and abrocitinib 100 mg QD treatment groups (6 subjects, 3.80/100 PY [95% CI: 1.39, 8.27]). These IRs were relatively comparable to background rates for serious infection in adults with AD (2.14/100 PY [95% CI: 2.10-2.18]) and for serious and severe events in the placebo group of randomised-controlled studies in AD (3.978/100 PY) (Narla et al, 2018; Eichenfield et al, 2019). However, the IRs above, for both placebo and abrocitinib treated subjects, were higher than those in the matched cohort studies.

Per protocol, subjects with serious infection were to discontinue treatment; approximately 90% of serious infections resolved during analysis period. There was 1 fatal infection after hospitalisation for COVID-19.

There were 10 subjects with adjudicated opportunistic infections, all were events of cutaneous multi-dermatomal herpes zoster [0.60/100 PY (95% CI: 0.29, 1.10)]. Among these events, 2 were serious, treated with IV antivirals. The non-serious events were treated with oral antivirals or did not require therapy, and most resolved with no change or interruption to study drug. There were no events of opportunistic infection that were bacterial, fungal, mycobacterial, or protozoan infections.

Figure 25 Time-to-Event: Cumulative Hazard Function Plot for Treatment-Emergent Serious Infections – All Exposure Pool



Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date (B7451014 & B7451015 only)]).

Herpes zoster

Herpes Zoster is an identified risk of treatment with JAK inhibitors (Winthrop et al, 2017). There was a higher incidence of herpes zoster (2.04/100 PY [95% CI: 1.09, 3.49] for 100 mg QD and 4.34/100 PY [95% CI: 3.15, 5.82] for 200 mg QD) (Table 12), including ophthalmic herpes zoster (4 subjects), in the abrocitinib-treated subjects compared to placebo as well as a dose response across the abrocitinib groups; across all abrocitinib-treated subjects the proportion of subjects with serious events of herpes zoster were uncommon (<0.2% for each). Herpes zoster events generally resolved without discontinuation of abrocitinib. The incidence rate of herpes zoster in patients ≥65 years of age treated with abrocitinib (7.40/100 PY) was higher that of patients 18 to <65 years of age (3.29/100 PY) and 12 to <18 years of age (2.12/100 PY).

Eczema herpeticum

There was no dose-related increase in the IR for eczema herpeticum (including events of Kaposi's varicelliform eruption) and no excess over placebo in the Primary Safety Pool (IR=3.46 (0.71, 10.12. In the All Exposure Pool the IR in the abrocitinib 200 mg QD group was lower than that in the 100 mg QD group although there were few events and, as such, the confidence intervals were relatively wide (IR 200 mg=0.78 [0.34, 1.53] and IR 100 mg = 2.34 [1.31, 3.86]). Among these events, there were 4 serious events all in the 100 mg QD group. Among all events of eczema herpeticum 91.7% of events resolved within the analysis period, 5 events led to study discontinuation (100 mg group: 4 subjects, 0.5%; 200 mg group: 1 subject, 0.1%). Among all events, 18 of 23 events were confirmed as an event of eczema herpeticum through adjudication

Cautions concerning viral activation, screening for tuberculosis and screening for viral hepatitis are addressed in the SmPC section 4.4. The risk of serious infections is addressed in sections 4.4 and 4.8 and in Table 2 of section 4.8. Herpes simplex and Herpes zoster including zoster ophthalmicus are inserted with frequency uncommon and common respectively, however, following the review process revised to frequency common for both. A clarification was needed if the cases reported as opportunistic infections have been included in the calculation of frequency of herpes zoster. It is stated in section 4.4 of the proposed SmPC that the most frequent serious infections in clinical studies were herpes simplex, herpes zoster, and pneumonia with a reference to section 4.8 and that the risks and benefits of treatment with abrocitinib should be carefully considered prior to initiating in patients and patients to be closely monitored for the development of signs and symptoms of infection. There seems to be no case of tuberculosis reported. Upon request from the CHMP and in view of the above and the important potential risk of serious infections the applicant agreed to add active serious systemic infections including TB as contraindication. Three cases of pneumonia occurred in the abrocitinib treated group although only one seem to have been classified as serious. Pneumonia is a recognised infection associated with use of other JAK inhibitors. Upon request from the CHMP, pneumonia was added in table 2 of the SmPC in section 4.8 with a frequency uncommon.

Malignancies except NMSC

There were 4 events of potential malignancy (2 events of prostate cancer and 2 events of ovarian neoplasm) in the clinical database at the time of release, adjudication was incomplete for these events. As such, the IR for all 4 events (0.24/100 PY [95% CI: 0.07, 0.61]) was assessed. Although adjudication was not complete for 3 of the events, 1 of the events of ovarian neoplasm was adjudicated as not malignant.

Non-melanoma skin cancer (NMSC)

Across all subjects treated with abrocitinib, there were 7 adjudicated cases of non-melanoma skin cancer [0.42/100 PY (95% CI: 0.17, 0.86)], 3 subjects in the abrocitinib 100 mg QD group and 4 subjects in the abrocitinib 200 mg QD group.

Comparisons were made with data from KPNC (Kaiser Permanente) and THIN databases. Overall, the IRs for malignancies (excluding NMSC) and NMSC in the KPNC and THIN databases were comparable to those seen in the AD clinical programme.

Major adverse cardiovascular events (MACE)

There were 3 adjudicated MACE events [IR 0.18/100 PY (95% CI: 0.04, 0.52)], 2 events of myocardial infarction in the abrocitinib 200 mg QD group and 1 event of sudden death in the abrocitinib 100 mg QD group. All events occurred in subjects older than 60 years with pre-existing CV risk factors. In the opinion of the Investigators, the events were considered to be unrelated to the study drug. There were no MACE events among adolescents.

In the All Exposure Pool, 1 subject in the abrocitinib 200 mg QD group had a QTcF of >500 msec, and 5 subjects in the abrocitinib 200 mg QD group had a change from screening >60 msec. None of these 5 subjects had a QTcF >462 msec.

A thorough QT study indicated a concentration dependent effect judged to have a lack of a clinically relevant effect on QTc interval (see section on secondary pharmacology). In the phase 3 studies, there were exclusion and discontinuation criteria related to QT duration. In addition, ECGs were monitored at 2-4 week intervals. In the Primary Pool, no subjects in any treatment group had a QTcF of >500 msec. One (1) subject in the abrocitinib 200 mg QD group had a change from screening >60 msec, with a screening value of 383 msec that increased to 452 msec (i.e., a change from screening of 69 msec). The subject's Day 1 QTcF was 452 msec and, as such, the change from baseline was 0. In the All

Exposure Pool, 1 subject in the abrocitinib 200 mg QD group had a QTcF of >500 msec, and 5 subjects in the abrocitinib 200 mg QD group had a change from screening >60 msec. None of these 5 subjects had a QTcF >462 msec. As all changes are described in the 200 mg QD a dose dependent effect seems likely and the applicant was requested to discuss the relevance of cautionary measures in the SmPC (see discussion section on clinical safety).

Overall, the IRs for MACE events in the KPNC (Kaiser Permanente) database were comparable to those seen in the AD clinical programme.

Deep venous thrombosis (DVT)

There were 2 adjudicated events of deep venous thrombosis (0.12/100 PY [95% CI: 0.01, 0.43]), all in the 200 mg QD group.

The first case concerned a 44-year-old female randomised to abrocitinib 200mg QD from 29 January 2019. The last dose of study drug was taken on 09 September 2019. On 12 September 2019 the subject underwent arthroscopic knee surgery under spinal anaesthesia. The subject received bemiparin sodium for 5 days as prophylaxis for thrombosis. On 17 September 2019 an ultrasound of the veins showed thrombosis of fibular veins and muscle branches. The study drug was permanently discontinued in response to the event of calf thrombosis. In the opinion of the Investigator, the event of calf thrombosis was considered to be unrelated to the study drug, concomitant medications, or a clinical trial procedure. The event was reported as related to arthroscopic surgery. The study Sponsor concurred with the Investigator's causality assessment.

The second case was a 50-year-old female. The subject received abrocitinib 200mg QD from 14 June 2019 to 06 September 2019. The subject experienced a non-serious adverse event of special interest of thrombophlebitis superficial on 31 July 2019 (Study Day 48). No action was taken with the study drug in response to the event of superficial thrombophlebitis. In the opinion of the Investigator, the event of superficial thrombophlebitis was considered to be not related to the study drug, but it was related to the history of a hypertension.

The IRs for DVT events in the KPNC database were lower than those seen in the AD clinical programme.

Pulmonary embolism (PE)

Across all subjects treated with abrocitinib, there were 3 adjudicated events of PE (0.18/100 PY [95% CI: 0.04, 0.52]).

One case concerned a 55-year old man who following approximately 2½ months of treatment with abrocitinib 200 mg once daily (QD) was reported with a serious adverse event (SAE), 'pulmonary embolism' with seriousness criteria of Important Medical Event. The study drug (abrocitinib) was permanently discontinued due to the event of PE with last dose received on 22 October 2016 (study Day 80). On 05 January 2017 (study Day 155), the subject had a follow-up appointment with his specialist for the result of a lung nuclear scan which was negative for blood clots. He was considered recovered from PE with sequelae on 05 January 2017.

The second case was a 69-year-old female who received study treatment abrocitinib 200mg QD for a bit more that 2½ months and experienced a serious adverse event of PE (bilateral pulmonary emboli). The Investigator considered the event of PE to be moderate in severity. The patient underwent cardiac computed tomography/angiography and chest x-ray, which confirmed the diagnosis of bilateral PE. The event of PE was considered resolved approx. 3 weeks later. The study drug was permanently discontinued. The concomitant medication estradiol was also permanently withdrawn as the physician suspected it to be the cause of the event.

The third case concerned a 17-year-old male who had class III obesity with a family history of PE and venous thromboembolism (VTE). He received study drug abrocitinib 200mg QD and experienced serious adverse events of PE on study Day 565, pneumothorax on study Day 574), and acute kidney injury on study Day 578. The study drug was permanently discontinued in response to the event of pneumothorax. The study Sponsor did not consider the event of acute PE related to the study drug but in the opinion of the Investigator, the event of PE was considered to be related to the study drug.

The IRs for PE events in the KPNC database were lower than those seen in the AD clinical programme.

The risk of venous thromboembolism is addressed in section 4.4 of the SmPC such that events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving Janus kinase (JAK) inhibitors. It is also included in Table 1 of section 4.8 as uncommon.

Other Adverse events of interest.

Hypersensitivity

Primary Safety Pool

The proportion of subjects with hypersensitivity events was similar across the treatment groups. Among these events, 2 subjects in the placebo group (anaphylactic reaction, dermatitis exfoliative) and 1 subject in the abrocitinib 200 mg QD group (anaphylactic shock) had serious events. The event in the abrocitinib-treated subject was related to food allergy.

Table 52 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Incidence of Treatment-Emergent Hypersensitivity (CMQ) Requiring Treatment by System Organ Class and Preferred Term – Primary Safety Pool

Number of Subjects Evaluable for AEs Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	Placebo (N=342) n (%)	Abrocitinib 100mg QD (N=608) n (%)	Abrocitinib 200mg QD (N=590) n (%)	All Abrocitinib (N=1198) n (%)
Subjects with events	7 (2.0)	15 (2.5)	9 (1.5)	24 (2.0)
Eye Disorders	1 (0.3)	5 (0.8)	2 (0.3)	7 (0.6)
Eye oedema	0	0	1 (0.2)	1 (0.1)
Eye swelling	0	1 (0.2)	0	1 (0.1)
Eyelid oedema	1 (0.3)	2 (0.3)	1 (0.2)	3 (0.3)
Swelling of eyelid	0	2 (0.3)	0	2 (0.2)
Gastrointestinal Disorders	1 (0.3)	1 (0.2)	0	1 (0.1)
Lip swelling	1 (0.3)	0	0	0
Tongue oedema	0	1 (0.2)	0	1 (0.1)
Immune System Disorders	1 (0.3)	1 (0.2)	3 (0.5)	4 (0.3)
Anaphylactic reaction	1 (0.3)	0	0	0
Anaphylactic shock	0	0	1 (0.2)	1 (0.1)
Hypersensitivity	0	1 (0.2)	2 (0.3)	3 (0.3)
Infections And Infestations	0	2 (0.3)	0	2 (0.2)
Kaposi's varicelliform eruption	0	2 (0.3)	0	2 (0.2)
Respiratory, Thoracic And Mediastinal Disorders	0	0	1 (0.2)	1 (0.1)
Rhinitis allergic	0	0	1 (0.2)	1 (0.1)
Skin And Subcutaneous Tissue Disorders	5 (1.5)	6 (1.0)	3 (0.5)	9 (0.8)
Angioedema	1 (0.3)	0	0	0
Dermatitis exfoliative	1 (0.3)	0	0	0
Drug eruption	1 (0.3)	1 (0.2)	0	1 (0.1)
Perioral dermatitis	0	0	1 (0.2)	1 (0.1)
Rash	0	1 (0.2)	0	1 (0.1)
Urticaria	2 (0.6)	4 (0.7)	2 (0.3)	6 (0.5)

Case of anaphylactic shock

Subject B7451013 200 mg QD: This 15-year-old white female subject experienced an SAE of anaphylactic shock (VT: anaphylactic shock) on study Day 79 after eating single cashew nut. The subject experienced anaphylactic shock with feeling sick, generalised rash, low blood pressure and collapse with fast recovery after IV adrenaline administration. The event was considered not related to study drug by the investigator, but to probably allergy. The subject remained in the study without change to study drug and the event was resolved on Day 81.

Table 53 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Incidence of Treatment-Emergent Hypersensitivity (CQM) Requiring Treatment by System Organ Class and Preferred Term – All Exposure Pool

Number of Subjects Evaluable for AEs	Abrocitinib 100mg QD (N=885)	Abrocitinib 200mg QD (N=1971)	All Abrocitinib (N=2856)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**
Subjects with events	34 (3.8)	48 (2.4)	82 (2.9)
Eye Disorders	7 (0.8)	6 (0.3)	13 (0.5)
Conjunctival oedema	0	1 (0.1)	1 (<0.1)
Eye allergy	1 (0.1)	0	1 (<0.1)
Eye oedema	0	1 (0.1)	1 (<0.1)
Eye swelling	1 (0.1)	0	1 (<0.1)
Eyelid oedema	2 (0.2)	3 (0.2)	5 (0.2)
Swelling of eyelid	3 (0.3)	1 (0.1)	4 (0.1)
Gastrointestinal Disorders	2 (0.2)	0	2 (0.1)
Lip swelling	1 (0.1)	0	1 (<0.1)
Tongue oedema	1 (0.1)	0	1 (<0.1)
General Disorders And Administration Site Conditions	0	1 (0.1)	1 (<0.1)
Swelling face	0	1 (0.1)	1 (<0.1)
Immune System Disorders	6 (0.7)	10 (0.5)	16 (0.6)
Anaphylactic reaction	2 (0.2)	1 (0.1)	3 (0.1)
Anaphylactic shock	0	1 (0.1)	1 (<0.1)
Atopy	1 (0.1)	0	1 (<0.1)
Drug hypersensitivity	0	1 (0.1)	1 (<0.1)
Hypersensitivity	3 (0.3)	7 (0.4)	10 (0.4)
Infections And Infestations	2 (0.2)	1 (0.1)	3 (0.1)
Kaposi's varicelliform eruption	2 (0.2)	0	2 (0.1)
Rash pustular	0	1 (0.1)	1 (<0.1)
Respiratory, Thoracic And Mediastinal Disorders	4 (0.5)	9 (0.5)	13 (0.5)
Bronchospasm	1 (0.1)	2 (0.1)	3 (0.1)
Rhinitis allergic	3 (0.3)	7 (0.4)	10 (0.4)
Skin And Subcutaneous Tissue Disorders	14 (1.6)	23 (1.2)	37 (1.3)
Acute generalised exanthematous pustulosis	0	1 (0.1)	1 (<0.1)
Angioedema	3 (0.3)	2 (0.1)	5 (0.2)
Drug eruption	1 (0.1)	1 (0.1)	2 (0.1)
Perioral dermatitis	1 (0.1)	3 (0.2)	4 (0.1)
Rash	2 (0.2)	4 (0.2)	6 (0.2)
Urticaria	7 (0.8)	12 (0.6)	19 (0.7)
Urticaria cholinergic	0	1 (0.1)	1 (<0.1)
Urticaria papular	0	1 (0.1)	1 (<0.1)

Urticaria, swelling of the face and rash have been identified as reactions associated with exposure to other JAK inhibitors. There are together seven cases of either swelling of eyes, swelling of eyelids, oedema of eyelids and oedema of eye reported for the abrocitinib treated subjects in the primary safety pool and only one case of eyelid swelling in the placebo group. In the All safety pool there are in total 13 cases of eye reactions, this includes the previous terms as well as conjunctival oedema and eye allergy.

Gastrointestinal (GI)

The GI perforation events were all upper GI events. There were 3 subjects (0.1%) reporting GI perforation in the All Exposure pool, 2 subjects (0.2%) in the abrocitinib 100 mg QD and 1 subject (0.1%) in the 200 mg QD group. The IR was 0.18/100 PY. Among these events, 1 was serious and led to study discontinuation.

Weight

Changes in weight are described using BMI to account for difference in age and gender. In the Primary Pool, the baseline median BMI was comparable in the placebo (25 kg/m2), the abrocitinib 100 mg and 200 mg QD groups (26 and 25 kg/m2, respectively). At week 12, there was no meaningful median change in the placebo (0 kg/m2), the abrocitinib 100 mg and 200 mg QD groups (0 and 1 kg/m2, respectively).

In the All Exposure Pool, the baseline median BMI was the same in the 100 mg QD and 200 mg QD treatment groups (25 kg/m2). There was no meaningful median change through Month 15 (27 kg/m2) for the 100 mg QD group; the median increased to 32 kg/m2 at Month 21. There was no meaningful median change for the 200 mg QD group (25 kg/m2 at Month 18 and Month 21).

Table 54 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Summary of Vital Signs, Height, Weight and BMI – All Exposure Pool Weight (kg)

		Abrocitinib 100mg QD (N=885)	Abrocitinib 200mg QD (N=1971)	All Abrocitinib (N=2856)
Visit	Summary Statistics			
Baseline	n	885	1971	2856
	Median (Min, Max)	74 (38, 164)	72 (36, 204)	73 (36, 204)
	Mean (Std. Dev.)	76.7 (19.0)	74.6 (19.7)	75.2 (19.5)
Week 2	n	19	30	49
	Median (Min, Max)	78 (44, 93)	70 (41, 150)	72 (41, 150)
	Mean (Std. Dev.)	75.4 (13.1)	72.2 (20.3)	73.5 (17.8)
Month 1	n	84	107	191
	Median (Min, Max)	75 (41, 135)	72 (48, 118)	74 (41, 135)
	Mean (Std. Dev.)	77.6 (19.7)	74.4 (16.6)	75.8 (18.0)
Month 3	n	793	1754	2547
	Median (Min, Max)	74 (40, 1155)	74 (41, 204)	74 (40, 1155)
	Mean (Std. Dev.)	78.8 (42.8)	76.0 (19.4)	76.9 (28.8)
Month 6	n	571	720	1291
	Median (Min, Max)	75 (36, 1280)	75 (41, 192)	75 (36, 1280)
	Mean (Std. Dev.)	80.0 (53.8)	77.1 (19.7)	78.4 (38.7)

Table 55 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Summary of Vital Signs, Height, Weight and BMI – All Exposure Pool Weight (kg)

		Abrocitinib 100mg QD (N=885)	Abrocitinib 200mg QD (N=1971)	All Abrocitinib (N=2856)
Visit	Summary Statistics			
Month 9	n	456	615	1071
	Median (Min, Max)	75 (46, 184)	75 (41, 178)	75 (41, 184)
	Mean (Std. Dev.)	78.3 (18.3)	78.6 (20.5)	78.5 (19.6)
Month 12	n	288	369	657
	Median (Min, Max)	76 (45, 8606)	75 (40, 159)	75 (40, 8606)
	Mean (Std. Dev.)	108.9 (502.8)	77.7 (18.9)	91.4 (333.2)
Month 15	n	150	197	347
	Median (Min, Max)	79 (51, 190)	76 (44, 219)	78 (44, 219)
	Mean (Std. Dev.)	83.1 (20.7)	80.3 (21.6)	81.5 (21.3)
Month 18	n	79	111	190
	Median (Min, Max)	84 (51, 188)	77 (46, 176)	80 (46, 188)
	Mean (Std. Dev.)	87.6 (23.7)	81.5 (21.5)	84.1 (22.6)
Month 21	n	32	46	78
	Median (Min, Max)	85 (57, 183)	76 (48, 171)	83 (48, 183)
	Mean (Std. Dev.)	91.0 (27.1)	82.3 (26.5)	85.9 (26.9)
Month 24	n	9	16	25
	Median (Min, Max)	100 (76, 184)	78 (49, 130)	86 (49, 184)
	Mean (Std. Dev.)	111.1 (39.4)	80.8 (21.5)	91.7 (32.1)
Month 27	n	3	6	9
	Median (Min, Max)	77 (74, 78)	75 (61, 94)	77 (61, 94)
	Mean (Std. Dev.)	76.1 (2.2)	75.4 (13.6)	75.7 (10.8)

Weight increase has been reported for other JAK inhibitors. The number of individuals according to the table above is limited at Months 24 and 27 but at Months 21 there seems to be an increase of the All abrocitinib group (median 83, mean 85.9) compared to baseline weight (median 73, mean 75.2.)

2.6.8.4. Laboratory findings

Haematological Laboratory Changes

Changes in haematology laboratory parameters were consistent with the mechanism of action, the non-clinical data, and suggest specificity of abrocitinib inhibiting the signalling of cytokines that use JAK1 heterodimers and sparing the JAK2 homo and heterodimer signalling cytokines given the clinically relevant changes in neutrophil counts and haemoglobin in the clinical studies. Changes in platelets after initiation of JAK inhibitors are likely to be the result of a balance between JAK2 mediated inhibition of thrombopoietin inhibition, decreasing platelet production, signalling and decreased IL-6 driven thrombopoietin hepatic production. These interactions are complex and, consequently, effects on platelets have been inconsistent across the class. The JAK1/2 inhibitor ruxolitinib is used to treat

post-polycythemia vera and has been associated with thrombocytopenia, while thrombocytosis has been associated with baricitinib treatment. A JAK1 inhibitor that preserves selectivity in the clinic has the potential to decrease platelet production by decreasing hepatic TPO synthesis resulting from IL-6 signalling (including rheumatoid arthritis). In fact, IL-6 inhibition with the monoclonal antibody tocilizumab is associated with a decrease in platelet counts (ACTEMRA prescribing information, 2013).

Haemoglobin changes with JAK inhibition have been thought to be due to inhibition of erythropoietin signalling through JAK2 homodimers. A JAK1 inhibitor that preserves selectivity in the clinic is not expected to produce significant haemoglobin decreases in a large percentage of patients and such changes were not seen with abrocitinib.

Lymphocyte decreases are thought to result from a complex set of interactions resulting from the inhibition of certain cytokines (IL-2, IL-7, IL-15) and since signalling of these is mediated by JAK1-containing signalling complexes (ie JAK1-JAK3), these are expected to be observed with a JAK1 selective inhibitor.

Neutrophil decreases have been linked to inhibition of G- and/or GM-CSF signalling that are mediated through JAK2 homodimers and/or resolution of inflammation. A JAK1 inhibitor that preserves selectivity in the clinic is not expected to produce clinically significant neutropenia in a large percentage of patients.

The results observed in the development programme for abrocitinib suggest that the biochemical JAK1 selectivity persists after administration of clinically efficacious doses in most patients:

Haemoglobin and neutrophils

- No population changes in haemoglobin and/or neutrophils are observed.
- Very few patients develop clinically meaningful low values of haemoglobin and no patient had a confirmed neutrophil count less than $1.0\times10^3/mm^3$.
- Although there are differences across JAK inhibitors with regard to the effect or extent of effect with regard to haematologic parameters, prescribing information for JAK inhibitors used for rheumatoid arthritis generally include the recommendation that they should not be initiated in patients with an ALC $<0.5\times10^3/mm^3$, ANC $<1\times10^3/mm^3$ and Hgb <8 gm/dL.

Table 56 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Proportion of Subjects Meeting Retest, Monitoring and Discontinuation Criteria for Hemoglobin – Primary Safety Pool

	Placebo N n (%)	Abrocitinib 100mg QD N n (%)	Abrocitinib 200mg QD N n (%)	All Abrocitinib N n (%)
Retest Criteria (Single Value)				
Hemoglobin (g/dL) [1] < 9 or drops >= 2 below baseline	282 8 (2.8)	546 17 (3.1)	530 36 (6.8)	1076 53 (4.9)
Hemoglobin (g/dL) [1] < 9	282 0	546 1 (0.2)	530 0	1076 1 (0.1)
Hemoglobin (g/dL) [2] < 11	56 0	55 4 (7.3)	55 7 (12.7)	110 11 (10.0)
Monitoring Criteria (Confirmed Value)				
Hemoglobin (g/dL) [1] < 9 or drops >= 2 below baseline [3]	282 3 (1.1)	546 5 (0.9)	530 9 (1.7)	1076 14 (1.3)
Hemoglobin (g/dL) [1] < 9 [3]	282 0	546 1 (0.2)	530 0	1076 1 (0.1)
Hemoglobin (g/dL) [2] < 11 [3]	56 0	55 2 (3.6)	55 3 (5.5)	110 5 (4.5)
Discontinuation Criteria (Confirmed Value)				
Hemoglobin (g/dL) [1] < 8 [3] or a decrease > 30% below baseline	282 0	546 0	530 0	1076 0
Hemoglobin (g/dL) [1] < 8 [3]	282 0	546 0	530 0	1076 0
Hemoglobin (g/dL) [2] < 10 [3]	56 0	55 0	55 1 (1.8)	110 1 (0.9)

Table 57 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Proportion of Subjects Meeting Retest, Monitoring and Discontinuation Criteria for Neutrophils – Primary Safety Pool

	Placebo N n (%)	Abrocitinib 100mg QD N n (%)	Abrocitinib 200mg QD N n (%)	All Abrocitinib N n (%)
Retest Criteria (Single Value)				
Neutrophils (10^3/mm^3) [1] < 1	282 0	546 0	530 2 (0.4)	1076 2 (0.2)
Neutrophils (10^3/mm^3) [2] < 2	56 2 (3.6)	55 5 (9.1)	55 11 (20.0)	110 16 (14.5)
Monitoring Criteria (Confirmed Value)				
Neutrophils (10^3/mm^3) [1] < 1 [3]	282 0	546 0	530 0	1076 0
Neutrophils (10^3/mm^3) [2] < 2 [3]	56 0	55 0	55 6 (10.9)	110 6 (5.5)
Discontinuation Criteria (Confirmed Value)				
Neutrophils (10^3/mm^3) [1] < 0.5 [3]	282 0	546 0	530 0	1076 0
Neutrophils (10^3/mm^3) [2] < 1 [3]	56 0	55 0	55 0	110 0

There was one SAE of pancytopenia and 2 AEs of pancytopenia exposed to abrocitinib 100 mg QD and 200 mg QD respectively reported in the All Exposure pool. All three patients discontinued the study although one did not meet the discontinuation criteria.

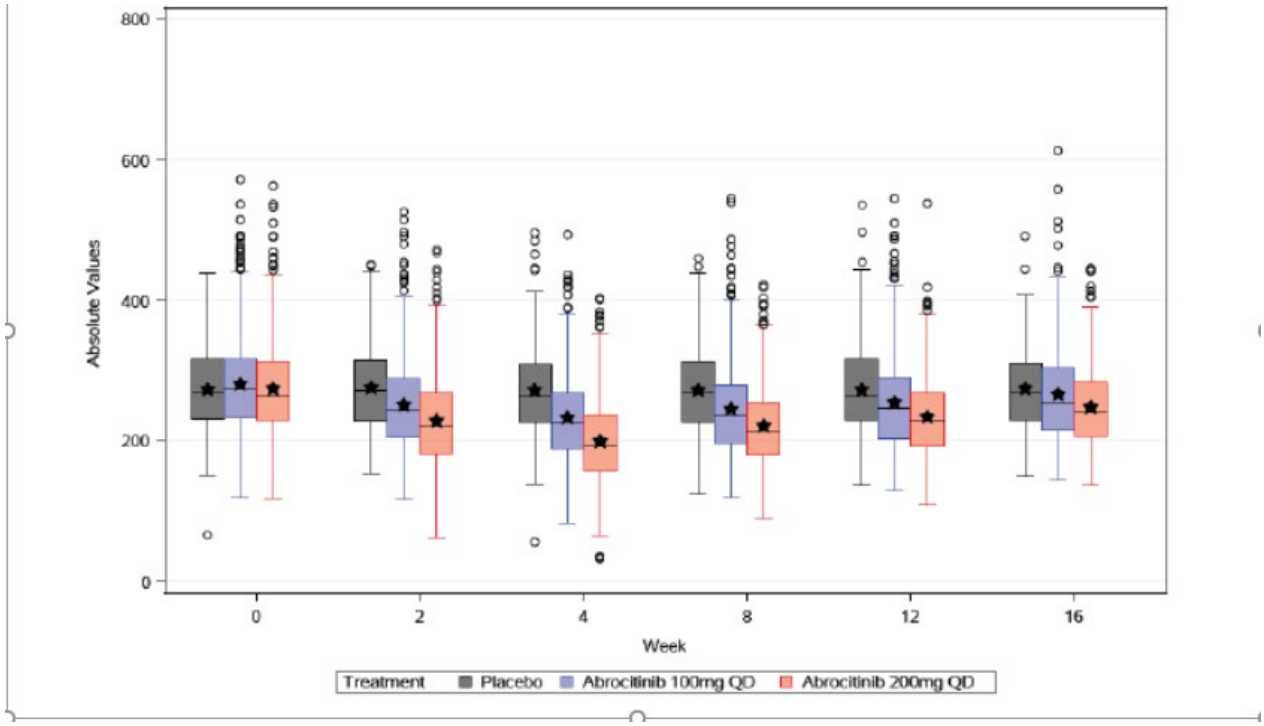
Platelets

After initiation of abrocitinib, there was a dose-related decrease in platelets with a nadir in median values at week 4; most values remained above the LLN ($140\times10^3/mm^3$). The median platelet counts in the population increased and reached a plateau at week 12 that was below the original baseline.

Across all subjects treated with abrocitinib, more than 95% of subjects in all treatment groups maintained a platelet value greater than $100\times10^3/mm^3$ throughout the treatment period. There were 9 subjects (0.3%) with a confirmed platelet values of $<75\times10^3/mm^3$, all values between week 2 and week 4 of exposure. Among the 9 subjects with low platelet counts, 2 (0.1%) subjects met the pre-

specified Phase 3 discontinuation criteria (confirmed <50×10^3/mm^3), both were in the abrocitinib 200 mg QD treatment group. Neither of these subjects had an AE related to bleeding.

Figure 26 Box Plot of Platelet (10^3/mm^3) Data by Visit – Primary Pool



Lymphocytes

In the Primary Pool, approximately 80% subjects in the abrocitinib treated groups maintained an ALC ≥ 1×10^3/mm^3. A higher percentage of subjects in the abrocitinib 100 mg (18.5%) and abrocitinib 200 mg (20.8%) QD groups had an ALC <1×10^3/mm^3 compared with the placebo group (11.9%). There was no change over time in absolute lymphocyte counts associated with abrocitinib treatment.

Per protocol, subjects included in Phase 2 and Phase 3 studies with abrocitinib, had lymphocyte counts at screening within the reference range in order to meet inclusion criteria. There were 4 subjects meeting discontinuation criteria for lymphopenia (confirmed <0.5×10^3/mm^3). These subjects were all older than 65 years of age and in 3 of the 4 subjects the confirmed decrease occurred in the first few weeks of therapy.

Table 58 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Proportion of Subjects Meeting Retest and Discontinuation Criteria for Lymphocytes – All Exposure Pool

	Abrocitinib 100mg QD N n (%)	Abrocitinib 200mg QD N n (%)	All Abrocitinib N n (%)
Retest Criteria (Single Value)			
Lymphocytes (10^3/mm^3) < 0.5	877 10 (1.1)	1955 21 (1.1)	2832 31 (1.1)
Discontinuation Criteria (Confirmed Value)			
Lymphocytes (10^3/mm^3) < 0.5 [1]	877 0	1955 4 (0.2)	2832 4 (0.1)

In summary, the clinical data are sufficient to determine that lymphopenia and thrombocytopenia are ADRs. Although there was no change over time in absolute lymphocyte counts associated with abrocitinib treatment, a higher percentage of subjects in the abrocitinib 100 mg (18.5%) and abrocitinib 200 mg (20.8%) QD groups had an ALC $<1\times10^3/mm^3$ compared with the placebo group (11.9%) and 4 subjects met discontinuation criteria for lymphopenia (confirmed $<0.5\times10^3/mm^3$). Thrombocytopenia and lymphopenia are labelled in Table 1 of section 4.8. No clear population changes in neutrophils were observed in the treatment groups of abrocitinib and no patient had a confirmed neutrophil count less than $1.0\times10^3/mm^3$. However, although no patient exposed to abrocitinib in the clinical studies experienced ANC 1.0 $x10^3/mm^3$ there was a dose-response effect in the number of subjects with ANC below 2 $x10^3/mm^3$. In addition, pancytopenia was one of the AEs leading to discontinuation that occurred in more than 2 subjects. Although there were no population changes in haemoglobin a limited number of patients developed clinically meaningful low values of haemoglobin. The proposed precautionary prescribing information for abrocitinib in section 4.2 as well as 4.4 is endorsed. The proposed text in section 4.2 presently reads: Treatment with abrocitinib should not be initiated in patients with a platelet count < 150 × $10^3/mm^3$, an absolute lymphocyte count (ALC) < 0.5 × $10^3/mm^3$, an absolute neutrophil count (ANC) < 1 × $10^3/mm^3$ or who have a haemoglobin value < 8 g/dL (see section 4.4).

Lipids

Changes in Lipid Parameters

In the Primary Pool, there was a dose-related percent change increase in LDL-c relative to placebo at week 4, which remained through the final visit in the treatment period (week 12 /week 16, Figure 17). The median change from baseline to last observation was higher in the abrocitinib 100 mg QD and 200 mg QD group (5 and 7 mg/dL, respectively) relative to placebo (-2 mg/dL). The percent change in LDL-c cholesterol at week 16 (B7451029) is higher for the abrocitinib and placebo arms than that of the other studies at week 12 (B7451012, B7451013, B7451006); however, the relationship between the arms remains similar.

In the All Exposure Pool, there was a continued increase in LDL though Month 9 (n = 617), afterwards there was more limited data. At Month 9 the median LDL was 114.0 mg/dL in the abrocitinib 100 mg QD group and 108.0 mg/dL in the abrocitinib 200 mg QD group.

Total cholesterol changes over time were consistent with that of LDL-c. In the All Exposure Pool, the LDL/HDL ratio decreases initially over the first 3 months and then increases by 5-10%, however, the number of subjects after Month 9 is more limited and, as such, there is less precision in the estimates. There was a dose-related percent change increase in HDL-c relative to placebo at week 4 which remained through the final visit in the treatment period (week 12 for studies B7451006, B7451012, B7451013 and week 16 for B7451029). The percent increase in HDL is larger than LDL. In the All Exposure Pool, the HDL remained above baseline throughout the analysis period.

Figure 27 Mean (+/-SE) Percent Change from Baseline in LDL-c by Visit – Primary Pool

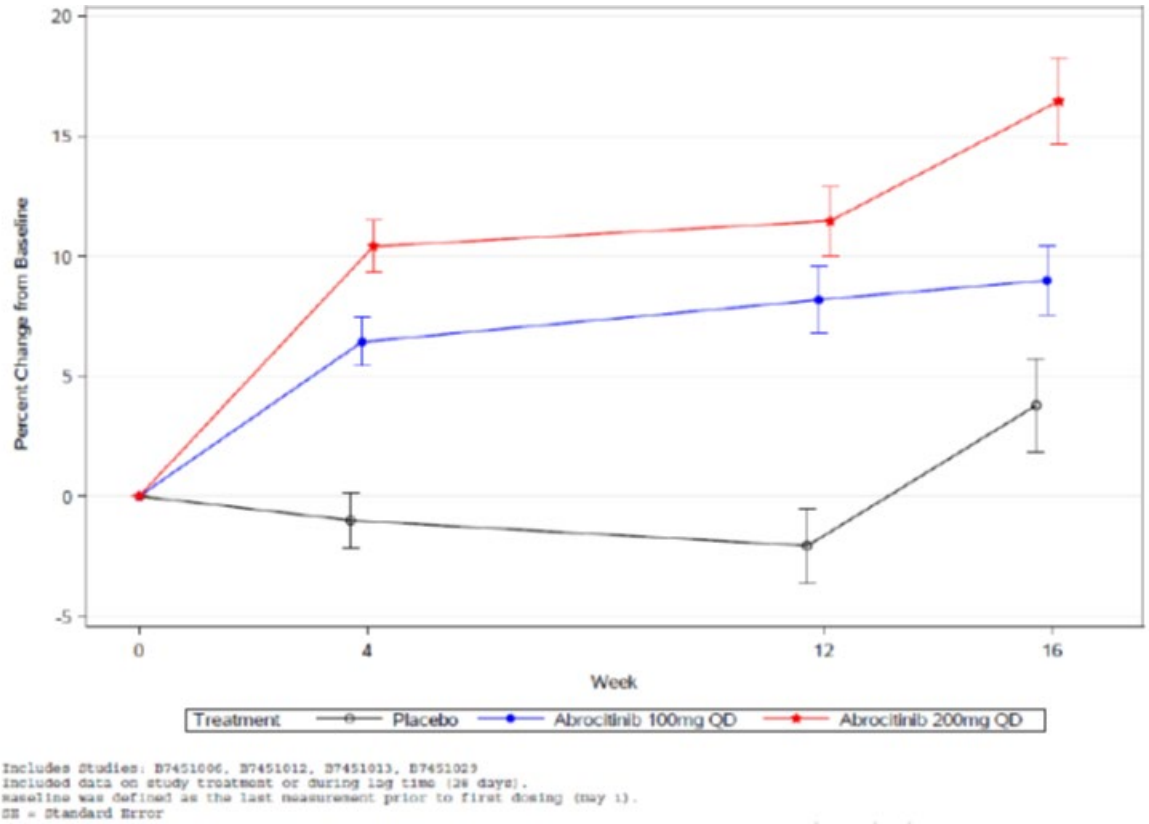
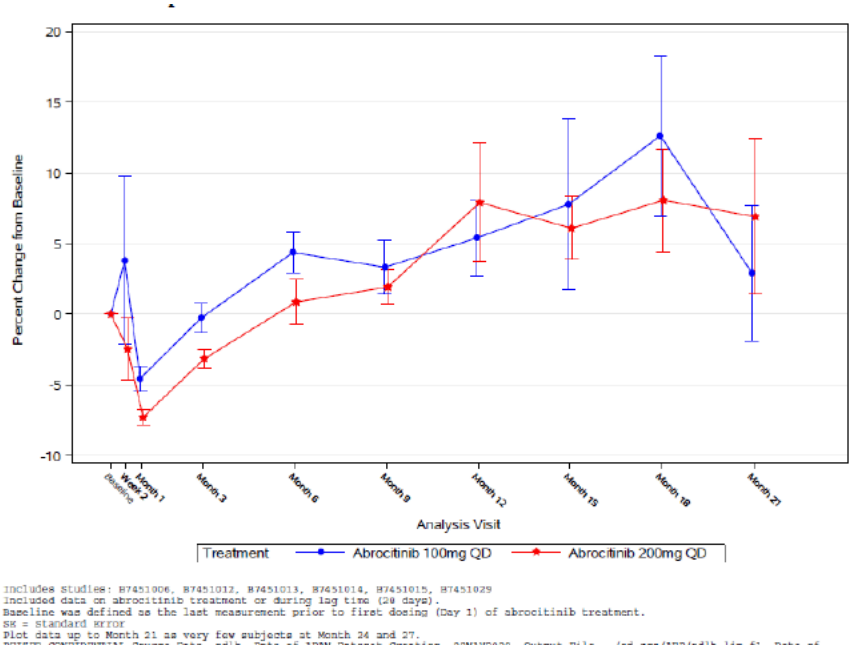


Figure 28 Mean (+/-SE) Percent Change from Baseline in LDL-c by Visit – All Exposure Pool



There was no meaningful change in triglycerides relative to placebo.

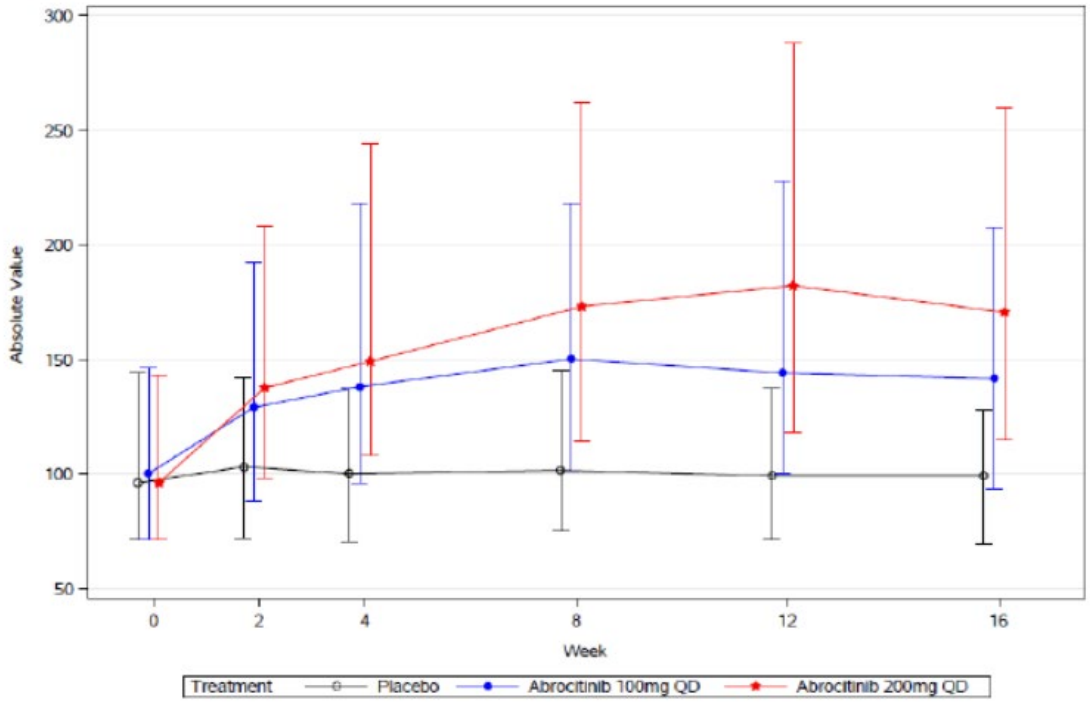
In the proposed SmPC section 4.4 it is initially stated that Dose dependent increase in blood lipid parameters were reported in patients treated with abrocitinib (see section 4.8). Lipid parameters should be assessed approximately 4 weeks following initiation of abrocitinib therapy and thereafter patients should be managed according to clinical guidelines for hyperlipidaemia. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

This recommendation is in line with other JAK 1 inhibitors though the time point of first recommended lipid assessment following initiation of therapy is earlier, 4 weeks. This is assumed to be linked to the shown dose-related percent change increase in LDL-c relative to placebo at week 4, which remained through week 12. Upon request from the CHMP, further information in relation to the known cardiovascular risk associated with hyperlipidaemia was included (see discussion section on clinical safety).

Creatine Kinase (CK)

Treatment with other JAK inhibitors has been associated with increases in CK. As such, CK was monitored in the abrocitinib programme. There was a dose-related increase in CK beginning at week 4 and having at plateau at week 8 (Figure 28). The median change at the last observation was increased in the abrocitinib 100 mg QD and 200 mg QD groups (53 U/L and 88 U/L, respectively) relative to the placebo group (-2 U/L). There was a dose-related increase in subjects reporting AEs of blood creatine phosphokinase increased in the Primary Pool. In the All Exposure Pool, CK remains increased throughout the study period and 5.4% of abrocitinib-treated subjects with CK >5xULN. There were no reported events of rhabdomyolysis.

Figure 29 Line Plot of Median (Q1, Q3) Creatine Kinase (U/L) Data by Visit – Primary Pool



There were 2 subjects with an SAE of myositis.

Creatine phosphokinase elevations increased is labelled in SmPC section 4.8 in SOC Investigations with frequency common. Upon request from the CHMP, the increase was specified as: Creatine phosphokinase increased > 5 x ULN.

Serum creatinine

There was no difference in the change over time of creatinine between the abrocitinib dose groups and the placebo group over 12 weeks. In the Primary Pool, the incidence was similar in abrocitinib treatment groups and the placebo group

CRP

There was a decrease over time in CRP in the abrocitinib treatment groups compared to placebo.

2.6.8.5. Safety in special populations

Safety in adolescents (12 - <18 years)

Short-term treatment

In the Primary safety pool, the safety profile for the TEAE overview (e.g., All AEs, SAEs, severe events, AEs leading to discontinuation) was generally similar across the subgroups.

Please refer to tables presented in the previous section summarising the TEAEs reported in adolescents of the Primary safety pool.

Long-term treatment

In the All Exposure Pool, 364 adolescent subjects were exposed representing 230.3 patient years. The median age of the adolescent subgroup was 15.0 years. In the All Exposure Pool, adolescent subjects were more likely to have any AE relative to the 18 - <65-year-old subgroup. There was no clustering of AEs driving the difference and, as such, the overall AE profile was similar. The proportions of adolescent subjects having serious and severe events as well as events leading to discontinuations were similar to those for subjects in the 18 - <65-year-old subgroup. In the All Exposure Pool, there were no meaningful differences in the proportions of adolescent subjects having serious infection relative to the other age groups. The IR for all herpes zoster infections was lowest in the adolescent subgroup relative to the other age groups.

Table 59 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Treatment-Emergent Adverse Events (All Causalities) by Baseline Age (<18, 18-<65, >=65, >=75 years) – All Exposure Pool

Number (%) of Subjects	Abrocitinib 100mg QD n (%)	Abrocitinib 200mg QD n (%)	All Abrocitinib n (%)
Baseline Age (years): < 18			
Subjects evaluable for adverse events	64	300	364
Number of adverse events	187	686	873
Subjects with adverse events	53 (82.8)	236 (78.7)	289 (79.4)
Subjects with serious adverse events	5 (7.8)	12 (4.0)	17 (4.7)
Subjects with severe adverse events	11 (17.2)	19 (6.3)	30 (8.2)
Subjects discontinued from study due to adverse events [1]	6 (9.4)	16 (5.3)	22 (6.0)
Subjects discontinued study drug due to AE and continue study [2]	1 (1.6)	2 (0.7)	3 (0.8)
Subjects with dose reduced or temporary discontinuation due to adverse events	5 (7.8)	30 (10.0)	35 (9.6)

Baseline Age (years): 18 -< 65			
Subjects evaluable for adverse events	770	1577	2347
Number of adverse events	1679	3408	5087
Subjects with adverse events	543 (70.5)	1121 (71.1)	1664 (70.9)
Subjects with serious adverse events	36 (4.7)	54 (3.4)	90 (3.8)
Subjects with severe adverse events	52 (6.8)	76 (4.8)	128 (5.5)
Subjects discontinued from study due to adverse events [1]	62 (8.1)	123 (7.8)	185 (7.9)
Subjects discontinued study drug due to AE and continue study [2]	9 (1.2)	9 (0.6)	18 (0.8)
Subjects with dose reduced or temporary discontinuation due to adverse events	73 (9.5)	162 (10.3)	235 (10.0)

Bone and Growth

Based on non-clinical data, monitoring was implemented and the potential growth effect risk to adolescents was analysed for height velocity SDS as well as AEs of fracture and growth disturbance in adolescents. Seenon-clinical assessment for further data. Height SDS was examined in adolescent subjects who entered the long-term safety study (B7451015).

Table 60 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Summary of Standard Deviation Score (SDS) for Height Measurement and Its Change from Baseline Overtime for Adolescent Subjects – All Exposure Pool

		Abrocitinib 100mg QD (N=885)		Abrocitinib 200mg QD (N=1971)		All Abrocitinib (N=2856)	
		Result	Change from Baseline	Result	Change from Baseline	Result	Change from Baseline
	Summary Statistics						
Baseline [1]	n	64		298		362	
	Mean (SD)	-0.2 (1.0)		-0.2 (1.1)		-0.2 (1.0)	
	Median (Q1, Q3)	0 (-1, 0)		0 (-1, 1)		0 (-1, 1)	
	Range (Min, Max)	(-4.2, 2.0)		(-3.4, 3.7)		(-4.2, 3.7)	
Day 180 (+/- 30 days) [2]	n	50	50	98	98	148	148
	Mean (SD)	-0.1 (0.9)	-0.0 (0.3)	-0.0 (1.0)	-0.0 (0.3)	-0.1 (1.0)	-0.0 (0.3)
	Median (Q1, Q3)	0 (-1, 0)	0 (0, 0)	0 (-1, 1)	0 (0, 0)	0 (-1, 1)	0 (0, 0)

	Range (Min, Max)	(-2.1, 2.4)	(-0.7, 1.1)	(-3.2, 2.8)	(-0.9, 1.3)	(-3.2, 2.8)	(-0.9, 1.3)
Day 360 (+/- 30 days) [2]	n	28	28	66	66	94	94
	Mean (SD)	-0.1 (0.9)	-0.0 (0.4)	-0.1 (1.0)	-0.0 (0.3)	-0.1 (1.0)	-0.0 (0.3)
	Median (Q1, Q3)	0 (-1, 0)	0 (0, 0)	0 (-1, 1)	0 (0, 0)	0 (-1, 1)	0 (0, 0)
	Range (Min, Max)	(-1.9, 1.5)	(-0.8, 1.2)	(-3.4, 1.7)	(-0.6, 1.1)	(-3.4, 1.7)	(-0.8, 1.2)
Day 540 (+/- 30 days) [2]	n	6	6	9	9	15	15
	Mean (SD)	0.4 (1.1)	0.3 (0.5)	-0.1 (1.1)	-0.1 (0.5)	0.1 (1.1)	0.0 (0.5)
	Median (Q1, Q3)	1 (0, 1)	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 1)	0 (0, 0)
	Range (Min, Max)	(-1.4, 1.5)	(-0.5, 1.2)	(-2.9, 1.0)	(-0.8, 0.7)	(-2.9, 1.5)	(-0.8, 1.2)
Day 720 (+/- 30 days) [2]	n	1	1	2	2	3	3
	Mean (SD)	-0.5 (NA)	0.2 (NA)	-1.0 (0.2)	-0.5 (0.2)	-0.8 (0.3)	-0.2 (0.4)
	Median (Q1, Q3)	0 (0, 0)	0 (0, 0)	-1 (-1, -1)	0 (-1, 0)	-1 (-1, 0)	0 (-1, 0)
	Range (Min, Max)	(-0.5, -0.5)	(0.2, 0.2)	(-1.1, -0.8)	(-0.6, -0.3)	(-1.1, -0.5)	(-0.6, 0.2)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029
SDS: Standardized to the US population by age and gender.
[1] Measurement on or prior to first abrocitinib dosing date.
[2] Relative to first abrocitinib dosing date.
PFIZER CONFIDENTIAL Source Data: advs Date of ADAM Dataset Creation: 01JUN2020 Output File: ./ad_scs/AEP/advs_s101_sds Date of Generation: 01JUN2020 (04:13)

Height SDS: The SDS standardised to the US population by age and gender was calculated at each time point where height measurement is available. As such the findings are normalised across age and gender. At Month 6 and Month 12, the SDS changes ranged from -0.9 to 1.3 with median of 0, suggesting no meaningful change in the subjects' growth curves. There were overall no events related to growth disturbance in the All Exposure Pool. It was considered that there was no meaningful change in measures of central tendency for height velocity SDS.

Abrocitinib seemed to be well-tolerated in the adolescent population when analysing submitted data. However, there was a higher percentage of TEAEs in adolescents compared to the total population in the analysis of the primary safety pool and higher compared to the 18 to <65 years age group of the All Safety Pool and it is questioned if provided clinical data are sufficient to address any potential bone effects in adolescents, in line with the signal indicated in pre-clinical studies. Based on this and the assumption of dose dependent TEAES, further discussion of safety were requested in relation to abrocitinib exposure in adolescents. Furthermore, as noted previously the discrepancy and increase of percentage of reported TEAEs within the SOC "Respiratory, Thoracic And Mediastinal Disorders" of abrocitinib treated subjects < 18 years of age compared to the total population was addressed upon request from the CHMP.

Safety in elderly (≥65 years)

Older subjects were more likely to discontinue treatment due to an AE relative to the younger age subgroups; the most frequent of these AEs were in the Investigations and Skin and subcutaneous structures SOCs. Older subjects were more likely to have herpes zoster, but not serious infections. Most subjects with CV and malignancy events were >60 years of age. Among patients exposed to abrocitinib including the long-term extension study, confirmed absolute lymphocyte count <0.5 × 10^3/mm^3 occurred only in patients ≥65 years of age. A higher proportion of patients ≥65 years of age

had platelets <75 × 10^3/mm^3.Most subjects meeting discontinuation criteria for haematology labs were ≥65 years of age.

Table 61 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Treatment-Emergent Adverse Events (All Causalities) by Baseline Age (<18, 18-<65, >=65, >=75 years) – All Exposure Pool

Number (%) of Subjects	Abrocitinib 100mg QD n (%)	Abrocitinib 200mg QD n (%)	All Abrocitinib n (%)
Baseline Age (years): 18 -< 65			
Subjects evaluable for adverse events	770	1577	2347
Number of adverse events	1679	3408	5087
Subjects with adverse events	543 (70.5)	1121 (71.1)	1664 (70.9)
Subjects with serious adverse events	36 (4.7)	54 (3.4)	90 (3.8)
Subjects with severe adverse events	52 (6.8)	76 (4.8)	128 (5.5)
Subjects discontinued from study due to adverse events [1]	62 (8.1)	123 (7.8)	185 (7.9)
Subjects discontinued study drug due to AE and continue study [2]	9 (1.2)	9 (0.6)	18 (0.8)
Subjects with dose reduced or temporary discontinuation due to adverse events	73 (9.5)	162 (10.3)	235 (10.0)
Baseline Age (years): ≥ 65			
Subjects evaluable for adverse events	51	94	145
Number of adverse events	102	221	323
Subjects with adverse events	31 (60.8)	63 (67.0)	94 (64.8)
Subjects with serious adverse events	7 (13.7)	8 (8.5)	15 (10.3)
Subjects with severe adverse events	6 (11.8)	7 (7.4)	13 (9.0)
Subjects discontinued from study due to adverse events [1]	9 (17.6)	16 (17.0)	25 (17.2)
Subjects discontinued study drug due to AE and continue study [2]	1 (2.0)	3 (3.2)	4 (2.8)
Subjects with dose reduced or temporary discontinuation due to adverse events	5 (9.8)	14 (14.9)	19 (13.1)
Baseline Age (years): ≥ 75			
Subjects evaluable for adverse events	10	15	25
Number of adverse events	35	32	67
Subjects with adverse events	7 (70.0)	11 (73.3)	18 (72.0)
Subjects with serious adverse events	2 (20.0)	2 (13.3)	4 (16.0)
Subjects with severe adverse events	2 (20.0)	1 (6.7)	3 (12.0)
Subjects discontinued from study due to adverse events [1]	2 (20.0)	6 (40.0)	8 (32.0)
Subjects discontinued study drug due to AE and continue study [2]	1 (10.0)	1 (6.7)	2 (8.0)
Subjects with dose reduced or temporary discontinuation due to adverse events	1 (10.0)	2 (13.3)	3 (12.0)

Below are specified tables of the cumulative pool of ages 65-<75, 75 - <85, ≥ 85 years as well as select adverse events by age.

Table 62 Treatment-Emergent Adverse Events (All Causalities) by Baseline Age (<65, 65 - <75, 75 - <85, ≥ 85 years) - Full Cumulative Pool

Number (%) of Subjects	Abrocitinib 100 mg QD		Abrocitinib 200 mg QD		All Abrocitinib	
	AEP n (%)	Updated AEP + B7451036 n (%)	AEP n (%)	Updated AEP + B7451036 n (%)	AEP n (%)	Updated AEP + B7451036 n (%)
Baseline Age (years): < 65						
Subjects evaluable for adverse events	834	972	1877	2011	2711	2983
Number of adverse events	1866	2356	4094	4654	5960	7010
Subjects with adverse events	596 (71.5)	716 (73.7)	1357 (72.3)	1481 (73.6)	1953 (72.0)	2197 (73.7)
Subjects with serious adverse events	41 (4.9)	50 (5.1)	66 (3.5)	76 (3.8)	107 (3.9)	126 (4.2)
Subjects with severe adverse events	63 (7.6)	71 (7.3)	95 (5.1)	107 (5.3)	158 (5.8)	178 (6.0)
Subjects discontinued from study due to adverse events [1]	68 (8.2)	84 (8.6)	139 (7.4)	158 (7.9)	207 (7.6)	242 (8.1)
Subjects discontinued study drug due to AE and continue study [2]	10 (1.2)	11 (1.1)	11 (0.6)	9 (0.4)	21 (0.8)	20 (0.7)
Subjects with dose reduced or temporary discontinuation due to adverse events	78 (9.4)	103 (10.6)	192 (10.2)	230 (11.4)	270 (10.0)	333 (11.2)
Baseline Age (years): 65 -< 75						
Subjects evaluable for adverse events	41	41	79	79	120	120
Number of adverse events	67	78	189	210	256	288
Subjects with adverse events	24 (58.5)	24 (58.5)	52 (65.8)	55 (69.6)	76 (63.3)	79 (65.8)
Subjects with serious adverse events	5 (12.2)	5 (12.2)	6 (7.6)	9 (11.4)	11 (9.2)	14 (11.7)
Subjects with severe adverse events	4 (9.8)	4 (9.8)	6 (7.6)	8 (10.1)	10 (8.3)	12 (10.0)
Subjects discontinued from study due to adverse events [1]	7 (17.1)	7 (17.1)	10 (12.7)	12 (15.2)	17 (14.2)	19 (15.8)
Subjects discontinued study drug due to AE and continue study [2]	0	0	2 (2.5)	3 (3.8)	2 (1.7)	3 (2.5)
Subjects with dose reduced or temporary discontinuation due to adverse events	4 (9.8)	4 (9.8)	12 (15.2)	13 (16.5)	16 (13.3)	17 (14.2)
Baseline Age (years): 75 -< 85						
Subjects evaluable for adverse events	10	10	15	15	25	25
Number of adverse events	35	39	32	34	67	73
Subjects with adverse events	7 (70.0)	7 (70.0)	11 (73.3)	11 (73.3)	18 (72.0)	18 (72.0)
Subjects with serious adverse events	2 (20.0)	2 (20.0)	2 (13.3)	3 (20.0)	4 (16.0)	5 (20.0)
Subjects with severe adverse events	2 (20.0)	2 (20.0)	1 (6.7)	2 (13.3)	3 (12.0)	4 (16.0)
Subjects discontinued from study due to adverse events [1]	2 (20.0)	2 (20.0)	6 (40.0)	7 (46.7)	8 (32.0)	9 (36.0)

Table 62 Treatment-Emergent Adverse Events (All Causalities) by Baseline Age (<65, 65 - <75, 75 - <85, ≥ 85 years) - Full Cumulative Pool

Number (%) of Subjects	Abrocitinib 100 mg QD		Abrocitinib 200 mg QD		All Abrocitinib	
	AEP n (%)	Updated AEP + B7451036 n (%)	AEP n (%)	Updated AEP + B7451036 n (%)	AEP n (%)	Updated AEP + B7451036 n (%)
Subjects discontinued study drug due to AE and continue study [2]	1 (10.0)	1 (10.0)	1 (6.7)	0	2 (8.0)	1 (4.0)
Subjects with dose reduced or temporary discontinuation due to adverse events	1 (10.0)	1 (10.0)	2 (13.3)	2 (13.3)	3 (12.0)	3 (12.0)

Table 63 Select Adverse Events by Age- Abrocitinib Safety Update Full Cumulative Pool

		Abrocitinib 100 mg		Abrocitinib 200 mg		All Abrocitinib	
Age (years) N		**18-< 65 N=771**	**≥65 N=51**	**18-< 65 N=1577**	**≥65 N=94**	**18-< 65 N=2348**	**≥65 N=145**
Serious Adverse Events	n (%) IR (CI)	42 (5.4) 6.40 (4.61, 8.65)	7 (13.7) 16.67 (6.70, 34.35)	59 (3.7) 6.32 (4.81, 8.15)	12 (12.8) 23.08 (11.92, 40.31)	101 (4.3) 6.35 (5.17, 7.71)	19 (13.1) 20.22 (12.17, 31.57)
TEAE Resulting in Permanent Discontinuation	n (%) IR (CI)	71 (9.2) 10.66 (8.33, 13.45)	9 (17.6) 20.92 (9.57, 39.72)	134 (8.5) 14.35 (12.02, 16.99)	19 (20.2) 35.49 (21.37, 55.42)	205 (8.7) 12.82 (11.12, 14.69)	28 (19.3) 29.00 (19.27, 41.91)
Serious Infections	n (%) IR (CI)	15 (1.9) 2.24 (1.25, 3.69)	1 (2.0) 2.29 (0.06, 12.75)	21 (1.3) 2.22 (1.37, 3.39)	2 (2.1) 3.63 (0.44, 13.11)	36 (1.5) 2.23 (1.56, 3.09)	3 (2.1) 3.04 (0.63, 8.87)
All Herpes Zoster Infections (CMQ)[1]	n (%) IR (CI)	13 (1.7) 1.95 (1.04, 3.34)	2 (3.9) 4.73 (0.57, 17.09)	43 (2.7) 4.63 (3.35, 6.23)	6 (6.4) 11.29 (4.14, 24.58)	56 (2.4) 3.51 (2.65, 4.56)	8 (5.5) 8.39 (3.62, 16.52)
Thrombotic events including pulmonary embolism[2]	n (%) IR (CI)	0 0.00 (0.00, 0.55)	0 0.00 (0.00, 8.43)	4 (0.3) 0.42 (0.11, 1.08)	1 (1.1) 1.81 (0.05,10.09)	4 (0.2) 0.25 (0.07, 0.63)	1 (0.7) 1.01 (0.03, 5.63)
Adjudicated Malignancies (excl. NMSC)	n (%) IR (CI)	0 0.00 (0.00, 0.55)	1 (2.0) 2.29 (0.06, 12.75)	0 0.00 (0.00, 0.39)	2 (2.1) 3.70 (0.45, 13.35)	0 0.00 (0.00, 0.23)	3 (2.1) 3.07 (0.63, 8.96)
NMSC	n (%) IR (CI)	3 (0.4) 0.45 (0.09, 1.31)	0 0.00 (0.00, 8.43)	1 (0.1) 949.78 0.11 (0.00, 0.59)	3 (3.2) 54.86 5.47 (1.13, 15.98)	4 (0.2) 1621.45 0.25 (0.07, 0.63)	3 (2.1) 98.63 3.04 (0.63, 8.89)
Major cardiovascular event	n (%) IR (CI)	0 0.00 (0.00, 0.55)	1 (2.0) 2.28 (0.06, 12.73)	3 (0.2) 0.32 (0.07, 0.92)	0 0.00 (0.00, 6.67)	3 (0.1) 0.18 (0.04, 0.54)	1 (0.7) 1.01 (0.03, 5.62)
Hyperlipidemia (CMQ)[3]	n (%) IR (CI)	6 (0.8) 0.89 (0.33, 1.95)	0 0.00 (0.00, 8.43)	23 (1.5) 2.44 (1.55, 3.66)	1 (1.1) 1.85 (0.05, 10.28)	29 (1.2) 1.80 (1.20, 2.58)2.29)	1 (0.7) 1.02 (0.03, 5.69)
Thrombocytopenia[4]	n (%) IR (CI)	0 0.00 (0.00, 0.55)	0 0.00 (0.00, 8.43)	1 (0.1) 0.11 (0.00, 0.59)	1 (1.1) 1.81 (0.05,10.08)	1 (<0.1) 0.06 (0.00, 0.34)	1 (0.7) 1.01 (0.03, 5.63)
Lymphopenia[5]	n (%) IR (CI)	0 0.00 (0.00, 0.55)	1 (2.0) 2.30 (0.06,12.81)	1 (0.1) 0.11 (0.00, 0.59)	5 (5.3) 9.11 (2.96,21.27)	1 (<0.1) 0.06 (0.00, 0.34)	6 (4.1) 6.10 (2.24,13.27)

It is stated in SmPC section 4.4 that the rate of herpes zoster infections was higher in patients 65 years of age and older with a cross reference to section 4.8. Most subjects meeting discontinuation criteria for haematology labs were also ≥65 years of age, seemingly absolute lymphocyte counts <0.5

$\times 10^3/mm^3$ occurred only in patients ≥65 years of age and a higher proportion of patients ≥65 years of age had platelets $<75 \times 10^3/mm^3$. Furthermore, according to Table 65 the percentage of subjects with SAEs exposed to combined strengths of 100mg QD abrocitinib and 200 mg QD abrocitinib were 3.8%, 10.3% and 16 % for individuals 18-≥65 years of age, >65 years of age and >75 years of age respectively. Based on these safety findings, the applicant was requested to further justify the exposure and dosing recommendations of abrocitinib in this subgroup.

Race

The number of subjects in the 'Other' subgroup was low and analyses in that subgroup had limited precision. As such, this section focuses on the White, Black, and Asian subgroups.

Table 64 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Treatment-Emergent Adverse Events (All Causalities) by RCE – All E

Number (%) of Subjects	Abrocitinib 100mg QD n (%)	Abrocitinib 200mg QD n (%)	All Abrocitinib n (%)
Race: White			
Subjects evaluable for adverse events	637	1426	2063
Number of adverse events	1456	2881	4337
Subjects with adverse events	446 (70.0)	1003 (70.3)	1449 (70.2)
Subjects with serious adverse events	35 (5.5)	55 (3.9)	90 (4.4)
Subjects with severe adverse events	56 (8.8)	88 (6.2)	144 (7.0)
Subjects discontinued from study due to adverse events [1]	62 (9.7)	115 (8.1)	177 (8.6)
Subjects discontinued study drug due to AE and continue study [2]	9 (1.4)	10 (0.7)	19 (0.9)
Subjects with dose reduced or temporary discontinuation due to adverse events	65 (10.2)	146 (10.2)	211 (10.2)
Race: Black			
Subjects evaluable for adverse events	49	121	170
Number of adverse events	105	270	375
Subjects with adverse events	31 (63.3)	81 (66.9)	112 (65.9)
Subjects with serious adverse events	1 (2.0)	7 (5.8)	8 (4.7)
Subjects with severe adverse events	3 (6.1)	4 (3.3)	7 (4.1)
Subjects discontinued from study due to adverse events [1]	4 (8.2)	14 (11.6)	18 (10.6)
Subjects discontinued study drug due to AE and continue study [2]	0	2 (1.7)	2 (1.2)
Subjects with dose reduced or temporary discontinuation due to adverse events	1 (2.0)	14 (11.6)	15 (8.8)
Race: Asian			
Subjects evaluable for adverse events	187	366	553
Number of adverse events	366	994	1360
Subjects with adverse events	141 (75.4)	293 (80.1)	434 (78.5)
Subjects with serious adverse events	11 (5.9)	10 (2.7)	21 (3.8)
Subjects with severe adverse events	8 (4.3)	8 (2.2)	16 (2.9)
Subjects discontinued from study due to adverse events [1]	10 (5.3)	24 (6.6)	34 (6.1)
Subjects discontinued study drug due to AE and continue study [2]	1 (0.5)	2 (0.5)	3 (0.5)
Subjects with dose reduced or temporary discontinuation due to adverse events	16 (8.6)	39 (10.7)	55 (9.9)
Race: Other			
Subjects evaluable for adverse events	12	58	70
Number of adverse events	41	170	211
Subjects with adverse events	9 (75.0)	43 (74.1)	52 (74.3)
Subjects with serious adverse events	1 (8.3)	2 (3.4)	3 (4.3)
Subjects with severe adverse events	2 (16.7)	2 (3.4)	4 (5.7)
Subjects discontinued from study due to adverse events [1]	1 (8.3)	2 (3.4)	3 (4.3)
Subjects discontinued study drug due to AE and continue study [2]	1 (8.3)	0	1 (1.4)
Subjects with dose reduced or temporary discontinuation due to adverse events	1 (8.3)	7 (12.1)	8 (11.4)

Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029
Includes data up to 28 days after last dose of study.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
[1] Subjects who had an AE record that indicated that the AE caused the subject to be discontinued from the study.
[2] Subjects who had an AE record that indicated that action taken with abrocitinib treatment was drug withdrawn but AE did not cause the subject to be discontinued from study.
MedDRA v23.0 coding dictionary applied.

As TEAEs when treated with abrocitinib 200 mg were more frequent in the Asian subgroup (80.1 %) compared to the Black subgroup (66.9%) and White subgroup (70.3 %) this will need further discussion concerning The applicant should comment and justify why no further any actions from the perspective of labelling concerning the Asian subgroup.

Hepatic

Transaminases

More than 80% of abrocitinib-treated subjects maintained AST and ALT within the normal range throughout the study period. The proportion of subjects with AST and/or ALT >3xULN was low (≤1.1%) and similar across the treatment groups. In total, 24 hepatic cases were adjudicated to determine the likelihood of a DILI case. Most (n = 17) cases were adjudicated as unlikely or unrelated. The other 7 were adjudicated as a possible DILI (probability 25-50%). No cases were adjudicated as a probable, highly likely, or definite DILI case. No subject met Hy's law criteria.

There were 2 SAEs of Drug-induced liver injury. One completed the adjudication process and the final assessment determined that DILI was unlikely. One event had not completed the adjudication process at the time of database release. The information proposed for the SmPC relates only to hepatic impairment and dose adjustments not being required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment and that abrocitinib has not been studied in patients with severe (Child Pugh C) hepatic impairment and therefore is contraindicated. There is no labelling in SmPC section 4.8. This is presently accepted though it is proposed that DILI is added in the safety specification of the RMP as important potential risk.

Renal

Baseline eGFR

Overall, the abrocitinib was safe and well tolerated regardless of baseline eGFR. No unique risks were identified based on baseline eGFR. There were 42 subjects (26.4 PY) in the eGFR <60 mL/min subgroup, 756(413.5 PY) in the 60 - <90 mL/min subgroup and 2053 (1172 PY) in the eGFR ≥90 mL/min subgroup. Subjects in the <60 mL/min subgroup were more likely to be in the age ≥65 years and female subgroups and had a lower weight. Subjects in the ≥90 mL/min subgroup had a higher proportion of subjects with severe disease. There was no meaningful difference in the proportions of subjects having all TEAEs, SAEs, severe AEs, and AEs (all causalities, all safety pool) leading to discontinuation in the eGFR subgroups. There was no meaningful difference in the IR for serious infection or herpes zoster by baseline eGFR subgroup.

Based on the recommendations in section 4.2 of the SmPC relating to dose reductions in patients with RI, the applicant was asked to clarify how many of the total number of 42 subjects (26.4 PY) in the eGFR <60 mL/min subgroup received 50mg QD and 100 mg QD abrocitinib respectively; and how many of these subjects experienced adverse events in each dosing group.

Treatment with other JAK inhibitors has been associated with increases in creatinine. Creatinine was monitored in the abrocitinib programme. Phase 3 protocols included a pre-specified discontinuation criterion of 2 sequential increases in serum creatinine that are >50% over the average of screening and baseline values and an absolute increase in serum creatinine ≥0.5 mg/dL. In the Primary Pool,

there was no meaningful change in creatinine over time in any treatment group. No subject met protocol pre-specified discontinuation criteria.

There was 1 event of acute kidney injury in the abrocitinib 100 mg QD group; the event was considered by the investigator as not related to the study drug. This event was not serious, severe, and did not lead to discontinuation. In the All Exposure Pool, there were 2 events of blood creatinine abnormal and 3 events of blood creatinine increased in abrocitinib-treated subjects. There were 3 events of acute kidney injury. One event of acute kidney injury was serious and concerned a 17-year old male who had serious events of pulmonary embolism and pneumothorax leading to discontinuation of therapy followed 5 days later by acute kidney injury. In this case there were concomitant medications vancomycin and piperacillin sodium/tazobactam sodium that were permanently withdrawn in response to the event of acute kidney injury. In the opinion of the Investigator, the event of acute kidney injury was considered to be unrelated to the study drug or a clinical trial procedure but was related to concomitant medications vancomycin and piperacillin sodium/tazobactam sodium. The study Sponsor concurred with the Investigator's causality assessment. There was 1 event of blood creatinine increased severe; 1 event of acute kidney injury and 1 event of blood creatinine increased led to discontinuation.

Pregnancy

Adverse effects on the musculoskeletal system (skeletal variation at ≥30 mg/kg/day) were observed in the embryo-foetal development study in rats. In the EFD study in rats, the developmental NOAEL was established at exposures of 2.4x the unbound human AUC at the clinical dose of 200 mg. In a rat PPND study, no effects on parturition and postnatal development were noted at NOAEL exposures of 2.4x the unbound human AUC. In the abrocitinib AD studies, based on the nonclinical data briefly described above, women of childbearing potential were expected to use effective contraception. While there are no substantial data on the use of abrocitinib in pregnant women, as of 22 April 2020, there have been 10 cases of exposure in utero reported in subjects exposed to abrocitinib in the AD clinical programme, 7 maternal exposures and 3 partner exposures. Of the 7 maternal exposers there were two miscarriages and five with outcome unknown.

In summary, there is very limited clinical pregnancy data. According to the proposed SmPC in section 4.3 abrocitinib is contraindicated during pregnancy and breast feeding and in section 4.6 it is recommended that women of reproductive potential should be advised to use effective contraception during treatment and for 1 month following the final dose of abrocitinib.

See non-clinical assessment for evaluation of effects on pregnancy and fertility. For other JAK inhibitors, treatment is contraindicated during pregnancy. Upon request from the CHMP and based on the non-clinical data and assessment, the applicant agreed to add pregnancy and breast-feeding as a contraindication for treatment with abrocitinib.

Lactation

There are no data on the presence of abrocitinib in human milk, the effects on the breast-fed infant, or the effects on milk production. Abrocitinib was secreted in milk of lactating rats. A risk to newborns/infants cannot be excluded and abrocitinib should not be used during breast-feeding. Therefore, abrocitinib is contraindicated during breast-feeding (see section 4.3 in the SmPC).

2.6.8.6. Immunological events

No data on immunological events were reported for AD patients exposed to abrocitinib. Abrocitinib is a small molecule product and antibody formation related to monoclonal antibody products is not relevant.

2.6.8.7. Safety related to drug-drug interactions and other interactions

Drug-drug interactions studies

Based on the results of the extrinsic factor studies, abrocitinib dose should be reduced by half to 50 mg or 100 mg once daily in patients receiving strong inhibitors of CYP2C19 alone (eg, fluvoxamine and ticlodipine) and in patients receiving one or more concomitant medicinal products that result in both moderate inhibition of CYP2C9 as well as strong inhibition of CYP2C19 (eg, fluconazole). The use of abrocitinib is not recommended concomitantly with moderate or strong inducers of CYP2C19/2C9 enzymes (eg, rifampin). Please also refer to the clinical pharmacology part of this report.

Overdose

Abrocitinib has been administered in Phase 1 and Phase 2 studies in doses as high as 800 mg in a single dose to healthy subjects (Study B7451001) and 200 mg BID and 400 mg QD for 4 weeks to subjects with psoriasis (Study B7451005).

Single doses of 800 mg (n = 16) were well tolerated in study B7451001. The most common AEs in that treatment group (reported in ≥3 subjects) were flatulence (n = 3), nausea (n = 3), vomiting (n = 4), pain in extremities (n = 3), and headache (n = 4). In the phase 2 study B7451005, subjects with psoriasis were treated with abrocitinib 200 mg BID and 400 mg QD for 4 weeks. Abrocitinib was generally well tolerated at those higher doses (Study B7451005). In this psoriasis Phase 2 study, the platelet counts for abrocitinib 400 mg QD and 200 mg QD were similar. The abrocitinib 200 mg QD dose group had platelet decreases in weeks 1-4 that were lower than that of 200 mg BID dose. There were no adverse events of overdose in the clinical programme.

Drug Abuse

There were no reports of drug abuse or dependence or other information relevant to the potential for drug abuse in these studies.

Withdrawal and Rebound

In the completed studies in the All Exposure Pool (B7451006, B7451012, B7451013, B7451029), no safety signal was identified in subjects who entered a follow-up period due to discontinuation from the study. In the All Exposure Pool, there were no AEs related to withdrawal and rebound.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

There were no reports of impairment of the senses, coordination, or other factors that would result in diminished ability to drive a vehicle or operate machinery or would impair mental ability.

2.6.8.8. Discontinuation due to adverse events

The primary safety pool

The proportion of subjects with AEs leading to discontinuations was similar across the abrocitinib treatment groups and the placebo group, with no dose relationship observed. The most frequent AEs leading to discontinuation were dermatitis atopic, occurring more frequently in the placebo treatment group (5.6%) than in abrocitinib treated subjects (1.2%). Other frequent AEs leading to discontinuation, occurring more frequently in the abrocitinib treated subjects, were nausea (4 of 1198 subjects: 0.3%) and headache (3 of 1198 subjects: 0.3%).

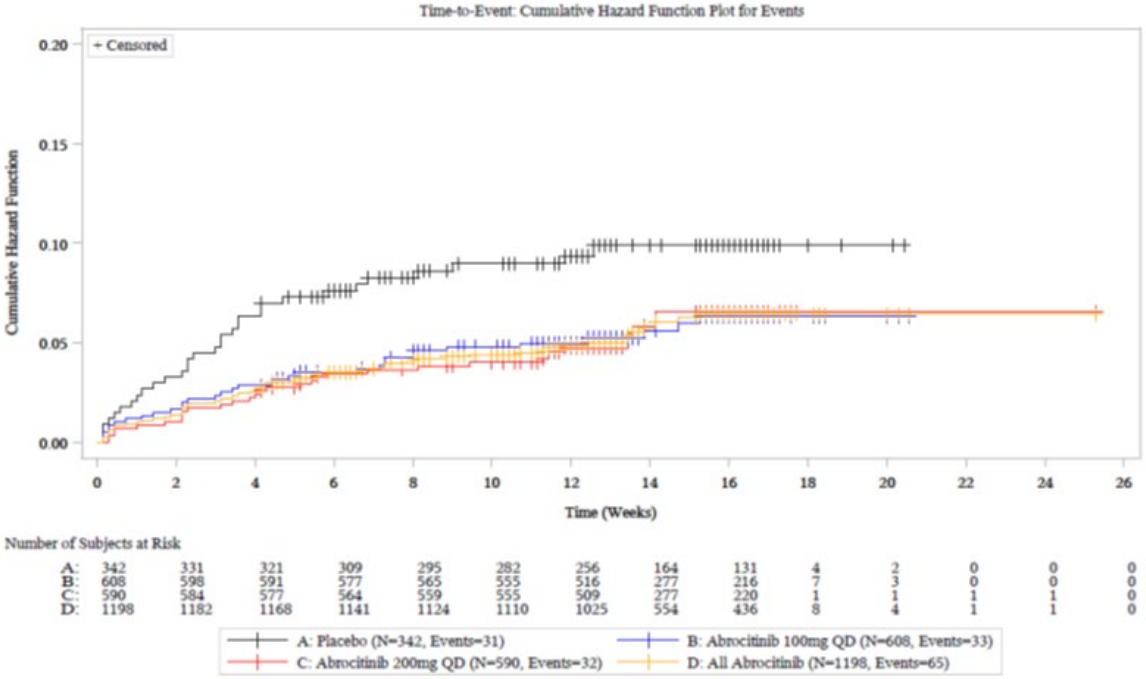
The proportion of subjects with temporary discontinuations was similar across treatment groups. The SOCs with the highest proportion of temporary discontinuations were Gastrointestinal disorders and Infections and infestations.

Table 65 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Incidence of Treatment-Emergent Adverse Events Resulting in Permanent Discontinuation from Study by System Organ Class and Preferred Term (All Causalities) – Primary Safety Pool

Number of Subjects Evaluable for AEs Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	Placebo (N=342) n (%)	Abrocitinib 100mg QD (N=608) n (%)	Abrocitinib 200mg QD (N=590) n (%)	All Abrocitinib (N=1198) n (%)
Subjects with events	31 (9.1)	33 (5.4)	32 (5.4)	65 (5.4)
Blood And Lymphatic System Disorders	1 (0.3)	1 (0.2)	1 (0.2)	2 (0.2)
Lymphadenopathy	1 (0.3)	0	0	0
Pancytopenia	0	1 (0.2)	0	1 (0.1)
Thrombocytopenia	0	0	1 (0.2)	1 (0.1)
Cardiac Disorders	0	0	1 (0.2)	1 (0.1)
Palpitations	0	0	1 (0.2)	1 (0.1)
Eye Disorders	1 (0.3)	0	0	0
Eyelid oedema	1 (0.3)	0	0	0
Lacrimation increased	1 (0.3)	0	0	0
Gastrointestinal Disorders	1 (0.3)	5 (0.8)	5 (0.8)	10 (0.8)
Abdominal pain	0	1 (0.2)	1 (0.2)	2 (0.2)
Abdominal pain upper	0	1 (0.2)	0	1 (0.1)
Cheilitis	1 (0.3)	0	0	0
Inflammatory bowel disease	0	0	1 (0.2)	1 (0.1)
Lip swelling	1 (0.3)	0	0	0
Nausea	0	2 (0.3)	2 (0.3)	4 (0.3)
Pancreatitis acute	0	1 (0.2)	0	1 (0.1)
Vomiting	0	0	1 (0.2)	1 (0.1)
General Disorders And Administration Site Conditions	0	2 (0.3)	3 (0.5)	5 (0.4)
Asthenia	0	1 (0.2)	0	1 (0.1)
Chills	0	0	1 (0.2)	1 (0.1)
Fatigue	0	0	2 (0.3)	2 (0.2)
Malaise	0	0	1 (0.2)	1 (0.1)
Sudden death	0	1 (0.2)	0	1 (0.1)
Immune System Disorders	0	1 (0.2)	0	1 (0.1)
Hypersensitivity	0	1 (0.2)	0	1 (0.1)
Infections And Infestations	4 (1.2)	4 (0.7)	7 (1.2)	11 (0.9)
Dermatitis infected	0	1 (0.2)	0	1 (0.1)
Eczema herpeticum	1 (0.3)	1 (0.2)	0	1 (0.1)
Eczema infected	1 (0.3)	0	0	0
Herpangina	0	1 (0.2)	0	1 (0.1)
Herpes simplex	1 (0.3)	0	1 (0.2)	1 (0.1)
Herpes zoster	0	0	1 (0.2)	1 (0.1)
Lower respiratory tract infection	0	0	1 (0.2)	1 (0.1)
Mastitis	0	0	1 (0.2)	1 (0.1)
Ophthalmic herpes simplex	0	0	1 (0.2)	1 (0.1)
Pneumonia	0	1 (0.2)	0	1 (0.1)
Pyelonephritis	0	0	1 (0.2)	1 (0.1)
Skin bacterial infection	1 (0.3)	0	0	0
Skin infection	0	0	1 (0.2)	1 (0.1)
Staphylococcal skin infection	1 (0.3)	0	0	0
Injury, Poisoning And Procedural Complications	0	1 (0.2)	0	1 (0.1)
Foot fracture	0	1 (0.2)	0	1 (0.1)
Investigations	1 (0.3)	3 (0.5)	3 (0.5)	6 (0.5)
Alanine aminotransferase increased	1 (0.3)	0	1 (0.2)	1 (0.1)
Aspartate aminotransferase increased	1 (0.3)	0	1 (0.2)	1 (0.1)

Bacterial test positive	0	1 (0.2)	0	1 (0.1)
Blood bilirubin increased	0	1 (0.2)	0	1 (0.1)
Electrocardiogram abnormal	0	1 (0.2)	0	1 (0.1)
Lymphocyte count decreased	0	0	1 (0.2)	1 (0.1)
Platelet count decreased	0	0	1 (0.2)	1 (0.1)
Musculoskeletal And Connective Tissue Disorders	0	1 (0.2)	0	1 (0.1)
Muscle spasms	0	1 (0.2)	0	1 (0.1)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	1 (0.3)	0	0	0
Neoplasm	1 (0.3)	0	0	0
Nervous System Disorders	0	2 (0.3)	3 (0.5)	5 (0.4)
Dizziness	0	1 (0.2)	1 (0.2)	2 (0.2)
Headache	0	1 (0.2)	2 (0.3)	3 (0.3)
Pregnancy, Puerperium And Perinatal Conditions	1 (0.3)	0	1 (0.2)	1 (0.1)
Pregnancy	1 (0.3)	0	1 (0.2)	1 (0.1)
Psychiatric Disorders	0	0	3 (0.5)	3 (0.3)
Depression	0	0	1 (0.2)	1 (0.1)
Depression suicidal	0	0	1 (0.2)	1 (0.1)
Schizophrenia	0	0	1 (0.2)	1 (0.1)
Reproductive System And Breast Disorders	0	0	1 (0.2)	1 (0.1)
Uterine haemorrhage	0	0	1 (0.2)	1 (0.1)
Respiratory, Thoracic And Mediastinal Disorders	0	1 (0.2)	1 (0.2)	2 (0.2)
Asthma	0	1 (0.2)	0	1 (0.1)
Pulmonary embolism	0	0	1 (0.2)	1 (0.1)
Skin And Subcutaneous Tissue Disorders	23 (6.7)	12 (2.0)	7 (1.2)	19 (1.6)
Dermatitis allergic	1 (0.3)	0	0	0
Dermatitis atopic	19 (5.6)	9 (1.5)	5 (0.8)	14 (1.2)
Eczema	1 (0.3)	1 (0.2)	2 (0.3)	3 (0.3)
Ingrowing nail	1 (0.3)	0	0	0
Perioral dermatitis	0	1 (0.2)	0	1 (0.1)
Urticaria	1 (0.3)	1 (0.2)	0	1 (0.1)
Vascular Disorders	0	1 (0.2)	0	1 (0.1)
Hypertension	0	1 (0.2)	0	1 (0.1)

Figure 30 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Time-to-Event: Cumulative Hazard Function Plot for Treatment-Emergent Adverse Events Resulting in Permanent Discontinuation from Study (All Causalities) – Primary Safety Pool

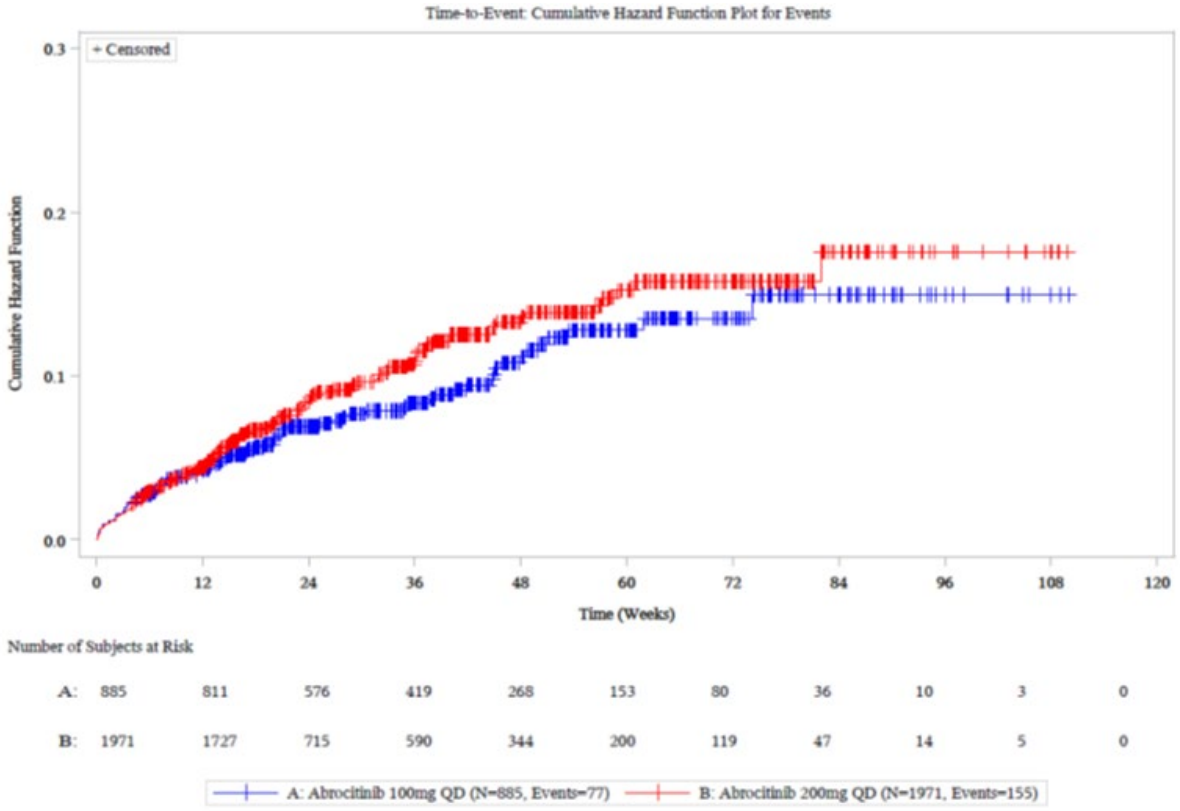


All Exposure Pool

In the All Exposure Pool, the proportion of subjects with AEs leading to discontinuation was similar across the abrocitinib treatment groups with no dose relationship observed. the discontinuations accumulated in a linear fashion over time with a slightly steeper curve in the 200 mg QD group. Discontinuations occurred more frequently in older subjects (≥65 years) compared to the other age subgroups. The proportion of subjects with temporary discontinuations was similar across treatment groups. The SOCs with the highest proportion of temporary discontinuations were Infections and infestations, Investigations, and Gastrointestinal disorders.

Figure 31 Abrocitinib Summary of Clinical Safety (Atopic Dermatitis)

Time-to-Event: Cumulative Hazard Function Plot for Treatment-Emergent Adverse Events Resulting in Permanent Discontinuation from Study (All Causalities) – All Exposure Pool



2.6.8.9. Post marketing experience

There is no post-marketing data for abrocitinib.

2.6.9. Discussion on clinical safety

Data from eight phase 2 and phase 3 studies in atopic dermatitis (AD) are included in the safety analysis of the initial submission. A total of 2856 subjects with AD were exposed to abrocitinib during the development programme. Among these subjects 885 were exposed to 100 mg QD and 1971 to 200 mg QD. Following a safety update as of April 2021 data-cut a total of 3128 subjects had been exposed to abrocitinib representing 3001.5 patient years. In addition, 46.4% of subjects (n = 1450) have at least 48 weeks of exposure.

Short-term safety

The evaluation of short-term safety of exposure to abrocitinib has been performed within the placebo-controlled studies during the first 12 weeks of therapy, the Primary Safety Pool.

The Primary Safety Pool has been used to compare the safety profile of individual abrocitinib doses of 100 mg QD and 200 mg QD with placebo and events with a dose-response relationship. The pool has been used to establish frequencies, seriousness, and severity of common AEs in the active treatment groups relative to placebo, including most commonly reported TEAEs and treatment related TEAEs, including TEAEs of special interest and laboratory data.

The Primary Safety Pool includes a total of 1540 subjects of the initial submission whereof 124 [8.1%] adolescents, with 608 exposed to abrocitinib 100 mg QD, 590 exposed to 200 mg QD, and 342 exposed to placebo. The median duration of exposure was 86.0 days. Among subjects in the Primary Pool, 945 (61.4%) were randomised to a monotherapy study (B7451006, B7451012, B7451013) and 595 (38.6%) were randomised in a study including background topical therapy (B7451029). The exposure in Black/African Americans is significantly lower compared to included subgroups of White and Asian Americans. It is understood that AD prevalence is at least similar or even higher in Black/African Americans compared to European Americans. The applicant was therefore requested by CHMP to discuss if labelling measures are justified for patients of the Black/African subgroup as data are limited. It has been clarified that according to the updated figures, the percentage of Black patients who experienced TEAEs and SAEs is not higher compared to patients of White Race. It is thus accepted that specific labelling measures related to the Black/African American sub-population is not warranted in the SmPC.

The percentage of included subjects experiencing TEAEs was for the placebo group 55.0%, for the abrocitinib 100 mg QD group 61.0%, and for the abrocitinib 200 mg QD group 68.3%. The proportion of subjects with TEAEs evaluated as treatment-related was similar between the abrocitinib 100 mg QD and placebo treatment groups and higher in the abrocitinib 200 mg QD treatment group. The SOCs with the highest proportion of events in abrocitinib treatment groups and greater frequency than placebo were Infections and infestations, Gastrointestinal disorders, Nervous system disorders, and Investigations. Although it is stated in the RMP that no unique risks were identified by race or ethnicity, it is noted that TEAEs when treated with abrocitinib 200 mg were more frequent in the Asian subgroup (80.1%) compared to Black/African subgroup (66.9%) and White subgroup (70.3%). Upon request from the CHMP, the applicant further elaborated on reasons for the incidences of AE, serious AEs, severe AEs and discontinuations due to AE being highest in Western Europe compared to all other geographic regions as well as the increased proportions in PT acne in Asian subjects and the high incidences of the SOC Infections and infestations as well as proportions of nausea in the race subgroup "Other". Cultural differences (e.g. health system and reporting habits), racial differences (increased incidences of acne in Asian subjects) as well as heterogeneity in subgroup definition (Others) are being presented as possible reasons for deviations in the mentioned subgroups. The applicant further discussed reasons for higher proportion of TEAEs in Asian subjects compared to subjects from other races, also considering the increased exposure (30% increased AUCinf after 200mg QD) in this subgroup. The applicant clarified that the increased proportion in Asian subjects was mainly driven by higher incidences in acne and nausea for this subgroup. While the issue is of less relevance for an EU population, the applicant was encouraged to follow up on this topic.

The requested analysis for safety events in the two main studies (B74510412 and B74510413) based on season during enrolment did not reveal striking differences related to season of enrolment/treatment. A higher exposure was suspected for patients with renal impairment and in patients with CYP inhibiting co-mediation as concluded from in silico data. Upon further elaboration, no safety concerns arise for these subjects being exposed to the reduced dose of 50mg abrocitinib. Upon request from the CHMP, the applicant listed incidences separately for long-term exposure (excluding data on short-term exposure) and provided the analysed incidence rates by 12-week periods for all AEs, SAEs and AESIs. No concerns arise from data review.

Common AEs

The most frequent events overall (≥2% in any treatment group) that occurred more commonly in the abrocitinib groups than placebo and in a dose-related fashion were nausea with frequencies 2%, 6.1% and 14.6% in the placebo group, abrocitinib 100 mg QD and abrocitinib 200 mg QD respectively and headache with frequencies 3.5%, 5.9% and 7.8% in the placebo group , abrocitinib 100 mg QD and abrocitinib 200 mg QD respectively, both TEAEs mainly occurring during the first two weeks of therapy.

The proportion of subjects having events in the Gastrointestinal disorders SOC was higher in female subjects, driven largely by nausea and vomiting which were reported in females in 18.1% and 4.2%, respectively, relative to male subjects (7.6% and 2.3%, respectively).

All reported proportions above relate to the initial submission of the primary safety pool (data cut-off date 22 April 2020). Upon request from the CHMP, the applicant provided an update on in total 3 safety data pools, the Full Cumulative Pool (adolescent and adult subjects from studies B7451006, B7451012, B7451013, B7451014 (open-label period only), B7451029 and B7451036), the Adolescent Short-Term Pool (adolescent patients from studies B7451006, B7451012, B7451013 and B7451036) and the Primary Safety Pool + B7451036 (adult and adolescent subjects from studies B7451006, B7451012, B7451013, B7451029 and B7451036). The provided safety update comprises data until data cut-toff date of 24 July 2020 and the updated Primary Safety Pool + B7451036 is the current source of reported data in the SmPC. However, further safety updates are pending and reported proportions refer to data from the initial submission. the applicant committed to provide a further update of safety data, with data cut in the second half of 2021, as part of a Type II variation in the first half of 2022, including an updated SmPC (section 4.8).

Nausea occurred only in subjects while they were in a fasted period. This has been considered in the implementation of a recommendation in SmPC section 4.2 that patients who experience nausea are to take abrocitinib with food. Further, nausea is listed as a very common ADRs in SmPC section 4.8. Vomiting, herpes simplex, blood creatine phosphokinase increase, and dizziness, also occurring in a dose-related fashion are labelled with frequency common. Upon request from the CHMP, the applicant clarified that acne is a concern for the treatment with JAK inhibitors under development for AD and that it is considered an adverse drug reaction. The reported DLQI (dermatology life quality index) change from baseline did not indicate a critical change in reported life quality from onset to resolution of acne in those patients that had treatment emergent acne. However, due to the high rate of observations and a clear dose related effect, patients and investigators should be informed about this effect of abrocitinib. Accordingly, treatment emergent acne is reported as a common adverse reaction in the proposed SmPC. Upper abdominal pain did also appear to have a dose response and also occurred more commonly in the abrocitinib groups compared to placebo though at a frequency <2%. Accordingly, treatment emergent upper abdominal pain is reported as a common ADR in SmPC section 4.8.

Laboratory

Haematologic abnormalities (based on the submission of the primary safety pool with data cut-off date 22 April 2020): Confirmed ALC < 0.5 × 103/mm^3 and platelet count < 50 × 103/mm^3 were observed in less than 0.5% of patients in clinical studies. A higher percentage of subjects in the abrocitinib 100 mg (18.5%) and abrocitinib 200 mg (20.8%) QD groups had an ALC <1×103/mm^3 compared with the placebo group (11.9%) and there were 4 subjects meeting discontinuation criteria for lymphopenia (confirmed <0.5×103/mm^3). These subjects were all older than 65 years of age. A dose-related decrease in platelet count with maximum effects observed within 4 weeks were seen. There were 9 subjects (0.3%) with a confirmed platelet values of <75×103/mm^3 (0.1% with confirmed platelet counts of < 50 × 10^3/mm^3), all values between week 2 and week 4 of exposure. Although no clear population changes in neutrophils were observed in the treatment groups of abrocitinib and no patient had a confirmed neutrophil count less than ANC 1.0×103/mm^3 there was a dose-response effect in the number of subjects with ANC below 2 x10 3/mm3. In addition, pancytopenia was one of the AEs leading to discontinuation that occurred in more than 2 subjects. A dose dependent increase in blood lipid parameters, both increases in LDL-c and HDL relative to placebo, were reported in patients treated with abrocitinib. The LDL/HDL ratio decreased initially over the first 3 months and then increased by 5-10%. There was a dose-related increase in subjects reporting AEs of blood creatine phosphokinase increased in the Primary Pool. There was a dose-related increase in CK beginning at

week 4 and having at plateau at week 8. The median change at the last observation was increased in the abrocitinib 100 mg QD and 200 mg QD groups (53 U/L and 88 U/L, respectively) relative to the placebo group (-2 U/L). There was a dose-related increase in subjects reporting AEs of blood creatine phosphokinase increased in the Primary Pool. Two cases of myositis exposed to abrocitinib was reported. Additional information was provided concerning thresholds for retest, monitoring as well as discontinuation criteria in haematology measures upon request from the CHMP. A statement in the SmPC on decreased NK-cell counts and increased B-cell counts was added. High general ALC counts were confirmed by the applicant to be temporary. It was clarified that suspected low ANC counts in patients ≥65 years and patients of Black/African American race compared to other respective subgroups only affected the ANC threshold of < $2x10^3/mm^3$. It is agreed that the clinical relevance of this threshold is not clear. No subject met the defined discontinuation threshold at ANC <1 × $10^3/mm^3$ and a respective statement regarding treatment discontinuation if ANC is <1 × $10^3/mm^3$ for all patients is included in the SmPC. A relative risk of hyperlipidaemia is associated with the treatment of abrocitinib (due to JAK inhibitor class effects) and the updated SmPC is appropriate to inform about the risk of increased blood-lipid parameters and potential cardiovascular complications that might be associated with those. The applicant included a statement in the SmPC that in patients with a higher burden of cardiovascular risk factors the benefit:risk ratio of abrocitinib compared to that of other available therapies for AD should be considered. The SmPC addresses the risks of haematologic abnormalities and lipid changes in section 4.4 and thrombocytopenia, lymphopenia and hyperlipidaemia are included in SmPC section 4.8 with frequency uncommon.

A clear dose-related increase in events reported for the SOC musculoskeletal and connective tissue disorders was observed within the group of patients with increased CK (55.6%, 35.2 and 9.3% for 200mg, 100mg and placebo treatment, respectively), whereas no meaningful difference in the proportion of subjects with events was observed for the general population (regardless of CK values) in the primary safety pool. The elevation of CK >5x ULN is reported as a common event for abrocitinib treatment in the SmPC (also, 16.4% of subjects treated with 200mg had a creatine kinase measure >2xULN, which would fall under very common incidences). However, a temporal relation to muscle injuries is observed only sparsely and no clear causality between elevated CK levels and muscle injuries can be concluded from data presented upon request. The uncertainty regarding the SOC musculoskeletal and connective tissue disorders is also not further substantiated by the presented data on Muscle disorders HLGT. Therefore, the potential of myopathies caused via JAK inhibition by abrocitinib will be monitored in the post approval setting (See RMP).

When analysing the All Exposure Pool, subjects with detected CK increase during the first 16 weeks experienced remaining CK increase throughout the study period and 5.4% of abrocitinib-treated subjects with CK >5xULN. There was no report of rhabdomyolysis in the clinical studies.

Other AEs

Other reported AEs were Herpes zoster as a common AE (see further discussion on this issue under the long-term safety); and thrombocytopenia, lymphopenia, hyperlipidaemia and venous thromboembolism, occurring with a frequency uncommon and initially labelled as such in section 4.8 of the SmPC.

SAEs

The incidence of SAEs was low and were reported in similar proportions of subjects across the abrocitinib (100 mg QD was 3.1%; and 200 mg QD was 1.9%) and placebo (3.2%) groups in the Primary Pool. They accumulated in a linear fashion over time. However, SAEs of pneumonia (3 subjects, 0.3%), asthma (3 subjects, 0.3%), and AD (2 subjects, 0.2%) occurred in more than 1 abrocitinib treated subject; all other SAEs occurred in 1 subject.

Long-term safety

The long-term safety was evaluated in the All Exposure Pool. This pool included 2856 subjects (12.7% adolescents) representing 1614 patient years. Among these subjects 885 were exposed to 100 mg QD and 1971 to 200 mg QD i.e. the abrocitinib 200 mg QD group contributed more patient-years of exposure relative to the 100 mg QD group (992.9 and 620.8 PY, respectively). There were 1248 subjects exposed for more than 24 weeks, 995 exposed for more than 36 weeks, and 606 exposed for more than 48 weeks (670 subjects with a 12-month visit). Data from this pool have been used to determine IRs over time for AEs of special interest, including laboratory parameter and assess dose-related differences. As discussed by the applicant a limitation of this pool is a lack of comparator, therefore external data sources have been used for risk contextualisation.

AEs

The proportion of subjects reporting TEAEs in the All Exposure pool were 70.8 % and 72.0 % in the abrocitinib 100 mg QD and abrocitinib 200 mg QD respectively. The proportion of subjects with TEAEs judged as treatment-related was higher in the abrocitinib 200 mg QD treatment group. Among all causality AEs, 38.6% were considered treatment-related by the Investigator. The SOCs with the highest proportion of events in abrocitinib treatment groups were Infections and infestations, Gastrointestinal disorders, Skin and subcutaneous tissue disorders, Nervous system disorders, and Investigations. The most frequent AEs by PT were similar to those in the Primary Pool.

The most frequent AEs leading to permanent discontinuation in abrocitinib treated subjects were dermatitis atopic (1.9%), nausea (0.5%), and headache (0.4%).

Herpes simplex was reported in 2.6% and 2.7% of the abrocitinib 100 mg QD and abrocitinib 200 mg QD respectively and Herpes zoster in 1.4% and 2.0% of the abrocitinib 100 mg QD and abrocitinib 200 mg QD respectively. Of the subjects who had an event of herpes simplex, approximately 50% of subjects had an initial event of herpes simplex in the first 3 months of therapy (48.2% in abrocitinib 100 mg QD group and 57.8% in abrocitinib 200 mg QD group. In the proposed SmPC, herpes simplex is labelled with frequency common and herpes zoster with frequency uncommon. The applicant was requested to clarify if the cases reported as opportunistic infections have been included in the calculation of frequency of herpes zoster. Upon request from the CHMP, the applicant clarified that the cases of opportunistic herpes zoster infection have been included with the frequency for herpes zoster. Furthermore, the applicant agreed to use the frequencies for the abrocitinib 200 mg dose for the tabular list of adverse reactions. As such, herpes zoster is now included as common with a frequency of 1.2% in SmPC section 4.8.

SAEs

Three fatal cases were reported, all in abrocitinib-treated subjects. One case of sudden CV death occurred 22 days after cessation of study drug, one case was associated with a COVID-19 infection, both events assessed as not related to study drug per the investigator. The third fatal case was diagnosed with a gastric Adenocarcinoma on Study Day 43. The time-event relationship is not in favour of a suspected causality association with abrocitinib. Following the safety update as of April 2021 two additional fatal events (Covid-19 and septic shock) were recorded. The fatal event of Covid-19 infection was considered unrelated to study drug (100mg). The event of septic shock was considered related to study drug by the investigator. Serious infections are an important potential risk and routine as well as additional risk minimisation measures (Prescriber Brochure and Patient Card) are proposed. See RMP section.

AEs seem to accumulate in a linear fashion over time and there was no dose response for SAEs. In the All Exposure Pool treatment-emergent SAEs were reported in 5.3 % and 3.6 % of the abrocitinib 100 mg QD and abrocitinib 200 mg QD, respectively. The Infections and Infestations SOC had the highest

incidence of SAEs. The most frequent adverse events were AD, asthma, pneumonia, eczema herpeticum, and intervertebral disc protrusion. There were 6 subjects with an SAE of asthma and 1 with an SAE of status asthmaticus. Among these, 5 subjects had a history of asthma and 1 subject had a history of bronchospasm. Of note though is that in the Primary Pool, overall events of asthma were not more frequent in the abrocitinib 100 and 200 mg QD groups (1.0 and 0.3%, respectively) compared to the placebo group (0.9%). Asthma was a common comorbidity in the population, being reported as ongoing in more than 30% of subjects. Of note, the assessment of asthma control via the Asthma Control Questionnaire (ACQ) in the scope of study B7451014 does not suggest worsening of asthma control for subjects treated with 200mg abrocitinib within the first 12-weeks of study treatment and the safety update of the full cumulative pool does not suggest a general increase in severe asthma with increasing dose of abrocitinib.

Upon request from the CHMP, case histories of five asthma events have been presented by the applicant Furthermore, a discussion of the cause relationship of asthma and abrocitinib exposure was requested in the subject experiencing status asthmaticus. The requested case history of the patient with status asthmaticus as well as a summary of case histories of the other five patients experiencing asthma plus two additional cases from the safety update have been presented. All patients had a history of asthma. In three of the eight cases, study drug was withdrawn while for the other five patients the asthma symptoms resolved, and they continued study drug. The adolescent male experiencing status asthmaticus had apparently been non-compliant with his asthma medication and the event was considered due to that.

Adverse events of special interest (AESI)

The reports on AESI by subgroup were limited to IRs for serious infections or all herpes zoster for some of the chosen factors. The applicant provided proportions and incidence rates for treatment-emergent SAEs, AEs resulting in permanent discontinuation, deaths, and AEs for infections, malignancies and cardiovascular events for the requested subgroups baseline age, gender and baseline disease severity, all for the Full Cumulative Pool and including data from the abrocitinib AD 2020 Safety Update. Upon request from the CHMP, a section on elderly patients is included in SmPC section 4.4 (with cross-reference to section 4.8) and an additional comment was added on the observation that elderly were more likely to have serious adverse events compared to younger patients. As a consequence of the potentially increased risk for elderly patients, the applicant proposed a starting dose of 100mg once daily for elderly patients aged ≥ 65 years. This has been adequately reflected in the SmPC.

Venous thromboembolism: There were 5 events reported; 3 events of PE and 2 events of DVT all in the 200 mg QD group. Although there were few events, the IR was higher than the background rates in patients with AD in cohort studies. In the initially proposed SmPC VTE is labelled as uncommon. Upon request from the CHMP, the applicant agreed to explicitly mention PE as an ADR (e.g. 'venous thromboembolism/pulmonary embolism') in SmPC section 4.8.

Serious infections: The most frequently reported serious infections were pneumonia, herpes zoster, and herpes simplex. A Higher incidence of herpes zoster including ophthalmic herpes zoster (4 cases), with abrocitinib compared to placebo as well as a dose response across the abrocitinib groups was shown. Upon request from the CHMP, the applicant agreed to include pneumonia in SmPC section 4.8 with a frequency uncommon. Furthermore, in view of the important potential risk of serious infections, active serious systemic infections including TB was added as contraindication in section 4.3 of the SmPC.

Malignancies: There were 7 cases of non-melanoma skin cancer [0.42/100 PY (95% CI: 0.17, 0.86)], 3 subjects in the abrocitinib 100 mg QD group and 4 subjects in the abrocitinib 200 mg QD group and 4 events of potential malignancy (2 events of prostate cancer and 2 events of ovarian neoplasm) in the

clinical database at the time of release. Comparisons were made with data from KPNC (Kaiser Permanente) and THIN databases. Overall, the IRs for malignancies (excluding NMSC) and NMSC in the KPNC and THIN databases were comparable to those seen in the AD clinical programme. However, although no direct evidence for a serious risk for malignancies was found yet, due to the potential lack of sensitive monitoring an increased risk cannot be excluded at this time of assessment. Upon request from the CHMP, the applicant provided an update from available long-term data with a contextualisation based on the Danish Registry and the THIN registry as well as pending adjudication data. Reported incidence rates do not suggest a causal relationship between the treatment with abrocitinib and the occurrence of malignancies, at least for the time period that was investigated. Although no direct evidence for a serious risk for malignancies was identified to date, the potential association between AD and malignancies as well as JAK inhibitor treatment and malignancies justifies the inclusion of malignancies as an important potential risk in the list of safety concerns of the RMP. A warning in this regard is also included in SmPC section 4.4.

Other AEs of interest

Hypersensitivity: There were together seven cases of either swelling of eyes, swelling of eyelids, oedema of eyelids and oedema of eye reported for the abrocitinib treated subjects in the primary safety pool and only one case of eyelid swelling in the placebo group. In the All safety pool there are in total 13 cases of eye reactions, this included the previous terms as well as conjunctival oedema and eye allergy. Upon request from the CHMP, the applicant commented that ocular comorbidities and symptoms are common in patients with AD, including conjunctivitis and keratitis and that there was an inverse dose response and events were less frequent in patients with well controlled disease (IGA 0 or 1). Therefore, the data suggest that there is no meaningful risk of increased ocular symptoms associated with abrocitinib therapy and thus no need to reflect those into SmPC section 4.8.

ECG measurement in the clinical studies: In the All Exposure Pool, all subjects with measured increase of QTcF were in the abrocitinib 200 mg QD (group1 subject in the abrocitinib 200 mg QD group had a QTcF of >500 msec, and 5 subjects in the abrocitinib 200 mg QD group had a change from screening >60 msec QTcF. As all changes are described in the 200 mg QD a dose dependent effect cannot be excluded, thus the applicant was requested to discuss the relevance of cautionary measures in the SmPC. The applicant acknowledged that analysis of outliers according to categorical responses (QTcF > 500 msec, delta QTcF > 60 msec) may provide insights into the potential of a drug to prolong the QT interval in a susceptible individual and hence to precipitate Torsades de Pointes. However, that these findings should be balanced with the performed *in vitro* studies of ion channels demonstrating no clinically meaningful inhibition of hERG channels indicating potential proarrhythmic effects and a performed controlled TQT study (B7451027) in healthy adult volunteers in which the mean effect on QTcF at peak plasma concentration was 7.12 msec indicating an unlikely potential of torsadogenic effect. Considering the outcome of the TQT study and additional justifications provided by the applicant, the conclusion not to introduce additional information in the SmPC concerning QT changes is acceptable.

Liver: There were 2 SAEs of drug-induced liver injury and 7 other liver AEs adjudicated as a possible DILI (probability 25-50%). No cases were adjudicated as a probable, highly likely, or definite DILI case. No subject met Hy's law criteria. Further, use in patients with severe (Child Pugh C) hepatic impairment is added as a contraindication in SmPC section 4.3 due to the lack of information regarding influence of severe hepatic impairment as these subjects were not included in the PK study of abrocitinib. This is agreed.

Renal: There was one case of acute renal injury reported. Based on the recommendations in SmPC section 4.2 with regards to dosing reductions in patients with renal insufficiency, the applicant was requested to clarify how many of the total number of 42 study subjects (26.4 PY) in the eGFR <60

mL/min subgroup, that received 50mg QD and 100 mg QD abrocitinib respectively. Furthermore, how many of these subjects that experienced adverse events in each dosing group. The applicant has clarified that in the development programme AD patients were randomised to receive 200 or 100 mg QD doses regardless of their renal function. It appears from presented data that subjects with serious adverse events are overrepresented in the baseline eGFR <60 mL/min group with 18.2%, 9.7% and 11.9% for exposure to abrocitinib 100 mg, 200mg and all abrocitinib, respectively compared to the 60-<90 mL/min group with 5.6% 2.5 and 3.4% for exposure to abrocitinib 100 mg, 200mg and all abrocitinib, respectively and the >90 mL/min group with 5.2%, 4.1% and 4.4% for exposure to abrocitinib 100 mg, 200mg and all abrocitinib, respectively. These findings would thus be in support of a dose reduction of abrocitinib in patients with eGFR < 60 mL/min. The proposed dose reductions reflected in SmPC section 4.2 are agreed.

Apart from the common AE abdominal pain upper, there were 3 subjects (0.1%) reporting GI perforation (all upper GI events) in the All Exposure pool, 2 subjects (0.2%) in the abrocitinib 100 mg QD and 1 subject (0.1%) in the 200 mg QD group. The applicant was requested by CHMP to further discuss the need for inclusion of this safety issue in the SmPC. Based on the review of events of upper abdominal pain, nausea, and vomiting in the All safety pool from the perspective of individual co-occurrence, timing, resolution incl. time to resolution, and cause of study discontinuation; the applicant considered a warning and precaution in the SmPC related to gastrointestinal perforation associated with abdominal pain/vomiting was not warranted. As GI perforation is added to the RMP as an important potential risk it will be closely monitored following post approval, bringing further information of this potential risk and the need of an SmPC update.

Weight increase has been reported for other JAK inhibitors. The number of individuals is limited at Months 24 and 27 but at Months 21 there seems to be an increase of the All abrocitinib group (median 86, mean 91.7) compared to baseline weight (median 73, mean 75.2.) Weight increase was requested to be further discussed for inclusion in the SmPC. The applicant clarified that there is a small increase in BMI but as there is no consistent dose response the proposal is not to include weight increase in section 4.8 of the SmPC. This is agreed.

Subgroups

Adolescents

The indication initially proposed for abrocitinib included adolescents 12-<18 years of age as well as adults.

In non-clinical studies, abrocitinib induced effects on bone development and the effect of abrocitinib on bone metabolism in humans is not clear. Permanent impact on skeletal development cannot be excluded. Abrocitinib exposure on bone development was evaluated clinically by HT SDS and fracture rate in adolescents ≥12 years of age. A safety update with data-cut April 2021 was submitted as part of the responses to D180 LoOI. The Full Cumulative Pool included 635 adolescents with 646.2 PY. In the April 2021 data there were 296 adolescent subjects with height data to Day 360. The rate of fracture in adolescent subjects in the 100 mg group was 0.78 per 100 PY (2 events; 95% CI: 0.09, 2.80)] and in the 200 mg was 1.50 per 100 PY (6 events; 95% CI: 0.55, 3.26). Those data may suggest a potential of a dose related effect on fractures. Furthermore, uncertainties still remained whether the applied clinical measures are sensitive enough to satisfactorily provide reassuring data for safe use in adolescents ≥12 years of age and the reported data on height SDS as well as for fractures was premature for final evaluation. 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 has been restricted to adults > 18 years of age only.

Further studies to investigate bone safety in adolescents have been proposed by the applicant. The same clinical measures/endpoints will be collected in the proposed post-authorisation safety B7451084 study (please refer to the RMP). The applicant also proposed to initiate a sub-study within the frame of the ongoing long-term extension study B7451015, in order to further investigate potential clinical implications on bone development for adolescent subjects ≥12 years of age that are exposed to abrocitinib. The proposed study concept aims for annual MRI images of the knee and is principally supported. These studies are planned to be performed post-approval.

Adults and elderly might suffer from consequences on bone physiology that would impact the benefit-risk evaluation and the applicant was thus asked to elaborate on bone effects for these age groups as well. Upon assessment of data provided by the applicant, no matter of concern arises from presented data on osteoporosis or fractures reported for adult (18 -<65 years) or elderly (≥65 years) that were treated with abrocitinib. It is recognised that the assessment of reported AEs might not be sensitive enough to detect unreported effects in bone physiology and study duration might not be sufficiently long for potential bone effects to be experienced as an AE. Further, non-clinical data on bone findings are described in the updated SmPC in section 5.3. Potential effects on bone physiology cannot be excluded, however, based on available data this risk appears specifically high for developing bones.

Although there was generally no significant difference in the safety profile of abrocitinib of adolescents as presented in the clinical data, there were some issues related to this subgroup that needed clarification. There was a higher percentage of TEAEs compared to the total population in the analysis of the Primary Safety Pool and compared to the age group 18-<65 years of age of the All Exposure group. Based on this and the assumption of dose dependent TEAES, the applicant was asked to discuss safety in relation to abrocitinib exposure in adolescents. Concerns based on slightly different exposure values calculated based on the initial adolescent dataset were further mitigated as updated results based on larger adolescent datasets indicate that there is no clinically relevant difference in exposure between the two age cohorts, also considering worst case scenario (light-weight adolescents). Furthermore, in the analyses of the updated safety pool TEAEs and SAEs do not seem to be overrepresented in adolescents compared to adults.

According to the table of Treatment-Emergent Adverse Events by System Organ Class (All Causalities) by Baseline Age Primary Safety Pool- there was a clear discrepancy and increase of the percentage of reported TEAEs within the SOC "Respiratory, Thoracic And Mediastinal Disorders" of abrocitinib treated subjects < 18 years of age compared to the total population. Upon request from the CHMP, the applicant clarified that pooled data of study B7451036 and the Primary Safety Pool in the safety update no longer demonstrate a discrepancy of percentage of reported TEAEs within the SOC "Respiratory, Thoracic And Mediastinal Disorders" of abrocitinib treated subjects < 18 years of age compared to placebo.

Elderly

Most subjects with malignancy events were >60 years of age. The rate of herpes zoster infections was higher in patients 65 years of age and older. Most subjects meeting discontinuation criteria for haematology labs were also ≥65 years of age, apparently absolute lymphocyte counts <0.5 × 103/mm^3 occurred only in patients ≥65 years of age and a higher proportion of patients ≥65 years of age had platelets <75 × 103/mm^3. Furthermore, the percentage of subjects with SAEs exposed to combined strengths of 100mg QD abrocitinib and 200 mg QD abrocitinib were 3.8%, 10.3% and 16 % for individuals 18-≥65 years of age, >65 years of age and >75 years of age respectively. Based on these safety findings, the exposure and dosing recommendations of abrocitinib in this subgroup were requested to be further justified by the applicant. As part of its responses, the applicant revised dosing in elderly to recommend a starting dose of abrocitinib 100 mg for patients aged ≥65 years. The proposed SmPC includes information about specific findings in elderly in SmPC section 4.8 incl. that

data is limited in elderly>75 years of age. Upon request from the CHMP, the applicant submitted a summary table of the abrocitinib 2020 Safety Update Full Cumulative Pool of the 100 mg and 200 mg treatment groups for the applied age subgroups <65, 65 - <75, 75 - <85, ≥ 85 years.

An increase in proportions of the SOC musculoskeletal and connective tissue disorders was observed with increasing age (2.2% in adolescent, 5.2% in adult and 12.4% in elderly across both doses). Contextualisation of reported incidences of musculoskeletal disorders with epidemiological references does not raise further concern for the treatment with abrocitinib in this aspect. A comment on increased serious and severe AEs as well as a higher rate of discontinuations due to AEs in elderly patients is included in section 4.4 of the SmPC.

There were no significant differences between the safety profile of abrocitinib as monotherapy or in combination with topical medicated therapy in terms of frequent events, serious and severe events, or AEs leading to discontinuation for subjects enrolled in the combination therapy study (B7451029).

Pregnancy

Ten cases of exposure in utero reported in subjects exposed to abrocitinib in the AD clinical programme, 7 maternal exposures and 3 partner exposures. Of the 7 maternal exposers there were two miscarriages and five with outcome unknown. Further data on these outcomes were requested. For other JAK inhibitors the use is contraindicated during pregnancy and based on the non-clinical data and assessment this would have been expected for abrocitinib as well. Upon request the applicant has implemented this as a contraindication in section 4.3 of the SmPC.

Overall, the demonstrated safety profile of abrocitinib showed similarities with other JAK inhibitors and is consistent with the mechanism of action. The exposure of patients to abrocitinib is considered sufficiently sized and the detected relevant adverse events at large adequately addressed in the SmPC.

2.6.10. Conclusions on the clinical safety

Abrocitinib is a Janus kinase (JAK) 1 inhibitor. The present safety profile of data derived from the performed phase 2 and phase 3 studies demonstrates similarities with other JAK inhibitors. These include common reactions such as nausea, headache, acne, vomiting, herpes simplex, blood creatine phosphokinase increase, and dizziness, haematological effects with a decrease in lymphocytes and platelets and cases of serious infections as well as opportunistic infections and venous thromboembolism reported. Overall, the exposure of patients to abrocitinib is considered sufficiently sized and the detected relevant adverse events are adequately addressed in the SmPC.

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 has been restricted to adults > 18 years of age only.

Abrocitinib is contraindicated in active tuberculosis (TB) or active serious infections, severe hepatic impairment, pregnancy and breast feeding.

2.7. Risk Management Plan

2.7.1. Safety concerns

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

2.7.2. 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 AD patients receiving abrocitinib and AD patients receiving appropriate systemic treatments including dupilumab for AD in a real-world setting.	The following are the endpoints of interest: • Thrombotic events including pulmonary embolism, • Herpes zoster, • Serious and opportunistic infection, • Rhabdomyolysis, • Gastrointestinal perforation, • Malignancy, and • MACE.	Draft protocol submission Interim report Final report	Within 6 months of abrocitinib approval in the EU (July 2022) December 2026 December 2034
B7451085: A Drug Utilisation Study to Evaluate the Effectiveness of RMMs for Abrocitinib in the EU using Electronic Healthcare Data Planned	The study objectives will be to evaluate indicators of HCP's adherence to the risk minimisation measures in accordance with the abrocitinib SmPC and prescriber brochure, specifically: • Indicators of adherence to performing laboratory tests of CBC, lipid panel, hepatitis B/C and TB screening prior to prescribing abrocitinib, • Indicators of adherence to performing laboratory tests of CBC and lipid panel at Week 4 (± 1 week) from initiation of abrocitinib treatment, • Indicators of adherence to consideration of risk factors for thrombotic events including pulmonary	Safety concerns addressed include: • Thrombotic events including pulmonary embolism • Serious and opportunistic infections, • MACE (lipid assessment,) • Impaired bone growth and development if used off-label in paediatric patients <18 years, and • Embryofoetal toxicity following exposure in utero.	Draft protocol submission Final report	Within 6 months of abrocitinib approval in the EU (July 2022) December 2028

	embolism 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 use in patients 18 years-of-age and older.			
B7451015: Long-term extension study Ongoing	To assess the long-term safety of 100 mg and 200 mg once daily of abrocitinib with or without topical treatments in adult and adolescent subjects who previously participated in qualifying abrocitinib AD trials.	This study will continue to describe safety data to include: • Thrombotic events including pulmonary embolism, • Serious and opportunistic infections, • Herpes zoster, • Malignancy, • Fracture in adolescents, • Myopathy (including rhabdomyolysis), • Gastrointestinal perforation, • MACE, • Height in adolescents, • Development in adolescents, and • Pregnancy outcomes.	Study Report	December 2025

B7451015: Adolescent Imaging Substudy Planned	To evaluate if abrocitinib has any clinically meaningful effects on bone growth and development	Primary endpoint • To detect the proportion of abnormal bone findings in knee MRI in adolescent subjects exposed to abrocitinib 100 mg and 200 mg Safety concerns addressed include: • Impaired bone growth and development if used off-label in paediatric patients <18 years	Draft protocol submission Interim Report Final Report	Within 6 months of abrocitinib approval in the EU (July 2022) December 2023 December 2025

2.7.3. Risk minimisation measures

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

	SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: Prescriber Brochure Patient card	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study
Important Potential Risks		
Serious and opportunistic infection	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: Prescriber Brochure Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study
Malignancy	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use PL Section 2 Additional risk minimisation measures: Prescriber Brochure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study
MACE	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use (lipid monitoring, including in the setting of a high burden of cardiovascular risk) SmPC Section 4.8 Undesirable effects (hyperlipidaemia only) PL Sections: Section 2 and 4 Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data

	Prescriber Brochure (lipid monitoring) Patient Card (lipid monitoring)	B7451015: Long-term Extension Study
Myopathies (including rhabdomyolysis)	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.8 Undesirable effects (Blood creatine phosphokinase increase) Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study
Gastrointestinal perforation	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study
Embryofoetal toxicity following exposure in utero	Routine risk minimisation measures: SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, Pregnancy and Lactation Additional risk minimisation measures: Prescriber Brochure Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study
Impaired bone growth and development if used off-label in paediatric patients <18 years-of-age	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration PL Section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study B7451015: Adolescent Imaging Substudy

Missing Information		
Long-term safety	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 08 September 2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Cibinqo (abrocitinib) is included in the additional monitoring list as it contains a new active substance.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The initially claimed indication was treatment of moderate-to-severe atopic dermatitis (AD) in adults and adolescents 12 years and older who are candidates for systemic therapy.

Atopic dermatitis 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 with the more severe forms of AD that respond inadequately to standard treatment, most often emollients and topical corticosteroids of different potency.

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 is not suitable for long-term use due to toxicities. Dupilumab (Dupixent) is approved within the EU for the treatment of moderate-to-severe AD from the age of 12 years old, and in children ≥6 years old in severe AD. Barititinib (Olumiant) and tralokinumab (Adtralza) have recently been approved for treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy. In addition, the JAK inhibitor upadacitinib (Rinvoq) is now approved for moderate to severe AD in adolescents and adults.

The applicant claims the proposed product to have a fast relief of itch, one of the most troublesome symptoms in AD.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is two Phase 3, randomised, double-blind, placebo-controlled, parallel-group studies with identical design; study **B7451012** (n=387) and study **B7451013** (n=391) the so-called monotherapy studies. Furthermore, a Phase 3, multi-centre active control study on background topical therapy study **B7451029** (n=838) has been performed (combination therapy study).

All three studies were performed in the US/Canada/EU/Asia/South America. The subjects included should have a clinical diagnosis of chronic AD with inadequate response to treatment with topical medication. The AD should be of moderate to severe degree (affected BSA ≥10%, IGA≥3, EASI≥16, and Pruritus NRS≥4 at the baseline visit).

The monotherapy studies B7451012 and B7451013 included adolescents (≥12 years of age), while study B7451029 was performed in adults only. The inclusion criteria of the performed clinical studies are considered adequate to reflect the proposed therapeutic indication. The exclusion criteria reflected general warnings for use of JAK inhibitors, e.g. with respect to infection, haematological abnormalities, viral reactivation and the risks for venous thromboembolism.

Eligible subjects were treated with abrocitinib 100 mg QD or 200 mg QD or placebo for 12 weeks in studies B7451012 and B7451013, and for 20 weeks in study B7451029. In study B7451029, dupilumab (Dupixent) was used as active comparator. Blinded dupilumab, 300 mg/ml, and its matching placebo were dosed according to label of the product. Duplimab was when the clinical programme of abrocitinib was designed and implemented, the only marketed product indicated for moderate to severe AD. The choice of comparator is therefore considered appropriate and of relevance in view of the EU approved treatment options. Recently, another JAK-inhibitor baricitinib (Olumiant) has received positive opinion for a new indication, treatment of moderate to severe AD in adults.

The co-primary efficacy endpoints, and key secondary efficacy endpoints used in the pivotal Phase 3 studies in the clinical development programme, are well established endpoints used for drug development in AD.

The following three supportive studies are considered important for this application:

B7451015 (EXTEND) is a phase 3 open-label, ongoing safety study in patients who completed the parent studies.

B7451014 (REGIMEN) is a phase 3 randomised withdrawal, double-blind, placebo-controlled study conducted in the target population. This study is now completed, and study documentation has been submitted within D120 LoQ responses upon request from the CHMP.

B7451036 (TEEN) is a phase 3, randomised, double-blind, placebo controlled, study in adolescent subjects 12 to <18 years of age with moderate-to-severe AD investigating abrocitinib co-administered with background medicated topical therapy. This study is now completed, and study documentation has been submitted within D120 LoQ responses upon request from the CHMP.

3.2. Favourable effects

Monotherapy studies

In study **B7451012**, the first co-primary efficacy parameter which evaluated the proportion of subjects who achieved an IGA response of clear or almost clear and a more than 2 points improvement from baseline at week 12, was statistically significant for both the 100 mg group 23.7 (17.0, 30.4) and the 200 mg group 43.8 (35.9, 51.7) compared with placebo 7.9 (1.8, 14.0). The corresponding values obtained in study **B7451013** was for the 100 mg group 28.4 (21.3, 35.5) and the 200 mg group 38.1 (30.4, 45.7) compared with placebo 9.1 (2.7, 15.5).

The second co-primary efficacy parameter was the proportion of subjects who achieved an EASI response of >= 75% improvement from baseline at week 12, and was for the abrocitnib 100 mg group 39.7 (32.1, 47.4) and for the 200 mg group 62.7 (55.1, 70.4) compared with placebo 11.8 (4.6, 19.1) in study **B7451012**. The corresponding results obtained in study **B7451013** was for the 100 mg group 44.5 (36.7, 52.3) and the 200 mg group 61.0 (53.3, 68.7) compared with placebo 10.4 (3.6, 17.2).

The key secondary efficacy endpoints were ≥4 points improvement from baseline in the peak pruritus NRS scale (PP-NRS4) at weeks 2, 4 and 12, and the change from baseline in Pruritus and Symptoms Assessment for AD (PSAAD). In study **B7451012**, results obtained with the PP-NRS4 scale were 37.7 (29.2, 46.3) for abrocitinib 100 mg, 57.2 (48.8, 65.6.) for abrocitinib 200 mg and 15.3 (6.6, 24.0) for the placebo group at week 12. The corresponding results obtained in study **B7451013** were 45.2 (37.1, 53.3) for abrocitinib 100 mg, 55.3 (47.2, 63.5) for abrocitinib 200 mg and 11.5 (4.1, 19.0) for placebo at week 12. In both studies, a statistically significant efficacy on itch was noted already at week 2. A dose-response relationship was obtained with a more pronounced efficacy on itch noted in

the 200 QD group compared with 100 mg QD group. Maximum efficacy evaluated as PP-NRS-4 was obtained during week 4 in study B7451012, and during week 4-8 in study B7451013.

In study **B7451012**, the change from baseline on itch evaluated by PSAAD at week 12 was -2.2 (-2.6, -1.9) for 100 mg and -3.2 (-3.6, -2.8) for 200 mg compared with -1.1 (-1.7, -0.6) for placebo. In study **B7451013**, the change from baseline on itch evaluated by PSAAD at week 12 was -2.4 (-2.8, -2.1) for 100 mg and -3.0 (-3.3, -2.7) for 200 mg compared with -0.8 (-1.3, -0.3) for placebo. Superiority of abrocitinib 100 mg QD ($p<0.001$) and 200 mg QD($p<0.001$) to vehicle were demonstrated also for itch evaluated by PSAAD in both the monotherapy studies.

To conclude, 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 which was superior to placebo. The results are considered of clinical relevance for the target population.

Subgroup analyses by intrinsic factors (age, sex, race ethnicity, weight and body mass index, disease severity by IGA and EASI, percent BSA affected by AD, and comorbidities) and extrinsic factors (geographic region and prior therapy for AD) demonstrated that effects of each dose of abrocitinib were similar across subgroups for the co-primary endpoints IGA and EASI-75. The effects of each dose of abrocitinib were similar across subgroups also for the key secondary efficacy endpoint PP-NRS4.

Both abrocitinib doses were efficacious regardless of the subject's baseline severity or extent of AD.

Combination therapy study

In the active control study **B7451029**, the efficacy of abrocitinib 100 mg QD and 200 mg QD was compared with that of dupilumab 300 mg/ml while all subjects where on medicated topical therapy (mainly TCS).

The results of the co-primary efficacy endpoint which evaluated the proportion of subjects who achieved an IGA response of clear or almost clear and a more than 2 points improvement from baseline at week 12, was statistically significant for both the 100 mg group 36.6 (30.4, 42.8), the 200 mg group 48.4 (41.8, 55.0) and dupilumab group 36.5 (30.4, 42.6) compared with placebo 14.0 (8.0, 19.9).

The corresponding results for the second co-primary efficacy parameter, the proportion of subjects who achieved an EASI response of >= 75% improvement from baseline at week 12, was for the 100 mg group 58.7 (52.4, 65.0), the 200 mg group 70.3 (64.3, 76.4), dupilumab 58.1 (51.9, 64.3) and for placebo 27.1 (19.5, 34.8).

The key secondary efficacy endpoint PP-NRS4 responder proportion at week 2 was statistically significantly higher for abrocitinib 100 mg 31.8 (25.8, 37.7) and for 200 mg 49.1 (42.6, 55.6) compared with placebo 13.8 (7.9, 19.8). Abrocitinib 200 mg QD had statistically significantly higher proportion of PP-NRS4 responders at week 2 compared with dupilumab 26.4 (20.8, 31.9), while the difference between abrocitinib 100 mg and dupilumab at week 2 did not reach statistical significance). PP-NRS4 responder proportion at weeks 12 and 16 were also higher for abrocitinib 100 mg and abrocitinib 200 mg compared with placebo.

IGA responder proportion at week 16, was statistically significantly higher for abrocitinib 100 mg 34.8 (28.6, 40.9) and for 200 mg 47.5 (40.9, 54.1) compared with placebo 12.9 (7.0, 18.8). When compared with dupilumab, treatment effect (IGA responder proportion corrected for placebo) at week

16 was greater with abrocitinib 200 mg QD than dupilumab 38.8 (32.5, 45.1), and similar between abrocitinib 100 mg QD and dupilumab.

For the third key secondary efficacy endpoint, proportion of EASI-75 responders, a statistically significantly higher efficacy for abrocitinib 100 mg 60.3 (53.9, 66.6) and for 200 mg 71.0 (65.1, 77.0) compared with placebo 30.6 (22.5, 38.8). When compared with dupilumab, treatment effect (IGA responder proportion corrected for placebo) at week 16 was greater with abrocitinib 200 mg QD than dupilumab 65.5 (59.4, 71.6), and similar between abrocitinib 100 mg QD and dupilumab.

Meaningful improvements in quality of life and psychosocial well-being were demonstrated, especially with the 200mg dose.

To conclude, superiority of abrocitinib 100 mg QD, 200 mg QD and dupilumab versus placebo was demonstrated. Interestingly, the level of efficacy was similar for abrocitinib 100 mg QD and for dupilumab, while in the first 12 weeks of treatment abrocitinib 200 mg QD was superior to dupilumab when dosed according to label. The efficacy of itch is also dose-dependent and can be noted earlier with abrocitinib than with dupilumab. These results are assessed to be of clinical relevance.

Adolescents

Adolescents were included in both the monotherapy studies, 84 subjects in study B7451012 and 40 subjects in study B7451013, but not in study B7451029. Study B7451036, assessing abrocitinib as add-on to concomitant medicated topical therapy in adolescents is now completed. Study B7451036 confirm efficacy findings from other trials and support inclusion of this age cohort into the target population from an efficacy perspective. However, there are safety concerns that led to the restriction of indication to adults only (see further below). Both co-primary endpoints of IGA and EASI-75 responses at Week 12 were met for both doses.

Maintenance of efficacy

In the maintenance study **B7451015**, the effect was maintained over 48 weeks in 502 subjects, including 73 adolescents. In the overall population of the long-term therapy pool, response rates for IGA, EASI-75 and PP-NRS4 at week 48 of abrocitinib treatment were similar to or higher than those at week 12 for either dose of abrocitinib. The mean percent change from baseline in EASI and PP-NRS scores were also similar between week 12 and week 48. Long-term analyses indicated also that there was a late-onset response among subjects who were previously non-responders at 12 weeks. The effect was largely maintained also beyond 48 (data up to 96 weeks are available).

Supportive studies

At week 12, the end of the open label run in period of **B7451014**, 64.3% of the 1233 patients achieved IGA response, 74.4% achieved EASI-75, and 67.3% achieved PP-NRS4.

3.3. Uncertainties and limitations about favourable effects

Methods including dosing of the product

The 50 mg dose has not been tested during the clinical development in any population and no PK data for the 50 mg strength are available. The respective dose recommendations are based on extrapolation and on the results from simulations performed with the population PK model.

Most of the data collected to describe abrocitinib long-term effects were collected in a single blinded manner (treatment assignment was disclosed to the investigators but not to the patients).

Results

In the combination therapy study B7451029, several treatment options were allowed (topical corticosteroids, calcineurin inhibitors (e.g., tacrolimus, pimecrolimus) or a PDE4 inhibitor (e.g., crisaborole) may be used instead of corticosteroids. The net efficacy result with abrocitinib 100 mg QD or 200 QD plus these medicated topical therapies used, and more precisely the extra efficacy in percent achieved when the patients are on combination therapy with TCS, calcineurin inhibitors or crisaborole is thus not known. As no specific claim were made on this in the SmPC section 5.1, this issue was not further pursued by the CHMP.

The applicant claims that in study B7451029 the 200 mg QD dose of abrocitinib demonstrated a larger treatment effect across multiple endpoints at week 16. However, data indicated that while the abrocitinib curves have reached a plateau, the dupilumab effect seems still on the rise for some endpoints. Overall, the 16-weeks study duration are too short to finally conclude on the cumulated effect of both treatments.

3.4. Unfavourable effects

Nausea occurred more commonly in females. The applicant is of the opinion that symptoms might be reduced when abrocitinib is taken in a fed state compared to fasted state. This conclusion appears reasonable although based on data from 2 Phase 1 studies (B7451004 and B7451032) with low numbers of healthy subjects and heterogeneity in tested doses as well as formulations of abrocitinib. The product information was updated to reflect that in patients who experience nausea, taking tablets with food may improve nausea.

The haematological profile of patients is vulnerable to the treatment with abrocitinib. Significant haematologic abnormalities compared to placebo with a dose-related decrease in platelet count with maximum effects observed within 4 weeks (median platelet values remained below baseline after 3 months) as well as subjects meeting discontinuation criteria for lymphopenia (confirmed $<0.5\times10^3/mm^3$) were seen. In the All Exposure Pool, 3 subjects were discontinued due to low platelet counts, all treated with 200mg. Furthermore, all subjects with reported AE of thrombocytopenia were treated with 200mg and all reported bleeding events were in the 200mg treatment group (5 events in the AEP with mild to moderate severity, one of these events led to discontinuation). Although no clear population changes in neutrophils were observed in the treatment groups of abrocitinib and no patient had a confirmed neutrophil count less than ANC $1.0\times10^3/mm^3$ there was a dose-response effect in the number of subjects with ANC below 2 $x10^3/mm^3$. In addition, pancytopenia was one of the AEs leading to discontinuation that occurred in more than 2 subjects. In Study B7451029 a B-cell increase and a substantial NK-cell decrease was observed.

All 7 reported subjects that met discontinuation thresholds for haematology measures in the AEP were in the 200mg treatment group and additionally 3 subjects (1 from 100mg and 2 from 200mg treatment groups) were discontinued due to pancytopenia. All patients meeting monitoring criteria for neutrophils in study B7451006 ($103/mm^3<2$) were treated with 200mg abrocitinib (10.9%). All patients meeting monitoring criteria for haemoglobin in study B7451006 (g/dL<11) were treated with abrocitinib (3.6% and 5.5% for 100mg and 200mg, respectively).

Elderly had a higher risk for haematology changes (especially low ALC, haemoglobin and platelets), herpes zoster infections and high LDL (>130 mg/dL).

A dose dependent increase in blood lipid parameters-both increases in LDL-c and HDL relative to placebo were reported in patients treated with abrocitinib as well as a dose-related increase in subjects reporting AEs of blood creatine phosphokinase increased in the Primary Pool. A higher proportion of subjects in the 200mg treatment group crossed the threshold of creatine kinase measure >5xULN

(3.8% for 200mg, 1.8% for 100mg and 1.8% for placebo, respectively). Two cases of myositis exposed to abrocitinib was reported but no report of rhabdomyolysis.

The incidence of SAEs was low and were reported in similar proportions of subjects across the abrocitinib (100 mg QD was 3.1%; and 200 mg QD was 1.9%) and placebo (3.2%) groups in the Primary Pool. They accumulated in a linear fashion over time. However, SAEs of pneumonia (3 subjects, 0.3%), asthma (3 subjects, 0.3%), and dermatitis atopic (2 subjects, 0.2%) occurred in more than 1 abrocitinib treated subject; all other SAEs occurred in 1 subject. Furthermore, serious and severe AEs are more likely to occur in elderly.

The long-term safety was evaluated in the All Exposure Pool. The proportion of subjects reporting TEAEs in the All Exposure Pool were 70.8 % and 72.0 % in the abrocitinib 100 mg QD and abrocitinib 200 mg QD respectively. The proportion of subjects with TEAEs judged as treatment-related was higher in the abrocitinib 200 mg QD treatment group.

Herpes simplex was reported in 2.8% and 4.8% of the abrocitinib 100 mg QD and abrocitinib 200 mg QD respectively and Herpes zoster in 0.6% and 1.2% of the abrocitinib 100 mg QD and abrocitinib 200 mg QD respectively. Serious infections with herpes simplex and herpes zoster were recorded for 200 mg in the AEP only (2 and 3 subjects, respectively). A statistically higher risk to suffer from herpes zoster infections upon treatment with 200 mg abrocitinib was concluded for subjects with age ≥65 years (proportions: 4.3%, 2.3% and 1.3% in subjects ≥65 years, 18-<65 and <18, respectively) and for patients with severe baseline AD disease (proportions: 3.2% and 1.6% in subjects with severe and moderate disease, respectively). Treatment emergent SAEs were reported in 5.3 % and 3.6 % of the abrocitinib 100 mg QD and abrocitinib 200 mg QD respectively. The Infections and infestations SOC had the highest incidence of SAEs with the most frequently reported serious infections being pneumonia, herpes zoster, and herpes simplex.

From subjects treated with 200mg, 4.7% developed acne (0% for placebo and 1.6% for 100mg) in the PP. It is recognised that Asian subjects could have a higher incidence of acne and nausea.

The proportion of subjects with elevated (supra-threshold) ALT values, AST values, or total bilirubin in the PP and AEP suggest a drug-related increase. Serious liver injuries and 7 potential liver injuries are reported in the clinical programme for abrocitinib. Serious injuries were recorded for 100mg treatment on Day 85 and 113 (incidences resolved at days 169 and 161, respectively). Potential liver injuries are reported for 100 mg and 200 mg treatment (1 and 6 cases, respectively). No incidence of liver-injury is reported for placebo treated subjects.

Three subjects treated with abrocitinib had GI perforations in the All Exposure Pool (AEP; 2 subjects treated with 100 mg and 1 subject treated with 200mg) with one serious incidence leading to study discontinuation.

Venous thromboembolism was reported in 5 events; 3 events of PE (all events of pulmonary embolism were serious) and 2 events of DVT all in the 200 mg QD group. Although there were few events, IRs of VTEs were higher in the AEP compared to all analysed cohorts. Apart from serious infections and VTE, Malignancies was included as an AESI. There were 7 cases of non-melanoma skin cancer and 4 events of potential malignancy (2 events of prostate cancer and 2 events of ovarian neoplasm) in the clinical database at the time of release. Comparisons were made with data from KPNC (Kaiser Permanente) and THIN databases. Overall, the IRs for malignancies (excluding NMSC) and NMSC in the KPNC and THIN databases were comparable to those seen in the AD clinical programme.

In non-clinical studies abrocitinib induces effects on bone development and the effect of abrocitinib on bone metabolism and bone development in humans is at present not clear. Permanent impact on skeletal development cannot be excluded. Abrocitinib exposure on bone development was evaluated clinically by HT SDS and fracture rate in children/adolescents >12 years of age. A safety update with

data cut April 2021 was provided by the applicant as part of their D180 LoOI responses. The Full Cumulative Pool included 635 adolescents with 646.2 PY. In the April 2021 data there were now 296 adolescent subjects with height data to Day 360. However, data from the provided April 2021 data cuts suggested a potential of a dose-related effect on fractures.

Finally, data are limited concerning pregnancies exposed to abrocitinib. However, data from preclinical studies, available data from other JAK inhibitors, as well as available clinical data for abrocitinib justify a contraindication, as depicted in section 4.3 of the SmPC.

Overall, the demonstrated safety profile of abrocitinib show similarities with other JAK inhibitors. Three deaths occurred in the abrocitinib treated subjects but there was no evidence on treatment related deaths. Demonstrated key unfavourable effects are haematological abnormalities, virus activation in terms of increased percentage of herpes simplex and herpes zoster whereof some serious, VTE and possibly pneumonia. The rate of herpes zoster infections was higher in the elderly.

3.5. Uncertainties and limitations about unfavourable effects

Important uncertainties relate to unfavourable effects of long latency and low frequency. Upon request from the CHMP, the applicant committed to update the information presented in the SmPC (where necessary) based on an update of safety data from the Full Cumulative Pool (April 2021 data cut) as part of a type II variation application (by Q1 2022).

In non-clinical studies abrocitinib induces effects on bone development and the effect of abrocitinib on bone metabolism in humans is not clear. Permanent impact on skeletal development cannot be excluded. The indication initially proposed for Cibinqo included children 12-<18 years of age as well as adults. Abrocitinib exposure on bone development was evaluated clinically by HT SDS and fracture rate in children/adolescents >12 years of age. A safety update with datacut April 2021 was submitted in the Day 180 response. The Full Cumulative Pool included 635 adolescents with 646.2 PY. In the April 2021 data there were now 296 adolescent subjects with height data to Day 360. However, data from the provided April 2021 data cuts suggested a potential of a dose-related effect on fractures. Furthermore, uncertainties still remained whether the applied clinical measures are sensitive enough to satisfactorily provide reassuring data for safe use in children $\geq$ 12 years of age and the reported data on height SDS as well as for fractures was premature for final evaluation. 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 treatment indication has been restricted to adults $\geq$ 18 years of age only.

Studies in animals have shown reproductive toxicity. Abrocitinib has been shown to cause embryo-foetal lethality in pregnant rats and rabbits, skeletal variations in the foetuses of pregnant rats and rabbits, and to affect parturition and peri/postnatal development in rats (see section 5.3). Cibinqo is contraindicated during pregnancy and breast feeding (see section 4.3). Women of reproductive potential should be advised to use effective contraception during treatment and for 1 month following the final dose of Cibinqo. Adequate risk minimisation measures and pharmacovigilance activities are included in the RMP to address the risk of foetal malformation following exposure in utero.

Finally, there are uncertainties regarding long-term safety beyond one year. The long-term effect on the risk of developing malignancies is presently unknown. There are also some uncertainties regards other events considered as class effects of JAK inhibitors. These concern myopathies (incl. rhabdomyolysis), GI-perforation and MACE. Those risks will be followed post approval (see RMP section).

3.6. Effects Table

Table 66 Effects Table for Abrocotinib-Pfizer for the treatment of moderate to severe Atopic dermatitis.

Effect	Short description	Unit	Regimen	Placebo	Abro 100 mg	Abro 200 mg	Dupi*	Uncertainties / Strength of evidence	References
Favourable Effects Study B7451012 (monotherapy trial)									
IGA 0/1	'Clear' or 'almost clear' according to Investigator's Global Assessment (and ≥2 points improvement)	%	Mono	7.9	23.7	43.8	N/A	Effects for abrocitinib 100 mg QD and 200 mg QD shown in 2 duplicate placebo-controlled monotherapy trials, and in one clinical trial of abrocitinib 100 mg QD and 200 mg QD with add-on to TCS on similar set of outcomes. Dupilumab (Dupixent) was used as active comparator in the combination therapy trial.	
EASI75	≥75% improvement in EASI score from baseline	%	Mono	11.8	39.7	62.7	N/A		
ΔItchNRS≥4	≥4 points improvement in Itch NRS from baseline	%	Mono	15.3	37.7	57.2	N/A	The strength of evidence is strong. Uncertainties are dosage, analysis of key secondary endpoints, additional effect of topical medicated treatment and long-term efficacy.	
Favourable Effects Study B7451013 (monotherapy trial)									
IGA 0/1	'Clear' or 'almost clear' according to Investigator's Global Assessment (and ≥2 points improvement)	%	Mono	9.1	28.4	38.1	N/A	Effects for abrocitinib 100 mg QD and 200 mg QD shown in 2 duplicate placebo-controlled monotherapy trials, and in one clinical trial of abrocitinib 100 mg QD and 200 mg QD with add-on to TCS on similar set of outcomes. Dupilumab (Dupixent) was used as active comparator in the combination therapy trial.	
EASI75	≥75% improvement	%	Mono	10.4	44.5	61.0	N/A		

Effect	Short description	Unit	Regimen	Placebo	Abro 100 mg	Abro 200 mg	Dupi*	Uncertainties / Strength of evidence	References
	in EASI score from baseline								
ΔItchNRS≥4	≥4 points improvement in Itch NRS from baseline	%	Mono	11.5	45.2	55.3	N/A	The strength of evidence is strong. Uncertainties are dosage, analysis of key secondary endpoints, additional effect of topical medicated treatment and long-term efficacy.	
Favourable Effects Study B7451029 (combination therapy trial)									
IGA 0/1	'Clear' or 'almost clear' according to Investigator's Global Assessment (and ≥2 points improvement)	%	Mono +TCS	 14.0	 36.6	 48.4	 36.5*	Effects for abrocitinib 100 mg QD and 200 mg QD shown in 2 duplicate placebo-controlled monotherapy trials, and in one clinical trial of abrocitinib 100 mg QD and 200 mg QD with add-on to TCS on similar set of outcomes. Dupilumab (Dupixent) was used as active comparator in the combination therapy trial.	
EASI75	≥75% improvement in EASI score from baseline	%	Mono +TCS	 27.1	 58.7	 70.3	 58.1*	The strength of evidence is strong. Uncertainties are dosage, analysis of key secondary endpoints, additional effect of topical medicated treatment and long-term efficacy.	
ΔItchNRS≥4	≥4 points improvement in Itch NRS from baseline	%	Mono +TCS	 13.8	 31.8	 49.1	 26.4		
Unfavourable Effects Studies B7451006, B7451012, B7451013, B7451029 (pooled)									
Adverse events		%	Mono and combi	55.0	61	68.3		Overall, the exposure of patients to abrocitinib is considered sufficiently sized for evaluation of common adverse events. Most of these occurred in a dose-related fashion. Uncertainties are the number of	
Serious adverse events		%		3.2	3.1	1.9			
Infections		%		26.3	35.2	34.6			
Serious infections		%		0.6	1.2	0.3			

Effect	Short description	Unit	Regimen	Placebo	Abro 100 mg	Abro 200 mg	Dupi*	Uncertainties / Strength of evidence	References
Thrombocytopenia, confirmed	$<75\times10^3/mm^3$	%		0	0	0.6		treatment-related adverse events in some subgroups, occurrence of some other specific adverse events, serious infections (pneumonia) and long-term events considered class effects of JAK inhibitors.	
Lymphocytes	ALC $<1\times10^3/mm^3$	%		11.9	18.5	20.8			
LDL-c cholesterol	Median change from baseline to last observation	%		-2 mg/dL	5 mg/dL,	7 mg/dL,			

Abbreviations: Abro = abrocitnib; Dupi = dupilumab; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; PP-NRS = Peak Pruritus Numerical Rating Scale

Notes: * the IGA 0/1 and EASI75 scores for dupilumab were evaluated as key secondary efficacy endpoints at week 16

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The most important effects noted in the monotherapy studies B7451012 and B7451013 are that subjects that well represent the target indication achieved clear or almost clear AD lesions in IGA score with abrocitinib 100 mg QD (24-28%) and 200 QD (44-38%) compared with placebo. An even more pronounced efficacy was seen for the other co-primary endpoint EASI-75 where 40-44% and 63-61% achieved a more than 75% improvement from baseline at week 12 with abrocitinib 100 mg QD and 200 mg QD, respectively. The clinical efficacy of abrocitinib is dose-dependent with approximately the double magnitude of efficacy obtained with 200 mg QD compared with 100 mg QD.

Furthermore, a combination therapy study has also been performed since the use of medicated topical therapy (mostly TCS) is the mainstay of AD treatment. In this study, dupilumab dosed according to label was used as the active comparator. The second most important finding is that the efficacy of dupilumab overall is like the efficacy of abrocitinib 100 mg QD, while 200 mg QD abrocitinib achieved a higher efficacy result in IGA and EASI-75 scores.

Itch is one of the major symptoms of AD that causes great distress for many patients. Abrocitinib has a dose-dependent and statistically significant efficacy on itch when evaluated with the PP-NRS4 score after 2 weeks of treatment but could be noted already after a few doses. Abrocitinib 200 mg QD has a superior efficacy on itch compared with abrocitinib 100 mg QD and dupilumab for which a similar efficacy level was obtained.

Overall, the clinical efficacy seems robust across subgroups and robust irrespective of different patient characteristics, intrinsic or extrinsic factors.

The dose recommendation has been changed and is now overall accepted.

The most important uncertainty is triggered by a safety signal from preclinical studies in rats. In these non-clinical studies, abrocitinib induces detrimental effects on bone development and the effect of abrocitinib on bone metabolism in humans is not clear. Permanent impact on skeletal development cannot be excluded. Abrocitinib exposure on bone development was evaluated clinically by HT SDS and fracture rate in adolescents $\geq$12 years of age. However, data from the provided April 2021 data cut suggested a potential of a dose-related effect on fractures and the reported data on height SDS as well as for fractures is considered by the CHMP to be premature for final evaluation. Furthermore, uncertainties still remain whether the applied clinical measures are sensitive enough to satisfactorily provide reassuring data for safe use in children >12 years of age. Consequently, the treatment indication has been restricted to adults >18 years of age only.

Further studies to investigate bone safety in adolescents have been proposed by the applicant. The same clinical measures/endpoints will be collected in the proposed safety B7451084 study-please refer to the RMP. The applicant also proposed to initiate a sub-study within the frame of the ongoing long-term extension study B7451015, in order to further investigate potential clinical implications on bone development for adolescent subjects >12 years of age that are exposed to abrocitinib. The proposed study concept aims for annual MRI images of the knee and is principally supported. These studies will be performed post-approval.

Other demonstrated key unfavourable effects are haematological abnormalities, virus activation in terms of increased percentage of herpes simplex and herpes zoster whereof some serious, VTE and

possibly pneumonia. The rate of herpes zoster infections was higher in the elderly. The knowledge on long-term safety is not complete but will be addressed post approval (see RMP section).

Overall, the impact of the important uncertainties of unfavourable effects of long latency and low frequency have been adequately addressed by presently limiting the therapeutic indication to adults only and by including appropriate information in the SmPC and RMP.

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 been observed in the target population moderate to severe atopic dermatitis. The proposed therapeutic indication initially reflected the population included in the clinical programme performed. Nevertheless, based on pre-clinical findings, there are uncertainties pertaining to potential detrimental effects on bone physiology and associated consequences on bone tissue formation and maintenance, in particular in growing bone. The clinical studies or the monitoring in these studies were likely insensitive to detect adverse events related to bone tissue formation. The therapeutic indication is therefore presently limited to adults only.

Contraindications for pregnancy, breast-feeding, severe hepatic impairment and ongoing serious infection (including TB) have been implemented in the product information. Additionally, hypersensitivity to the active substance or to any of the excipients is included as contraindication.

Other adverse events that pertain mostly to known drug-class effects for JAK inhibitors were also recorded, such as haematological changes which could be associated with a higher risk for VTEs and infections. Potential effects on cardiovascular safety must be assumed. Those risks will be followed up post approval (see RMP section).

Overall, the exposure of patients to abrocitinib is considered sufficiently sized. The demonstrated safety profile of abrocitinib including dose related common adverse events, show similarities with other JAK inhibitors and is consistent with the mechanism of action.

3.7.3. Additional considerations on the benefit-risk balance

N/A.

3.8. Conclusions

The overall benefit/risk balance of Cibinqo is positive in the adult population.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Cibinqo is favourable in the following indication:

Cibinqo is indicated for the treatment of moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

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

The educational programme is aimed at increasing awareness about the safety concerns of the product, including, infections (including herpes zoster and serious and opportunistic infections), thrombotic events including pulmonary embolism, malignancy, major adverse cardiovascular event (MACE), and embryo-foetal toxicity following exposure in utero.

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

The physician educational material should contain:
- The Summary of Product Characteristics
- Package leaflet
- Prescriber Brochure
- Patient card (PC)

The Prescriber Brochure shall contain the following key elements:
- Language for HCPs to inform patients of the importance of the PC.
- *Risk of infections (including herpes zoster and serious and opportunistic infections)*
  - Describe that Cibinqo must not be used in patients with active serious systemic infections.
  - Language on the risk of infections during treatment with Cibinqo.

    - Details on how to reduce the risk of infection with specific clinical measures (what laboratory parameters should be used to initiate Cibinqo, screening for TB, screening for hepatitis B and hepatitis C, getting patients immunised as per local guidelines, and temporary interruption of Cibinqo if an infection is not responding to standard therapy until the infection resolves).
    - Language stating the use of live, attenuated vaccines should be avoided during or immediately prior to treatment along with examples of live, attenuated vaccines.
- *Risk of thrombotic events including pulmonary embolism*
    - Language on the risk of thrombotic events, including pulmonary embolism, during treatment with Cibinqo.
    - Examples of the risk factors which may put a patient at higher risk for thrombotic events, including pulmonary embolism, and in whom caution is needed when using Cibinqo.
    - Language on the response if clinical features of thrombotic events, including pulmonary embolism, occur including the need for discontinuation of Cibinqo, prompt evaluation, and appropriate treatment for thrombotic events, including pulmonary embolism.
- *Potential risk of malignancy*
    - Language describing that malignancies, including non-melanoma skin cancer, have been observed in studies with Cibinqo.
    - Details of how to reduce the potential risk with specific clinical measures (that the risks and benefits of Cibinqo treatment should be considered prior to initiating in patients with a known malignancy or when considering continuing Cibinqo therapy in patients who develop a malignancy and that periodic skin examination is recommended for patients who are at increased risk for skin cancer).
- *MACE*
    - Language that lipids should be monitored prior to initiation, after 4 weeks of therapy and thereafter according to clinical guidelines. Lipids should be managed according to clinical guidelines.
- *Embryo-foetal toxicity following exposure in utero*
    - Language describing that there are no or limited data on the use of Cibinqo in pregnant women.
    - Details on how to reduce the risk of exposure during pregnancy for women of childbearing potential based on the following: Cibinqo is contraindicated during pregnancy, women of childbearing potential should be advised to use effective contraception both during treatment and for 1 month after cessation of Cibinqo oral administration, and to advise patients to inform their HCP immediately if they think they could be pregnant or if pregnancy is confirmed.

The patient information pack should contain:

- Package leaflet
- Patient card

- **The patient card** shall contain the following key messages:
    - Contact details of the Cibinqo prescriber.
    - Language that the PC should be carried by the patient at any time and to share it with HCPs involved in their care (i.e. non-Cibinqo prescribers, emergency room HCPs, etc.).
    - Description of signs/symptoms of infections the patient needs to be aware of, so that they can seek attention from their HCP:
        - Language to advise patients and their HCPs about the risk of live vaccinations when given immediately before and during Cibinqo therapy with examples of live vaccines.
    - Description of signs/symptoms of thrombosis including pulmonary embolism which the patient needs to be aware of, so that they can seek immediate attention from an HCP.
    - Description of targeted risks for awareness by the patient and for HCPs involved in their care including:
        - The need for laboratory monitoring, including for high cholesterol.
        - A reminder to use contraception, that Cibinqo is contraindicated during pregnancy, and to notify their HCPs if they become pregnant while taking Cibinqo.

- ***New Active Substance Status***

Based on the CHMP review of the available data, the CHMP considers that abrocitinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

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.