20 July 2023
EMA/357337/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Litfulo

International non-proprietary name: ritlecitinib

Procedure No. EMEA/H/C/006025/0000

Note

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

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

Abbreviation	Term
AA	alopecia areata
AAD	American Academy of Dermatology
AAPPO	alopecia areata patient priority outcomes
AASc	Alopecia Areata Scale
ACE	AA Consensus of Experts
ADME	absorption, distribution, metabolism, elimination
ADR	adverse drug reaction
AE	adverse event
AEC	all exposure cohort
AEDC	participants discontinued from study or study drug due to adverse events
AEP	all-exposure pool
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AT	alopecia totalis
ATE	arterial thromboembolic events
AU	alopecia universalis
AUC	area under concentration-time curve
AUC_{24}	area under the concentration-time curve from 0 to 24 hr
AUC_{inf}	area under concentration-time curve to infinity
AUC_{ss}	area under the concentration-time curve during a dosing interval at steady state
AUC_{tau}	area under the concentration-time curve over dosing interval tau
AZP	azathioprine
BA	bioavailability
BAD	British Association of Dermatologist
BAEP	brainstem auditory evoked potential
BCC	basal cell carcinoma
BCRP	breast cancer resistance protein
BCS	biopharmaceutics classification system
BE	bioequivalence
BfArm	Federal Institute for Drugs and Medical Devices
BHT	butylated hydroxytoluene
BID	twice a day
BL	baseline
BMI	body mass index
BMX	bone marrow tyrosine kinase on chromosome X
BR	benefit risk
BRA	benefit-risk analysis
BRI	behavior regulation index
BRIEF 2	behavior rating inventory of executive function 2
BTK	Bruton's tyrosine kinase
C_{av}	averaged plasma concentration at steady-state
C_{cs}	corticosteroids
CD	cluster of differentiation
CFB	change from baseline
CI	confidence interval
CK	creatine kinase
ClinRo	clinician-reported outcomes
C_{max}	maximum observed concentration
C_{min}	lowest concentration observed during the dosing interval
CMQ	customized MedDRA query
CNS	central nervous system
CO	clinical overview

Abbreviation	Term
COVID-19	coronavirus disease 2019
CQA	critical quality attribute
CRI	cognitive regulation index
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CV	cardiovascular
CYP	cytochrome
DDI	drug-drug-interaction
De novo participants	individuals not exposed to ritlecitinib prior to entering Study B7981032
Diff	difference
DoE	design of experiments
DPCP	2,3-diphenylcyclopropenone
DR	dose ranging (period)
DVT	deep vein thrombosis
EBA	eyebrow assessment
EE	ethinyl estradiol
eGFR	estimated glomerular filtration rate
EC_{50}	median effective concentration
ELA	eyelash assessment
EMA	European Medicines Agency
E_{max}	maximal effect
EOI	event of interest
EPO	erythropoietin
ER	estrogen receptor
ERI	emotional regulation index
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FIMEA	Finnish Medicines Agency
F-VASI	facial-vitiligo area scoring index
GC	gas chromatography
GSH	glutathione
GST	glutathione-S-transferase
HADS	hospital anxiety and depression scale
HALMED	Agency for Medicinal Products and Medical Devices of Croatia
HCP	health care professional
HDL-C	high density lipoprotein cholesterol
HDPE	high density polyethylene
HER2	human epidermal growth factor receptor 2
Hgb	hemoglobin
HLT	high level term
HPLC	high performance liquid chromatography
HPMC	hypromellose
HRQoL	health-related quality of life
HS	herpes simplex
HV	healthy volunteers
HZ	herpes zoster
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IENF	intraepidermal nerve fiber
IENFD	intraepidermal nerve fiber density
IFN	interferon
Ig(X)	immunoglobin (X)
IL	interleukin
ILCS	intralesional corticosteroids
IMT	immunotherapy
IR	incidence rate
IR	immediate release

Abbreviation	Term
ITK	interleukin-2 inducible T-cell kinase
JAK	Janus kinase
LC	liquid chromatography
LCR	longitudinal concentration response
LDL-C	low density lipoprotein cholesterol
LDPE	low density polyethylene
LFT	liver function test
LLN	lower limit of normal
LN	levonorgestrel
LS	least squares
LSM	least squares means
MACE	major adverse cardiac events
MAR	maximal acceptable risk
MATE	multidrug and toxin extrusion transporter
MCMC	Markov chain Monte Carlo
MEB	Medicines Evaluation Board
MDN	modified de novo
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MIDD	model informed drug development
MN	Miettinen and Nurminen
MPA	Swedish Medical Product Agency
MS	mass spectrometry
MTX	methotrexate
N	number of participants
nbUVB	narrow band ultraviolet B
NCA	non-compartmental analysis
NDA	new drug application
NICE	The National Institute for Health and Care Excellence
NK	natural killer
NMR	nuclear magnetic resonance
NMSC	non-melanoma skin cancer
NRS	numeric rating scale
NSEAC	Neurosafety Event Adjudication Committee
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OI	opportunistic infection
OPA/Al/PVC/Al	oriented polyamide/aluminum foil/polyvinyl chloride/aluminum
OYEP	one-year exposure pool
PASS	post-authorisation safety study
Pbo	placebo
PCI	percutaneous coronary intervention
PCP	placebo-controlled pool
PCPAA	placebo-controlled pool (AA)
PCPAAV	placebo-controlled pool (AA + Vitiligo)
PD	pharmacokinetics
PDCO	Paediatric Committee
PE	pulmonary embolism
PGI-C	patient global impression of change
Ph. Eur.	European Pharmacopoeia
PIP	paediatric investigation plan
PK	pharmacokinetics
PMAR	pharmacometric analysis report
PNS	peripheral nervous system
POPPK	population pharmacokinetics
PPS	patient preference study
PR	progesterone receptor

Abbreviation	Term
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	patient reported outcome
P-Sat	patient satisfaction with hair growth
PSD	particle size distribution
PT	(MedDRA) preferred term
PTCA	percutaneous transluminal coronary angioplasty
PV	pharmacovigilance
PY	person-years
QbD	quality by design
QC	quality control
QD	once daily
QoL	quality of life
QTPP	quality target product profile
RA	rheumatoid arthritis
rBA	relative bioavailability
RH	relative humidity
Roll-over participants	participants in Study B7981032 previously exposed to ritlecitinib in either Study B7931005 or Study B7981015.
RWE	real-world experience
SADBE	squaric acid dibutylester
SAE	serious adverse event
SALT	severity of alopecia tool
$SALT_{\#}$	at least #% improvement in SALT score from baseline
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	systemic corticosteroids
SCC	squamous cell carcinoma
SCE	summary of clinical efficacy
SDS	standard deviation score
SE	standard error
SF-36v2	36-Item Short Form Health Survey version 2
SmPC	summary of product characteristics
sNDA	supplemental New Drug Application (NDA)
SMQ	standardized MedDRA query
SOC	system organ class
TAMC	total aerobic microbial count
TB	tuberculosis
TC	total cholesterol
TCR	T cell receptor
TCS	topical corticosteroids
TE	thromboembolic events
TEAE	treatment-emergent adverse event
TEC	tyrosine kinase expressed in hepatocellular carcinoma
TG	triglycerides
THIN	The Health Improvement Network
TPO	thrombopoietin
TS	trial-similar
TSE	transmissible Spongiform Encephalopathy
TXK	tyrosine kinase expressed in T cells
TYK2	tyrosine kinase 2
TYMC	total combined yeasts/moulds count
UC	ulcerative colitis
UK	United Kingdom
ULN	upper limit of normal
URTI	upper respiratory tract infection
US	United States
UTI	urinary tract infection
UV	ultraviolet
vs	versus

Abbreviation	Term
V_{ss}	steady state volume of distribution
VTE	venous thromboembolism
VZV	varicella-zoster virus
WPAI-AA	work productivity and activity impairment: alopecia areata

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 26 July 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Litfulo, 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 14 October 2021.

The applicant applied for the following indication: Litfulo is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older (see section 5.1).

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 test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0147/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0147/2021 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(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance ritlecitinib 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
26 July 2018	EMEA/H/SA/3875/1/2018/HTA/III	André Elferink, Andreas Kirisits
12 December 2019	EMEA/H/SA/3875/1/FU/1/2019/III	André Elferink, Walter Janssens, Karl-Heinz Huemer
23 July 2020	EMEA/H/SA/3875/1/FU/2/2020/II	Mario Miguel Rosa, Karl-Heinz Huemer

The scientific advice pertained to the following non-clinical and clinical aspects:

Initial SA EMEA/H/SA/3875/1/2018/HTA/III:

- Non-clinical: Issues raised concerned whether the provided, ongoing, and planned nonclinical toxicity studies with PF-06651600 may be sufficient for MAA purposes. Specifically, whether the collective nonclinical toxicity package supports clinical doses up to 200 mg QD for 16 weeks and 100 mg QD for chronic dosing.
- Clinical: The initial advice concerned the clinical pharmacology package, QT analyses ,medical need and inclusion criteria, placebo comparator, the selected dose(s) and dose regimen(s) to be evaluated, primary endpoint, key secondary endpoint, handling of emergence or re-emergence of androgenetic (male or female pattern) baldness, appropriate time-point to demonstrate efficacy, the proposed numeric rating scales (below) to assess the treatment effect on eyebrows and eyelashes, adequacy of the withdrawal-retreatment design of the ongoing Phase 2a study (B7931005) with extension to demonstrate the need for continuous treatment, adequacy of the proposed clinical data support the proposed posology statement, the proposed sample size for the Phase 2b/3 study, the key data to be collected at baseline for the Phase 2b/3, safety assessments and safety monitoring plans. Acceptability that an initial submission package for PF-06651600, based on 2 studies (the ongoing Phase 2a proof-of-concept study, followed by the proposed pivotal Phase 2b/3 dose ranging study), could be sufficient to support an initial conditional approval for AA with 50% or greater scalp hair loss, provided the evidence of positive benefit:risk profile was clear and compelling. Acceptability of the projected safety databases. Appropriateness of inclusion of adolescents. Whether a single Phase 3B study coupled with results from the LTE study and post-approval RWE is adequate to support full authorisation. Patient reported outcomes (PROs).

Follow-up (FU) advice EMEA/H/SA/3875/1/FU/1/2019/III:

- The clinical relevance of the treatment-related axonal dystrophy observed in dogs. Clarification in how far the relative CNS immaturity in humans, especially with regards to continued myelination and synaptogenesis, resembles the one in the dog during adolescence. The proposed approach for additional characterisation of the clinical relevance of the finding of axonal dystrophy observed in the 9-month toxicity studies in dogs with PF-06651600 adequately addresses the Agency's request for clinical risk characterisation. Agreement that the totality of evidence from the PF-06651600 programme (including the nonclinical data, the clinical safety data from studies B7981015 and B7981032, and data from the ex-EU Study B7981037), that the clinical relevance of the nonclinical finding of axonal dystrophy in dogs will be adequately characterised to support a future MAA filing for adolescents. Agreement that that based on the totality of evidence from the PF-06651600 programme (including adolescents), additional clinical risk characterisation in the

younger paediatric subjects (from 6 to <12 years of age) is not warranted.

FU advice EMEA/H/SA/3875/1/FU/2/2020/II:

- Revision of the primary endpoint of Study B7981015 to the proportion of patients achieving SALT ⩽20 at Week 24. Adequacy of the proposed safety data package to support initial MAA review. Discussion of an 'extrapolation study' to support adolescent subjects in the EU PIP (in addition to all the studies that include [ex-EU] adolescent subjects). Modifications of the design of Study B7981027 including inclusion of a lower dose and a mandatory psychological counselling run-in period in the paediatric Study B7981027.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Margareta Bego

The application was received by the EMA on	26 July 2022
The procedure started on	18 August 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 November 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 November 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 December 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 March 2023
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	2 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 May 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 May 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	15 June 2023
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	5 July 2023
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 July 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting	20 July 2023

a marketing authorisation to Litfulo on	
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	20 July 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed therapeutic indication was as follows:

Litfulo is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older (see section 5.1).

2.1.2. Epidemiology

Studies on the prevalence of alopecia areata (AA) are limited and estimates vary considerably. A meta-analysis including articles published up to 2018 calculated the overall pooled incidence (95%CI) of AA in Europe as 4.9% (2.4% -8.3%) and the pooled prevalence (95%CI) of AA was estimated as 0.58% (0.49% - 0.66%); (Lee 2020).

The onset of AA can occur at any age; however, 82.6% to 88.0% of patients develop the condition before the age of 40 years and 40.2% by the age of 20 years, with a mean age of onset between 25 and 36 years (Villasante 2015). In a UK population, the annual incidence of AA peaked at 5.1 per 10,000 (males) and 4.3 per 10,000 (females) in patients aged 25-29 years and subsequently decreased with age (Harries, 2022). It is uncertain whether there is a gender predominance in patients with AA (Harries, 2022).

2.1.3. Aetiology and pathogenesis

AA is an autoimmune T-cell disease that causes non-scarring hair loss, which may be chronic with unpredictable relapses, affecting all ages, races, and genders. The complex pathophysiology of AA is still not completely understood. CD8+ T cells, NK cells and mast cells are likely involved in the pathogenesis of AA and their development and function are known to be regulated by both JAK3 and TEC kinases (such as ITK). Mouse models have shown that IL-2, and IL-15 play a role in the initiation of auto-reactive CD8+ cells (Dai 2021; Xing 2014). Also, data from patients with AA demonstrated that IL-15 plays a critical role in the pathogenic pathways of AA (Suarez-Farinas 2015).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The three main variants of AA are patchy AA (localised hairless areas), alopecia totalis (AT) (entire scalp affected), and alopecia universalis (AU) (affecting all body surface area). Nearly all AA patients experience more than one episode of scalp hair loss, and 14-25% progress to AT or AU (Messenger 2012). The onset of AA can occur at any age. Disease duration >1 year and extensive hair loss (> 50% scalp involvement) are predictors of poorer prognosis, with <17% of AT and AU patients reaching

remission with fully regrown lost hair (Messenger 2012; Pratt 2017; Jang 2017; Tosti 2006). A study assessing the long-term course of AA across age groups reported that the proportion of patients with relapses after diagnosis was high overall (52%, 44% and 30% in childhood-onset, adult-onset and late-onset, respectively); however, relapses declined over time, with the majority (79%) occurring within the first 4 years after initial diagnosis (Lyakhovitsky 2019).

Hair loss is emotionally challenging and results in higher incidences of psychosocial impacts in patients with AA compared to healthy people, including detrimental effects on emotional wellbeing, self-esteem, social interactions, and health-related quality of life.

Treatment guidelines vary but generally distinguish between "acute" or "active" versus "chronic" AA (Messenger 2012; Meah 2020; Rossi 2019). While some treatment guidelines and consensus statements define AA involving ⩾50% scalp hair loss as "extensive" or "severe" AA, there is no agreed upon definition of severity.

2.1.5. Management

Baricitinib (a selective inhibitor of JAK 1 and 2) was centrally approved in the EU on 19 May 2022 for the treatment of severe AA in adults. No other products are centrally approved for the treatment of AA. However, some authorised medications are available in individual member states (e.g., methylprednisolone and triamcinolone intra-lesion injections are approved for AA indication in NL). Current guidelines advise on topical (corticosteroids and minoxidil) or systemic therapies (corticosteroids, corticosteroid-sparing agents such as cyclosporin and methotrexate, and biological such as ustekinumab) (European Dermatology Forum (EDF): Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and men, 2017; British Association of Dermatologists (BAD): Guidelines for the management of alopecia areata, 2012). However, some of those treatments are used off-label.

2.2. About the product

Ritlecitinib is an oral covalent irreversible inhibitor of the 5 TEC family kinases (BMX, BTK, ITK, TEC, TXK) and JAK3. The covalent mechanism of inhibition confers high selectivity over the remaining three JAK isoforms (JAK1, JAK2 and TYK2) and the broader kinome. Ritlecitinib is characterised by its lack of activity against JAK1 and JAK2 leading to a narrower spectrum of cytokine inhibition, inhibiting only the 6 γ-common cytokines IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. Consequently, in human whole blood, ritlecitinib inhibits signalling of the common-γ chain receptors but does not inhibit signalling of cytokines that are JAK3 independent such as the JAK1 dependent cytokines (including type 1 & 2 interferons, the IL-6 family of cytokines, the IL-10 family of cytokines). Ritlecitinib does not inhibit the JAK2-dependent hematopoietic factors such as EPO and TPO. Ritlecitinib additionally inhibits the TEC family of kinases leading to the inhibition of cytolytic functions in CD8+ T cells and NK cells (Telliez 2016; Xu 2019). Thus, ritlecitinib aims to inhibit the signalling of JAK3-dependent cytokines and TEC family-dependent immune receptors that are considered to contribute to the pathophysiology of AA.

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 received EMA scientific advice on the clinical development programme of ritlecitinib in the treatment of AA (see section 1.5. 'Scientific advice').

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as hard capsules containing ritlecitinib tosylate equivalent to 50 mg of ritlecitinib as an active substance.

Other ingredients are:

hard capsule content: cellulose microcrystalline, lactose monohydrate, crospovidone, glycerol dibehenate;

hard capsule shell: hypromellose (E464), titanium dioxide (E171), yellow iron oxide (E172), brilliant blue FCF (E133);

printing ink: shellac, propylene glycol, ammonia solution concentrated, black iron oxide (E172), potassium hydroxide.

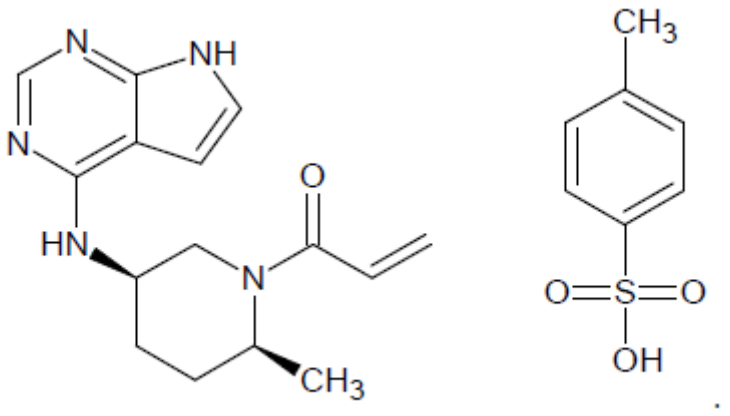
The product is available in high-density polyethylene (HDPE) bottle with a silica gel desiccant and polypropylene closure or in Oriented Polyamide/Aluminum Foil/Polyvinyl chloride/Aluminum (OPA/Al/PVC/Al) foil blisters.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of ritlecitinib tosylate is 1-{(2*S*,5*R*)-2-Methyl-5-[(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl}prop-2-en-1-one 4-methylbenzene-1-sulfonic acid corresponding to the molecular formula $C_{22}H_{27}N_5O_4S$. It has a relative molecular weight of 457.55 Daltons and the following structure:

Figure 1: active substance structure



The structure has two chiral centres, giving four possible diastereomeric isomers. The chiral pure (2*S*,5*R*) isomer is used in the finished product. The diastereomeric purity is introduced with one of the starting materials and is not changed during the manufacturing process. Enantiomeric purity is controlled routinely by chiral HPLC. Properties of the active substance were measured by infrared (IR) spectroscopy, mass spectrometry (MS), Nuclear Magnetic Resonance (NMR) spectroscopy, X-Ray Diffraction, Ultraviolet/Visible (UV/Vis) spectroscopy.

The active substance is a non-hygroscopic white to off-white to pale pink solid. Ritlecitinib tosylate is classified as a BCS class III active substance (high solubility and low permeability). It exists in a single crystal form (Form 1). This form is physically and chemically stable under normal manufacturing and storage conditions as well as under accelerated stability conditions. No other polymorphs or hydrated forms have been observed during development or in stability studies.

2.4.2.2. Manufacture, characterisation and process controls

The synthesis of ritlecitinib tosylate consists of 4 synthetic steps using three well-defined, custom-synthesised starting materials with acceptable specifications, one salt formation step, and one recrystallisation step. In the first three steps, the key structural features are built up. The final steps include the tosylate salt formation and recrystallisation. Part of the last step is a milling process, in which the particle size distribution of the active substance is controlled.

The manufacturing process is sufficiently described. The control strategy (including specification of starting materials and intermediates, in-process controls and monitoring of critical process parameters) is provided in section 3.2.S.2.6.

- The choice of the starting materials is adequately justified by the applicant in line with ICH Q11. As mentioned above, the enantiomeric purity is adequately controlled in one of the starting materials. Batch data of the active substance manufactured from each source of starting materials has been provided to demonstrate quality equivalence between different sources of starting materials.
- A list of raw materials was provided with specifications. No class 1 solvents are used. Residual benzene in ethanol and toluene is controlled by specification in these solvents.
- Two intermediates are identified . The proposed specifications for both intermediates are acceptable. Structural characterisation of intermediates was provided by the applicant.
- Four critical parameters were specified in the development , and in-process controls are established.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. A structural analysis and a schematic overview of the origin, fate and purge of the specified organic impurities is included in the dossier.

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

The development of the manufacturing procedure is described in detail.

The applicant established critical quality attributes (CQAs), which include specified organic impurities (based on batch history and impurities identified in the later steps), particle size distribution (PSD), and residual solvents. The in-process controls and manufacturing controls to control the CQAs have been described. Following commercial route selection and design, ritlecitinib tosylate development was focused on building an understanding of the functional relationships between material attributes, process parameters, and the critical quality attributes (CQAs). A structured quality risk management approach was employed to identify potential critical process parameters and critical material attributes based on risk of impact to the ritlecitinib tosylate CQAs. The reaction parameters of each step were investigated using risk assessment, univariate and DoE studies. Based on this, the control strategy was established. Based on these studies, design spaces have been proposed for several steps of the

manufacturing process, and provided the required data from DoE studies to justify the proposed operating ranges.

The impact of scale and equipment dependent parameters has been assessed for all experiments, including impact of several parameters on scale-up. In addition to the scale and equipment understanding, a variety of pilot and commercial scale batches of each step of the manufacturing process have been performed during development. These batches serve as confirmation of the scale and equipment understanding and support the validity of the design spaces at commercial scale. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design spaces.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Changes introduced have been presented in sufficient detail and have been justified. It has been demonstrated that the change(s) did not have a significant impact on the quality of the product.

Ritlecitinib tosylate is packaged in two sealed, low-density polyethylene (LDPE) anti-static liners. The bagged material is then inserted into a high-density polyethylene (HDPE) drum. The LDPE anti-static liner is suitable for pharmaceutical or "in contact with food" use and comply with EU regulation No. 10/2011.

2.4.2.3. Specification

The active substance specification includes tests for appearance (visual), identity (IR), chiral identification (LC), assay (LC), impurities (LC), water content (Ph. Eur.), residual solvents (GC), counter ion, residue on ignition (Ph. Eur.) and particle size distribution (laser diffraction).

The active substance specification is based on the active substance CQAs. The CQAs identified include organic impurities, PSD, and residual solvents.

Identification is performed with two tests, IR by comparing with a reference standard and LC to establish the chiral identity by comparing with a reference standard.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate limits have been set.

The proposed acceptance criterion for particle size distribution is solely based on finished product manufacturability. Impact of the particle size on finished product bioavailability and dissolution is considered negligible because of the high solubility of the active substance.

The applicant provided rationales for omitting tests for the opposite enantiomer of ritlecitinib, polymorphic form, benzene, elemental impurities, BHT, microbial enumeration, and class 1-3 impurities from the active substance specification; these are acceptable.

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 of ritlecitinib tosylate Form 1 and ritlecitinib to show that the correct structure is present, chromatography to establish assay and impurity profile, x-ray diffraction to establish crystal form and other tests to define its purity has been presented. Reference standards for related substances and the counter ion, and for chiral identity testing have also been described.

Batch analysis data of 41 batches produced during development using the synthetic route in use at the time, and 18 pilot scale batches and 4 commercial scale batches of the active substance manufactured

with the synthetic route proposed for commercial manufacture are provided. The results are within the specification limits and consistent from batch to batch.

2.4.2.4. Stability

The primary stability programme consists of a formal programme comprising three batches manufactured at the development site using the commercial process without an auxiliary material to limit impurity formation at commercial scale. Thirty months stability data at long term conditions (25ºC / 60% RH) and six months at accelerated conditions (40ºC / 75% RH) are provided.

A supplementary registration stability programme in which one batch manufactured at the development site using the commercial process including an additional auxiliary material at commercial scale is provided. Data through twenty-four months at 25°C / 60% RH and six months at the accelerated condition of 40°C / 75% RH is included. As indicated above, an auxiliary material was added to the process to mitigate impurity formation. This change was made to the process after the manufacture of the primary stability active substance lots. Data presented showed that the material generated using the final commercial manufacturing route, in which the auxiliary material is added, is chemically equivalent to that produced when the auxiliary material is not present and show the same stability behaviour.

In addition, data from the commercial stability programme on three batches manufactured at the site proposed for commercial manufacture at commercial scale is available. Twelve months stability data at 25°C / 60% RH and six months at the accelerated condition of 40°C / 75% RH are provided.

All batches were stored in the primary packaging proposed for marketing.

For the primary stability programme 30 months data are completed of 3 pilot scale batches without the additional auxiliary material, and for the supplementary stability programme 24 months data are completed of 1 batch with the additional auxiliary material, stored under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines.

The following parameters were investigated: appearance, assay, degradation products, API Polymer, chiral purity, water content, particle size, polymorph form and microbiological quality.

The analytical procedures used in the primary and supplementary stability programs are the same as the release procedures, with the exception of chiral purity, solid form and microbial quality. The additional analytical procedures have been described.

For all the data provided, no significant upward or downward trend was observed for all parameters measured including assay and related substances. No differences in stability are observed between the primary and supplementary stability studies.

Photostability testing following the ICH guideline Q1B was performed on one batch from the primary stability study. Samples were tested for appearance, assay, achiral purity, polymer impurity, water content, solid form and chiral purity. No degradation was observed.

Therefore, it is accepted that no light restriction for storage of the active substance is applied.

Samples of ritlecitinib tosylate active substance were subjected to forced degradation conditions (thermal, thermal/humidity; acid; base; light exposure; heat; and oxidation) to confirm the suitability of the assay and purity procedure and to identify potential primary degradation products. The only forced conditions that caused any degradation to occur were basic conditions in solution and high

temperature/high humidity in the solid state. The study showed that the assay/purity procedure proposed for commercial production is specific, selective, and stability-indicating.

The post-approval stability protocol and stability commitments are accepted.

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 36 months in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Litfulo is presented as immediate release (IR) hypromellose (HPMC) opaque hard capsules containing 50 mg of ritlecitinib (as tosylate). The capsules are size #3 (approximately 16 mm in length x 6 mm width), with a yellow body and blue cap. The body is printed with "RCB 50" and the cap is printed with "Pfizer" in black.

The development was also performed with 30 mg and 100 mg capsules manufactured from a common blend, as well as other clinical development formulations, including extemporaneously prepared (EP) oral solutions, non-film coated immediate release (IR) tablet for oral administration and a solution for intravenous administration. Only the 50 mg capsule strength is proposed for commercialisation.

The formulation and process development of ritlecitinib capsules focused on the quality attributes defined in the Quality Target Product Profile (QTPP) .

The Quality Target Product Profile (QTPP) has been established as immediate release dosage form containing ritlecitinib capsules, that meets compendial and other relevant quality standards for CQAs appearance, identity, assay, impurities, uniformity of dosage units, water activity, dissolution and microbial limits.

An enhanced development programme was executed in accordance with ICH Q8(R2). A combination of risk-based assessments, small-scale multivariate studies and manufacturing experience at the proposed commercial manufacturing site has resulted in a comprehensive understanding of the formulation and process conditions and their impact on the quality attributes of the finished product. Attributes and parameters have been categorised as either critical or non-critical, based on their impact on product quality. The proposed commercial ritlecitinib finished product manufacturing process is supported by a control strategy that assures each quality attribute meets the acceptance criteria required to deliver a finished product with the desired efficacy, safety and quality.

The active substance is the ritlecitinib tosylate salt, crystalline Form 1. The highest ritlecitinib clinical dose (200 mg) assessed in the pivotal clinical study is soluble over the entire physiological pH range. The acceptance criterion for active substance particle size distribution was developed considering the impact on dissolution, bio performance and manufacturability (blend and content uniformity) of the finished product.

All the excipients used in the proposed commercial formulation are globally acceptable and are present at pharmaceutically precedented levels. All excipients quality is compliant with Ph. Eur standards, except yellow iron oxide (E172) and Brilliant blue FCF – FD&C Blue 1 (E133), which comply with the specifications described in Regulation 231/2012. The list of excipients is included in section 6.1 of the SmPC. Functionality-related characteristics of the excipients are discussed acceptably. No additional tests are necessary in the specifications of the excipients, given the lack of criticality of the aspects on the quality of the finished product.

The proposed patient population includes paediatric patients (12 years of age and older). The applicant has provided a discussion on the suitability of the excipients for this patient group, as per *CHMP guideline on Pharmaceutical development of medicines for paediatric use.*

The 10 mg and 50 mg strengths of the ritlecitinib IR tablet were used to support the pivotal Phase 2b/3 efficacy and safety study (B7981015) and long-term safety study (B7981032) as well as clinical pharmacology studies. The ritlecitinib IR tablets were unsuitable for commercial development due to instability of the formulation (shelf-life was less than 2 months when stored at 30°C / 65% in an open dish, likely caused by the degradation of the ritlecitinib tosylate, resulting in the formation of the less stable ritlecitinib free base) as well as the multiple units (up to 4 tablets) potentially required to support the proposed doses.

A preliminary excipient screen was conducted using binary mixtures (1:1 ratio) of ritlecitinib tosylate and a range of common pharmaceutical excipients stored for one week at 70°C / 75% RH. The results indicated that the highest level of impurity formation occurred when ritlecitinib tosylate was mixed with excipients with the following attributes – microenvironment pH greater than the pH max of ritlecitinib tosylate (~4.0) and proton accepting capacity (i.e. croscarmellose sodium, sodium starch glycolate and magnesium stearate). Out of the filler excipients assessed microcrystalline cellulose, lactose and starch provided an environment that minimised the degradation of the ritlecitinib tosylate active substance. Microcrystalline cellulose and lactose were selected as the fillers based on prior experience. The concentration of crospovidone and glyceryl dibehenate was selected based on precedence in other solid dosage form products. Additionally, the results confirmed the suitability of crospovidone as the disintegrant and glyceryl dibehenate as the lubricant.

Following the identification of excipients for the proposed commercial finished product, formulation understanding experiments were conducted and focused on assessing the impact of drug loading and active substance particle size on stability, manufacturability and dissolution on the finished product. Based on the data generated, a capsule formulation was nominated as the proposed commercial formulation.

To bridge between the clinical tablets and the proposed commercial capsules, a relative bioavailability (rBA) study (B7981022) and a pivotal bioequivalence study (B7981029) were conducted. A biowaiver for the lower capsule strengths of 50 mg and 30 mg has been applied because the composition of the strengths is quantitatively proportional, (i.e. common blend and manufacturing process) between the three capsule strengths. The BE/PK similarity between products and strengths is supported by *in vivo* and *in vitro* evaluations.

The bioequivalence study (B7981029) demonstrated that the clinical 50 mg tablet formulation used in the pivotal Phase 2b/3 study is equivalent to the intended 100 mg 'commercial' capsule formulation (not subject of the marketing authorisation application). Dissolution results of the 50 mg tablets and 100 mg capsules used in the BE study have been provided, although the results could not be compared directly due to the difference in dissolution procedure set-up. However, as *in vivo* results prevail, this issue was not further pursued.

A biowaiver for the lower strength of 50 mg capsules has been applied because the composition of the strengths is quantitatively proportional, (i.e. common blend and manufacturing process) between the 30 mg, 50 mg and 100 mg capsule strengths. The same common blend (identical active and inactive ingredients) is used to fill the 30 mg, 50 mg and 100 mg ritlecitinib capsules. Following a Major Objection from the CHMP, dissolution testing of the 30 mg capsules, 50 mg capsules and 100 mg capsules in three different pH media (pH 1.2, pH 4.5 and pH 6.8) using USP Apparatus II (paddle) at 50 rpm with 500 ml of test medium, was performed and the profiles are compared. The actual numerical results have been provided and show that the dissolution profiles of the 100 mg vs 50 mg and 100 mg vs 30 mg are not similar in all pH media. The profiles show that dissolution is rapid, with

all capsules reaching greater than 85% mean release by 30 minutes in all media. The applicant claimed that although the 100 mg capsule has a similar profile shape to the 30 mg and 50 mg capsules, it has a delayed start due to a slower capsule rupturing time (larger capsule shells take longer to rupture and release the active substance). F2 calculations cannot be performed due to high %RSD values at early time points, and F2-bootstrap results are below 50.

The applicant argued that the observed delay in capsule rupturing in dissolution is justified by disintegration data (different strength ritlecitinib capsules disintegrate at different rates according to their capsule size, with the size #3 (50 mg) capsules disintegrating faster than the size #1 (100 mg) capsule) but that different capsule rupture times have no *in vivo* relevance, based on the results of the rBA study B7981022. In this study, a standard ritlecitinib 100 mg capsule with an over-encapsulated 100 mg capsule (inside a size #0 capsule shell) showed the same relative bioavailability, despite the significant difference in capsule rupture times highlighted by the dissolution conditions. This was not considered a relevant study as it only justifies that a (100 mg) capsule with a slower dissolution/longer disintegration time had the same relative bioavailability as a regular (100 mg) capsule. It does not justify if a capsule with a faster disintegration also has the same bioavailability as a regular (100 mg) capsule. A PBPK model was used to simulate BE trials comparing 100 mg capsules to 2 x 50 mg capsules. The PBPK model was developed using Simcyp® platform (version 22, release 1) with input parameters derived from *in vitro* and *in vivo* studies and was based upon physiologically based principles and justifiable assumptions. Model verification shows a good prediction, i.e. observed and predicted ratios for the capsule formulations fell within 1.08 – 1.20 for Cmax and 0.99 – 1.36 for AUC. Simulations showed that the 50 and 100 mg capsule can be considered bioequivalent. In addition, comparative performance of ritlecitinib 50 mg and 100 mg capsules was assessed using the TIM-1 gastrointestinal simulator. Although the TIM-1 gastric dissolution profiles confirmed the faster dissolution from the 50 mg capsule, the cumulative bio-accessibility of 50 mg and 100 mg ritlecitinib capsule was comparable.

Overall, pharmacokinetic data and simulations showed that, although the faster *in vitro* dissolution observed for the 50 mg capsule compared to the 100 mg capsule, the 50 and 100 mg capsule can be considered bioequivalent *in vivo*. Therefore, the bridge between the 50 mg clinical trial tablet and the 50 mg capsule intended to be marketed is supported and the biowaiver is acceptable.

The QC dissolution test conditions have been adequately justified. The discriminatory power of the dissolution method has been demonstrated.

A discussion related to the observed discrepancies in dissolution profiles between six batches of the final finished product formulation was provided. The applicant justifies that the observed differences between the dissolution profiles are linked to the variability in the disintegration time of individual HPMC capsule shells (which causes high variability of dissolution results in the first sampling points) and not to the lack of reproducibility of the manufacturing process. Considering the manufacturing process (direct encapsulation) and that it has been demonstrated that the slower disintegration of capsule shells does not significantly impact the bioavailability of ritlecitinib (rBA study B7981022), the provided justification is considered acceptable.

The proposed manufacturing process for ritlecitinib capsules is a conventional encapsulation process consisting of three main steps – blending, screening and encapsulation. Risk assessment was used to investigate the potential relationship between the processing step and quality attributes.

The finished product manufacturer performed an intermediate holding time study on the final blend stage of ritlecitinib 50 mg capsules. The storage time was 63 days. The storage time confirms that a total production time of 60 days can be applied for ritlecitinib 50 mg capsules.

The primary packaging is a high-density polyethylene (HDPE) bottle with a silica gel desiccant and polypropylene closure or OPA/Al/PVC/Al blisters. The packaging materials are commonly used for capsules. The specifications are acceptable as they contain tests for Identity, and IR spectra results have been provided. Certificates of Analysis / Conformity have been provided. The materials comply with EU directive EU 10/2011 and, where applicable, with Ph. Eur. requirements. This is considered acceptable.

The amount of desiccant of 1 gram of silica gel has been justified. The effectiveness of the nature and the recorded quantity of desiccant has been discussed in relation to the maximum expected moisture retention during packing, the shelf life and normal use. The risk of accidental swallowing of the desiccant capsule is negligible, as it was demonstrated (with pictures) that the HDPE desiccant canister is sufficiently visually distinguishable from the product and bears a warning statement ('DO NOT EAT').

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 finished product is manufactured at Pfizer Manufacturing Deutschland GmbH, Freiburg im Breisgau, Germany. The manufacturing process consists of six main steps: blending, screening, blending, encapsulation, weight sorting and packaging. The process is considered to be a standard manufacturing process.

The typical drug product blend batch size manufactured at Pfizer Freiburg, Germany, is a defined batch size range. As the manufacturing process is considered a standard process, the concept of a batch size range is acceptable.

Factorisation (i.e. adjusting the quantity of the active substance for potency) is applied, with cellulose microcrystalline as the excipient used to compensate. This is acceptable as cellulose microcrystalline is a filler of the capsule blend. The capsule shells are ready-made.

The proposed in-process controls are adequate for this type of manufacturing process and are acceptable.A validation protocol has been provided for the validation of the manufacturing process using three consecutive batches. The protocol is acceptable. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. As per the Guideline on manufacture of the finished dosage form, the applicant does not apply prolonged storage of the bulk capsules.

2.4.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (LC, UV), assay (LC), degradation products (LC), dissolution (UV), uniformity of dosage units by weight variation (Ph. Eur.), water activity (Ph. Eur.), microbial limits (TAMC, TYMC and *E. coli*) (Ph. Eur.).

The limit for assay at release and shelf-life are acceptable. Based on the maximum daily dose of 50 mg (one capsule per day), the ICH identification threshold is 0.2%. The limit for total impurities is acceptable based on the limits for individual impurities and stability data.

The limit for dissolution is acceptable based on the results of the 100 mg capsule batch used in the BE study.

Two degradation products have been specified. Limits are stated to have been based on batches used in toxicological studies.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches of 50 mg and 100 mg ritlecitinib capsules using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested in a Major Objection) 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). Specific details of the expected nitrite level in each component of the finished product have been provided and the details on the analytical procedure (LC-UV/MS) used for the analysis of nitrosamines in WHO NAP test and acetic acid standard conditions, such as the limit of detection and limit of quantitation, as well as the results of the experiments performed to test the reactivity of the active substance and its impurities towards nitrosation, have been provided. The results of these experiments have been discussed in the context of the conditions existing in the finished product and are considered extreme / forced degradation conditions. The potential risk of nitrosamine formation from packaging has also been addressed. The overall risk for nitrosamine formation is negligible. The API-specific nitrosamine impurity has been shown to be not detected (LOD < 10% of AI of 18 ng/day), and no further control is considered necessary. Overall, based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The omission of tests for water content and chiral purity has been adequately justified.

Water content is not included on the specification since water activity has been selected as the analytical test to measure moisture levels for the product.

Ritlecitinib has two chiral centres, neither of which is adjacent to a strong electron withdrawing group. Both chiral centres have to isomerise to form the enantiomer. The finished product HPLC impurity method is capable of detecting the two diastereomers, which have not been observed under long term, accelerated stability studies or forced degradation studies. Based on the above, no control or acceptance criterion for the enantiomer of ritlecitinib is proposed.

The analytical procedures used have been adequately described and appropriately validated in accordance with the ICH guidelines, including the microbiological procedures for which suitability in the presence of the finished product has been shown. The stability indicating the nature of the proposed analytical procedure for assay and degradation products in the finished product has been demonstrated. Satisfactory information regarding the reference standards has been presented.

Batch analysis results are provided for six batches of ritlecitinib 50 mg capsules, supplemented by data from seven batches of 30 mg capsules and six batches from 100 mg capsules 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

The primary registration programme consists of three pilot scale batches of the 50 mg strength, plus three pilot scale batches of each of the 30 mg (not proposed for marketing), and 100 mg (not proposed for marketing) capsule strengths. The batches were manufactured at Pfizer, Freiburg, Germany using the commercial formulation process and contain active substance lots prepared using the commercial processes. The batches of Litfulo are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Eighteen months stability data at 25°C / 60% RH and 30°C / 65% RH (HDPE bottle) or 30°C / 75% RH (blister) and six months at the accelerated condition of 40°C / 75% RH are provided.

A supplementary stability programme is also included, referred to as Process Understanding, which consists of one batch of each of the 30 mg, 50 mg and 100 mg capsule strength, manufactured at Pfizer, Freiburg, Germany, containing an active substance lot prepared using the commercial processes. Twelve months stability data at 25°C/60% RH and 30°C / 65% RH (HDPE bottle) or 30°C / 75% (blister) RH and six months at the accelerated condition of 40°C / 75% RH are provided.

Samples were tested for appearance, assay, degradation products, dissolution, water content, water activity and microbiological attributes. The analytical procedures used are stability indicating. Except for the assay and degradation products procedure, the analytical procedures proposed for release are used during the stability study. An earlier version of the HPLC procedure for assay and degradation products was used up to 12 months of the stability study and for the forced degradation study. Validation data are provided for the analytical procedure that was used during the first 12 months of the stability study.

The primary registration and supplementary stability studies have demonstrated that degradation products are the only attributes trending on stability. No stability trends have been observed for appearance, assay and dissolution.

In addition, one batch of each capsule strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples were tested for appearance, assay, degradation products and dissolution. No significant changes were observed in assay, degradation products and dissolution for samples directly exposed to light. Some fading of the blue capsule color was observed for samples directly exposed under ICH Option 2 and 2 x ICH Option 1 conditions. This justifies the proposed storage condition "Store in the original package in order to protect from light".

Forced degradation experiments were performed on ritlecitinib 30 mg, 50 mg and 100 mg capsules to establish the extent and nature of potential degradation pathways and to confirm the suitability of the LC assay and purity method. The stress conditions included thermal/low humidity, thermal/mild humidity, thermal/high humidity, and photolysis studies. Samples were analysed for potency and degradation products, as well chiral purity. The studies showed an increase in degradation under thermal stress conditions. The degradation was more pronounced under thermal / high humidity stress conditions. These studies confirm that the assay and purity method is selective and stability indicating. There was no chiral conversion observed in any of the forced degradation studies.

In-use stability studies have been performed with several batches of 50 mg capsules packaged in HDPE bottles, in line with the *CHMP Note for Guidance on in-use stability testing of human medicinal products*. The current in-use study lasted 60 days, which is acceptable given of EMA Q & A on the design of in-use stability studies (2 containers x 28 count). The capsules were tested for appearance, assay, degradation products and dissolution and water content. Acceptable appearance, assay, degradation products and dissolution data were obtained after the bottles were left opened for 60 days

stored at 30°C/65% RH for each of the time points. Water content did not significantly increase. Based on the data available, an in-use period is not considered necessary for the SmPC.

Based on available stability data, the proposed shelf-life of 30 months without any special temperature storage condition, but stored in the original package in order to protect from light as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

2.4.3.5. Adventitious agents

It is confirmed that the lactose 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.

No other excipients derived from animal or human origin have been used.

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. Two major objections were raised by the CHMP during the procedure on: 1) the biowaiver of strength, and the supporting *in vitro* dissolution comparisons, and on 2) the risk assessment concerning the potential presence of nitrosamine impurities in the finished product. These were satisfactorily addressed by the applicant by providing additional data and further justifications.

The applicant has applied QbD principles in the development of the active substance Design spaces have been proposed for several steps in the manufacture of the active substance. The design spaces have been adequately verified.

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. Recommendations for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

Ritlecitinib (PF-06651600) is an orally bioavailable, selective, covalent, irreversible inhibitor of JAK3 and the TEC kinase family.

Within the scope of the pharmacodynamics assessment of ritlecitinib, the applicant conducted a series of primary, secondary and safety pharmacology studies. At the time of marketing authorisation application, the dossier consisted of eighteen *in vitro* and four *in vivo* primary pharmacology studies, four *in vitro* secondary pharmacodynamics studies and two *in vitro* and four *in vivo* safety pharmacology studies. In addition, a research article from Dai et al., 2021 was attached discussing the effect of ritlecitinib in an AA animal model of disease.

In addition, the applicant submitted an extensive non-clinical programme to examine the pharmacokinetics (PK) in relevant non-clinical animal species and in humans, including investigations on ADME and the potential of ritlecitinib and its major plasma metabolite M2 to induce PK drug-drug interactions (DDI). In particular, 5 study reports on analytical methods and validations, 4 absorption studies, 7 distribution studies, 7 metabolism studies, one excretion study, and 19 non-clinical PK drug interaction studies were submitted.

The applicant submitted an extensive toxicological programme. Specifically, 4 single dose toxicity studies, 7 repeated dose toxicity studies in rats and dogs (including one *in vivo* micronucleus study), 3 *in vitro* genotoxicity studies, 4 carcinogenicity studies (including 2 dose-range finding studies) in rats and mice, 1 fertility study in rats, 4 embryo-fetal development (EFD) studies (dose-range finding and pivotal) in rats and rabbits, 1 pre- and postnatal development (PPND) study in rats, 1 immunotoxicity mouse study, 5 exploratory mechanistic studies, 15 impurity qualification studies (*in vivo* and *in vitro*), and 1 phototoxicity study in rats were submitted.

Genetic toxicity studies included a standard battery of *in vitro* assays (bacterial reverse mutagenicity, micronucleus in TK6 cells), mechanistic follow-up testing for *in vitro* micronucleus test results, and an *in vivo* blood reticulocyte micronucleus assay in rats conducted as part of the 8-week pivotal repeat-dose toxicity study.

The potential for carcinogenicity was assessed in a 6-month study in transgenic rasH2 (tg/wt) mice and a 2-year study in rats in accordance with ICH Guidelines M3(R2), 2009. Doses for the 6-month study in transgenic mice were selected based on results from a 2-week study in C57BL/6NTac mice and a 1-month study in rasH2 (wt/wt) mice. Design and doses for the 2-year carcinogenicity study in rats were selected based on results from the 6-month toxicity study in rats.

Developmental and reproductive studies were completed in rats and rabbits. These included a fertility and early embryonic development study in male and female rats, DRF and pivotal EFD studies in pregnant rats and rabbits, and a pre- and postnatal development study in rats. Rats and rabbits were selected for the evaluation of reproductive and developmental toxicity because of the extensive background knowledge accumulated in these species, and because they have been proven susceptible to the effects of developmental and reproductive toxicants. A GLP-compliant juvenile toxicity study in juvenile male and female rats with dose administration on PND 10-60 with a 2-month recovery to examine postnatal growth and development and potential effects on bone and nervous system was submitted upon CHMP's request.

An *in vivo* immunotoxicity study was conducted in mice (mouse allergy model) to characterise the risk for hypersensitivity reactions, and phototoxicity was evaluated in rats based on light absorbance within 290-700 nm. In line with ICH M7(R1), 2018, a 13-week impurity qualification toxicity study was

conducted in rats to qualify potential drug substance and drug product impurities. Several potential impurities were evaluated in *in vitro* bacterial mutagenicity assays. Other impurities were evaluated and qualified or appropriately controlled based on ICH quality guidelines and process knowledge.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Potency and selectivity of ritlecitinib and its main metabolite PF-07034562 against human Janus kinases (JAK1, JAK2 and JAK3) and tyrosine kinase (TYK2) was investigated in a calliper enzyme assay (study number 184021 and 123643, respectively). In addition, activity of ritlecitinib against a panel of further protein kinases (>300) was evaluated in kinase screening assays (Z'-LYTE Screening Assay and LanthaScreen assay; study number 151236).

Inhibitor potency of ritlecitinib by covalent inactivation (k_{inact}/K_i) was determined for JAK3 and several other kinases such as BTK, BLK, BMX, ITK, TEC, SLK, FGR, and FLT3 by a time-resolved Förster resonance energy transfer (TR-FRET) assay, except for TXK where a classic pyruvate kinase/lactate dehydrogenase (PK/LDH) coupled enzyme assay was utilised (study number 184157).

In study number 101033, the nonspecific chemical reactivity of ritlecitinib to recombinant human serum albumin (HSA) was investigated by detecting covalent adduct formation via mass spectrometry.

Generally, the primary cell potency of ritlecitinib was investigated in lymphocytes and whole blood. The potency of ritlecitinib to inhibit cytokine-mediated STAT phosphorylation was investigated in human peripheral blood mononuclear cells (PBMC; study number 184605), human whole blood (hWB; study number 184417) and whole blood of rats and dogs (study number 102317) by flow cytometry.

The effect of ritlecitinib on proinflammatory cytokine production was investigated in LPS stimulated human monocytes and macrophages by measuring levels of IL-1β, IL-6, and TNFα using a Meso Scale Discovery (MSD) multiplex cytokine kit and compared to the effect of JAK1 and pan-JAK inhibitors (study number 185220). In addition, study 185307 examined the influence of ritlecitinib on IL-27 primed and with TNFα or IL-1β stimulated macrophages, again compared to a JAK1 inhibitor.

In study number 044630, ritlecitinib's effect on differentiation and expansion of human Th1, Th2, Th17 and B cells was evaluated by monitoring the production of IFNγ, IL-5/IL-13, IL-17A and IgG, respectively.

Cellular potency of ritlecitinib against BTK and ITK, both members of the TEC family kinases, was assessed by measuring B cell receptor (BCR) and T cell receptor (TCR) mediated upregulation of the cell surface marker CD69 in human peripheral blood mononuclear cells (PBMC) and $CD4^+$ T cells (study number 023747).

The potency of ritlecitinib to inhibit the *in vitro* functional activity of activated human NK cells and CD8+ T cells was investigated by flow cytometry, measuring the cytolytic granule protein (CD107a) on the cell surface, and intracellular IFN-γ (study number 011358).

In study number 090414, the potency of ritlecitinib on cytokine-mediated phosphorylation of signal transducer and activator of transcription (STAT) proteins was evaluated in various cell types.

The occupancy of JAK3 and TEC kinase family by ritlecitinib in human peripheral blood mononuclear cell (PBMC) lysates was measured by using a clickable probe (a close analogue of ritlecitinib/PF-06651600) in a TMT-10plex mass spectrometry assay (study number 023828).

Kinase domains of Human JAK3 and TEC kinase family proteins were defined by databases (e.g. UniProt, NCBI RefSeq) and/or derived from Gnomon-predicted gene models (Souvorov, 2010) and compared to their corresponding canine and rat orthologous.

Study number 094745 compared the effects of several JAK inhibitors (pan JAKi, JAK1i, JAK1/TYK2i and ritlecitinib as JAK3 inhibitor) on thrombopoietin and interleukin 6 signalling and cell expansion in megakaryocyte precursor cells by flow cytometry.

The effect on the clearance of thrombopoietin (TPO) by human platelets was investigated for five JAK inhibitors, including ritlecitinib (study number 033455), because JAK2 is known to be mainly involved in TPO and platelet homoeostasis.

To assess the efficacy and pharmacodynamics (PD) response of ritlecitinib *in vivo*, several animal models of inflammatory and autoimmune diseases were used (e.g., rats with adjuvant-induced arthritis (study number 090652), chemically induced inflammatory bowel disease (IBD) mouse models (study number 181316), a mouse adoptive transfer model of inflammatory bowel disease (IBD) (study number 100542) and an experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis (study number 085612).

The research article of Dai et al., 2021 discussed the PD of JAK inhibitors in a mouse model of AA. The effect of ritlecitinib at a dosage of 30mg/kg/day, intravenously administered via an osmotic pump, on disease onset (4 weeks treatment) and disease progression/revision (12 weeks treatment) was investigated in C3H/HeJ skin-grafted mice. Furthermore, topical administration of ritlecitinib [2% (w/w)], twice daily for 12 weeks in C3H/HeJ mice with long-standing AA, was also investigated.

The results of the potency and selectivity assays (study numbers 184021 and 151236) indicate a high selectivity of ritlecitinib for JAK3 (IC_{50} of 0.346 nM at the apparent ATP and IC_{50} of 33.1nM at 1mM ATP) and, to a lesser extent, for protein kinases as TXK, TEC, BMX and BTC with a CYS at the same position as CYS 909 in JAK3. The lowest selectivity ratios over JAK3 could be determined, with 83.8 for BMX at the apparent K_m for ATP and 5.9 for TXK at 1mM ATP. The results of study number 123643 revealed no PD activity for the main metabolite M2.

Kinetic parameters (k_{inact}, K_i and k_{inact}/K_i), describing the covalent adduct formation and; therefore, inhibitor potency of ritlecitinib with selected kinases, underline the selectivity of ritlecitinib for JAK3 (k_{inact}/K_i ratio of $3.68x10^5 M^{-1}s^{-1}$). Only kinases containing a cysteine proximal to the ATP binding pocket at the same position as JAK3 showed irreversible covalent adduct formation to ritlecitinib, but with lower k_{inact}/K_i ratios (e.g. $1.03x10^4 M^{-1}s^{-1}$ for BMX) compared to JAK3 (study number 184157).

2% of human serum albumin (HSA) was found to form adducts at the highest concentration of 320µM ritlecitinib, whereas the positive control canertinib even showed traces of adduct formation at the lowest tested concentration of 1µM (study number 101033). Therefore, no adduct formation with HSA was noticed at the expected unbound Cmax of 1.1µM ritlecitinib for a clinical daily dose of 50 mg.

Ritlecitinib inhibited the JAK1/JAK3 signalling pathway in IL-15 stimulated human PBMCs (IC_{50} 51.7nM) and hWB (IC_{50} 198nM) and in IL-21 stimulated hWB (IC_{50} of 362nM). Minor or almost negligible inhibition was observed for JAK1/TYK2 (IC_{50} 12106nM) and JAK1/JAK2/TYK2 (IC_{50} 17823nM) signalling pathways in PBMCs. No effect could be demonstrated for other cytokines/signalling pathways, neither in PBMCs nor in hWB. Comparison of IC_{50} values obtained in IL-15 and IL-21 stimulated whole blood of humans (IC_{50} 198nM and IC_{50} of 362nM, respectively), rats (137nM and 302nM, respectively) and dogs (170nM and 212nM, respectively) indicate a similar potency of ritlecitinib to inhibit STAT phosphorylation (study numbers 184605, 184417 and 102317).

Ritlecitinib as JAK3 selective inhibitor did not change proinflammatory cytokine levels (IL-1β, IL-6, and TNFα) in LPS-stimulated macrophages. Furthermore, ritlecitinib could not reverse the IL-27-mediated effects in study 185307, compared to a JAK1 inhibitor.

As shown in study 044630, ritlecitinib potently inhibited the production of IFNγ, IL-5/IL-13, IL-17A and IgG in Th1, Th2, and Th17 (during the differentiation phase) and human B cells (IC_{50} values of 34, 17.1/24.1, 211 and 86nM, respectively), as well as in Th1 and Th17 differentiated cells (49 and 278 nM, respectively).

Some inhibitory potential of ritlecitinib for the TEC family kinase members BTK (IC_{50} of 344nM) and ITK (IC_{50} of 380nM) was observed in human PBMC and $CD4^+$ T cells (study number 023747).

Ritlecitinib inhibited human NK and CD8+ T cell activity in study number 011358, represented by IC_{50} values for CD107a+ of 509nM and 210nM in NK and CD8+ cells, respectively and an IC_{50} value of 188nM for intracellular IFN-γ production in both cell types. This effect was supposed to be ITK dependent, according to the applicant.

In the cellular potency assay (study number 090414), ritlecitinib showed its most inhibitory activity on IL-4-induced STAT6 phosphorylation (via JAK1/JAK3 signalling) in T-cells (IC_{50} value of 226nM), whereas in B-cells an IC_{50} of 1000nM was observed and in monocytes and HT-29 cells the IC_{50} values increased up to >20000nM. Only a minor effect was observed on IL-31 mediated STAT3 inhibition in THP1 cells (IC_{50} of 4400nM, JAK1/JAK2 signalling) and no inhibitory potential was found on IL-13 (via JAK1/JAK2/TYK2, STAT6) and IL-22 (via JAK1/TYK2, STAT3) induced STAT phosphorylation (IC_{50} >20000nM).

The occupancy assay (study number 023828) revealed an OC_{50} of 73nM ritlecitinib for JAK3, and similar values for the TEC kinase family members BTK, BMX and TEC, whereas for ITK and RLK OC_{50} values were observed to be 2-fold higher.

Within the scope of the sequence homology analysis, canine JAK3 was found to be 94% identical to human JAK3 and rat JAK3 to 87% identical to human JAK3.

As demonstrated in study 094745, ritlecitinib led to weak inhibition of TPO-induced STAT5 and IL-6-induced STAT3 phosphorylation and expansion of $CD41a^+$ cells, with IC_{50} values greater than 20000 (in contrast to the other JAK inhibitors used in this assay).

The inhibitory potential of ritlecitinib on TPO clearance investigated in study number 033455 was low (IC_{50} value of >20000nM), which is supported by the minor potential to inhibit JAK2 (IC50 of >10000nM reported in study number 184021). Overall, the higher the inhibitory concentration at 50% activity for JAK2 of a compound, the lower the inhibitory potential on TPO clearance. However, the more potent JAK2 inhibitors showed only a maximum of about 10% inhibition of TPO clearance.

In terms of the PD *in vivo* data, ritlecitinib showed to have immunosuppressive potential, reflected by improvements of disease parameters, in the adjuvant-induced arthritis rat model (study number 090652), in the chemically induced inflammatory bowel disease mouse model (study number 181316) and the mouse model of multiple sclerosis (study number 085612).

Intravenously administered ritlecitinib at 30mg/kg prevented the onset of AA by effectively reducing AA-associated skin inflammation (e.g. supported by data from immunofluorescence and flow cytrometric analysis) and avoiding hair loss in C3H/HeJ skin grafted mice. Additionally, i.v. treatment with ritlecitinib at 30mg/kg effectively reversed AA, again by reducing AA-associated skin inflammation, demonstrated by suppression of T cell proliferation and function. Interestingly, twice daily topical administration of ritlecitinib (2% w/w) showed to be highly effective in the reversal of AA in C3H/HeJ skin-grafted mice as well (Dai et al., 2021).

2.5.2.2. Secondary pharmacodynamic studies

Secondary PD studies included a screening panel for possible (off) targets, including several receptors, ion channels, transporters and enzymes (study number 100009194), an *in vitro* assay in PAE-KDR cells, investigating the effect on VEGFR2 phosphorylation (study number PF-06651600-00-0010 pVEGFR_6-1-2013) and a Z´-LYTE screening assay for Abl kinase (study number 4647_31278). In addition, further secondary PD activities of ritlecitinib were investigated within the scope of primary PD studies (studies 151236, 184021 and 184157).

Data of the screening panel for off-target effects of ritlecitinib (at 10µM) revealed a >50% of a maximal inhibitory response for Abl kinase (83.2%), EGFR kinase (83.0%) and VEGFR2 kinase (93.5%) with corresponding IC_{50} values of 2800nM, 2200nM and 1300nM, respectively (study number 100009194). In the InCell Kinase assay, ritlecitinib did not inhibit VEGFR2 phosphorylation (IC_{50} >30µM) (study number PF-06651600-00-0010 pVEGFR_6-1-2013), and only a minor inhibitory potential of ritlecitinib for Abl kinase was observed (about 15% inhibition at 30µM), with an IC_{50} >30µM (study number 4647_31278).

2.5.2.3. Safety pharmacology programme

Two GLP-compliant and two non-GLP-compliant safety pharmacology *in vivo* studies and one GLP- and one non-GLP-compliant *in vitro* assay were submitted.

Neurofunctional and pulmonary effects of ritlecitinib were investigated in male Wistar Han IGS rats with each 24 animals receiving vehicle or ritlecitinib at 75, 175, or 400 mg/kg as a single dose via oral gavage (6 animals/group) (study number 14GR139).

Two *in vitro* safety pharmacology studies were conducted in hERG gene transfected Chinese Hamster Ovary (CHO) cells (study number 14GR206) and hERG cDNA stably transfected human embryonic kidney cells (HEK293) (study number 180319.QHJ) to assess ritlecitinib's potential to inhibit the hERG potassium channel current to predict *in vivo* QT prolongation.

Cardiovascular effects of ritlecitinib were investigated in Wistar Han Rats (n = 8/group), receiving 0 or 125 mg/kg of the study drug on three consecutive days by oral gavage (study number 13LJ074).

Two cardiovascular safety studies, one compliant to GLP, were conducted in conscious, unrestrained, radiotelemetry implanted male beagle dogs.

In study 14GR078, each of the four dogs received vehicle control, 6mg/kg ritlecitinib or 20mg/kg ritlecitinib on two consecutive days and within one week.

Then, in the GLP-compliant study 14GR140, each dog (n=4) received four treatments of single doses of 0, 3, 15, and 45 mg/kg of ritlecitinib via oral gavage with a washout phase of at least 6 days between the treatments.

With one exception, the results of the safety pharmacology study 14GR139 revealed no statistically significant changes between the control group and treatment groups, neither in neurofunctional nor in pulmonary effects, measured by functional observational battery (FOB), body temperature and locomotor activity or tidal volume, respiratory rate and minute volume, respectively. One value of a single animal of the 400 mg/kg ritlecitinib dosage group led to a higher mean respiratory rate at 240 minutes post-dose, which was not considered relevant due to its late occurrence.

In study 14GR206, significant inhibition (12.9%) of the hERG potassium current in hERG gene transfected CHO cells was achieved with the highest tested concentration of ritlecitinib at 30µM with an IC_{50} value for hERG current inhibition of >30µM ritlecitinib. In hERG cDNA stably transfected HEK293

cells (study number 180319. QHJ), hERG was statistically significantly inhibited at concentrations of 100µM and 300µM ritlecitinib (16.5% and 31.0%, respectively), but not at the lowest concentration of 30µM. The IC_{50} value of ritlecitinib on hERG inhibition was estimated to be >300µM in this study.

In the non-GLP cardiovascular (CV) study in rats (study number 13LJ074), an increase in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) was noticed after the first administration of 125mg/kg ritlecitinib on day 1 (max. of +5mmHg for SBP), whereas a decrease in SBP, MBP (max. of-4.2mmHg for SBP) and temperature (max. of -0.5°C) was observed on study day 3, each compared to vehicle control.

In the non-GLP CV safety study in dogs (study number 14GR078), significant and test-article-related decreases in systolic (-4 to -7 mmHg), diastolic (-3 to -4 mmHg) and mean blood pressure (-3 to -5 mmHg) were noticed for animals treated with 20mg/kg ritlecitinib and in heart rate values (-5 to -11 bpm and -4 to -12 bpm, respectively) for both doses at 6 and 20mg/kg. Some increases (+4 to +7 msec) in the QT-Interval were seen as well (6 and 20mg/kg); however, for the corrected QT-Interval (QTc) no changes were observed.

Data from the GLP-compliant CV safety study in beagle dogs (study number 14GR140) revealed no ritlecitinib-related, significant changes in telemetry data at the lower doses of 3 and 15mg/kg. A significant and test-article-related increase in heart rate (HR, +15 bpm) and a decrease in QT-Interval (-11 msec) was observed 0.5 to 3.5 hours post-dose. However, the corrected QT Interval (QTc) did not indicate any ritlecitinib-related changes compared to values obtained from vehicle-treated animals. Ritlecitinib concentrations in plasma increased dose-proportionally 4 hours post-dose. A C_{max} of 12800ng/ml and T_{max} of 1.7 hours at 45mg/kg could be determined.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamics drug interaction studies were performed by the applicant.

2.5.3. Pharmacokinetics

Methods of analysis

In terms of non-clinical analytical methods and validations, the applicant submitted five GLP-compliant validation reports on the LC-MS/MS analyses applied for the detection of ritlecitinib in mouse, rat, rabbit and dog plasma (study 021727, study 095401, study 083814 and study 095221, respectively), the non-clinical animal species used for experimentation in the submitted dossier. Furthermore, a qualification assay was submitted for the detection of M2 in rat plasma (study 202346MQSMB_PGC).

In the submitted validation reports, intra- and inter-assay accuracy and precision (evaluated with regular QC samples, dilution QC samples, and transparency assessments), calibration linearity, reproducibility, stability (processed sample stability, benchtop stability, freeze/thaw stability, long-term storage stability, working solution stability), matrix effects, selectivity and carryover were examined. Finally, in the submitted qualification study of M2 in Wistar Han rat plasma, the applicant qualified accuracy and precision (of regular QC and dilution QC samples), linearity of the calibration range, inter-lot selectivity, benchtop stability, freeze/thaw stability, matrix effects, extraction recovery and reinjection reproducibility. The submitted validation reports generally demonstrated that the evaluated validation endpoints generally proved to be acceptable when compared with their pre-specified limits. Therefore, the applied LC-MS/MS methods can reliably detect ritlecitinib in non-clinical animal plasma.

Absorption

In terms of absorption, the applicant submitted 3 single dose pharmacokinetics (PK) studies and one repeated dose PK study. Absorption after oral administration was also assessed in the frame of toxicokinetic evaluations.

In study 152020, the PK of ritlecitinib were examined in male SD rats (n=2 per group) after i.v. injection (0.71 mg/kg) or after oral administration (3 mg/kg). Furthermore, in one of the groups in this study (n=4), biliary and urinary excretion of ritlecitinib was studied after i.v. bolus administration of 1 or 1.5 mg/kg ritlecitinib. Similarly, in study 145444, the PK of ritlecitinib were examined after i.v. (3 mg/kg) or oral (30 mg/kg) administration to male C57BL6 mice (n=3). In study 132012, the applicant examined the PK of ritlecitinib when orally (3 mg/kg) or intravenously (1 mg/kg) administered to male Beagle dogs (n=2 per group). In study 105110, the applicant investigated the PK of ritlecitinib and its metabolite M2 in JVC/CAC surgerised Wistar Hannover rats (n=5 per sex and dose group and sampling point) after oral QD administration of 200 mg/kg ritlecitinib for 7 consecutive days.

Mean oral Tmax levels were rapidly attained in the submitted absorption studies and ranged from 0.25 hours post-dose in the mouse and dog study to 0.42 hours in the repeated dose rat study 105110 and 0.5 hours post-dose in the single dose rat study 152020. This demonstrates rapid enteral absorption of orally administered ritlecitinib in the tested non-clinical species. The Tmax of the major plasma metabolite M2 in the repeated dose rat study 105110 was attained already 1.4 hours post-dose, demonstrating the rapid conversion of ritlecitinib to M2 after gastrointestinal absorption. Efficient gastrointestinal absorption is supported by high calculated oral bioavailabilities in the submitted non-clinical absorption studies, which ranged from 61% in male mice to 85% in male rats and 100% in male dogs. At an equal oral dose (3 mg/kg), these oral bioavailabilities translated into a Cmax at 4100 ng/mL and an AUC_{inf} at 1250 ng*h/mL in male dogs, and a Cmax at 173 ng/mL and AUC_{inf} at 446 ng*h/mL in male rats. In subgroups of these experiments to which ritlecitinib was intravenously administered, clearance, the volume of distribution and plasma $T_{1/2}$ were calculated. Plasma clearance in rodents was high, amounting to 45 mL/min/kg in male mice and even 69 mL/min/kg in rats. These rates are below or similar to the mean liver blood flow in these species, amounting to 90 mL/min/kg in mice and 68.7 mL/min/kg in rats (Davies and Morris 1993). In male dogs, plasma clearance or ritlecitinib was clearly smaller, only amounting to 13 mL/min/kg. This rate is below the hepatic blood flow of dogs, being 30.9 mL/min/kg (Davies and Morris 1993). The fact that clearance in these species is similar to or lower than their respective hepatic blood flow suggests that absorbed ritlecitinib may rapidly be cleared by hepatic pathways (in the case of ritlecitinib through hepatic metabolism). The calculated volumes of distribution were similar between the different species and ranged from 0.84 L/kg in male mice to 1.1 L/kg in male dogs to 1.4 L/kg in male rats. These values suggest that ritlecitinib partitions throughout the total body water. Plasma $T_{1/2}$ values in the investigated species were low and ranged from 0.33 hours in male rats and 1.1 hours in male dogs to 1.3 hours in male mice. These rapid plasma elimination half-lifes together with the rapid Tmax value of M2 in male rats (1.4 hours post-dose) support the notion of rapid hepatic elimination of ritlecitinib via metabolic conversion. Finally, the excretion of unchanged ritlecitinib in urine and bile in male rats proved to be negligible. This further supports that hepatic elimination of ritlecitinib predominates plasma clearance of ritlecitinib in non-clinical animal species.

Distribution

In regard to distribution, 7 studies were submitted.

In the *in vitro* study YDP/067/018, the applicant investigated the partitioning of ritlecitinib between red blood cells and plasma in rat, dog and human whole blood. Similarly, in study YDP/067/369, the

applicant examined the partitioning of M2 in mouse, rat, rabbit, dog and human whole blood. In the *in vitro* study YDP067/032, the applicant examined the protein binding capacity of ritlecitinib in mouse and rabbit plasma. The protein binding capacity of ritlecitinib in rat, dog, monkey and human plasma was evaluated in the *in vitro* study YDP/067/368. Similarly, the plasma protein binding capacity of M2 was evaluated in mouse, rat, dog, rabbit and human plasma in the *in vitro* study YDP/067/368. In study 103503, the applicant conducted a more detailed *in vitro* assessment of the binding of [^{14}C] PF-06651600 to particular human plasma proteins. Specifically, ^{14}C-labelled ritlecitinib was either added to aliquots of pooled human plasma specimens or preparations of albumin, high-density alpha-lipoprotein, fibrinogen, γ-globulin and α1-Acid glycoprotein (at physiologically relevant concentrations). Finally, in study 15647, the applicant examined tissue distribution of ^{14}C-labelled ritlecitinib at 10 mg/kg after oral gavage administration to male pigmented Long-Evan rats in a quantitative whole body autoradiography setup (evaluation of one carcass per time point at 0.25, 0.5, 1, 2, 4, 8, 24, 48, 96, 168, 336 and 672 hours post-dose, and evaluation in separate samples of blood, plasma and the liver of two animals per sampling point at 1, 4 and 24 hours post-dose). No repeated dose tissue distribution study was submitted.

The mean whole blood to plasma concentration ratios for ritlecitinib were 0.985, 1.57 and 1.62 in rats, dogs and humans, respectively (after 1 hour of incubation). Contrarily, the whole blood to plasma concentration ratios of M2 in these experiments ranged between 0.545 in rats and 0.829 in rabbits after 1 hour of incubation. These data demonstrate that ritlecitinib either equally partitioned between red blood cells and plasma (in rat whole blood) or preferably partitioned to red blood cells in dog and human whole blood, whereas its metabolite M2 rather remained in the plasma compartment in all examined species.

Ritlecitinib had a high binding capacity to proteins in mouse and rabbit plasma; specifically, only 22.4% and 28.8% (%CV values of 18.2% and 20.8%) constituted unbound ritlecitinib in mouse or rabbit plasma. Contrarily, the unbound fraction of ritlecitinib in rat, dog, monkey and human plasma in study 154304 amounted to 67.4, 81.9, 86.0 and 86.4, respectively (with the corresponding %CV values being 12.9%, 13.2%, 7.4% and 14.9%). This indicates species-specific differences in the binding capacities of ritlecitinib to plasma proteins, particularly with large laboratory animals (dogs and monkeys) and humans having high unbound fractions of ritlecitinib in plasma. M2 did not bind to plasma proteins; in the plasma specimens of the analysed species, unbound fractions of M2 were all not distinguishable from 1. In human blood, the applicant established that ritlecitinib binding to high-density alpha-lipoprotein, fibrinogen, γ-globulin and α1-acid glycoprotein was below 0.5% of the tested concentration; binding to platelets similarly amounted to <1%. However, binding to albumin amounted to approximately 6% of the total added radioactivity in study 103503. Interestingly, all protein pellet extractions had [^{14}C] counts that were similar to blank incubations after 5 extractions. This suggests that the bound ritlecitinib to plasma proteins in this study was irreversibly bound to plasma proteins. The applicant described that the observed selective binding of ritlecitinib to HSA (human serum albumin) may be explained by the reactivity of ritlecitinib with the free cysteine 34 in HSA, presumably by covalent binding to HSA. This irreversible binding to albumin is not entirely unexpected, as ritlecitinib was designed to react with cysteine 909 within the JAK3 ATP binding pocket and might, therefore, also covalently bind with cysteine residues of other body proteins such as albumin. Furthermore, the TEC family kinases (BTK, BMX, ITK, RLK, TEC) also present a cysteine residue in their catalytic domain at the equivalent position of Cys909 in JAK3 and were also inhibited to various degrees by PF-06651600 in biochemical and cellular assays. The potential safety concerns that might be related to covalent binding of ritlecitinib to off-target body proteins is discussed below.

In the single-dose administration quantitative whole body autoradiography rat study, most Tmax values of the investigated tissues were already reached within the first hour after administration, supporting the rapid enteral absorption of the orally administered ritlecitinib (as was already concluded

in the submitted *in vivo* absorption studies). At the end of the experiment at 672 hours post-dose, radioactivity was still above the quantification in the adrenal gland and its substructures, aorta, blood (cardiac), eye, heart, lens, liver, lung, kidney and its substructures, spleen and uveal tract. However, plasma elimination $T_{1/2}$ was considerably shorter, amounting only to 55.1 hours. As in the LC-MS/MS based rat absorption study 152020, the $T_{1/2}$ after i.v. administration only amounted to 0.33 hours, most of the circulating radioactivity in the whole-body autoradiography rat study were presumably metabolites. The short plasma elimination $T_{1/2}$ in the whole-body autoradiography rat study contrasts considerably with the very long $T_{1/2}$ values measured in many of the investigated tissues. e.g. in plasma and blood, Cmax & Tmax were already reached at 0.25 hours post-dose (being the first sampling point in this study), whereas the AUC_{0-t} value in plasma was much lower than in blood (12.3 vs 476 µg equivalents*hr/g in the liquid scintillation count investigation of group 2 animals, respectively). This demonstrates that within whole blood, ritlecitinib has a much higher tendency to reside (and presumably also accumulate) in blood cells than in plasma. Of note, the irreversible binding of ritlecitinib to haemoglobin could explain this considerable difference. The tissue half-life of the radioactivity associated with ritlecitinib (i.e. originating either from ritlecitinib or from its metabolites) was only 55.1 hours in plasma, but much higher in many investigated organs such as, e.g. the eyes (439.1 hours), the adrenal gland (approximately 488 hours), the cardiac blood (396.7 hours), the spleen (478.1 hours), the pancreas (560.0 hours) and the lung (382.7 hours).

Furthermore, the AUC_{0-t} levels of ritlecitinib and/or its metabolites were only 12.3 µg equivalents*hr/g in plasma, but were much higher in most other organs (e.g. 184 µg equivalents*hr/g in the lungs, 193 µg equivalents*hr/g in the liver, 203 µg equivalents*hr/g in the kidney, 476 µg equivalents*hr/g in the blood, and even 1597 µg equivalents*hr/g in the uveal tract). Both the clearly higher elimination half-lifes and AUC exposures in most of the investigated tissues compared to the plasma demonstrate a strong potential for high steady-state exposure and accumulation of ritlecitinib and/or its metabolites in the tissue compartment at chronic dosing. Also see non-clinical discussion section.

Except for the brain (0.04), spinal cord (0.05), bone (0.56), white inguinal fat (0.84), thymus (0.69), testes (0.58), and nasal turbinates (0.83), the tissue: plasma AUC_t ratios of all evaluated tissues were higher than 1. This demonstrates that partitioning of ritlecitinib to the tissue compartment is, in most cases, favoured. However, the low brain: plasma AUC ratio at ~0.04 demonstrates that penetration of the blood-brain barrier is inefficient in the rat.

The high AUC and long excretion $T_{1/2}$ in the uveal tract suggest melanin-related accumulation. However, this is not associated with phototoxicity, as evaluated in a phototoxicity rat study (study 20075773, presented further below). Furthermore, contrarily to the very high exposure of ritlecitinib and/or its metabolites in the uveal tract (AUC_{0-t} of 1597 µg equivalents*hr/g), AUC_{0-t} levels in the skin were much lower, only amounting to 50 and 63 µg equivalents*hr/g in non-pigmented and pigmented skin, respectively. The low difference in exposure of ritlecitinib and/or its metabolites between non-pigmented and pigmented skin further supports that generalised melanin binding unlikely explains the high measured exposure in the uveal tract. Finally, it was noted that in the lens, the ritlecitinib-related radioactivity did de facto not decrease at all between 8 hours and 672 hours post-dose in study 152020. This was unique in the rat whole body autoradiography study and was not discussed by the applicant. However, as no adverse ocular effects were observed in any of the submitted toxicity studies, no concern was raised.

Metabolism

The applicant submitted 7 metabolism studies.

In the preliminary study 085839, the applicant examined the metabolism of ritlecitinib in rat, dog and human hepatic liver microsomes and isolated cryopreserved hepatocytes, estimated the hepatic burden of covalent binding of ritlecitinib in human hepatocytes, and profiled plasma, urine and bile for metabolites in bile-duct cannulated rats (single i.v. dose 3 mg/kg, from study JAK3-0100-BDC)) and one dog (15-day multiple oral 75 mg/kg/day dose, from study 13LJ111). In study 033226, the applicant attempted to identify the glutathione S-transferase isoforms involved in the metabolism (*in vitro*) of ritlecitinib. Furthermore, in study 011706, the applicant phenotyped the CYP450 isoforms involved in the *in vitro* transformation of ritlecitinib in human liver microsomes into its major oxidative metabolites 302-3 and M4. In study 092809, the applicant performed metabolite scouting with pooled samples from plasma and brain tissues (superior olivary nucleus, cochlear nucleus and left and right hippocampus) collected from the 3-day Beagle dog toxicokinetics study 17GR131 (40 mg/kg/day of ritlecitinib administered to female Beagle dogs (n=4) for 3 consecutive days by oral gavage). In study 040703, the applicant examined the major circulating metabolites of ritlecitinib in pooled human plasma (n=16, day 14 plasma pools) and urine samples (an aliquot from each subjects Day 14 post-dose urine sample was pooled for metabolic profiling) from the multidose clinical study B7981001. Furthermore, in study 085448, the applicant evaluated the routes of excretion and metabolic profiles of ^{14}C-labelled ritlecitinib (200 mg) in plasma and excreta in healthy male human subjects (n=6) after single oral administration. Finally, the applicant examined whether the major human metabolites of ritlecitinib, specifically M2, but potentially also M1, M3 and M4, are formed during the incubations used for bacterial reverse mutation assays in study 111222.

Low levels of glutathione-conjugation related (glutathione, N-acetyl-cysteine, cysteine-glycine and cysteine) and oxidative (single hydroxylations) metabolites were identified in rat, dog and human liver microsomes and isolated cryopreserved hepatocytes. In terms of glutathione S-transferase isoforms involved in the metabolism (*in vitro*) of ritlecitinib, GST A3, GST P1, GST T2, GST Z1, MGST1,2&3 were the most effective isoforms to initiate glutathione conjugation of ritlecitinib (all more than 3-fold than the chemical reactivity of the buffer control). CYP450-mediated hydroxylations of ritlecitinib were observed with the following recombinant human isozymes: CYP 1A1, 1A2, 1B1, 2C8, 2C9, 2C18, 2C19, 2D6 2J2, 3A4, 3A5 and 3A7. CYP3A4/5 caused the largest contribution to oxidative turnover of ritlecitinib in human liver microsome preparations, and CYP2C8 and CYP1A2 contributed to a relevant extent to oxidative metabolism of ritlecitinib in human liver microsomes.

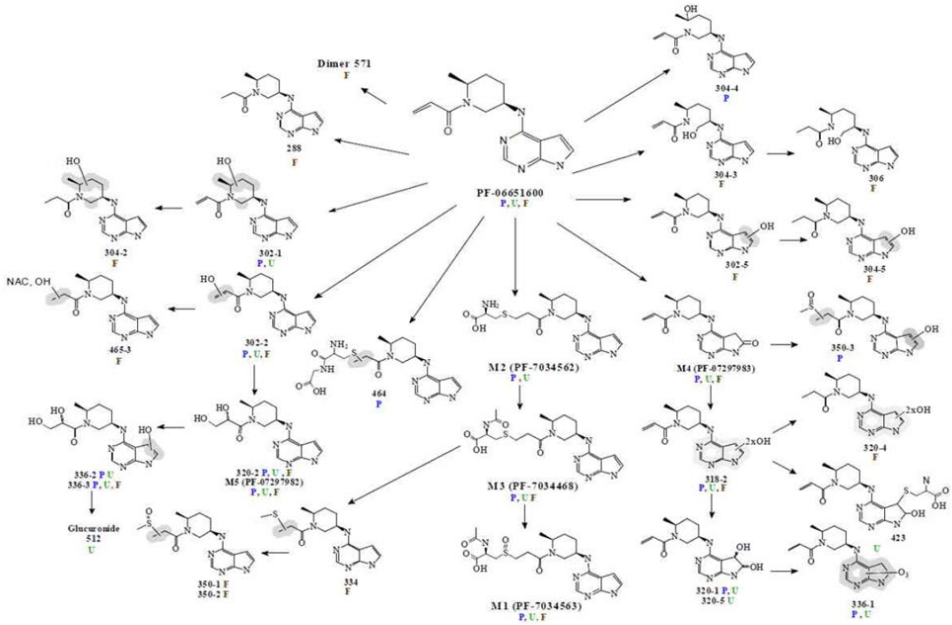
The most important metabolites of ritlecitinib in the rat were hydroxylated metabolites in plasma and glutathione-related metabolites in urine and bile. In the dog, the major metabolites were cysteine conjugates in plasma (specifically the cysteine conjugate M2 and the cysteine-glycine conjugate metabolite 464), a cysteine conjugate in urine, and glutathione, N-acetyl-cysteine, cysteine-glycine, cysteine, and hydroxyl-thiol conjugates in bile. Regarding coverage of human metabolites in non-clinical species, M2 was sufficiently present in plasma and urine in mouse, rat and dog. However, M1 (N-acetylcysteine sulfoxide conjugate) and M3 (N-acetylcysteine conjugate) were only detected in plasma and urine in rodents (rats and mice), but not in dog plasma and urine (with the exception of M3 that was detected in dog urine). Nonetheless, the non-clinical coverage of the main human metabolites in the investigated non-clinical species appears sufficient, as sufficient exposure of the major metabolites was achieved in at least two of the non-clinical species used. Finally, the applicant considered that the chemical conversion of ritlecitinib into M1, M2 and M3 (glutathione conjugation with subsequent derivatisation of the glutathione moiety) does not harbour a toxifying effect (but rather leads to de-toxification and enhanced excretion).

In the dog brain tissues (superior olivary nucleus, cochlear nucleus and left and right hippocampus) that were gathered in study 17GR131, the applicant predominantly detected M2 and ritlecitinib. However, also trace metabolites were detected in the dog brain tissues, specifically the cysteine-glycine conjugate metabolite 464 and different single hydroxylated metabolites. Of note, the

distribution of ritlecitinib was similar between the studied brain tissues. In the dog study 092809, the brain: plasma fraction was 10%, contrasting the clearly lower levels determined in the quantitative whole body autoradiography rat study 15647 in which the radioactivity of ritlecitinib and/or its metabolites in the brain and the spinal cord only made 4% or 5% of the radioactivity in plasma, respectively. As, in addition to ritlecitinib, also its metabolites partitioned to the CNS in dog study 092809, it can be expected that the difference in BBB crossing between the rat and the dog is higher than 2-fold. Based on this comparison, it is apparent that BBB crossing of ritlecitinib and/or its metabolites can vary between species.

The metabolic pathways identified in humans following oral administration of 200 mg are depicted in the Figure 2 below.

Figure 2: Proposed biotransformation of ritlecitinib in humans following oral administration of 200 mg



Furthermore, parent and metabolite profiling of ritlecitinib in humans, mice, rats, and dogs is summarised in the Table 1 below:

Table 1: Parent and metabolite profiling of ritlecitinib in humans, mice, rats, and dogs

Metabolite[a]	m/z	Human[b]			Mouse[c]		Rat[d]		Dog[e]	
		Plasma (% total [^{14}C])	Urine (% [^{14}C] dose)	Feces (% [^{14}C] dose)	Plasma	Urine	Plasma	Urine	Plasma	Urine
PF-06651600	286	30.4	2.7	0.2	√	√	√	√	√	√
M2 (PF-07034562)	407	16.5	4.6	0	√	√	√	√	√	√
M1 (PF-07034563)	465	7.2	4.0	0.1	√	√	√	√	nd	nd
M3 (PF-07034468)	449	6.9	10.3	0.3[f]	√	√	√	√	nd	√
336-3	336	5.9	6.5	0.2	nd	nd	nd	nd	nd	nd
M4 (PF-07297983)	302	5	16.3	0.2	√	√	√	√	√	√
464	464	3.9	nd	nd	nd	nd	nd	nd	√	√
304-4	304	3.5	0	0	nd	nd	nd	nd	nd	nd
M5 (PF-07297982)	320	2.8	3.3	0.3	√	√	nd	√	nd	nd
336-1	336	2.2	0.6	0	nd	nd	nd	nd	nd	nd
320-1	320	2.1	2.3	0.2	nd	nd	nd	nd	nd	nd
336-2	336	1.2	0.7	0	nd	nd	nd	nd	nd	nd
350-3	350	0.9	trace	nd	nd	nd	nd	nd	nd	nd
318-2	318	0.6	1.5	0.2	nd	nd	nd	√	nd	nd
302-1	302	0.2	0.2	0	nd	nd	nd	nd	√	√
320-2	320	0.2	0.6	0.1	nd	√	nd	nd	nd	nd
512	512	Trace	1.1	0	nd	nd	nd	nd	nd	nd
320-5	320	Trace	0.6	0	nd	nd	nd	nd	nd	nd
304-2	304	Trace	0	0.1	nd	nd	nd	nd	nd	nd
304-3	304	Trace	0	0.3	nd	nd	nd	nd	nd	nd
423	423	Trace	2	0	nd	nd	nd	nd	nd	nd
302-5	302	Trace	0	0.1	nd	nd	nd	nd	nd	nd
350-1	350	Trace	0	0.1	nd	nd	nd	nd	√[g]	√[g]
302-2	302	Trace	trace	trace	nd	nd	nd	nd	nd	nd
350-2	350	Trace	trace	0.3[f]	√	√	√	√	√[g]	√[g]
304-5	304	Trace	0	0.2	nd	nd	nd	nd	nd	nd

a. Metabolites listed in order of highest to lowest % total [^{14}C] in human plasma (4 metabolites not detected in plasma shown in Tabulated Summary 2.6.5.9D).
b. Human 200 mg single dose, total recovered dose = 85.6 % (66.1% Urine and 19.5% Feces) (B7981011).
c. CB6F1/Jic-TgrasH2 mouse dosed 200 mg/kg/day PO QD for 3 days (PF-06651600_13Dec17_040703).
d. Wistar Han rat dosed 200 mg/kg/day PO QD for 3 days (PF-06651600_13Dec17_040703).
e. Beagle dog dosed 75 mg/kg/day on Day 15 from Study 13LJ111 (PF-06651600_13Jun14_085839).
f. 350-2 and M3 co-eluted.
g. 350 metabolite seen in dog, but 350-1 and/or 350-2 not resolvable.

In both pooled human plasma and urine, the main metabolites were M1 (N-acetylcysteine sulfoxide conjugate), M2 (cysteine conjugate) and M3 (N-acetylcysteine conjugate). In urine, also minor metabolites were identified, specifically di-hydroxylation, di-hydroxylation with hydrolysis, methyl sulfoxide, hydroxy-methyl sulfoxide and hydroxy N-acetylcysteine metabolites. Of note, no chiral inversion of ritlecitinib was observed in human plasma.

After administration of 200 mg of ^{14}C labelled ritlecitinib to six healthy male volunteers, the mean total recovery of the administered radioactivity was 85.6 % (with a SD of 9.2%) over a period of 240 hours. This indicates an almost complete mass balance but also renders the possibility of long-term retention or even accumulation of a fraction of the administered ritlecitinib and/or its metabolites. 66.1% (SD±13.4%) of the administered radioactivity was detected in urine and 19.5% (SD±4.4%) in faeces, demonstrating that renal clearance of the administered radioactivity predominates in humans. Tmax after oral administration was 0.75 hours, supporting rapid absorption of ritlecitinib after oral administration as already established in the non-clinical absorption studies. The primary plasma clearance pathway was metabolism of the administered ritlecitinib, specifically glutathione-conjugation with subsequent derivatisation of the conjugated moiety and CYP450-mediated oxidation. The predominating ritlecitinib species (ritlecitinib and its metabolites) measured in human plasma (within 48 hours post-dose), urine (within 24 hours post-dose) and faeces (24-96 hours post-dose) are summarised in the Table 1 presented above. Of note, in human urine, ritlecitinib and M2 only made low fractions of the totally administered radioactivity (all below 5%), demonstrating that while both are the major source of radioactivity in the systemic circulation of humans, they are still not effectively excreted (probably demonstrating tubular re-uptake in the kidneys).

Approximately 35% of the plasma-associated radioactivity in healthy male volunteers was non-extractable and associated with the pellet and remains unidentified. This presumably indicates covalent association of ritlecitinib with plasma proteins, as was already identified in the *in vitro* human plasma protein binding study 103503 and suggested in several other studies throughout the non-clinical dossier. Similarly, 49.8% of the total radioactivity detected in faeces was not extractable from the pellet. It is conceivable that this pool partly constitutes covalent adducts of ritlecitinib with proteins from the gastrointestinal passage (e.g. originating from food, or shredded contents of the gastrointestinal mucosa) and covalent conjugates of ritlecitinib with body proteins that have been excreted via bile and ultimately excreted via faeces. Furthermore, from the excretion kinetics of the administered radioactivity in healthy human volunteers, it is apparent that from 96 hours until the end of the experiment (240 hours), no relevant excretion occurred. Therefore, it appears that an important fraction of the administered ritlecitinib had long retention times in humans and is liable for accumulation. This is also presumably related to the already identified covalent binding of ritlectinib to proteins and to the slow tissue elimination half-lives measured in the rat quantitative whole body autoradiography study 15647. Finally, it is noted that excretion of the administered radioactivity considerably varied among the six recruited subjects in study 103503. For example, in one subject, only 58.2% of the administered radioactivity was excreted, whereas in another subject, already 96.2% of the administered radioactivity was excreted between 168- and 192-hours post-dose. Of note, the applicant clarified that low recoveries in this study can be explained by e.g. a documented urine leakage from a collection container, and by non-compliance of a subject with urine collection instructions.

Finally, the major human circulating metabolite M2 is formed in bacteria incubation media that were also used in the conducted Ames tests. While M4 was additionally detected, M1 and M3 were not detected. However, as M1 and M3 are similar glutathione conjugation derivatives than M2, and as for M1-M3 negative bacterial mutagenicity is predicted with the latest Derek Nexus and Sarah Nexus software packages, the applicant does not consider that these conjugation reactions introduce alerting moieties to the ritlecitinib structure.

Excretion

In terms of excretion, one study was submitted.

In study 8448335, the applicant examined whether ritlecitinib is actually excreted after a single oral administration (30 mg/kg) in lactating SD rats (n=16). For that purpose, milk and blood were collected from n=4 rats per time point at 1, 3, 8, and 24 hours post-dose. Excretion into milk was found up to 8 hours post-dose. The milk: plasma ratio was 2.21 (expressed in terms of AUC_{0-t}), demonstrating a net flux of ritlecitinib from plasma into milk. In terms of Cmax, the milk: plasma mean concentration ratio was even 3.63 1-hour post-dose.

Pharmacokinetic drug interactions

In terms of non-clinical pharmacokinetic drug interactions, the applicant submitted 19 *in vitro* studies.

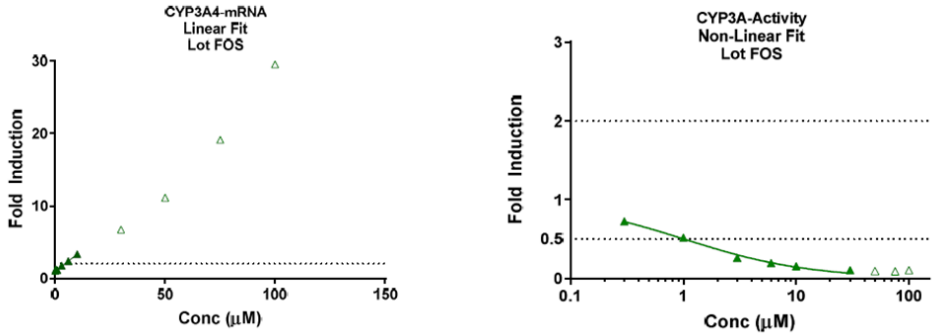
In study XT135092, the applicant examined the *in vitro* potential of ritlecitinib and its metabolites to directly inhibit CYP450 isoforms in human liver microsomes. Then, in study XT133107, the applicant investigated the potential of ritlecitinib to induce CYP1A2, CYP2B6 and CYP3A4 in cultured cryopreserved human hepatocytes. Similarly, in study 022301, the applicant examined the potential of ritlecitinib to induce CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C19 in cultured human hepatocytes. In study 121415, the applicant examined whether ritlecitinib can lead to time-dependent inhibition of the CYP3A4/5 activity in human microsomes. Similarly, in study 123341, the applicant investigated whether CYP1A2 is subject to time-dependent inhibition by ritlecitinib in human liver microsomes. Apart from CYP450 isoforms, the applicant also studied whether ritlecitinib (and/or potentially its metabolites) act as inhibitors of UGT enzyme isoforms in human liver microsomes (study 135124). Additionally, the applicant studied whether human recombinant glutathione S-transferase isoforms are susceptible to inhibition by ritlecitinib (study 094951). Then, the applicant examined whether ritlecitinib could inhibit sulfotransferase-mediated metabolism in human liver cytosol (study 111809). In addition to ritlecitinib, also enzyme inhibition and induction studies were conducted with M2. Specifically, in study 111635 the applicant examined whether M2 acts as a reversible and time-dependent inhibitor of CYP1A2, 2B6, 2C8, 3A4/5, CYP2C9, 2C19, and 2D6 in human liver microsomes. Then, in study 090107, the applicant investigated whether M2 induces CYP3A4, CYP2B6, CYP1A2 and CYP2C in cultured human hepatocytes. Finally, in study 034526, the applicant examined whether M2 is an inhibitor of UGT enzyme activities in human liver microsomes. In terms of transporter protein mediated drug interactions, the applicant examined whether ritlecitinib is an inhibitor of the MDR1, OATP1B1, OAT1B3, OCT2, MATE1, and MATE2K transporters in *in vitro* cellular apical to basolateral transport assays with MDCKII and HEK293 cells (that stably expressed the relevant transporter proteins) (study 103701). Similarly, the applicant examined whether ritlecitinib inhibits the transporter proteins BCRP, OAT1, OAT3, OATP1B1, OATP1B3 and OCT1 in HEK293 cells (which stably expressed the respective transporter proteins) and in BCRP vesicles (study 101345). Then, in study 090524, the applicant assessed whether ritlecitinib is a substrate of the human transporter proteins OATP1B1 and OATP1B3 in an incubation experiment using HEK293 cells that stably express these proteins. Also, in study 112105 (or study 18PFIZP1R1S1), the applicant investigated whether ritlecitinib is a substrate of BCRP (ABCG2) in transfected MDCK cells. Finally, in study Pfizer-76-09Jan2018, the applicant examined whether ritlecitinib is a substrate of BCRP (ABCG2) in transfected MDCK cells. Transporter inhibition studies were also conducted with M2. In study 073254, the applicant examined whether M2 is an inhibitor of the transporters BCRP, MATE1, MATE2K, MDR1, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2 (in HEK293 cells vesicles that express or contain these transporters). Similarly, in study 063458, the applicant examined whether M2 is an *in vitro* transporter substrate of human MDR1 in a bidirectional permeability assay using MDCK cells that over-express human MDR1. Finally, in the

PBPK study 032218, the applicant modelled whether ritlecitinib as a perpetrator could cause clinically relevant DDIs of concomitantly administered drugs.

In human liver microsomes, no relevant inhibitions (IC_{50} close or higher than 100 µM) of CYP1A2, 3A4/5, 2B6, 2C8, 2C9, 2C19 and 2D6 were observed when ritlecitinib was concomitantly incubated with the isoform-specific test substrates. Similar low inhibitions were observed when the human liver microsomes were pre-incubated with ritlecitinib in the absence of NADPH for 30 minutes. However, clear inhibitions of CYP1A2 (IC_{50} of 65 µM) and CYP3A4/5 (IC_{50} ranging from 11 to 14 µM) were observed when the human liver microsomes were pre-incubated with ritlecitinib and NADPH. This indicates that for CYP1A2 and CYP3A4/5, ritlecitinib has a time- and NADPH-dependent inhibition potential. In human hepatocytes cultures, ritlecitinib induced increases in CYP3A4 and CYP2B6 mRNA levels and CYP2B6 activity at 50 µM or higher when incubated 3 days in the hepatocyte cultures prior to activity evaluation of the respective CYP450 enzymes. In a subsequent CYP450 induction study in cultured human hepatocytes (study 022301), addition of ritlecitinib to human hepatocytes for 2 consecutive days resulted in the induction of CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C19. Of note, the applicant estimates that the theoretical unbound liver inlet ritlecitinib concentration at the proposed clinical dosing regimen is 8 µM. The ritlecitinib levels at which CYP450 induction was identified in this study were already in the same range. For example, induction of CYP3A4 already started in the range of 6-30 µM depending on the cell lot. Also, for CYP1A2, induction was already observed at 3 - 6 µM depending on the cell lot. Similarly, for CYP2C8, induction was already observed from 3 - 10 µM in all three cell lots.

Interestingly, the ritlecitinib concentration added to the human hepatocytes during the first phase of the experiment, and the subsequent CYP3A4-mediated turn-over kinetics of the isoform-specific test substrate (midazolam) in the second phase of the experiment, proved to be inversely proportional. Conversely, the incubations with ritlecitinib caused substantial enzyme induction of CYP3A4, as measured by CYP3A4 mRNA levels. A direct influence of ritlecitinib on enzyme activity in the second phase of the conducted experiment in study 022301 can, however, be excluded, as the cell media of the first experimental phase (in which ritlecitinib was added to the incubation) were removed and as the cells were subsequently rinsed before enzyme activities toward the test substrates were evaluated. This effect is illustrated in one of the cell lots used in study 022301 in the Figure 3 below:

Figure 3: Effect of ritlecitinib on CYP3A4 mRNA and enzyme activity in cultured human hepatocytes



Of note, similarly to CYP3A4/5 induction and time-dependent inhibition of CYP3A4/5 by ritlecitinib in the human hepatocyte culture study 022301, this particular isoform also showed strong time-dependent inhibition by ritlecitinib in human liver microsomes (however, only in the presence of NADPH, study 121415). Finally, time-dependent (and NADPH dependent) inhibition of CYP1A2 by ritlecitinib was similarly observed as for CYP3A4/5, albeit at clearly lower potency. However, in contrast to human liver microsomes, no clear time-dependent inhibition was observed in the induction study 022301 in human hepatocyte cultures.

In respect to the inhibition of UGT isoforms, the applicant found that UGT1A1 and UGT1A4 activity was inhibited by ritlecitinib with an IC_{50} value of 54 and 81 µM in human liver microsomes (in the absence of bovine serum albumin (BSA), in the presence of BSA IC_{50} values were higher).

No relevant inhibition of human recombinant glutathione S-transferases was detected by ritlecitinib. Similarly, no relevant inhibitions of the tested SULT isoforms 1E1, 1A1, and 2A1 by ritlecitinib were observed in human liver cytosol. Finally, M2 did not inhibit or induce the tested CYP450 isoforms in human liver microsomes or cultured human hepatocytes to a relevant extent (also, no time-dependent inhibition was observed), and did not inhibit the tested UGT isoforms in human liver microsomes to a relevant extent.

In terms of transporter protein inhibition, ritlecitinib did not cause relevant inhibitions of MDR1, OATP1B1 and OATP1B3 (IC_{50} values above 300 µM). However, ritlecitinib inhibited OCT2 (IC_{50} of 55.2 µM), MATE1 (IC_{50} of 51.4 µM) and MATE2K (IC_{50} of 48.3 µM). Furthermore, ritlecitinib was not a relevant inhibitor of OAT1, OATP1B1 and OATP1B3 (IC_{50} values of 156.0, 311.8 and 933.6 µM, respectively). However, ritlecitinib inhibited BCRP and OAT3 at IC_{50} values of 27.0 and 41.3 µM, respectively, and very strongly inhibited OCT1 at an IC_{50} value of only 3.74 µM. Similarly, ritlecitinib was a substrate of BCRP at 0.5 and 2 µM. Finally, ritlecitinib was not an inhibitor of the BSEP efflux transporter (IC_{50} value >200 µM). Additionally, M2 inhibited OCT1 (IC_{50} at 0.86 µM), OATP1B1 (IC_{50} at 2.0 µM), BCRP (IC_{50} at 5.6 µM), OATP1B3 (IC_{50} at 8.4 µM) and MDR1 (IC_{50} at 44.1 µM), but did not inhibit MATE1, MATE2K, OAT1, OAT3 and OCT2 to a relevant extent (IC_{50} at >300 µM). M2 also proved to be a substrate of MDR1 (at 0.3, 1, and 3 µM). Considering that the applicant estimates the steady state unbound Cmax of ritlecitinib at 1.1 µM and its theoretical unbound liver inlet concentration at 8 µM, many of these IC_{50} values could translate into clinically relevant PK drug interactions. For the clinical assessment of transporter-mediated pharmacokinetic interactions, see section 2.6 on clinical aspects.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

In terms of single-dose toxicity studies, the toxicokinetics of ritlecitinib after oral gavage administration were evaluated in rats (n=3) at 0, 250, 500 and 1000 mg/kg ritlecitinib (study 13MA012). Then, 1-day oral dose exploratory toxicity was evaluated in dogs (n=1 per sex) at 20, 90 and 300 mg/kg ritlecitinib (study 13LJ078). Additionally, single-dose oral toxicokinetics were analysed in male Wistar Han IGS rats (n=3) at 25, 75 and 200 mg/kg ritlecitinib (study 14MA133). Finally, single dose modified release capsule toxicokinetics were studied in Beagle dogs (n=3 per sex) at 65 mg (study 16GR208). All studies were non-GLP compliant.

Ritlecitinib was well tolerated in the submitted single-dose toxicity studies. Clinical effects related to ritlecitinib administration were emesis and partially closed eyes in dogs (study 13LJ078) and watery faeces in the dog study 16GR208. Tmax was rapidly attained in the single-dose toxicity studies (with the exception of the release capsule study) both in rats (ranging from 1 to 1.67 hours post-dose) and in dogs (ranging from 0.5 to 3 hours post-dose).

2.5.4.2. Repeat-dose toxicity

Repeat-dose toxicity (after oral gavage administration) was examined in rats and in Beagle dogs. In total, seven studies were submitted. In the non-GLP compliant study 13MA039, ritlecitinib was administered at 0, 125, 300 and 500 mg/kg/day for a consecutive period of 14 days to male Wistar

Han rats (n=5). Then, in the GLP-compliant study 14GR132, 0, 75 and 175 mg/kg/day of ritlecitinib were administered for 8 consecutive weeks (and at 400 mg/kg/day for 31 consecutive days) to Wistar HAN (Crl:WI[Han]) rats (n=10 per group and sex). Note that a micronucleus evaluation was included in study 14GR132. Finally, in the pivotal and GLP-compliant rat repeated dose toxicity study 20070067, 0, 50, 100 and 200 mg/kg//day of ritlecitinib were administered for six consecutive months to Crl:WI(Han) rats (n=15 animals per group and sex). In this pivotal rat toxicity study, the reversibility of effects was assessed in n=5 animals per group and sex in the vehicle and the highest dose group. Of note, toxicokinetics in the submitted rat repeated dose toxicity studies were investigated in satellite groups (n=3 per sex and group, treated at the same dosing regimens used in the main study fraction) at 1-, 3-, 8- and 24-hours post-dose. In Beagle dogs, repeated dose toxicity was at first studied in the non-GLP compliant exploratory study 13LJ111, in which ritlecitinib was administered at 0, 15, 45 and 75 mg/kg/day to Beagle dogs (1 dog per sex and group at 15 and 75 mg/kg/day and 2 dogs at 0 and 45 mg/kg/day) for 15 consecutive days. Then, repeated dose toxicity was evaluated in a GLP compliant study in Beagle dogs (n=3 per group and sex) that received 0, 5, 15, or 45 mg/kg/day for 8 consecutive weeks (study 14GR135).

Finally, two GLP-compliant pivotal 9-months repeated dose toxicity studies were submitted (the second study was submitted to test the reproducibility of the critical ritlecitinib-related axonal dystrophies in dogs exposed to ritlecitinib for 9 months, vide infra). In the first pivotal dog repeated dose toxicity study 20070068, ritlecitinib was administered to Beagle dogs (n=4 per main phase group and sex) at 0, 5, 20 and 40 mg/kg/day for 9 consecutive months. Recovery of effects in the vehicle and the highest dose groups was studied for 3 dosing-free months (n=2 per group and sex). Finally, in the follow-up pivotal dog repeated dose toxicity study 20099163, ritlecitinib was administered to Beagle dogs (n=4 per group and sex in the main dosing phase) at 0, 10, 20 q.d., 20 b.i.d. (two times 10 mg/kg/day approximately 6 hours apart), and 40 mg/kg/day for 9 consecutive months. Recovery was examined in additional groups (n=3 per group and sex) at 0, 20 q.d. and 40 mg/kg/day for 6 months.

Rats

In rats, repeated dose administration of ritlecitinib was generally well tolerated.

In terms of test-article-related effects in rats pertaining to the pharmacology of ritlecitinib, decreased peripheral counts of white blood cells, lymphocytes, monocytes, eosinophils and basophils were commonly observed. Similarly, considerable dose-dependent organ weight decreases, and macroscopic organ size decreases were noted for the thymus and/or the spleen, correlating with dose-dependent decreases in lymphoid cellularity in these organs. Decreased lymphoid cellularity was also commonly observed in lymph nodes (mesenteric, inguinal), GALT, and bone marrow. These effects were commonly observed down to the lowest applied dosing regimens. In addition, these (exaggerated) pharmacology effects commonly resulted in secondary effects that are presumably also related to the immunosuppressive mode of action of ritlecitinib, e.g. decreased globulin levels, decreased hematopoietic tissue in the bone marrow, and increases in peripheral neutrophil counts. In study 20070067, all ritlecitinib-related findings pertaining to exaggerated pharmacology proved to be fully reversible after 3 month of dosing cessation.

In terms of off-target effects of ritlecitinib in rat repeated dose toxicity studies, decreases in body weight and body weight gain, and decreases in food consumption were commonly observed. Alterations in body weight largely reversed after 3 months of recovery in study 20070067. In study 14GR132, 400 mg/kg/day ritlecitinib proved to be above the maximal tolerated dose, as severe morbidities (e.g. poor clinical condition, failure to gain body weight, increases in peripheral neutrophils and monocytes, gastrointestinal mucosa inflammation) and cases of mortality were identified.

Additionally, in the 8 weeks and the 6 months rats repeated dose toxicity studies, ritlecitinib-related alterations of erythrocyte endpoints were observed in the high-exposure groups. Specifically,

microscopic erythrocyte abnormalities (poikilocytosis, eccentrocytes and pyknocytes), a higher red cell distribution width and an increase of reticulocytes were observed at 175 mg/kg/day in study 14GR132. In study 20070067, a lower red blood cell mass at ≥100 mg/kg/day, a higher mean corpuscular volume and red cell distribution width at 200 mg/kg/day, minimally higher absolute reticulocyte counts at ≥100 mg/kg/day, poikilocytosis (specifically eccentrocytes and pyknocytes) and hypochromasia at 200 mg/kg/day were observed. Of note, poikilocytosis was also observed in male rats of the impurity qualification study 8413430. Eccentrocytes are RBCs that appear in a peripheral blood smear to have their haemoglobin shifted to one side of the cell (Caldin et al. 2005). Pyknocytes are small erythrocytes (occasionally with atypical membrane projections) resulting from the removal of damaged membranes from eccentrocytes.

Furthermore, other minor ritlecitinib-related alterations were frequently observed in the rat repeated dose toxicity studies. Specifically, decreases in mean serum potassium, cholesterol, AST, triglyceride and glucose levels were observed in one or in both of the long-term rat studies 14GR132 and 20070067. These mostly did not follow a dose-response and were of minor magnitude; therefore, no concern was raised on these test-article related alterations.

In addition, in the rat repeated dose toxicity study 14GR132, ritlecitinib-related increases in urine volumes were observed at 75 and 175 mg/kg/day. Importantly, in the pivotal rat study 20070067, proteinuria was identified in rats at ≥50 mg/kg/day ritlecitinib. Even after 3 months of recovery, the identified proteinuria did not fully reverse at 200 mg/kg/day. Also in the impurity qualification study 8413430, similar cases of proteinuria were identified, demonstrating reproducibility. These cases of proteinuria were correlated with microscopic incidences of hyaline droplet accumulation in renal tubular epithelial cells of ritlecitinib-treated rats (in study 20070067 in males from 50 mg/kg/day and in females from 100 mg/kg/day onwards). These droplets stained positive for lipofuscin or alpha2µ-globulin. While the latter is a common response to high exposures of xenobiotics in male rats, renal lipofuscin droplets are uncommon. Similar renal droplets were occasionally identified in the 8 weeks rat study 14GR132, the impurity qualification Study 8413430, and in the 2-year rat carcinogenicity Study 8384525. Of note, the ritlecitinib-related renal hyaline droplets in rats proved to fully reverse after 3 months of recovery in study 20070067.

Importantly, in the micronucleus assessment that was incorporated in the rat Study 14GR132, no ritlecitinib-related signs of clastogenicity or aneugenicity were observed.

Finally, the toxicokinetics investigations in rat repeated dose toxicity studies generally demonstrated rapid Tmax values at approximately 1 to 1.4 hours post-dose. This supports rapid enteral absorption of ritlecitinib in rats. Furthermore, Cmax values mostly increased approximately dose-proportionally, while AUC_{24} mostly increased greater than dose-proportionally. No sex-related differences in toxicokinetics were observed in the submitted rat studies.

Dogs

In dogs, a range of potentially worrisome ritlecitinib-related on-target and off-target effects were identified.

As already observed in the submitted rat repeated dose toxicity studies, similar test-article-related effects pertaining to the immunosuppressive mode of action of ritlecitinib were identified in Beagle dog studies 13LJ111, 14GR135, 20070068 and 20099163. Specifically, decreased counts of peripheral total white blood cells, lymphocytes (total T cells, T helper cells, cytotoxic T cells, NK cells and B cells), basophils and eosinophils were associated with the administration of ritlecitinib and were generally observed in all test-article groups. Furthermore, ritlecitinib-related alterations of immune organs ranged from decreased organ weights (of especially the thymus) and macroscopically small thymi to decreased lymphoid cellularity in the thymus, the spleen, (mesenteric and popliteal) lymph nodes, and

the GALT. These alterations generally followed a dose-response relationship. Similarly, as observed in the rat repeated dose toxicity studies, also in Beagle dog studies, decreased cellularities of all lineages were observed in the (sternal) bone marrow. These are (similarly as in the rat) presumed to be related to the pharmacological mode of action of ritlecitinib. Note that these exaggerated pharmacology findings proved to partially or fully reverse during the recovery periods implemented in the dog studies 20070068 and 20099163.

Importantly, however, in the two pivotal dog repeated dose toxicity studies 20070068 and 20099163, adverse over-immunosuppression was observed at high supra-therapeutic doses at 20 (q.d. and 2x10 b.i.d.) mg/kd/day and at 40 mg/kg/day, which was manifested by systemic skin infections. Specifically, generalised red skin, skin papules, thin fur and interdigital cysts as well as marked microscopic hyperplasia of the epidermis were observed. In affected dogs, the observed opportunistic skin (and sometimes ear) infections were, according to the applicant, triggered by Demodex mites and/or papilloma viruses. Of note, these infections even progressed in severity over the cessation of the treatment period, required up to several months of dosing cessation for partial or full recovery, and demanded veterinary care (with both an antiparasitic agent and a broad-spectrum antibiotic). While the observed over-immunosuppression pertains to the pharmacological mode of action of ritlecitinib, the extent and the inefficient recovery (in selected cases not even 6 months sufficed for total recovery) of this finding in the dog studies 20070068 and 20099163 were still unexpected. This is further elaborated in the discussion section below.

According to the microscopic findings report from study 20070068, Demodex was only presumed in males, while in the affected females, parasites were not observed. In addition, it is reported that no ectoparasites were found following a deep skin scrapings procedure performed by the DVM (animals 6992/M, 6993/M, 6998/F, 6999/F). In the confirmatory study 20099163, similar clinical signs were found. The appointed DVM treated the affected animals, but no antiparasitic drug was administered. No data on skin scrapings were found in the study report. In the pathology report, viral inclusions were found (Papilloma virus). However, it is not considered likely that Papilloma virus could solely cause the observed effects. In addition, dogs were received from Marshall BioResources – according to health monitoring reports these beagles should be free from subclinical infestation with Demodex mites.

Considering these facts, there is no clear evidence of Demodex being the core reason for skin findings. General skin inflammation is present with no clear cause at this time point. This is further elaborated upon in the discussion section below.

In addition to test-article-related exaggerated pharmacology, also increases in neutrophils, platelets and fibrinogen were observed in the dog studies 20070068 and 20099163. These changes might be connected with the observed immunosuppression and concomitant (opportunistic) infections and could therefore be a secondary manifestation of exaggerated pharmacology. Note that these findings also proved to be completely reversible after the recovery phases in both studies. Because of these aspects and the small magnitude of these alterations, no concern was raised.

In terms of off-target effects in Beagle dogs related to ritlecitinib administration, the applicant occasionally observed test-article-related emesis and mucoid/discoloured faeces that were considered non-adverse. Furthermore, ritlecitinib-related decreases in body weight and body weight gains (up to conditions necessitating feed supplementation) were observed. This condition correlated with decreased food consumption and with the clinically apparent thin condition of dogs at high dosing regimens. However, these test-article-related clinical effects proved to reverse during the recovery periods of the dog studies 20070068 and 20099163.

Additionally, a range of test-article-related haematological and clinical chemistry alterations were identified in the submitted dog toxicity studies 20070068 and 20099163. Similarly, as observed in the rat, also in dogs, erythrocyte endpoints were altered after chronic administration of ritlecitinib.

Specifically, decreases in RBCs, haemoglobin, haematocrit and reticulocytes were observed. Also, increases in red cell distribution width were noted. However, no poikilocytosis was observed in this study (as was observed in the preceding rat repeated dose toxicity studies). It might be presumed that these erythrocytic alterations are based on a similar ritlecitinib-related effect as observed in the submitted rat repeated dose toxicity studies. In terms of clinical chemistry, test-article-related decreases in phosphorous, calcium, total cholesterol and serum creatinine as well as increases in fibrinogen and globulin, were observed in dogs. As many of these findings followed no dose-response relationship, as the findings were not considered adverse, and as these findings were not clearly observed in the preceding rat repeated dose toxicity studies, no concern was raised. Of note, these haematology and clinical chemistry findings in dogs proved to be completely reversible after cessation of ritlecitinib administration. Finally, in study 20099163, AST levels were frequently increased (statistically significant) in test-article group animals, and this often followed a dose-response relationship. However, as no microscopic signs of hepatotoxicity were noted, no concern was raised.

Finally, the applicant observed ritlecitinib-related decreases in albumin and the albumin/globulin ratio in the pivotal dog studies 20070068 and 20099163. The applicant speculates that these decreases were related to the infections of dogs affected by over-immunosuppression. This notion is supported. An increased incidence and severity of mixed cell perivascular/alveolar infiltrations in the lungs was observed in test article groups in both pivotal dog toxicity studies 20070068 and 20099163; in the latter study, this finding was already identified from the lowest ritlecitinib groups onwards. Furthermore, also (non-adverse) pinpoint pale foci with or without microscopic correlate (mixed cell infiltration) were observed in the post-mortem investigations in animals of the highest dose groups. The applicant similarly hypothesises that these alterations were secondary to ritlecitinib-related over-immunosuppression and were a sign of infection. In the dog study 20099163, test-article-related hypoplasia/atrophy of the seminiferous tubular epithelium and/or hypospermatogenesis were observed in animals of all test-article groups. Additionally, it appears that testis maturation in dogs of test-article groups was delayed, as the fraction of adolescent testes was increased in animals of most test-article groups, whereas all investigated testes of dogs of the control group were mature. While these findings did not follow a dose-response relationship, they were nonetheless only observed in dogs of test-article groups. Interestingly, also after 6 months of recovery, still cases of immature testes, hypoplasia/atrophy of the seminiferous tubular epithelium and hypospermatogenesis were observed in test-article group animals. Of note, no such alterations were observed in the preceding Beagle dog repeated dog toxicity study 20070068. The implications of these ritlecitinib-related alterations in the male genital tract in dogs in study 20099163 are further elaborated in the discussion section below.

In both 9-month pivotal repeated dose dog toxicity studies 20070068 and 20099163, ritlecitinib-related widespread axonal dystrophy was observed in the CNS and PNS of treated dogs from 10 mg/kg/day onwards. The microscopic correlate to these axonal dystrophies were “spheroids”, which are known to form in response to various degenerative triggers such as oxidative stress and neurotoxic molecules (i.e. disease-related proteins) (Yong et al. 2021). Overall, ritlecitinib-related axonal dystrophies were observed in the brainstem (e.g. in the superior olivary nucleus and the lateral lemniscus), cerebellum (specifically in the cerebellar rostral vermis), sciatic nerve, branches of the vagus nerve that innervate multiple visceral organs and the mesenteric and submucosal plexuses of the gastrointestinal tract, vagina, and urinary bladder. Furthermore, axonal dystrophies were found in autonomic nerves of the adrenal gland in animals of the 20 mg/kg/day q.d. group (study 20099163).

In most examined dog CNS and PNS specimens, ritlecitinib-related axonal dystrophies were observed from 20 mg/kg/day onwards. However, importantly, also clear increases in axonal dystrophies in investigated specimens of the cerebellar vermis (in 100% of the investigated animals per sex, n=4) were already observed at 10 mg/kg/day in study 20099163. In the Table 2 below, incidences of axonal

dystrophies in the cerebellar rostral vermis from 10 mg/kg/day ritlecitinib onwards in study 20099163 are summarised:

Table 2: Group incidences (with severities) of test article-related microscopic findings in the dog brain in Study 20099163

Finding	Males Dose (mg/kg/day)					Females Dose (mg/kg/day)				
	0	10	20	20[a]	40	0	10	20	20[a]	40[b]
Axonal dystrophy; Rostral Vermis Cerebellum (white matter)	-	4	4	4	4	-	4	4	4	4
Minimal (Grade 1)	-	2	3	4	-	-	2	3	3	2
Mild (Grade 2)	-	2	1	-	3	-	2	1	1	2
Moderate (Grade 3)	-	-	-	-	1	-	-	-	-	-

- = No finding present.

[a] 10 mg/kg BID (twice daily).

[b] Early euthanized animal (Female 6588) findings were included.

[c] Number examined.

Furthermore, the following Table 3 summarises axonal dystrophies in harvested dog brain tissues (superior olivary nucleus and lateral lemniscus and/or ventral nucleus) from the dog study 20099163:

Table 3: Group incidences (with severities) of test article-related microscopic findings in the dog brain in Study 20099163

Finding	Males Dose (mg/kg/day)					Females Dose (mg/kg/day)				
	0	10	20	20[a]	40	0	10	20	20[a]	40[b]
Brain[c]	4	4	4	4	4	4	4	4	4	4
Axonal dystrophy; Lateral superior olivary nucleus	-	-	3	4	3	1	1	3	1	3
Minimal (Grade 1)	-	-	3	3	-	1	1	3	1	1
Mild (Grade 2)	-	-	-	1	-	-	-	-	-	1
Moderate (Grade 3)	-	-	-	-	3	-	-	-	-	1
Axonal dystrophy; Lateral lemniscus and/or ventral nucleus	-	-	3	4	4	-	-	2	3	4
Minimal (Grade 1)	-	-	3	4	3	-	-	2	3	4
Mild (Grade 2)	-	-	-	-	1	-	-	-	-	-

Importantly, the test-article-related axonal dystrophies in the brain stem (especially in the superior olivary nucleus) also led to severe functional impairments. This was demonstrated in BAEP (brainstem auditory evoked potential) investigations of dogs affected by ritlecitinib-mediated axonal dystrophies. Mild to severe hearing capacity loss and waveform defects was detected in BAEP investigations of animals at 40 mg/kg/day in both dog toxicity studies 20070068 and 20099163. Contrarily, no abnormalities of the tested BAEPs were identified in control animals. Additionally, statistically significant shorter mean latency to wave I and V at 46 and/or 82 db was observed in animals from the 10 mg/kg/day groups onwards in study 20099163. The applicant considered these BAEP alterations in affected dogs test-article related and adverse. Examples of ritlecitinib-mediated alterations in the BAEP investigations of study 20099163 is demonstrated in the Figure 4 and Figure 5 below:

Figure 4: Representative waveform of a normal pattern BAEP at baseline (Dog # 6544F – Left -82 dB). The first 5 seconds of the BAEP include a complex set of waves reflecting activity ranging from of the cochlea (Wave I) to the olivary complex (Waves IV and V)

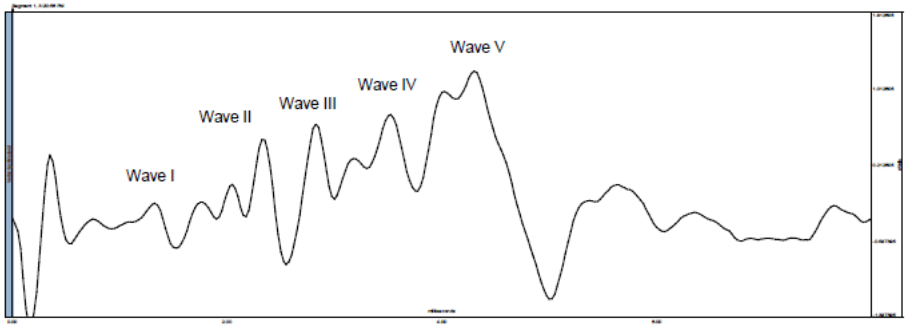
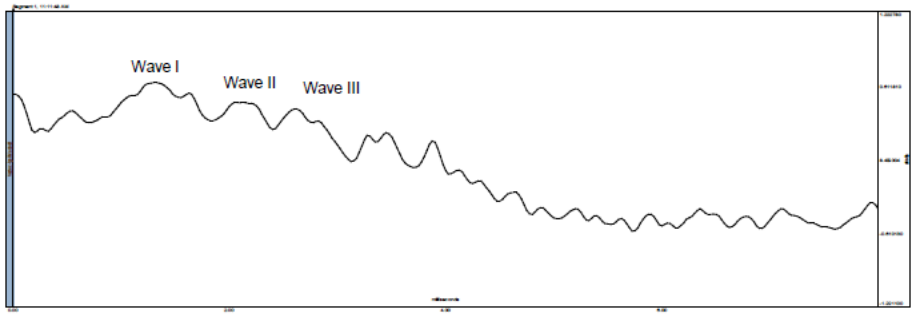


Figure 5: Waveform reflecting significant deficit in auditory processing at Month 9 (Dog # 6589F – Left 40 dB). Note the reduced amplitude, but the presence, of Waves I-III, and the virtual absence of the later responses (Waves IV-V)



Importantly, the ritlecitinib-related BAEP alterations and the identified axonal dystrophies in the nervous system in dogs showed full (BAEP) or partial (axonal dystrophies) reversibility after 6 months of recovery. Regarding the latter, incomplete recovery from axonal dystrophies was noted for the lateral lemniscus, the lateral superior olivary nucleus and the rostral vermis in the cerebellum. Specifically, for the lateral lemniscus, spheroids were still observed in one animal of the 20 and 40 mg/kg/day groups in males and in the 40 mg/kg/day group in one female, in the lateral superior olivary nucleus in one male and female of the 40 mg/kg/day group, and in the rostral cerebellar vermis in one female animal of the mg/kg/day group. Therefore, the applicant's notion that full recovery of axonal dystrophies was observed apart from the rostral cerebellar vermis is not supported.

According to the applicant, the margins between the clinical exposure and the exposures in the lowest dose group at which ritlecitinib-related axonal dystrophies were observed (rostral cerebellar vermis at 10 mg/kg/day, study 20099163) are only 6.0-fold in terms of Cmax and 7.4-fold in terms of AUC_{24}. Importantly, in the second pivotal 9-month dog toxicity study 20099163, axonal dystrophies were observed at all applied dose levels, rendering the possibility that even at lower exposure multiples to the clinically anticipated exposure axonal dystrophies might be formed.

In the frame of the Beagle dog study 20070068, the applicant also conducted transmission electron microscopy (TEM) investigations of superior olivary (SON) and cochlear nucleus specimens from dogs of the dosing- and recovery phase to investigate the identified ritlecitinib-related axonal dystrophies more specifically. In SON specimens from the end of the dosing phase of the 40 mg/kg/day group (n=2), axosomatic bouton enlargements were frequently found. However, no such alterations were found in one of the control dogs after the dosing phase had ended (n=1). Of note, synapses between these bouton enlargements were still intact. Importantly, after recovery (3 months), no bouton enlargements were found in brain specimens of dogs of the 40 mg/kg/day groups, demonstrating the reversibility of this finding. Interestingly, the applicant also describes that in the TEM investigation of

dog brains at 40 mg/kg/day, poorly demarcated non-membrane bound oval to spherical structures were observed which were moderately electron-dense, either single or merged and with a homogenous internal appearance without further visible internal organisation. Furthermore, one of the brain sections examined ultra-structurally from 1 of the 2 dogs administered 40 mg/kg/day at the end of the dosing phase had 1 instance of a well-demarcated irregularly shaped membrane-bound electron dense focus of compacted rough endoplasmic reticulum and mitochondria.

Finally, in terms of toxicokinetics in Beagle dogs, Tmax was attained at approximately 1-hour post-dose in the dog toxicity studies, supporting rapid enteral absorption of ritlecitinib after oral administration. Cmax generally increased dose-proportionally, while AUC_{24} generally increased greater than dose-proportionally. No sex differences were noted.

2.5.4.3. Genotoxicity

In total, three *in vitro* genotoxicity studies were submitted. Specifically, a GLP-compliant bacterial reverse mutation assay (Ames test, study WIL-655100), a GLP-compliant *in vitro* micronucleus test in TK6 cells (a human lymphoblast cell line, study WIL-655099), and a non-GLP compliant mechanistic follow up study to this *in vitro* micronucleus assays in TK6 cells (study 13GTX10) were submitted. Note that an *in vivo* micronucleus evaluation was included in the 8 weeks rat repeated dose toxicity study 14GR132 (vide supra).

Ritlecitinib proved to be negative in the bacterial reverse mutation assay. In the *in vitro* micronucleus study WIL-655099, a statistically significant increase in micronucleated cells was observed without metabolic activation at the highest concentration of this study (125 µg/mL, or 437 µM). In the follow-up study 13GTX10, the applicant found that ritlecitinib did not cause clastogenicity, but caused aneugenicity (hypodiploidy, hyperdiploidy and polyploidy) at concentrations from at 90.8 to 669 µM at incubations for 27 hours. While ritlecitinib was unequivocally an *in vitro* aneugen, the *in vivo* relevance of this finding is considered to be low, especially as aneugenicity is generally considered to be a threshold effect and as *in vitro* aneugenicity was only observed at exceedingly high supra-therapeutic exposures. This notion was supported by the *in vivo* micronucleus rat study 14GR132, in which no increases in micronucleated cells were observed in test-article groups at relevant exposures. This is substantiated by the fact that even at 400 mg/kg/day in study 14GR132 (corresponding to an exposure that is 130-fold higher than the expectable clinical exposure in terms of unbound AUC_{24}), no increase in peripheral micronucleated cells was observed. The applicant considers that ritlecitinib – at high doses – functionally inhibited kinases that are involved in mitosis, which subsequently led to *in vitro* aneugenicity. Importantly, this constitutes another example of an off-target protein reaction by ritlecitinib with subsequent impairment of protein function.

Finally, no signs of genotoxic carcinogenicity were noted throughout the submitted dossier. While in study 8384525, benign and malignant neoplasms of the thymus (also one case of benign thymoma in the highest dose group of the dog study 20099163) and benign neoplasms of the thyroid gland were observed, these neoplasms were presumably not of genotoxic origin, and in the case of benign and malignant thymomas presumably related to the pharmacology of ritlecitinib.

2.5.4.4. Carcinogenicity

The applicant submitted an extensive carcinogenicity programme, consisting of the pivotal and GLP-compliant rat 2 year carcinogenicity study 8384525 and the 0.5 year pivotal rasH2 transgenic mouse study 8400625. In addition, the applicant also performed two toxicity studies in the rasH2 transgenic mouse to examine tolerability (in the 2 week study 18GR117, non-GLP compliant) and dose range finding (in the 4 weeks study 8392586, GLP-compliant). The 2-year carcinogenicity study was

conducted in Crl:WI(Han) rats (n=60 per group and sex) at 0, 10, 30 and 100 mg/kg/day ritlecitinib, whereas the 0.5 year study was performed in rasH2 transgenic mice (n=25 per group and sex) at 0, 30, 100 and 300 mg/kg/day. In the 0.5 year study, an appropriate positive control group was included. In the preceding rasH2 transgenic mouse tolerability study 18GR117, 0, 30, 100, 300, and 1000 mg/kg/day ritlecitinib were administered to 12 mice per group and sex, whereas in the dose range finding study 8392586, 0, 75, 225 and 450 mg/kg/day ritlecitinib were administered to 10 mice per sex and group. Toxicokinetics were examined in these studies in appropriate satellite groups.

While survival in the 2-year rat carcinogenicity study was similar between control males and females at the end of the study (60% vs. 65%, respectively), % survival appeared clearly lower in male rats than in female rats (53%, 57% and 52% in males vs. 75%, 67% and 67% in females at 10, 30 and 100 mg/kg/day, respectively). However, upon request, the applicant submitted a statistical analysis in which this difference in survival was only statistically significant at the lowest dose level of ritlecitinib. Additional ritlecitinib-related clinical findings were decreases in body weight and thin appearances. Interestingly, increases in parasites were observed in the colon of animals treated with ritlecitinib (in females approximately dose-dependent). Similarly, as the observed systemic skin infections by opportunistic pathogens in the dog repeated dose toxicity studies 20070068 and 20099163, this finding presumably results from ritlecitinib-mediated immunosuppression.

Similarly, as observed in the rat repeated dose toxicity studies, in the 2-year rat carcinogenicity study 8384525, ritlecitinib-related findings pertaining to exaggerated pharmacology were also identified. These included decreased lymphoid cellularities in the thymus, the spleen and the mesenteric lymph node at 100 mg/kg/day. In addition, lipofuscin depositions were identified in the kidneys of animals treated with ritlecitinib (as was also observed in preceding rat repeated dose toxicity studies, vide supra).

In the 2-year rat carcinogenicity study 8384525, significantly increased incidences of benign thymomas were observed in male and female rats at 100 mg/kg/day. Increased incidences of thymus hyperplasia were also observed in female rats at 100 mg/kg/day. Importantly, however, also malignant thymomas were observed in this study; specifically, 1 male at 100 mg/kg/day, 1 female at 30 mg/kg/day and 2 females at 100 mg/kg/day were affected. At least one of the malignant thymomas in one of the affected females at 100 mg/kg/day also metastasised, as apparent by malignant thymoma metastases found in the heart of the affected animal. While these data hint at a dose-response relationship in females, these low incidences were not statistically significant due to the limited group size in this study.

Interestingly, in a comparative study of data from long-term studies in the National Toxicology Program database, the incidence of malignant thymomas of all identified thymoma cases in Wistar Han rats (n=129) was only 2%, 98% of the identified thymomas were benign (Moore et al. 2019). However, clearly higher ratios of malignant thymomas out of all identified thymomas per affected group were identified in study 8384525 (specifically, 1 out of 8 thymomas in males at 100 mg/kg/day = 12.5%; 1 out of 15 thymomas in females at 30 mg/kg/day = 6.15%; and 2 out of 18 thymomas in females at 100 mg/kg/day = 11.1%). Furthermore, Taylor and Mowat 2020 described that out of 860 male and 871 female control Crl:WI(Han) rats, only 2 males and 5 females had malignant thymomas, resulting in incidences of 0.23% and 0.57%, respectively. The incidences in study 8384525 were, however, clearly higher, amounting to 1.89% in males of the 100 mg/kg/day group (1 out of 53 animals), to 1.72% in females of the 30 mg/kg/day group (1 out of 58 animals), and to 3.57% in females of the 100 mg/kg/day group (2 out of 56 animals). These translate into 8.2-fold, 3.0-fold and 6.3-fold increases over the incidences described in the Taylor and Mowat 2020 study. Finally, and most importantly, in the historical database of control Crl:WI(Han) rats used in study 8384525, not a single malignant thymoma was identified in 543 control males (0.0%), and only 1 malignant thymoma was observed in 574 control females (0.18%). Therefore, the incidence of malignant thymomas in females

of the 30 (1 out of 58 animals = 1.72%) and 100 mg/kg/day (2 out of 56 animals = 3.57%) groups in study 8384525 were 9.6-fold and 19.8-fold higher than in the historical control database of the CRO in which the study was conducted.

In addition to thymomas, a statistically significantly increased incidence of thyroid adenomas was observed in males in study 8384525 at 100 mg/kg/day (specifically, 19 out of 59 animals were affected). Of note, the incidences of benign thyroid adenomas also increased dose proportionally from 11.7% (vehicle group) to 20.0% (10 mg/kg/day), 21.7% (30 mg/kg/day) and 32.2% (100 mg/kg/day) in males, and from 3.3% (vehicle group) to 6.7% (10 and 30 mg/kg/day) to 10.0% (100 mg/kg/day) in females. No clear trends in thyroid carcinomas were identified. Additionally, a slight trend of increasing severities (males) or increasing incidences (females) of thyroid hyperplasias was observed in test-article groups. The applicant considers that these increased thyroid adenoma incidences are an exacerbation of these common background tumours in rats due to ritlecitinib-mediated immunosuppression.

In the 6-month hemizygous rasH2 transgenic (tg/wt) Study 8400625, no test-article related neoplasms were observed. The validity of this study was demonstrated by the included positive control group. Interestingly, no decreased lymphoid cellularities or organ weights were observed in the thymus and the spleen, even though these were observed in all preceding mouse, rat, and dog repeated dose toxicity studies.

2.5.4.5. Reproductive and developmental toxicity

In terms of reproductive and developmental toxicity, the applicant submitted 6 studies. Specifically, in the GLP-compliant fertility and early embryonic development until development (FEED) study 00655209, ritlecitinib was administered to Wistar rats (n=20 per sex and group) at 0, 20, 60 and 200 mg/kg/day, whereby breeding was initiated between non-dosed naïve animals and dosed animals. Specifically, male rats received ritlecitinib (or vehicle) for 28 days or 84 days prior to mating, and dosing in females started 14 days before initiation of mating, was continued during mating, and lasted until gestation day (GD) 7. In terms of embryo-fetal toxicity (EFD), non-GLP compliant dose-finding studies were conducted with Wistar Han rats (receiving 0, 75, 175 and 325 mg/kg/day ritlecitinib between GD 6 to 17 at n=6 animals per group; study 20069224) and NZW rabbits (receiving 0, 10, 75, 175, or 325 mg/kg/day between GD 7 to 19 at n=6 animals per group; study 20069228). Pivotal GLP-compliant studies were then similarly conducted in Wistar Han rats (receiving 0, 75, 175, and 325 mg/kg/day ritlecitinib between GD 6 to 17 at n=22 animals per group; study 20075271) and NZW rabbits (receiving 0, 5, 25 and 75 mg/kg/day ritlecitinib between GD 7 to 19 at n=20 animals per group; study 20075272). Pre- and postnatal natal development (PPND) was investigated in study 00655232, in which ritlecitinib was administered at 0, 25, 75 and 175 mg/kg/day from GD 6 until lactation day (LD) 20. In the postnatal part of this study, 1 male and 1 female/litter from the F1 generation were randomly selected prior to weaning (at PND 4) for postnatal evaluation of vaginal patency (PND 25 onwards), balanopreputional separation (PND 35 onwards), auditory startle response (PND 60), locomotor activity (PND 61), learning and memory (using a water-filled 8-unit T-maze; PND 62) and breeding (minimum age of PND 85). Scheduled euthanasias were at either LD 21 (F0 mothers), PND 21 (pre-weaning F1 litters), PND 115-120 (post-weaning F1 males) or GD 14 (F1 post-weaning females). Adequate toxicokinetics investigations were included in these six studies. Finally, ritlecitinib was administered to Wistar Han rats in a juvenile toxicity study (study 00655269) once daily at 25, 50, and 100 mg/kg/day from post-natal day (PND) 10 until PND60. In this study, a 2-month dose-free phase was additionally examined in a subset of animals. Appropriate toxicokinetics satellite groups were included in this juvenile toxicity study. Apart from the regular battery of investigations,

also landmarks of reproductive development, neurobehavior, and femur length were examined in this study.

In terms of FEED, no effects on male reproductive performance (mating and copulation) were detected. However, an adverse increase in mean litter proportion of pre-implantation loss in test-article naïve females that were mated with test-article treated males was detected after the first and second breeding phases. Specifically, an approximately 10-fold increased pre-implantation loss was noted in females that were sired by males of the 200 mg/kg/day group in relation to the vehicle group (20.2% vs. 2.0%, respectively) after the first mating phase, and an approximately 5.2-fold increase in pre-implantation loss in the same groups after the second breeding phase (27.1% vs. 5.2%, respectively). Secondary to the ritlecitinib-related pre-implantation loss, the mean implantation sites and the mean number of viable embryos were lower than in ritlecitinib-naïve females sired by males from the 200 mg/kg/day group as from males of the vehicle group. Apart from these findings, no test-article-related effects on sperm endpoints (counts, motility and morphology) or male organ weights were detected. It should be noted that also test-article related effects on male reproductive tract were detected in the Beagle dog repeated dose toxicity study 20099163 (as described before). These aspects are further elaborated in the non-clinical discussion section of this document (vide supra). Of note, clinical safety margins to the male fertility NOAEL established in the FEED study 00655209 were 14-fold based on unbound AUC_{24}, and 23-fold based on unbound Cmax.

No relevant effects on female fertility and early embryonic development until implantation were detected when test-article treated females were mated with test-article naïve males in the FEED study 00655209.

In the pivotal rat EFD study, mean foetal body weights (sexes combined) were decreased in the 175 and 325 mg/kg/day groups (specifically 0.94 and 0.80-fold in respect to the control groups). Furthermore, the applicant identified test-article-related malformations and variations at 175 and/or 325 mg/kg/day that followed a dose-response relationship (i.e. malformed vertebrae and ribs and variations in the development of the digits, vertebrae (cervical, thoracic, and lumbar), ribs, and sternebrae). Specifically, one foetus with skeletal malformations of the vertebrae and/or ribs was identified in the 175 mg/kg/day group, and 3 foetuses had such malformations in the 325 mg/kg/day group. In the pivotal rabbit EFD study 20075272, in the highest dose group at 75 mg/kg/day, a test-article-related increase in post-implantation loss was noted (13.08% compared with 8.25% in controls). Furthermore, ritlecitinib-related visceral malformations in 3 fetuses of the 75 mg/kg/day group (mal-positioned kidneys), and skeletal malformations in 3 fetuses (malformed vertebrae and sternebrae) of the 75 mg/kg/day group, were identified. The incidence of malformed kidneys might have followed a dose-response relationship and was identified in 1 fetus of the 5 and 25 mg/kg/day groups and 3 fetuses of the 75 mg/kg/day groups. Additionally, in the 75 mg/kg/day group of study 20075272, an increased incidence of test-article-related variations was identified, specifically ossification delays (digits, pubes, skull, thoracic vertebrae, and sternebrae) and variations in the development of the skull and vertebrae.

Overall, ritlecitinib proved to be a developmental toxicant in gestating Wistar Han rats (study 20075271) and NZW rabbits (study 20075272), with identified test-article-related cases of visceral and skeletal fetal malformations, fetal skeletal variations, decreased fetal body weights and post-implantation losses. Safety margins from animal studies at the claimed no observed adverse effect levels to clinical exposures only ranged between 12 and 24-fold. Upon CHMP's request, the applicant issued a contra-indication for pregnancy in the SmPC section 4.3.

In regard to PPND (study 00655232), ritlecitinib-related increases in pups that were found dead or were missing (presumably due to cannibalisation) were detected in the 175 mg/kg/day group compared to the control group (e.g. 14(7) vs. 2 (1) pup(litters) were found dead, and 20 (8) vs. 3 (2)

and pups (litters) were missing, respectively). Furthermore, an adverse effect of ritlecitinib on post-natal survival in the highest dose group at 175 mg/kg/day was noted between post-natal day (PND) 1-4 (93.7% in the 175 mg/kg/day group vs. 99.6% in the control group) and PND 4-7 (95.5% in the 175 mg/kg/day group vs. 99.4% in the control group). Additionally, ritlecitinib-related effects in the F1 generation of the 175 mg/kg/day group included decreased male and female pup birth weight at PND 1 (0.82-fold and 0.80-fold of the control group, respectively) and statistically significantly decreased body weights and body weight gains (up to decreases of 20%) in the 175 mg/kg/day group and frequently in the 75 mg/kg/day group throughout large parts of the post-natal development. Then, also test-article-related delayed sexual maturation was observed in the F1 generation at 175 mg/kg/day. Statistically significantly increased times until balanopreputioal separation was noted in the 25, 75 and 175 mg/kg/day groups, amounting to 45.8, 46.4 and 47.4 days, respectively, compared to 43.8 days in the control group. Similarly, attainment of vaginal patency was delayed in females of the 175 mg/kg/day group (37.8 days vs. 34.0 days in the vehicle group). Finally, F1 females demonstrated an adverse test-article-related decrease in corpus lutea numbers at 175 mg/kg/day (12.6 vs. 14.2 per dam in the vehicle group, respectively). This led to a decreased number of implantation sites and viable embryos per dam in the high dose group compared to the vehicle control group (11.0 vs. 13.3 implantation sites and 10.5 vs. 12.5 viable embryos, respectively). Of note, the exposure at the claimed NOAEL of this study at 75 mg/kg/day in rats relates to a clinical safety margin of 14-fold in terms of unbound AUC_{24}, and to 25-fold in terms of unbound Cmax. Upon CHMP's request, the applicant agreed to issue a contra-indication for breast-feeding in the SmPC section 4.3, also see the discussion on non-clinical aspects.

In the juvenile rat toxicity study 00655269, administration of ritlecitinib to juvenile rats led to an adverse lower mean body weight gain (with a corresponding decreased food consumption) at 100 mg/kg/day in males during the dosing phase. Also at lower dose levels, decreases in mean body weight were noted that also occasionally proved to be statistically significant. These translated into lower mean body weights and lower food consumption, mainly at 100 mg/kg/day, but also at lower dosing regimens. Of note, this condition partly or fully reversed during the recovery period in the affected animals. Decreases in mean body weights, mean body weight gains and mean food consumption were only considered adverse in males' 100 mg/kg/day doses. Secondary to these alterations, the age of balanopreputial separation in males at 100 mg/kg/day was delayed by two days as compared to the control group. Also, femur length differences were noted in males at 100 mg/kg/day after the dosing and recovery phases. However, the applicant considers these effects secondary to the observed decrease in mean body weight and weight gain in this group. This hypothesis is supported because no alterations of femur length were observed in females at the same dosing regimen and because no particular macroscopic or microscopic abnormalities were associated with this finding. Importantly, no ritlecitinib-related neurological and skeletal alterations were recognised in this study.

2.5.4.6. Local Tolerance

No local tolerance studies were submitted. As Litfulo will be administered orally, this is acceptable.

2.5.4.7. Other toxicity studies

No antigenicity studies were submitted. This is acceptable.

In terms of immunotoxicity, one dedicated immunogenicity / antigenicity study was submitted, specifically a mouse allergy model with the purpose of determining whether ritlecitinib administration

can lead to hypersensitivity reactions due to covalent binding to off-target proteins with subsequent haptenisation.

In the mouse allergy model of study 14GR446, no ritlecitinib-mediated hypersensitivity was observed.

In terms of dependence, no studies were submitted. However, the applicant summarised that the primary pharmacology of ritlecitinib is not associated with molecular pathways liable for dependency and that secondary pharmacology studies did not demonstrate activity towards relevant targets that induce dependency. Additionally, the applicant concluded that no test-article effects on functional observational batteries were observed in the conducted non-clinical studies. The applicant's positions are supported.

No non-clinical safety studies with metabolites were submitted. The applicant summarised that the most important metabolites of ritlecitinib are presumably of lower risk concern, as many of them are conjugate metabolites and are of little toxicological concern. This was explained because their pharmacology potential was considerably decreased regarding ritlecitinib because CNS penetration of these metabolites is very low and because the metabolites of ritlecitinib show an unproblematic in silico profile in Derek and Sarah Nexus predictions. This is supported; no studies are needed.

In total, 15 non-clinical impurity qualification studies were submitted. At first, in the GLP-compliant study 8413430, male and female Crl: WI(Han) rats (10 animals per group and sex) received batches of ritlecitinib at 0 and 200 mg/kg/day for 13 consecutive weeks that either were pure or that were blended with impurities (at a total extent of 4.37%). Note that five impurities (PF-06763318, PF-06757444, PF-06837196, PF-07103942 and PF-06763172) are specified above their respective ICH Q3A/Q3B qualification thresholds and that these impurities consequently demanded non-clinical qualification. In the ritlecitinib batch used in study 8413430 these impurities were concentrated at levels higher than their intended qualification threshold. In addition, 11 non-GLP compliant exploratory bacterial reverse mutation assays were submitted (studies 20GR280, 20GR189, 20GR190, 20GR191, 20GR192, 20GR139, 20GR140, 19GR162, 15GR004, 14GR556 and 21GR240 for the impurities PF-07313152/PF-07313153, PF-07226176, PF-07226177, PF-07268908, PF-07268909, PF-07299318, PF-07268909, PF-01403876, PF-06837196, PF-06757444 and PF-07308030, respectively). Finally, 3 GLP-compliant bacterial reverse mutation assays (studies 20232598, 20232562 and 1149304 for the impurities PF-06715298, PF-07202371-S7 and CP-902684, respectively) were submitted.

In the *in vivo* rat study 8413430, no relevant differences between batches of ritlecitinib with or without impurities were observed when rats were administered 200 mg/kg/day ritlecitinib for a consecutive period of 13 weeks. In the exploratory reverse bacterial mutation (Ames) assays, only PF-07299318 and PF-07308030 (a potential N-nitrosamine impurity of ritlecitinib) proved to be bacterial mutagens. The necessary control strategy of these impurities is discussed in the quality section.

For the (potential) impurities PF-07812857, PF-07812862, PF-07256812, PF-07243943 and PF-07289082, the applicant obtained either equivocal or even positive Sarah Nexus calls for bacterial mutagenicity (Sarah Nexus is a statistically-based prediction software used for predicting bacterial mutagenicity). According to the ICH M7(R1), these impurities would classify as class 3 impurities that need to be controlled below the TTC of 1.5 µg/day. However, for these 5 impurities, no Ames test data were submitted. Instead, the applicant performed a read-across assessment for these impurities (by using structurally similar compounds for which Ames test data were available) and concluded that these 5 impurities possess no mutagenic hazard and can therefore be classified as class 5 impurities. No detailed structure-activity relationship (SAR) assessment was submitted that would allow to de-risk these untested impurities by already tested substances that share exactly the same structural alerts. However, an own Derek Nexus (recent version 2.5.2) SAR assessment supports that these 5 impurities can indeed be classified as class 4 impurities, as all their structural alerts were already contained in the

already negatively-tested impurities PF-07313153, PF-07313152, PF-06837196 and PF-01403876. Therefore, no non-clinical concern was raised about these impurities.

Finally, also for the impurity PF-06685960, no reverse bacterial mutation assay was submitted. According to the applicant's in silico predictions, this impurity had an equivocal Sarah Nexus call for bacterial mutagenicity. However, in an own Derek Nexus (recent version 2.5.2) prediction, this substance tested negative for bacterial mutagenicity. Consequently, this impurity can be considered a class 5 impurity and non-mutagenic.

In addition, 5 non-GLP compliant mechanistic studies on the axonal dystrophy findings in the Beagle dog toxicity studies 20070068 and 20099163 were submitted. Specifically, the goal of study 17GR131 was to examine the plasma and brain tissue concentrations of ritlecitinib (superior olivary nucleus, cochlear nucleus and hippocampus) after oral gavage administration to female Beagle dogs (n=4 per group) at 0 and 40 mg/kg/day when administered for 3 consecutive days. Then, the objective of study 19GR193 was to examine potential off-target proteins in the dog CNS that might be causally related to the observed axonal dystrophies identified in the 9-month repeated dose toxicity studies 20070068 and 20099163. Specifically, a click chemistry-based chemoproteomic method was used to examine potential off-target proteins in Beagle dog (18-21 months old) brain tissue homogenates (hippocampus (n=5) and rostral cerebellar vermis (n=3)). Furthermore, in study 19GR372, the applicant's goal was to examine the binding affinities of ritlecitinib towards MAP2K7 in overexpressing HEK 293F cells (as the applicant identified MAP2K7 as a potential off-target of ritlecitinib in dog brain homogenates in the preceding study 19GR193). Then, in study 19GR142, the applicant's goal was to examine the relative mRNA expression of different kinases and oxidative stress genes in brain regions of untreated male Beagle dog (approximately 4 years old) brain tissue (specifically, of the superior olivary nucleus vs. the cochlear nucleus and the hippocampus). This was to examine the hypothesis that differences in gene expression in the cochlear nucleus compared with the superior olivary nucleus in terms of differences in oxidative stress genes might have led to the observed axonal dystrophy in the superior olivary nucleus in the dog repeated dose toxicity studies 20070068 and 20099163. Finally, in study 21GR164, the applicant's objective was to examine DOCK10 expression in the cerebellum of humans, dogs, rats, and mice (as the applicant identified DOCK10 as a potential off-target of ritlecitinib in dog brain homogenates in the preceding study 19GR193).

In study 17GR131, approximately 10% of the ritlecitinib plasma levels were detected in the superior olivary nucleus, cochlear nucleus and hippocampus (when normalised to ng/mL or ng/g). This study demonstrates that blood-brain barrier penetration of ritlecitinib in the Beagle dog is clearly higher than in the rat quantitative whole body autoradiography study 15647, in which after single dose administration a brain: plasma ratio of 4% was established. As metabolites of ritlecitinib also likely contributed to this signal (only radioactivity was measured, but not its exact source), the real blood-brain barrier penetration of ritlecitinib might be smaller than 4%. Therefore, the dog is a more relevant species in determining the neurotoxic potential of ritlecitinib than the rat.

In study 19GR193, potential off-target proteins of ritlecitinib in the hippocampus and the rostral cerebellar vermis were BTK, DOCK10, BMX and MAP2K7 (the latter only in the rostral cerebellar vermis). Of note, JAK3 was not among the identified off-targets in the investigated dog brain areas, suggesting that JAK3 is not involved in the ritlecitinib-related axonal dystrophies in dogs. Furthermore, the applicant concludes that BTK and BMX (2 kinases of the TEC family) binding by ritlecitinib in the dog brain is unlikely the cause of the observed axonal dystrophies, as no similar neurological toxicities as noted with ritlecitinib were observed with dedicated TEC inhibitors. Interestingly, in the hippocampus homogenates and in the rostral cerebellar vermis homogenates in the dog study 19GR193, also ritlecitinib-binding to Protein Kinase C (PKC) isoform was detected and proved statistically significant. As PKC signalling alterations are involved in neurodegenerative disease, this finding is further elaborated upon in the non-clinical discussion section of this report.

In study 19GR372, binding affinities of ritlecitinib towards human, dog and rat versions of MAP2K7 in overexpressing HEK 293F cells proved to fall within a factor-2 range between the three species. Of note, dysfunction of MAP2K7 signalling is suspected to be correlated to the aetiology of neurological diseases such as schizophrenia (Winchester et al.); therefore, ritlecitinib-mediated inactivation of MAP2K7 might potentially be of neurological concern. This is further discussed in the discussion section below. In study 21GR164, the applicant found that expression (only on the mRNA level) of DOCK10 in the cerebellum of dog, rat, and mouse was significantly different and higher than expression in the human cerebellum.

Finally, a GLP-compliant phototoxicity study in Crl: LE (Long-Evans) pigmented rats (n=5 per dose group) was submitted. Rats in this study received 0, 50, 100 and 200 mg/kg/day ritlecitinib for 3 consecutive days and were exposed to light in the UVA, UVB and VIS wavelength. Toxicokinetics were studied in satellite groups. No signs of dermal or ocular phototoxicity were observed in this study.

2.5.5. Ecotoxicity/environmental risk assessment

The applicant submitted an extensive assessment in which the environmental risk of ritlecitinib was evaluated in phase I persistency and phase II tier A and B ecotoxicity and environmental fate studies. All submitted studies were conducted in GLP compliance and in line with relevant OECD guidelines. Specifically, a PBT phase I PBT screening was performed in study 260K-108. Then, in phase II tier A, a sludge die away study (study 260E-336, according to OECD 314B) and an adsorption study (adsorption to soils, sediments and activated sludge, study 260E-337) were carried out. In terms of environmental fate, the applicant conducted a 100 days water-sediment degradation study (study 260E-339) and a 28-day surface-water and suspended sediment biodegradation study (study 260E-340) with radiolabelled ritlecitinib. In terms of ecotoxicity, the applicant submitted an activated sludge respiratory inhibition test (study 260E-341, according to OECD 209), a 72-hour toxicity study with fresh water green algae (study 260P-117, according to OECD 201), a daphnia toxicity test (study 260A-275, according to OECD 211) and an early life-stage toxicity test with fish (study 260A-276, according to OECD 210). Finally, in phase II tier B, a prolonged sediment toxicity tests with the midge (Chironomus riparius) using spiked sediment was conducted (study 260A-280, according to OECD 218).

In the phase I PBT screening, log D values of ritlecitinib at pH 4, 7 and 9 were far below the trigger value of 4.5 (specifically, log D values were 0.45, 1.50 and 1.40, respectively). Therefore, no PBT assessment was warranted. However, the PEC_{SW} calculation resulted in a value of 0.25 µg/L, which clearly exceeds the trigger value of 0.01 µg/L, necessitating a phase II ERA. In the sludge die away study, ritlecitinib had a moderate biodegradation half-life of 1.1 days, and complete mineralisation after 28 days amounted to approximately 20%. Sorption to sludge was found to be negligible, therefore phase II studies in terrestrial environments were waived. Input into the environment was subsequently considered to mainly result by discharge of effluents from wastewater treatment facilities. In terms of environmental fate in the water-sediment compartment, the half-life of ritlecitinib ranged between 11.5 and 44 days, whereas complete mineralisation was inefficient (e.g. 3.5% in 100 days). Importantly in this context ritlecitinib tosylate exceeded the persistence criterion > 40 d for water (DT50 water 12 °C = 44 d, DT50 total system, 12°C = 91 d) in the Choptank water sediment system.

Additionally, the applicant found a strong tendency of ritlecitinib to irreversibly bind to environmental reactants in the sediment (probably organic matter that contains sulfhydryl groups). As this irreversible binding sequesters ritlecitinib in the environment, its environmental persistency of ritlecitinib might get considerably prolonged. In terms of ecotoxicity, no adverse effects on activated sludge microorganisms were detected. While high concentrations of ritlecitinib were toxic to algae, led

to reproduction and growth impairments in daphnia, influenced post-hatch and overall survival as well as growth in fish, and influenced larval emergence of Chiromomus riparius, all calculated PEC/PNEC ratios were clearly below 1. Specifically, the PEC/PNEC ratio of the most sensitive endpoint in the most sensitive species (reproduction in daphnia) only amounted to 0.033. Therefore, no relevant ecotoxicological risks of ritlecitinib are expected in the environment.

Table 4: Summary of main study results

Substance (INN/Invented Name): ritlecitinib tosylate			
CAS-number (if available): 2192215-81-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	0.45 at pH 4 1.50 at pH 7 1.40 at pH 9	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	0.45 at pH 4 1.50 at pH 7 1.40 at pH 9	not B
Persistence	DT50 (at 12°C)	DT50water 44 d	P in water
Toxicity	$NOEC_{surface\ water}$ $NOEC_{ground\ water}$ $NOEC_{microorganism}$	0.074 mg a.i./L 0.074 mg a.i./L >1000 (615) mg (a.i.)/L	not T
PBT-statement:	The compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default	0.25	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Mean slugde K_{oc} = 61.4 Mean soil K_{oc} = 10449 Mean sediment K_{oc} = 4209	Sludge 1 64.1 L/kg Sludge 2 58.8 L/kg Soil 1 2750 L/kg (Soil 2 39700 L/kg (4.37) Sediment 1 6920 L/kg Sediment 2 2560 L/kg
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 314 B OECD 308	$14CO_2$: 20.1 % (d 28) $DT_{50,\ water}$ = 3.7 d (1), 20.7 d (2) $DT_{50,\ sediment}$ = 20.9 d (1), 19 d (2) $DT_{50,\ totalsystem}$ = 11.5 d (1), 42.5 d (2) (1) = Brandywine Creek sediment, (2) = Choptank River sediment % shifting to sediment = 76.7%	at 20°C

		% CO_2 = 3.2% (1), 3.5% (2) % NER = 74.9% (1), 32.9% (2) Transformation products >10% = NO.			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ Raphidocelis subcapitata	OECD 201	NOEC EC10	8.0 >20	mg a.i./ L	*Raphidocelis subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC EC10	0.074 0.076	mg a.i./ L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*pimephales promelas*	OECD 210	NOEC EC10	1.7 1.7	mg a.i./ L	*pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC15	1000 (615 a.i.)	mg a.i./ L	Respiration
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC EC10	79.4 166	mg a.i./ kg	*Chironomus riparius, o.c. 1.4%*

2.5.6. Discussion on non-clinical aspects

Pharmacodynamics (PD)

An extensive programme of primary *in vitro* pharmacology studies was conducted.

IL-2 induced STAT5 phosphorylation and GM-CSF-induced STAT5 phosphorylation were not investigated in human PBMCs and rat, dog and human whole blood. Nevertheless, as expected of JAK3-dependent cytokines, the applicant provided adequate data on IL-2 inhibition by ritlecitinib in human whole blood. Based on comparable IC_{50} values for IL-15 and IL-21 between human, rat and dog (198, 137 and 170 nM for IL-15 and 362, 302 and 212 nM for IL-21, respectively), as well as for IL-2, IL-4, IL-7, IL-15 and IL-21 in human whole blood (244, 340, 407, 266 and 355 nM, respectively), the applicant regarded the inhibition of IL-15 and IL-21 by ritlecitinib as surrogate for the comparison of IL-2 inhibition across species. Furthermore, ritlecitinib did not inhibit many other JAK3-independent cytokines and growth factors (e.g., IL-6, IL-10, IL-12, IL-23, IL-27, IFNα, IFNγ, G-CSF and EPO), suggesting that inhibition of GM-CSF (JAK2-dependent) was not expected. Indeed, ritlecitinib did not affect GM-CSF in CD3+ cells in C3H/Hej mice.

In order to demonstrate that exposures achieved after systemic administration of ritlecitinib selectively inhibited JAK3, but not other JAK kinases, the applicant provided projected IC_{50} values for JAK1, JAK2 and TYK2 (17.4 µM, 42.6 µM and 99.9 µM, respectively), indicating more than 2 orders of magnitude weaker inhibitory potency than for JAK3 and, thus, having presumably no significant contribution to the pharmacological effect of ritlecitinib. Taking into account that lower average unbound concentrations (C_{av} values) are more predictive for *in vivo* effects than higher maximum concentrations (C_{max}), as indicated by *in vivo* and *ex vivo* studies in rats (Telliez et al., 2016), the applicant claimed

that exposures after systemic administration in AA mice were still below those required for inhibition of other JAK members.
In study 011358, inhibition of human NK and CD8+ T cell activity by ritlecitinib was dependent on ITK. The applicant provided literature references to underline that TEC kinases, rather than JAK kinases, regulate CD8+ T cell and NK cell function. It was pointed out that the markers of CD8+ and NK cell activation, IFNɣ and CD107a-induced expression, depend on TEC kinases. Ritlecitinib inhibits ITK, TEC and TXK, which belong to the TEC kinases family and are all expressed on T lymphocytes, but ITK at a significantly higher level. To confirm these conclusions, the applicant demonstrated results from a published article (Xu H. et al., 2019) in which ritlecitinib potently inhibited CD107a and IFNγ expression in both CD8+ T cells and NK cells, while ITK-selective inhibitor showed a similar effect in CD8+, but lower in NK cells and JAK1/3-selective inhibitor did not react. Similar results were demonstrated by Sung L. (2021), who concluded that ITK-selective inhibitors reduced activity in CD8+ T cells but not in NK cells. These data suggest that ritlecitinib influences CD8+ T and NK cells activity by inhibiting not only ITK, but also other members of TEC kinases family. This information was adequately reflected in the section 5.1. of the SmPC *(Mechanism of Action).*

Generally, *in vivo* PD studies should confirm the efficacy and mode of action of an active substance in the proposed clinical indication. Therefore, experiments performed by the applicant in animal models of diseases for different indications are considered as supportive only. Studies and assays submitted by the applicant are acknowledged and considered acceptable to the CHMP.

The results of the studies reported in the research article of Dai et al., 2021, support the function of ritlecitinib being a potent JAK3 inhibitor and restoring hair growth by decreasing skin inflammation in an AA mouse model. Ritlecitinib was intravenously and topically administered to the AA mice. Upon CHMP's request, the applicant justified that exposure data of ritlecitinib after oral administration (the proposed route of administration in human) in AA mice and data on symptoms, markers of neuroinflammation and molecular data upon ritlecitinib withdrawal were not available as the study in AA mice was performed solely with the intention to demonstrate that JAK3 inhibition would improve symptoms of AA. Regarding the missing data upon ritlecitinib withdrawal in AA mice, the applicant refers to results from the rat model of experimental autoimmune encephalomyelitis (EAE) (study 085612), where a neuroprotective effect could be demonstrated after oral administration of ritlecitinib. This result does not clarify possible effects following treatment cessation, especially when considering that EAE model and AA model are not interchangeable. To conclude, the lack of PK parameters in AA mice do not allow to confirm whether there are differences in exposures between healthy and AA mice, as different exposures were observed between healthy volunteers and AA patients in clinical studies as well. Consequently, possible inhibition of other JAK kinases in AA mice is not clearly excluded. However, from a clinical viewpoint, a proof of concept has been adequately addressed and therefore, this concern is not further pursued.

In terms of the PD *in vivo* data, ritlecitinib showed to have immunosuppressive potential, reflected by improvements of disease parameters, in the adjuvant-induced arthritis rat model (study number 090652), in the chemically induced inflammatory bowel disease mouse model (study number 181316) and the mouse model of multiple sclerosis (study number 085612).

Intravenously administered ritlecitinib at 30mg/kg prevented the onset of AA by effectively reducing AA-associated skin inflammation (e.g. supported by data from immunofluorescence and flow cytrometric analysis) and avoiding hair loss in C3H/HeJ skin grafted mice. Additionally, i.v. treatment with ritlecitinib at 30mg/kg effectively reversed AA, again by reducing AA-associated skin inflammation, demonstrated by suppression of T cell proliferation and function. Interestingly, twice daily topical administration of ritlecitinib (2% w/w) showed to be highly effective in the reversal of AA in C3H/HeJ skin-grafted mice as well (Dai et al., 2021).

For the Lck kinase, known to play an important role in immunity, T cells and antigen receptor signal transduction, a mean % inhibition of control value of 34.6 was noticed in the screening assay for possible off-targets of ritlecitinib (study number 100009194). The applicant concluded that due to much higher ATP concentrations in cells, inhibition of Lck kinase would be expected to be even less, resulting in an IC_{50} of >10µM. Furthermore, in a follow-up study (study 151236) at 1µM ritlecitinib and low ATP concentrations, even lower inhibition of 22.3% was reached, confirming that off-target binding to Lck kinase is not expected at clinically relevant concentrations of ritlecitinib, with the projected IC_{50} value of >10µM.

Overall, the safety pharmacology programme submitted by the applicant is considered complete and adequate.

Comparing both CV safety studies in dogs (study number 14GR078 and 14GR140), different effects on blood pressure, heart rate and QT-interval were noticed. While in the non-GLP compliant study SBP, DBP and MBP, as well as heart rate, decreased, leading to an increase in QT-interval, an increase in heart rates and a corresponding decrease in QT-interval was observed in the GLP-compliant study. No changes were observed in both studies for the corrected QT-Intervals (QTc). Unbound C_{max} values of 7084ng/ml of the 20mg/kg dose group in the non-GLP compliant study and 10483ng/ml of the 45mg/kg dose group in the GLP-compliant study were determined, corresponding to ritlecitinib concentrations of 24,83µM and 36,74µM, respectively. Assuming an unbound C_{max} of 1,1µM at steady-state following a clinically intended dosing regimen of 50 mg QD ritlecitinib (study PMAR-1157), a broad safety margin of more than 22- and 33-fold the human exposure was calculated for the 20mg/kg and 45mg/kg dose groups in dogs. A NOEL of 15mg/kg was settled in the GLP-compliant dog study by the applicant, assuming a 13-fold unbound C_{max} which can be expected at the clinical dose of 50mg. As the PK was not conducted at 15 mg/kg in the GLP-compliant CV safety study in dogs (study 14GR140); the safety margin at NOEL was calculated using the Day 1 mean unbound C_{max} of 4185ng/ml from the GLP-compliant 8-week dog toxicity study (study 14GR135). However, the very small sample size of 4 beagle dogs, actually 3 in the GLP-compliant study, since the data of one dog could not be evaluated, poses an issue with the informative value of the results. Although the results of these cardiovascular safety studies in beagle dogs can be regarded as supportive information only, possible CV effects are not expected with ritlecitinib due to selectivity towards JAK3. This is further discussed in the clinical safety section of this report.

No PD drug interaction studies were performed by the applicant, which is accepted by the CHMP.

Pharmacokinetics

An extensive non-clinical programme to examine the pharmacokinetics in relevant non-clinical animal species and in humans, including investigations on ADME and the potential of ritlecitinib and its major plasma metabolite M2 to induce pharmacokinetic drug-drug interactions (DDI) was conducted.

Extraction recoveries of ritlecitinib from Beagle dog plasma in the validation study 095221 ranged from 69.1% to 74.9%; the recovery for the internal standard was 75.2%. In the validation reports for the LC-MS/MS detection methods of ritlecitinib in mouse, rat and rabbit plasma, extraction recoveries were within 20% of the targeted value (i.e. 100%). Consequently, the extraction recoveries in dog plasma appear to be worse than in the plasma of the other species. Upon CHMP's request, the applicant explained that despite the low extraction recoveries from dog plasma, the established LC-MS/MS method met all key validation acceptance criteria. This is acknowledged; however, it should be considered that the true ritlecitinib concentrations in dog plasma are likely higher than the ones reported by the LC-MS/MS method.

No repeated dose tissue distribution study was submitted by the applicant. According to the ICH S3B guideline, repeated dose tissue distribution studies may be required if certain circumstances are fulfilled, e.g. when single-dose tissue distribution studies suggest that the apparent half-life of the test compound (and/or metabolites) in organs or tissues significantly exceeds the apparent half-life of the elimination phase in plasma and if it is also more than twice the dosing interval in the toxicity studies. In the whole body autoradiography rat study 15647, considerably higher tissue elimination half-lifes were observed versus the half-life in plasma: tissue half-life of the radioactivity associated with ritlecitinib (i.e. originating either from ritlecitinib or from its metabolites) was only 55.1 hours in plasma, but much higher in many investigated organs such as, e.g. the eyes (439.1 hours), the adrenal gland (approximately 488 hours), the cardiac blood (396.7 hours), the spleen (478.1 hours), the pancreas (560.0 hours) and the lung (382.7 hours). Furthermore, these tissue elimination half-lives clearly exceeded the daily dosing intervals in the submitted toxicity studies. Therefore, a repeated dose tissue distribution study would have been indicated. However, as a such study would presumably not add more relevant information regarding ritlecitinib's potential to accumulate in tissues due to high tissue half-lives (probably due to off-target protein binding, as ritlecitinib contains an α,β-unsaturated carbonyl moiety designed to target a covalent interaction with the cysteine residue of the JAK3 enzyme to achieve high selectivity), no additional study was deemed necessary.

Additionally, from the excretion kinetics of the administered radioactivity in healthy human volunteers (study 103503), it is apparent that no relevant excretion of the administered radioactivity occurred from 96 hours until the end of the experiment (240 hours). Furthermore, in the same study, large fractions of the administered radioactivity (35% in plasma and 49.8% in faeces) were non-extractable. These observations also suggest that a fraction of the administered ritlecitinib covalently binds to off-target proteins throughout the body.

Regarding the higher AUC_{0-t} levels of ritlecitinib and/or its metabolites in whole blood than in plasma measured in the rat quantitative whole body autoradiography study 15647, it is presumed that blood cells act as a sink for ritlecitinib and/or its metabolites. While the Cmax levels between plasma and blood were approximately similar in the rat quantitative whole body autoradiography study 15647, the considerably increased AUC_{0-t} demonstrates that elimination of ritlecitinib is slower in blood cells. It is conceivable that ritlecitinib and/or its metabolites are retained in blood cells by covalent protein binding within blood cells (as was, e.g. already identified in the *in vitro* human plasma protein binding study 103503 for human albumin). Haemoglobin contains cysteine residues (Viturri et al. 2013) which might be accessible for covalent reaction with ritlecitinib and/or its metabolites. This could explain the retention of ritlecitinib in red blood cells observed in the rat quantitative whole body autoradiography study 15647, and could also explain the rapid partitioning of ritlecitinib (but not of M2) into the cellular compartment of whole canine and human blood (study YDP/067/018). These findings are further discussed below, under toxicology sub-heading.

Further, even in phosphate buffer alone, glutathione conjugation of ritlecitinib was observed, demonstrating that adduct formation is, to a certain extent, not dependent on enzymatic activation. This is another example of covalent reactivity of ritlecitinib towards thiol groups of cysteine residues in polypeptides (as in this case observed with glutathione), as was observed for human serum albumin and can also be hypothesised for haemoglobin (vide supra). Furthermore, this observation demonstrates that covalent reaction of ritlecitinib with thiol groups of cysteine residues in polypeptides does not need to be enzymatically triggered in order to occur, which explains the covalent reaction capacity of ritlecitinib with cysteine residues of off-target proteins observed throughout the submitted non-clinical studies. Additionally, the applicant reports that approximately up to 2% of ^{14}C-labelled ritlecitinib added to human hepatocytes cultures in study 085839 was covalently bound to proteins in the cells demonstrating off-target covalent binding in hepatocytes. However, it should be noted that

only a single dose was administered, thus this experiment cannot account for the potential accumulation of such protein adducts in hepatocytes at a chronic dosing regimen.

Based on the quantitative whole body autoradiography rat study 15647 and the dog study 092809, it can be expected that the difference in BBB crossing of ritlecitinib and its metabolites between these two species is clearly higher than 2-fold. Based on this comparison, it is apparent that BBB crossing of ritlecitinib and/or its metabolites can vary between species.

Regarding the inhibition of CYP450 isoforms by ritlecitinib (as observed in cultured human hepatocyte studies), the applicant agreed that the time-dependent inhibition by ritlecitinib of CYP3A (study 121415) and CYP1A2 (study 123341) is likely mediated through irreversible binding to a cysteine within the reactive site of each of the enzymes.

Similarly, the applicant agreed that the observed inhibitions of UGT1A1 and UGT1A4 by ritlecitinib in study 135124 could possibly be another example of off-target protein reactivity by ritlecitinib. The functional inhibitions of these enzymes are examples of irreversible reactions of ritlecitinib with off-target proteins.

Overall, an extensive study programme examined non-clinical ADME and PK drug interactions. Notably, throughout the submitted non-clinical PK and toxicology programme, binding of ritlecitinib to off-target proteins or polypeptides (presumably via covalent reaction with thiol groups of cysteine residues) was observed or is presumed. This was, apart from the pharmacological targets JAK3 and TEC kinases, observed or suspected for the following off-target polypeptides or proteins or in the following studies: human serum albumin (study 103503); glutathione (study 085839); CYP3A4 and potentially CYP1A2 (studies XT135092, 022301, 121415 and 123341); UGT1A1 (study 135124); the proteins MAP2K7, DOCK10 and different PKC isoforms in dog brain homogenates (study 19GR193); haemoglobin (presumed based on the results in the quantitative whole body autoradiography rat study 15647); protein nucleophiles in general in cultured human hepatocytes (study 085839). Study 103503 demonstrates that large fractions of the administered ritlecitinib (35% in plasma and 49.8% in faeces) are non-extractable (associated with the pellet) and therefore presumably related to irreversible protein binding. In the whole-body autoradiography rat study 15647, the exceedingly long tissue elimination half-lives could suggest sequestering of ritlecitinib by off-target proteins. Off-target protein binding at very high ritlecitinib exposures might have caused the aneugenicity of ritlecitinib in the *in vitro* studies WIL-655100 and 13GTX10 and the decreased fertility of rat spermatozoa in the rat fertility study 00655209. In the ERA, ritlecitinib irreversibly reacted with environmental reactants in sediments (presumably with thiol-containing organic matter).

For CYP3A4 (and potentially CYP1A2) as well as UGT1A1 and some of the inhibitions in toxicity studies (e.g. aneugenicity and decreased fertility of rat spermatozoa), these interactions decreased the functional activity of the altered protein.

The ritlecitinib concentration added to the human hepatocytes during the first phase of the experiment, and the subsequent CYP3A4-mediated turn-over kinetics of the isoform-specific test substrate (midazolam) in the second phase of the experiment, proved to be inversely proportional. This effect appears counterintuitive, as enzyme induction is supposed to translate into increased overall enzyme activity. However, it is presumed that the decreased enzymatic activity of CYP3A4 when pre-incubated with ritlecitinib is related to covalent interaction of ritlecitinib with the enzyme, which subsequently decreases its catalytic efficacy. As CYP3A4 possess accessible cysteine residues near their active site cavities, it is presumed that ritlecitinib can react with delicate cysteine residues in CYP3A4 and could thereby render it catalytically less active or even inactive. This notion could well explain the time-dependent inhibition of CYP3A4/5 by ritlecitinib, and ultimately constitutes another example of covalent reaction of ritlecitinib with off-target proteins.

In respect to the inhibition of UGT isoforms, the applicant found that UGT1A1 and UGT1A4 activity was inhibited by ritlecitinib with an IC_{50} value of 54 and 81 μM in human liver microsomes (in the absence of bovine serum albumin (BSA), in the presence of BSA IC_{50} values were higher). While these IC_{50} values are not clinically relevant (as they clearly exceed expectable ritlecitinib exposures), these findings are interesting from a mechanistic perspective, as in study 135124, no glucuronide conjugation of ritlecitinib is expected. Therefore, inhibition of these enzymes was probably not caused by a substrate-mediated mechanism. As free thiol groups of cysteine residues within the intracisternal region of human UGT1A1 are important for its catalytic activity, it is well conceivable that, as already described for CYP450 isoforms (vide supra), ritlecitinib might have covalently reacted with cysteine residues of UGT isoforms and thereby decreased its catalytic efficacy to turn over the test substrates used in this study. Therefore, the observed inhibitions of UGT1A1 and UGT1A4 by ritlecitinib could be another example of off-target protein reactivity by ritlecitinib.

In general, these findings demonstrate that reaction of ritlecitinib with off-target proteins is ubiquitous and common. Upon CHMP's request, the applicant adequately amended the section 5.2 of the SmPC to mention the potential of ritlecitinib to covalently react with off-target proteins.

Toxicology

As discussed above, the ritlecitinib-related erythrocyte effects observed in the rat repeated dose toxicity studies 14GR132, 20070067 and 8413430 could indicate that the accumulation of ritlecitinib (and potentially the reaction of ritlecitinib with haemoglobin) might lead to adverse erythrocytic effects. As especially eccentrocytes and pyknocytes are associated with increased cellular oxidative stress (Caldin et al. 2005; Berardi et al. 2017;), and as cysteine residues in haemoglobin act as important antioxidants (Viturri et al. 2013), covalent reaction of ritlecitinib with cysteine groups of haemoglobin may critically decrease the anti-oxidative capacity of erythrocytes. This could explain the observed erythrocytic cell abnormalities, the subsequent increased red cell distribution width, and ultimately the increased reticulocytes as a compensatory response. The applicant also communicated that the increased reticulocytes, mean corpuscular volume, RBC distribution width, hypochromatophilic RBC, and the presence of eccentrocytes and pyknocytes were consistent with oxidative damage to RBC and an appropriate erythroid regenerative response. The applicant thus hypothesised that the erythrocyte abnormalities in rats at very high ritlecitinib exposures were caused by metabolite trapping of ritlecitinib via glutathione conjugation in erythrocytes with subsequent decreases of the cellular anti-oxidative capacity. However, such metabolites are usually excreted by ATP-dependent efflux transporters. Therefore, it is considered more plausible that in erythrocytes ritlecitinib reacts with haemoglobin at high exposures. However, no signs of anaemia were observed in clinical studies, suggesting that the erythrocytic rat findings at high ritlecitinib exposures have no clinical relevance for patients.

Regarding the observed proteinuria in the rat repeated dose toxicity studies 14GR132, 20070067 and 8413430, the applicant considered this finding as not adverse because the incidence and degree of proteinuria decreased during the experiment; and there were no corresponding adverse clinical pathology changes, clinical signs, or microscopic findings indicative of renal injury. Furthermore, upon CHMP's request, the applicant concluded that the observed cases of proteinuria cannot be translated to sub-microscopic minimal change glomerulopathy. As no clinical correlates were found, the observed test-article-related proteinuria and increased urine volumes in the rat studies 14GR132, 20070067 and 8413430 are considered to have no clinical relevance for patients.

Regarding the hyaline droplets (containing lipofuscin and alpha2μ-globulin) identified in the kidneys of ritlecitinib-treated rats in the repeated dose toxicity studies 14GR132, 20070067, 8413430 and 8384525, the applicant discussed that a relation between these renal droplets to off-target protein

reaction of ritlecitinib is unlikely, as such accumulations were, e.g. not observed in post-mitotic cells (e.g. neurons, cardiomyocytes) in rats. Notably, no similar findings were observed in mice and dogs at high ritlecitinib dosing regimens. Furthermore, the applicant also explained upon CHMP's request that the identified renal alpha2µ-globulin droplets are a (male) rat-specific finding in studies in which high amounts of xenobiotics are administered. Considering these aspects, the formation of these renal droplets in rats are considered of low clinical relevance for patients.

Regarding the test-article-related opportunistic skin infections observed in the dog repeated dose toxicity studies 20070068 and 20099163 as a complication of over-immunosuppression, a concern was originally raised on the long recovery duration from this condition after ritlecitinib dosing cessation. The applicant responded that the significant over-immunosuppression observed at high ritlecitinib dosing of dogs was similarly observed in dog studies conducted for the development of other JAK inhibitors (JAKis). Therefore, this finding can be considered an expected effect of exaggerated pharmacology at high exposures of JAKis in dogs. As over-immunosuppression is an established clinical risk factor of JAKis, this concern was therefore not further pursued from a non-clinical viewpoint. See clinical safety section.

According to the applicant, the observed opportunistic skin infections were triggered by Demodex mites and/or papilloma viruses in affected dogs. Nevertheless, there is no clear evidence of Demodex being the core reason for the observed skin findings in dogs. In the first 9-month dog study, deep skin scraping was performed but no ectoparasites were found in the skin of the affected dogs. In the confirmatory study, no Demodex diagnostics were performed. The applicant was asked to present a reason for not performing deep skin scraping for Demodex in the confirmatory dog 9-month study. The applicant persisted in explaining the skin findings as a clinical onset of demodicosis while using some arguments as why the parasite was not actually found. The applicant's arguments were however, found inadequate. Nevertheless, given that the clinical skin findings are manageable, this issue was not further pursued from a non-clinical viewpoint. See clinical safety section for further discussion on infections.

Regarding the identified neurotoxicity of ritlecitinib in the Beagle dog studies 20070068 and 20099163, the molecular pathogenesis of this finding is still not understood. Microscopically, the axonal dystrophies were identified as spheroids, which are *"bubble-like biological features that form on most degenerating axons"* (Yong et al. 2021). Upon CHMP's request, the applicant clarified that no signs of neurodegeneration were observed. Importantly, no alterations of synapses and myelination were observed apart from the axonal dystrophies.

It is conceivable that ritlecitinib led to axonal dystrophy generation in dog toxicity studies by three distinct mechanisms (either separately or by combinations of them): a.) by functional impairment of delicate neuronal proteins after covalent reaction with ritlecitinib; b.) by covalently reacting with delicate axonal proteins which could lead to aggregation of protein-ritlecitinib adducts and subsequent proteinopathy; or c.) by covalently reacting to free thiol groups of cysteine residues in the CNS or PNS and therefore depleting anti-oxidative capacity, which ultimately increases oxidative tissue damage. The applicant however considers that the reaction of ritlecitinib with an off-target protein in the dog brain caused the formation of the observed axonal dystrophies.

Furthermore, regarding the TEM investigations in study 20070068, a similar electron-dense appearance as found in the brain specimens of dogs affected by axonal dystrophies has been described for amyloid plaques in Alzheimer's disease (El Haji et al. 2019). However, upon CHMP's request, the applicant rejected that the identified electron-dense structures in dog brains affected by axonal dystrophies had a similar morphology than the one encountered in neurodegenerative diseases.

Of note, the applicant considers the axonal dystrophies in the cerebellar vermis of the 10 mg/kg/day groups in study 20099163 not adverse. However, considering that none of the control animals had

axonal dystrophies in this area of the cerebellum and considering the apparent neurotoxicity of ritlecitinib that also leads to functional neurological impairments (i.e. hearing loss), this interpretation is not supported by the CHMP.

Importantly, axonal dystrophy incidences in the dog study 20099163 showed similar magnitudes when ritlecitinib was administered at 20 mg/kg/day q.d. and 10 mg/kg/day b.i.d. As the b.i.d. doses were administered approximately 6 hours apart, the two doses per day in the 10 mg/kg/day b.i.d. can be considered as two independent administrations considering the short plasma $T_{1/2}$ of ritlecitinib in Beagle dogs (1.1 hours, study 132012). Therefore, the similar incidence of axonal dystrophies in the 20 mg/kg/day q.d. and 10 mg/kg/day b.i.d. groups suggests that the administered cumulative total dose determined the observed formation of axonal dystrophies in the dog study 20099163. On a cellular level, this finding appears plausible, as the CNS/PNS parenchyma is in a post-mitotic state, allowing cumulative ritlecitinib-mediated lesions. However, this notion could be worrisome, as after prolonged administration, patients could reach cumulative doses that had led to axonal dystrophies in the pivotal dog toxicity studies. The applicant responded to this concern that normal protein turnover (neuronal protein $T_{1/2}$ of approximately 5.4 days) would limit the amount of off-target binding of ritlecitinib in dogs to within 4-5 half-lives (approximately 20-25 days) and prevent indefinite accumulation with time. However, following this hypothesis, one would expect axonal dystrophies in the 8-weeks dog study 14GR153. As no axonal dystrophies were observed in this study, the applicant's hypothesis is not fully supported. It is not apparent why the formation of axonal dystrophies would take months while this equilibrium is attained much sooner. Therefore, a risk of accumulation of ritlecitinib protein adducts in the nervous system of patients can ultimately not fully be rejected in the absence of long-term safety data. This is further discussed in the clinical safety section.

Furthermore, the applicant was not able to calculate the cumulative ritlecitinib amounts that had partitioned to the dog CNS/PNS and caused axonal dystrophies in the pivotal dog toxicity studies 20070068 and 20099163 (for all dose groups), and to estimate after what time of chronic ritlecitinib administration patients would obtain similar cumulative brain exposures.

Overall, the observed neurotoxicity in dogs was unambiguously caused by ritlecitinib, as axonal dystrophies a.) were observed at high incidences in test-article groups (frequently in 100% of the animals), b.) proved to be perfectly reproducible in the dog studies 20070068 and 20099163, c.) generally increased in severity and incidence in a dose-dependent manner, and d.) were correlated with functional impairments (hearing loss). In addition, the occurrence of axonal dystrophies depended on cumulative rather than threshold exposures.

Furthermore, ritlecitinib strongly tends to covalently react with off-target proteins throughout the body (including proteins expressed in the nervous system that are connected with neurological diseases such as MAP2K and PKCs), often leading to functional impairment. It is therefore assumed that the axonal dystrophies in dogs are a result of covalent reactions of ritlecitinib with proteins in the nervous system, which could lead to impaired function of delicate neuronal proteins and/or accumulation of neurotoxic protein-ritlecitinib adducts. Since ritlecitinib demonstrated a high potential to accumulate in tissues and penetrate the BBB, and that ritlecitinib-mediated lesions might accumulate in the post-mitotic nervous system parenchyma, an adverse neurotoxic outcome pathway cannot be fully rejected at the molecular level.

Notably, these findings largely reversed during 6 months of ritlecitinib-free recovery in dogs. The applicant thus concluded that the reversal of the axonal dystrophies in dog upon dosing cessation might likely be related to intracellular protein turn-over and subsequent clearance of ritlecitinib adducts with off-target proteins. Assuming that the same mechanism would also apply to patients, this could be an important de-risking factor.

Nonetheless, based on the data available thus far, a potential risk for patients receiving a chronic ritlecitinib treatment cannot be fully excluded. This is supported by a.) the unambiguity of this signal in chronic dog toxicity studies, b.) the lack of understanding of its pathogenesis, c.) the reactivity of ritlecitinib to covalently and irreversibly react with off-target proteins (including the nervous system), d.) the suspected accumulative aetiology of the axonal dystrophies as suggested in study 20099163, and e.) the fact that no such effects were found in non-clinical studies of similar covalent inhibitor products. Therefore, upon CHMP's request, a warning was added in section 4.4 of the SmPC, and a summary of the axonal dystrophy findings in dogs was included in the section 5.3 of the SmPC. Furthermore, given the limited availability of long-term clinical safety data, this safety concern will be followed-up post-approval (see clinical safety and RMP sections below).

Taking into consideration the abundantly established binding of ritlecitinib to off-target proteins, hypersensitivity reactions towards ritlecitinib and autoimmunity would be, in theory, a realistic side effect of ritlecitinib administration; although, such reactions might not be observed during chronic ritlecitinib treatment due to its pharmacologic immunosuppression. However, upon CHMP's request, the applicant considers the potential of ritlecitinib to induce autoimmunity as small. This is agreed.

Chronic administration of ritlecitinib in the long-term rat study 8384525 led to statistically significant increased incidences of mostly benign neoplasms of the thymus and the thyroid gland. However, increased incidences of malignant thymomas were also observed in test-article group animals. As these incidences were considerably higher than the incidences of malignant thymomas in control rats of the same strain (CRO historical database; Moore et al. 2019; Taylor and Mowat 2020), and as the occurrences of these malignant thymomas followed a dose-response, these malignant neoplasms are possibly test-article related. Upon CHMP's request, the applicant added in section 5.3 of the SmPC that an increased incidence of malignant thymomas after ritlecitinib administration to female rats in study 8384525 could not be excluded.

The submitted toxicology studies demonstrated that ritlecitinib affects the fertility of male rats at high exposures. Regarding the decreased male fertility in the FEED study 00655209, the applicant considered that ritlecitinib did not affect spermatogenesis. Therefore, the applicant hypothesised that ritlecitinib impacted sperm function and capacity to fertilise the egg (through effects on sperm capacitation or acrosome reaction). Specifically, the applicant communicated that JAK/STAT family members are present in sperm and potentially also active in signalling in sperm capacitation and/or the acrosome reaction. Inhibition by ritlecitinib could therefore inhibit these functions. However, the applicant also noted that numerous other proteins, including kinases, are important in capacitation and acrosome reaction processes, all of which might be susceptible to inhibition by ritlecitinib at high exposures. Both hypotheses are supported by the CHMP. Importantly, the applicant concluded that the effect of very high ritlecitinib exposures on sperm functionality in rats did not progress with the duration of dosing and that the adverse effect of high ritlecitinib exposures on sperm functionality is expected to be transient and reversible after dosing cessation. Finally, as these effects were only observed at considerably supra-therapeutic exposures, a clinical impact is considered to be of little likelihood. This is supported by the CHMP.

Regarding the submitted embryo-foetal development studies, no contra-indication for pregnancy was initially issued in the SmPC in section 4.3. Nevertheless, in view of the available non-clinical data and in line with other products in the same class, the applicant agreed to add a pregnancy (and breast-feeding) contra-indication in the SmPC, upon CHMP's request. In addition, the applicant also provided a recommendation for a sufficiently long ritlecitinib-free period prior to pregnancy initiation. Specifically, the applicant proposed that women of childbearing potential be advised to use effective means of contraception during treatment up to at least 1 month following the final dose of ritlecitinib. This is agreed. This recommendation was adequately included in section 4.6 of the SmPC. Also see discussion on clinical safety.

Regarding the click chemistry-based chemoproteomic study 19GR193, ritlecitinib-binding to Protein Kinase C (PKC) isoform was detected in areas of the dog brain that were affected by ritlecitinib-mediated axonal dystrophies in the dog toxicity studies 20070068 and 20099163. This is interesting, as PKC signalling alterations are involved in neurodegenerative disease e.g., PKC activation exhibits a beneficial effect on amyloid pathology at several levels and is therefore an important signalling pathway in the pathogenesis complex of Alzheimer disease (Talman et al. 2016). Consequently, alterations of PKC isoforms by covalent ritlecitinib-binding might lead to neurodegenerative changes similar as occur in Alzheimer. Additionally, alteration of PKC isoforms is known to lead to the neurodegenerative disease spinocerebellar ataxia type 14, which can also lead to neuronal hearing impairment (Shirajuji et al. 2019). The neurological hearing losses observed in the dog repeated dose toxicity studies 20070068 and 20099163 could subsequently be related to ritlecitinib-mediated PKC signalling alterations. Finally, reactions of PKC isoforms by substances that react with cysteine residues in its structure are well described in the literature (e.g. Ward et al. 1995), rendering a cysteine-mediated reaction of ritlecitinib with PKC isoforms conceivable. Of note, in the kinase selectivity panel assay in study 151236, inactivation of PKC isoforms by ritlecitinib proved little efficient (maximally approximately 13% inhibition at 1 μM concentrations). However, as the applicant estimates that the unbound liver inlet ritlecitinib concentration at the proposed clinical dosing regimen is 8 μM, also in the brain, ritlecitinib levels might be attained that lead to a relevant extent of PKC inhibition. Additionally, it is also conceivable that a reaction with ritlecitinib with PKC isoforms in the brain could lead to an increased proteolytic degradation of PKC-ritlecitinib adducts, rendering an overall decreased PKC activity in the brain. The alteration of PKC signalling by ritlecitinib might explain the neurological alterations observed in the dog repeated dose toxicity studies 20070068 and 20099163. However, the applicant responded that the binding of PKC isoforms by ritlecitinib is not aetiologically or biologically relevant to the ritlecitinib-related axonal dystrophy formation in dogs. According to the applicant, ritlecitinib has a relatively low binding affinity to PKC compared to other potential off-targets and showed minimal inhibition in the Invitrogen kinase selectivity panel. Specifically, the applicant concluded that the binding of ritlecitinib to PKC can be predicted to be even lower than MAP2K7. The applicant also concluded that there is no *in vitro* or *in vivo* evidence suggesting that there is an alteration in PKC signalling by ritlecitinib or that it could contribute to axonal dystrophies. These aspects are acknowledged by the CHMP; a risk to patients is therefore considered low.

As demonstrated by a mechanistic toxicity study (study number 19GR193) of ritlecitinib, DOCK10 and MAP2K7 were identified as potential off-target binding proteins in the dog central nervous system.

Regarding the binding of ritlecitinib to MAP2K7 as identified in study 19GR372, the applicant was expected to discuss the pathological and especially neurological relevance of this finding for patients, considering that dysfunction of MAP2K7 signalling is suspected to be correlated with the aetiology of neurological diseases such as schizophrenia (Winchester et al.). The applicant responded that the off-target binding of ritlecitinib with MAP2K7 does not lead to axonal dystrophies in dogs, and that this off-target reaction at clinically relevant exposures is not considered to impose a safety relevance for the clinical use of ritlecitinib. The latter was based on a provided literature review and a summary of the relevant non-clinical data. Specifically, the applicant concluded that the off-target MAP2K7 binding noted after incubation with very high concentrations of ritlecitinib in brain homogenates obtained from normal dogs is not considered of neuropathological relevance to patients at clinically relevant doses of ritlecitinib. Importantly, the applicant also communicated that there were no reported events or evidence of schizophrenia or potential associated symptoms such as delusions, hallucinations, or disorganised thinking associated with ritlecitinib treatment in clinical studies. Considering these aspects, the relevance of MAP2K7 inhibition by ritlecitinib is considered to be low for patients.

According to findings from an article (Ruiz-Lafuente N. et al., 2019), DOCK10-knockout mice showed slower coat loss due to reduced senescence gene set expression. There is no evidence of DOCK10

involvement in the pathophysiology of autoimmune AA since known genes linked to DOCK10 are associated with morphogenesis and differentiation (HOXA5), epidermal growth factor (EGF) signalling and chromatin condensation. Furthermore, the only immune cells shown to be reduced in DOCK10-knockout (KO) mice were Splenic B cells, considered as irrelevant in AA (Ruiz-Lafuente N. et al., 2019). In addition, DOCK10 was identified as a potential off-target binding protein only in the CNS of dogs; however, ritlecitinib potency against DOCK10 was not investigated due to the lack of a cysteine at the same position as JAK3, indicating low probability of covalent binding. Therefore, to the existing knowledge, DOCK10 is probably not included in the pathogenesis of AA, and the ability of ritlecitinib to inhibit DOCK10 remains questionable, especially in mice and humans.

Ritlecitinib's covalent nature of binding to JAK3 was demonstrated by adequate mass spectrometry and x-ray crystallography data.

The ICH M7(R1) specifies that bacterial mutagenicity assays are expected to be performed in compliance with Good Laboratory Practices (GLP) regulations and that lack of full GLP compliance does not necessarily mean that the data cannot be used to support clinical trials and marketing authorisations. As the submitted exploratory Ames tests were nonetheless in line with appropriate guidance (e.g. highest tested concentrations 5 mg/plate, cytotoxicity and solubility assessments, 5 relevant strains, adequate positive controls etc.), the non-GLP assays submitted in the dossier are considered sufficient for mutagenicity evaluation of (potential) impurities.

Ritlecitinib was not mutagenic in the bacterial mutagenicity assay (Ames assay). Ritlecitinib was not aneugenic or clastogenic at exposures equal to 130 times the MRHD on an unbound AUC basis based on the results of the *in vivo* rat bone marrow micronucleus assay.

In addition, 5 non-GLP compliant mechanistic studies on the axonal dystrophy findings in the Beagle dog toxicity studies 20070068 and 20099163 were submitted.

Specifically, the goal of study 17GR131 was to examine the plasma and brain tissue concentrations of ritlecitinib (superior olivary nucleus, cochlear nucleus and hippocampus) after oral gavage administration to female Beagle dogs (n=4 per group) at 0 and 40 mg/kg/day when administered for 3 consecutive days. Then, the objective of study 19GR193 was to examine potential off-target proteins in the dog CNS that might be causally related to the observed axonal dystrophies identified in the 9-month repeated dose toxicity studies 20070068 and 20099163. Specifically, a click chemistry-based chemoproteomic method was used to examine potential off-target proteins in Beagle dog (18-21 months old) brain tissue homogenates (hippocampus (n=5) and rostral cerebellar vermis (n=3)). Interestingly, the superior olivary nucleus was not investigated, even though this brain area in the pons was especially affected by ritlecitinib-mediated axonal dystrophies in the dog studies 20070068 and 20099163. As the axonal dystrophies in this brain area of the dog also led to functional impairments (up to severe neuronal hearing loss), sparing this brain area in the investigations of Study 19GR193 is unfortunate. While it is appreciated that the applicant examined potential off-target proteins for ritlecitinib in the dog brain in this study, all affected brain areas by ritlecitinib-mediated axonal dystrophies (especially the superior olivary nucleus) would have been needed to be analysed in such studies. Finally, albeit such studies might give some mechanistic understanding of the pathology underlying the observed ritlecitinib-related axonal dystrophies in dogs, their translatability to humans remains elusive, especially as the possibility of human-specific neurologic off-targets of ritlecitinib cannot be addressed by studies using dog brain homogenates.

However, regarding the observed ritlecitinib-mediated axonal dystrophies in the dog repeated dose toxicity studies 20070068 and 20099163, study 21GR164 did not seem relevant in elucidating the pathogenesis of the observed axonal dystrophies. This stems from the methodological weaknesses of this study (expression was only studied on the mRNA level), and from the fact that DOCK10 is not known to be a target liable for eliciting neurodegenerative diseases. Quite on the contrary, recent

investigations suggest that knock-out of this protein in mice actually might have beneficial effects in neuroinflammatory disorders and is therefore even proposed to be used in the treatment of multiple sclerosis (Namekata et al. 2020). However, no concerns were identified in this study.

Environmental Risk Assessment

The CHMP originally raised some concerns on the irreversible binding of ritlecitinib to environmental reactants. Specifically, in the 100 days water-sediment degradation study (study 260E-339), the fraction of non-extractable, irreversibly bound radioactivity (that had originally been added as labelled ritlecitinib) in the Brandywine Creek and Choptank River sediments at test termination were 74.9% and 39.2%, respectively. Similarly, in the 28-day surface-water and suspended sediment biodegradation study (study 260E-340) of ritlecitinib in Brandywine Creek surface water and in sediment amended surface water (containing approximately 1002 mg/L total suspended sediment), the main pathway for the disappearance of parent from both test systems was also transformation into non-extractable residues. This affected 40.8 to 49.1% of the added ritlecitinib. Note that the kinetics of this irreversible binding to sediment were fast: in study 260E-340, a quarter to two fifth of the irreversibly bound ritlecitinib-associated radioactivity pool was already bound to the sediment 1 minute after addition to the batch experiment. As widespread covalent reactivity of ritlecitinib with off-target proteins was observed throughout the submitted non-clinical dossier, it appears plausible that also in sediments and surface water, ritlecitinib covalently binds to organic structures (that presumably contain sulfhydryl moieties). This suggests that the covalent binding of ritlecitinib to organic matter is an ubiquitous chemical reaction not limited to humans and animals. The binding of ritlecitinib to environmental reactants could therefore considerably increase the persistence of ritlecitinib in the environment. However, as ritlecitinib proved to possess a very low ecotoxic potential at the environmentally expected concentrations, this potential for increased persistency presumably bears no or only little ecotoxicologic relevance.

Overall, ritlecitinib is not a PBT substance. Considering the above data, ritlecitinib is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

In conclusion, the applicant provided a comprehensive evaluation of pharmacologic, pharmacokinetic and toxicologic properties of ritlecitinib. Studies in animal have shown neurologic and reproductive toxicities. The impact on neurotoxicity is further discussed in the clinical safety section. Ritlecitinib is contraindicated in pregnancy and breast-feeding. Women of childbearing potential have to use effective contraception during treatment and for 1 month following the final dose of ritlecitinib. Overall, ritlecitinib is 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.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

21 pivotal studies in healthy subjects were submitted to support the pharmacokinetics (PK) of ritlecitinib. In addition, PK data were included in population PK analyses.

Ritlecitinib is formulated as a single enantiomer. Ritlecitinib has a high solubility in aqueous solutions. The recommended dose is 50 mg once daily. Considering this dose, ritlecitinib tosylate is a high solubility drug, in accordance with the ICH M09 Biowaiver guideline. The estimated absorption of ritlecitinib tosylate is less than 85%. The absolute bioavailability is 64% and the absorbed fraction of the dose was estimated to be 89% in the labelled ADME study. However, as for the latter no complete mass balance could be obtained, which may imply uncertainties in the absorbed fraction; by taking a conservative approach, ritlecitinib tosylate should be considered a BCS Class III drug, according to the Biopharmaceutics Classification System (BCS).

Analytical methods

For the analysis of ritlecitinib in plasma and urine, validated LC-MS/MS methods were applied, showing acceptable accuracy and precision. Validation/analysis in plasma were carried out at 2 analytical sites. Cross-validation was carried out between both plasma analytical methods, using spiked QC samples and 40 incurred study samples from study B7981054. QC accuracy showed a negative bias at Labcorp Shanghai compared to York Bioanalytical Services, ranging from -9.7 to -20.1%. Further, for the incurred sample analysis a trend to a negative bias was observed at Labcorp Shanghai, although analysis showed that 92.5% was within the acceptable 20% difference between the 2 labs and passing the acceptance criteria. According to EMA guideline on bioanalytical method validation, for QC samples, inter-laboratory differences for mean accuracy should be within ±15%. The applicant was asked to justify that the negative bias of the method, and especially the large negative bias observed for QCDIL would not significantly affect PK results from corresponding clinical studies or results from the population PK analysis. New QCs were prepared and analysed, and the results showed that the difference between the 2 labs was well within the criteria. The applicant attributed the difference between the first and second analyses to variability in preparation. The results of the second analysis align with those obtained for incurred sample reanalysis at both labs. Therefore, this issue is considered resolved.

Validated LC-MS/MS methods with acceptable accuracy and precision were applied for the analysis of the co-administered drugs midazolam in plasma, efavirenz in plasma, levonorgestrel and ethinyl estradiol in plasma, rosuvastatin in plasma, sumatriptan in plasma, tolbutamide and 4-hydroxytolbutamide in plasma, caffeine in plasma and for the biomarker N1-methylnicotinamide in plasma and urine.

Accuracy and precision during study sample analysis were within normal criteria. ISR data showed good reproducibility. Furthermore, study samples were analysed within the established stability periods.

PopPK analyses

PopPK analysis has been conducted iteratively as ritlecitinib concentration information became available from completed studies.

PopPK model PMAR-EQDDB798h-Proof of Concept-1091 encompasses all studies included in the previously developed models PMAR-EQDD-B798d-Other-1023 and PMAR-EQDD-B798d-PrePoC-859;

therefore, the results supersede those of the previous iterations. The final model described in PMAR-EQDD-B798d-DP4-1157 was developed using PMAREQDD-B798h-Proof of Concept-1091.

Model PMAR-EQDDB798h-Proof of Concept-1091 was a popPK model of ritlecitinib in healthy volunteers and patients with moderate-to-severe rheumatoid arthritis, moderate-to-severe AA, moderate-to-severe ulcerative colitis, or active non-segmental vitiligo. The PK of ritlecitinib could be adequately described by a 2-compartment model with first-order oral absorption with a direct-response non-stationary clearance and bioavailability driven by peripheral concentrations in the analysis population of healthy volunteers, subjects with moderate hepatic impairment, moderate-to-severe RA, AA, vitiligo, and moderate-to-severe UC patients. Goodness-of-fit plots of the model and the pcVPC demonstrated that the model adequately described the time course of ritlecitinib plasma concentrations and its associated variability after oral dosing.

A final model PMAR-EQDD-B798d-DP4-1157 was developed, including healthy volunteers, subjects with severe renal impairment, and patients with AA. The final model was a 2-compartment model with first-order absorption with inter-individual variance on apparent clearance and apparent central volume of distribution, a proportional random unexplained variability model, and non-stationary clearance and bioavailability directly driven by peripheral concentrations. Goodness-of-fit plots of the model and the pcVPC demonstrated that the model adequately described the time course of ritlecitinib plasma concentrations and its associated variability after oral dosing.

The final model addresses ritlecitinib non-linear PK by introducing a non-stationary effect of ritlecitinib concentrations from the peripheral compartment on both CL/F and F. Different structural models were tested in the development, and the model with peripheral concentration dependent CL and F provided the best fit. Goodness-of-fit plots of the model and the pcVPC demonstrated that this model adequately described the time course of ritlecitinib plasma concentrations and its associated variability after oral dosing.

Absorption

After oral dosing, maximal plasma concentrations were reached at about 1 h after administration.

The absolute bioavailability of ritlecitinib is about 64%. Based on oral and intravenous administration of the labelled active substance, the relative urinary recovery (oral/intravenous) of the labelled compounds was about 89%, indicating a high fraction absorbed (fa).

Ritlecitinib is a substrate for P-gp and BCRP. Dose normalised C_{max} was independent of dose within the range of 5 to 800 mg, and considering the relatively high bioavailability, the impact of intestinal P-gp or BCRP efflux on the PK is considered limited by the applicant. Additionally, inhibition of P-gp and BCRP due to drug interactions is unlikely to impact the absorption of ritlecitinib significantly.

After a single dose, ritlecitinib AUC_{inf} increased more than dose-proportional over the 20 – 800 mg dose range, however, dose-proportional increases were observed up to 200 mg. C_{max} increased dose proportional after a single dose. After q.d. dosing, popPK analysis showed dose-proportional increases in AUC_{tau} and C_{max} from 30 mg to 200 mg compared to 50 mg q.d. at steady-state as median geometric mean ratios were within 0.8 to 1.25.
After q.d. oral dosing, a steady state was achieved after about 4 days, and the accumulation ratio was about 1.45 (popPK estimation). Considering the elimination half-life of about 2 h, the unexpected accumulation indicates non-stationary PK characteristics, where ritlecitinib CL changes following multiple doses resulting in a lower CL than after single doses. The mechanism contributing to this change in CL after multiple dosing is not clear.

The inter-subject variability observed after 50 mg q.d. administration in AA patients showed an inter-subject variability of about 47 and 44% for AUC_{tau} and C_{max}, respectively. The intra-subject variability

or within-subject standard deviations estimated in study B7981022 were 12 % and 24 % for AUC_{inf} and $C_{max,}$ respectively. The intrasubject variability or within-subject standard deviations estimated in study B7981029 were 11.9 % and 25.2 % for AUC_{inf} and $C_{max,}$ respectively. Pooled across treatments, intra-subject variability was estimated using ANOVA. The final popPK estimated intra-subject variability in Cl/F was about 18%, indicating that ritlecitinib is not subject to high intra-subject variability.

Both non-compartmental and population PK analyses show higher exposures in AA patients than healthy subjects. The underlying cause is unknown, but it is hypothesised that inflammatory condition in AA patients leads to reduced ritlecitinib clearance. At the recommended 50 mg QD dose, the non-compartmental analysis (NCA) showed a 2.6-fold higher exposure in AA patients, while popPK analyses showed a 1.5-fold higher exposure. Upon CHMP' request, the applicant clarified the discrepancy between NCA and Pop PK results due to the limited sample sizes, uncontrolled demographic factors across different treatment groups, and different sampling schemes in healthy participant studies compared to AA patient studies. In addition, a difference in body weight may have additionally contributed. The disease state (alopecia areata, alopecia totalis and alopecia universalis) had no significant impact on ritlecitinib clearance.

Population PK estimates indicate for the recommended dosing scheme of 50 mg q.d. the following exposure data in AA patients (geometric mean (%CV): AUC_{tau} 1249 (73) and C_{max} 370 (39).

In clinical studies, a loading dose of 200 mg was also used, i.e. a loading dose of 200 mg q.d. for 4 weeks followed by 50 mg q.d.. The longitudinal concentration-response analysis of the SALT score (see section Pharmacodynamics) demonstrated that although the corresponding loading dose regimen achieves SALT $\leqslant$10 response faster (about 3 weeks faster for 200/50 vs 50 mg dose), by week 48 there was no significant additional benefit of the loading dose regimen. Therefore, no loading dose is recommended. Furthermore, the longitudinal concentration-response analysis also demonstrated that the doses of 50 mg and 30 mg are in the ascending linear part of the dose-response curve, with the concentrations associated with 50 mg approximating the EC_{50}. Hence, 50 mg is predicted to provide more benefit over the 30 mg dose in terms of efficacy response (see further sections Pharmacodynamics and Efficacy).

Based on a log-normal distribution and observed variability in PK and taking into account analysis on exposure-response relationships of ritlecitinib for safety endpoints and exposure-response relationship of ritlecitinib for efficacy, mean exposure differences because of intrinsic or extrinsic factors, which fall within the range of 0.5- to 2-fold of the mean for the reference group, are considered not clinically relevant. However, the longitudinal concentration-response analysis indicated that a 30 mg q.d. dose would provide less efficacy. The suggested acceptable 0.5-fold difference in exposure, which would translate in a 25 mg q.d. dose, will thus also provide less efficacy. Therefore the 0.5-fold cut-off being not clinically relevant was further justified, i.e. both the 30 mg and 50 mg doses have been shown to be efficacious; however, the 50 mg group had a higher efficacy (proportion of participants who achieved severity of alopecia tool [SALT]$\leqslant$10) compared to 30 mg. A subject receiving a 50 mg dose and ending at the lower 0.5-fold exposure due to variability (and covariates) would fall in the higher exposure and still efficacious range of a 30 mg dose.

In clinical studies, the main formulation used was a 50 mg tablet. Intake of the 50 mg tablet after a high fat, high caloric meal decreased C_{max} by about 39%, while AUC was unaffected. Intake of a 100 mg capsule after a high-fat high caloric meal decreased C_{max} by about 32%, while AUC increased by 11% (not statistically significant). The 100 mg capsule formulation is dose-proportional (same blend) to the proposed 50 mg capsule formulation. Therefore, the results can be extrapolated to the commercial 50 mg capsule, as the criteria for a biowaiver for additional strengths have been fulfilled (see Bioequivalence/bioavailability).

Ritlecitinib was administered as tablets in the pivotal Phase 2b/3 efficacy and safety study and long-term safety study without regard to the timing of meals. The lower C_{max} is considered not clinically relevant. The SmPC recommends the capsule intake once daily with or without food, which is agreed upon.

Bioavailability/bioequivalence

In the development, the pivotal formulation was a 50 mg immediate-release tablet. In addition, 10 mg tablets were used in some studies. However, due to cold chain storage requirements, the ritlecitinib immediate-release tablets were unsuitable for commercial development. Therefore, the applicant developed a 50 mg capsule as the commercial formulation.

Bioequivalence between a 100 mg capsule formulation and the 50 mg tablet under fasting conditions could be shown. The 100 mg capsule is dose-proportional (same blend) to the proposed 50 mg commercial formulation. Applying a biowaiver for additional strengths, using paddle apparatus at 50 rpm, 500 ml media pH 1.2, 4.5 and 6.8, comparable dissolution could not be shown, as the 100 mg capsule showed a slower dissolution, according to the applicant, attributed to a slower disruption of the capsule. To be noted, individual results and f2 calculations were provided in the applicant's response. In addition, new dissolution data were provided with 900 ml media showing comparable results.

To support that the slower dissolution has no impact *in vivo*, the 100 mg capsule was over-encapsulated, creating a capsule with a slower *in vitro* dissolution. The 100 mg capsule and the 100 mg over-encapsulated capsule appeared to be bioequivalent *in vivo*. However, it is questionable whether this can be extrapolated to the 50 mg capsule, as the over-encapsulated capsule is not bioequivalent to 2 x 50 mg tablets, while these tablets were bioequivalent to the 100 mg (normal) 100 mg capsule formulation. Furthermore, the strategy applied includes an indirect comparison, i.e., first bridging the 50 mg tablet to the 100 mg capsule and additionally a waiver of additional strengths for the 50 mg capsule.

The bridging strategy was therefore not fully understood, and the applicant has provided an additional justification, i.e.:

- as a 200 mg loading dose was intended to be applied, the 100 mg capsule, being the highest strength, was used for comparisons, instead of the 50 mg capsule,

- Bioequivalence has been shown between the 50 mg clinical trial tablet and the 100 mg capsule. This 100 capsule contained the same blend as the 50 mg capsule intended to be marketed. Linear pharmacokinetics has been shown over at least the 20 – 100 mg single dose range. In principle, bioequivalence may also be expected between the 50 mg capsule intended to be marketed and the 50 mg clinical trial tablet if the similarity in dissolution between the 50 and 100 mg capsule has been shown. However, dissolution appeared to be faster for the 50 mg capsule compared to the 100 mg capsule (and even faster for the 30 mg capsule which was also used in clinical trials). As the same blend is used in both capsules, this difference can be attributed to the capsule shell. Still, as comparable *in vitro* dissolution has not been shown, it may be of concern that results cannot be extrapolated between the 50 mg clinical trial tablet and the 50 mg capsule intended to be marketed. However, plasma concentration data were available for the 30, 50 and 100 mg capsules from different clinical studies, although for the 50 mg capsule, only sparse sampling data from a recently completed target occupancy study (study B7981045). Dose normalised concentration-time curves showed comparable curves.

- With regard to dissolution, the 100 mg and the 30 mg capsule are the extremes, and the dissolution profile for the 50 mg capsule is bracketed by those two strengths. Statistical analysis by inter-study

comparison for the 30 and 100 mg capsule showed that ratios of adjusted geometric means of dose-normalised AUCinf and Cmax were close to 1, indicating only 5-6% difference (to be noted, the data on the 50 mg capsule were not taken into account in this analyse as due to sparse sampling Cmax could have been missed). Additionally, a PBPK model was developed using Simcyp platform (version 22, release 1) with input parameters derived from *in vitro* and *in vivo* studies and was based upon physiologically based principles and justifiable assumptions. Model verification shows a good prediction. Simulations predicted that the 50 and 100-mg capsules could be considered bioequivalent. Additionally, the comparable extent of absorption from the 50 and 100 mg capsules was confirmed using the TIM-1 gastrointestinal simulator. Although the TIM-1 gastric dissolution profiles confirmed the faster dissolution from the 50 mg capsule, the cumulative bio-accessibility of 50 mg and 100 mg ritlecitinib capsules was comparable.

Therefore, the bridge between the 50 mg clinical trial tablet and the 50 mg capsule intended to be marketed is supported.

With regard to the dose-proportional 10 mg tablet, no dissolution data could be retrieved to support the waiver for the 10 mg tablet vs. the 50 mg tablet. These data were additionally provided, showing comparable dissolution at pH 1.2, 4.5, and 6.8, paddle, 50 rpm, using 900 ml media.

Distribution

Ritlecitinib binding to plasma proteins is low, with a free fraction of 86% (14% unbound). Binding is mainly to serum albumin.

The blood to plasma ratio was 1.62, indicating distribution to red blood cells.

After i.v. administration, a volume of distribution is observed of 74 l, indicating considerable tissue distribution.

Based on rat data, biliary excretion of ritlecitinib is limited, distribution to brain tissue is limited and ritlecitinib is excreted into the milk.

Metabolism

In vitro, metabolite profiling of ritlecitinib in liver microsomes and hepatocytes indicated that CYP3A4/5 was identified as the primary CYP contributing to ritlecitinib metabolism through combined formation fractions of 302-2 and PF-07297983 (302-3, M4) with an overall CYP3A fm 0.29. Lesser contributions to ritlecitinib metabolism identified were CYP2C8 fm 0.091, CYP1A2 fm 0.068, and CYP2C9 fm 0.016. Furthermore, multiple glutathione S-transferases are involved in the metabolism (i.e., cytosolic GST A1/3, M1/3/5, P1, S1, T2, Z1, and microsomal Membrane Associated Proteins involved in Eicosanoid and glutathione metabolism MAPEG 1/2/3). However, functional variants in GST P1 (*B, *C) and null genotypes in GST M1 and T1 did not show significant differences in AUC compared to wild-type GST P1*A, M1, or T1.

The *in vivo* mass balance of ritlecitinib was evaluated after a single oral dose of ^{14}C-ritlecitinib 200 mg containing approximately 300 nCi ^{14}C (i.e., radio-labelled ritlecitinib). In a second period, subjects received a single oral dose of unlabelled ritlecitinib 200 mg followed at t_{max} (about 0.5 h post-oral dose) by an i.v. dose of ^{14}C-ritlecitinib 60 µg containing approximately 300 nCi ^{14}C (i.e., radio-labelled ritlecitinib) to evaluate the absolute bioavailability. In both periods, fasting conditions were applied.

In plasma, ritlecitinib was the most abundant drug compound (about 30% of total drug-related materials), with the M2 (cysteine conjugate) as the major circulating metabolite showing abundance of about 17%. Other minor circulating drug-related components included glutathione-related metabolites and downstream oxidations. The abundance of the other metabolites identified in human plasma was

trace or minor (<10%). No individual clearance pathway contributed ⩾25% of systemic clearance. However, approximately 35% of the plasma-associated radioactivity was non-extractable, associated with a protein pellet, and could not be identified. This raises a concern that major or some other metabolites may be circulating in plasma. However, the applicant explained the high percentage of non-extractable radioactivity plasma by off-target binding of ritlecitinib to albumin. The total binding of ritlecitinib to albumin only makes a low fraction of the available albumin in patients, and only 0.6% of the administered dose in the human ADME study is bound to albumin. These estimations support that binding to albumin will be clinically negligible (see further pre-clinical section).

The total recovery of the orally administered radioactive dose for 240 h post-dose (n=5) was 85.6±9.2%, with 66.1±13.4% in the urine and 19.5±4.0% in the faeces.

In urine, hydroxylated M4 and N-acetyl cysteine conjugate M3 were the main metabolites, representing 16.3 and 10.3 % of the administered dose, respectively. Other minor metabolites observed in urine were the glutathione-related M2 (4.6%), M1(4.0%) and 423(2.0%), downstream oxidative metabolites 336-3 (6.5%), M5 (3.3%), 320-1 (2.3%), 318-2 (1.5%), oxidative glucuronide 512 (1.1%) and ritlecitinib (2.7%). Renal clearance of ritlecitinib accounted for approximately 4% of total clearance.

In faeces, glutathione-related remnants and various hydrolytic and oxidative metabolites were identified, but no single metabolite was greater than 1% of the administered dose. Half of the fraction in faeces could not be identified as being non-extractable and associated with a protein pellet.

The main circulating metabolite in plasma is the cysteine conjugate M2, but it represents only about 17% of drug-related material in plasma. After once-daily dosing of 200 mg ritlecitinib, a steady state for the M2 metabolite is achieved at day 6. T_{max} at steady state was about 2 h and C_{min} about 2.8 ng/ml. Cysteine conjugate M2 is pharmacologically inactive against JAK1, JAK2, JAK3, TYK2 and TEC family kinases.

Elimination

Ritlecitinib is eliminated with an elimination half-life of about 1.3 - 2.3 h. Clearance after a single iv dose was estimated to be about 44 l/h and CL/F 66 – 77l/h. However, PopPK analysis (final model) indicated a Cl/F of 107 l/h. It is observed that ritlecitinib shows non-stationary PK characteristics, where ritlecitinib CL changes following multiple doses resulting in a lower CL relative to after single doses. This would not be in line with the observed data from the single-dose study and the final popPK analysis. The difference has been clarified because the CL/F in the popPK model represents the clearance without inhibition. Comparison with Cl/F at the low dose of 5 mg, a dose at which concentration inhibition is considered minimal, indicated comparable clearance values. Furthermore, the non-stationary PK was accounted for in the popPK model.

Special populations

PK data and population PK analysis were used to evaluate the impact of covariates on the PK of ritlecitinib.

Renal impairment: The PK of ritlecitinib has been evaluated in subjects with severe renal impaired function. The ANOVA analysis indicated that AUC_{tau} and C_{max} were 55% and 44% higher in subjects with severe renal impairment, respectively, compared to healthy subjects.

The difference in exposure falls within the estimated 0.5 – 2.0-fold range of clinical insignificance. The SmPC indicates that no dose adjustment is required for subjects with mild, moderate and severe renal impairment, which is agreed from a PK point of view.

Hepatic impairment: The PK of ritlecitinib has been evaluated in subjects with a moderate hepatic impaired function (Child-Pugh B score). The ANOVA Inclusion of the data in popPK analysis indicated

that AUC_{tau} and C_{max} in subjects with moderate hepatic impairment were 18.5% and 4% higher, respectively, compared to healthy subjects.

The difference in exposure falls within the estimated 0.5 – 2.0-fold range of clinical insignificance. The SmPC indicates that no dose adjustment is required for subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, which is agreed from a PK point of view. Ritlecitinib is contraindicated in patients with severe (Child-Pugh C) hepatic impairment.

In study B7981016, 1 subject with moderate hepatic impairment showed a very pronounced higher exposure than the other subjects with moderate hepatic impairment. No clear explanation could be given for the pronounced higher result. However, considering variability in the total population, such a higher value may be expected by coincidence.

Gender: The popPK analysis identified gender as a non-significant covariate on ritlecitinib pharmacokinetics.

Ethnicity/Race: The popPK analysis identified race/ethnicity (Asian/Black/White/Other, Japanese/non-Japanese, Asia/Europe/North America/Rest of the world) as a non-significant covariate on ritlecitinib PK.

Age Elderly/adolescents: The popPK analysis identified age (12 – 73 years) as a non-significant covariate on ritlecitinib PK. The SmPC indicates that no dose adjustment is required for adolescents 12 to < 18 years of age and for the elderly, which is agreed from a PK point of view.

In the popPK analysis, 69 subjects of age 65–74 years were included, and no subject over 75 years of age was available in the analysis dataset.

Bodyweight: The popPK analysis identified body weight as a significant covariate on ritlecitinib PK. A subject with a body weight of 47 kg had a 45% higher exposure, while a subject with a body weight of 101 kg had a 30% lower exposure. These differences fall within the estimated 0.5 – 2.0-fold range of clinical insignificance. As requested, the clinical relevance of exposures of subjects with an extreme body weight outside this 47 – 101 kg range, especially for adolescents, has been justified, i.e. based upon simulations, patients with a body weight of 32.6 – 131 kg would fall within the 0.5 – 2.0 exposure range, which is considered still efficacious and safe.

Pharmacokinetic interaction studies

Ritlecitinib is metabolised by multiple isoforms of GSTs and CYPs (CYP3A4 is the predominant CYP responsible for the metabolism with contributions from CYP2C8, CYP1A2, and CYP2C9). Regarding GSTs, functional variants in GST P1 (*B, *C) and null genotypes in GST M1 and T1 did not show significant differences in AUC compared to wild-type GST P1*A, M1, or T1, indicating a low potential of interaction with this pathway.

Administration of 200 mg q.d. itraconazole (strong CYP3A/P-gp inhibitor) with ritlecitinib (30 mg, single dose) resulted in a 15% and 3% increase in AUC_{inf} and C_{max} of ritlecitinib.

Administration of 600 mg q.d. rifampin (strong CYP3A and P-gp/UGT inducer, 2C19, 2C9 and 2B6 inducer, *in vitro* inducer GSTs) resulted in a 44% decrease in AUC_{inf} and a 25% decrease in C_{max} of ritlecitinib.

These differences in exposure fall within the estimated 0.5 – 2.0-fold range of clinical insignificance.

Co-administration of ritlecitinib with acid-reducing agents is highly unlikely to impact its solubility and subsequent absorption, given its high solubility profile across a range of pH levels.

In vitro, ritlecitinib was not a significant competitive inhibitor of CYP enzymes. Ritlecitinib showed *in vitro* time-dependent inhibition versus CYP3A and CYP1A2. Ritlecitinib exhibited a potential to induce

CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19. A low inhibition towards glutathione S-transferase isoforms is observed *in vitro*, suggesting no significant impact *in vivo*; however, the quantitative translation to *in vivo* is currently not understood.

The M2 inactive metabolite was not a significant competitive inhibitor of CYP enzymes. M2 did not exhibit *in vitro* time-dependent inhibition versus CYP3A and CYP1A2 or other CYPs, and did not exhibit a potential to induce CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19.

In vitro studies have shown the inhibitory potential of ritlecitinib for hepatic transporters (e.g., OCT1 [IC_{50}=3.7 µM]), renal transporters (e.g., OCT2 [IC_{50}=55 µM], OAT3 [IC_{50}=41.3 µM], MATE1 [IC_{50}=51 µM] and MATE2K [IC_{50}=48 µM]) and BCRP [IC_{50}=27.0 µM].

In vitro, ritlecitinib and M2 demonstrated no significant inhibition of the major UGT enzymes. And ritlecitinib did not significantly inhibit SULT or GST enzymes.

The time-dependent inhibition versus CYP3A was confirmed *in vivo*, showing an increased AUC_{inf} and C_{max} of the CYP3A4 substrate midazolam (single 2 mg dose) by 169 and 81%, respectively, after 200 mg q.d. administration of ritlecitinib. Although *in vitro*, ritlecitinib may also induce CYP3A4, these data indicate that ritlecitinib is *in vivo* a time-dependent moderate inhibitor for CYP3A.

The time-dependent inhibition versus CYP1A2 was confirmed *in vivo*, showing an increased AUC_{inf} and C_{max} of the CYP1A2 substrate caffeine (single 100 mg dose) by 165 and 10%, respectively, after 200 mg q.d. administration of ritlecitinib. Although *in vitro*, ritlecitinib may also induce CYP1A2, these data indicate that ritlecitinib is *in vivo* a time-dependent moderate inhibitor for CYP1A2.

The potential to induce CYP2C9 was not confirmed *in vivo*, as AUC_{inf} and C_{max} of the CYP2C9 substrate tolbutamide (single 500 mg dose) were not significantly affected after 200 mg q.d. administration of ritlecitinib. These data indicate that ritlecitinib is *in vivo*, not an inducer of CYP2C9.

The potential to induce CYP2B6 was not confirmed *in vivo*, as 200 mg q.d. administration of ritlecitinib did not significantly affect the pharmacokinetics of efavirenz (CYP2B6 substrate, single 50 mg dose). These data indicate that ritlecitinib is *in vivo*, not an inducer of CYP2B6.

Ritlecitinib 200 mg qd decreased the BCRP, OATP1B1 and OAT3 substrate rosuvastatin (10 mg single dose) AUC_{inf} and C_{max} by 13 and 27%, respectively, and urinary rosuvastatin excretion was not affected (Clr ratio 106%). Intestinal BCRP acts as an efflux transporter limiting rosuvastatin absorption, while liver BCRP actively excretes rosuvastatin into the bile. OATP1B1 is an uptake transporter expressed on the sinusoidal side of hepatocyte, providing rosuvastatin access to hepatocyte and subsequent metabolism and elimination. Hence, potential inhibition of BCRP and OATP1B1 by ritlecitinib would be expected to increase rosuvastatin plasma exposure. However, rosuvastatin exposures did not increase when rosuvastatin was co-administered after multiple doses of ritlecitinib. Hence, the inhibition potential of ritlecitinib for BCRP and OATP1B1 transporters is low.

Furthermore, rosuvastatin is a substrate for OAT3, contributing to its active renal secretion. Any OAT3 inhibition is expected to reduce the renal clearance of rosuvastatin significantly. However, renal clearance of rosuvastatin was comparable in the absence and presence of multiple doses of ritlecitinib, suggesting minimal inhibition potential risk of ritlecitinib for the OAT3 transporter.

Furthermore, the biomarkers coproporphyrin 1 for OATP1B1/1B3, N1-methylnicotinamide for OCT2/MATE1/MATE2K and pyridoxic acid for OAT1/3 biomarker were not significantly affected, indicating a low inhibition potency towards these transporters.

The inhibitory potential of ritlecitinib for the hepatic transporter OCT1 was confirmed *in vivo*, as AUC_{inf} and C_{max} of the OCT1 substrate sumatriptan (single 25 mg dose) increased with 30 and 13%, respectively, after co-administration of 400 mg ritlecitinib. When ritlecitinib was administered 8 h

before sumatriptan, the sumatriptan exposure increased by 50%. These data indicate that ritlecitinib is an inhibitor of OCT1 *in vivo*.

To exclude a possible interaction with oral contraceptives, *in vivo* ethinyl estradiol/levonorgestrel 30/150 µg (single dose) was co-administered with 50 mg q.d. ritlecitinib. Ritlecitinib decreased the ethinyl estradiol AUC_{inf} and C_{max} by 2 and 8%, respectively, and decreased the levonorgestrel AUC_{inf} and C_{max} by 12 and 20%, respectively. These changes were not considered clinically relevant.

The potential for interactions has been adequately reflected in the SmPC section 4.5.

2.6.2.2. Pharmacodynamics

Mechanism of action

Ritlecitinib irreversibly and selectively inhibits Janus kinase (JAK) 3 and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family by blocking the adenosine triphosphate (ATP) binding site. In cellular settings, ritlecitinib specifically inhibits γ-common cytokines (IL-2, IL-4, IL-7, IL-15 and IL-21) signalling through JAK3-dependent common-γ chain receptors. Additionally, ritlecitinib inhibits TEC family of kinases, resulting in reduced cytolytic activity of NK cells and CD8+ T cells.

JAK3 and TEC family mediated signalling pathways are both involved in alopecia areata pathogenesis, although complete pathophysiology is still not understood.

Primary and Secondary pharmacology

Data from the main clinical study B07981015 in participants with AA were used for the exploration of pharmacodynamics (PD). The pathophysiology of AA as an auto-immune disease supports the relevance of JAK inhibition in the treatment of this disorder. Ritlecitinib is an oral covalent irreversible inhibitor of the 5 TEC family kinases (BMX, BTK, ITK, TEC, TXK) and JAK3. It lacks activity against JAK1 and JAK2, leading to a narrower spectrum of cytokine inhibition. JAK3 and TEC kinases regulate the response of CD8+ T, NK and mast cells thought to be involved in the pathophysiology of AA. Ritlecitinib lacks activity against JAK1 and JAK2, inhibiting only the 6 γ-common cytokines IL-2, IL-4, IL-7, IL-9, IL-15 and IL-2. The spider graphs in Figure 6 and Figure 7 represent the theoretical projected inhibition profiles of various signalling pathways, some of which have been shown to be important in autoimmune diseases. Values on the axes represent the projected average percent inhibition of each cytokine during a dosing period. These values are calculated based on the IC50 values obtained in whole blood for each cytokine and the average concentration measured in the plasma of subjects dosed with JAK inhibitors. Although the relevance of selective inhibition of a specific JAK enzyme to clinical effects is not currently known, ritlecitinib shows a pattern of effects on immune cell signalling that is differentiated from approved JAK inhibitors by sparing JAK1, JAK2 and TYK2.

Since the pivotal study was dose-ranging, the relationship between concentration and its effect on symptoms (i.e. hair loss) was analysed in that study (see the section on Clinical Efficacy for details). In the pivotal study, the participants were randomised to 6 treatment arms: ritlecitinib 50 or 30mg QD (either with or without loading dose of 200mg QD during the first 4 weeks, referred to as 200/50 of 200/30), ritlecitinib 10 mg QD and placebo. The placebo-controlled phase lasted 24 weeks after which participants of the placebo arm were blindly assigned to either 200/50 mg or 50 mg treatment group. The participants of other arms remained on the originally assigned dose. This extension phase lasted another 24 weeks (through week 48).

Changes in biomarkers

In addition to assessing the clinical manifestations of AA, the pivotal study also measured several PD biomarkers such as a change from baseline in interferon gamma-induced protein 10 (IP-10) up to

Week 24, percentage and absolute numbers of lymphocyte subsets and change from baseline in immunoglobulins (IgA, IgG, IgM) up to Week 48.

All treatment groups showed small and variable changes in IP-10 from baseline up to Week 24. At Week 24, the mean change from baseline was dose-dependent, ranging from a maximum (ng/mL) of -37.4 in 200/50 mg to -6.8 in placebo. A decrease of absolute lymphocyte (subset) levels of CD3, CD4 and CD8 were observed. After the initial dose-dependent decrease, the levels partially recovered and remained stable up to week 48, not always in a dose-dependent way. CD19 (B lymphocyte) did not appear to decrease in either treatment group. There was a dose-dependent early decrease in CD16/56 (NK cells), which was the most apparent in groups that had received a 200 mg loading dose (200/50 mg and 200/30 mg) of ritlecitinib. The dose-dependent effect was less obvious in subsequent weeks. Finally, there were no clinically concerning changes in immunoglobulins (IgA, IgG, IgM) up to Week 48 across all groups.

Figure 6: Projected spectrum of cytokine inhibition by ritlecitinib

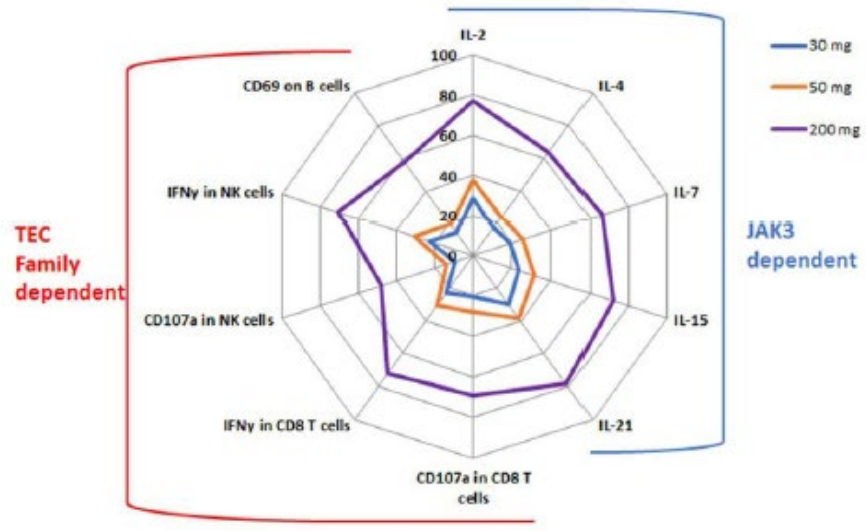
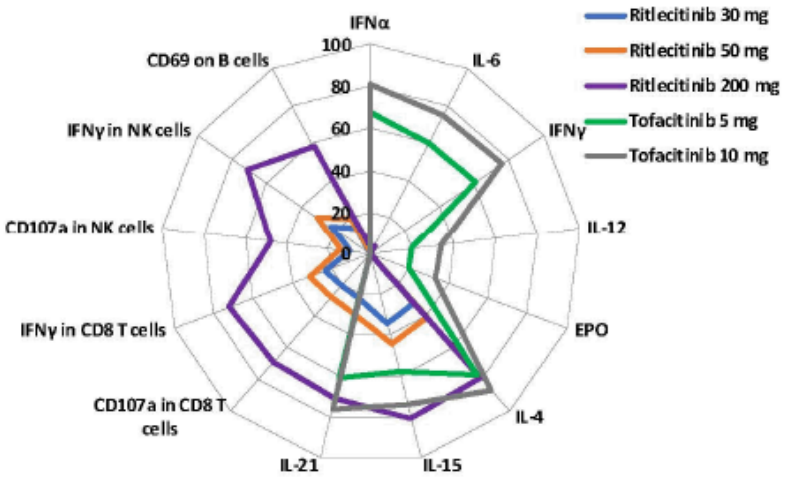
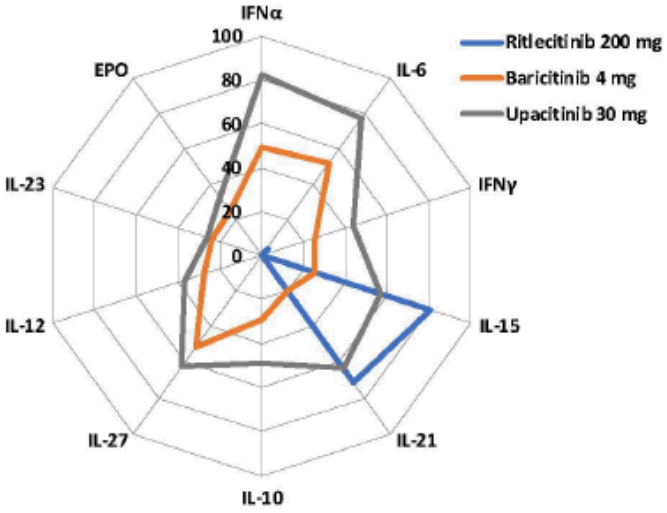


Figure 7: Spectrum of cytokine inhibition and other cellular readouts. (A) Ritlecitinib versus Tofacitinib.(B) Ritlecitinib versus Baricitinib and Upadacitinib.

A



B



Concentration response analyses

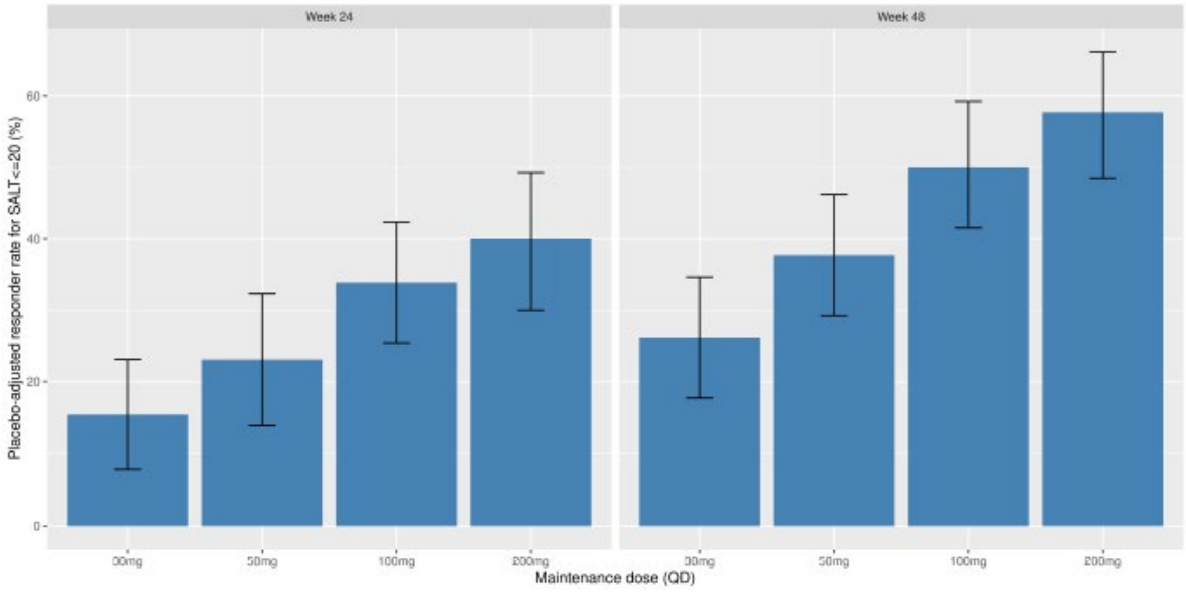
A longitudinal concentration-response analysis using Cav and the raw SALT score was conducted to characterise the concentration-response relationship, temporal characteristics of the response and covariates in the study population, which can account for variability in SALT score reduction. A combined data set which included data from completed studies (B7931005 and B7981015) and ongoing study B7981032 (data cutoff date of 02 Jun 2021) was used for the analysis.

As the SALT score represents a bounded scale (0 to 100), the non-boundary data were scaled between 0 to 1 and transformed using Aranda-Ordaz flexible link function to normalise the skewed distribution of a bounded SALT score data. A general nonlinear mixed-effects model was then constructed based on the transformed SALT score. The final model was a semi-mechanistic model that described the placebo and drug response utilising indirect response models with transit compartments to characterise the delay in response. The drug effect was described by a 2 parameter Emax-EC_{50} model.

The C_{av} during the time interval between the previous SALT score and the current SALT score were used as the PK concentration metric for the efficacy. Given that ritlecitinib irreversibly inhibits JAK3/TEC kinases and the improvement in SALT score is the gradual outcome of their modulation of the downstream signalling pathways, the applicant assumed that the efficacy is not sensitive to the short-time fluctuation in concentration, such as Cmax, and is rather influenced by average concentration over a period of time (i.e., Cav).

The concentration at half maximum effect (EC_{50}) estimated as in Cav was 53.6 ng/ml, similar to the Cav of a 50 mg q.d. dose (52 ng/ml). Simulations indicated that an additionally improved efficacy is expected by increasing the maintenance dose to greater than 50 mg q.d. (see Figure 8).

Figure 8: Placebo-adjusted responder rate for SALT ⩽20 for various maintenance doses



The use of a loading dose (200 mg q.d. for 4 weeks) resulted only in an earlier onset of effect. The clinical onset times were 6 weeks with loading dose vs. 9 weeks with non-loading for 50 mg q.d.. The loading dose of 200 mg for 4 weeks achieved the clinical onset of SALT ⩽20, 3 weeks faster for 50 mg q.d. dose group. However, the differentiation in the SALT ⩽20 response was diminished by week 48, such that the responder rates were similar between loading vs non-loading dose regimens at week 48.

Further, to evaluate the possibility of maintenance therapy with ritlecitinib 30 mg after remission has been achieved with 50mg, a model-based clinical trial simulation approach was used to quantitatively assess the potential exposure-driven decrease in efficacy when the ritlecitinib dose is reduced from 50 mg to 30 mg. A simulation was conducted utilising the final longitudinal concentration-response (LCR) model of the SALT score based on data from studies B7931005, B7981015, and B7981032 to predict the proportion of SALT ⩽20 responders on 50 mg maintaining their SALT ⩽20 response after a dose reduction to 30 mg. The modelling data indicate that loss of response should be expected when the dose is reduced from 50 mg to 30 mg: more patients on the 50 mg dose maintained the response at week 156 as compared to patients whose dose was lowered (95%, 95%CI [90, 99] vs. 81%, 95%CI [72, 88]) (Table 5).

Table 5: Model-predicted proportion of responders maintaining SALT ⩽20 response after dose tapering

	Proportion of responders maintaining SALT ≤20 response (%, median [95% prediction interval])	
Time after re-randomization (Week)	50 mg→50 mg	50 mg→30 mg
24	94 (89,98)	85 (77,92)
36	94 (89,98)	83 (75,90)
52	94 (90,98)	82 (74,89)
104	95 (89,98)	81 (72,88)
156	95 (90,99)	81 (72,88)

The **effect of dose interruption** on SALT≤20 was analysed using a simulation analysis, from which it was concluded that dose interruptions in the 50 mg dose of ≥6 weeks could lead to decreases in average population response rates at Week 24. For the no dose interruption scenario, the responder rate for SALT ≤20 was 23.1%. This is the expected value for the responder rate when no participant missed a study visit, and no one skipped any ritlecitinib doses. The estimate was very similar to the observed value for 50 mg group in the B7981015 study (23.39%), after the exclusion of 6 participants missing due to COVID 19 and treating 5 participants missing due to reasons unrelated to COVID-19 as non-responders.

The responder rate decreased for each of the various dose interruption scenarios, reflecting the impact of dose interruption on SALT ⩽20 at Week 24 (Table 6). The impact of dose interruption was dependent upon both 1) the dose interruption start time and 2) the duration of the interruption. The impact was generally larger when the duration of interruption was ⩾6 weeks.

Table 6: Predicted proportions of patients with SALT ⩽20 at week 24 for various dose interruption scenarios for ritlecitinib 50 mg

Dose interruption start time (week)	RR for no dose interruption (%)	RR for 2 weeks of dose interruption (%)	RR for 4 weeks of dose interruption (%)	RR for 6 weeks of dose interruption (%)	RR for 8 weeks of dose interruption (%)
0	23.1	-	-	-	-
4	-	17.7	15.4	11.5	8.5
6	-	17.7	15.4	10.0	8.5
8	-	19.2	14.6	10.8	7.7
10	-	19.2	13.8	10.0	9.2
12	-	19.2	16.2	10.0	9.2
14	-	19.2	16.9	13.8	13.1
16	-	18.5	16.9	16.9	16.9
18	-	18.5	16.2	16.2	-
20	-	20.0	19.2	-	-
22	-	22.3	-	-	-

RR='response rate', or proportion of patients with SALT⩽20.

The effect of dose interruptions after the target clinical response (SALT ≤10) is achieved was also analysed using simulation, concluding that after the target clinical response of SALT ≤10 is achieved, dose interruptions of ≥6 weeks will result in the loss of the SALT ≤10 response in some patients. Simulations assumed that the offset rate was equal to the onset rate of the patient. The final model was used to simulate responses up to 96 weeks to ensure a stable target clinical response. The dose was interrupted following 96 weeks, and changes in SALT score were collected. The proportion of responders losing SALT ≤10 response was further summarised according to the duration of treatment

interruption in Table 7. Based on the model prediction, ≥14% of the responders were predicted to lose response when treatment was discontinued for ≥6 weeks, and almost half of the responders were predicted to lose response when treatment was discontinued for ≥16 weeks.

Table 7: Proportion of responders losing SALT≤10 response for various dose interruption durations

Treatment interruption duration (weeks)	Proportion of responders losing SALT ≤10 response (%)
4	7.1
6	14
8	21
10	29
12	36
14	41
16	45

The applicant has updated the above analysis with the simulation to evaluate times to lose SALT ⩽20 response for SALT ⩽10 responders. Also, in this updated simulation, all the participants were treated with ritlecitinib 50 mg QD until Week 96 to ensure the SALT response had reached a plateau. However, the SALT score was now simulated for every week up to Week 144 (up to 48 weeks of treatment interruption) to capture any changes in SALT score after treatment withdrawal. The proportion of SALT ⩽10 responders losing SALT ⩽20 response for various treatment interruption durations is summarised in Table 8. Based on this summary, 66% of SALT ⩽10 responders are predicted to lose SALT ⩽20 response and 70% are predicted to lose SALT ⩽10 response with up to 48 weeks of treatment interruption. The risk of losing SALT ⩽20 response is <5% after treatment withdrawal for up to 6 weeks, and it is >10% if treatment withdrawal is for 10 weeks or longer.

Table 8: Cumulative proportion of SALT⩽10 responders to 96 weeks of ritlecitinib 50mg QD treatment who lost SALT ⩽20 or SALT⩽10 responses for various interruption durations

Treatment interruption duration (weeks)	Proportion of SALT ≤10 responders losing SALT ≤20 response (%)	Proportion of SALT ≤10 responders losing SALT ≤10 response (%)
4	1.4	5
6	3.9	9.9
8	8	15
10	13	20
12	17	26
14	22	29
16	25	32
24	38	46
36	54	62
48	66	70

Regarding the effect of ritlecitinib on **platelets**, a mean reduction from baseline counts of less than 25% was observed for all ritlecitinib doses with respect to placebo (see Safety section). However, the effect appears to be saturated as all doses demonstrated a similar response without a clear dose-response relationship. This level of change in platelet counts was not considered clinically significant in this population and is unlikely to result in increased risk of thrombocytopenia. Therefore, no further concentration-response modelling was conducted.

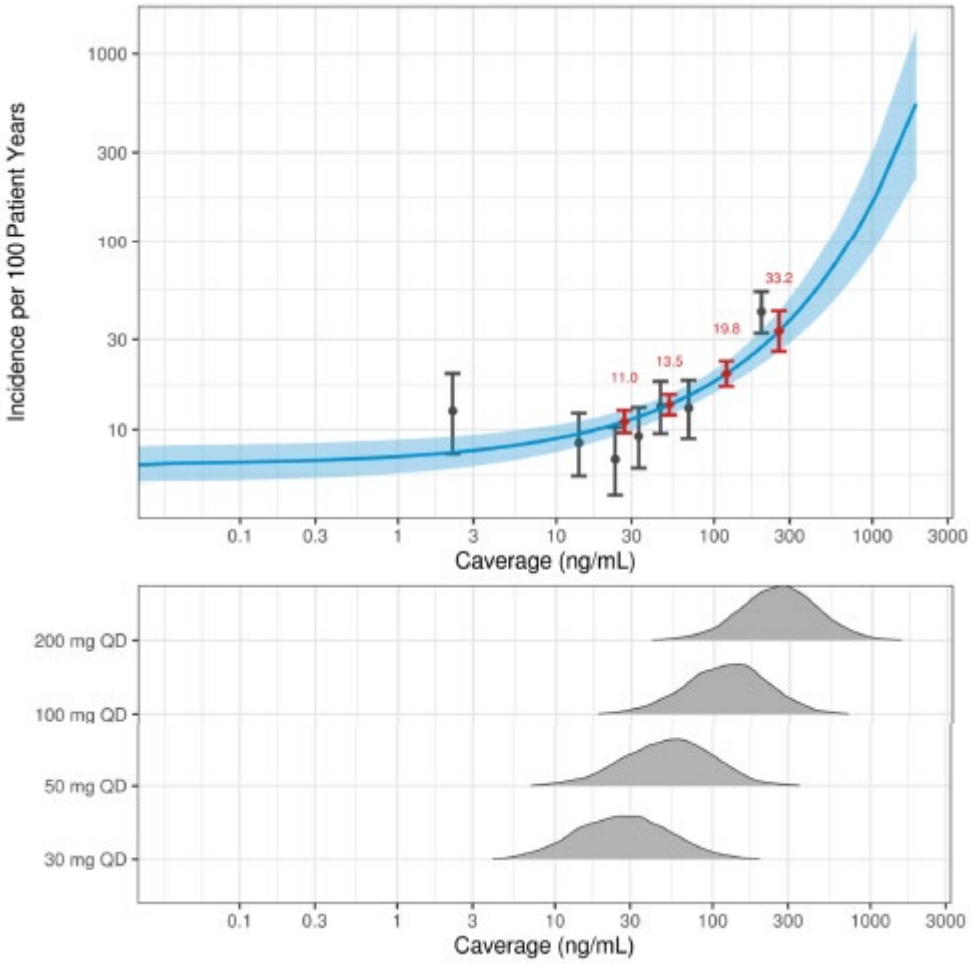
Regarding the effect on **lymphocytes**, in the exposure-response modelling analysis showed that the 200 mg loading dose regimen with 50 maintenance dosing was associated with a higher risk of lymphopenia than 50 flat dosing regimens. The prediction interval for Grade 2 lymphopenia contains 0

for the flat dosing but not for the matching loading doses dose regimens. The simulated probabilities (95%CI) for a lymphopenia when being on the 50 mg dose were: 15% (9.2% - 22%) for grade 1; 2.9% (0 – 6.7%) for grade 2; 0 (0 – 0.8%) for grade 3; 0 for grade 4. For flat dosing regimens, the model describes a gradual descent to steady-state, where lymphocyte counts are predicted to remain until the end of dosing.

For the analysis of first occurrences of **treatment-emergent AEs**, data were used from studies in healthy participants (B7981001, B7981003, B7981008, B7981022, B7981036), in AA participants (7931005, B7981015, B7981032) and Vitiligo participants (B7981019). The concentration metric used for the analysis was a time-weighted Cav which was determined as the cumulative AUC divided by the time of the adverse event. It was time-weighted to account for the assumed delay in PD effects following the change in ritlecitinib dose. The relationship between ritlecitinib concentration and treatment-emergent clinical safety endpoints, such as infections, were characterised using Poisson regression.

For **infections,** the AE categories of interest were identified as moderate infections, severe infections and infections leading to discontinuation. The model-estimated slope for the effect of time-weighted Cav on the mean incidence of infection events was statistically significant (95% CI of estimate did not include zero). Over the range of relevant doses, an approximately 10-fold increase in ritlecitinib concentration (geometric mean Cav of 27 ng/mL [30 mg QD] vs. 257 ng/mL [200 mg QD]), was predicted to demonstrate an approximately 3-fold increase in the mean incidence of infections per 100 patient-years (11.0 vs. 33.2, respectively). The mean (95% CI) incidence of infections per 100 patient years for chronic ritlecitinib administration of 30 mg and 50 mg QD was 11.0 (9.61, 12.7) and 13.5 (11.9, 15.3), respectively.

Figure 9: Incidence of infections per 100 patient years over the range of time-weighted observed Cav



Top: Gray circles and error bars are the observed mean and 95% CI, respectively, of the incidence of infections (moderate, severe, leading to discontinuation) per 100 patient years for each bin of C_{av} in the analysis population (n = 7). The blue line, (and blue shaded area) are the model-predicted mean (and 95% CI) incidence per 100 patient years for the range of observed C_{av} in the analysis population. Red circles and error bars are the model-predicted mean and 95% CI, respectively, incidence of infection per 100 patients years at the geometric mean steady-state C_{av} for 30 mg, 50 mg, 100 mg, and 200 mg QD in AA patients. *Bottom:* Gray distributions represent the predicted distribution of steady-state C_{av} for 10,000 AA patients chronically administered 30 mg, 50 mg, 100 mg, and 200 mg QD with randomly drawn random effect parameters for CL/F and Vc/F as described by the final population PK model (PMAR-EQDD-B798d-DP4-1157) and body weights sampled from those observed in B7981015.

Effect on the QT/QTc interval

On the basis of the preclinical assessments and clinical assessments along with the concentration QT analysis, no evidence of any clinically meaningful QTc interval prolongation has been observed. The CQTc analysis results in humans indicated that the treatment with ritlecitinib is not associated with QTc prolongation. The upper bound of 90% CI for the ΔΔQTcF estimate was less than 10 msec across the entire investigated concentration range of ritlecitinib, including anticipated supratherapeutic concentrations (up to 3 times the Cmax of the highest dose currently being evaluated in Phase 3 trials).

The applicant requested a waiver for the Thorough QTc study for ritlecitinib based on the recommendations in E14 ICH Guideline (ref). The CHMP concurred with the applicant rationale to waive the Thorough QTc study under the condition that the marketed clinical dose does not exceed 200 mg.

A prespecified LME model was fitted to the SAD period data from study B7981001. The upper bounds of 90% CI for ΔΔQTcF estimates across the entire concentration range were all below 10 msec, which is the threshold for regulatory concern. The upper bound of 90% CI for ΔΔQTcF estimate at the supratherapeutic concentration was 3.06 msec and the value at the mean Cmax of the highest dose in study B7981001, 3-fold higher than the mean Cmax,ss for the highest therapeutic dose in AA population, was 4.13 msec (Table 9).

Table 9: Model derived ΔΔQTcF prediction for concentrations of ritlecitinib

	Concentration (ng/mL)	Mean ΔΔQTcF (90% CI) (msec)
Supratherapeutic concentration in AA[a]	3202	0.33 (−2.40, 3.06)
800 mg single-dose mean C_{max} in B7981001	4990	0.71 (−2.71, 4.13)

a. Two times the steady-state C_{max} of the 200 mg QD dose regimen.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

By applying a longitudinal concentration-response analysis using Cav and raw SALT score to characterise the concentration-response relationship, an EC50 of 53.6 ng/ml (as the Cav) was estimated, which was comparable to the Cav after a 50 mg q.d. dose (i.e., 52.0 ng/ml).

Simulation of various maintenance doses indicated that an additionally improved efficacy is expected by increasing the maintenance dose to greater than 50 mg q.d.. Mean exposure differences were considered acceptable because of intrinsic or extrinsic factors, which fall within the range of 0.5- to 2-fold of the mean for the reference group. However, the longitudinal concentration-response analysis indicated that a 30 mg q.d. dose would provide less efficacy. The suggested acceptable 0.5-fold difference in exposure, which would translate in a 25 mg q.d. dose, will thus also provide less efficacy.

Therefore the 0.5-fold cut-off being not clinically relevant was further justified, i.e. both the 30 mg and 50 mg doses have been shown to be efficacious; however, the 50 mg group had a higher efficacy (proportion of participants who achieved severity of alopecia tool [SALT]⩽10) compared to 30 mg. A subject receiving a 50 mg dose and ending at the lower 0.5-fold exposure due to variability (and covariates) would fall in the higher exposure and still efficacious range of a 30 mg dose.

Simulations of a loading dose indicated that a loading dose would achieve the onset of efficacy faster, but the effect of the loading dose is not sustained on the long-term efficacy, as the response rates converge regardless of the presence of loading dose in the dose regimen. A loading dose of 200 mg for 4 weeks followed by 50 mg q.d., resulted in a 3 weeks (6 vs 9 weeks) faster clinical onset (see further clinical efficacy and safety).

In light of the above, the proposed dose recommendation of 50 mg once daily is supported by the CHMP. Also see clinical efficacy section for further results/discussion on the recommended dose.

Ritlecitinib was administered as tablets in the pivotal Phase 2b/3 efficacy and safety study and long-term safety study without regard to the timing of meals. The SmPC recommends the capsule intake once daily with or without food, which is agreed by the CHMP.

Special populations

PK data and population PK analysis were used to evaluate the impact of covariates on the PK of ritlecitinib.

Renal impairment: The SmPC indicates that no dose adjustment is required for subjects with mild, moderate and severe renal impairment, which is agreed from a PK point of view.

Hepatic impairment: The SmPC indicates that no dose adjustment is required for subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, which is agreed from a PK point of view. Ritlecitinib is contraindicated in patients with severe (Child-Pugh C) hepatic impairment.

In study B7981016, 1 subject with moderate hepatic impairment showed a very pronounced higher exposure than the other subjects with moderate hepatic impairment. No clear explanation could be given for the pronounced higher result. However, considering variability in the total population, such a higher value may be expected by coincidence.

Gender: The popPK analysis identified gender as a non-significant covariate on ritlecitinib pharmacokinetics.

Ethnicity/Race: The popPK analysis identified race/ethnicity (Asian/Black/White/Other, Japanese/non-Japanese, Asia/Europe/North America/Rest of the world) as a non-significant covariate on ritlecitinib PK.

Age Elderly/adolescents: The popPK analysis identified age (12 – 73 years) as a non-significant covariate on ritlecitinib PK. The SmPC indicates that no dose adjustment is required for adolescents 12 to < 18 years of age and for the elderly, which is agreed from a PK point of view.

In the popPK analysis, 69 subjects of age 65–74 years were included, and no subject over 75 years of age was available in the analysis dataset. The section 4.2 of the SmPC was updated to reflect that there are limited data in patients ⩾65 years of age.

Bodyweight: The popPK analysis identified body weight as a significant covariate on ritlecitinib PK. A subject with a body weight of 47 kg had a 45% higher exposure, while a subject with a body weight of 101 kg had a 30% lower exposure. These differences fall within the estimated 0.5 – 2.0-fold range of clinical insignificance. As requested, the clinical relevance of exposures of subjects with an extreme body weight outside this 47 – 101 kg range, especially for adolescents, has been justified, i.e. based upon simulations, patients with a body weight of 32.6 – 131 kg would fall within the 0.5 – 2.0 exposure range, which is considered still efficacious and safe.

The potential for interactions has been adequately reflected in the SmPC section 4.5.

Pharmacodynamics (PD)

Ritlecitinib is a JAK-inhibitor with selective activity against JAK3 and TEC kinases, as opposed to JAK1 and JAK2 activity.

Although the choice of lymphocytes, immunoglobulins and IP-10 as PD biomarkers can be theoretically deduced from the mechanism of action of ritlecitinib, no explicit rationale was given by the applicant for the choice of these specific biomarkers. The data provided by the applicant do not allow for differentiation between different classes of JAK-inhibitors. Nevertheless, since this information does not currently provide additional information for this application, the issue was not further pursued. The decrease in lymphocytes which might be relevant for safety is discussed in the Safety section. Information on lymphocyte subsets and immunoglobulins were reflected in the section 5.1 of the SmPC. This is agreed.

Limited data are available on the effect of treatment interruption, and loss of response after the treatment target of SALT≤10 has been reached. The applicant, therefore, chose a modelling approach, which is acknowledged. The exposure-efficacy analysis characterised the longitudinal relationship between ritlecitinib exposure and SALT score based on studies B7931005, B7981015 and B7981032. Cavg (the average drug concentration during the time interval between the previous and current SALT

score) was selected as the exposure metric, which is acceptable. Goodness-of-fit and VPC plots indicate that the developed model adequately described the observed data. Based on the simulations, the response rate at Week 24 could be influenced by dose interruption. The reduction in effect was larger when the interruption was longer than 6 weeks. The proposed statement in SmPC section 4.2, stating that 'a treatment interruption for less than 6 weeks is not expected to result in significant loss of regrown scalp hair', is acceptable.

A simulation analysis indicated that a loss of response would be expected when the dose is reduced from 50 mg to 30 mg. Considering the greater efficacy seen with a dose of 50 mg as compared to 30 mg, the relatively low infection risk for both 50 and 30 mg of ritlecitinib in the general AA population and in the elderly; that elderly is not a major target population for ritlecitinib given the demographic characteristics and the presence of a warning in Section 4.4 regarding the infection risk, a maintenance dose of 50 mg is, overall, considered appropriate.

The relationship between ritlecitinib exposure and lymphocyte count was explored using the developed semi-mechanistic Friberg model. The results suggest that a 200 mg loading dose regimen was associated with a higher risk of lymphopenia than 30 or 50 mg flat dosing regimen. Changes in B lymphocytes were only marginal and tended to return to baseline. The applicant considered decreased platelets and lymphocytes as ADRs, and this is agreed upon (see Safety section). In addition, monitoring advice is given in the SmPC. Upper respiratory tract infections are considered ADRs, given the differences in the occurrence of upper respiratory tract infections between placebo and ritlecitinib 50 mg, and the dose-response relation in the 48-week data.

A positive exposure-response relationship was identified for the incidence of infection and rash events. For herpes zoster infections, the relationship was not statistically significant. However, this should be interpreted cautiously since only a limited number of herpes zoster infections were available for analysis.

The applicant has provided concentration-QT modelling using time-matched PK-ECG data from SAD/MAD study B7981001 as a waiver for the TQT study, in line with the previously received CHMP scientific advice.

For model development, the general principles laid out in the white paper by Garnett et al. (2017) were followed, which is endorsed. The data were fitted to a pre-specified linear mixed-effects model. Sufficiently high multiple clinically relevant concentrations were tested.

2.6.4. Conclusions on clinical pharmacology

Overall, the pharmacokinetics of ritlecitinib have been adequately characterised. The exposure-response analyses support the choice of 50 mg QD flat dose without needing a 200 mg loading dose.

2.6.5. Clinical efficacy

The clinical programme to support the efficacy of ritlecitinib in Alopecia Areata (AA) consisted of 3 studies: 1 pivotal phase 2/3 study (B7981**015**), 1 supportive phase 2a study (B7931**005**), and 1 long-term phase 3 study (B7981**032**), all in participants with AA (see Table 10). In this section, clinical studies will be denoted with the last 3 digits of their identifier.

Table 10: Studies included in the efficacy investigation of ritlecitinib

Study Number	Study Design, Objectives and Endpoints (Primary)	Treatment/Duration Actual Number of participants/ Status
Phase 3 Studies		
B7981015 Module 2.7.3.1.1.1.1	A Phase 2b/3 randomized, double-blind, placebo-controlled, dose-ranging study. Objective: To evaluate the efficacy of ritlecitinib compared to placebo in adult and adolescent (≥12 years of age) AA participants with 50% or greater scalp hair loss on regrowth of lost hair (measured by an absolute SALT Score ≤20) (adolescents were not enrolled in the EU [Section 2.5.1.9.1]). Primary Endpoints: For the EMA, the primary efficacy endpoint was absolute SALT score ≤10 at Week 24 as it was agreed with the CHMP during initial advice as reflective of 'near complete remission'. For the FDA, the primary endpoint was absolute SALT score ≤20 at Week 24. For the EMA, PGI-C response defined as a score of "moderately improved or greatly improved" at Week 24 was a key secondary (Type I error controlled) endpoint. For the FDA, there were no key secondary endpoints. The B7981015 trial was designed to meet two objectives: i) to provide compelling evidence of efficacy and safety as a single pivotal Phase 3 trial (this was the primary objective), and ii) to provide dose-ranging data (which was a secondary objective) (Table 3).	Study B7981015 tested multiple dose regimens, including the same ritlecitinib dose regimen (200 mg/50 mg) demonstrated to be efficacious and safe in the completed AA Phase 2a Study B7931005. Ritlecitinib Placebo-controlled 24 weeks (Loading/Maintenance) A: 200 mg/50 mg QD B: 200 mg/30 mg QD C: 50 mg/50 mg QD D: 30 mg/30 mg QD E: 10 mg/10 mg QD F: Placebo → 200 mg/50 mg QD G: Placebo → 50 mg QD Extension 24 Weeks A, C, and G: 50 mg QD B and D: 30 mg QD E: 10 mg QD F: 200 mg QD/50 mg QD Maximal study duration was approximately 57 weeks that included a 5-week screening period, 48-week treatment period and 4-week follow-up period A 10 mg dose was only included in the study to support the characterization of the exposure response. 718 participants Complete
B7981032 Module 2.7.3.1.1.1.2	A Phase 3 open-label, multi-center, long-term study. Objective: To evaluate the long-term safety and tolerability of ritlecitinib in adult and adolescents (≥12 years of age) (adolescents were not enrolled in the EU [Section 2.5.1.9.1]) participants with AA. Due to immunomodulating effects of ritlecitinib, a vaccine substudy is being conducted as part of Study B7981032. The purpose of this substudy is to evaluate the effect of 50 mg QD of ritlecitinib on primary immune responses to the meningococcal group C polysaccharide of a meningococcal vaccine and on secondary (booster) immune responses to tetanus toxoid in adult participants with AA. This substudy is currently ongoing and is not included in this submission dossier. Primary Endpoint: Incidence of TEAEs, incidence of SAEs and AEs leading to discontinuation signs; incidence of clinically significant abnormalities and clinical laboratory values	De novo Participants: 200 mg ritlecitinib for 4 weeks QD followed by 50 mg ritlecitinib QD for 35 months Roll-over participants from Study B7981015 and B7931005: 50 mg ritlecitinib QD for 36 months. 449 de novo participants, and 603 participants who rolled over from studies B7931005 and B7981015, total 1052 participants. Ongoing (CSR with data up to the 28 Feb 2022 efficacy and safety data-cut included)
Phase 2 studies		
B7931005 Module 2.7.3.1.1.1.3	A Phase 2a randomized, double-blind, placebo-controlled, multicenter study. Objective: To evaluate the efficacy of ritlecitinib and PF-06700841 (brepocitinib, a TYK2/JAK1 inhibitor) compared to placebo at Week 24 in adult participants with moderate to severe AA. Primary Endpoint: Change from baseline of SALT score at Week 24.	PF-06700841 60 mg QD (4 weeks) to 30 mg QD (20 weeks), PF-06651600 200 mg QD (4 weeks) to 50 mg QD (20 weeks), Placebo QD (24 weeks) The maximum duration was approximately 113 weeks consisting of 3 periods: a 24-week double-blind treatment period, 48-week treatment with ritlecitinib in the single-blind extension period 24-week cross-over extension period. 142 participants Complete

2.6.5.1. Dose response study

Dose-response has been studied within the single pivotal trial (015). Instead of a dose-response study, the pivotal study was preceded by a proof-of-concept study (005), including ritlecitinib in a single dose regimen (200/50 mg QD) in comparison to placebo.

A Phase 2a randomised, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety profile of PF-06651600 and PF-06700841 in subjects with moderate to severe alopecia areata with a single-blind extension period and a cross-over open label extension period.

The primary objective of study B7931**005** was to evaluate the efficacy of ritlecitinib (PF-06651600) and of brepocitinib (PF-06700841) as compared to placebo, on change in SALT score from 0-24 weeks (primary outcome), in adults with severe AA (SALT≥50). Results of the brepocitinib study arm are not reported here.

The design of study 005 consisted of 3 periods: a 24-week double-blind treatment period, a 4-week 'drug holiday' followed by a 24-week single-blind extension period, and a 24-week cross-over open-label period. Patients who had at least 50% hair loss of the scalp (SALT score ≥50%) without evidence of hair regrowth within the previous 6 months and a current episode of hair loss not over 7 years were randomised (2:1) to ritlecitinib or to matching placebo (cq. brepocitinib and placebo, the placebo groups were combined for analysis). Patients and investigators were blinded for treatment allocation.

The primary endpoint was the change in SALT score from weeks 0-24. Secondary outcomes calculated post-hoc included improvements >2 grade in Numeric Rating Scale (NRS) for eyelash and eyebrow hair growth and SALT10. The induction dose of ritlecitinib was 200 mg QD for 4 weeks, followed by 20 weeks of 50 mg QD. The dosing regimen for the proof-of-concept study was informed by the non-clinical safety results in dogs and by *in vitro* percent inhibition of IL-15 and IL-21.

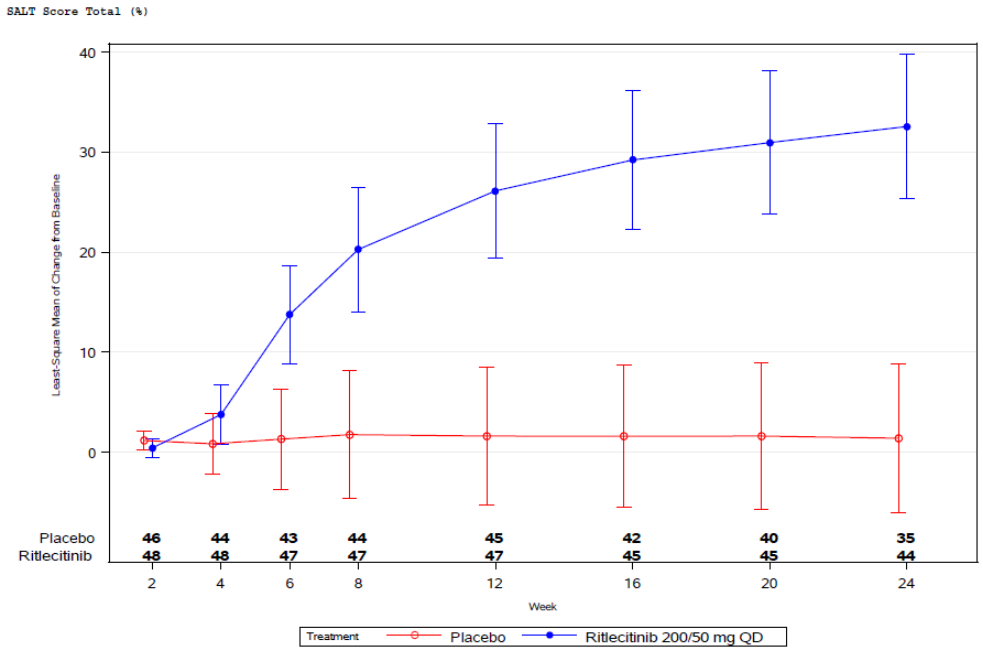
The 24-week double-blind phase was followed by a 4-week period without treatment ('treatment holiday'). Only patients who had completed the double-blind phase were eligible for the single-blind extension phase. Patients who were responders (change from baseline in SALT>30%) were treated with placebo up to 24 weeks but were retreated with their original compound (ritlecitinib or brepocitinib) in case of an increase in SALT of >30%. Non-responders continued to receive the original compound they had been allocated to. In the cross-over part of the study, patients who were non-responders in the single-blind extension phase, and were still non-responders at week 52, were switched to the alternative experimental compound. Responders, however, directly entered the 4 weeks follow-up period.

At baseline, there were 48 participants included in the ritlecitinib group and 47 participants included in the placebo group. The mean age of the participants in the ritlecitinib group and placebo group was similar, with 37 and 38 years of age, respectively. In the ritlecitinib group, 77% of participants were female, as compared to 62% in the placebo group. Most patients were of Caucasian origin, in ritlecitinib (79%) and placebo (96%) groups. The median duration of the current AA episode was about 2,5 years in both groups. The baseline SALT score was at least 50% in both treatment groups, and the average SALT score at baseline was about 89%. About 40% of patients in each group had AT or AU.

After 24 weeks, 34 (72%) of the patients in the placebo group and 45 (94%) of the patients in the ritlecitinib group had completed the study. In each group, 2 patients had discontinued treatment due to an AE.

The Least Squares Means (LSM) difference (95%CI) in SALT score (primary outcome) from baseline up to week 24 between ritlecitinib 200/50 and placebo was 31% (19% - 44%) with a $p<0.0001$. The change from baseline in SALT score in the placebo group was 1.4% (Figure 10).

Figure 10: Change in SALT score from baseline to week 24 in study 005



The proportion of patients who had a SALT10 response at week 24 (post-hoc calculation of primary endpoint in the pivotal study), was 25% in the ritlecitinib 200/50 group and 0% in the placebo group, with a p<0.001. Also, in a post-hoc analysis, among participants with an abnormal eyebrow assessment (EBA) score at baseline, 20% of participants in the 200/50 mg group had at least a 2-grade improvement in or normal EBA at Week 24, compared with 7.5% for the placebo group. Similarly, among participants with an abnormal eyelash (ELA) at Baseline, 22% of participants in the 200/50 mg group had at least a 2-grade improvement in or normal ELA at Week 24, compared with 8.6% for the placebo group.

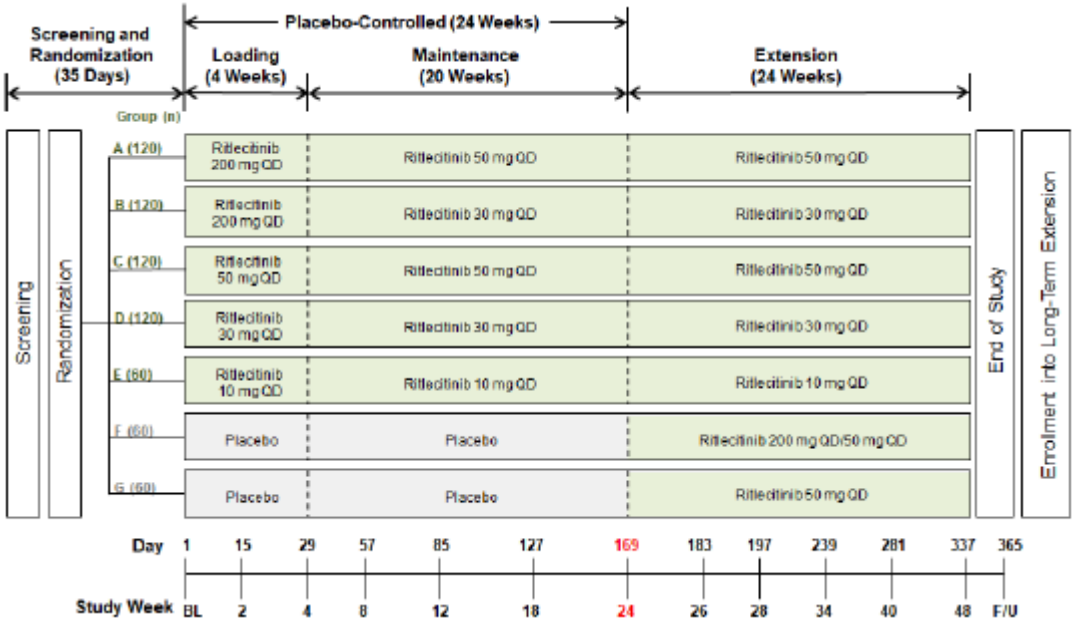
2.6.5.2. Main study

Title of study

A phase 2b/3 randomised, double-blind, placebo-controlled, dose-ranging study to investigate the efficacy and safety of PF-06651600 in adult and adolescent Alopecia Areata (AA) subjects With 50% or greater scalp hair loss

The participants were randomised to 6 treatment arms: ritlecitinib 50 or 30mg mg QD (either with or without loading dose of 200mg QD during the first 4 weeks, referred to as 200/50 of 200/30), ritlecitinib 10 mg QD and placebo (Figure 11). The placebo-controlled phase lasted 24 weeks, after which participants of the placebo arm were blindly assigned to either 200/50 mg or 50 mg treatment group. The participants of other arms remained on the originally assigned dose. This Extension Phase lasted another 24 weeks, through Week 48.

Figure 11: Design of pivotal study 015



Methods

- **Study Participants**

The study participants were adults and adolescents with a diagnosis of AA. Adolescent participants, between 12 and <18 years of age, were recruited outside of the EU.

The main inclusion criteria were:

- Male or female participants ⩾12 years of age at the time of informed consent/assent.
- A clinical diagnosis of AA with no other aetiology of scalp hair loss (e.g. telogen effluvium, androgenic alopecia).
- At least 50% hair loss of the scalp as measured by SALT, including alopecia totalis (complete scalp hair loss) and alopecia universalis (complete scalp, facial, and body hair loss), without evidence of terminal hair regrowth within 6 months at both screening and baseline visits.
- The current episode of scalp hair loss is less than 10 years.

The main exclusion criteria were:

- Active systemic diseases that could cause hair loss (e.g., lupus erythematosus, thyroiditis, systemic sclerosis, lichen planus, etc.).
- Certain psychiatric conditions such as suicidality in the past year of a current major psychiatric disorder. Participants with a suicidal risk in the past underwent a risk assessment in order to participate in the study.
- Hearing loss with progression over the previous 5 years, sudden hearing loss, middle or inner ear disease, or other auditory condition considered acute, fluctuating, or progressive.
- Previous use of any JAK inhibitor for use in any disease indication or any non-B-cell selective lymphocyte-depleting agent.
- Current or recent history of clinically significant severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine (particularly thyroid disease

which can be associated with hair loss), pulmonary, cardiovascular, immunologic/rheumatologic or neurologic disease.

- Any present solid or hematological malignancies or history of malignancies, except for adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.
- History (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localised, dermatomal herpes zoster.
- Adolescent participants 12 to <18 years old without a documented history of VZV vaccination or presence of VZV IgG Ab.
- 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.
- Active acute or chronic infection requiring treatment with oral antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to Day 1 or superficial skin infection within 1 week prior to Day 1.
- Known immunodeficiency disorder, including positive serology for HIV at Screening or a first-degree relative with a hereditary immunodeficiency.
- Infection with HBV or HCV according to protocol-specific testing algorithm.
- Evidence of untreated or inadequately treated active or latent Mycobacterium tuberculosis (TB) infection as evidenced by any of the criteria listed in the Protocol.

- **Treatments**

Study treatment

Both ritlecitinib and placebo were provided as tablets for oral administration. The 50 mg and 10 mg tablets and their matching placebos were supplied in blister cards such that all participants took the same number of tablets per day.

Compliance

Compliance was monitored by accounting the unused medication that was returned by the subject at the study visits. By compliance <80% or >120%, a participant was counselled by the investigator to improve compliance. Non-compliance of the investigational product between visits of <80% or >120% was to be reported as a protocol violation (referred to as "protocol deviation" by the applicant). Non-compliance was dealt with in the analysis as follows: first the primary analyses of the primary and key secondary endpoints were conducted according to the intent-to-treat principle, on the Full Analysis Set (FAS), which included all participants (regardless of non-compliance issues). The same analyses were then repeated on the Per Protocol Analysis Set (PPAS), which excluded participants who had major protocol deviation related to inclusion/exclusion criteria, compliance regarding investigational product, or any other major protocol deviations that, in the opinion of the sponsor study team, might have affected the efficacy data through Week 24. Participants were excluded from PPAS if prior to the date of the Week 24 visit, subject had a dosing interruption of $\geqslant$6 weeks for any reason.

Treatment discontinuation

Treatment with the study drug was discontinued in case of adverse effects such as serious infections requiring parenteral antimicrobial therapy or hospitalisation for treatment, treatment-related SAEs or ECG abnormalities. The following laboratory abnormalities (confirmed by retesting) were a reason to discontinue the drug:

- Absolute Neutrophil Count <750/mm^3 (<0.75 × 10^9/L).
- Hemoglobin <9.0 g/dL (<5.59 mmol/L or <90 g/L) or a decrease of >30% from baseline (either criterion or both).
- Platelet count <75,000/mm^3 (<75.0 × 10^9/L).
- Absolute Lymphocyte Count <500/mm^3 (<0.5 × 10^9/L).
- Creatine kinase >10 × ULN.
- Increased aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (any of the following: >3 times the upper limit of normal with at least one total bilirubin value >2 times the upper limit of normal; >3 times the upper limit of normal accompanied by signs or symptoms consistent with hepatic injury (eg, new onset elevated PT/INR); two sequential AST or ALT elevations >5 times the upper limit of normal, regardless of total bilirubin or accompanying signs or symptoms).

Other reasons for discontinuation were pregnancy, suicidal ideation and non-compliance (under certain circumstances).

Concomitant treatment

Topical or systemic treatments which could affect AA such as other JAK-inhibitors, immunosuppressants including steroids, and phototherapy, were prohibited medications during the study. Further, medication with potential drug-drug interactions or potential safety concerns was prohibited (e.g. lymphocyte-depleting agents, live attenuated vaccines, moderate to potent CYP3A inducers, and specific sensitive to moderate sensitive CYP3A substrates).

Any other locally approved medication for other indications in an appropriate dose was allowed. Subjects were instructed to refrain from starting new or changing doses of permitted drugs (including vitamins and dietary supplements) within 7 days or 5 half-lives to Day 1 and prior to study visits throughout the study unless it was considered medically essential.

Rescue medication

No rescue medication was foreseen in the protocol.

- **Objectives**

The primary objective of study B7931015 was to evaluate the efficacy of ritlecitinib compared to placebo in adult and adolescent AA participants with 50% or greater scalp hair loss, on regrowth of lost hair, measured as SALT Score ⩽10 at Week 24. The key secondary objective was to evaluate the effect of ritlecitinib on patient-centered outcomes as assessed by PGI-C score of 'moderately improved' or 'greatly improved' at Week 24. Other secondary objectives were to evaluate the efficacy of ritlecitinib on regrowth of scalp hair at different time points (using SALT ⩽20 at week 24, SALT ⩽10 up to week 48 and SALT ⩽20 up to week 48); to evaluate the efficacy of ritlecitinib on regrowth of eyelashes and of eyebrows up to week 48 as measured by ELA and EBA; and to evaluate patient-reported outcomes as assessed by PGI-C and Alopecia Areata Patient Priority Outcomes (AAPPO) up to week 48.

- **Outcomes/endpoints**

The primary endpoint was the Severity of Alopecia Tool (SALT) Score ⩽10 at Week 24.

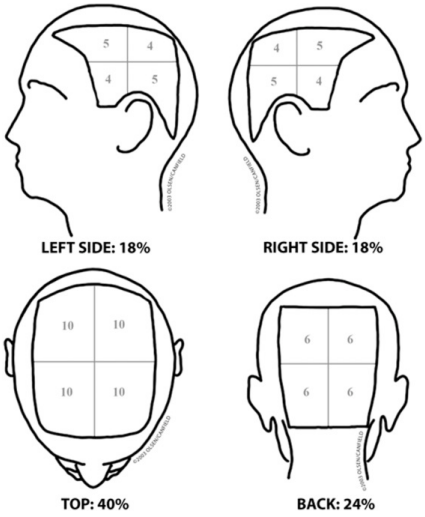
The key secondary endpoint was the proportion of participants with a PGI-C score of 'moderately improved' or 'greatly improved' at week 24.

Other main secondary endpoints were: regrowth of scalp hair using SALT ⩽20 at week 24, SALT ⩽10 up to week 48 and SALT ⩽20 up to week 48; regrowth of eyelashes and of eyebrows up to week 48 as

measured by at least a 2-grade improvement from baseline or a score of 3 in Eyelash Assessment (ELA) and Eyebrow Assessment (EBA); the proportion of participants with PGI-C score of 'moderately improved' or 'greatly improved' up to Week 48 and change in baseline in AAPPO scales up to week 48.

Description of tools used to measure outcomes

Severity of Alopecia Tool (SALT) is a quantitative assessment tool of AA severity based on scalp terminal hair loss. The score can vary between 0% (no hair loss) to 100% (100% hair loss) and represents an absolute value. Use made of reference values and a mannequin.



Patient's Global Impression of Change (PGI-C) is a patient-reported outcome measure asking the subject to evaluate the improvement or worsening of their AA as compared to the start of the study. The subject is requested to complete the following sentence 'Since the start of the study, my alopecia areata has: …' using one of seven responses ranging from 'greatly improved' to 'greatly worsened'. PGI-C response was defined as a proportion of patients with PGI-C score of 'moderately improved' or 'greatly improved'.

Eyelash Assessment (ELA) is a numeric rating scale (NRS) developed to characterise eyelash hair loss; the ELA is rated by the investigator. The numeric rating scale ranges from 0 (none) to 3 (normal) as described below. ELA response was defined as at least a 2-grade improvement from baseline or a score of 3 on the ELA in participants without normal ELA score at baseline.

Score	Description
0	None Eyelash • No eyelashes of both right and left upper and lower eyelashes.
1	Minimal Eyelash • Modestly or severely decreased density of and/or large gap(s) in one or both upper eyelashes.
2	Moderate Eyelash • Normal density of both upper eyelashes without gap(s), and decreased density or gap(s) is present in one or both lower eyelashes, OR • Normal density of both upper eyelashes with short gap(s), OR • Mildly decreased density of one or both upper eyelashes with or without short gap(s).
3	Normal Eyelash • Normal density of both right and left upper and lower eyelashes from near medial canthus to near lateral canthus without any gap(s).

NOTE:
- Density of lower eyelashes is usually less than upper eyelashes.
- A short gap does not significantly distort the appearance of the eyelash(es).
- Moderate Eyelash score does not require presence of lower eyelashes.

Eyebrow Assessment (EBA) is an NRS developed to characterise eyebrow hair loss; the EBA is rated by the investigator. The numeric rating scale ranges from 0 (none) to 3 (normal). EBA response was

defined as at least a 2-grade improvement from baseline or a score of 3 on the EBA in participants without normal EBA score at baseline.

Score	Description
0	None Eyebrow • No eyebrow hair.
1	Minimal Eyebrow • Normal or decreased density of one or both eyebrows with large gap(s). • Severely decreased density of one or both eyebrows with or without gap(s).
2	Moderate Eyebrow • Normal density of both eyebrows with short gap(s) that does not significantly distort the appearance of the eyebrows, OR • Mildly decreased density of eyebrows with or without short gap(s), OR • Moderately decreased density of eyebrows without short gap(s). There is visual definition of eyebrows at a distance of 3 feet.
3	Normal Eyebrow • Normal density of both right and left eyebrows spanning usual length (ie, from glabella to near temple) and width. There are no gap(s).

NOTE:
- Density of lateral aspect of eyebrows may be mildly less than medial eyebrows.
- A short gap does not significantly distort the appearance of the eyebrow(s).

Before implementation of the EBA and ELA in study B7981015, the scales were validated by the applicant using data from study B7931005 demonstrating the following properties:

- Test-retest reliability: intraclass correlation coefficient (ICC) values for EBA and ELA scores using screening and baseline data were 0.98 for both scales.

- Convergent validity: At baseline and Week 24, moderate to strong correlations were observed between the EBA and ELA scores and scores of the individual item of the Alopecia Areata Symptom Impact Scale (AASIS) assessing body or eyelash hair loss (|r| =0.45-0.56) and SALT scores (|r| = 0.46-0.70).

- Known-groups evidence: Using all available data from baseline to Week 24 it was shown that EBA and ELA scores discriminated between levels of SALT scores (all p <0.0001).

- Ability to detect change (responsiveness): Using all available post-baseline data up to Week 24, the relationship between change in EBA (ELA) scores and change in SALT scores was investigated. It was shown that when SALT score is changing, then EBA and ELA scores are also changing. For example, a 10% improvement in SALT score is associated with 0.1-point (p-value <0.0001) improvement in ELA. Complimentary analysis of correlations between changes in EBA and ELA scores and the Investigator Global Assessment were also supportive of the ability of EBA and ELA to detect change and were more than 0.4 starting at Week 4 for EBA and at Week 16 for ELA.

Alopecia Areata Patient Priority Outcomes (AAPPO) scale is a self-administered questionnaire to assess hair loss, emotional symptoms, and activity limitations over the past week. The questionnaire is described as follows: The first four items of the tool, which cover hair loss from the scalp, eyebrows, eyelashes, and body, ask the patient to describe the current amount of hair loss using a 5-point response scale that ranges from 'no hair loss' to 'complete (do not have any hair on my [insert body area]).' The remaining items ask the patient to rate the impact of AA over the past week on a 5-point scale ranging from 'never' to 'always'.

The development of the AAPPO followed the recommendations of the Food and Drug Administration (FDA. Draft Guidance: Patient-focused drug development: methods to identify what is important to patients guidance for industry, food and drug administration staff, and other stakeholders; 2019). Specifically, concepts were initially identified from a targeted literature review, an instrument review, and an FDA Patient-Focused Drug Development public meeting about AA. Subsequently, the identified concepts were tested in concept elicitation interviews in adults with AA, after which a final 11-item

instrument was created that demonstrated content validity in the target population of adults and adolescents with AA (Winnette et al., 2021). RTI-HS and the applicant conducted a validation study to assess the additional measurement properties of the AAPPO (Wyrwich et al., 2021). Results demonstrated moderate to strong correlations of the high-level terms (HL) items with the Alopecia Areata Symptoms and Impacts (AASIS) and the Patient's Global Impression of Severity.

- **Sample size**

The sample size of 120 per treatment arm (and 120 in the two placebo arms combined) provides more than 90% power for the SALT ≤10 at Week 24 endpoint, assuming that the 200 mg/50 mg QD group is superior to placebo by a difference of 20% in the proportion of subjects achieving SALT ≤10 and assuming a placebo response rate of no more than 5% at the more stringent significance level of 1% requested by the CHMP. The planned sample size of 120 subjects per group also provides more than 90% power for PGI-C response, assuming a difference of 35% and a placebo response rate of 20%, at a two-sided significance level of 1% requested by the CHMP.

- **Randomisation and Blinding (masking)**

Subjects were allocated to treatment groups using an interactive response technology (IRT) system. Randomisation was stratified on age (<18 years and ≥ 18 years) and AT/AU versus not AT/AU used for operational purposes to achieve a global target composition for AT/AU and adolescent subjects in the enrolled population.

Subjects were randomised in a 2:2:2:2:1:1:1 manner to blinded 200 mg/50 mg once daily (QD), 200 mg/30 mg QD, 50 mg/50 mg QD, 30 mg/30 mg QD, 10 mg/10 mg QD, placebo loading and maintenance followed by 200 mg/50 mg QD during extension and placebo loading and maintenance followed by 50 mg/50 mg QD during extension.

Investigators, subjects, and the sponsor study team were blinded to treatment throughout the study. A blinded screening independent photo review (IPR) of participant scalp photos was used to verify eligibility (eg, ⩾50% hair loss of the scalp, hair loss due to AA). Once the photos had been uploaded into the Canfield Data Management System (DMS), the Canfield Clinical Services Project Management Team (CSPMT) reviewed the photos for quality. The Canfield CSPMT was not blinded in terms of site ID, participant ID, and visit but were blinded to study intervention assignment. Once the screening photos were approved by the Canfield CSPMT, the IPR procedures described in the response were followed. All photos were reviewed by the Canfield CSPMT for quality; however, an IPR was never utilised to confirm site SALT scores at any post-screening visit. The IPRs were blinded with respect to subject identifiers (save for sequence numbering) and investigator information. Although the IPR may have calculated a SALT score to determine eligibility unless the IPR noted the SALT score in the optional comments, the SALT score was neither communicated back to the site nor was it stored in the Canfield system.

Blinded ritlecitinib and matching placebo were provided as tablets for oral administration. The tablets and their matching placebos were supplied in blister cards labelled according to local regulatory requirements. All participants took 7 tablets/day during the Loading Period, 4 tablets/day during the Maintenance Period, 7 tablets/day during the first 4 weeks of the Extension period, and 4 tablets/day for the remainder of the Extension Period.

- **Statistical methods**

Statistical methods were detailed in Statistical Analysis Plan (SAP) version 5.0 dated 09 July 2021. Version history listed changes to the SAP related to the specification of the primary and key secondary endpoint (based on FDA and EMA recommendations), update of power analyses, the definition of per protocol analysis set, the addition of stratified randomisation procedure used and introduction of

testing procedures to account for multiple testing and use of more stringent significance level for regulatory submission. In addition, it was added that the study may be unblinded for internal decision-making purposes.

Analysis populations

The Full Analysis Set (FAS) is defined as all subjects who have been randomised, regardless of whether they received study medication. Subjects were analysed in the treatment groups as they were randomised. If a subject was randomised but received the incorrect treatment, then the subject was reported under their randomised treatment group for all efficacy analyses. If a subject was treated but not randomised, then the subject was excluded from the FAS. Comparisons of SALT scores and PGI-C were done in the FAS. In addition, a Per Protocol Analysis Set (PPAS), a Safety Analysis Set (SAS) and PK Analysis Set were defined (Table 11). Data from the two treatment arms that start with the 24-week placebo period were pooled in the analyses for endpoints defined up to week 24.

Table 11: Overview and definition of analysis sets

Analysis Set	Description	Analysis Set Applies to Following Endpoints
FAS	All participants who were randomized regardless of whether they received study intervention. Participants were analyzed in treatment groups as randomized.	Efficacy
PPAS	All randomized participants who did not have any major protocol deviation related to inclusion/exclusion criteria, compliance with investigational product, or any other major protocol deviations that could affect the efficacy data through Week 24.	Primary Efficacy
SAS	All participants who received at least 1 dose of study intervention, classified according to actual study intervention received for most of the time during the study.	Treatment Administration/Compliance and Safety
PK Analysis Set	All enrolled participants who received at least 1 dose of ritlecitinib and in whom at least 1 ritlecitinib concentration value was reported.	Pharmacokinetics

For the primary endpoint of SALT ≤ 10 response at week 24, a generalised linear mixed model (GLMM) for longitudinal binary data of response based on SALT ≤ 10 over time up to Week 24 was used. Fixed factors in this model are treatment (6 levels), visit (5 levels) and treatment-by-visit interaction. Visit is included as a categorical covariate, and a subject-specific random intercept was used. The key secondary endpoint of PGI-C response at week 24 was analysed similarly to the primary endpoint.

The evaluation of the effect of loading versus no loading dose on the response at Week 24 was assessed by logistic regression applied to the data from the 30 mg and 50 mg maintenance doses, with and without the loading dose. In addition, the interaction between the two effects (loading y/n and maintenance dose) was tested.

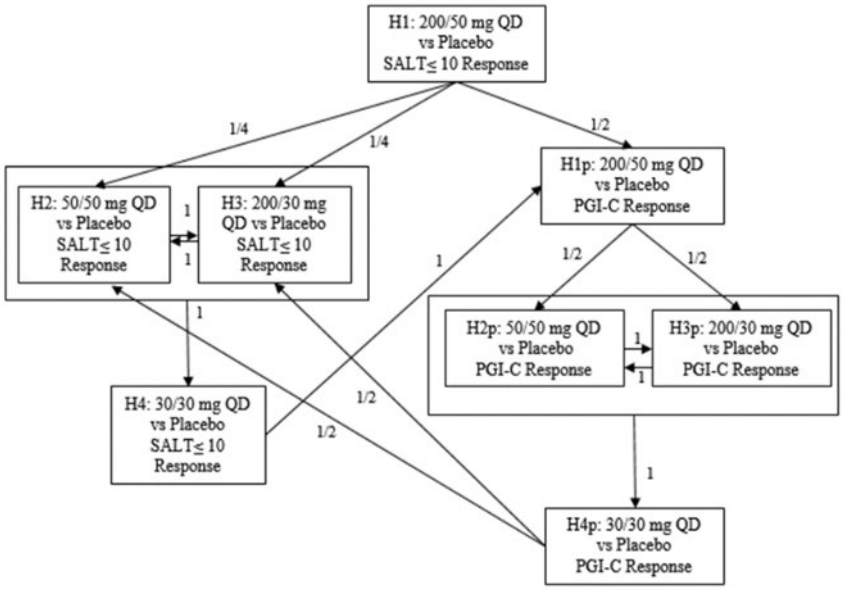
For continuous secondary endpoints up to Week 24, a mixed-effect model with repeated measures (MMRM) was used. The MMRM method was also applied to the continuous data up to Week 48 (over the entire study) for initial active treatment groups. LSM, standard error and 95% CI were presented for each treatment group without treatment comparison.

Multiple testing strategies for the primary and key secondary endpoint

The SALT ≤10 response at Week 24 was the primary endpoint and the PGI-C response at Week 24 was analysed as a key secondary endpoint. There were a total of 8 hypotheses (primary endpoint and key secondary endpoint in combination with 4 dosing schemes) that was tested as part of a hierarchical

testing strategy. The family-wise type I error was strongly controlled over the hypotheses at a two-sided 1% significance level using a gate-keeping approach as shown in the following Figure 12:

Figure 12: Overview of the hierarchical testing procedure used for primary and key secondary endpoints



Hypothesis H1 is tested first at a significance level of α = 0.01. The Familywise error rate is controlled over the eight hypotheses for primary and key secondary endpoint at the (two-sided) 1% significance level.

For some secondary endpoints (SALT ≤ 20 at week 48 and SALT ≤10 at weeks 18, 12, 8, and 4), additional multiple testing strategies were specified outside of the gate-keeping strategy for primary and key secondary endpoint.

Missing data and estimands

Primary and supplementary analyses for the primary and key secondary endpoints are given in Table 12. The primary analysis of the primary endpoint (SALT ≤ 10) and key secondary endpoint (PGI-C) is based on a MAR assumption and uses multiple imputation methods for missing SALT scores due to COVID-19. A composite estimand strategy is used for SALT scores missing due to other reasons, in which case subjects are considered non-responders (Analysis 4). Three supplementary analyses are performed for the primary endpoint using the Miettinen and Nurminen (MN) method and considering different strategies for handling missing data due to COVID-19.

Table 12: Overview of predefined statistical analyses for primary and key secondary endpoint

Study or Region	Endpoint/ designation	Analysis #	Analysis Designation	Statistical Method	Missing due to COVID-19	Missing due to other reasons
EMA and competent authorities in VHP countries	SALT ≤10 at Week 24/ primary	Analysis 4	Primary	GLMM	MAR	non-responders
		Analysis 4a	Supplementary	GLMM/TP	MNAR	non-responders
		Analysis 1	Supplementary	MN	exclude	non-responders
		Analysis 3	Supplementary	MN	non-responders	non-responders
	PGI-C Response at Week 24/ key secondary	Analysis 4	Key Secondary	GLMM	MAR	non-responders

Abbreviations: GLMM = Generalized linear mixed model; MN = Miettinen and Nurminen; MAR = Missing at random; MNAR = Missing not at random; TP = Tipping point

Results

- **Participant flow**

A total of 1097 participants were screened. The most frequent reasons for screen failures are presented in Table 13. Subsequently, 718 participants were randomised to treatment (Figure 13).

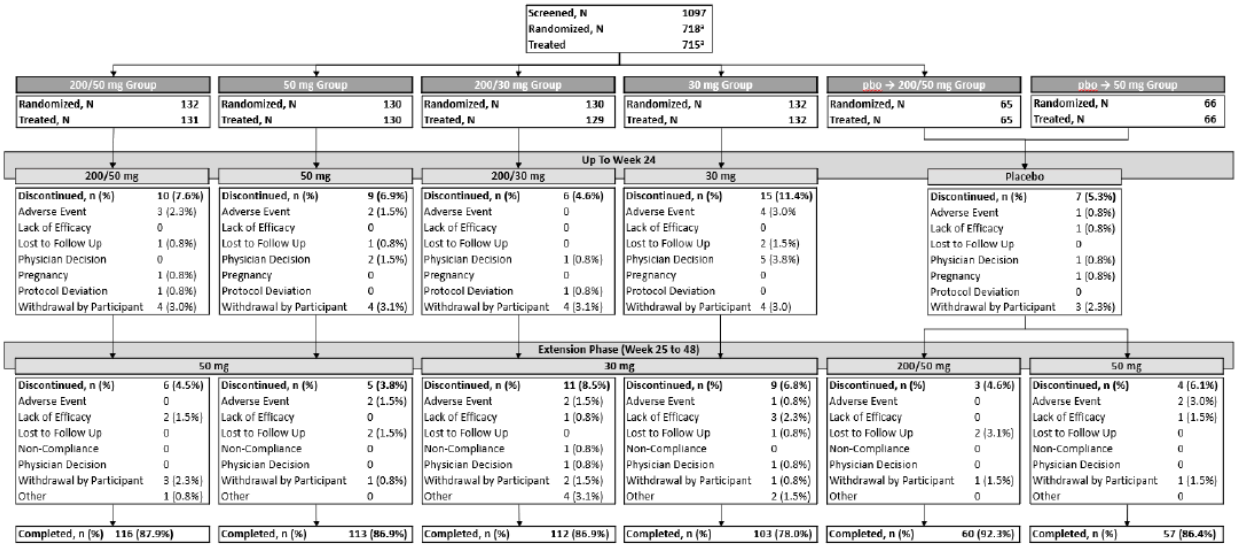
Table 13: The most frequent reasons for screen failures

Exclusion criterion	Screen Failure (N=379)	Reasons for Screen Failure
21: Have evidence of untreated or inadequately treated active or latent Mycobacterium tuberculosis (TB) infection	46 (12.1%)	• All the 46 subjects were QuantiFERON-TB Gold (QFT)-G tuberculosis (TB) test positive.
24: Any of the abnormalities in clinical laboratory tests at screening as described in protocol exclusion criterion 24	40 (10.6%)	• 12 had abnormal haemoglobin (Hgb) level (9 with low Hgb; 3 were reported as out of range) • 7 had abnormal platelet count (6 with low platelet count; 1 was reported as out of range) • 5 were excluded due to abnormal/elevated alanine aminotransferase (ALT)/aspartate aminotransferase (AST) results • 5 had total bilirubin >1.5× ULN (upper limit of normal) • Others include positive QuantiFERON, low glomerular filtration rate (GFR), low HCT, low absolute neutrophil count (ANC), low lymphocyte and, urinary tract infection.
7: Have hearing loss with progression over the previous 5 years, sudden hearing loss, or middle or inner ear disease, or other auditory condition that is	29 (7.7%)	• 14 had hearing loss • 8 with neurosensorial hearing loss • 2 had fluctuation in hearing loss • 2 didn't complete hearing test • Others include otosclerosis, tympanitis

Of these randomised participants, 715 (99.6%) received treatment and 101 (14%) discontinued treatment. The proportions of participants discontinuing during the Placebo-Controlled Period (week 0-24) were similar across treatment groups with 5-8%, except for the 30 mg group in which 11% of patients discontinued. During the Extension Period (weeks 25-48), discontinuation ranged from 3.8% (50 mg) to 8.5% (200/30 mg). Overall, 614 (86%) of participants completed treatment.

The reasons for discontinuation were adverse effects, lack of efficacy, the physician's decision to withdraw. These numbers were not different between treatment groups. There were 2 cases of protocol deviation and 2 cases of pregnancy.

Figure 13: Participant flow in study B7981015



Protocol deviations are presented in Table 14 and Table 15. A total of 96% of participants had at least one protocol deviation and 68% had at least one important protocol deviation. There was roughly comparable distributions of protocol deviations and important protocol deviations among study arms. The most prominent sources of protocol deviations pertain to the following categories: procedures/tests (76% in total), laboratory (72% in total), investigational product (52% in total), and visit schedule (42.5% in total). The most prominent sources of important protocol deviations pertain to the following categories: investigational product (43%), procedures/tests (31%), laboratory (16%).

Table 14: Summary of all protocol deviations in Study B7981015

Protocol Deviation Category	Ritlecitinib 200/50 mg QD (N=132)	Ritlecitinib 200/30 mg QD (N=130)	Ritlecitinib 50 mg QD (N=130)	Ritlecitinib 30 mg QD (N=132)	Ritlecitinib 10 mg QD (N=63)	Placebo→ Ritlecitinib 200/50 mg QD (N=65)	Placebo→ Ritlecitinib 50 mg QD (N=66)	Total (N=718)
Number of participants with at least one PD	124(93.9)	126(96.9)	127(97.7)	127(96.2)	59(93.7)	61(93.8)	64(97.0)	688(95.8)
Concomitant Medications	11(8.3)	11(8.5)	14(10.8)	13(9.8)	3(4.8)	7(10.8)	7(10.6)	66(9.2)
Inclusion/ Exclusion	14(10.6)	11(8.5)	16(12.3)	10(7.6)	10(15.9)	8(12.3)	8(12.1)	77(10.7)
Informed Consent	29(22.0)	27(20.8)	28(21.5)	33(25.0)	14(22.2)	15(23.1)	11(16.7)	157(21.9)
Investigational Product	62(47.0)	62(47.7)	79(60.8)	62(47.0)	38(60.3)	34(52.3)	35(53.0)	372(51.88)
Laboratory	93(70.5)	99(76.2)	91(70.0)	100(75.8)	40(63.5)	46(70.8)	47(71.2)	516(71.9)
Other	6(4.5)	1(0.8)	3(2.3)	6(4.5)	0	1(1.5)	1(1.5)	18(2.5)
Procedures/Tests	101(76.5)	101(77.7)	96(73.8)	105(79.5)	46(73.0)	49(75.4)	47(71.2)	545(75.9)
Protocol Specific Discontinuation Criteria	0	0	0	0	0	0	1(1.5)	1(0.1)
Randomization	16(12.1)	10(7.7)	10(7.7)	10(7.6)	6(9.5)	1(1.5)	5(7.6)	58(8.1)
Safety Reporting	2(1.5)	1(0.8)	0	0	0	1(1.5)	0	4(0.6)
Visit Schedule	57(43.2)	51(39.2)	58(44.6)	57(43.2)	29(46.0)	31(47.7)	22(33.3)	305(42.5)

Table 15: Summary of all important protocol deviations in Study B7981015

Protocol Deviation Category	Ritlecitinib 200/50 mg QD (N=132)	Ritlecitinib 200/30 mg QD (N=130)	Ritlecitinib 50 mg QD (N=130)	Ritlecitinib 30 mg QD (N=132)	Ritlecitinib 10 mg QD (N=63)	Placebo→ Ritlecitinib 200/50 mg QD (N=65)	Placebo→ Ritlecitinib 50 mg QD (N=66)	Total (N=718)
Number of participants with at least one PD	87(65.9)	89(68.5)	93(71.5)	89(67.4)	42(66.7)	41(63.1)	48(72.7)	489(68.1)
Concomitant Medications	11(8.3)	11(8.5)	14(10.8)	13(9.8)	3(4.8)	7(10.8)	7(10.6)	66(9.2)
Inclusion/ Exclusion	14(10.6)	11(8.5)	16(12.3)	10(7.6)	10(15.9)	8(12.3)	8(12.1)	77(10.7)
Informed Consent	0	1(0.8)	2(1.5)	0	0	0	0	3(0.4)
Investigational Product	50(37.9)	54(41.5)	65(50.0)	51(38.6)	31(49.2)	27(41.5)	31(47.0)	309(43.0)
Laboratory	18(13.6)	25(19.2)	13(10.0)	23(17.4)	9(14.3)	14(21.5)	10(15.2)	112(15.6)
Other	2(1.5)	0	0	1(0.8)	0	0	0	3(0.4)
Procedures/Tests	35(26.5)	54(41.5)	36(27.7)	39(29.5)	23(36.5)	20(30.8)	17(25.8)	224(31.2)
Protocol Specific Discontinuation Criteria	0	0	0	0	0	0	1(1.5)	1(0.1)
Randomization	1(0.8)	0	0	0	0	0	0	1(0.1)
Safety Reporting	2(1.5)	1(0.8)	0	0	0	1(1.5)	0	4(0.6)
Visit Schedule	1(0.8)	2(1.5)	3(2.3)	1(0.8)	0	3(4.6)	0	10(1.4)

A total of 20 participants had compliance <80% between Day 1 through Week 24, and the numbers were similar between the groups. Of these 20 participants, 15 were excluded from the PPAS (13 due to non-compliance and 2 due to missing SALT score at Week 24), and 5 were not excluded from the PPAS (although these participants had a documented potentially important protocol deviation of weekly non-compliance <80%, they did not meet the criterion of a dosing interruption of ⩾6 weeks prior to the Week 24 visit).

- **Recruitment**

The recruitment started 3 December 2018, and the data collection ended June 24, 2021. The study included participants from 118 sites in 18 countries (Australia, Argentina, Canada, Chile, China, Colombia, Czech Republic, Germany, Hungary, Japan, South Korea, Mexico, Poland, Russian Federation, Spain, Taiwan, United Kingdom and the United States).

- **Conduct of the study**

The study was performed in accordance with ethical principles originating in the Declaration of Helsinki, in compliance with all ICH Good Clinical Practice Guidelines and with applicable laws and country-specific regulations in which the studies were conducted. Protocol amendments were made at five different time points, the most relevant concerned adjustments in the secondary endpoint and adjustments in the analysis to account for missing data due to COVID-19. The PGI-C became a key secondary endpoint. Both amendments were implemented after this was recommended during the Scientific advice.

- **Baseline data**

In total, 718 patients were included in the pivotal trial (Table 16). The majority (85%) of the participants were adults (≥18 years of age), and 15% were adolescents. The mean age of the participants was 34 years. The study included 105 adolescents (12 to 17 years of age) who all were recruited outside of the EU. There was a limited proportion (<5%) of elderly (>65 years of age) participants in the study. There were more female (62%) than male (38%) participants. Most (60-70%) participants were Caucasian. Age, gender, and race were evenly distributed over treatment groups.

The disease characteristics such as the median duration since AA diagnosis (6.9 years), a median duration of the current episode (2.5 years), the proportion of AT/AU participants (46%) and the mean SALT score (88-93) were also similar across the groups.

Over treatment groups, on average 69% (60-77%) of participants had received prior pharmacologic treatment for AA. The most frequent prior pharmacological treatment for AA were: topical corticosteroids (38%); oral/IV/IM steroids (29%); intralesional corticosteroid injection (28%); and topical vasodilator (24%). On average, 25% of participants had received prior non-drug treatments/procedures for AA. About 30% of participants across treatment groups received prior treatments not considered a prior pharmacological treatment for AA; these numbers were similar between the groups.

Concomitant medication for conditions other than AA was taken by about 80% of the participants during the double-blind period in the main study, without differences between the placebo and ritlecitinib groups. A maximum of 1 participant in each group reported using AA medication.

Table 16: Baseline Demographics and Disease Characteristics (study B7981015)

	Ritlecitinib 200/50 mg QD (N=132)	Ritlecitinib 200/30 mg QD (N=130)	Ritlecitinib 50 mg QD (N=130)	Ritlecitinib 30 mg QD (N=132)	Ritlecitinib 10 mg QD (N=63)	Placebo (N=131)
Age (Years), n (%)						
Mean (SD)	34.5 (14.98)	33.7 (13.75)	32.4 (13.36)	33.7 (14.83)	34.3 (13.88)	34.0 (14.96)
12-17	20 (15.2)	19 (14.6)	18 (13.8)	20 (15.2)	9 (14.3)	19 (1456)
≥18	112 (84.8)	111 (85.4)	112 (86.2)	112 (84.8)	54 (85.7)	112 (85.5)
≥65	4 (3.0)	1 (0.8)	3 (2.3)	7 (5.3)	0	5 (3.8)
Female	81 (61.4)	85 (65.4)	71 (54.6)	80 (60.6)	43 (68.3)	86 (65.6)
Weight (kg)						
Mean (SD)	71.0 (16.78)	71.4 (17.90)	70.1 (17.19)	69.7 (16.22)	68.8 (17.64)	69.8 (21.38)
Race, n (%)						
White	92 (69.7)	90 (69.2)	79 (60.8)	91 (68.9)	42 (66.7)	94 (71.8)
Asian	33 (25.0)	28 (21.5)	43 (33.1)	34 (25.8)	17 (27.0)	31 (23.7)
Severity of AA n(%)						
AT/AU	60 (45.5)	60 (46.2)	60 (46.2)	61 (46.2)	29 (46.0)	60 (45.8)
Baseline SALT Score Mean (SD)						
All	90.3 (15.05)	90.5 (14.28)	90.3 (14.69)	90.0 (15.07)	88.3 (16.87)	93.0 (11.50)
Non AT/AU	82.2 (16.48)	82.4 (15.39)	82.0 (15.90)	81.5 (16.27)	78.3 (17.61)	87.0 (12.93)
Duration Since Diagnosis (Years)						
Mean (SD)	9.9 (10.79)	11.6 (11.69)	8.7 (8.67)	8.8 (8.94)	10.8 (10.65)	11.0 (11.77)
Duration of Onset of Current Episode (Years)						
Mean (SD)	3.4 (2.93)	3.4 (2.89)	3.2 (2.67)	3.6 (2.82)	3.3 (2.65)	3.2 (2.65)

- **Numbers analysed**

Data from the intention to treat (ITT) population constituted the full analysis set and included all randomised participants. Out of the randomised 718 participants, 715 were treated. The groups consisted of n=132 (ritlecitinib 200/50 mg), n=130 (ritlecitinib 200/30 mg), n=130 (ritlecitinib 50 mg), n=132 ritlecitinib 30 mg), n=63 (ritlecitinib 10mg), n=131 (placebo). The placebo group was divided in the Extension phase into 2 groups: n=65 (ritlecitinib 200/50 mg) and n=66 (ritlecitinib 50 mg).

Per protocol population (defined as all randomised subjects who do not have any major protocol deviation) consisted of n=115 (ritlecitinib 200/50 mg), n=116 (ritlecitinib 200/30 mg), n=120 (ritlecitinib 50 mg), n=126 ritlecitinib 30 mg), n=55 (ritlecitinib 10mg), n=124 (placebo). The placebo group was divided in the Extension phase into 2 groups: n=60 (ritlecitinib 200/50 mg) and n=64 (ritlecitinib 50 mg).

- **Outcomes and estimation**

Primary endpoint

The primary endpoint was met. The responses in SALT≤10 in the ritlecitinib 200/50 mg (21%), 200/30 mg (13%), 50 mg (13%) and 30 mg (11%) groups were larger than placebo (1.5%) at week 24, at a significance level of p< 0.005 (Table 17). The mean difference (95%CI) with placebo was 20% (12-28) for the 200/50 mg group, 11% (5-18) for the 200/30 mg group, 12% (5-18) for the 50 mg group, and 9% (3-15) for the 30 mg group. The effect in the ritlecitinib 10 mg group did not differ from the effect in the placebo group; the 10 mg group was a priori not included in the estimations for the primary endpoint.

Table 17: Response based on SALT⩽10 at Week 24

Analysis Visit		Ritlecitinib 200/50 mg QD (N=132)	Ritlecitinib 200/30 mg QD (N=130)	Ritlecitinib 50 mg QD (N=130)	Ritlecitinib 30 mg QD (N=132)	Ritlecitinib 10 mg QD (N=63)	Placebo (N=131)
Week 24	Participants with SALT < 10 response (before imputation)	27	16	17	13	1	2
	Participants with non-missing SALT score (N1)	118	119	119	114	55	125
	Missing due to COVID-19 (N2), assumed MAR	8	9	6	13	4	1
	Missing due to reasons unrelated to COVID-19 (N3), considered non-responders	6	2	5	5	4	5
	Estimated Response Rate (%)	21.29	12.87	13.42	10.62	1.65	1.54
	SE (%)	3.64	3.01	3.03	2.79	1.64	1.08
	Difference from Placebo						
	Difference	19.75	11.33	11.88	9.09	0.12	
	SE of Difference	4.00	3.27	3.29	3.05	1.93	
	95% CI	(11.91, 27.59)	(4.93, 17.74)	(5.42, 18.33)	(3.10, 15.07)	(-3.67, 3.91)	
	p-value	<0.000001	0.000526	0.000311	0.002922	0.950947	

Key secondary endpoint

The key secondary endpoint was met. The response in PGI-C in the ritlecitinib 200/50 mg (52%), 200/30 mg (45%), 50 mg (49%) and 30 mg (42%) groups was larger than in placebo (9%) at week 24, at a significance level of p< 0.005 (Table 18). The mean difference (95%CI) with placebo was 43% (32-54) for the 200/50 mg group, 36% (25-47) for the 200/30 mg group, 40% (29-51) for the 50 mg group, 33% (22-43) for the 30 mg group. The effect in the ritlecitinib 10 mg group did not differ from that in the placebo group.

Table 18: PGI-C response based at Week 24

Analysis Visit		Ritlecitinib 200/50 mg QD (N=132)	Ritlecitinib 200/30 mg QD (N=130)	Ritlecitinib 50 mg QD (N=130)	Ritlecitinib 30 mg QD (N=132)	Ritlecitinib 10 mg QD (N=63)	Placebo (N=131)
Week 24	Participants with PGI-C response (before imputation)	67	57	62	51	7	12
	Participants with non-missing PGI-C score (N1)	120	119	120	116	55	125
	Missing due to COVID-19 (N2), assumed MAR	6	9	5	11	3	1
	Missing due to reasons unrelated to COVID-19 (N3), considered non-responders	6	2	5	5	5	5
	Estimated Response Rate (%)	52.19	45.40	49.17	41.95	11.36	9.23
	SE (%)	4.43	4.46	4.44	4.43	4.04	2.54
	Difference from Placebo						
	Difference	42.96	36.18	39.96	32.72	2.15	
	SE of Difference	5.76	5.59	5.67	5.50	4.62	
	95% CI	(31.68, 54.25)	(25.22, 47.14)	(28.85, 51.06)	(21.95, 43.50)	(-6.91, 11.22)	
	p-value	<0.000001	<0.000001	<0.000001	<0.000001	0.641652	

Other secondary endpoints

Also, for **SALT ⩽20** response at week 24, ritlecitinib 200/50 mg, 200/30 mg, 50 mg and 30 mg were significantly different from placebo ($p < 0.01$). Compared to placebo, the ritlecitinib 10 mg group was not included in the Type I error-controlled testing procedure for efficacy.

The response rates for SALT ⩽20 were higher than those using the SALT ⩽10 given that SALT ⩽20 is a less stringent measure of hair regrowth (Table 19).

Table 19: Response based on SALT≤20 at Week 24

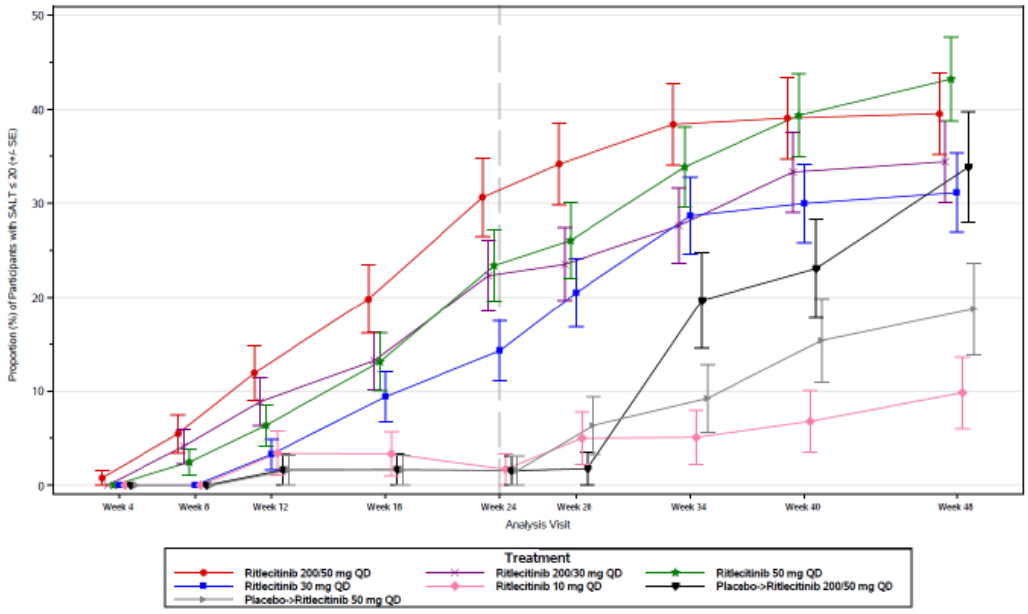
Analysis Visit		Ritlecitinib 200/50 mg QD (N=132)	Ritlecitinib 200/30 mg QD (N=130)	Ritlecitinib 50 mg QD (N=130)	Ritlecitinib 30 mg QD (N=132)	Ritlecitinib 10 mg QD (N=63)	Placebo (N=131)
Week 24	Participants with SALT ≤ 20 response (before imputation)	38	27	29	17	1	2
	Participants with non-missing SALT score (N1)	118	119	119	114	55	125
	Missing due to COVID-19 (N2), assumed MAR	8	9	6	13	4	1
	Missing due to reasons unrelated to COVID-19 (N3), considered non-responders	6	2	5	5	4	5
	Estimated Response Rate (%)	29.89	21.69	22.98	13.83	1.62	1.55
	SE (%)	4.07	3.70	3.75	3.12	1.61	1.09
	Difference from Placebo						
	Difference	28.34	20.15	21.43	12.29	0.09	
	SE of Difference	4.57	4.04	4.11	3.40	1.91	
	95% CI	(19.39, 37.30)	(12.23, 28.07)	(13.37, 29.48)	(5.64, 18.95)	(-3.66, 3.84)	
	p-value	<0.000001	<0.000001	<0.000001	0.000294	0.962973	

The proportion of participants with **SALT ⩽20** further increased **after week 24** (Figure 14). The response became statistically different from placebo at Week 8 (for the ritlecitinib 200/50mg group), Week 12 (200/30 mg group), and Week 18 (50 mg and 30 mg groups).

At Week 24, the proportion of participants with SALT ⩽20 was larger in participants who had received a 200 mg **loading dose** for 4 weeks than in participants treated for 24 weeks without a loading dose: 200/50 mg (31%) versus 50 mg (23%); 200/30 mg (22%) versus 30 mg (14%). By Week 48, the proportion of participants with SALT ⩽20 was similar between the participants who had received a 200 mg loading dose for 4 weeks and those who were treated for 48 weeks without a loading dose: 200/50 mg (40%) versus 50 mg (43%); 200/30 mg (34%) versus 30 mg (31%).

Those participants who, by design, **switched from placebo** to ritlecitinib after Week 24 showed an average response at week 48 which was similar to that of participants at Week 24 treated with the same regimen from the start (placebo->200/50 mg [35%] and placebo -> 50 mg [19%] vs. 200/50 mg [31%] and 50 mg [23%]).

Figure 14: Response based on SALT⩽20 up to Week 48

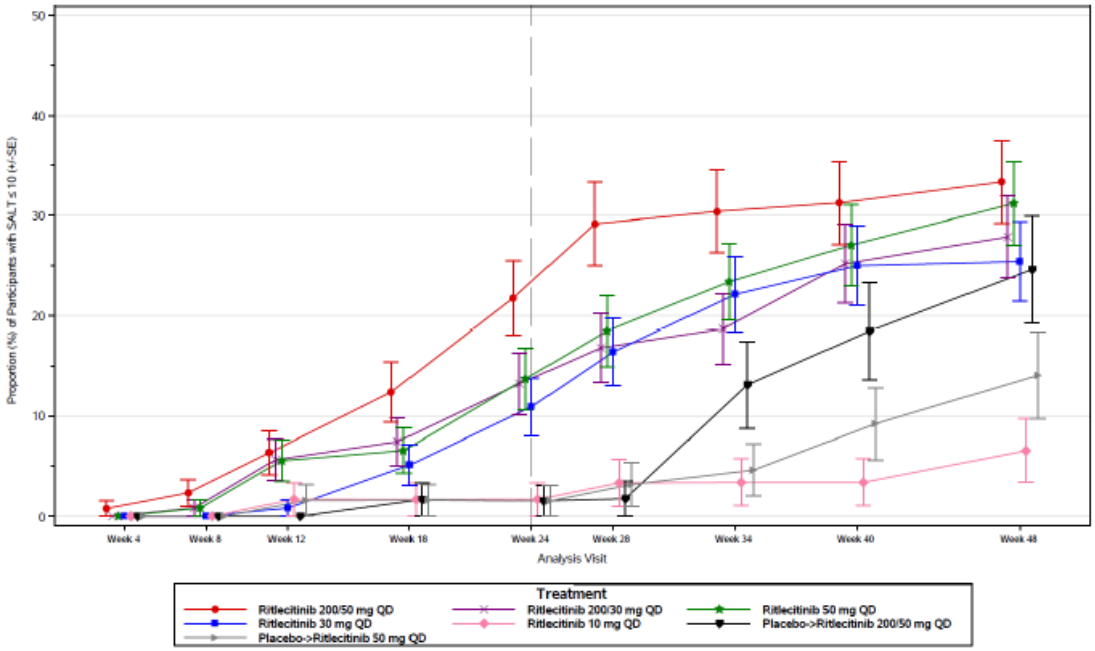


After week 24 the proportion of participants with **SALT ⩽10** increased (Figure 15). The absolute responses were lower for SALT ⩽10 than SALT ⩽20. The response became statistically different from placebo at Week 18 for the ritlecitinib 200/50 mg group, other groups (ritlecitinib 200/30 mg, 50 mg, and 30 mg) became significantly different from placebo at Week 24.

Similarly to the response SALT⩽20, at Week 24, the proportion of participants with SALT ⩽10 was greater in participants who had received a 200 mg **loading dose** for 4 weeks than in participants treated for 24 weeks without a loading dose: 200/50 mg (22%) versus 50 mg (14%). By Week 48, the proportion of participants with SALT ⩽10 was similar between the participants who received a 200 mg loading dose for 4 weeks and those who were treated for 48 weeks without a loading dose: 200/50 mg (33%) versus 50 mg (31%); 200/30 mg (28%) versus 30 mg (25%).

Those participants who **switched from placebo** to ritlecitinib after Week 24 demonstrated a response at Week 48 which was similar to that of participants at Week 24 treated with the same regimen from start (placebo->200/50 mg [25%] and placebo -> 50 mg [14%] vs. 200/50 mg [25%] and 50 mg [14%]).

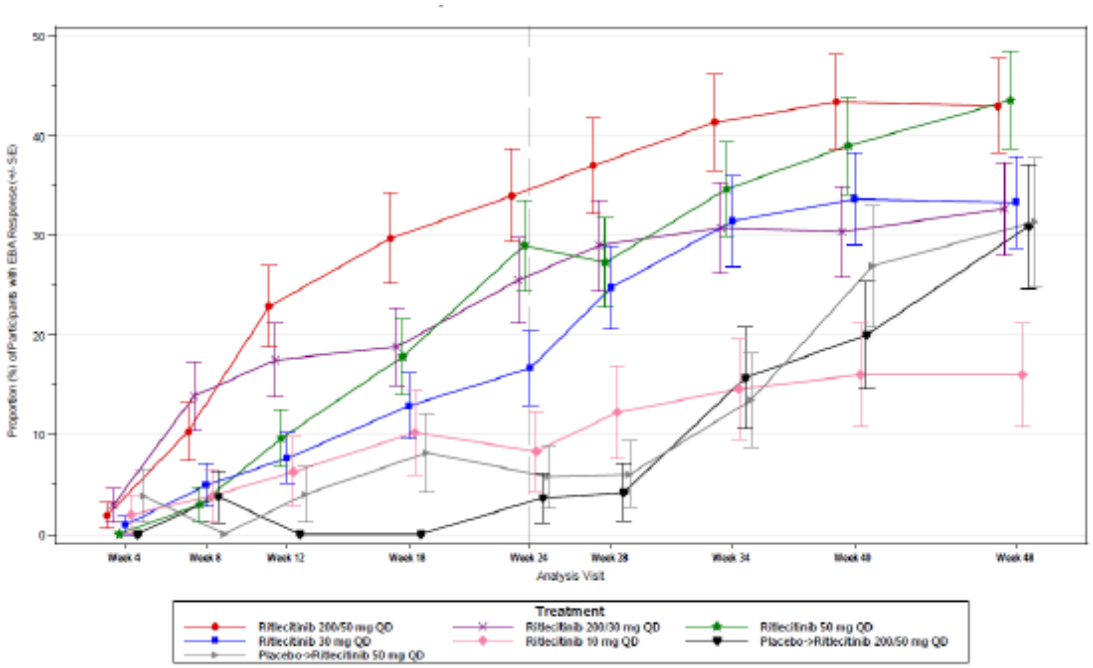
Figure 15: Response based on SALT⩽10 up to Week 48



The proportion of participants with **EBA response** increased from week 4 to week 24 in ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg and continued to increase after Week 24 (Figure 16). At 24 weeks the proportion of participants with EBA response was significantly higher in ritlecitinib 200/50 mg (34%), 200/30 mg (25%), 50 mg (29%) and 30 mg (17%) groups than in the placebo group (4.7%).

By Week 48, the proportion of participants with EBA response was similar between the participants who received a 200 mg loading dose for 4 weeks and those who were treated for 48 weeks without a loading dose: 200/50 mg (43%) versus 50 mg (44%); 200/30 mg (33%) versus 30 mg (33%). In participants who had received placebo during the first 24 weeks, after transitioning to active treatment (placebo->200/50 mg; placebo->50 mg), the proportion of participants with EBA response increased from Week 28 to Week 48. At Week 48, the proportion of participants with EBA response in participants first treated with placebo was similar to that of participants at Week 24 treated with the same regimen (placebo->200/50 mg [31%] and placebo->50 mg [31%] vs. (200/50 mg [34%] and 50 mg [29%]).

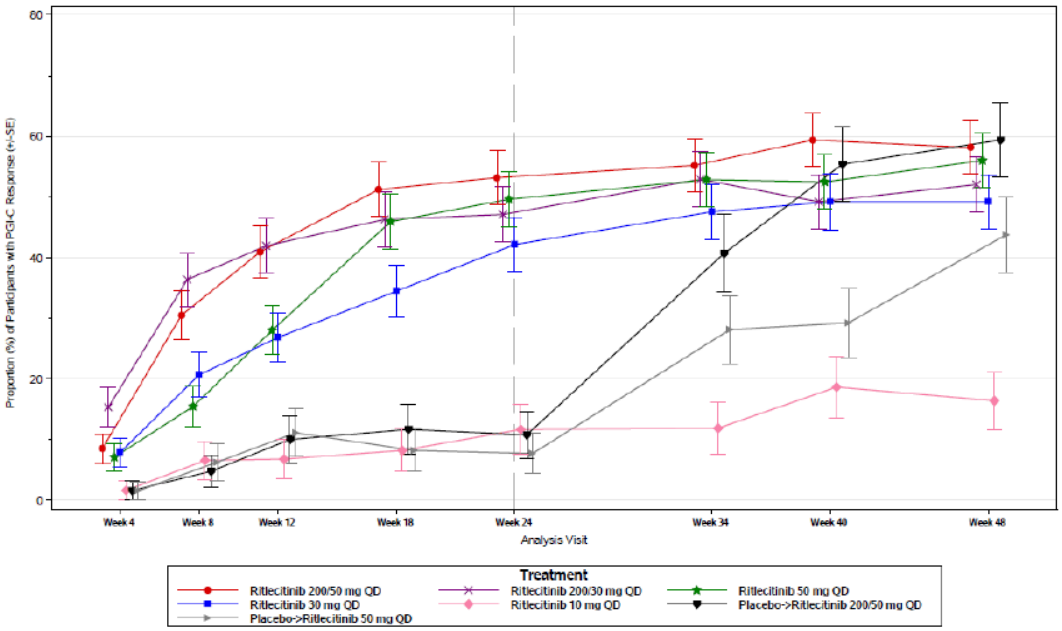
Figure 16: EBA response based on at least a 2-grade improvement from baseline or a normal EBA score up to Week 48



The proportion of participants with **ELA response** increased from Week 4 to Week 24 in ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg and continued to increase after Week 24. At Week 24, the proportion of participants with ELA response was larger in 200/50 mg (30%), 200/30 mg (21%), 50 mg (29%), and 30 mg (26%) than 10 mg (4.9%) or placebo (5%). The proportion of participants in the first 4 groups was also significantly higher than in the placebo group. At both Week 24 and Week 48, the proportion of participants with ELA response was similar with and without a loading dose for 4 weeks (Week 24: 200/50 mg (30%) versus 50 mg (29%); 200/30 mg (21%) versus 30 mg (26%); Week 48: 200/50 mg (38%) versus 50 mg (40%); 200/30 mg (30%) versus 30 mg (31%). Similarly to other endpoints, transitioning from placebo to active treatment after 24 weeks increased the response by Week 48.

The proportion **of PGI-C responders** increased from Week 4 to Week 24 in ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg (Figure 17). This increase continued to a lesser degree up to week 48. The proportion of PGI-C responders in ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg was larger than in placebo starting at Week 4. In participants who had received placebo during the first 24 weeks, after transitioning to active treatment, the proportion of PGI-C responders increased from Week 24 to Week 48. At Week 48, the proportion of PGI-C responders in groups first treated with placebo was generally consistent with that of participants at Week 24 treated with the same regimen.

Figure 17: PGI-C response to Week 48



Patient-reported impression of improvement (defined as achieving a score of 0 [no hair loss] or 1 [little hair loss]) on each of **AAPPO** hair loss items 1-4 (scalp, eyebrows, eyelash, body hair) was assessed in participants with a baseline score of 2-4 (indicating moderate-complete hair loss). Up to week 24, the proportion of participants reporting an improvement on AAPPO hair loss items 1-4 increased in ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg groups; the increase was greater than in 10 mg and placebo. In participants who had received placebo, after transitioning to active treatment, the proportion of participants with improvement on AAPPO items 1-4 increased from week 24 to week 48. At week 48 the proportion of participants who were first treated with placebo until Week 24 was similar to that of participants at week 24 treated with the same regimen. In the AAPPO, the Emotional Symptoms domain score is defined as mean of items 5-8, and the Activity Limitations subscore is defined as the mean of items 9-11. Up to Week 24, the least square mean change from baseline indicated mean Emotional Symptoms scores improved modestly in all groups, including placebo. There was no difference between any active treatment group and placebo.

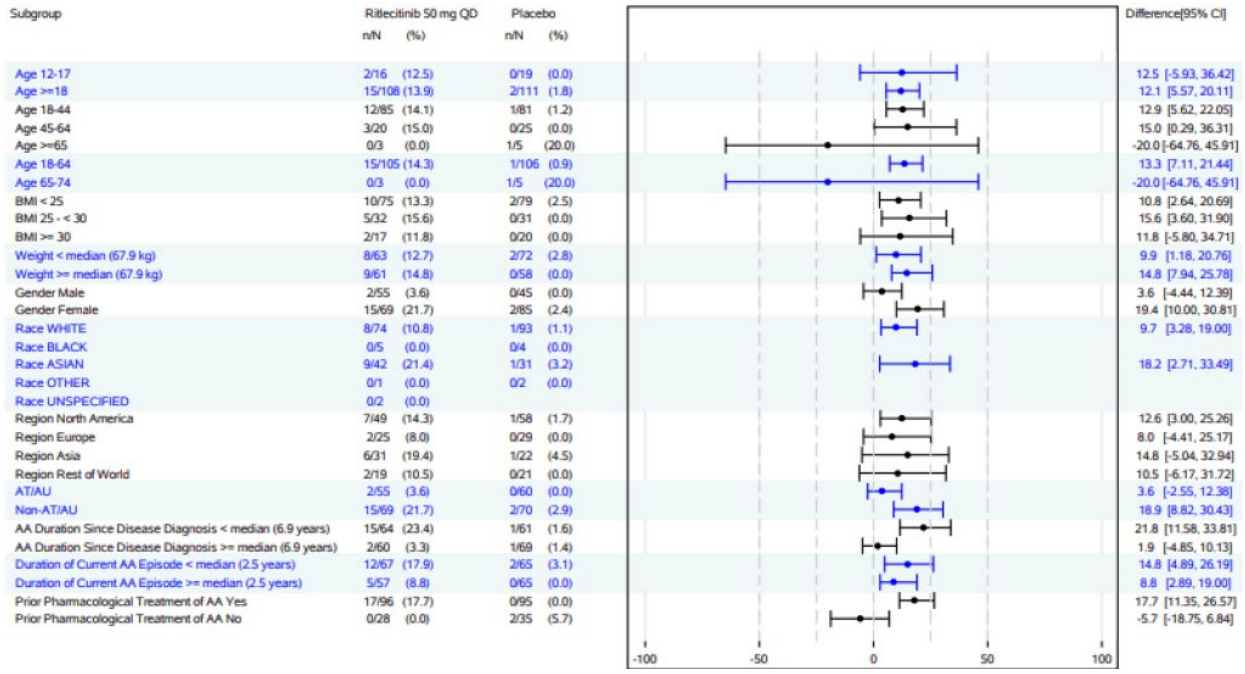
- **Ancillary analyses**

Subgroup analyses

Subgroup analyses have been performed using the SALT10 and the PGI-C at week 24 (primary and key secondary outcomes).

Subgroup data with respect to **SALT ⩽10** score for ritlecitinib 50mg, the dose proposed by the applicant, are visualised in a forest plot (Figure 18). Treatment with ritlecitinib 50 mg resulted in a higher proportion of SALT ⩽10 responders than placebo in most subgroups. The differences in proportions of SALT ⩽10 responders at Week 24 between ritlecitinib and placebo were similar in adolescents and adults. Some subgroups were small, such as patients >65 years of age, which is reflected in large standard errors. Placebo-adjusted SALT ⩽10 responses at week 24 were similar for White and Asian participants; the numbers of participants of other races were low. The difference in SALT ≤10 response of ritlecitinib versus placebo was lower in participants with AT/AU than in those without AT/AU at Week 24.

Figure 18: Response based on SALT ≤10 at Week 24 with ritlecitinib 50mg by subgroups

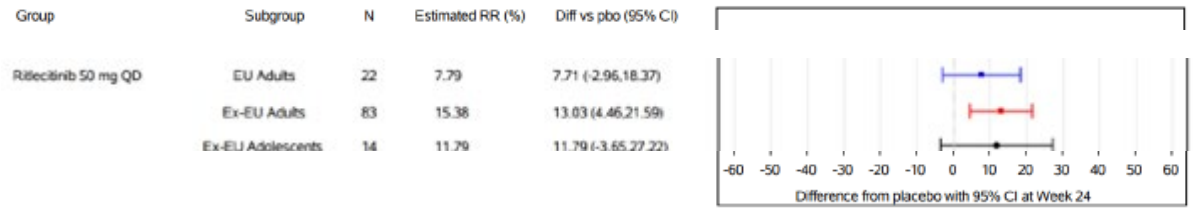


Subgroup data with respect to **PGI-C** response for 50mg, the dose proposed by the applicant, were visualised in a forest plot. Treatment with ritlecitinib 50 mg resulted in a higher proportion of PGI-C improvement than placebo in most subgroups. The subgroup of elderly participants (above 65 years of age) was small. The differences in proportions of participants with PGI-C improvement was similar between AT/AU and non-AT/AU participants.

Adolescents

There were no separate studies conducted in adolescents. Adolescent data was incorporated into study B7981015 (efficacy and safety) and B7981032 (safety). The applicant conducted extrapolation analyses to investigate the generalisation of data from the non-EU adolescents to the EU adolescent population. These analyses compared age groups (adults and adolescents) and regions (EU vs non-EU). Data derived from adolescent (non-EU only) and adult (non-EU and EU) AA participants in study B7981015 indicate that the efficacy of ritlecitinib, as measured by improvements in scalp hair loss (SALT score) and patient-reported treatment benefits (PGI-C and AAPPO), in non-EU adults is similar to that of EU adults, and ritlecitinib efficacy in non-EU adolescents is consistent with that in non-EU adults. Figure 19 shows that there was a similar SALT⩽10 response (primary outcome) for ritlecitinib 50 mg between EU/non-EU adults and non-EU adolescents with overlapping 95% confidence intervals. Similar results are shown for SALT⩽20 and PGI-C responses at week 24. The dose-response relationship is similar for SALT⩽10 in adolescents and adults at week 24.

Figure 19: Response based on SALT ⩽10 at Week 24 for EU adults, non-EU adults and non-EU adolescents



Elderly participants

No separate studies were conducted on elderly participants (≥65 years of age). Only a few elderly participants were enrolled in the main study (<5%).

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main study 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 20: Summary of efficacy for the main study 015

<table>
<tr><td colspan="3"><u>Title:</u> A phase 2b/3 randomised, double-blind, placebo-controlled, dose-ranging study to investigate the efficacy and safety of ritlecitinib in adult and adolescent Alopecia Areata (AA) participants with 50% or greater scalp hair loss</td></tr>
<tr><td>Study identifier</td><td colspan="2">B7981015
EudraCT number: 2018-001714-14</td></tr>
<tr><td>Design</td><td colspan="2">Randomised (2:2:2:2:1:1:1):, double-blind, placebo-controlled (24 weeks), dose-ranging study In 718 adult and adolescent (15%) with Alopecia areata with ≥50% scalp hair loss. Randomisation was stratified for age (<18 years vs. ≥ 18 years) and alopecia totalis/alopecia universalis (y/n). There were 7 dose regimens (study arms):
<table>
<tr><th>Loading (0-4 wks)</th><th>Maintenance 4-24 wks</th><th>Extension 25-48 wks</th></tr>
<tr><td>Ritlecitinib 200 mg QD</td><td>Ritlecitinib 50 mg QD</td><td>Ritlecitinib 50 mg QD</td></tr>
<tr><td>Ritlecitinib 200 mg QD</td><td>Ritlecitinib 30 mg QD</td><td>Ritlecitinib 30 mg QD</td></tr>
<tr><td>Ritlecitinib 50 mg QD</td><td>Ritlecitinib 50 mg QD</td><td>Ritlecitinib 50 mg QD</td></tr>
<tr><td>Ritlecitinib 30 mg QD</td><td>Ritlecitinib 30 mg QD</td><td>Ritlecitinib 30 mg QD</td></tr>
<tr><td>Ritlecitinib 10 mg QD</td><td>Ritlecitinib 10 mg QD</td><td>Ritlecitinib 10 mg QD</td></tr>
<tr><td>Placebo</td><td>Placebo</td><td>Ritlecitinib 200/50 QD</td></tr>
<tr><td>Placebo</td><td>Placebo</td><td>Ritlecitinib 50 mg QD</td></tr>
</table>
Duration of main phase: 24 weeks
Duration of Run-in phase: not applicable
Duration of Extension phase: 24 weeks</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Superiority</td></tr>
<tr><td>Treatments groups</td><td>ritlecitinib 200/50 mg</td><td>200 mg for 4 weeks followed by 50 mg for 44 weeks; 132 randomised</td></tr>
<tr><td></td><td>ritlecitinib 200/30 mg</td><td>200 mg for 4 weeks followed by 30 mg for 44 weeks; 130 randomised</td></tr>
<tr><td></td><td>ritlecitinib 50 mg</td><td>50 mg for 48 weeks; 130 randomised</td></tr>
<tr><td></td><td>ritlecitinib 30 mg</td><td>30 mg for 48 weeks; 132 randomised</td></tr>
</table>

	ritlecitinib 10 mg		10 mg for 48 weeks; 63 randomised
	Placebo ritlecitinib 200/50 mg		Placebo for 24 weeks and then 200 mg for 4 weeks followed by 50 mg for 20 weeks; 65 randomised
	Placebo ritlecitinib 50 mg		Placebo for 24 weeks and then 50 mg for 20 weeks; 66 randomised
Endpoints and definitions	Primary endpoint	SALT ≤10 response at Week 24	Severity of Alopecia Tool (SALT) SALT score is a quantitative assessment of AA severity based on scalp hair loss. SALT ≤10 response represents less than or equal to 10% of scalp hair loss.
	Key Secondary endpoint	PGI-C at Week 24	Patient Global Impression of Change (PGI-C) is a patient reported outcomes measure of treatment benefit used to assess if there has been a global improvement or worsening in clinical status compared to baseline. PGI-C response is defined as a score of "moderately improved" or "greatly improved."
	Secondary endpoint	SALT ≤10 at Week 48	Severity of Alopecia Tool (SALT) SALT score is a quantitative assessment of AA severity based on scalp hair loss. SALT ≤10 response represents less than or equal to 10% of scalp hair loss.
	Secondary endpoint: PGI-C response at Week 48	PGI-C at Week 48	Patient Global Impression of Change (PGI-C) is a patient reported outcomes measure of treatment benefit used to assess if there has been a global improvement or worsening in clinical status compared to baseline. PGI-C response is defined as a score of "moderately improved" or "greatly improved."
	Secondary endpoint: Response based on an absolute SALT Score ≤20 at Week 24 and Week 48	SALT ≤20 at Week 24 and Week 48	Severity of Alopecia Tool (SALT) SALT score is a quantitative assessment of AA severity based on scalp hair loss. SALT ≤20 response represents less than or equal to 20% of scalp hair loss.
	Secondary endpoint: Response based on at least a 2-grade improvement from Baseline or a score of 3 in EBA score at Week 24 and Week 48	EBA at Week 24 and Week 48	The Eyebrow Assessment (EBA) is a ClinRO numeric rating scale developed by the applicant in collaboration with AA experts to characterise eyebrow hair loss. The numeric rating scale ranges from 0 (none) to 3 (normal). EBA response was defined as at least a 2-grade improvement or a normal score (score of 3) (ie, achievement of moderate or normal eyebrows) in EBA in participants who had an abnormal eyebrow score (ie, scores <3) at Baseline.
	Secondary endpoint: Response based on at least a 2-grade improvement from Baseline or a score of 3 in ELA score at Week 24 and Week 48	ELA at Week 24 and Week 48	The Eyelash Assessment (ELA) is a ClinRO numeric rating scale developed by the applicant in collaboration with AA experts to characterise eyelash hair loss. The numeric rating scale ranges from 0 (none) to 3 (normal). ELA response was defined as at least a 2-grade improvement or a normal score (score of 3) (ie, achievement of moderate or normal eyelashes) in ELA in participants who had an abnormal eyelash score (ie, scores <3) at Baseline.

Database lock	10 July 2021 (Database snapshot date 12 July 2021)

Results and Analysis

Results of treatment comparison between the ritlecitinib 10 mg dose group and the placebo group are not presented. The 10 mg group was included in the study only to support the characterisation of the exposure response; it was not planned for comparison versus placebo, as it was not expected to have meaningful efficacy.

Analysis description	**Primary Analysis**						
Analysis population and time point description	Full Analysis Set (FAS): All participants who were randomised regardless of whether they received study intervention. Week 24						
Descriptive statistics and estimate variability	Treatment group	Ritlecitinib 200/50 mg QD	Ritlecitinib 200/30 mg QD	Ritlecitinib 50 mg QD	Ritlecitinib 30 mg QD	Ritlecitinib 10 mg QD	Placebo
	Number of subjects	132	130	130	132	63	131
	SALT ≤10 Response at Week 24 (%)	21.29	12.87	13.42	10.62	1.65	1.54
	SE (%)	3.64	3.01	3.03	2.79	1.64	1.08
Effect estimate per comparison	Primary endpoint	Comparison groups		Ritlecitinib 200/50 mg QD and Placebo			
		Difference from Placebo		19.75			
		95% CI		(11.91, 27.59)			
		P-value		<0.000001			
		Comparison groups		Ritlecitinib 200/30 mg QD and Placebo			
		Difference from Placebo		11.33			
		95% CI		(4.93, 17.74)			
		P-value		0.000526			
		Comparison groups		Ritlecitinib 50 mg QD and Placebo			
		Difference from Placebo		11.88			
		95% CI		(5.42, 18.33)			
		P-value		0.000311			
		Comparison groups		Ritlecitinib 30 mg QD and Placebo			
		Difference from Placebo		9.09			
		95% CI		(3.10, 15.07)			
		P-value		0.002922			
Notes	In this analysis, a generalised linear mixed effect model without imputation using observed data up to Week 24 was used as the imputation model. Estimation of model parameters was performed assuming MAR using Bayesian framework with non-informative/weakly informative prior densities and MCMC. For a participant with missing response at Week 24 due to COVID-19, imputation was done based on predictive Bernoulli distribution with a probability equal to the probability under MAR calculated using the sampled parameters. Participants with missing SALT score at Week 24 due to reasons other than COVID-19 were considered non-responders. A single complete imputed data set for Week 24 was analysed using the Miettinen and Nurminen method as the analysis model.						

Analysis description	**Key Secondary Analysis (pre-specified)**						
Analysis population and time point description	Full Analysis Set (FAS): All participants who were randomised regardless of whether they received study intervention. Week 24						
Descriptive statistics and estimate variability	Treatment group	Ritlecitinib 200/50 mg QD	Ritlecitinib 200/30 mg QD	Ritlecitinib 50 mg QD	Ritlecitinib 30 mg QD	Ritlecitinib 10 mg QD	Placebo
	Number of subjects	132	130	130	132	63	131
	PGI-C Response at Week 24 (%)	52.19	45.40	49.17	41.95	11.36	9.23
	SE (%)	4.43	4.46	4.44	4.43	4.04	2.54
Effect estimate per comparison	Key secondary endpoint	Comparison groups			Ritlecitinib 200/50 mg QD and Placebo		
		Difference from Placebo			42.96		
		95% CI			(31.68, 54.25)		
		P-value			<0.000001		
		Comparison groups			Ritlecitinib 200/30 mg QD and Placebo		
		Difference from Placebo			36.18		
		95% CI			(25.22, 47.14)		
		P-value			<0.000001		
		Comparison groups			Ritlecitinib 50 mg QD and Placebo		
		Difference from Placebo			39.96		
		95% CI			(28.85, 51.06)		
		P-value			<0.000001		
		Comparison groups			Ritlecitinib 30 mg QD and Placebo		
		Difference from Placebo			32.72		
		95% CI			(21.95, 43.50)		
		P-value			<0.000001		
Notes	In this analysis, a generalised linear mixed effect model without imputation using observed data up to Week 24 was used as the imputation model. Estimation of model parameters was performed assuming MAR using Bayesian framework with non-informative/weakly informative prior densities and MCMC. For a participant with missing response at Week 24 due to COVID-19, imputation was done based on predictive Bernoulli distribution with a probability equal to the probability under MAR calculated using the sampled parameters. Participants with missing PGI-C score at Week 24 due to reasons other than COVID-19 were considered non-responders. A single complete imputed data set for Week 24 was analysed using the Miettinen and Nurminen method as the analysis model.						

Analysis description	Secondary Analysis (pre-specified)							
Analysis population and time point description	FAS at Week 48							
Descriptive statistics and estimate variability	Treatment group	Ritlecitinib 200/50 mg QD	Ritlecitinib 200/30 mg QD	Ritlecitinib 50 mg QD	Ritlecitinib 30 mg QD	Ritlecitinib 10 mg QD	Placebo→ Ritlecitinib 200/50 mg QD	Placebo→ Ritlecitinib 50 mg QD
	Number of subjects	129	122	125	122	61	65	64
	SALT ≤10 response at Week 48 (%)	33.33	27.87	31.20	25.41	6.56	24.62	14.06
	SE (%)	4.15	4.06	4.14	3.94	3.17	5.34	4.35
Note	Subjects with missing data due to reasons unrelated to COVID-19 were considered as non-responders; subjects with missing data due to COVID-19 were excluded from the analysis. Treatment comparison to Placebo group was not conducted post Week 24, as subjects initially randomised to receive placebo treatment were randomised to receive either ritlecitinib 200/50 mg QD or ritlecitinib 50 mg QD at Week 24.							

Analysis description	Secondary Analysis (pre-specified)							
Analysis population and time point description	FAS at Week 48							
Descriptive statistics and estimate variability	Treatment group	Ritlecitinib 200/50 mg QD	Ritlecitinib 200/30 mg QD	Ritlecitinib 50 mg QD	Ritlecitinib 30 mg QD	Ritlecitinib 10 mg QD	Placebo→ Ritlecitinib 200/50 mg QD	Placebo→ Ritlecitinib 50 mg QD
	Number of subjects	129	123	125	122	61	64	64
	PGI-C response at Week 48 (%)	58.14	52.03	56.00	49.18	16.39	59.38	43.75
	SE (%)	4.34	4.50	4.44	4.53	4.74	6.14	6.20
Note	Subjects with missing data due to reasons unrelated to COVID-19 were considered as non-responders; subjects with missing data due to COVID-19 were excluded from the analysis. Treatment comparison to Placebo group was not conducted post Week 24, as subjects initially randomised to receive placebo treatment were randomised to receive either ritlecitinib 200/50 mg QD or ritlecitinib 50 mg QD at Week 24.							

Analysis description	Secondary Analysis (pre-specified)						
Analysis population and time point description	FAS Week 24						
Descriptive statistics and estimate variability	Treatment group	Ritlecitinib 200/50 mg QD	Ritlecitinib 200/30 mg QD	Ritlecitinib 50 mg QD	Ritlecitinib 30 mg QD	Ritlecitinib 10 mg QD	Placebo
	Number of subjects	132	130	130	132	63	131
	SALT ≤20 Response at Week 24 (%)	29.89	21.69	22.98	13.83	1.62	1.55
	SE (%)	4.07	3.70	3.75	3.12	1.61	1.09
Effect estimate per comparison	Secondary endpoint	Comparison groups		Ritlecitinib 200/50 mg QD and Placebo			
		Difference from Placebo		28.34			
		95% CI		(19.39, 37.30)			
		P-value		<0.000001			
		Comparison groups		Ritlecitinib 200/30 mg QD and Placebo			
		Difference from Placebo		20.15			
		95% CI		(12.23, 28.07)			
		P-value		<0.000001			
		Comparison groups		Ritlecitinib 50 mg QD and Placebo			
		Difference from Placebo		21.43			
		95% CI		(13.37, 29.48)			
		P-value		<0.000001			
		Comparison groups		Ritlecitinib 30 mg QD and Placebo			
		Difference from Placebo		12.29			
		95% CI		(5.64, 18.95)			
		P-value		0.000294			
Notes	In this analysis, a generalised linear mixed effect model without imputation using observed data up to Week 24 was used as the imputation model. Estimation of model parameters was performed assuming MAR using Bayesian framework with non-informative/weakly informative prior densities and MCMC. For a participant with missing response at Week 24 due to COVID-19, imputation was done based on predictive Bernoulli distribution with a probability equal to the probability under MAR calculated using the sampled parameters. Participants with missing SALT score at Week 24 due to reasons other than COVID-19 were considered non-responders. A single complete imputed data set for Week 24 was analysed using the Miettinen and Nurminen method as the analysis model.						

Analysis description	Secondary Analysis (pre-specified)							
Analysis population and time point description	FAS Week 48							
Descriptive statistics and estimate variability	Treatment group	Ritlecitinib 200/50 mg QD	Ritlecitinib 200/30 mg QD	Ritlecitinib 50 mg QD	Ritlecitinib 30 mg QD	Ritlecitinib 10 mg QD	Placebo→ Ritlecitinib 200/50 mg QD	Placebo→ Ritlecitinib 50 mg QD
	Number of subjects	129	122	125	122	61	65	64
	SALT ≤20 response at Week 48 (%)	39.53	34.43	43.20	31.15	9.84	33.85	18.75
	SE (%)	4.30	4.30	4.43	4.19	3.81	5.87	4.88
Note	Subjects with missing data due to reasons unrelated to COVID-19 were considered as non-responders; subjects with missing data due to COVID-19 were excluded from the analysis. Treatment comparison to Placebo group was not conducted post Week 24, as subjects initially randomised to receive placebo treatment were randomised to receive either ritlecitinib 200/50 mg QD or ritlecitinib 50 mg QD at Week 24.							

Analysis description	Secondary Analysis (pre-specified)						
Analysis population and time point description	All participants without Normal EBA at Baseline in FAS. Week 24						
Descriptive statistics and estimate variability	Treatment group	Ritlecitinib 200/50 mg QD	Ritlecitinib 200/30 mg QD	Ritlecitinib 50 mg QD	Ritlecitinib 30 mg QD	Ritlecitinib 10 mg QD	Placebo
	Number of subjects	103	102	100	102	48	107
	EBA Response at Week 24 (%)	33.98	25.49	29.00	16.67	8.33	4.67
	SE (%)	4.67	4.32	4.54	3.69	3.99	2.04
Effect estimate per comparison	Secondary endpoint	Comparison groups		Ritlecitinib 200/50 mg QD and Placebo			
		Difference from Placebo		29.31			
		95% CI		(19.47, 39.50)			
		P-value		<0.000001			
		Comparison groups		Ritlecitinib 200/30 mg QD and Placebo			
		Difference from Placebo		20.82			
		95% CI		(11.70, 30.67)			
		P-value		0.000023			
		Comparison groups		Ritlecitinib 50 mg QD and Placebo			
		Difference from Placebo		24.33			
		95% CI		(14.82, 34.48)			
		P-value		0.000002			
		Comparison groups		Ritlecitinib 30 mg QD and Placebo			
		Difference from Placebo		11.99			
		95% CI		(3.89, 21.02)			
		P-value		0.004741			
Notes	Cases with missing data at Week 24 due to COVID-related reasons are excluded from the analysis; cases with missing data at Week 24 due to reasons unrelated to COVID-19 are considered as non-response. Confidence Interval of the estimated treatment difference and p-value are calculated using the Miettinen and Nurminen (MN) method.						

Analysis description	Secondary Analysis (pre-specified)							
Analysis population and time point description	All participants without Normal EBA at Baseline in FAS. Week 48							
Descriptive statistics and estimate variability	Treatment group	Ritlecitinib 200/50 mg QD	Ritlecitinib 200/30 mg QD	Ritlecitinib 50 mg QD	Ritlecitinib 30 mg QD	Ritlecitinib 10 mg QD	Placebo→ Ritlecitinib 200/50 mg QD	Placebo→ Ritlecitinib 50 mg QD
	Number of subjects	107	101	101	105	50	55	51
	EBA response at Week 48 (%)	42.99	32.67	43.56	33.33	16.00	30.91	31.37
	SE (%)	4.79	4.67	4.93	4.60	5.18	6.23	6.50
Note	Subjects with missing data due to reasons unrelated to COVID-19 were considered as non-responders; subjects with missing data due to COVID-19 were excluded from the analysis. Treatment comparison to Placebo group was not conducted post Week 24, as subjects initially randomised to receive placebo treatment were randomised to receive either ritlecitinib 200/50 mg QD or ritlecitinib 50 mg QD at Week 24.							

Analysis description	**Secondary Analysis**						
Analysis population and time point description	All participants without Normal ELA at Baseline in FAS. Week 24						
Descriptive statistics and estimate variability	Treatment group	Ritlecitinib 200/50 mg QD	Ritlecitinib 200/30 mg QD	Ritlecitinib 50 mg QD	Ritlecitinib 30 mg QD	Ritlecitinib 10 mg QD	Placebo
	Number of subjects	96	89	90	92	41	97
	ELA Response at Week 24 (%)	30.21	21.35	28.89	26.09	4.88	5.15
	SE (%)	4.69	4.34	4.78	4.58	3.36	2.25
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ritlecitinib 200/50 mg QD and Placebo				
		Difference from Placebo	25.05				
		95% CI	(15.00, 35.56)				
		P-value	0.000005				
		Comparison groups	Ritlecitinib 200/30 mg QD and Placebo				
		Difference from Placebo	16.19				
		95% CI	(6.86, 26.49)				
		P-value	0.000999				
		Comparison groups	Ritlecitinib 50 mg QD and Placebo				
		Difference from Placebo	23.73				
		95% CI	(13.61, 34.50)				
		P-value	0.000013				
		Comparison groups	Ritlecitinib 30 mg QD and Placebo				
		Difference from Placebo	20.93				
		95% CI	(11.15, 31.43)				
		P-value	0.000066				
Notes	Cases with missing data at Week 24 due to COVID-related reasons are excluded from the analysis; cases with missing data at Week 24 due to reasons unrelated to COVID-19 are considered as non-response. Confidence Interval of the estimated treatment difference and p-value are calculated using the Miettinen and Nurminen (MN) method.						

Analysis description	Secondary Analysis (pre-specified)							
Analysis population and time point description	All participants without Normal ELA at Baseline in FAS. Week 48							
Descriptive statistics and estimate variability	Treatment group	Ritlecitinib 200/50 mg QD	Ritlecitinib 200/30 mg QD	Ritlecitinib 50 mg QD	Ritlecitinib 30 mg QD	Ritlecitinib 10 mg QD	Placebo→ Ritlecitinib 200/50 mg QD	Placebo→ Ritlecitinib 50 mg QD
	Number of subjects	99	88	90	95	43	51	45
	ELA response at Week 48 (%)	38.38	29.55	40.00	30.53	20.93	37.25	35.56
	SE (%)	4.89	4.86	5.16	4.72	6.20	6.77	7.14
Note	Subjects with missing data due to reasons unrelated to COVID-19 were considered as non-responders; subjects with missing data due to COVID-19 were excluded from the analysis. Treatment comparison to Placebo group was not conducted post Week 24, as subjects initially randomised to receive placebo treatment were randomised to receive either ritlecitinib 200/50 mg QD or ritlecitinib 50 mg QD at Week 24.							

2.6.5.3. Supportive studies

Three studies (B7931**005**, B7981**037** and B7981**032**) provide additional information about efficacy over time and for the duration of treatment with ritlecitinib.

Two studies (B7981**048** and B7981**072**) provide information about AA patient preferences for treatment attributes. Study 048 was performed in adults; patient preferences were elicited using a discrete choice experiment and applied to the trial results in AA in a quantitative Benefit/Risk analysis. Study 072 was a similar discrete choice experiment performed in adolescents.

Study B7931005

The placebo-controlled part of study B7931005 (Week 1-24) is described in the section Proof of Concept Study above. The single-blinded period of this study evaluated the course of hair loss following week 24 and could provide information on the duration of treatment with ritlecitinib.

As described above, after the 4-week drug holiday (starting immediately after Week 24) **responders** (those having achieved at least a 30% improvement in the SALT score from Baseline at Week 24) were treated with placebo and monitored every 2 weeks. In case of hair loss of more than 30% with respect to week 24 (i.e. change in SALT >30%) participants were started on ritlecitinib (4 weeks 200 mg QD and 20 weeks of ritlecitinib 50mg QD). The **non-responders** (from either the placebo or ritlecitinib group from Week 1-24) were treated with ritlecitinib throughout the entire single blinded period. The non-responders group included 33 participants, respectively 17 and 16 from the placebo and ritlecitinib group from Week 1-24.

A total of 22 participants who met the responder criteria entered the withdrawal/retreatment period. Of the 22 ritlecitinib responders, 15 participants met the retreatment criterion, 3 discontinued before meeting the retreatment criterion, and 4 completed the withdrawal segment without meeting the retreatment criterion. One of the 15 participants who met the criterion for retreatment voluntarily withdrew from the study upon meeting the retreatment criterion.

The minimum time to meet the retreatment criterion was 4.3 weeks; the median time to meet the retreatment criterion was 16.1 weeks, including the 4-week drug holiday. Among the participants who met the retreatment criterion, 7/14 (50%) had at least a 30% improvement in SALT score at treatment re-initiation compared to the study baseline. At the end of the retreatment period (after 24 weeks of retreatment), 8/14 participants (57%) had at least a 30% improvement in SALT score compared to study Baseline. Of 6 remaining participants, 5 did not have SALT data available at the end of the retreatment period.

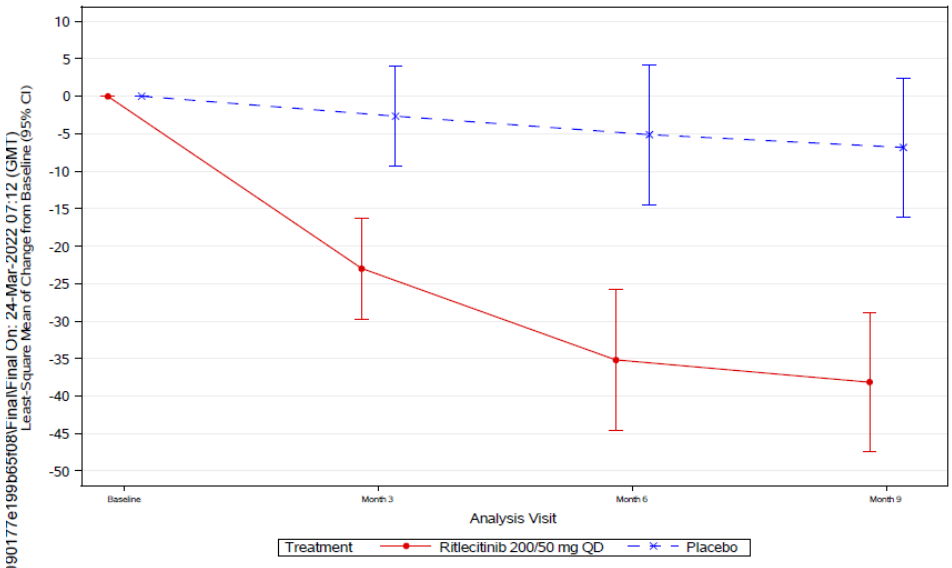
The effect of ritlecitinib treatment in non-responders in the single blinded period was compared to placebo group of the Initial 24-Week Treatment Period. The non-responders who were treated with ritlecitinib in both the Initial phase and in the single blinded phase ("active non-responders") showed only a slight improvement in SALT score compared to the placebo group from the Initial phase. Participants treated with the placebo in the first 24 weeks and with ritlecitinib during the single blinded phase ("placebo non-responders")" demonstrated an improvement in SALT score similar to the ritlecitinib group in the Initial 24-Week Treatment Period (LSM difference from placebo 29%; 90% CI [20%, 38%] at p-value <0.0001).

B7981037

Study B7981037 is phase 2a, randomised, double-blind, parallel-group, placebo-controlled safety study designed to evaluate the safety and tolerability of ritlecitinib (for more information, see Safety section). However, two secondary efficacy endpoints were included: change from baseline in SALT score over time and of PGI-C score response ('greatly improved' or 'moderately improved') over time. The Placebo-Controlled Treatment Phase, which included 2 groups (ritlecitinib and placebo) lasted for 9 months. The dose of ritlecitinib consisted of 4 weeks of loading dose 200 mg QD and 8 months of ritlecitinib 50mg QD. There were 36 participants in the ritlecitinib and 35 participants in the placebo group. The inclusion criterion with respect to the extent of AA was ⩾25% hair loss. This was different than in Study 005 and 015.

At Months 3, 6, and 9, the decrease in LSM change from baseline in SALT scores was larger in the ritlecitinib group than in placebo (-23 vs. -2.7, -35 vs. -5.1, and -38 vs. -6.8 , respectively), see Figure 20. The 95% CI for the difference between groups excluded 0 at all timepoints. The findings were similar for the PGI-C outcome: a larger proportion of participants in the ritlecitinib group mg were PGI-C responders (defined as 'greatly improved' or 'moderately improved') compared to placebo at Months 3, 6, and 9 (56%, 58%, and 53%, respectively). The 95% CI for the difference between groups excluded 0 at all timepoints.

Figure 20: Least-square mean of change from baseline in SALT score up to month 9



B7981032

Study B7981032 is an ongoing Phase 3, open-label, multi-centre, long-term study to evaluate the safety and efficacy of ritlecitinib in adults and adolescents ⩾12 years of age with AA. The study

included a 36-month open-label treatment period. This study included rollover participants from B7931005 and B7981015 who received open-label 50 mg ritlecitinib QD for 36 months, and de novo participants who received open-label 200 mg loading dose for 4 weeks, followed by the open-label 50 mg ritlecitinib QD dose for 35 months. An additional treatment period (of variable length for individual participants) was later added in Protocol Amendment 6 to allow participants not requiring discontinuation per protocol to continue to receive study intervention for a maximum of an additional 24 months or until the availability of the commercial product in their country, or until the Sponsor terminates the study in that country, whichever occurs first. The total treatment duration of study B7981032 will therefore be 60 months. A Primary Completion Date (PCD) Clinical Study Report (CSR) with data through Month 36 is expected to be finalised in November 2024. A Supplemental CSR with final study data through the last visit of the last participant in the study, including available data up to Month 60, is expected to be final by May 2026. The final CSR will be submitted post approval once available.

The original submission was based on the data cut-off date of 28 February 2022. Efficacy data has been updated based on a cut-off date of 07 November 2022.

Although the primary endpoints were focused on safety, secondary efficacy outcomes were included: SALT score ⩽10 and ⩽ 20 through Month 36, response based on achieving at least a 2-grade improvement from Baseline or a score of 3 in EBA or ELA score through Month 36; and PGI-C response defined as PGI-C score of 'moderately improved' or 'greatly improved' through Month 36.

This study included rollover participants from studies B7931005 and B7981015 who received open-label 50 mg ritlecitinib QD for 36 months, and de novo participants who received open-label 200 mg loading dose for 4 weeks, followed by the open-label 50 mg ritlecitinib QD dose for 35 months.

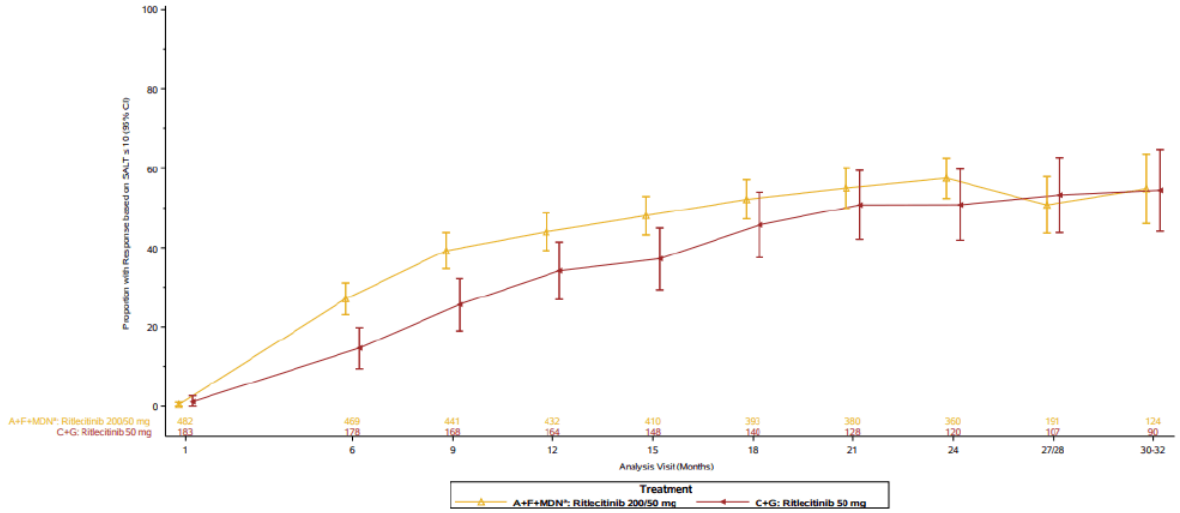
Unlike in studies B7981015 and B7931005 where the inclusion criterion was ⩾50% terminal scalp hair loss, the inclusion criterion for the de novo participants was ⩾25% terminal scalp hair loss due to AA.

Efficacy analyses were descriptive in nature; there was no formal hypothesis testing, though 95% two-sided confidence intervals were reported. Missing data were not imputed. The results through Month 30-32 are presented. Data are not presented after Month 30-32 as there were only a limited number of participants with efficacy data beyond that timepoint as of the 07 November 2022 data cut.

Data from studies B7981015 and B7981032 were combined to form the All Exposure Cohort (AEC) which are presented below.

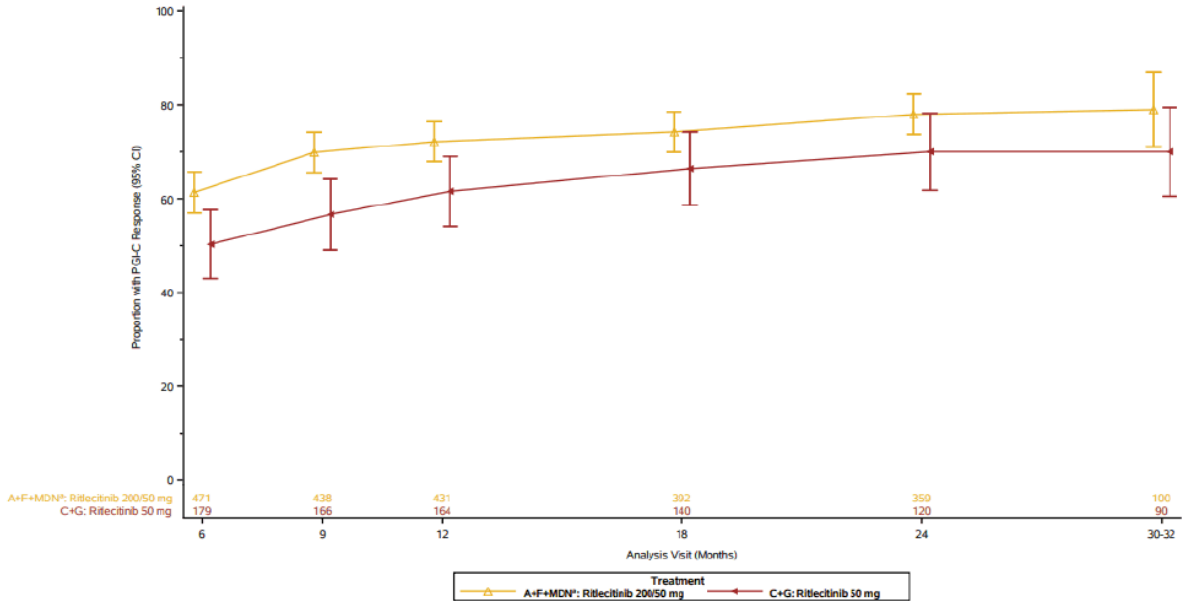
SALT ⩽10 response rate continued to increase through Month 24 and then remained generally stable through Month 30-32 for both the 200/50 mg Combined and the 50 mg Combined groups. For the 200/50 mg Combined group, 58% of participants at Month 24 and 55% at Month 30-32 had SALT ⩽10 response. For the 50 mg Combined group, 51% of participants at Month 24 and 54% at Month 30-32 had SALT ⩽10 response (Figure 21).

Figure 21: SALT ⩽10 response based on pooled efficacy data from Studies B7981015 and B7981032 (AEC)



PGI-C response (defined as a PGI-C score of 'moderately improved' or 'greatly improved') was maintained from Month 12 to Month 30-32 for the 200/50 mg Combined group and from Month 18 to Month 30-32 for the 50 Combined group. For the 200/50 mg Combined group, 78% of participants at Month 24 and 79 % at Month 30-32 had PGI-C response. For the 50 mg Combined group, 70 % of participants at both Month 24 and Month 30-32 had PGI-C response (Figure 22).

Figure 22: PGI-C response based on pooled efficacy data from Studies B7981015 and B7981032 (AEC)



Similar patterns were seen for the SALT ⩽20 and EBA/ELA response through Month 30-32 for both the 200/50 mg Combined and 50 mg Combined groups in the AEC.

Regarding the subgroup of **adolescents**, 42 adolescent participants were withdrawn for the reason of 'no longer meets eligibility criteria'. The majority were withdrawn because they did not meet the study continuation criteria for adolescents, which were added in study B7981032 Protocol Amendment 4 following FDA's advice to amend the protocol to limit exposure to the drug product in adolescent participants if limited treatment effects were observed. To assess the potential impact of these early withdrawals, additional analyses using non-responder imputation (NRI) and last observation carried

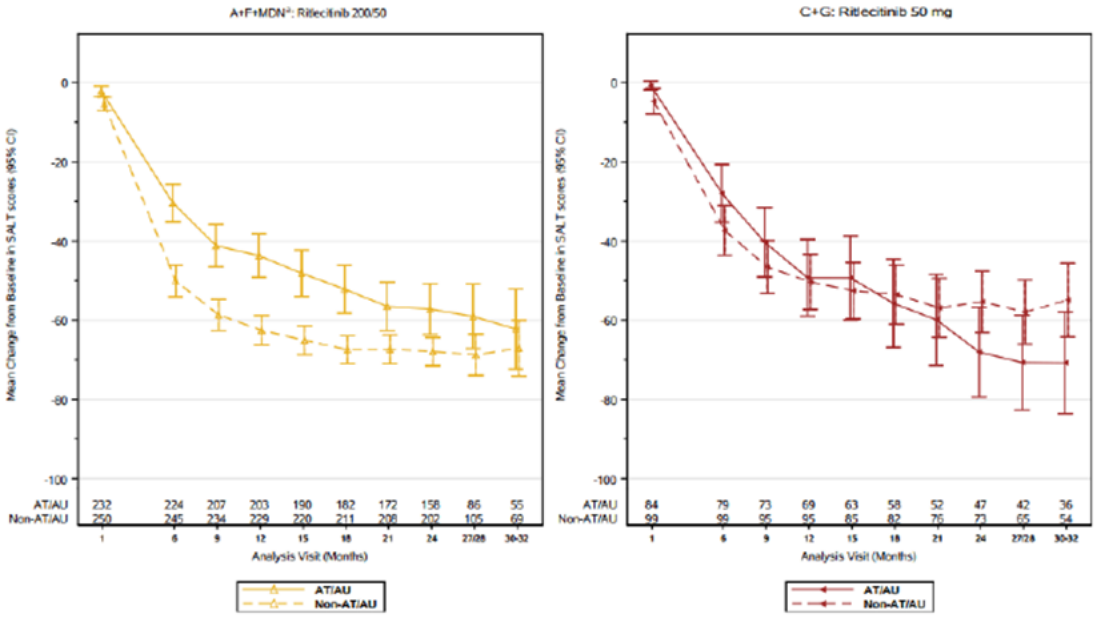
forward (LOCF) methods were also performed for SALT response rates and CFB in SALT scores, respectively.

In both adults and adolescents in the All Exposure Cohort SALT≤ 10 responders increased and SALT change from baseline decreased up to Month 24 in both adults and adolescents indicating regrowth of the lost hair. NRI and LOCF analysis showed similar trends, and the results were further supported by SALT ≤ 20 and PGI-C responses.

With respect to **AT/AU vs non-AT/AU groups**, SALT ⩽10 response rates generally increased over time in AT/AU and non-AT/AU for the ritlecitinib 200/50 mg Combined group and the 50 mg Combined group. For the ritlecitinib 200/50 mg Combined group, the non-AT/AU subgroup had higher SALT ⩽10 response rates than the AT/AU subgroup through Month 30-32 with nonoverlapping 95% CIs for all timepoints. For the ritlecitinib 50 mg Combined group, SALT ⩽10 response rates tended to be higher for participants with non-AT/AU than for those with AT/AU through Month 18. At the Month 21 through Month 30-32 visits, response rates were similar for participants with and without AT/AU for ritlecitinib 50 mg. Similar observations were made for SALT ⩽20 response over time for the AT/AU and non-AT/AU subgroups.

The change from baseline in SALT scores for the 200/50 mg Combined group for the non-AT/AU subgroup had greater reduction from baseline than the AT/AU subgroup through Month 30-32, with non-overlapping 95% CIs at all timepoints except Month 27/28 and Month 30-32 (Figure 23). The change in baseline in SALT score over time for the ritlecitinib 50 mg Combined group was similar for the AT/AU and non-AT/AU subgroups through Month 21, with continued decreases (i.e., improvement) through Month 30-32 for the AT/AU subgroup.

Figure 23: Change from baseline in SALT score over time by AA severity (observed data)



NRI and LOCF analysis for AT/AU and non-AT/AU subgroups showed similar trends as the observed data.

In order to identify an appropriate time to consider **discontinuation** of ritlecitinib in AA patients who are **non-responders**, additional analysis was conducted in patients who rolled over from study B7981015 to study B7981032. Three periods of possible response were identified: early (up to week 24), middle (week 24-48) and late (after week 48). SALT response trajectories were constructed for Late Responders to identify those participants who achieved SALT⩽20 response after week 48.

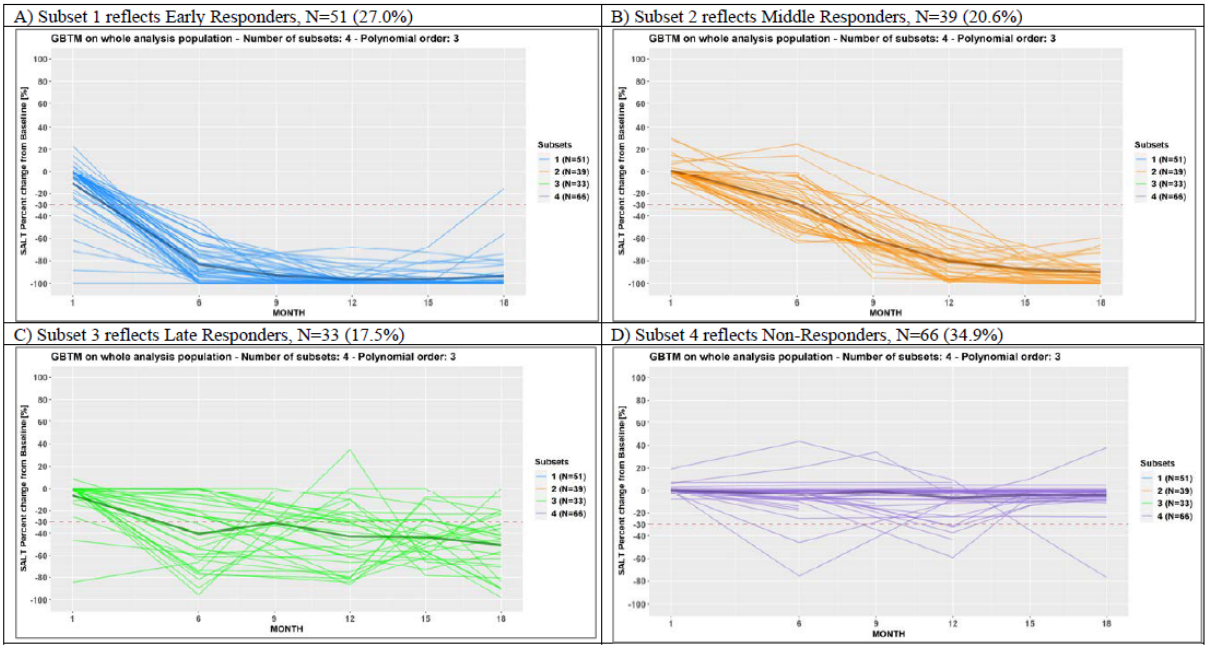
An additional predictive analysis of SALT response at Month 18 based on earlier SALT scores was carried out in ritlecitinib-treated participants. In this analysis, 'no response' was defined as the failure to reach a reduction of at least 30% from baseline on SALT scores (SALT30) during the 18-month period of treatment with ritlecitinib.

To evaluate a potential stopping rule for the non-responder group, 2 parameters were tested to predict the lack of response up to Month 18: i) magnitude of SALT improvement (10%, 20%, 25%, and 30% improvement from baseline), and ii) time points (namely Months 6, 9, and 12). Predictors were evaluated by how well they could identify potential non-responders.

The highest probability of being a non-responder (failure to reach a reduction of at least 30% from baseline on SALT scores) at Month 18 based on percent change from baseline at an earlier visit (negative predictive value) was 77% and 75% at Month 9 and 77% and 73% at Month 12, based on SALT improvement of 10% and 20% respectively.

Finally, Group Based Trajectories Modeling was employed to visualise trajectories which can be used to identify subsets of participants in the Ritlecitinib 50 mg Combined Group who followed similar longitudinal patterns of response based on SALT scores at Months 1, 6, 9, 12, 15, and 18 (Figure 24).

Figure 24: Individual SALT trajectories (percent change from baseline) for each subset from the GBTM analysis selected model (4 Subsets and Polynomial Order 3) for ritlecitinib 50 mg



B7981048: Alopecia Areata Benefit-risk trade-off study in adults

The main **objectives** of this study were to: elicit patient preferences for AA treatment attributes and to estimate maximum acceptable risks (MARs) of potential safety concerns associated with JAK inhibitors that AA patients are willing to tolerate for specific treatment benefits, and to assess the net benefit-risk profile of oral ritlecitinib 50 mg QD compared to 30 mg QD and to placebo.

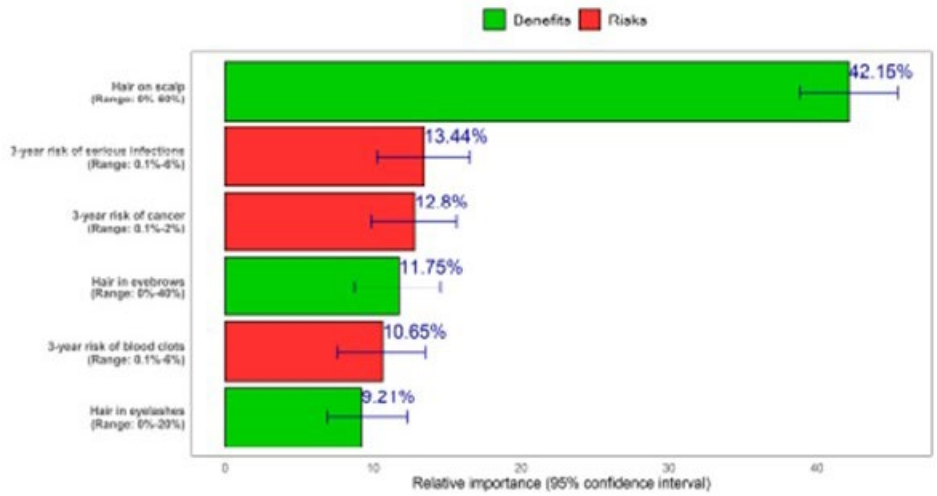
The **design** of the study was a cross-sectional quantitative survey administered online to patients in the United States (US), United Kingdom (UK), France, Germany, Italy and Spain. Patient preferences were elicited using a discrete-choice experiment in which patients were asked to choose between two hypothetical AA treatment profiles and no treatment in a series of questions. Each hypothetical treatment profile was defined by six attributes: the probability of 80% to 100% scalp hair regrowth over 24 weeks of treatment, the probability of moderate or normal eyebrows after 24 weeks of

treatment, probability of moderate or normal eyelashes after 24 weeks of treatment, 3-year risk of serious infection due to treatment, 3-year risk of cancer (including non-melanoma skin cancer) due to treatment, and 3-year risk of blood clot due to treatment. The profiles and profile pairs in the series of questions were determined using an experimental design. Preferences were then combined with clinical data for ritlecitinib 50 mg QD, ritlecitinib 30 mg QD, and placebo from clinical studies in a quantitative benefit-risk assessment model.

The **sample** consisted of 201 adult patients (age 18 years and older) with a dermatologist-confirmed diagnosis of AA recruited from the US (n=62), UK (n=22), France (n=3), Germany (n=30), Italy (n=59), and Spain (n=25). The mean (SD) age of patients in the sample was 41 (14) years and 130 (65%) were female. Most patients had been diagnosed with AA at least two years ago (80%) and were not currently on treatment (52%). The most common area of hair loss was on the scalp (95% of patients) followed by eyebrows (67% of patients) and eyelashes (60% of patients). Very few patients had prior serious infection (10%), cancer (2%), or blood clot (4%).

Relative attribute importance (RAI) values showed that the most important attribute for AA patients was the benefit of increasing the chance (from 0% to 50%) of getting back most or all of the hair on the scalp after 24 weeks of treatment (RAI 42%); (Figure 25). This was followed by a reduction in the risk of serious infection from 6% to 0.1% during three years of treatment (RAI 13%), a decrease in the risk of getting cancer from 2% to 0.1% during three years of treatment (RAI 13%), and the benefits of increasing the chance of getting moderate or normal eyebrows from 0% to 40% after 24 weeks (RAI: 12%). The reduction from 6% to 0.1% in the risk of getting blood clots during three years of treatment (RAI 11%), and benefits of increasing the chance from 0 % to 40% of getting moderate or normal eyelashes after 24 weeks (RAI 9.2%) were less important. Overall, patients placed more value on benefits, with a sum (95%CI) of benefit attribute RAIs of 63% (59% - 67%) than the treatment risks, with a sum (95%CI) of risk attribute RAIs of 37% (33% - 41%).

Figure 25: Relative attribute importance (RAI) as valued by AA patients (n=201) in the discrete choice experiment



Abbreviations: DCE = discrete choice experiment; ECL = error-component multinomial logit; RAI = relative attribute importance.

The percentage-point increase in each 3-year risk that respondents were willing to accept in exchange for a 20% chance of getting regrowth of most or all scalp hair (corresponding to SALT ⩽20) after 24 weeks of treatment are presented in Table 21. The combinations of these three risks (i.e., a simultaneous increase in all three risks) that would be acceptable to patients (US and EU) exceed the actual combinations of these three risks, as observed in the All-exposure pool.

Table 21: Maximum acceptable risks (MAR) in exchange for a 20% increase in the probability of SALT≤20

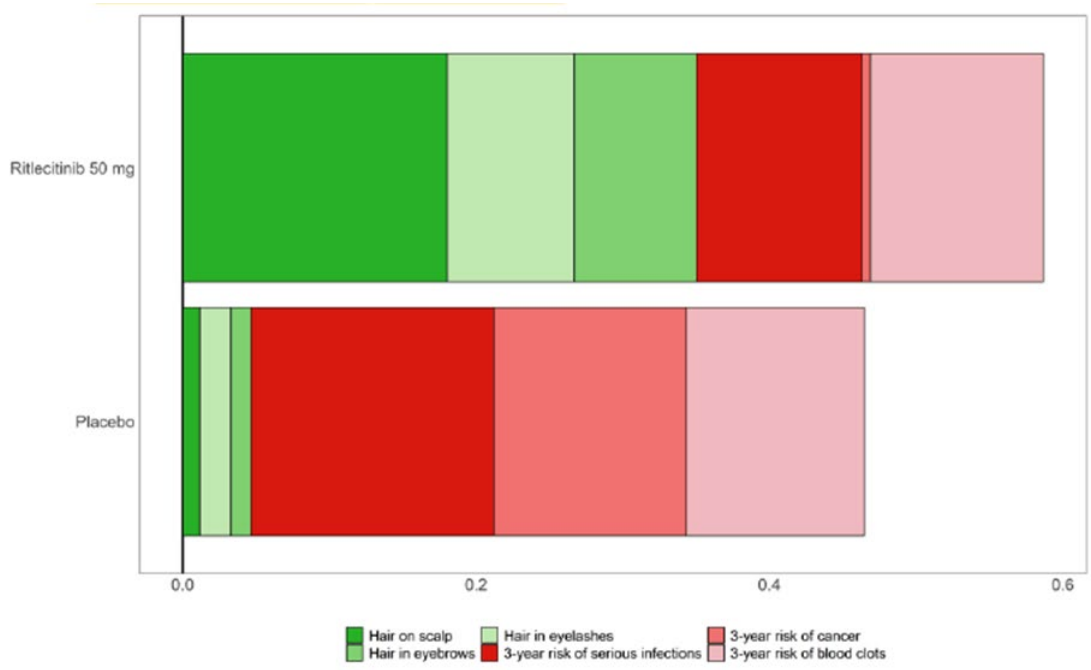
3-Year Risk	Overall Sample	US Sample
Serious Infection	7.40 [5.47; 9.33]	3.71 [2.62; 4.79]
Cancer (including NMSC)	2.50 [1.87; 3.14]	2.12 [1.19; 3.05]
Blood Clot	9.34 [6.42; 12.26]	5.65 [3.43; 7.87]

The MAR for a given 3-year risk is the percentage-point increase in the individual risk that will yield a utility loss that will exactly offset the utility gain from a 20 percentage-point increase in the probability of achieving SALT≤20 from the patient perspective.

Clinical efficacy and safety data in the quantitative Benefit/Risk analysis included the probability of hair regrowth on the scalp, eyebrows and eyelashes for the 50 mg QD, 30 mg QD and placebo arms in study B7981015, and the probabilities of serious infection, malignancy (including NMSC) and venous thromboembolism, from the All-Exposure Pool for all 50 mg. The risk probabilities for the AEP (expressed as risk per patient-year) were assumed to be 1-year risks and were converted to 3-year risks by multiplying these probabilities by 3. The risk probabilities for the placebo arm were assumed to be zero. For the purpose of comparing the net benefit of 50 mg QD to the net benefit of 30 mg QD it was assumed that the risk probabilities for the 30 mg QD dose were 0.60 times the observed risk of the 50 mg QD dose (proportional to dose).

The mean net benefit of 50 mg QD exceeded the mean net benefit of placebo. Ritlecitinib 50 mg has 0.122 higher NBR score than placebo, indicating a positive benefit-risk profile for the active treatment (Figure 26). The highest positive contribution to this difference is from the hair on the scalp (0.168), whereas the highest negative contribution is from the risk of cancer (-0.126). In simulations reflecting uncertainty in clinical outcomes, the probability that the mean net benefit of ritlecitinib 50 mg QD was greater than the mean net benefit of placebo was 99.8%. The predicted choice probability that any patient (US and EU combined) would choose ritlecitinib 50 mg QD over no treatment for AA was 65.9%.

Figure 26: Attribute contribution to weighted net Benefit/Risk



B7981072: A Discrete Choice Experiment for Alopecia Areata treatments with adolescents

A similar experiment was conducted in adolescents. Relative attribute importance (RAI) values showed that the most important attribute for AA adolescent patients was the benefit of increasing from 0% to 50% the chance of getting back most or all of the hair on their scalps after 24 weeks of treatment (RAI: 61.6%; 95% CI: [56.8; 66.4]). This was followed by a reduction in the risk of cancer from 6% to 0.1% during three years of treatment (RAI: 14.1%, 95% CI: [10.4; 17.7]), the benefits of increasing the chance of getting moderate or normal eyebrows from 0% to 40% after 24 weeks (RAI: 13.2%; 95% CI: [9.7; 16.6]), and the benefits of increasing the chance from 0 % to 40% of getting moderate or normal eyelashes after 24 weeks (RAI: 9.1%; 95% CI: [5.7; 12.6]). The reduction in the risk of serious infection from 6% to 0.1% during three years of treatment (RAI: 1.4%; 95% CI: [-2.7; 5.6]) and the risk of getting blood clots during three years of treatment (RAI: 0.6%; 95% CI: [-3.4; 4.6]) were less important.

In addition, differences in preferences between the adolescents and adults were tested in an Error-Component Multinomial Logit (ECL) model including additional interaction terms between the age group (adolescent vs adult) and the attributes' levels. The chance to obtain hair on most or all of scalp was the most important attribute for both adults and adolescents, but adolescents patients cared significantly more about the scalp hair benefit than adult patients ($p<0.001$). Adult patients valued the 'no treatment' option significantly more than adolescents ($p<0.001$), meaning they were more averse to the treatment burden solely for having to take a treatment, and not due to any benefits or risks it may provide. Adult patients were also significantly more averse to risks of serious infections and blood clots than adolescents ($p<0.001$).

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical programme to evaluate the efficacy of ritlecitinib in Alopecia Areata (AA) consists of 3 studies: 1 pivotal study (B7981015), 1 supportive Phase 2a study (B7931005), and 1 long-term study (B7981032), all in participants with AA. The comparative safety study (B7981037) also included efficacy data.

The applicant received CHMP Scientific Advice on the clinical development programme of ritlecitinib for the treatment of AA (EMEA/H/SA/3875/1/2018/HTA/III). The main points of the Advice regarding efficacy included to follow the recommendations of the EMA guideline for single pivotal studies such as setting a more stringent Type I error rate for the primary endpoint. The main inclusion criteria for the pivotal trial and the primary efficacy endpoint (SALT score $\leqslant$10) were deemed adequate by CHMP. Upon the advice of CHMP a measure of subjective treatment benefit, Patient Global Impression of Change (PGI-C), was included as a key secondary endpoint. With respect to safety, following the observation of axonal dystrophy in the 9-month toxicity studies in dogs, the CHMP advised continuing audiological and neurological events as well as audiometry assessments in the phase 3 trial. This was implemented by the applicant in study 015. Furthermore, phase 2 safety study 037 addressed this issue by measuring brainstem auditory evoked potential (BAEP) and intraepidermal nerve fibre (IENF) sampling. CHMP also recommended to consider a longer duration of the placebo-controlled study given that successful treatment of severe AA is expected to take longer than 24 weeks, especially if SALT10 is the primary outcome. CHMP also proposed a staggered approach for the inclusion of adolescents so that adults' safety would be known first. As a consequence, adolescents had not been included in the EU, as agreed with the PDCO (as part of the agreed EU PIP); an indication for adolescents in the EU could be supported by an extrapolation approach to meet the applicable guidelines and regulations (ICH-E5, ICH E11-R1, the EMA's Reflection paper on the use of extrapolation in the development of

medicines for paediatrics (EMA/189724/2018) and the EU Paediatric Regulation (EC) No 1901/2006). The CHMP Scientific advice has, overall, been followed.

Main study

The pivotal study B7981015 had a randomised, placebo-controlled period of 24 weeks followed by a non-placebo-controlled treatment extension phase of 24 weeks. As previously stated in the CHMP Scientific Advice, 24 weeks of a placebo-controlled trial might be too short for the treatment of AA, especially for a stringent primary outcome such as SALT≤10. The relatively short duration of the placebo-controlled phase would thus limit the interpretation of the (favourable and unfavourable) long-term effects of ritlecitinib. The applicant kept the placebo-controlled period to 24 weeks but added an extension phase up to week 48. Overall, the length of the 24-week placebo-controlled period in combination with the follow-up phase to in total 48 weeks of exposure is considered acceptable.

The dose-ranging design of the pivotal trial is also considered acceptable, although it yielded a low number of participants in each treatment group. Due to the difference in study designs between the pivotal and supportive studies, a pooled analysis couldn't be performed for efficacy. The main efficacy study should thus be interpreted as a single pivotal trial.

The CHMP SA to conduct a separate dose-ranging and confirmatory studies was not followed by the applicant. Nevertheless, the pivotal study complies with the EMA guideline (CPMP/EWP/2330/99) on single pivotal trial. There is a well-grounded pharmacologic rationale for the plausibility of ritlecitinib's efficacy in AA and sufficient internal and external validity (demonstrated by, e.g. adequate blinding of all parties, randomisation of participants, well-justified inclusion and exclusion criteria). The proof of concept is considered established in study B7931005 for ritlecitinib 200/50 mg dose regimen. The effect sizes of primary and secondary outcomes are statistically significant at a level sufficient for a single pivotal trial and considered clinically relevant. Lastly, longer-term data indicated that the effect of ritlecitinib increases up to 24 months.

Study participants

The selected study population is representative of the target population, as reflected in the proposed indication. Even if there is no universally adopted definition of 'severe AA', this definition was also used for the indication of Olumiant in AA. Including participants with AT and AU is considered relevant. The exclusion criteria mainly concern safety measures and are not considered overly restrictive being in accordance with the known class effects of JAK inhibitors (e.g. serious infections, thromboembolic events, and malignancies). Since the renal route plays only a minor role in the elimination of ritlecitinib, excluding participants with renal impairment is unlikely to be a concern. Participants with a moderate hepatic impairment had a 30% (90% CI: 26% – 33%) higher Cmax and a 35% (90% CI: 28% - 42%) higher AUCtau, which does not appear clinically relevant (see pharmacokinetic discussion).

Study treatments

The 5 ritlecitinib regimens in the main study consisted of ritlecitinib 200/50 mg, 50mg, 200/30 mg, 30 mg and 10mg. Regarding the treatment received, ritlecitinib was administered by the participants, which inherently introduced dosing and compliance issues. It is, however, considered that reasonable effort was paid to evaluate compliance. The criteria for drug discontinuation and concomitant medication can be agreed upon. Incidences of protocol deviations and important protocol deviations in study B7981015 were high (96% and 68%, respectively) but similar across study groups. There was a comparable distribution of protocol deviations over study. Sensitivity analyses indicated that there was no substantial impact on the results i.e. the internal validity of the study is not compromised.

Outcomes

The endpoints chosen in the pivotal study B7981015 are in line with the CHMP Scientific Advice and are considered acceptable. The primary endpoint was a response in SALT≤10 (≤10% scalp hair loss) at week 24. The key secondary endpoint was the proportion of participants with patient-reported outcome PGI-C response defined as a score of 'moderately improved' or 'greatly improved' at Week 24. Other main secondary endpoints were: response based on SALT≤20 (i.e. ≤20% scalp hair loss) at week 24, SALT≤10 and ≤20 up to Week 48; change in eyebrow and eyelash response (EBA and ELA) with at least a 2-grade improvement from baseline or a score of 3 in EBA/ELA score through week 4-48; PGI-C response defined as a PGI-C score of 'moderately improved' or 'greatly improved' through week 4-48 and change in baseline from another patient-reported outcome AAPPO response up to Week 48. SALT is a validated measure used in AA. SALT ≤10 is a stringent primary endpoint which, however, is supported by a less stringent secondary endpoint (i.e. SALT ≤20).

Following the CHMP SA, a patient-reported outcome measure PGI-C response was included as a key secondary endpoint at 24 weeks. PGI-C is considered a valid tool for a key secondary outcome in the pivotal trial in AA. PGI-C is broadly used, and its outcomes are easily interpretable. EBA and ELA are a validated set of clinician-reported outcomes identical to the one reported in Wyrwich et al. (2020) and used for the registration of Olumiant in AA. Supportive studies used an identical set of outcomes. AAPPO was developed and validated by the applicant and the validation process is described in the Methods section above.

Sample size, randomisation, and blinding

Sample size calculations have been provided, including calculations for the primary and key secondary endpoints at the more stringent significance level of 1% in line with the NfG on single pivotal trial. The sample size for the pivotal is sufficiently motivated and considered acceptable with sufficient statistical power for the primary and key secondary endpoint. The analysis provided in this application requested primary and key secondary endpoints were controlled at the more stringent significance level of 1% and accounted for multiplicity using a closed testing procedure.

A stratified randomisation was used with strata defined by adults versus adolescents and AT/AU versus not AT/AU. A block randomisation was used in the strata with blocks of size 11. Targets for overall and stratum-specific enrolment were monitored using blinded interactive response reports allowing for adjustment of the randomisation caps to keep numbers within limits specified in protocol.

Planned unblinding only occurred after all Week 24 outcomes has been observed or patient discontinued before Week 24 visit. Unblinded data were restricted to the applicable unblinded reporting team members only. Investigators, subjects, and the sponsor study team were blinded to treatment throughout the duration of the study. Blinding is considered acceptable.

Statistical analyses

Statistical methods are generally considered acceptable. The family-wise type I error rate is controlled over the primary and key secondary endpoints for hypotheses regarding four treatment sequences. Multiple imputation under a missing-at-random and non-missing at random assumption for outcomes missing due to COVID-19 was used for analyses of the primary endpoint for SALT $\leqslant$ 10 and key secondary endpoint PGI-C at week 24. Patients with missing Week 24 outcomes not due to COVID-19 were regarded non-responders. The strategy to consider subjects whose outcomes are missing for other reasons, such as discontinuation, as non-responders is acceptable.

Several sensitivity analyses have been provided for the primary and key secondary endpoints to assess robustness to assumptions related to handling missingness due to COVID-19. The robustness of results to assumptions has been shown. The power of interaction test for loading dose is likely to be low.

Efficacy data and additional analyses

Study population

The most frequent reasons for screen failure were exclusion criteria. Demographic characteristics were well balanced between the placebo and the ritlecitinib groups. Adolescents comprised about 15% of the study sample. The group of participants aged 65 years or older comprised less than 5%. Most patients had used prior therapies, in line with a severe AA population that is eligible for systemic treatment. The low proportion of elderly patients may hamper the interpretation of efficacy for in this sub-population but is representative of the target population. A priori, there is no reason to believe that ritlecitinib will not be effective in the elderly, apart from confounding due to age-related androgenic alopecia. Correct diagnosis and prescription is, however, the responsibility of the prescribing physician.

Completion

A total of 718 participants was included in the pivotal study. The numbers of withdrawals in the ritlecitinib groups are low (5-8%), and the reasons for discontinuation or withdrawal were similar between ritlecitinib and placebo groups. The per-protocol population (defined as all randomised subjects with no major protocol deviation) consisted of 656 participants.

Adherence and drug exposure

Non-compliance of the investigational product between visits of <80% or >120% was to be reported as a protocol violation (referred to as 'protocol deviation' by the applicant). A total of 20 participants had compliance <80% between Day 1 through Week 24, and the numbers were similar between the groups. No participants had compliance >120%. Non-compliance was dealt with in the analysis as follows: first, the primary analyses of the primary and key secondary endpoints were conducted according to the intent-to-treat principle on the Full Analysis Set (FAS), which included all participants (regardless of non-compliance issues). The same analyses were then repeated on the Per Protocol Analysis Set (PPAS), which excluded participants who had major protocol deviations related to inclusion/exclusion criteria, compliance regarding the investigational product, or any other major protocol deviations that, in the opinion of the sponsor study team, might have affected the efficacy data through Week 24. Participants were excluded from PPAS if, prior to the date of the Week 24 visit, the subject had a dosing interruption of ⩾6 weeks for any reason. This approach is considered adequate.

Prior and concomitant medication

On average, 69% of participants had received prior pharmacologic treatment for AA. The most frequent treatment for AA were topical corticosteroids, oral/IV/IM steroids, intralesional corticosteroid injection and topical vasodilators, which is representative of a current treatment strategy of AA. These numbers were similar between the groups.

Concomitant medication for conditions other than AA was taken by about 80% of the participants during the double-blind period in the main study, without differences between the placebo and ritlecitinib groups. It is unlikely that the use of concomitant medication has affected the outcome since it was equally divided between the groups and is unlikely to interfere with the treatment. A maximum of 1 participant in each group reported using AA medication.

Treatment effects

The primary endpoint (SALT ≤10 at week 24) and the key secondary endpoint (PGI-C response at week 24) in the single pivotal trial were both met, with $p<0.005$ while correcting for multiplicity. Regarding SALT10 at week 24, the mean difference with placebo was the largest for the 200/50 mg group (20%) compared to the 200/30 mg group (11%), the 50 mg group (12%) and the 30 mg group

(9%). The treatment effects were more pronounced with SALT≤20 at week 24 (secondary outcome) with 200/50 mg group (28%) compared to the 200/30 mg group (20%), the 50 mg group (21%) and the 30 mg group (12%); all differences with placebo were statistically significant.

PGI-C outcome (key secondary outcome) was also significantly different from placebo at week 24 with effect size comparable between 200/50 and 50mg groups (40%) and between 200/30 and 30 mg groups (33%).

Other secondary endpoints and the results on SALT and PGI-C in supportive studies corroborate these findings. By week 48 (at the end of the extension phase), the proportion of participants with SALT ⩽10 was similar between the participants who received a 200 mg loading dose for 4 weeks and those who were treated for 48 weeks without a loading dose: 200/50 mg (33%) versus 50 mg (31%); 200/30 mg (28%) versus 30 mg (25%). This supports the proposed posology of ritlecitinib 50mg QD.

Although the treatment effect in SALT≤10 as the primary outcome appears numerically small (21.29% vs 1.54% for ritlecitinib 200/50 dose and placebo respectively), it is considered clinically relevant. The reason is that SALT≤10 is a rather stringent measure ('near remission'), and 24 weeks is relatively short, while the clinical relevance is also supported by the larger treatment effects in SALT≤20 and PGI-C.

Long-term treatment effect

The duration of treatment of AA is likely to constitute more than 24 weeks. The data from the extension phase showed that the proportion of participants with a low SALT score continues to increase beyond 24 weeks with ritlecitinib 50 mg. This notion is further corroborated by supportive studies B7981037 and B7981032. In study B7981037, the difference between ritlecitinib and placebo in SALT response further increases between 6 and 9 months. The preliminary results from the open-label study B7981032 in the rollover group (i.e. the group of participants who had already had ritlecitinib either in study B7981015 or B7931005) suggest that the number of participants with SALT ≤10 continues to increase up to additional 15-18 months.

Based on the available clinical data, the treatment effect does not appear to fade away on prolonged treatment.

Dose

As the most appropriate dose (30 mg or 50 mg, with or without a loading dose of 200 mg for 4 weeks) was not apparent before the pivotal study began, the applicant chose not to perform a dose-finding study before starting the pivotal study. The choice for the dose in the proof-of-concept study (200/50 mg) was based on non-clinical safety margins.

The applicant proposes the 50 mg dose without loading dose as the recommended dose in the SmPC, mainly for safety reasons. From the efficacy point of view, it can be agreed that 50 mg without loading dose is an effective alternative to the 200/50 mg regimen. From the 0–24-week data of the pivotal study, it appears that for SALT≤10 and SALT≤20, the 50 mg QD with 200 mg loading dose for 4 weeks (200/50) is the most effective dose. The effect of 200/30 mg resembles that of 50/50 mg and is less prominent than of 200/50 mg. For PGI-C at week 24 however, the 200/50 mg and 50/50 mg doses were similarly effective. At 48 weeks of treatment, the 200/50 mg dose and the 50/50 mg dose were equally effective, which is conceivable as the effect of the loading dose will diminish over time. At 24 and 48 weeks, the 30 mg dose was less effective than the 50 mg dose in all outcomes. A longer-term simulation analysis also indicated that a 14% loss in SALT ⩽20 response at week 156 would be expected when the dose is reduced from 50 mg to 30 mg. The most important rationale for dose reduction would be to lower the risk of adverse drug effects, mostly infections, in a vulnerable population, such as the elderly. A warning regarding this risk is already incorporated in Section 4.4 of

the SmPC. Further, the analysis of predicted choice probability in the adult patient preference study revealed that a predicted choice probability for the 30 mg dose was either similar to 50 mg (with overlapping confidence intervals) or lower than for the 50 mg dose, indicating no patient preference for a lower dose. Overall, considering a greater efficacy of 50 mg as compared to 30 mg, a relatively low infection risk for both 50 and 30 mg of ritlecitinib in the general AA population and in the elderly, elderly not being a major target population for ritlecitinib given the demographic characteristics and the presence of a warning in Section 4.4 of the SmPC regarding the infection risk, a maintenance dose of 50 mg is considered appropriate.

Treatment withdrawal

In the SmPC, it was initially proposed to discontinue patients who show no evidence of therapeutic benefit after 48 weeks. There is, however, a paucity of data to support this discontinuation criterion. The results from the single-blinded phase of study B7931005 show that additional treatment in non-responders (previously treated with ritlecitinib) after week 24 does not lead to a substantial response. The difference from baseline in SALT score was only 7% more than placebo (90% CI 0.75-13) after additional 24 weeks of treatment. The number of analysed participants is, however, very small (N=13). Given the current paucity of data, the duration of treatment of responders with ritlecitinib cannot be established. The inclusion of a stopping rule in the SmPC in case of non-response is endorsed. Based on the updated data from study 032, 9 months (36 weeks) is a more adequate moment for discontinuation. The SmPC section 4.2 was updated accordingly. Furthermore, the probability of being a non-responder (failure to reach a reduction of at least 30% from baseline on SALT scores) at Month 18 based on percent change from baseline at an earlier visit (negative predictive value) was similar for 9 and 12 months. The two highest negative predictive values associated with not meeting the percent change from baseline of 10% and 20% were 77% and 75% at Month 9 and 77% and 73% at Month 12. Further, stopping ritlecitinib appears to lead to a loss of response. A simulation analysis showed that 66% of SALT ≤10 responders are predicted to lose SALT ≤20 response and 70% are predicted to lose SALT ≤10 response with up to 48 weeks of treatment interruption (after being treated with ritlecitinib for 96 weeks). After treatment withdrawal for up to 6 weeks, the risk of losing SALT ≤20 response was, however, low (<5%), which is reflected in the SmPC, section 4.2.

Adolescents

The proposed indication includes adolescents (≥12 years of age), and in the pivotal study, 105 adolescents (12 to 17 years of age) were included. All adolescents were recruited outside of the EU. The applicant has performed an extrapolation exercise to compare efficacy in ex-EU adolescents with ex-EU adults and EU adults. The extrapolation is acceptable, and it can be assumed that the pathophysiology of AA is not different in adolescents as compared to adults. The analysis in the pivotal study shows that the effects on SALT≤10 and PGI-C in adolescents are in accordance with the findings in ex-EU adults and EU adults and are further supported by the similarity in less stringent SALT≤20 response and dose-response relationship for SALT≤10 at week 24 between adolescents and adults. Furthermore, the absolute SALT score decreases similarly in adolescents as compared to adults up to week 48 and further up to month 24 (as shown by All Exposure Cohort based on pooled efficacy data from studies B7981015 and B7981032). Therefore, it is considered that the effects on adults can be generalised to EU adolescents.

Elderly participants

Only a few elderly participants were enrolled in the main study (<5%). The SmPC section 4.2 was updated to reflect that there are limited data in patients ⩾ 65 years of age.

AT/AU patients

The effect size in AT/AU patients for ritlecitinib is smaller than for non-AT/AU patients for both SALT ≤ 10 and SALT ≤20 endpoints at week 24. This is reflected in the section 5.1 of the SmPC.

Other subgroups

While for the subgroup 'AA Duration Since Disease Diagnosis' the difference between ritlecitinib and placebo was not significant for the stringent SALT ⩽10 outcome at week 24, this difference was significant for other relevant endpoints SALT ⩽20 and PGI-C at various timepoints.

Other subgroup analysis by age, BMI , gender, race, region, prior treatment did not indicate an effect modification.

Patient preferences

The performance of studies to acquire patient preferences for AA treatments in adults and adolescents is appreciated. Both studies appear to be well-performed using standard methodologies, including relevance of attributes, understandability of questions in the Discrete Choice Experiment (DCE), appropriate figures for observed favourable and unfavourable treatment effects, and use of statistical methods and approaches. The samples of adults and adolescents are considered representative of the target population and large enough. Data for the preferences of favourable and unfavourable effects were acquired from the DCE. Data for favourable effects on the return of scalp hair (SALT≤20) and return of eyebrows (EBA) and eyelashes (ELA) came from the 24-week data of pivotal study 015. For unfavourable effects regarding the 3-years risks for serious infections, cancer, and blood clots, incidence rates of exposure to 50 mg in the All-exposure pool were used.

The probabilities for favourable effects are realistic, though the treatment effect of ritlecitinib has not been completed at week 24, as the effect increases up to week 48. The risk estimates for the unfavourable effects are endorsed, although the size of the risk is still uncertain due to the low frequencies and the relatively short period of observation.

According to the results, the by far most important attribute to patients is a return of most or all scalp hair (42%), which was valued much more than the return of eyebrows (12%) or eyelashes (9.2%). In ranking, the return of scalp hair was followed by the 3-year acceptable risk for infections (13%) and 3-year risk of cancer (13%), while the 3-year risk for blood clots (11%) was valued as less important. When coupled with the actual trial results in the quantitative Benefit/Risk analysis, it showed that ritlecitinib 50 mg has 0.122 higher Net Benefit/Risk score than placebo, which indicates a positive benefit-risk profile for the active treatment from the patient perspective. Mathematically, this returns in a predicted choice probability of 66%. This means that more than half, or a small majority, of the 'average' adult patients with AA can be expected to prefer ritlecitinib 50 mg over no treatment when making an informed choice. Based on the patient preference study in adolescents, it can be expected that the Net Benefit/Risk ratio in adolescents also shows a preference for ritlecitinib 50 mg over no treatment. Although no quantitative Benefit/Risk analysis in adolescents was performed, compared with adults, they placed more value on the return of scalp hair and less (virtually no) value on the risk for serious infections and blood clots. Given the high value that patients with severe AA place on scalp hair regrowth, the NBR difference of 0.12 and predicted choice probability of 66% are probably on the low side, though the net B/R for ritlecitinib 50 mg, as compared to no treatment, is positive from the patient perspective.

2.6.7. Conclusions on the clinical efficacy

In the single pivotal study in adolescent and adult participants with AA treated with ritlecitinib, the primary endpoint (SALT ≤10 response at week 24) and the key secondary endpoint (PGI-C response at week 24) were both met, with multiplicity corrected p-values <0.005. The treatment effect is supported by the results of the secondary outcomes, by a clear dose-response effect, and is consistent over virtually all predefined sub-populations, including adolescents. The treatment effect continues to increase after week 24, up to 24 months and is maintained on treatment beyond 24 months.

Although the treatment effect in SALT≤10 as a primary outcome appears numerically small, SALT ≤10 is a stringent measure indicating a near remission. The responses in the secondary outcomes (PGI-C, SALT ≤20, EBA, ELA) are larger and support clinical relevance. From an efficacy point of view, it is agreed that 50 mg without loading dose is an effective alternative to the 200/50 mg regimen over time.

Although this application is based on a single pivotal trial**,** this trial is considered methodologically adequate and sufficiently demonstrated efficacy as revealed by primary and secondary outcomes at various time-points and across various subgroups.

Based on the patient preference studies in adults and adolescents, it is estimated that a small majority of the 'average' patient with AA can be expected to prefer ritlecitinib 50 mg over no treatment when making an informed choice.

The CHMP concluded that the efficacy data supports the following indication: 'Litfulo is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older (see section 5.1)'.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Main safety studies

The clinical development programme of ritlecitinib in AA was a global programme including 21 phase 1 studies, 4 phase 2/phase 3 studies in AA and 1 phase 2b study in vitiligo (Table 22). The study in vitiligo was considered relevant for the evaluation of safety in AA due to similarities between the AA and vitiligo populations, similar ritlecitinib dosing regimens to those in the AA studies, and similar safety monitoring in vitiligo and AA study protocols.

Table 22: Phase 2 and 3 Ritlecitinib clinical studies in alopecia areata and vitiligo

Protocol	Study Design	Treatment	Safety Population
Phase 3 Study			
B7981015 AA	Placebo-controlled RCT Adults and Adolescents	**Treatment duration:** 48 Weeks <u>Double-Blind 24 Weeks +</u> <u>Extension 24 Weeks</u> 200 mg/50 mg ritlecitinib[b] 200 mg/30 mg ritlecitinib[e] 50 mg ritlecitinib 30 mg ritlecitinib 10 mg ritlecitinib Placebo-200 mg/50 mg ritlecitinib Placebo-50 mg ritlecitinib	Total = **715** n = 131 n = 129 n = 130 n = 132 n = 62 n = 65 n = 66

Phase 2 Studies			
B7931005 AA	Placebo-controlled RCT with a single-blind extension period and a cross-over open label extension period. Adults	**Treatment duration:** Up to 48 Weeks[a] Double-Blind: 24 Weeks 200 mg/50 mg ritlecitinib [b] Placebo (ritlecitinib group) Single-Blind Extension: Up to 48 Weeks[c] 200 mg/50 mg ritlecitinib[b]	Total =**142**[d] n = 48 n = 24 n = 33
B7981037 (Ongoing) AA Data cutoff date: 04 Jan 2022	Placebo-controlled, safety study with active extension Adults	**Treatment duration: 24 months** Double-Blind: 9 Months plus Extension up to 15 Months 200 mg/50 mg ritlecitinib (200 mg loading dose for 1 month, 50 mg maintenance dose for 23 months). Placebo 9 months **–** ritlecitinib 200 mg loading dose for 1 month/50 mg maintenance dose for 14 months.	Total = **71** n = 36 n = 35
B7981019 Vitiligo	Placebo-controlled RCT with a partially blinded extension period to evaluate the efficacy and safety of ritlecitinib and brepocitinib Adults	**Treatment duration:** 48 Weeks Double-Blind: 24 Weeks 200 mg/50 mg ritlecitinib[b] 100 mg/50 mg ritlecitinib[f] 50 mg ritlecitinib 30 mg ritlecitinib 10 mg ritlecitinib Placebo Double-Blind or Open-Label Extension (depends on treatment group): 24 Weeks 200 mg/50 mg ritlecitinib[b] 50 mg ritlecitinib 30 mg ritlecitinib	Total = **364** n = 65 n = 67 n = 67 n = 50 n = 49 n = 66 Total = 293[g] n = 187 n = 6 n = 2
Phase 3 Long Term Study			
B7981032 (Ongoing) AA Data cutoff date: 28 Feb 2022	Open-label, long term study Adults and Adolescents	**Treatment duration:** 36 Months Open-Label: 36 Months 50 mg ritlecitinib. 200 mg/50 mg ritlecitinib (200 mg loading dose first 4 weeks, 50 mg maintenance dose thereafter).	Estimated Total = **1052**

a. Cross-Over Open Label Extension Period is not included.
b. 200 mg loading dose first 4 weeks, 50 mg maintenance dose for 20 weeks
c. Single-Blind Extension noted here only includes the Non-Responder Segment.
d. Brepocitinib group included, therefore total number of participants is greater than the placebo and ritlecitinib groups combined.
e. 200 mg loading dose first 4 weeks, 30 mg maintenance dose for 20 weeks
f. 100 mg loading dose first 4 weeks, 50 mg maintenance dose for 20 weeks
g. Brepocitinib and ritlecitinib + nbUVB included, therefore total number of participants is greater than the ritlecitinib groups combined.

Supportive study (B7981037)

This study was designed to investigate the clinical relevance of non-clinical findings of axonal dystrophy with audiological consequences. In dog chronic toxicity studies, axonal dystrophy was associated with brainstem auditory evoked potential (BAEP) changes at the highest exposure in those studies. Therefore, the BAEP interwave I-V latency was the primary endpoint for this study. Axonal

swelling and intraepidermal nerve fiber density (IENFD) were evaluated in peripheral skin biopsies. The technique allowed direct assessments of both morphological features (such as axonal swellings) and IENFD in nerve endings.

The **objective** was to assess I-V interwave latency of brainstem auditory evoked potential (BAEPs) and to assess axonal swellings in intraepidermal nerve endings (IENF), in adult participants with AA treated with ritlecitinib.

The **design** was a phase 2a, randomised, double-blind, parallel group, placebo-controlled safety study designed to evaluate the safety and tolerability of ritlecitinib, including the assessments of BAEP and IENF, in adults 18 to ≤50 years of age with ≥25% scalp hair loss due to AA. Approximately 60 adults were randomised (1:1) to either ritlecitinib 200/50 mg or placebo. The placebo-controlled phase lasted for 9 months, followed by an active treatment phase of 15 months and a safety follow-up of 4 weeks. At month 6, all participants with a baseline SALT ⩽75 and an increase (worsening) in SALT⩾25 points could already enter the active treatment phase.

Main **inclusion criteria** were: ≥25% hair loss due to AA as measured by SALT; normal hearing and BAEP; normal neurological examination. Patients were **excluded** if having clinically significant neurological diseases, diseases that may lead to hearing loss, or had first-degree relatives with hereditary neuropathy.

The **primary endpoint** was change from baseline in I-V interwave latency on BAEP at a stimulus intensity of 80 dB at Month 9. **Secondary** outcomes included: the I-V interwave latency at month 6 and 15; change from baseline in axonal dystrophy and of intraepidermal nerve endings density in skin punch biopsies at months 9 and 15; absence of wave V on BAEP at stimulus intensities ranging from 80 dB to 40 dB at months 6, 9 and 15; occurrence of TEAS, SAEs, and AEs leading to discontinuation. For the primary safety endpoint, there was no formal hypothesis testing; summary statistics for each group with 95% confidence intervals were provided.

Data pools

There were 4 study pools to summarise the clinical safety of ritlecitinib: 2 pools (PCPAA and PCPAAV) focused on short-term (up to 24 weeks) placebo-controlled treatment, 1 pool (OYEP) focused on 1-year (up to 48 weeks) treatment, and 1 pool (AEP) focused on participants from the same studies as in the other pools with a longer duration of exposure to ritlecitinib, as well as the LTE study. The data of the phase 1 studies were not pooled, due to differences in study design, doses studied, short study durations and the inconsistent availability of a placebo comparator.

The placebo-controlled pools **PCPAA** (and **PCPAAV**) included studies B7931005 (0-24 weeks), B7981015 (0-24 Weeks), and B7981037 (0 24 weeks), with similar doses of ritlecitinib, similar patient populations, and comparable safety outcome assessments, as well as study B7981019 (0-24 weeks) in Vitiligo. This cohort included participants who were randomised and received: 200/50 mg QD from all studies; 50/50 mg QD from B7981015 (and B7981019); All 50 mg (200/50 mg QD and 50/50 mg QD combined) from all studies; All 30 mg (200/30 mg QD and 30/30 mg QD combined) from B7981015 (and B7981019); 10 mg QD from B7981015 (and B7981019); placebo QD from all studies.

The one-year exposure pool (**OYEP**) included only the ritlecitinib-treated participants from B7981015 who received a continuous dose regimen (0-48 weeks). Participants who were randomised to placebo up to Week 24 and then switched to active treatment were not included in this pool.

The all-exposure pool (**AEP**) included the same studies (B7931005, B7981015, B7981019, B7981037) included in the placebo-controlled pools, but not limited to their 24-week placebo-controlled portions. 'Rollover' data from the long-term, open-label study B7981032 plus data from 'de novo' participants enrolled into study B7981032 were included. All participants who received ritlecitinib, from the start of

their first dose of ritlecitinib in one of these studies, were included in this pool. The ritlecitinib exposure to 50 mg treatment was evaluated from the time a participant started the 50 mg dose or the preceding loading dose. For example, for participants who received 30 mg QD in B7981015 and then 50 mg in B7981032, the summary for these participants starts from the time they first received 50 mg.

In addition to AA and vitiligo, ritlecitinib is also being investigated for RA (completed Phase 2 study B7981006 and Phase 2 study B7921023 in combination with another kinase inhibitor), UC (completed Phase 2 study B7981005), and Crohn's disease (ongoing Phase 2 study B7981007). These studies in non-dermatological indications were not pooled due to the differences in patient characteristics.

Data collection and adjudication

AEs presented in the pooled datasets have been coded using the MedDRA version 24.1. Adjudication committees independent of the applicant were established to review potential AEs of opportunistic infections (Ois), malignancies/histopathology, CV events, and neurological and audiological events of interest. Each of these committees consisted of experts in the relevant field, with charters in place to describe the details of event definitions and the committee's purpose.

In study B7981015, to assess for potential changes in hearing status, routine audiologic testing (including pure tone audiometry, speech audiometry and immittance audiometry) was implemented throughout the study at pre-specified time points (at Screening or within 8 weeks prior to Study Day 1, and at Study Days 169 and 337 or early termination visit). TEAEs reported as audiologic events of interest reflect the outcome of the protocol-specified audiologic testing (there were no spontaneously reported events of hearing loss).

Real World Data cohorts of patients with hospital-treated Alopecia Areata (AA) to characterise the patient population and contextualise safety events within the Ritlecitinib AA clinical development programme (B7981049)

To better understand the epidemiology of hospital-treated AA, including AT/AU, a population-based cohort study was conducted using real-world data collected from Denmark's national health registries.

The main **objectives** were to estimate background rates of safety events of interest in the AA Cohort and AA trial-similar (TS) Sub-cohort (overall, by AA subtype and age subgroup); and to estimate the prevalence of comorbidities with known/potential associations with AA.

The study **design** was a historical population-based cohort study based on routinely collected data from administrative and health registers in Denmark. Patients with hospital-treated AA were identified based on primary or secondary diagnoses between 1995 and 2016, recorded at inpatient hospital stays or during outpatient visits to hospital-based specialist clinics. In addition, a subset of those who were similar to the ritlecitinib AA clinical trial programme were also identified as a sub cohort. The follow-up was extended through the end of 2016 for all endpoints except major adverse cardiovascular events (MACE) and cardiovascular deaths; the follow-up for MACE and cardiovascular death was extended through the end of 2011, the date of the last update of cause-of-death data. The lookback period extended to 01 January 1977 for diagnoses and to 01 January 2004 for medications, based on available data from the relevant sources. The variables of interest included AA diagnosis at a hospital encounter; demographic and clinical characteristics; and select safety events of importance to the ritlecitinib clinical programme. The following data sources were used in this study: the Danish Civil Registration System, the Danish National Patient Registry (DNPR), Danish Health Services Prescription Database, and the Danish Register of Causes of Death (updated through 2011).

Between 1995 and 2016, 4,014 cases of hospital-treated AA were identified, the AA incident cohort included 2,778 patients (472 AT/AU, 2306 non-AT/AU), 60.4% of the patients were between 18 – 50 years old at first hospital AA diagnosis, and men comprised 36.9% of the total incident AA cohort. The

trial-similar sub cohort (TS) included 2,232 (80% of the incident cohort) patients, with characteristics similar to those of the total AA cohort. Crude incidence rates for the trial-similar sub cohort are given and discussed within the section on Adverse events of special interest.

Epidemiology and risk characterisation of Alopecia Areata via external patient cohorts within a US administrative database (B7981051)

The aim of this study, conducted retrospectively within a US healthcare claims database, was to inform risk characterisation efforts in support of the ritlecitinib clinical trial programme and product registration. For that purpose, data were collected in three cohorts of patients: a) AA cohort, b) a subset of the AA cohort that is similar to the ritlecitinib AA clinical trial programme and c) non-AA cohort.

The main **objectives** were to estimate background incidence rates of safety events of interest identified in the ritlecitinib AA clinical programme; and to estimate the prevalence of comorbidities with known/potential associations with AA.

The study **design** was a retrospective descriptive cohort study of patients 12 years of age and older within the United States embedded within the Optum Claims Database. A study period from October 1, 2016 to September 30, 2020, was selected to reflect the most current and complete data in the Optum Claims Database. The study population consisted of patients diagnosed with AA from the administrative database and a subset of those who were similar to the characteristics of the patients enrolled in the ritlecitinib AA clinical trial programme. In addition, a non-AA cohort was utilised in this study to provide descriptive analysis of characteristics and background rates of selected safety events of a general population without AA who were matched by age, sex and race to patients in the AA cohort. Outcome variables included selected safety events (eg, sensorineural hearing loss, serious infections, cancer, cardiovascular events, all cause death) and immunologic and psychiatric co-morbidities (eg, atopic dermatitis, rheumatoid arthritis, anxiety, depression).

The final cohorts identified for this study were 8,784 patients with $\geqslant$2 diagnosis codes for AA and 26,352 non-AA patients matched by age, sex and race to patients in the AA cohort. In addition, a **trial-similar sub cohort** of AA patients (n= 5,370) met the criteria set for similarity to the ritlecitinib AA clinical trial study B7981015. Among the trial-similar AA sub cohorts the ranges in IR per 1,000 Pys were 11.4 for serious infections to 5.5 for herpes zoster and 12.9 for herpes simplex infections; 10.0 for any primary malignancies; 12.0 for MACE; and 27.2 for sensorineural hearing loss. Crude incidence rates for the trial-similar sub cohort are further given and discussed within the section on Adverse events of special interest.

Exposure

In the phase 2/3 studies, there were 1521 participants (1763 patient years) exposed to ritlecitinib 50 mg or higher. There were 1011 participants with at least 12 months (48 weeks) exposure and there were 1334 participants who had $\geqslant$6 months exposure to ritlecitinib 50 mg or higher. Among these participants, 172 were adolescents, including 133 adolescents with at least 48 weeks of exposure to ritlecitinib 50 mg or higher.

Table 23: Cumulative exposure during AA and Vitiligo phase 2/3 studies

Cumulative Exposure[a]	All Participants		Adolescents	
	All 50 mg (N=1521/ 1763.3 PY)	Any Ritlecitinib (N=1628/2084.6 PY)	All 50 mg (N=172/228.9 PY)	Any Ritlecitinib (N=181/272.7 PY)
≥6 months	1334	1436	157	173
≥12 months	1011	1152	133	153
≥18 months	585	757	90	111
≥24 months	279	461	44	67

a. 1 month is equivalent to 4 weeks.

During the procedure, additional safety data from the ongoing studies with a data cut-off of 30 May 2022 were provided. This updated All exposure pool included 1630 participants with 2303 PY of exposure to ritlecitinib.

2.6.8.2. Adverse events

The **placebo-controlled AA pool** consists of the data from 0-24 weeks of studies 005, 015 and 037. There were n=130 patients who were treated with the 50 mg QD dose as is applied for (denoted as 50/50 mg), n=215 patients who were treated with 50 mg QD preceded by the 4 week loading dose of 200 mg (200/50 mg), which makes n=345 for these two regimens combined (50 mg) and n=261 for the 30 mg regimens with and without loading dose combined (30 mg); n=213 patients were treated with placebo (Table 24).

The proportion of patients with at least 1 **TEAE** was 75% in the 50/50 mg group and 70% in the placebo group. Over all dose regimens (placebo, 10 mg, 30 mg, 50/50 mg and 200/50 mg) the proportion of patients with at least 1 TEAE was quite similar with ~70% for most dose regimens, except for the 50/50 mg group where this was 5%-point higher. The proportion of patients with at least 1 treatment-related TEAE was 33% in the 200/50 mg group, 36% in the 50/50 mg group and 32% in the placebo group.

The proportions of patients with at least 1 **SAE** or at least 1 severe AE were 0 and 1.5% in the 50/50 mg group and 1.9% and 2.3% in the placebo group. Over all dose regimens, the 50/50 mg group had the lowest numbers of patients with SAEs, in the 200/50 mg group, 4 patients (1.9%) had at least 1 SAE/severe AE.

The proportions of patients who **discontinued** permanently or temporary with the study drug due to AEs were 1.5% and 10% in the 50/50 mg group and 2.3% and 3.8% in the placebo group. Over all dose regimens, the number of permanent discontinuations was lowest in the 50/50 mg group, but the number of patients with temporary discontinuations was highest.

Table 24: Summary of treatment-emergent adverse events in the placebo-controlled AA pool (0-24 weeks)

	Ritlecitinib 200/50 mg (N=215) n (%)	Ritlecitinib 50/50 mg (N=130) n (%)	Ritlecitinib 50 mg (N=345) n (%)	Ritlecitinib 30 mg (N=261) n (%)	Ritlecitinib 10 mg (N=62) n (%)	Placebo (N=213) n (%)
Participants evaluable for adverse events	215	130	345	261	62	213
Number of adverse events	404	243	647	513	113	370
Participants with adverse events	151 (70.2)	98 (75.4)	249 (72.2)	186 (71.3)	43 (69.4)	148 (69.5)
Participants with serious adverse events	4 (1.9)	0	4 (1.2)	1 (0.4)	2 (3.2)	4 (1.9)
Participants with severe adverse events	4 (1.9)	2 (1.5)	6 (1.7)	10 (3.8)	2 (3.2)	5 (2.3)
Participants discontinued from study or study drug due to adverse events[a]	6 (2.8)	2 (1.5)	8 (2.3)	4 (1.5)	2 (3.2)	5 (2.3)
Participants with temporary discontinuation due to adverse events	19 (8.8)	13 (10.0)	32 (9.3)	18 (6.9)	5 (8.1)	8 (3.8)

Placebo-Controlled AA Pool includes the placebo-controlled portion of studies B7931005 (0-24 weeks), B7981015 (0-24 weeks) and B7981037 (0-24 weeks).
Ritlecitinib 50 mg: participants from Ritlecitinib 200/50 mg and 50/50 mg QD combined; Ritlecitinib 30 mg: participants from Ritlecitinib 200/30 mg and 30/30 mg QD combined.
Except for the Number of Adverse Events, participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment
a. Participants who had an AE record that indicated that the AE caused the participant to be discontinued from the study or study drug.
MedDRA v24.1 coding dictionary applied.
B7981037 data cutoff date: 04JAN2022.
PFIZER CONFIDENTIAL Source Data: adae Source Dataset Creation: 24MAR2022 (08:52) Table Generation: 29APR2022 (12:48)
Output File: ./aa_scs_nda/PCPAA/adae_s010a

In the **placebo-controlled AAV pool**, with the addition of the data from the vitiligo trial, the proportion of patients with at least 1 TEAE became 77% in the 50/50 mg group, 74% in the 200/50 mg group, and 71% in the placebo group. The proportions of patients with at least 1 SAE were 0.5% (n=1) in the 50/50 mg group, 1.4% (n=4) in the 200/50 mg group, and 1.8% (n=5) in the placebo group. The proportions of patients with at least 1 severe AE were 3.6% (n=7) in the 50/50 mg group, 2.1% (n=6) in the 200/50 mg group, and 2.5% (n=7) in the placebo group. The proportions of patients who discontinued permanently or temporarily with the study drug due to AEs were 3.6% and 9.6% in the 50/50 mg group and 2.9% and 5.0% in the placebo group, while these were 2.9% and 8.2% in the 200/50 mg group.

In the **one-year exposure pool**, of the 0-48 week data of pivotal study 015, the proportion of patients with at least 1 TEAE was 84% in the 50 mg group, 80% in the 30 mg group, and 77% in the 10 mg group (Table 25). The proportion of patients with at least 1 treatment-related TEAE was 44% in the 50 mg group, 41% in the 30 mg group and 39% in the 10 mg group. The proportions of patients with at least 1 SAE or at least 1 severe AE were 2.3% and 2.7% in the 50 mg group, 1.1% and 5.7% in the 30 mg group, and 3.3% and 3.3% in the 10 mg group. The proportions of patients who permanently discontinued the study drug due to AEs were 3% in all three dose groups. The proportions of patients who discontinued the study drug temporarily due to AEs were 14% and 12% in the 50 mg and 30 mg dose groups, and 8% in the 10 mg group.

Table 25: Summary of treatment-emergent adverse events in the one-year exposure pool (0-48 weeks) of study 015

	Ritlecitinib 50 mg (n=261)	Ritlecitinib 30 mg (n=261)	Ritlecitinib 10 mg (n=62)
Participants evaluable for adverse events	261	261	62
Number of adverse events	766	744	157
Participants with adverse events	218 (84%)	210 (80%)	46 (77%)
Participants with serious adverse events	6 (2.3%)	3 (1.1%)	2 (3.3%)
Participants with severe adverse events	7 (2.7%)	15 (5.7%)	2 (3.3%)
Participants discontinued from study or study drug due to adverse events	8 (3.0%)	8 (3.0%)	2 (3.3%)
Participants with temporary discontinuation due to adverse events	37 (14%)	32 (12%)	5 (8.1%)

Common Adverse Events

In the **placebo-controlled AA pool**, the most frequent events (2% in any treatment group) that occurred more commonly (>1%) in the ritlecitinib 50/50 mg group than in the placebo group included: nasopharyngitis, diarrhoea, headache, acne, urticaria, rash, upper abdominal pain, pyrexia, folliculitis, SARS-CoV-2 test positive and Covid-19, dizziness, and atopic dermatitis (Table 26). In addition, tinnitus, gastroenteritis, nasopharyngitis, blood creatinine phosphokinase increased, and back pain, were more common in the 50 mg dose groups as compared to placebo. Lower respiratory tract infections and pneumonia did not occur in the PCPAA pool.

Regarding audiological AEs, there were 6 cases (2.8%) of tinnitus in the 200/50 mg group, no cases in the 50/50 mg group, one case each in the 30 mg and 10 mg groups, and 2 cases (0.9%) in the placebo group. Hypoacusis was found in 1 case in the placebo group, not in the ritlecitinib groups.

Infections and infestations (SOC) occurred in 38% of patients in the combined 50 mg group, in 37% in the 30 mg group, in 32% in the 10 mg group and in 31% of the placebo group; this proportion was higher in the 200/50 mg group (41%) as compared to the 50/50 mg group (33%). Herpes zoster was infrequent, but occurred in 2 patients (1.5%) of the 50/50 mg group and in 2 patients (0.8%) of the 30 mg group, but not in the 10 mg group or the placebo group.

Fractures were uncommon. In 3 patients fractures had occurred: an occasion of hand fracture in the 30 mg group, a rib fracture in the 10 mg group, a humerus fracture in the placebo group.

In the **placebo-controlled AAV pool**, the pattern of common TEAEs was similar as compared to the AA pool. In the **placebo-controlled Vitiligo trial**, the most common (≥5%) TEAEs were similar as occurred in the AA pool. Acne, urticaria, and diarrhoea were more frequent in the ritlecitinib treatment groups, as compared to placebo.

Table 26: Common (≥2%) treatment-emergent adverse events in the placebo-controlled AA pool (0-24 weeks), in all treatment groups

Number of Participants Evaluable for AEs	Ritlecitinib 200/50 mg (N=215)	Ritlecitinib 50/50 mg (N=130)	Ritlecitinib 50 mg (N=345)	Ritlecitinib 30 mg (N=261)	Ritlecitinib 10 mg (N=62)	Placebo (N=213)
SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
EAR AND LABYRINTH DISORDERS						
Tinnitus	6 (2.8)	0	6 (1.7)	1 (0.4)	1 (1.6)	2 (0.9)
GASTROINTESTINAL DISORDERS						
Abdominal discomfort	1 (0.5)	1 (0.8)	2 (0.6)	2 (0.8)	0	6 (2.8)
Abdominal pain upper	1 (0.5)	4 (3.1)	5 (1.4)	5 (1.9)	0	2 (0.9)
Diarrhoea	14 (6.5)	12 (9.2)	26 (7.5)	10 (3.8)	0	8 (3.8)
Nausea	12 (5.6)	3 (2.3)	15 (4.3)	12 (4.6)	3 (4.8)	15 (7.0)
Vomiting	6 (2.8)	2 (1.5)	8 (2.3)	6 (2.3)	0	5 (2.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Fatigue	1 (0.5)	4 (3.1)	5 (1.4)	12 (4.6)	2 (3.2)	5 (2.3)
Pyrexia	4 (1.9)	4 (3.1)	8 (2.3)	3 (1.1)	1 (1.6)	0
INFECTIONS AND INFESTATIONS						
COVID-19	1 (0.5)	3 (2.3)	4 (1.2)	2 (0.8)	0	2 (0.9)
Folliculitis	12 (5.6)	4 (3.1)	16 (4.6)	11 (4.2)	2 (3.2)	4 (1.9)
Gastroenteritis	3 (1.4)	2 (1.5)	5 (1.4)	3 (1.1)	2 (3.2)	0
Influenza	6 (2.8)	2 (1.5)	8 (2.3)	1 (0.4)	2 (3.2)	3 (1.4)
Laryngitis	0	0	0	0	2 (3.2)	1 (0.5)
Nasopharyngitis	21 (9.8)	13 (10.0)	34 (9.9)	34 (13.0)	6 (9.7)	15 (7.0)
Upper respiratory tract infection	21 (9.8)	8 (6.2)	29 (8.4)	21 (8.0)	2 (3.2)	16 (7.5)
Urinary tract infection	8 (3.7)	0	8 (2.3)	7 (2.7)	0	6 (2.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS						
Fall	1 (0.5)	2 (1.5)	3 (0.9)	1 (0.4)	2 (3.2)	2 (0.9)
Ligament sprain	1 (0.5)	3 (2.3)	4 (1.2)	3 (1.1)	0	0
INVESTIGATIONS						
Blood creatine phosphokinase increased	7 (3.3)	2 (1.5)	9 (2.6)	6 (2.3)	2 (3.2)	0
SARS-CoV-2 test positive	0	4 (3.1)	4 (1.2)	4 (1.5)	0	1 (0.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
Arthralgia	2 (0.9)	1 (0.8)	3 (0.9)	6 (2.3)	2 (3.2)	6 (2.8)

Back pain	3 (1.4)	2 (1.5)	5 (1.4)	4 (1.5)	2 (3.2)	0
Myalgia	5 (2.3)	1 (0.8)	6 (1.7)	6 (2.3)	5 (8.1)	3 (1.4)
NERVOUS SYSTEM DISORDERS						
Dizziness	11 (5.1)	3 (2.3)	14 (4.1)	10 (3.8)	1 (1.6)	3 (1.4)
Headache	20 (9.3)	12 (9.2)	32 (9.3)	30 (11.5)	11 (17.7)	17 (8.0)
PSYCHIATRIC DISORDERS						
Insomnia	4 (1.9)	1 (0.8)	5 (1.4)	0	1 (1.6)	5 (2.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
Oropharyngeal pain	3 (1.4)	4 (3.1)	7 (2.0)	7 (2.7)	0	6 (2.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Acne	12 (5.6)	8 (6.2)	20 (5.8)	14 (5.4)	3 (4.8)	10 (4.7)
Dermatitis atopic	5 (2.3)	3 (2.3)	8 (2.3)	1 (0.4)	0	1 (0.5)
Dermatitis contact	1 (0.5)	0	1 (0.3)	3 (1.1)	3 (4.8)	2 (0.9)
Pruritus	4 (1.9)	1 (0.8)	5 (1.4)	8 (3.1)	1 (1.6)	5 (2.3)
Rash	3 (1.4)	5 (3.8)	8 (2.3)	4 (1.5)	0	2 (0.9)
Urticaria	11 (5.1)	6 (4.6)	17 (4.9)	10 (3.8)	1 (1.6)	3 (1.4)

Placebo-Controlled AA Pool includes the placebo-controlled portion of studies B7931005 (0-24 weeks), B7981015 (0-24 weeks) and B7981037 (0-24 weeks).
Ritlecitinib 50 mg: participants from Ritlecitinib 200/50 mg and 50/50 mg QD combined; Ritlecitinib 30 mg: participants from Ritlecitinib 200/30 mg and 30/30 mg QD combined.
Participants are only counted once per treatment per event.
MedDRA v24.1 coding dictionary applied.
B7981037 data cutoff date: 04JAN2022.

In the **one-year exposure pool**, the most common TEAEs in the ritlecitinib groups were similar to those in the placebo-controlled AA pool, including diarrhoea, nausea, folliculitis, nasopharyngitis, urinary tract infections, headache, and acne (Table 27). Diarrhoea, nasopharyngitis, upper respiratory tract infections, dizziness, acne and urticaria were more frequent in the highest, 50 mg and 30 mg dose groups compared to the 10 mg group.

Pyrexia was more frequent in the 50 mg group (3.8%) as compared to the 30 mg (1.5%) and 10 mg (1.6%) groups.

There were 4 (1.5%) cases of tinnitus in the 50 mg group, 3 (1.1%) in the 30 mg group, and 1 (1.6%) in the 10 mg group. Neurosensory deafness occurred in 4 (2.6%) participants in the 50 mg group, 5 (1.9%) in the 30 mg group, and 0 participants of the 10 mg group. There was 1 case of unilateral deafness in the 50 mg group. Dizziness occurred in 13 (5%) of the participants in the 50 mg group, 16 (6.1%) in the 30 mg group, and 1 (1.6%) in the 10 mg group.

Infections and infestations (SOC) were more frequent in the 50 mg group (51%), as compared to the 30 mg (47%) and the 10 mg (40%) groups. Of the most frequent infections, nasopharyngitis (14% and 16% versus 9.7%), upper respiratory tract infections (11% and 11% versus 3.2%), and urinary tract infections (4.6% and 3.1% versus 0), were more frequent in the 50 mg and 30 mg groups, versus the 10 mg group. In analysing the concentration-response relationship of ritlecitinib with infections, there appeared to be a statistically significant relationship of exposure with the occurrence of infections. The included AE categories of interest were moderate, severe, and infections leading to discontinuation.

No additional fractures occurred as compared to the placebo-controlled period of 0-24 weeks.

Dose-response for infections

In the all-exposure pool, the model-estimated slope for the effect of time-weighted Cav on the mean incidence of infection events was statistically significant (95% CI of estimate did not include zero). Over the range of relevant doses, an approximately 10-fold increase in ritlecitinib exposure (geometric mean Cav of 27 ng/mL [30 mg QD] vs 257 ng/mL [200 mg QD]), was predicted to demonstrate a less than 2-fold increase in the mean incidence of infections per 100 patient-years (11.0 vs 33.2, respectively). The IR/100 PY (95% CI) of infections for chronic ritlecitinib administration of 30 mg and 50 mg QD was 11.0 (9.61, 12.7) and 13.5 (11.9, 15.4), respectively. The IR/100 PY (95% CI) following 1-year of ritlecitinib treatment for 200/50 mg was 14.9 (13.1, 16.9) compared with that for a 50 mg QD continuous dosing regimen of 13.5 (11.9, 15.3).

Table 27: Common (⩾5%) treatment-emergent adverse events in the one-year exposure pool (0-48 weeks) of study 015

Number of Participants Evaluable for AEs	Ritlecitinib 50 mg (N=261)			Ritlecitinib 30 mg (N=261)			Ritlecitinib 10 mg (N=62)		
SYSTEM ORGAN CLASS and Preferred Term	n (%)	PY	IR (95% CI) [a]	n (%)	PY	IR (95% CI) [a]	n (%)	PY	IR (95% CI) [a]
GASTROINTESTINAL DISORDERS									
Diarrhoea	21 (8.0)	215.37	9.75 (6.20, 14.66)	12 (4.6)	220.18	5.45 (2.95, 9.27)	0	55.32	0.00 (0.00, 5.42)
Nausea	14 (5.4)	222.92	6.28 (3.57, 10.29)	15 (5.7)	216.48	6.93 (4.02, 11.18)	3 (4.8)	52.95	5.67 (1.44, 15.43)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS									
Fatigue	10 (3.8)	227.39	4.40 (2.23, 7.85)	12 (4.6)	218.36	5.50 (2.97, 9.35)	4 (6.5)	53.20	7.52 (2.39, 18.14)
INFECTIONS AND INFESTATIONS									
Folliculitis	19 (7.3)	221.30	8.59 (5.32, 13.17)	16 (6.1)	217.37	7.36 (4.35, 11.71)	4 (6.5)	54.00	7.41 (2.35, 17.87)
Nasopharyngitis	37 (14.2)	209.58	17.65 (12.61, 24.08)	42 (16.1)	200.39	20.96 (15.30, 28.07)	6 (9.7)	50.31	11.93 (4.83, 24.81)
Upper respiratory tract infection	29 (11.1)	211.94	13.68 (9.33, 19.40)	28 (10.7)	212.49	13.18 (8.93, 18.80)	2 (3.2)	53.76	3.72 (0.62, 12.30)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS									
Myalgia	9 (3.4)	227.06	3.96 (1.93, 7.28)	8 (3.1)	222.41	3.60 (1.66, 6.83)	6 (9.7)	51.40	11.67 (4.72, 24.28)
NERVOUS SYSTEM DISORDERS									
Dizziness	13 (5.0)	223.16	5.83 (3.23, 9.71)	16 (6.1)	218.56	7.32 (4.32, 11.64)	1 (1.6)	54.57	1.83 (0.09, 9.05)
Headache	33 (12.6)	212.04	15.56 (10.88, 21.60)	38 (14.6)	202.19	18.79 (13.49, 25.54)	12 (19.4)	47.00	25.53 (13.83, 43.41)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS									
Nasal congestion	3 (1.1)	229.93	1.30 (0.33, 3.56)	4 (1.5)	224.01	1.79 (0.57, 4.32)	4 (6.5)	54.09	7.39 (2.34, 17.84)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS									
Acne	18 (6.9)	220.56	8.16 (4.99, 12.66)	22 (8.4)	215.02	10.23 (6.57, 15.24)	3 (4.8)	53.03	5.66 (1.44, 15.41)
Urticaria	16 (6.1)	222.33	7.20 (4.25, 11.44)	14 (5.4)	218.37	6.41 (3.65, 10.51)	1 (1.6)	54.29	1.84 (0.09, 9.09)

One-Year Exposure Pool includes participants initially randomized to active ritlecitinib treatment in study B7981015 (0-48 weeks).
Ritlecitinib 50 mg: participants from Ritlecitinib 200/50 mg and 50/50 mg QD combined; Ritlecitinib 30 mg: participants from Ritlecitinib 200/30 mg and 30/30 mg QD combined.
Participants are only counted once per treatment per event.
Included data up to the end of risk period.
Risk period is defined as period from the first dose of ritlecitinib to the smallest of [last dose date in B7981015 + 35 days], [first dose date in B7981032 - 1 day], or [death date].
PY (Patient-Year): Total follow up time calculated up to the day of the first event for participants with events, and up to the end of risk period for participants without events.
n: Number of participants with the event.
a. Results per 100 PY and mid-p gamma intervals.
MedDRA v24.1 coding dictionary applied.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

No deaths were reported in the placebo-controlled phases (0-24 weeks) of the AA trials (005, 015, 037) or in the Vitiligo trial (019), or in the one-year follow-up phase of the AA pivotal trial (015). In the phase 1 programme, no deaths occurred.

In the All-Exposure Pool, there were 2 deaths (breast cancer (spindle cell carcinoma) of a patient in her 60's; acute respiratory failure and cardiorespiratory arrest in a patient in her 50's) both on 50 mg, and there was one death (severe myocardial infarction on Study Day 50 of a patient in his 50's) in the clinical study programme for Ulcerative Colitis. The three events were considered as unrelated to treatment by the investigators.

Serious Adverse Events

In the **Placebo-controlled AA pool**, there were 4 (1.9%) participants with at least one SAE in the 200/50 mg group, none in the 50/50 mg group, 1 (0.4%) in the 30 mg group, 2 (3.2%) in the 10 mg group, and 4 (1.9%) in the placebo group. Across treatment groups, the SOC that included the highest number of participants with SAEs was Infections and Infestations (4 events, in n=3 participants). No individual PT SAE was reported for more than 1 participant in any treatment group.

The SAEs in the 200/50 mg group were: three instances of serious infections (appendicitis, empyema, and sepsis), a case of breast carcinoma, and a spontaneous abortion.

Three participants discontinued the study due to an SAE: eczema (10 mg), invasive lobular breast carcinoma (200/50 mg), and sepsis (200/50 mg).

In the **Placebo-controlled Vitiligo trial**, there was one SAE in the 50/50 mg group and also one additional SAE in each of the 30 mg group, the 10 mg group and the placebo group. These were additional SAEs of migraine (2 participants, 1 each in 50/50 mg and 10 mg, oesophageal spasm (1 participant, 30 mg), and neurogenic bladder (1 participant, placebo).

One participant had discontinued the study due to an SAE: migraine (10 mg).

In the **one-year exposure pool**, the SOCs of 'Infections and Infestations' and of 'Neoplasms' included the highest proportions of participants with SAEs (Table 28). There were relatively more participants with an SAE in the 50 mg group (n=6, 2.3%) as compared to the 30 mg group (1.1%) but not the 10 mg group (3.2%). SAEs that had occurred in the 50 mg group were: appendicitis, empyema, sepsis, breast cancer and invasive lobular breast cancer, spontaneous abortion, and pulmonary embolism. SAEs of appendicitis, diverticulitis, chemical poisoning, and suicidal behaviour had occurred in the 30 mg group. In the 10 mg group, there was a SAE of suicidal behaviour and one of eczema.

Compared with the placebo-controlled AA pool/period, 3 additional participants with SAEs were discontinued from pivotal study 015: 1 each with pulmonary embolism (50 mg), breast cancer (50 mg), and suicidal behaviour (30 mg).

Table 28: Serious adverse events in the one-year exposure pool of study 015

Number of Participants Evaluable for AEs	Ritlecitinib 50 mg (N=261)			Ritlecitinib 30 mg (N=261)			Ritlecitinib 10 mg (N=62)		
SYSTEM ORGAN CLASS and Preferred Term	n (%)	PY	IR (95% CI) [a]	n (%)	PY	IR (95% CI) [a]	n (%)	PY	IR (95% CI) [a]
Participants with events	6 (2.3)			3 (1.1)			2 (3.2)		
INFECTIONS AND INFESTATIONS	2 (0.8)	231.54	0.86 (0.14, 2.85)	2 (0.8)	226.20	0.88 (0.15, 2.93)	0	55.32	0.00 (0.00, 5.42)
Appendicitis	1 (0.4)	231.63	0.43 (0.02, 2.13)	1 (0.4)	226.97	0.44 (0.02, 2.18)	0	55.32	0.00 (0.00, 5.42)
Diverticulitis	0	232.07	0.00 (0.00, 1.29)	1 (0.4)	226.47	0.44 (0.02, 2.18)	0	55.32	0.00 (0.00, 5.42)
Empyema	1 (0.4)	231.98	0.43 (0.02, 2.13)	0	227.23	0.00 (0.00, 1.32)	0	55.32	0.00 (0.00, 5.42)
Sepsis	1 (0.4)	231.98	0.43 (0.02, 2.13)	0	227.23	0.00 (0.00, 1.32)	0	55.32	0.00 (0.00, 5.42)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	232.07	0.00 (0.00, 1.29)	1 (0.4)	227.14	0.44 (0.02, 2.18)	0	55.32	0.00 (0.00, 5.42)
Chemical poisoning	0	232.07	0.00 (0.00, 1.29)	1 (0.4)	227.14	0.44 (0.02, 2.18)	0	55.32	0.00 (0.00, 5.42)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2 (0.8)	231.84	0.86 (0.14, 2.85)	0	227.23	0.00 (0.00, 1.32)	0	55.32	0.00 (0.00, 5.42)
Breast cancer	1 (0.4)	231.93	0.43 (0.02, 2.13)	0	227.23	0.00 (0.00, 1.32)	0	55.32	0.00 (0.00, 5.42)
Invasive lobular breast carcinoma	1 (0.4)	231.97	0.43 (0.02, 2.13)	0	227.23	0.00 (0.00, 1.32)	0	55.32	0.00 (0.00, 5.42)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1 (0.4)	232.05	0.43 (0.02, 2.13)	0	227.23	0.00 (0.00, 1.32)	0	55.32	0.00 (0.00, 5.42)
Abortion spontaneous	1 (0.4)	232.05	0.43 (0.02, 2.13)	0	227.23	0.00 (0.00, 1.32)	0	55.32	0.00 (0.00, 5.42)
PSYCHIATRIC DISORDERS	0	232.07	0.00 (0.00, 1.29)	1 (0.4)	227.14	0.44 (0.02, 2.18)	1 (1.6)	54.75	1.83 (0.09, 9.02)
Suicidal behaviour	0	232.07	0.00 (0.00, 1.29)	1 (0.4)	227.14	0.44 (0.02, 2.18)	1 (1.6)	54.75	1.83 (0.09, 9.02)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.4)	231.97	0.43 (0.02, 2.13)	0	227.23	0.00 (0.00, 1.32)	0	55.32	0.00 (0.00, 5.42)
Pulmonary embolism	1 (0.4)	231.97	0.43 (0.02, 2.13)	0	227.23	0.00 (0.00, 1.32)	0	55.32	0.00 (0.00, 5.42)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	232.07	0.00 (0.00, 1.29)	0	227.23	0.00 (0.00, 1.32)	1 (1.6)	55.22	1.81 (0.09, 8.94)

One-Year Exposure Pool includes participants initially randomized to active ritlecitinib treatment in study B7981015 (0-48 weeks).
Ritlecitinib 50 mg: participants from Ritlecitinib 200/50 mg and 50/50 mg QD combined; Ritlecitinib 30 mg: participants from Ritlecitinib 200/30 mg and 30/30 mg QD combined.
Participants are only counted once per treatment per event.
Totals for the No. of Participants at a higher level are not necessarily the sum of those at the lower levels since a participant may report two or more different adverse events within the higher level ca
Included data up to the end of risk period.
Risk period is defined as period from the first dose of ritlecitinib to the smallest of [last dose date in B7981015 + 35 days], [first dose date in B7981032 - 1 day], or [death date].
PY (Patient-Year): Total follow up time calculated up to the day of the first event for participants with events, and up to the end of risk period for participants without events.
n: Number of participants with the event.
a. Results per 100 PY and mid-p gamma intervals.
MedDRA v24.1 coding dictionary applied.

In the **All-exposure pool**, the IR/100 PY (95% CI) of SAEs in the AEP All 50 mg group was 2.72 (2.03 – 3.57) which was 2.69 (0.85, 6.48) in the All 50 mg group of the placebo-controlled AA pool.

In the All 50 mg group, the 'Infections and Infestations' SOC included the highest proportion (n=12, 0.8%) of participants with SAEs, followed by 'Neoplasms' (n=9, 0.6%); there were 2 cases of 'Cardiac disorders' (acute myocardial infarction and cardio-respiratory arrest), and 1 case of pulmonary embolism, classified within 'Respiratory disorders'.

SAEs that were reported by ≥2 participants in Any Ritlecitinib included (preferred term): appendicitis (n=5), breast cancer and invasive lobular breast carcinoma (n=3 and n=1, respectively), abortion spontaneous (n=3), acute respiratory failure (n=3), COVID-19 (n=2), COVID-19 pneumonia (n=2), migraine (n=2), and suicidal behaviour (n=2).

2.6.8.4. Adverse events of special interest

Infections, malignancies and NMSC, MACE and thromboembolic events, neurological and audiological findings were handled as Adverse Events of Special Interest (Table 29).

Table 29: Occurrence of AESIs by safety pool

	PCPAA B7981015 Sub-pool				PCPAAV B7891015 +B7981019 Sub-pool				OYEP		AEP	
	Ritlecitinib 50/50 mg N=130		Placebo N=131		Ritlecitinib 50/50 mg N=197		Placebo N=197		Ritlecitinib All 50 mg N= 261		Ritlecitinib All 50 mg N=1521	
Adverse Events	n[a] (%)	IR[b] (95% CI)	n[a] (%)	IR[b] (95% CI)	n[a] (%)	IR[b] (95% CI)	n[a] (%)	IR[b] (95% CI)	n[a] (%)	IR[b] (95% CI)	n[a] (%)	IR[b] (95% CI)
Infections												
Serious infections	0	0.00 (0.00, 5.06)	0	0.00 (0.00, 4.97)	0	0.00 (0.00, 3.34)	0	0.00 (0.00, 3.48)	2 (0.8)	0.86 (0.14, 2.85)	12 (0.8)	0.66 (0.35, 1.14)
OIs[c]	0	0.00 (0.00, 5.06)	0	0.00 (0.00, 4.97)	1 (0.5)	1.11 (0.05, 5.50)	0	0.00 (0.00, 3.48)	0	0.00 (0.00, 1.29)	2 (0.1)	0.10 (0.01, 0.35)
HZ[d]	2 (1.5)	3.42 (0.56, 11.30)	0	0.00 (0.00, 4.97)	3 (1.5)	3.37 (0.86, 9.20)	1 (0.5)	1.17 (0.05, 5.78)	6 (2.3)	2.61 (1.06, 5.44)	21 (1.4)	1.17 (0.74, 1.76)
HS[d]	2 (1.5)	3.43 (0.57, 11.34)	3 (2.3)	5.06 (1.28, 13.77)	4 (2.0)	4.51 (1.43, 10.89)	4 (2.0)	4.51 (1.43, 10.95)	3 (1.1)	1.30 (0.33, 3.55)	32 (2.1)	1.72 (1.19, 2.41)
Malignancy												
Malignancy (excluding NMSC)[c]	0	0.00 (0.00, 5.06)	0	0.00 (0.00, 4.97)	0	0.00 (0.00, 3.34)	0	0.00 (0.00, 3.48)	2 (0.8)	0.86 (0.14, 2.85)	7 (0.5)	0.37 (0.16, 0.75)
NMSC (BCC-SCC)[c]	0	0.00 (0.00, 5.06)	0	0.00 (0.00, 4.97)	0	0.00 (0.00, 3.35)	0	0.00 (0.00, 3.48)	0	0.00 (0.00, 1.29)	5 (0.3)	0.26 (0.09, 0.59)
CV												
All MACE[c]	-[e]	-	-	-	-	-	-	-	0	0.00 (0.00, 1.29)	3 (0.2))	0.15 (0.03, 0.43)
Thromboembolic events[c,f]	0	0.00 (0.00, 5.06)	0	0.00 (0.00, 4.97)	0	0.00 (0.00, 3.34)	0	0.00 (0.00, 3.48)	1 (0.4)	0.43 (0.02, 2.13)	1 (<0.1)	0.06 (0.00, 0.29)
Neurological												
Peripheral neuropathy[c]	0	0.00 (0.00, 5.06)	0	0.00 (0.00, 4.97)	0	0.00 (0.00, 3.34)	0	0.00 (0.00, 3.48)	0	0.00 (0.00, 1.29)	3 (0.2)[g]	0.16 (0.03, 0.45)[g]
Audiological												
Sensorineural hearing loss[c]	1 (0.8)	1.69 (0.08, 8.34)	0	0.00 (0.00, 4.97)	1 (0.5)	1.12 (0.05, 5.51)	0	0.00 (0.00, 3.48)	3 (1.1)	1.30 (0.33, 3.55)	15 (1.0)	0.85 (0.49, 1.39)

PCPAA and PCPAAV included data up to the end of risk period. Risk period is defined as period from the first dose of placebo or ritlecitinib to the smallest of (last dose in the placebo-controlled period + 35 days), (first dose date in the extension period - 1 day), or (death date).
OYEP included data up to the end of risk period. Risk period is defined as period from the first dose of ritlecitinib to the smallest of (last dose date in B7981015 + 35 days), (first dose date in B7981032 - 1 day), or (death date).
AEP included data up to the end of risk period. Risk period is defined as period from the first dose of ritlecitinib to the earliest of (last dose date + 35 days), (death date), or (data cutoff date).

a. n: Number of participants with the event
b. Results per 100 PY and mid-p gamma intervals (PY: Total follow up time calculated up to the day of the first event for participants with events, and up to the end of risk period for participants without events.)
c. Adjudicated events

Neurological and audiological events

In **safety study 037**, the PD safety outcomes did not show differences between the ritlecitinib (200/50 mg) group and the placebo group over 9 months. Events of neurosensory hearing loss or deafness did not occur in the study.

A total of 71 participants were included: 36 participants were randomised to 200/50 mg and 35 were randomised to placebo. Of these, 6 (8.5%) participants discontinued during the placebo-controlled phase: 4 in 200/50 mg and 2 in placebo.

There was no effect of ritlecitinib compared to placebo on BAEP I-V interwave latency at 80dB nHL at month 9 (primary outcome), and there was no effect of ritlecitinib on BAEP Wave V amplitude at 80dB nHL or on the absence of BAEP wave V, on intraepidermal nerve fiber density, or on percentage of intraepidermal nerve fibers with axonal swellings (secondary outcomes). There were no events adjudicated by the neurological adjudication committee as meeting criteria for sensorineural hearing loss or central hearing disorder.

The baseline mean (SD) value (ms) of I-V interwave latency on BAEP at 80 dB was 4.085 (0.1614) in 200/50 mg and 3.989 (0.1946) in placebo on the right side, and 4.103 (0.1531) in 200/50 mg and 3.988 (0.2235) in placebo on the left side. There were no within-group changes and no statistically significant differences in change from baseline in I-V interwave latency between 200/50 mg and placebo on either side (Table 30, Figure 27). The mean I-V interwave latency values remained within the range of published normative data of mean (SD) 4.0 (0.21) ms. The 6 months data gave the same picture. There also were no within- or between group changes in mean (SD) value (µV) of amplitude of Wave V on BAEP at 80 dB on right or left sides, at 6 or 9 months. All participants had Wave V on BAEP present at stimulus intensities ranging from 80 dB to 40 dB up to Month 9 except for 1 participant.

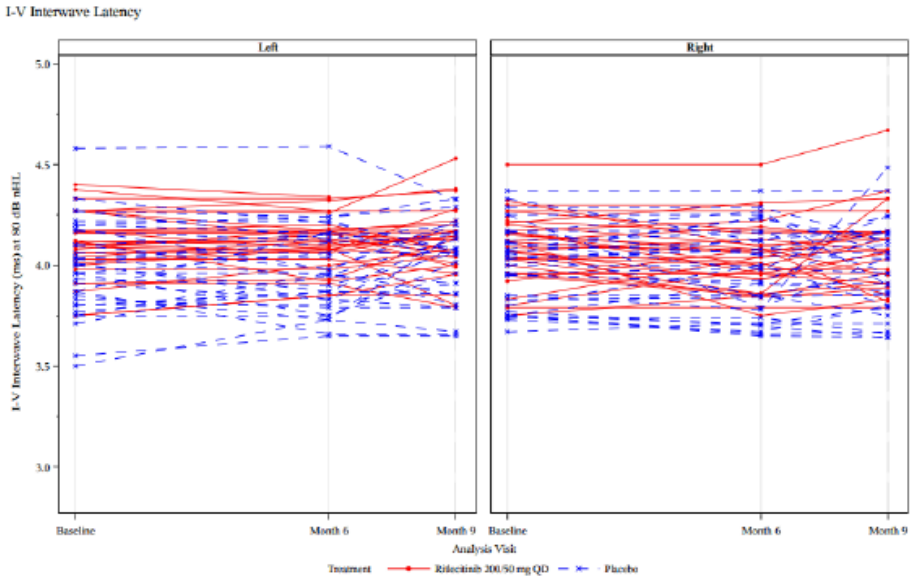
The intraepidermal nerve fiber density (IENFD) values for ritlecitinib 200/50 mg and placebo were consistent with published normal ranges both at baseline and Month 9. Change from baseline to month 9 in mean and median IENFD was minimal and similar between ritlecitinib 200/50 mg and placebo groups. Change from baseline to month 9 in percentage of IENFs with axonal swellings was minimal and similar between ritlecitinib 200/50 mg and placebo groups.

Table 30: Least-square mean of change from baseline in I-V Interwave Latency (ms) on BAEP at 80 dB from the right and left sides at month 9 of study 037

Analysis Visit	Summary Statistics	Ritlecitinib 200/50 mg QD (N=36)	Placebo (N=35)
Month 9	n	31	32
	Estimated LS Mean (SE)	0.011 (0.0270)	-0.010 (0.0266)
	95% CI	(-0.043, 0.065)	(-0.063, 0.043)
	Difference From Placebo		
	LS Mean Difference (SE)	0.021 (0.0382)	
	95% CI	(-0.056, 0.097)	
Month 9	n	31	32
	Estimated LS Mean (SE)	0.031 (0.0217)	0.022 (0.0214)
	95% CI	(-0.012, 0.075)	(-0.020, 0.065)
	Difference From Placebo		
	LS Mean Difference (SE)	0.009 (0.0307)	
	95% CI	(-0.052, 0.070)	

Upper half: right side; lower half: left side.

Figure 27: Individual participant data of I-V Interwave Latency (ms) at 80 dB nHL from the left side and the right side up to month 9 in study 037



In the **placebo-controlled AA pool**, the occurrence of adjudicated **neurological events** (i.e.. Meeting adjudication criteria for being a neurological event of interest), were 2.8% in the 200/50 mg group, 1.5% in the 50/50 group, 2.3% in the 50 mg group, 4.6% in the 30 mg group, 6.5% in the 10 mg group and 4.2% in the placebo group. The most frequently reported adjudicated events of interest (n ≥2 in any treatment group) were Paraesthesia and Dysesthesia, Headache, Syncope,

and Dizziness (not vertigo or presyncope). Paraesthesia and dysaesthesia occurred in 1.7% of the combined 50 mg group, 1.5% of the 30 mg group, not in the 10 mg group and in 0.9% of the placebo group. The occurrence was highest (1.9%) in the 200/50 mg group. Peripheral neuropathy occurred in 1 patient in the 30 mg group. The occurrence of adjudicated sensorineural **hearing loss** was: 0 patients of the 200/50 group, in 1 patient in the 50/50 mg group, 1 patient in the 30 mg group, and 0 patients in both the 10 mg and placebo groups.

In the **Placebo-controlled AAV pool**, there were 10 additional neurological events of interest meeting criteria for adjudication, as compared with the PCPAA pool. Of these, 3 were events of Paresthesia and dysesthesia in the 50 mg group. In the combined 50 mg group, there were 1.7% of patients with adjudicated paraesthesia/dysaesthesia, compared to 0.7% in the placebo group (Table 31). In the 30 mg group there were 1.3% of patients with paraesthesia/dysesthesia, but none in the 10 mg group. There were no additional adjudicated events of Peripheral neuropathy. Most dys-/hyper-/hypo-/paraesthesia's were mild and resolved while being on study drug. Most events that were resolved did so within 2.5 – 8 weeks.

Treatment-emergent tinnitus was most frequent in the 200/50 mg group (2.5%), less frequent in the 50/50 mg group (0.5%), and overall as frequent in the 50 mg group (1.5%) as in the placebo group (1.4%), (Table 31). Neurosensory deafness/hypoacusis (unadjudicated) occurred in 1-2 cases in all treatment groups.

Table 31: Occurrence of dysaesthesias and of audiological events in the Placebo-controlled AAV pool

	Ritlecitinib (200/50 mg) (N=280)		Ritlecitinib (50/50 mg) (N=197)		Ritlecitinib (50 mg)[a] (N=544)		Ritlecitinib (30 mg)[b] (N=311)		Ritlecitinib (10 mg) (N=111)		Placebo (N=279)	
	n (%)	IR (95% CI)	n (%)	IR (95% CI)	n (%)	IR (95% CI)	n (%)	IR (95% CI)	n (%)	IR (95% CI)	n (%)	IR (95% CI)
Events Meeting Adjudication EOI Criteria												
Paraesthesia and dysesthesia	4 (1.4)	1.40 (0.44, 4.67)	3 (1.5)	2.90 (0.73, 7.90)	9 (1.7)	3.32 (1.61, 6.26)	4 (1.3)	1.96 (0.63, 6.28)	0	0.00 (0.00, 6.08)	2 (0.7)	0.71 (0.12, 3.87)
Sensorineural Hearing Loss	0	0.00 (0.00, 2.94)	1 (0.5)	0.96 (0.04, 4.73)	1 (0.2)	0.48 (0.02, 2.35)	1 (0.3)	0.49 (0.02, 4.41)	1 (0.9)	1.29 (0.06, 8.06)	0	0.00 (0.00, 2.99)
TEAE Preferred Terms (Non-adjudicated)												
Dysaesthesia	0	0.00 (0.00, 2.94)	1 (0.5)	0.96 (0.04, 4.73)	1 (0.2)	0.48 (0.02, 2.35)	0	0.00 (0.00, 3.79)	0	0.00 (0.00, 6.06)	0	0.00 (0.00, 2.99)
Hyperaesthesia	2 (0.7)	0.69 (0.11, 3.79)	0	0.00 (0.00, 2.87)	2 (0.4)	0.69 (0.11, 2.53)	0	0.00 (0.00, 3.80)	0	0.00 (0.00, 6.06)	0	0.00 (0.00, 2.99)
Hypoaesthesia	1 (0.4)	0.35 (0.01, 3.38)	3 (1.5)	2.90 (0.73, 7.89)	4 (0.7)	1.62 (0.50, 4.05)	4 (1.3)	1.96 (0.62, 6.27)	0	0.00 (0.00, 6.06)	2 (0.7)	0.71 (0.12, 3.88)
Paraesthesia	2 (0.7)	1.30 (0.16, 5.12)	0	0.00 (0.00, 2.87)	4 (0.7)	1.47 (0.46, 3.74)	3 (1.0)	1.47 (0.37, 5.65)	0	0.00 (0.00, 6.06)	2 (0.7)	1.29 (0.16, 5.14)
Deafness neurosensory	0	0.00 (0.00, 2.94)	2 (1.0)	1.92 (0.31, 6.33)	2 (0.4)	0.95 (0.16, 3.15)	2 (0.6)	0.97 (0.16, 5.03)	1 (0.9)	1.29 (0.06, 8.06)	1 (0.4)	0.36 (0.01, 3.45)
Deafness unilateral	0	0.00 (0.00, 2.94)	0	0.00 (0.00, 2.87)	0	0.00 (0.00, 1.42)	0	0.00 (0.00, 3.79)	1 (0.9)	1.29 (0.06, 8.05)	0	0.00 (0.00, 2.99)
Hypoacusis	0	0.00 (0.00, 2.94)	0	0.00 (0.00, 2.87)	0	0.00 (0.00, 1.42)	0	0.00 (0.00, 3.79)	0	0.00 (0.00, 6.06)	1 (0.4)	0.94 (0.04, 4.76)
Tinnitus	7 (2.5)	4.93 (1.99, 10.52)	1 (0.5)	0.96 (0.04, 4.73)	8 (1.5)	3.14 (1.45, 6.12)	2 (0.6)	1.75 (0.23, 6.78)	2 (1.8)	3.34 (0.53, 11.8)	4 (1.4)	3.33 (0.98, 8.51)

a. Ritlecitinib 50 mg: participants from Ritlecitinib 200/50 mg, 100/50 mg, and 50/50 mg QD combined.
b. Ritlecitinib 30 mg: participants from Ritlecitinib 200/30 mg and 30/30 mg QD combined.

In the **one-year exposure pool** of pivotal study 015, the occurrence of adjudicated paraesthesia/ dysaesthesia was infrequent, and higher in the 30 mg group (1.5%) as compared to the 50 mg (0.8%) and placebo (1.6%) groups (Table 32). Adjudicated sensorineural hearing loss occurred in more cases in the 50 mg group (1.1%) and 30 mg group (0.8%), as compared to the 10 mg group. Unadjudicated deafness was registered for 5 participants in the 50 mg group and 30 mg group each, not in the 10 mg group. Especially in the 50 mg and 30 mg group, there were additional unadjudicated cases of dysaesthesia/paraesthesia/hypoaesthesia. Most dys-/hyper-/hypo-/paraesthesia's were mild and resolved while being on study drug.

Table 32: Occurrence of dysaesthesias and of audiological events in the one-year exposure pool of study 015

Preferred Term	Ritlecitinib (50 mg)[a] (N=261)		Ritlecitinib (30 mg)[b] (N=261)		Ritlecitinib (10 mg) (N=261)	
	N (%)	IR (95% CI)	N (%)	IR (95% CI)	N (%)	IR (95% CI)
Events Meeting Adjudication EOI Criteria						
Paraesthesia and dysesthesia	2 (0.8)	0.87 (0.14, 2.86)	4 (1.5)	1.78 (0.56, 4.29)	1 (1.6)	1.82 (0.09, 9.00)
Sensorineural Hearing Loss	3 (1.1)	1.30 (0.33, 3.55)	2 (0.8)	0.88 (0.15, 2.92)	0	0.00 (0.00, 5.42)
TEAE Preferred Terms (Non-adjudicated)						
Dysaethesia	1 (0.4)	0.43 (0.02, 2.13)	0	0.00 (0.00, 1.32)	0	0.00 (0.00, 5.42)
Hypoaesthesia	2 (0.8)	0.87 (0.14, 2.86)	4 (1.5)	1.78 (0.56, 4.29)	1 (1.6)	1.82 (0.09, 9.00)
Paraesthesia	1 (0.4)	0.43 (0.02, 2.13)	4 (1.5)	1.78 (0.57, 4.31)	1 (1.6)	1.82 (0.09, 8.99)
Deafness neurosensory	4 (1.5)	1.74 (0.54, 4.19)	5 (1.9)	2.22 (0.81, 4.92)	0	0.00 (0.00, 5.42)
Deafness unilateral	1 (0.4)	0.43 (0.02, 2.13)	0	0 (0.00, 1.32)	0	0 (0.00, 5.42)
Tinnitus	4 (1.5)	1.74 (0.54, 4.20)	3 (1.1)	1.33 (0.33, 3.62)	1 (1.6)	1.81 (0.09, 8.95)

a. Ritlecitinib 50 mg: participants from Ritlecitinib 200/50 mg, 100/50 mg, and 50/50 mg QD combined.
b. Ritlecitinib 30 mg: participants from Ritlecitinib 200/30 mg and 30/30 mg QD combined.

In the **All-exposure pool**, 75 (4.9%) participants in the 50 mg group had an event that met adjudication criteria for neurological safety. Paraesthesia and dysaesthesia was the most commonly adjudicated events of interest, reported in 24 (1.6%) participants in the 50 mg group and in 29 (1.8%) on Any Ritlecitinib dose. The IR/100 PY (95% CI) for Paraesthesia and dysaesthesia in the 50 mg group was 1.28 (0.84 – 1.89). Peripheral neuropathy was reported in 3 (0.2%) participants in the 50 mg group and 4 (0.2%) in the Any Ritlecitinib group. The IR/100 PY (95% CI) for Peripheral neuropathy in the 50 mg group was 0.16 (0.03 – 0.45). According to the listings, several cases occurred with paraesthesia/dysaesthesia/hypoaesthesia that was considered related, for whom the dysaesthesia was not resolved, or that did resolve, and the drug was withdrawn.

There were 15 (1.0%) participants with TEAEs adjudicated to meet the criteria for adjudicated Sensorineural hearing loss in the 50 mg group, with an IR (95%CI) of 0.85/100 PY (0.49 – 1.39); there were 18 participants with sensorineural hearing loss in the any dose of ritlecitinib group. For comparison, in the AA subcohort in US study B7981051, the IR (95%CI) was 2.72 (2.4 – 3.09), and in the AA subcohort in Danish Study s7981049, the IR (95%CI) was 0.32 (0.24 – 0.41).

In the 50 mg group, the IR/100 PY (95% CI) in participants ≥65 years old (n=30) was 8.50 (2,15 – 23.1), which was higher than in participants ⩾18 years old (n=1349) with 0.98 (0.57 – 1.59). No adolescent participant had an adjudicated event of Sensorineural hearing loss.

Of the 18 patients in the Any Ritlecitinib dose group with sensorineural hearing loss, in 13/18 cases, the hearing loss was considered related. In 7/18 cases, the hearing loss was related and was resolved; in 6/18 cases, the hearing loss was considered related and not resolved.

MACE

In the ritlecitinib Phase 2/3 development programme, CV events were adjudicated by a blinded external adjudication committee. MACE was defined as a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

No treatment-emergent AEs of MACE (fatal or non-fatal) were reported in the **placebo-controlled AA pool**, in the placebo-controlled vitiligo trial, or in the **one-year follow-up** of the pivotal AA trial.

In the **All-exposure pool**, there were 3 SAEs in the All 50 mg group with an IR/100 PY (95% CI) of 0.15 (0.03 – 0.43) with events adjudicated as a MACE event: 1 acute myocardial infarction, 1 ischaemic stroke (retinal artery occlusion), and 1 sudden cardiac death (acute respiratory failure and cardio-respiratory arrest). The IR/100 PY (95% CI) for 2 events of non-fatal MACE was 0.09 (0.01 – 0.30), and for 1 fatal MACE, it was 0.05 (0.00 – 0.23).

The IR/100 PY (95% CI) of MACE in the All-exposure 50 mg group of 0.15 (0.03 – 0.43) was lower than reported in the TS AA sub cohorts in US study B7981051 with 1.2 (0.99 – 1.45) and the Danish study B7981049 with 0.58 (0.44 – 0.74).

Venous Thromboembolic Events

Adjudicated venous thromboembolic events (VTE) included pulmonary embolism (PE) and deep venous thrombosis (DVT).

There was 1 participant in the **All-exposure pool** who had an SAE which met adjudication criteria for PE; IR/100 PY (95% CI) of 0.06 (0.00 – 0.29). There were no cases of DVT in the data. The patient was treated with ritlecitinib 50 mg and had an SAE of **PE** of moderate severity on study Day 169. Potential risk factors included morbid obesity, sleep apnoea and cardiovascular disease (hypertension, hyperlipidemia). The event was considered not related to study treatment by the investigator but related by the sponsor. The participant was discontinued from the study as a result of the event; outcome of the event was resolved.

Serious infections

Serious infections were defined as SAEs in the Infections and Infestation SOC. This included infections that required parenteral antimicrobial therapy or required hospitalisation for treatment or met other criteria that required the infection to be reported as an SAE. All serious infections required discontinuation from the study, as per protocol.

In the **placebo-controlled AA pool**, the proportion of participants with serious infections was ≤0.9% in ritlecitinib treatment groups (200/50 mg, 0.9%; All 50 mg, 0.6%; All 30 mg, 0.4%), with no events in 50/50 mg, 10 mg or placebo groups (Table 33). In the 200/50 mg group there were 2 participants with in total 3 serious infections: appendicitis, empyema, and sepsis. In the 30 mg group, there was 1 participant with a serious infection: diverticulitis. In the **placebo-controlled Vitiligo study**, no serious infections occurred.

In the **one-year follow-up data** of the pivotal AA trial, in addition to the 3 serious infections in the 0–24-week data, one serious infection occurred in a participant on 30 mg: appendicitis. Time to onset of serious infections varied: 2 participants experienced serious infections (empyema and sepsis, and diverticulosis) that occurred on study day 50 and 56, respectively; 2 events of appendicitis occurred on study day 173 and study Day 240. All events resolved. The overall occurrence of serious infections in the 50 mg group was 0.8% with an IR (95%CI) of 0.86 (0.14 – 2.85).

In the **All-exposure pool**, there were 14 participants on 50 mg ritlecitinib who had at least one serious infection. The proportion and IR/100 PY (95% CI) of participants experiencing serious infections in the All 50 mg group were: 0.8% and 0.66 (0.35 – 1.14); and in the Any Ritlecitinib group these were 0.9% and 0.64 (0.36 – 1.05). The most frequently occurring serious infections on 50 mg were appendicitis (n=4) and coronavirus infections (n=4), (Table 33).

The IR/100 PY (95% CI) of serious infection in the All exposure pool All 50 mg group of 0.66 (0.35 – 1.14) was lower than reported in the AA subcohorts in the observational US Study B7981051 of 1.15 (0.95 – 1.39) and the Danish observational study B7981049 of 1.8 (1.61 – 2).

No participant who experienced a serious infection had an ALC <LLN at baseline or prior to the event.

Table 33: Occurrence of treatment-emergent serious infections in the AA All-exposure pool

Number of Participants Evaluable for AEs	Ritlecitinib 50 mg (N=1521)	Any Ritlecitinib (N=1628)
SYSTEM ORGAN CLASS, High Level Term, and Preferred Term	n (%)	n (%)
Participants with events	12 (0.8)	14 (0.9)
INFECTIONS AND INFESTATIONS	12 (0.8)	14 (0.9)
Abdominal and gastrointestinal infections	4 (0.3)	6 (0.4)
Appendicitis	4 (0.3)	5 (0.3)
Diverticulitis	0	1 (0.1)
Coronavirus infections	4 (0.3)	4 (0.2)
COVID-19	2 (0.1)	2 (0.1)
COVID-19 pneumonia	2 (0.1)	2 (0.1)
Female reproductive tract infections	1 (0.1)	1 (0.1)
Vulval abscess	1 (0.1)	1 (0.1)
Infections NEC	1 (0.1)	1 (0.1)
Empyema	1 (0.1)	1 (0.1)
Sepsis, bacteraemia, viraemia and fungaemia NEC	2 (0.1)	2 (0.1)
Sepsis	1 (0.1)	1 (0.1)
Septic shock	1 (0.1)	1 (0.1)
Staphylococcal infections	1 (0.1)	1 (0.1)
Staphylococcal sepsis	1 (0.1)	1 (0.1)
Urinary tract infections	1 (0.1)	1 (0.1)
Pyelonephritis	1 (0.1)	1 (0.1)

All-Exposure Pool includes all participants who received ritlecitinib in B7931005, B7981015, B7981032, B7981019 and B7981037 from the start of their first dose of ritlecitinib.
Any Ritlecitinib: participants taking any dose of Ritlecitinib; Ritlecitinib 50 mg: participants from Ritlecitinib 200/50 mg, 100/50 mg and 50/50 mg QD combined.
Participants are only counted once per treatment per event.
Totals for the No. of Participants at a higher level are not necessarily the sum of those at the lower levels since a participant may report two or more different adverse events within the higher level category.
MedDRA v24.1 coding dictionary applied.
B7981032 data cutoff date: 28FEB2022; B7981037 data cutoff date: 04JAN2022.

Herpes Zoster (HZ)

This section describes all events of HZ, regardless of whether they were reviewed and confirmed as an opportunistic infection (if it was multi-dermatomal HZ (nonadjacent or >2 adjacent dermatomes) or disseminated HZ.

In the **placebo-controlled AA pool**, the proportion of participants with HZ was ⩽1.5% in ritlecitinib (50/50 mg, 1.5%; All 50 mg, 0.9 %; All 30 mg, 0.8%) and no HZ events were reported in placebo. All HZ events were non-serious, mild, or moderate, and all resolved; 1 participant (All 30 mg) had HZ resulting in temporary discontinuation from the study drug.

In the **one-year follow-up** data, the proportion and IR/100 PY of participants with HZ increased with increasing dose across the All 50 mg group with 2.3% and IR (95%CI) of 2.61 (1.06 – 5.44), compared with All 30 mg with 0.8% and an IR of 0.88 (0.15 – 2.92) and 10 mg with 0.0% and an IR of 0 (0.00 - 5.42). There was no participant with an event of HZ adjudicated as an OI. All events were mild or moderate, resolved or resolving, and non-serious, 3 participants with HZ were temporarily discontinued from the study drug. The IR/100 PY (95% CI) in the All 50 mg group of the OYEP was 2.61 (1.06 – 5.44), which was higher than in the All 50 mg group in the PCPAA with 1.86 (0.47 – 5.14).

Malignancy (excluding NMSC)

Malignancy events were adjudicated by a blinded external adjudication committee consisting of experts in their field. In addition, a Histopathology Review Committee that included a central laboratory pathologist review of biopsies also assisted in the evaluation of potential malignancies. NMSC events are discussed separately from other malignancies.

In the **placebo-controlled AA pool**, 1 participant (0.5%) in the 200/50 mg group had an adjudicated malignancy of lobular carcinoma of the breast. In the **placebo-controlled Vitiligo trial**, no cases of malignancies (excluding NMSC) occurred.

In the **one-year follow-up period** of the pivotal AA trial, 2 (0.8%) participants in All 50 mg experienced malignancies (excluding NMSC) compared with no participant in the 30 mg or 10 mg groups. In both participants, the events were SAEs of breast cancer (invasive lobular breast carcinoma, breast cancer).

In the **all-exposure pool**, there were 7 participants with adjudicated malignancies (excluding NMSC), all in the 50 mg group (N=1521). The proportion and IR/100 PY (95% CI) in the 50 mg group was 0.5% and 0.37 (0.16 – 0.75) and in the Any Ritlecitinib group this was 0.4% and 0.32 (0.14 – 0.63). The adjudicated malignancies were lobular breast carcinoma (n=1), breast cancer (n=3), testis cancer (n=1) and papillary thyroid cancer (n=1). One additional adjudicated event of malignant melanoma was reported after the 35-day reporting period. Three of the 8 events were considered related by the investigator.

The IR/100 PY (95% CI) for malignancy (excluding NMSC) in the 50 mg group of 0.37 (0.16 – 0.75) was lower than reported for the AA subcohorts in US study B7981051 of 1.0 (0.82 – 1.23) and lower as compared with the IR of 0.56 (0.46 – 0.68) in the Danish study B7981049.

Non-melanoma skin cancer

In the **placebo-controlled AA pool**, there were no occurrences of NMSC (basal cell carcinoma or squamous cell carcinoma). In the **placebo-controlled Vitiligo trial**, there were 2 participants with NMSC; 1 participant in the 200/50 mg group experienced SCC, a participant in the 100/50 mg group experienced BCC. In the All 50 mg group, there thus were 2 cases (0.4% of NMSC).

In the **one-year follow-up period** of the pivotal AA trial, there were no occurrences of NMSC (basal cell carcinoma or squamous cell carcinoma).

In the **all exposure pool**, there were 5 (0.3%) participants with NMSC, all in the All 50 mg group (N=1521) with an IR (95%CI) of 0.26/100 PY (0.09 – 0.59). This included 3 (0.2%) events of BCC, 1 (0.1%) event of SCC, and 1 (0.1%) event of Bowen's disease. One event of BCC was severe and

reported as a SAE, resulting in the interruption of study treatment; the outcome was resolved. Four of the 5 events were considered as unrelated, for one, the assessment is unknown.

In the All 50 mg in the all-exposure pool, the IR/100 PY (95% CI) for BCC and SCC was 0.16 (0.03 – 0.45) and 0.06 (0.00 – 0.29), respectively, and comparable or lower than those reported in patients ⩾18 years in US study B7981051 with an IR (95%CI) for BCC of 0.63 (0.49 – 0.83] and for SCC of 0.42 (0.3 – 0.58) and comparable to the Danish study B7981049 with 0.13 (0.08 – 0.19) and for SCC 0.02 (0.01 – 0.06). The overall BCC:SCC ratio of 3:2 is within expected range for the general population and differs from the ratio expected in an immunosuppressed population.

2.6.8.5. Laboratory findings

Treatment with ritlecitinib was associated with changes in haematological parameters and lipids, some of which were larger with increasing doses. Decreases in haemoglobin, lymphocytes, and lymphocyte subsets were larger in the first 4 weeks in the 200/50 mg compared with 50/50 mg. Haematological parameters and lipids remained stable during long-term treatment. There were no clinically meaningful trends for hepatic laboratory parameters. There were no Hy's Law cases.

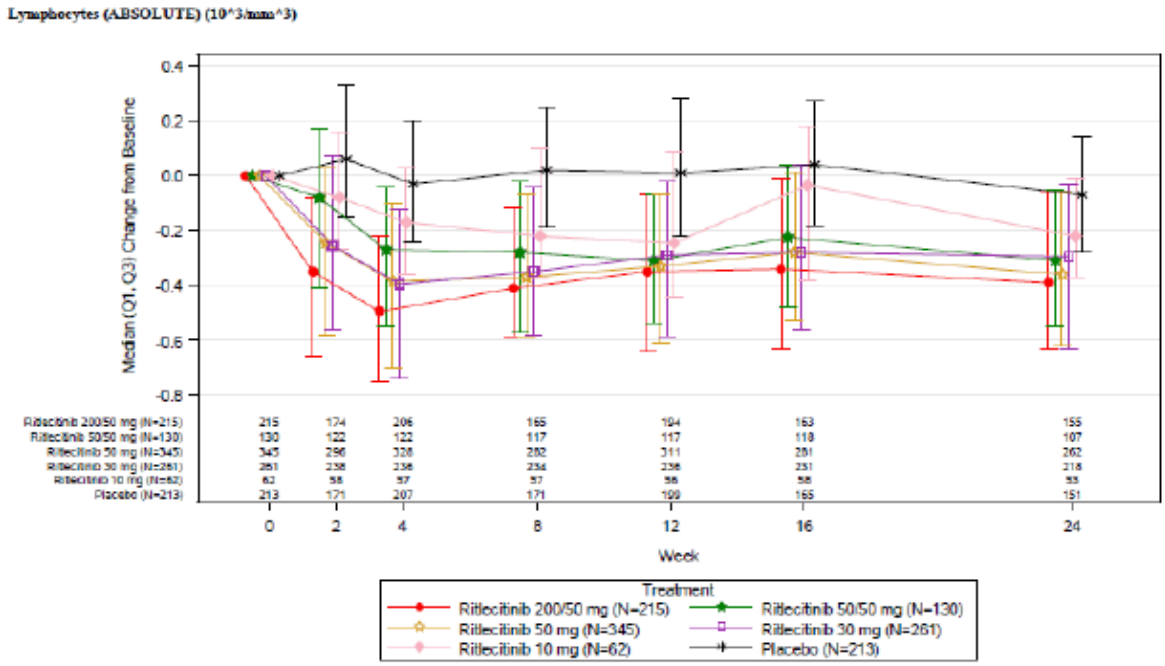
Lymphocytes

In the **placebo-controlled AA pool**, there was a median decrease from baseline in absolute ALC in all ritlecitinib groups compared with placebo up to Week 4, which was more apparent in 200/50 mg, All 50 mg, and All 30 mg. At Week 24, the median ALC in all groups reached a plateau that was lower than the baseline value (Figure 28).

In the 50/50 mg group, there were no events of lymphocyte count decreased considered CTCAE Grade 3 (<500 to 200/mm^3) or Grade 4 (<200/mm^3). However, 6 participants (4 [1.9%] in 200/50 mg [same participants in All 50 mg, 1.2%] and 2 [0.8%] in All 30 mg) had lymphocyte count decreased considered CTCAE Grade 3, and 1 [0.5%] participant (200/50 mg [had lymphocyte count decreased considered CTCAE Grade 4. No participant was permanently discontinued from the study or study drug or temporarily discontinued from study drug due to a TEAE of lymphopenia.

In the **one-year exposure pool**, the lower lymphocyte counts remained on the lower level. TEAEs of lymphopenia were reported for 7 participants (2 [0.8%] in All 50 mg, 4 [1.5%] in All 30 mg, and 1 [1.6%] in 10 mg). TEAEs of lymphocyte count decreased were reported for 6 participants (All 50 mg [2, 0.8%], All 30 mg [4, 1.5%]). A TEAE of lymphocyte count abnormal was reported for 1 (0.4%) participant (All 50 mg).

Figure 28: Change from baseline in lymphocyte counts in the PCPAA pool



Platelet counts

In the **placebo-controlled AA pool**, there was a median decrease from BL at Week 2 in all ritlecitinib groups, which remained stable at the lower level up to Week 24; changes were similar across ritlecitinib groups. No participant had platelet counts considered CTCAE Grade 3 (<50 to 25 × 10^3/mm^3) or Grade 4 (<25 × 10^3/mm^3). A TEAE of thrombocytopenia was reported for 1 (1.6%) participant (10 mg). TEAEs of platelet count decreased were reported for 5 participants (1 [0.8%] in 50/50 mg [same participant 1 (0.3%) in All 50 mg] and 4 [1.5%] in All 30 mg). 1 (0.4%) participant (All 30 mg) was permanently discontinued from study or study drug and 1 (0.4%) participant (All 30 mg) temporarily discontinued study drug due to a TEAE of platelet count decreased.

In the **one-year follow-up** data, the median decrease in the ritlecitinib groups remained stable up to week 48. TEAEs of thrombocytopenia were reported for 2 participants (1 [0.4%] in All 30 mg and 1 [1.6%] in 10 mg). TEAEs of platelet count decreased were reported for 6 participants (2 [0.8%] in All 50 mg; 4 [1.5%] in All 30 mg). 1 [0.4%] participant in All 30 mg was permanently discontinued from study or study drug and no participant temporarily discontinued from study drug due to a TEAE of thrombocytopenia.

Lipids

In the **placebo-controlled AA pool**, there were small increases from BL at Week 4 in median TC, HDL-C, and LDL-C and variable changes in TG relative to placebo. Up to Week 24, levels of HDL-C were similar to placebo across all ritlecitinib groups; there were small increases in median CFB in TC, LDL-C, and TG in ritlecitinib groups compared with placebo.

TEAEs of hyperlipidaemia were reported for 2 participants (1 each: All 30 mg [0.4%], 10 mg [1.6%]). No participant was permanently discontinued from study or study drug due or temporarily discontinued study drug to hyperlipidaemia.

In the **one-year follow up** data, the changes in lipids were variable and small as compared to baseline. TEAEs of hyperlipidaemia were reported for 3 participants (2 [0.8%] in All 30 mg and 1

[1.6%] in 10 mg). No participant was permanently or temporarily discontinued from study or study drug due to hyperlipidaemia.

Creatine phosphokinase

In the **placebo-controlled AA pool**, baseline median values (U/L) for CK (range: 88.0-101.0) were comparable between ritlecitinib and placebo. Median change from baseline to the Week 24 was 8.0 in in 50/50 mg and 0.5 in placebo. The proportion of participants with CK increases considered CTCAE Grade 3 (>5× ULN to 10× ULN) or Grade 4 (>10× ULN) was similar across the ritlecitinib groups, but higher than placebo in 200/50 mg, 50/50 mg, All 50 mg, All 30 mg, and 10 mg. Five (3.9%) participants in 50/50 mg and 2 (0.9%) participants in placebo had CK increases considered CTCAE Grade 3 or 4. 5 participants (200/50 mg, 2 [0.9%]; 50/50 mg, 1 [0.8%]; [same participants in All 50 mg (0.9%)]; 30 mg, 1 [0.4%], 10 mg, 1 [1.6%]) temporarily discontinued study drug due to TEAEs of blood CK increased. No events of rhabdomyolysis were reported.

In the **one-year follow up data**, there was no clinically meaningful change over time in CK levels in ritlecitinib groups. The proportion of participants with CK increases considered CTCAE Grade 3 was higher in All 50 mg compared with All 30 mg and 10 mg. The proportion of participants with CK increases considered CTCAE Grade 4 was higher in All 50 mg and All 30 mg compared with 10 mg. 14 participants had CK increases considered CTCAE Grade 3: 11 (4.3% [All 50 mg]), 2 (0.8% [All 30 mg]), and 1 (1.6% [10 mg]). 15 participants had CK increases considered CTCAE Grade 4: 6 (2.3% [All 50 mg]), 8 (3.1% [All 30 mg]), and 1 (1.6% [10 mg]). No events of rhabdomyolysis were reported.

Liver enzymes

In the **placebo-controlled AA pool**, baseline values (U/L) for AST (median range: 19.0-19.5) and ALT (median range: 15.0-17.0) were comparable between ritlecitinib and placebo groups. There was no meaningful change over time: median change from baseline (U/L) to the Week 24 in 50/50 mg (AST: 0; ALT: 1) and placebo (AST: -1; ALT: 0). TEAEs of hyperbilirubinaemia were reported for 1 (1.6%) participant (10 mg) and liver function test increased for 3 (1.4%) participants (200/50 mg [same participants in All 50 mg, 0.9%]), 1 (0.6%) participant on 200/50 mg temporarily discontinued study drug due to liver function test increased; there were no potential Hy's Law cases.

In the **one-year follow up data**, there were some cases with raised hepatic enzymes above 2 time the ULN or more, especially in the higher dose groups. In the 50 mg ritlecitinib group: 1 TEAE of liver function increased, 2 TEAE of Transaminases increased, 2 TEAE of ALT increased, 1 TEAE of AST increased, 2 TEAE of bilirubin increased (1 moderate TEAE as well as 1 TEAE not recovered). In the 30 mg ritlecitinib group: 1 TEAE of Transaminases increased, 4 TEAE of ALT increased, 2 TEAE of AST increased, 1 TEAE of bilirubin increased (1 severe TEAE and all events recovered). In the 10 mg ritlecitinib group: 1 TEAE of Hepatic enzymes increased and 1 TEAE of Hyperbilirubinemia.

2.6.8.6. Safety in special populations

Elderly patients

The number of patients of 65 years and older was limited. In the All-exposure pool, there were 33 (2.0%) elderly participants, of which there were 30 (2.0%) elderly participants on the 50 mg dose.

The proportion of elderly participants experiencing **TEAEs** (all causality and treatment-related) was similar to adults (⩾18 years) across the ritlecitinib groups (Table 34). The proportion of elderly participants experiencing severe AEs, **SAEs**, and AEs leading to permanent **discontinuations** was

higher than adults. The proportion of elderly participants experiencing AEs leading to temporary discontinuations was similar to the overall adult population.

In the 50 mg group of the All-exposure cohort, compared with adults, additional frequent TEAEs (⩾ 10% and higher than adults) in elderly participants included urinary tract infections (elderly 16.7%; adults 5.3%), lymphocyte count decreased (elderly 10.0%; adults 1.3%), and arthralgia (elderly 13.3%; adults 3.4%). Five (16.7%) elderly participants experienced SAEs: COVID-19, thermal burn, BCC, breast cancer, and aortic aneurysm (1 participant each). There were no events adjudicated as OI, TB, MACE, or ATE.

The proportion and IR/100 PY (95% CI) of elderly participants experiencing **serious infection** and HZ was higher than in adults. One (3.3%; IR 2.11 [0.10, 11.52]) elderly participant experienced serious infection and 3 (10.0%, 8.23 [2.09, 22.41]) experienced HZ, compared with 10 (0.7%; 0.64 [0.32, 1.16]) for serious infections and 21 (1.6%, 1.34 (0.85, 2.03] for HZ in the adult population.

There was 1 (3.3%; IR 2.58/100 PY [95% CI: 0.13, 12.79]) elderly participant experienced adjudicated **malignancies** (excluding NMSC) and 2 (6.7%; IR 4.81/100 PY [95% CI: 0.79, 16.41]) experienced **NMSC** (BCC). No elderly participant experienced SCC. The proportion and IR of elderly participants experiencing malignancies (excluding NMSC), NMSC, and BCC were higher in the elderly than adults in both All 50 mg and Any Ritlecitinib.

There were 3 (10.0%; IR 7.63/100 PY [95% CI: 1.92, 21.16]) elderly participants in All 50 mg with an event of an adjudicated event of **Disorders of integrative motor functions** (excluding CN and peripheral neuropathies) (2 events of sciatica, 1 of peroneal nerve palsy).

There were 3 (10.0%) elderly participants in All 50 mg who experienced **sensorineural hearing loss** (1 event each of deafness, deafness unilateral/neurosensory, and hypoacusis). The proportion and IR/100 PY (95% CI) of adjudicated audiological events of interest of sensorineural hearing loss was higher in elderly participants (10%, 8.50 [2.15, 23.14]) than in adults (1.1%, 0.98 [0.57, 1.59]).

Table 34: Summary of TEAEs by baseline age in the All-exposure cohort

	12 to <18 years old		≥18 years old		18 to <50 years old		≥50 years old		≥65 years old	
	All 50 mg	Any Ritlecitinib	All 50 mg	Any Ritlecitinib	All 50 mg	Any Ritlecitinib	All 50 mg	Any Ritlecitinib	All 50 mg	Any Ritlecitinib
Participants evaluable for AEs (n)	172	181	1349	1447	1051	1125	298	322	30	33
Number of adverse events	521	646	4035	4963	3099	3794	936	1169	117	132
Participants with AEs (%)	76.2	80.7	77.4	81.5	76.4	80.8	80.9	84.2	76.7	81.8
Participants with serious AEs (%)	2.3	3.9	3.4	3.5	3.0	3.0	4.7	5.0	16.7	15.2
Participants with severe AEs (%)	4.7	5.5	4.7	5.5	4.5	5.4	5.4	5.9	16.7	15.2
Permanently discontinued from study or study drug due to AE (%)	4.1	4.4	5.0	5.7	4.6	5.4	6.4	6.8	16.7	18.2
Temporarily discontinued from study drug due to AE (%)	15.7	17.7	17.1	17.9	17.7	18.4	15.1	16.1	16.7	15.2
Participants with treatment-related AEs (%)	34.3	40.9	34.5	40.4	35.2	41.2	32.2	37.6	40.0	42.4

Females and males

In the **placebo-controlled AA pool**, the proportion of patients with at least one TEAE in the combined 50 mg group was 62% for males and 78% for females. The proportions of patients with SAEs was similar, but more females (11%) than males (6.1%) temporarily discontinued medication.

In the **all-exposure pool** on 50 mg, the proportion of participants experiencing TEAEs (all causality or treatment-related) was higher in females (80.0% and 36.7%, respectively) than males (72.9% and 31.0%, respectively). SAEs were more frequently experienced by female (4.2%) than

male (1.9%) participants. The proportion of participants experiencing severe AEs, or AEs leading to permanent or temporary discontinuation was similar in males and females. A higher proportion and IR/100PY (95% CI) of females of 3.3% had HZ compared with males with 0.9%. A higher proportion of females of 2.0% [3 participants] experienced sensorineural hearing loss compared with males (no events reported). In All 30 mg and 10 mg, the proportion of sensorineural hearing loss in males and females was similar.

Adolescents

In the **placebo-controlled AA pool**, there were n=105 (15%) adolescents included, with n=18 in the 50/50 mg group and n=20 in the 200/50 mg group, and n=19 on placebo (Table 35). In the combined 50 mg group (n=38), the proportion of adolescents with at least 1 TEAE was 79% (71% in adults), SAEs did not occur (1.3% in adults), there were 2.6% (2.3% in adults) adolescents who permanently discontinued study drug due to an AE, and 7.9% of adolescents temporary discontinued (9.4% in adults) due to an AE.

Table 35: Overview of adverse events for adolescents and adults in the PCPAA pool

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

TEAEs reported by the largest number of adolescents (⩾10% of participants) and at a frequency higher than in placebo included nasopharyngitis (All 50 mg 13.2%, placebo 0%) and acne (All 50 mg 13.2%, placebo 5.3%), with no increase in frequency with increasing dose. In adults, the proportion of participants with acne (All 50 mg 4.9%, Placebo 4.6%) and nasopharyngitis (All 50 mg 9.4%, Placebo 7.7%) were similar to placebo. Infections and infestations (SOC) were more frequent on 50 mg as compared to placebo in adolescents (All 50 mg 42%, placebo 20%) as well as adults (All 50 mg 38%, placebo 32%). Upper respiratory tract infections and urinary tract infections did not occur in adolescents on ritlecitinib.

No adolescent in the combined 50 mg group had an SAE; there were two adolescents in the 10 mg group who had an SAE (suicidal behaviour, eczema).

There were no reports of serious infections, HZ, TB, NMSC, BCC, SCC, MACE, thromboembolic events, or ATE in adolescents. There were no events adjudicated as neurologic or audiologic event of interest in adolescents. Also, tinnitus, par-/dys-/hypoaesthesia, did not occur in adolescents on ritlecitinib.

In the **one-year exposure pool** of the pivotal AA trial, the proportions of participants with at least 1 TEAE increased with dose, in adults as well as in adolescents. The proportion of adolescents with at least 1 TEAE in the 50 mg group was 82% (84% in adults), SAEs did not occur on 50 mg (2.7%% in adults), there were 2.6% (3.1% in adults) adolescents who permanently discontinued study drug due to an AE, and 13.2% of adolescents temporary discontinued (14.3% in adults) due to an AE.

Compared to the placebo-controlled period, there was one additional adolescent with a SAE, of appendicitis in the 30 mg group.

In adolescents, there were no reports of adjudicated HZ, TB, OI, NMSC, BCC, SCC, MACE, thromboembolic events or ATE. There were no adjudicated audiologic events of interest in adolescents, and no events of tinnitus, par-/dys-/hypoaesthesia.

In the **All exposure pool**, there were 172 adolescents included. The proportion of adolescents in the 50 mg group with at least 1 TEAE was 76% (76% in 18 < 50 years old), there were 2.3% with an SAE (4.7% in 18<50 yrs), while 4.1% and 15.7% permanently or temporary discontinued ritlecitinib due to AEs (4.6% and 18% in 18 < 50 yrs). The IR/100 PY (95% CI) of SAEs in the 50 mg group was 1.73 (0.54 – 4.23) in adolescents and 2.86 (2.11 – 3.80) in adults. In the adolescents on 50 mg and as compared with adults, TEAEs frequently experienced in adolescents (⩾5% and >5% higher than adults) included nausea (adolescents 8.1%, adults 3.1%) and acne (adolescents 17.4%, adults 7.0%).

There were no reports of HZ, HS, or adjudicated events of OI, TB, MACE, malignancy, ATE, or audiologic events of interest in adolescents. In the 50 mg group, 2 (1.2%) with an IR (95%CI) of 0.81 (0.13 – 2.79) adolescents had at least one serious infection (appendicitis, COVID 19 pneumonia, septic shock), compared with 10 (0.7%) with an IR (95%CI) of 0.64 (0.32 – 1.16) in adults.

In the 50 mg group, in adolescents, there was 1 case of unilateral deafness (2 cases or 0.1% in adults), 1 case of hypoacusis (10 cases or 0.7%) in adults), 1 case of tinnitus (34 cases or 2.5% in adults), and 1 adjudicated event of Paresthesia and dysesthesia (21 cases or 1.6% in adults).

In the ritlecitinib clinical trials which enrolled adolescents (015 and 032), the **height** SDS (SD standardised to the US population by age and gender) was calculated at each time point where height and weight measurement was available. As such, the findings were normalised across age and gender. At Month 6 and Month 12, the Height SDS changes in All 50 mg ranged from -1.1 to 2.2 with mean and median SDS close to 0, suggesting no meaningful change in the participants' growth curves (Table 36).

Table 36: Standardised deviation score (SDS) for height and change from baseline for adolescents in studies 015 and 032

		Height SDS		Weight SDS	
		Ritlecitinib 50 mg (N=172)	Any Ritlecitinib (N=181)	Ritlecitinib 50 mg (N=172)	Any Ritlecitinib (N=181)
Analysis Visit	Summary Statistic				
Day 180 (+/- 30 days)[a]	n	152	167	153	168
	Mean (SD)	0.1 (0.34)	0.0 (0.56)	0.0 (0.39)	0.0 (0.39)
	Median (Q1, Q3)	0.0 (-0.1, 0.2)	0.0 (-0.1, 0.2)	0.0 (-0.1, 0.2)	0.0 (-0.1, 0.2)
	Range (Min, Max)	(-1.1, 2.0)	(-5.8, 2.0)	(-3.5, 1.3)	(-3.5, 1.3)
Day 360 (+/- 30 days)[a]	n	130	147	130	146
	Mean (SD)	0.0 (0.38)	0.0 (0.37)	0.0 (0.55)	0.0 (0.54)
	Median (Q1, Q3)	0.0 (-0.1, 0.2)	0.0 (-0.1, 0.2)	0.0 (-0.2, 0.3)	0.1 (-0.2, 0.3)
	Range (Min, Max)	(-1.0, 2.2)	(-1.0, 2.2)	(-4.0, 1.7)	(-4.0, 1.7)
Day 540 (+/- 30 days)[a]	n	96	114	102	119
	Mean (SD)	0.0 (0.41)	0.0 (0.38)	0.0 (0.66)	0.0 (0.61)
	Median (Q1, Q3)	0.0 (-0.2, 0.2)	0.0 (-0.2, 0.2)	0.1 (-0.2, 0.3)	0.1 (-0.2, 0.3)
	Range (Min, Max)	(-0.9, 2.1)	(-0.9, 2.1)	(-3.9, 1.7)	(-3.9, 1.4)
Day 720 (+/- 30 days)[a]	n	45	61	48	63
	Mean (SD)	-0.1 (0.58)	0.0 (0.52)	0.0 (0.74)	0.0 (0.70)
	Median (Q1, Q3)	-0.1 (-0.2, 0.1)	-0.1 (-0.2, 0.2)	0.1 (-0.3, 0.4)	0.1 (-0.3, 0.4)
	Range (Min, Max)	(-2.2, 2.0)	(-2.2, 2.0)	(-3.3, 1.6)	(-3.3, 1.6)
Day 900 (+/- 30 days)[a]	n	10	19	10	20
	Mean (SD)	0.0 (0.39)	-0.1 (0.50)	-0.1 (0.61)	0.0 (0.74)
	Median (Q1, Q3)	-0.2 (-0.3, 0.1)	-0.2 (-0.3, 0.1)	0.0 (-0.6, 0.4)	0.1 (-0.5, 0.4)
	Range (Min, Max)	(-0.6, 0.7)	(-0.6, 1.5)	(-1.4, 0.6)	(-1.4, 2.4)

All-Exposure Pool includes all participants who received ritlecitinib in B7931005, B7981015, B7981032, B7981019 and B7981037 from the start of their first dose of ritlecitinib.
Any Ritlecitinib: participants taking any dose of Ritlecitinib; Ritlecitinib 50 mg: participants from Ritlecitinib 200/50 mg, 100/50 mg and 50/50 mg QD combined.
SDS: Standardized to the US population by age and gender.
[a] Relative to first dosing date.
Study B7981032 data cutoff date: 30MAY2022.

Similarly, the summary of **weight** SDS did not identify any meaningful change in weight. Weight SDS changes at Month 6 and Month 12 ranged from -4.0 to 1.7, with median of 0 at Month 6 and Month 12. In AEP, 2 (1.2%) adolescents in All 50 mg had an AE of weight increased.

AEs associated with **fractures** were identified using a CMQ. There were 4 (2.2%) adolescents with a fracture in the All-Exposure Pool on Any Ritlecitinib treatment. The IR/100 PY (95% CI) for fracture was 1.35 (0.43 – 3.33) which is within the range for the general adolescent population (1.33/100 PY). The cases were: a hand fracture (metacarpal fracture) attributed to an accident; a tibia fracture (minimally left tibial plateau fracture) attributed to an injury playing basketball; a clavicle fracture (right collar bone) related to injury and a radius fracture (right closed fracture, distal radius, intra-articular) being related to injury while playing basketball; a hand fracture (fractured right pinky finger) attributed to a weightlifting injury.

In the All-exposure pool, there were no events related to **growth disturbance** (PTs of growth disorder, growth failure, growth retardation, body height below normal, body height abnormal, body height decreased).

Tanner staging documents the development of secondary sexual characteristics in children and adolescents. The changes from baseline in Tanner stage assessments at Month 12 and Month 24 by age for participants <18 years old in study 032 indicated a progression of puberty among adolescents from Baseline to Month 12. There are too few participants at Month 24 to make any meaningful observations.

Pregnancy and lactation

The applicant claimed that there was no risk for genotoxicity at ritlecitinib doses relevant to human exposure in non-clinical studies; mainly based on the safety margins related to the unbound AUC at the chronic human dose of 50 mg (also see non-clinical AR).

Based on the non-clinical data, women of childbearing potential were required to use effective contraception in the clinical programme. While there are no substantial data on the use of ritlecitinib in pregnancy, as of 28 February 2022, there have been 21 cases of exposure during pregnancy reported in participants exposed to ritlecitinib: 12 maternal exposures and 9 partner exposures. Among the maternal cases in ritlecitinib treated participants, there was a live birth in 1 participant, spontaneous abortion in 4 participants, elective abortion in 6 participants, and 1 participant with unknown outcomes. Outcomes of the partner exposures were live births in 5 participants, elective abortion in 1 participant, and 3 participants with unknown outcomes.

There are no data on the presence of ritlecitinib in human milk, the effects on the breast-fed infant, or effects on milk production. According to the applicant, a risk to newborns/infants cannot be excluded and ritlecitinib should not be used during breast-feeding.

In the non-clinical studies, the applicant claims that ritlecitinib had no effects on female rat fertility at exposures up to 55× the unbound AUC at the chronic human dose of 50 mg.

According to the applicant, women of reproductive potential should be advised to use effective contraception during treatment with ritlecitinib and for at least 1 month after the last dose. It is also recommended to consider pregnancy planning and prevention for females of reproductive potential.

2.6.8.7. Safety related to drug-drug interactions and other interactions

The applicant considers that there is no clinically relevant potential for other medicines to affect the PK of ritlecitinib; and that there is a reason for caution as ritlecitinib has some potential to affect the PK of CYP3A4 inhibitors, CYP1A2 substrates, OCT1 substrates where small concentration changes may lead to serious adverse events. This information has been reflected in the product information.

2.6.8.8. Discontinuation due to adverse events

Permanent discontinuation

In the **placebo-controlled AA pool**, the proportions of patients who permanently discontinued treatment with the study medication due to AEs were roughly similar across treatment groups. In the combined 50 mg group, 2.3% of patients had discontinued; in the placebo group, this was similar with 2.3%; the highest proportions occurred in the 200/50 mg (2.8%) and 10 mg (3.2%) groups. Urticaria was the commonest reason for permanent discontinuation.

In the **one-year follow-up pool**, the proportions of patients who permanently discontinued treatment were similar across dose groups (50 mg, 30 mg, 10 mg).

In the **all-exposure pool**, pregnancy, urticaria and rash, and deviations in laboratory values (CPK increased, ALC decreased, ALAT increased, AST increased) were common reasons for permanent discontinuation, but there also were serious AEs such as breast cancer and acute respiratory failure and pneumonia.

Temporary discontinuation

In the **placebo-controlled AA pool**, the proportions of patients who temporary discontinued treatment with the study medication due to AEs was highest in the patients treated with 50 mg (9.3%) and lowest in the placebo group (3.8%). The commonest AEs were diarrhoea, vomiting, gastroenteritis, headache and urticaria; but were also Covid-19 related.

In the **one-year follow up pool**, the proportions of patients who permanently discontinued treatment were highest in the 50 mg group and lowest in the 10 mg group.

In the **all-exposure pool**, the commonest reasons for temporary discontinuation were: SARS-CoV-2 test positive, headache, pyrexia, cough, urticaria, vomiting and nausea, blood CPK increased, but also infections like latent tuberculosis and upper respiratory tract infections or herpes zoster.

2.6.8.9. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

Litfulo (ritlecitinib) is an orally bioavailable small molecule that inhibits JAK3 and the TEC kinase family (BTK, BMX, ITK, TXK and TEC) by irreversibly binding to the conserved cysteine in the ATP binding site. The applicant claims that ritlecitinib showed high selectivity over the other three JAK isoforms, JAK1, JAK2, and TYK2, by more than 300-fold, and over the broader human kinome.

Class effects

In the recently concluded Article 20 referral on JAKis authorised in the treatment of chronic inflammatory disorders (EC decision issued on 10 March 2023), several serious AEs were considered as class effects of oral JAK inhibitors: MACE, VTE, malignancies and NMSC, serious infections, and overall mortality. It is not known in how far those class effects considered for approved JAKis apply to ritlecitinib, despite its selectivity for JAK3, the clinical PD effects and available clinical safety data. Long-term follow-up is currently limited, and thus class effects cannot be fully discarded. The inclusion of serious and opportunistic infections and malignancies in the warnings in the RMP is agreed upon, based on the inhibiting effect of ritlecitinib on the immune system. The exact mechanism by which JAK inhibition would lead to thromboembolic events is not known, although JAK2 has haematologic downstream effects (e.g. Liu et al. 2012; Zarrin et al. 2021). Therefore, the inclusion of thromboembolic events as a warning in the SmPC and in the RMP is also endorsed due to the uncertainty stemming from effects found for other JAKis and the lack of long-term clinical safety data. Moreover, MACE was added in the context of thromboembolic adverse events, in line with the RMP's of other JAK-inhibitors. Those adverse events are further discussed below under AESIs subsection.

Design

Two repeated chronic toxicity studies in dogs noted a species-specific finding of axonal dystrophy (swelling). In CHMP Scientific Advice, it was recommended to consider these events in the pivotal clinical study. The applicant performed audiological testing in pivotal study 015, long-term study 032, and the dedicated safety study 037; nerve fibre measurements were performed in study 037. Potential neurologic and audiologic events of interest in both studies were adjudicated by a blinded external adjudication committee.

The design of the additional safety study on PD safety outcomes (BAEP and axonal dystrophy and swelling) is agreed. The sample size is, albeit small, large enough for PD outcomes, and it used a relevant dose (200/50 mg) and an adult population similar to the target population, although without pre-existing hearing loss or nerve disorders. This is agreed not to confound the study.

The pooling of the studies to safety data pools is agreed upon, as it increases sample sizes and is based on the similarity of dose regimens, indications/underlying disorders, and data collection.

Exposure

The exposure in the phase 2/3 studies, exceeds the normal expectations of 100 participants (for both adolescents and adults) exposed for > 1 year and aligns with a number of 1000-1500 participants to be exposed (ICH Guideline E1). It is endorsed that the data of patients treated with 200/50 mg and with the proposed posology of 50/50 mg are generally pooled. However, the data set is considered too limited for infrequent serious AEs considered class effects of JAK inhibitors (MACE, VTE, malignancies, serious infections). Accordingly, these were included as important potential risks in the Safety Specification of the RMP. In addition, the database may be insufficient for the follow-up of probable long-term unfavourable effects on the (central) nervous system (see non-clinical discussion) and a warning on neurotoxicity was added.

Generalisation to clinical practice

The main exclusion criteria considered the type of AA and inadequate wash-out of therapies, and the discontinuation criteria were in line with the safety profile for JAKis in general. Therefore, it is considered that these criteria were not overly selective, which is supportive for generalisation to clinical practice.

Ritlecitinib should be avoided in patients with an active, serious infection, and it should not be given to patients with active TB, as already indicated in the warnings. Opportunistic infections are an important potential risk based on the mechanism of action of ritlecitinib. Therefore, active tuberculosis and active serious infections were included as contra-indications in the section 4.3 of the SmPC.

Patients with evidence of HIV infection or hepatitis B or C infection were excluded from studies with ritlecitinib. Screening for viral hepatitis was already recommended in the warnings. The warning also included that monitoring for reactivation of viral hepatitis is recommended.

Pregnancy and lactation were included in the SmPC as contra-indications. This is further discussed below, under Safety in special populations.

Discontinuations

The proportions of patients who permanently discontinued due to AEs during the placebo-controlled phase were similar for the treatment groups and placebo; urticaria was a relatively common reason for permanent discontinuation. Pregnancy, urticaria and rash, and deviations in laboratory values (CPK increased, ALC decreased, ALAT increased, AST increased) were common reasons for permanent discontinuation in the all-exposure pool. However, there were also serious AEs such as breast cancer, acute respiratory failure and pneumonia. The proportion of patients who temporarily discontinued due to AEs during the placebo-controlled phase was highest for patients treated with 50 mg. In the all-exposure pool, the commonest reason for temporary discontinuation was 'SARS-CoV-2 test positive', otherwise the reasons for temporary discontinuations were a mixture of AEs with impactful symptoms (including pain and urticaria, vomiting and nausea, diarrhoea), deviations in laboratory values (blood CPK increased, aspartate increased, ALC decreased), and infections (including latent TB, upper respiratory tract infections, herpes zoster).

Stopping rules in case of deviation of laboratory values and infection are appropriately reflected in the posology and the warnings sections of the SmPC.

Adverse events

The applicant initially proposed to include 'herpes zoster', 'dizziness', 'diarrhoea', 'acne', 'urticaria', 'rash', 'blood CPK increased', 'platelet count decreased', and 'lymphocyte count decreased', as ADR in section 4.8 of the SmPC. Based on the differences in the placebo-controlled AA pool between the 50/50 mg and the combined 50 mg (200/50 mg and 50/50 mg) groups with the placebo group, the inclusion of those ADRs is agreed.

Based on the PCPAA and the OYEP data and supported by the modelled dose-response relationship, 'upper respiratory tract infections' were considered as ADRs for inclusion in section 4.8 of the SmPC. 'Folliculitis' had been included as an ADR as well and this is agreed upon. Infections were more frequent in the 50 mg group compared to placebo, and the occurrence of overall infection appeared to be dose-related in the placebo-controlled and one-year follow-up data. In the PCPAA pool, infections and infestations (SOC) occurred in 38% of patients in the combined 50 mg group, 37% in the 30 mg group, 32% in the 10 mg group and 31% of the placebo group; this proportion was higher in the 200/50 mg group (41%) as compared to the 50/50 mg group (33%). In the OYEP data, infections and infestations (SOC) were more frequent in the 50 mg group (51%), as compared to the 30 mg (47%) and the 10 mg (40%) groups. In the PCPAA pool, several infections at the PT level were more frequent in the combined 50 mg dose group as compared to placebo: folliculitis (4.6% *versus* 1.9%), gastroenteritis (1.4% *versus* 0), nasopharyngitis (9.9% *versus* 7.0%) and upper respiratory tract infections (8.4% *versus* 7.5%). These infections did not show a clear dose-response relationship in the PCPAA data. However, in the OYEP data (50 mg *versus* 30 mg *versus* 10 mg), folliculitis (7.3% *versus* 6.1% *versus* 6.5%), nasopharyngitis (14.2% *versus* 16.1% *versus* 9.7%) and upper respiratory tract infections (11.1% *versus* 10.7% *versus* 3.2%) were more frequent in the higher dose groups; such a dose-response relation was not apparent for gastroenteritis (1.5% *versus* 1.9% *versus* 3.2%). In the OYEP data, urinary tract infections were more frequent in the highest dose groups (4.6% and 3.1% versus 0). According to the dose-response analysis performed by the applicant, there was a small but statistically significant dose-response effect. Over the range of relevant doses, an approximately 10-fold increase in ritlecitinib exposure, with a geometric mean Cav of 27 ng/mL for 30 mg QD as compared to 257 ng/mL for 200 mg QD, was predicted to lead to a 3-fold increase in the mean incidence of infections per 100 patient-years (11.0 versus 33.2, respectively). Although SARS-CoV-2 test positive was more frequent in the 50 mg group, Covid-19 was not, and the frequencies were low. Also, considering the nature of the pandemic, it is considered that these events are quite appropriately covered within the discussion of infections in general.

Pyrexia was more frequent in the combined 50 mg group (2.3%) as compared to placebo (0); the occurrence was highest in the 50/50 mg group (3.1%), but pyrexia also occurred in the 200/50 mg (1.9%), 30 mg (1.1%) and 10 mg (1.6%) groups. Also, in the OYEP data, pyrexia was more frequent in the highest dose group. It, however, appeared that pyrexia was not an event 'on its own' but was explained by underlying causes, notably infection. Therefore. it is not included as an ADR.

Headache, upper abdominal pain, and back pain were numerically more common in the 50 mg dose groups than in the placebo group. Based on the relatively small difference in occurrence between the combined 50 mg group and placebo, and the lack of a dose-response relationship in the placebo-controlled and one-year follow-up data, it is concluded that headache, upper abdominal pain, and back pain are not considered as ADR.

Serious adverse events and deaths

SAEs and deaths were infrequent in the AA studies, though it must also be considered that the study population was young: 85% of the patients were <50 years of age and the mean (SD) age was 34 (14) years.

In the 200/50 mg group, there were 5 SAEs, while there were none in the 50 mg group. This supports the choice of 50 mg as the recommended dose instead of 200/50 mg, also given the nature of the SAEs that were infectious (n=3) or malignant (n=1). Most SAEs were infections or infestations, followed by neoplasms in the 50 mg All Exposure pool. In the All-Exposure Pool, there were 2 deaths, and one death in the clinical study programme for Ulcerative Colitis. The deaths were due to breast cancer, acute respiratory failure/cardio-respiratory arrest, and severe myocardial infarction. The period of exposure was relatively short for two of the deaths, making an important causal role for ritlecitinib unlikely.

The occurrence of infections and malignancies are in line with the mode of action of ritlecitinib. When combining all exposures to 50 mg ritlecitinib in the All 50 mg group, the 'Infections and Infestations' SOC included the highest proportion (n=12, 0.8%) of participants with SAEs, followed by 'Neoplasms' (n=9, 0.6%); there were 2 cases of 'Cardiac disorders' (acute myocardial infarction and cardio-respiratory arrest), and 1 case of pulmonary embolism.

Adverse events of special interest (AESI)

Following the non-clinical finding in dogs of **axonal dystrophy**, the applicant has implemented regular audiometry assessments in the phase2/3 studies in AA, had eligible audiological AEs and nervous system AEs adjudicated by an independent committee of experts in neurology and audiometry, and performed a placebo-controlled PD safety study (037) with audiological (BAEPs) and nervous system (IENF density and axonal swelling in skin punch biopsies) outcomes. The measures taken in the clinical study programme to detect nervous system and audiological adverse events are acknowledged.

The non-clinical finding in dogs of axonal dystrophy was found in the peripheral nervous system and at exposures ≥14 x the proposed human dose of 50 mg, and functional effects on hearing, tested using BAEP, were found at exposures ≥33 x the proposed human dose (see non-clinical discussion). From a clinical perspective, it is considered that the safety margins for axonal dystrophy are relatively low (7x to 14x), although the safety margin for apparently reversible, adverse hearing effects is much larger (33x).

The PD safety outcomes of study 037 did not show differences between the ritlecitinib 200/50 mg (n=36) group and the placebo group (n=35) over 9 months. This is reassuring in the short term. The occurrence of (adjudicated) usually mild, dys-/hyper-/hypo-/paraesthesia's was infrequent in the placebo-controlled data of the combined AA and vitiligo data, and this frequency was only slightly (~1%) higher in the ritlecitinib 50 mg group as compared to placebo. There were few participants with adjudicated neurosensory deafness, unilateral deafness, hypoacusis, or tinnitus, in the PCPAAV data set, with no difference between treatment groups. Overall, most neurological and audiological events, whether adjudicated or before adjudication was applied, that occurred when being treated with ritlecitinib 50 mg were considered treatment-related, and resolved while on treatment. However, based on the identified axonal dystrophies in the two dog toxicity studies 20070068 and 20099163, a potential risk for patients receiving a chronic ritlecitinib dosing regimen cannot be fully rejected. This stems from a.) the unambiguity of the findings in chronic dog toxicity studies, b.) the lack of understanding of its pathogenesis, c.) the reactivity of ritlecitinib to covalently and irreversibly react with off-target proteins (including the nervous system), d.) the suspected accumulative aetiology of the axonal dystrophies as suggested in study 20099163, and

e.) from the fact that no such effects were found in non-clinical studies of similar covalent inhibitor products.

While the applicant's position that the reversibility of the axonal dystrophies in the two dog toxicity studies 20070068 and 20099163 is reassuring is supported, a risk to patients on a chronic dosing regimen cannot be fully excluded. Consequently, the applicant agreed to include a warning in SmPC section 4.4 and to follow-up on this safety concern post approval (see RMP). In addition, the applicant will closely monitor neurological and audiological events in future PSURs.

The applicant has performed two retrospective observational studies in patients with AA, in Denmark and the US, to acquire background rates of AESI, such as serious infections, thrombotic events, and malignancy Limitations, however, are that the Danish cohort was hospital-based (inpatient and outpatient) and the US cohort claims based, which makes it more likely that especially severe cases are collected. To some extent, this matches the proposed indication for ritlecitinib, being severe AA (SALT>50%), while SALT or extent of hair loss was not available in the observational data. For serious adverse events such as death and malignancy or myocardial infarction, a lower degree of ascertainment bias can be assumed than that for events like hearing loss. It is doubted whether the estimates of the occurrence of hearing loss in the observational data is unbiased and can be meaningfully compared to the trials where auditory assessment had been performed. Although the bias will be conservative (to the disadvantage of ritlecitinib), the meaning of a between-group difference remains unclear.

MACE was infrequent in the clinical data; three cases of MACE occurred after one year of exposure in 3 patients: acute myocardial infarction, retinal artery occlusion, and sudden cardiac death. In addition, there was 1 event of a fatal myocardial infarction in an UC study. The IR/100 PY (95% CI) of MACE in the All-exposure 50 mg group of 0.15 (0.03 – 0.43) was lower than reported in the TS AA subcohorts in US study B7981051 with 1.2 (0.99 – 1.45) and the Danish study B7981049 with 0.58 (0.44 – 0.74). All three cases of MACE in the AA study also had other risk factors for MACE. There was a single event of **VTE** (PE) in the data of the All-exposure cohort on 50 mg (N=1521). Although the patient had multiple risk factors for PE, the event was considered related by the sponsor.

According to the non-clinical data (see non-clinical discussion), there were no definite findings of MACE and VTE. According to the laboratory data, ritlecitinib is associated with decreased platelet counts and a small increase in blood lipids. However, the average changes were small and only in a few cases led to clinically meaningful changes, and do not seem to be relevant in causing MACE or VTE.

Therefore, a causal relation between ritlecitinib and MACE cannot be concluded based on the currently available non-clinical and clinical data. It, however, has to be considered that the clinical studies were relatively short and that the AA and vitiligo study populations are relatively young without strong accumulation of other risk factors for MACE, as compared to, e.g. the average population with other auto-immune diseases, such as rheumatoid arthritis. Given the consideration of MACE as a class effect of oral JAK inhibitors authorised for the treatment of chronic inflammatory disorders, risks for MACE and VTE cannot be totally discarded. Therefore, MACE and thromboembolic events, including MI and VTE, were considered an important potential risk in the RMP and will be followed up post-approval (see RMP). In addition, appropriate warnings on MACE and VTE were included in the section 4.4 of the SmPC, in line with those included for Sotyktu.

The occurrence of **serious infections** in the ritlecitinib group treated with 50 mg can be appreciated as low, while it must be recognised that the AA study population is relatively young and presumably overall healthy. The occurrence of serious infections in the AA trials was lower than seen in the US and Danish AA cohorts used as reference. However, based on the

immunosuppressive mechanism of action of ritlecitinib and based on the occurrence of serious infection that especially occurred in the higher doses of 50 mg and 30 mg, a causal relation of ritlecitinib and infections, potentially including serious infections, cannot be excluded. The applicant considered serious infections and opportunistic infections as 'important potential risk' in the RMP, and this is agreed. Active serious infections, including tuberculosis are considered as contra-indications, in line with the warnings.

The occurrence of **malignancies, including NMSC**, in the ritlecitinib group treated with 50 mg can be appreciated as low, while it must be recognised that the AA study population is relatively young and presumably overall healthy, and follow-up is relatively short. In the placebo-controlled AA trial, two cases of breast cancer occurred within the first year of exposure; both patients used the 50 mg dose. In the all-exposure pool, there were 7 participants with adjudicated malignancies (excluding NMSC): lobular breast carcinoma (n=1), breast cancer (n=3), testis cancer (n=1) and papillary thyroid cancer (n=1). One additional adjudicated event of malignant melanoma was reported after the 35-day reporting period.

The occurrence of malignancies in the AA trials was lower than seen in the US and Danish AA cohorts used as reference. However, based on the immunosuppressive mechanism of action of ritlecitinib and based on the occurrence of malignancies that especially occurred in the higher doses of 50 mg, a causal relation between ritlecitinib and malignancies cannot be excluded. In addition, malignancies are considered a class effect of oral JAKis (Art. 20 referral), this is also in line with other immunomodulating treatments. Occurrences of malignancies in the non-clinical data align with the mode-of-action of ritlecitinib, although it generally occurred at supratherapeutic exposures (see non-clinical discussion). NMSC is included as an important potential risk in the RMP and will be followed-up post-approval (see RMP). In addition, appropriate warning on malignancies was included in the section 4.4 of the SmPC.

Regarding **laboratory values**, the applicant proposed that 'platelet count decreased', 'lymphocyte decreased' and 'blood creatine phosphokinase increased' as ADRs. This is agreed upon based on the available data of the placebo-controlled pool and the one-year follow-up data. Blood lipids showed a net increase over time in TC and LDL-C that was numerically higher than placebo, but overall, there was no clear dose-response relationship, and the changes are small. Therefore, it can be accepted that blood lipid changes are not considered as ADR. Cases with increases in liver enzymes over the ULN were relatively infrequent but were more frequent on ritlecitinib than placebo, and in the follow-up data, cases with hepatic AEs clustered in the higher (50 mg) dose group. Therefore, liver enzymes elevated were considered as ADR and were thus included in section 4.8 of the SmPC.

Safety in special populations

Adolescents

Data on adolescents had not been collected in the EU as agreed as part of the CHMP Scientific Advice received. Therefore, the applicant included an extrapolation report comparing EU adults with ex-EU adults and ex-EU adolescents. Data on growth (height, weight), AEs (fractures), and development (Tanner scale, neuropsychological development) of adolescents were included in the dossier. The non-clinical data in juvenile animals were completed during the procedure. According to the non-clinical data, in short- and long-duration toxicity studies in non-pregnant animals (dogs and rats) of comparable age to adolescents, there were no bone findings (macroscopically or microscopically) observed following administration of reflectional during a developmental period in which rats have open growth plates and growing long bones (also see non-clinical section). Nevertheless, as clinical follow-up data are still limited, growth and bone safety in adolescents will be followed-up post-approval (see RMP).

There were ~130 **adolescents** exposed to ritlecitinib 50 mg for at least one year in studies 015 and 032. In the placebo-controlled data of study 015, the overall safety profile of ritlecitinib was similar for adolescents and adults. In the combined 50 mg group (n=38), the proportion of adolescents with at least 1 TEAE was 79% (71% in adults), SAEs did not occur on 50 mg (1.3% in adults), there were 2.6% (2.3% in adults) adolescents who permanently discontinued study drug due to an AE, and 7.9% of adolescents temporary discontinued (9.4% in adults) due to an AE. Acne and nasopharyngitis occurred more frequently in adolescents on ritlecitinib as compared to adolescents on placebo and adults. However, this is not valued as a safety concern, and can partly be understood from the propensity for these events in the age group. On the short- (24 weeks) as well as longer (48 weeks) term, there were no reports of HZ, TB, NMSC, BCC, SCC, MACE, thromboembolic events, or ATE in adolescents, and 1 serious infection (appendicitis on 30 mg). Although the latency time for these kinds of events is usually long, in adolescents and adults, this is reassuring. A priori, these events are unlikely in adolescents.

No events were adjudicated as neurologic or audiologic events of interest in adolescents. From the measurements of height, weight and Tanner staging, there appeared to be no abnormalities. This is supported by the non-clinical data in juvenile rats, in which no relevant adverse events were found, including no signs of adverse bone homeostasis or bone growth (see non-clinical discussion).

As long-term data are still limited, 'long-term safety in adolescent patients including growth and bone development, and maturation and pubertal development' will be followed up post approval (see RMP section).

Pregnancy

There have been 21 cases of exposure during **pregnancy** reported in participants exposed to ritlecitinib: 12 maternal exposures and 9 partner exposures. The spontaneous abortion rate in ritlecitinib for all doses-treated patients was 30% (3/10), and in ritlecitinib 50 mg-treated patients was around 37% (3/8). Given that use of ritlecitinib 50 mg in the clinical programme (maternal and partner exposure) was very limited and that other JAKis authorised in the treatment of chronic inflammatory disorders are also contraindicated for use during pregnancy, and also for non-clinical reasons, pregnancy and lactation were included in the SmPC as contra-indications. In addition, the applicant also provided a recommendation for a sufficiently long ritlecitinib-free period prior to pregnancy initiation. Specifically, the applicant proposes that women of childbearing potential be advised to use effective means of contraception during treatment up to at least 1 month following the final dose of ritlecitinib. Note that this recommendation was also included in the SmPC in section 4.6, this is agreed. Embryofoetal toxicity following exposure in utero will be followed-up post approval (see RMP).

Elderly

Data on the elderly were scarce, which is in line with the target population encountered in clinical practice. It, however, limits the interpretation of safety data in the elderly. In the recently concluded Art. 20 referral, it appeared that for other oral JAKis, risks for MACE, VTE, malignancy, and serious infections were increased in the elderly (>65 years of age). Therefore, the lack of safety data on the elderly was reflected in a warning in section 4.4. of the SmPC. In addition, healthcare professionals were informed about the higher incidence of infections in elderly and in the diabetic population in general and thus caution should be exercised when treating the elderly and patients with diabetes, and that particular attention should be paid with respect to occurrence of infections.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The safety profile of ritlecitinib is overall acceptable. The applicant preferred the 50/50 mg regimen over the 200/50 mg regimen, which is accepted, as there were several SAEs, including infections and malignancy, in the highest dose regimen, which were absent in the 50 mg dose group. Regarding the common AEs, the safety profile of ritlecitinib 50 mg is considered manageable.

SAEs considered class effects of oral JAKis did occur in patients exposed to ritlecitinib in the proposed dose of 50 mg QD (MACE, VTE, malignancy, serious infections), albeit at a low frequency, however causality cannot be concluded. Given the limited availability of long-term safety data and in view of the recently concluded Article 20 referral on JAK inhibitors, the risk of malignancies, NMSC, MACE and other cardiovascular AEs cannot be fully discarded. MACE, thromboembolic events (which include MI and VTE), and malignancies including NMSC will be followed-up post-approval (see RMP). Appropriate warnings were included in the section 4.4. of the SmPC.

While the reversibility of the axonal dystrophies seen in the two dog toxicity studies 20070068 and 20099163 is reassuring, a risk to patients on a chronic dosing regimen cannot be fully excluded. Consequently, a warning was included in SmPC section 4.4 and this safety issue will be followed-up post approval (see RMP).

Pregnancy and lactation were included as contra-indication in SmPC section 4.3. Women of childbearing potential have to use effective contraception during treatment and for 1 month following the final dose of Litfulo.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	Herpes zoster
Important potential risks	Serious and Opportunistic infections
	Malignancy
	Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis
	Embyrofoetal toxicity following exposure in utero
	MACE
	Neurotoxicity
Missing information	Long-Term Safety
	Long-Term safety in adolescent patients including growth and bone development, and maturation and pubertal development

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 (by the competent authority)				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates

An Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Patients with Alopecia Areata in Europe (Secondary Databases)
 	
Planned
	The primary objective is to estimate the incidence rates (IRs) of safety events of interest among patients with alopecia areata (AA) receiving ritlecitinib and patients with AA receiving other approved systemic treatments for AA in a real-world setting. The following are the primary safety events of interest:
	• Thromboembolic events (including deep vein thrombosis [DVT], pulmonary embolism [PE], and arterial thrombosis [AT]);
	• Herpes zoster;
	• Serious infections;
	• Opportunistic infections;
	• Malignancy;
	  ○ Malignancy excluding nonmelanoma skin cancer (NMSC); and
	  ○ NMSC.
	• Major adverse cardiovascular events (MACE);
	• Neurological events of interest;
	• Bone fractures; and
	• Growth metrics in adolescents (e.g., height and weight; Denmark only).
		The following are the safety concerns addressed:
		• Thromboembolic events (including DVT, PE, AT);
		• Herpes zoster;
		• Serious and opportunistic infections;
		• Malignancy;
		• Long-term safety;
		• MACE;
		• Neurotoxicity;
		• Long-term safety in adolescent patients including growth and bone development.
			Draft protocol submission	March 2024

			Interim report	September 2028 September 2030 September 2032 September 2034
			Final report	March 2036
A Prospective Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Adolescents with Alopecia Areata (Primary Data Collection) Planned	The primary objectives are to: ○ Describe growth and bone development metrics among adolescent patients treated with ritlecitinib and, separately, among adolescent patients with AA who are unexposed to ritlecitinib, including those exposed to other approved systemic treatments for AA; ○ Describe maturation and pubertal development metrics among adolescent patients treated with ritlecitinib and, separately, among adolescent patients with AA who are unexposed to ritlecitinib, including those exposed to other approved systemic treatments for AA; and	The following are the safety concerns addressed: • Neurotoxicity; • Long-Term safety in adolescent patients including growth and bone development, and maturation and pubertal development	Draft protocol submission	March 2024
			Interim report	September 2026 September 2028 September 2030 September 2032 September 2034
			Final report	March 2037

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	○ Estimate the incidence rate of neurological events of interest among adolescent patients treated with ritlecitinib and, separately, among adolescent patients with AA who are unexposed to ritlecitinib, including those exposed to other approved systemic treatments for AA. Exploratory objectives are to: ○ Compare growth and bone development metrics among adolescent patients treated with ritlecitinib with adolescent patients with AA who are unexposed to ritlecitinib, including those exposed to other approved systemic treatments for AA; ○ Compare maturation and pubertal development metrics among adolescent patients treated with ritlecitinib with adolescent patients with AA who are unexposed to ritlecitinib, including those exposed to other approved systemic treatments for AA; and ○ Compare the incidence rate of neurological events of interest among adolescent patients treated with ritlecitinib to the incidence rate among adolescent patients with AA who are unexposed to ritlecitinib, including those exposed to other approved systemic treatments for AA.			
A Drug Utilisation Study to Evaluate the Effectiveness of Risk Minimization Measures for Ritlecitinib in Europe Using Electronic Healthcare Data Planned	The study objectives are: 1) To evaluate, to the extent measurable in the available routinely collected data, indicators of healthcare professional's (HCPs) adherence to the risk minimization measures (RMMs) in accordance with the ritlecitinib Summary of Product Characteristics (SmPC), HCP guide and patient card, specifically: • Indicators of adherence to performing laboratory tests of lymphocyte count, platelet count, hepatitis B/C, and tuberculosis (TB) screening prior to	The following are the safety concerns addressed: • Herpes zoster; • Serious and opportunistic infections; • Malignancy; • Thromboembolic events (including DVT, PE, AT); and • Embryofoetal toxicity following exposure in utero.	Draft protocol submission Interim report Final report	March 2024 September 2028 March 2031

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	initiation of ritlecitinib treatment; • Indicators of adherence to performing laboratory tests of lymphocyte count and platelet count at week 4 (± 2 weeks) from initiation of ritlecitinib treatment; • Indicators of adherence to avoid live attenuated vaccines shortly prior to and during treatment with ritlecitinib; • Indicators of adherence to no use during pregnancy; • Indicators of adherence to no use in patients aged < 12 years; and • Indicators of adherence to no use during serious infections. 2) Describe the characteristics of patients prior to initiation of ritlecitinib treatment, in terms of: • Risk factors for thromboembolic thrombotic events (including deep vein thrombosis, pulmonary embolism, and arterial thrombosis); • Risk factors for malignancy; and • Risk factors for cardiovascular (CV) disease.			
A Phase 3 Open-Label Multi-Center Long-Term study investigating the Safety and Efficacy of ritlecitinib in Adult and Adolescent Participants with Alopecia Areata. On-going	The primary objective is: To evaluate the long-term safety and tolerability of ritlecitinib in adult and adolescent participants with AA. The secondary objectives are: To evaluate the long-term efficacy of ritlecitinib in adult and adolescent participants with AA. To evaluate the effect of ritlecitinib on patient-centered outcomes and payer relevant measures to assess treatment benefit from the patient perspective and to demonstrate value.	This study will collect safety data for • Serious infections, • Opportunistic infections, • Herpes zoster, • Malignancy, • Thromboembolic events (including DVT, PE, AT) • MACE • Neurotoxicity • Long-Term safety • Long-Term safety in adolescent patients including growth and bone development, and maturation and pubertal development	LSLV for PCD PCD CSR LSLV for the study	(28 days after the Month 36 visit) - July 2023 November 2024 July 2025 or until market availability of ritlecinib in all countries in which the study is being conducted, whichever occurs first.

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
Herpes zoster	**Routine risk minimisation measures:** SmPC section 4.4 Special Warnings and Precautions for use SmPC section 4.8 Undesirable Effects **Additional risk minimisation measures**. Healthcare Professional Guide Patient Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Active surveillance study in secondary databases Final study report: March 2036 Drug utilisation study Final study report: March 2031 B7981032 Long-term study
Important Potential risk		
Serious and Opportunistic infections	**Routine risk minimisation measures:** SmPC section 4.2 Posology and Method of Administration SmPC section 4.3 Contraindications SmPC section 4.4 Special Warnings and Precautions for use SmPC section 4.8 Undesirable Effects **Additional risk minimisation measures**. Healthcare Professional Guide Patient Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Active surveillance study in secondary databases Final study report: March 2036 Drug utilisation study Final study report: March 2031 B7981032 Long-term study
Malignancy	**Routine risk minimisation measures:** SmPC section 4.4 Special Warnings and Precautions for use **Additional risk minimisation measures.** Healthcare Professional Guide Patient Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Active surveillance study in secondary databases Final study report: March 2036 Drug utilisation study Final study report: March 2031 B7981032 Long-term study
Thromboembolic events including deep vein thrombiosis, pulmonary embolism and arterial thrombosis	**Routine risk minimisation measures:** SmPC section 4.4 Special Warnings and Precautions for use	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures. Healthcare Professional Guide Patient Card	**Additional pharmacovigilance activities:** Active surveillance study in secondary databases Final study report: March 2036 Drug utilisation study Final study report: March 2031 B7981032 Long-term 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** Healthcare Professional Guide Patient Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Drug utilisation study Final study report: March 2031
MACE	**Routine risk minimisation measures:** SmPC section 4.4 Special Warnings and Precautions for use **Additional risk minimisation measures** Healthcare Professional Guide Patient Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Active surveillance study in secondary databases Final study report: March 2036 B7981032 Long-term study
Neurotoxicity	**Routine risk minimisation measures:** SmPC section 4.4 Special Warnings and Precautions for use SmPC section 5.3 Pre-clinical Safety Data **Additional risk minimisation measures** Healthcare Professional Guide Patient Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Active surveillance study in secondary databases Final study report: March 2036 Active surveillance study in adolescents (primary data collection) Final study report: Mar 2037 B7981032 Long-term study
Missing Information		

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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:** Active surveillance study in secondary databases Final study report: March 2036 Active surveillance study in adolescents (primary data collection) Final study report: Mar 2037 B7981032 Long-term study
Long-Term safety in adolescent patients including growth and bone development, and maturation and pubertal development.	**Routine risk minimisation measures:** None **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Active surveillance study in secondary databases Final study report: March 2036 Active surveillance study in adolescents (primary data collection) Final study report: Mar 2037 B7981032 Long-term study

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.2 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 23.06.2023. 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, Litfulo (ritlecitinib) 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 proposed indication for ritlecitinib is 'for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older'.

Ritlecitinib is an oral covalent irreversible inhibitor of the 5 TEC family kinases (BMX, BTK, ITK, TEC, TXK) and JAK3. It lacks activity against JAK1 and JAK2, leading to a narrower spectrum of cytokine inhibition. JAK3 and TEC kinases regulate the response of CD8+ T, NK and mast cells thought to be involved in the pathophysiology of alopecia areata (AA).

Alopecia areata is a chronic immune-mediated disorder that targets hair follicles and causes nonscarring hair loss. Although AA most commonly affects the scalp presenting with discrete patches of alopecia, other hair-bearing areas, such as the eyebrows, eyelashes and body, can also be involved. In severe AA, patients may experience loss of all scalp hair (alopecia totalis - AT) or all hair (alopecia universalis - AU). AA prevalence is independent of a geographic region, and AA affects males and females equally. Both children and adults can be affected. Spontaneous hair regrowth is common, although most patients suffer more than one episode of the disease. Approximately 10% of patients with AA progress to AT or AU.

AA is a disease with a high psychological burden, and the aim of treatment is to reach durable hair regrowth in affected areas with an acceptable appearance from the patient's perspective.

3.1.2. Available therapies and unmet medical need

In May 2022, baricitinib (inhibitor of JAK 1 and 2) has been centrally approved in the EU for the treatment of severe AA in adults. No other products are centrally approved for the treatment of AA. However, some authorised medications (e.g., methylprednisolone and triamcinolone intra-lesion injections) are available in individual member states. Current guidelines advise on topical (corticosteroids and minoxidil) or systemic therapies (corticosteroids, corticosteroid-sparing agents such as cyclosporin and methotrexate, and biologicals such as ustekinumab) (European Dermatology Forum, S3 guideline 2017; British Association of Dermatologists (BAD): Guidelines for the management of alopecia areata, 2012). The response to treatment varies widely; few well-designed clinical trials have evaluated these therapies. Therefore, there still is an unmet medical need for patients with severe AA.

3.1.3. Main clinical studies

The clinical programme to support the efficacy of ritlecitinib in AA consists of 3 studies: one single pivotal study (B7981**015**), one supportive Phase 2a study (B7931**005**), and a long-term study (B7981**032**), all in participants with AA. In addition, the comparative safety study (B7981**037**) also included efficacy data. Only the main study i.e. pivotal study (B7981**015**) is discussed here.

The single pivotal phase 2b/3 study (B7981**015**) was a randomised, double-blind, placebo-controlled, parallel-group, multicentre study to compare the efficacy and safety of 5 regimens (200/50 mg QD, 50 mg QD, 200/30 mg QD, 30 mg QD, 10 mg QD) of ritlecitinib to placebo in adults and adolescents ≥12 years of age with AA and ≥50% of scalp hair loss. The doses of 30 mg

QD and 50 mg QD were both also studied with a loading dose of 200 mg QD for 4 weeks; the 10 mg dose was included for dose-ranging. The placebo-controlled phase lasted 24 weeks; the complete study lasted 48 weeks. The primary efficacy outcome was SALT≤10 at week 24, with PGI-C response (patient-reported change) as a secondary outcome. There were N=718 patients included, and of those n=130 were treated with 50 mg QD, 131 with 200/50 mg QD, and 131 with placebo.

3.2. Favourable effects

Placebo-controlled phase

The primary endpoint and the key secondary endpoint were both met. The response in SALT⩽10 (primary outcome) in the ritlecitinib 200/50 mg (21%), 200/30 mg (13%), 50 mg (13%) and 30 mg (11%) groups was larger than placebo (1.5%) at week 24, at a significance level of p< 0.005, corrected for multiplicity. The mean difference (95%CI) with placebo was 20% (12% - 28%) for the 200/50 mg group and 12% (5% - 18%) for the 50 mg group.

The response in PGI-C in the ritlecitinib 200/50 mg (52%), 200/30 mg (45%), 50 mg (49%) and 30 mg (42%) groups was larger than in placebo (9%) at week 24, at a significance level of p< 0.005 corrected for multiplicity. The mean difference (95%CI) with placebo was 43% (32% - 54%) for the 200/50 mg group and 40% (29% - 51%) for the 50 mg group.

Also, for SALT ⩽20 response at week 24, ritlecitinib 200/50 mg, 200/30 mg, 50 mg and 30 mg were significantly different from placebo, at a significance level of < 0.01. The mean difference (95%CI) with placebo was 28% (19% - 37%) for the 200/50 mg group and 21% (13% - 29%) for the 50 mg group.

Maintenance of effect

From week 24 to week 48, the proportion of participants with a response in SALT≤10, PGI-C response, or SALT⩽20 further increased (respectively 31%, 56%, and 43%). Those participants who, by design, switched from placebo to ritlecitinib after Week 24 showed an average response at week 48 (SALT≤10:14%; SALT≤20:19%), which was similar to that of participants at Week 24 treated with the same regimen from the start (SALT≤10:14%; SALT≤20:23%).

Supportive outcomes

These effects are supported by similar effects in the regrowth of eyebrows (EBA) and eyelashes (ELA), in patients who had hair loss at these sites and by the patient-reported impression of improvement (AAPPO), defined as achieving a score of 0 (‘no hair loss’) or 1 (‘little hair loss’) on each of the 4 AAPPO hair loss items.

Consistency over subgroups

According to the forest plots, treatment with ritlecitinib 50 mg resulted in a higher proportion of SALT⩽10 responders and of PGI-C responders than placebo in most subgroups, including adolescents.

There was a similar SALT⩽10 response (primary outcome) and PGI-C response (key secondary outcome) for ritlecitinib 50 mg as compared to placebo in ex-EU adolescents, ex-EU adults and EU adults.

3.3. Uncertainties and limitations about favourable effects

The dose-ranging design of the pivotal study is considered acceptable, although it yielded a low number of participants in each treatment group. The effects in the 50/50 mg group are to some extent supported by the effects in the 200/50 mg group and the dose-response relation seen over the treatment groups. The recommended dose of 50 mg once daily is thus supported.

The effect in the AT/AU group was smaller. Nevertheless, this clinical finding was adequately reflected in the SmPC section 5.1.

Although this application is based on a single pivotal study, this study is considered methodologically adequate, and the efficacy has been sufficiently demonstrated as revealed by primary and secondary outcomes at various time-points and across most subgroups.

From the simulation analysis results and the limited data in the proof-of-concept study, it seems that treatment cannot be stopped in case of good response, without losing response, which is expected given the pathophysiology of AA. The benefit-risk of treatment should nevertheless be re-assessed at regular intervals on an individual basis.

The inclusion in the SmPC of a stopping rule in case of non-response is supported; however, based on the updated analysis from study B7981032, 36 weeks is a more appropriate time point to stop treatment in non-responders. Therefore, section 4.2 of the SmPC has been updated as follows: *'Consideration should be given to discontinuing patients who show no evidence of therapeutic benefit after 36 weeks.'*

Only a few elderly participants were enrolled in the main study (<5%); the lack of efficacy data in the elderly has been reflected accordingly in the SmPC.

3.4. Unfavourable effects

In the phase 2/3 studies, 1521 participants (1763 patient-years) were exposed to ritlecitinib 50 mg or higher. There were 1011 participants with at least 12 months (48 weeks) of exposure, and there were 1334 participants who had ⩾6 months of exposure to ritlecitinib 50 mg or higher. Among these participants, 172 were adolescents, including 133 adolescents with at least 48 weeks of exposure to ritlecitinib 50 mg or higher.

Common adverse events

In the placebo-controlled AA pool, the most frequent events (2% in any treatment group) that occurred more commonly (>1%) in the ritlecitinib 50/50 mg group than in the placebo group included: nasopharyngitis, diarrhoea, headache, acne, urticaria, rash, upper abdominal pain, pyrexia, folliculitis, SARS-CoV-2 test positive and Covid-19, dizziness, and atopic dermatitis. In addition, tinnitus, gastroenteritis, nasopharyngitis, blood creatinine phosphokinase increased, and back pain were numerically more common in the 50 mg dose groups as compared to placebo. Lower respiratory tract infections and pneumonia did not occur. In the one-year exposure data, the most common TEAEs in the ritlecitinib groups were similar to those in the placebo-controlled AA pool. Diarrhoea, nasopharyngitis, upper respiratory tract infections, dizziness, acne and urticaria, and pyrexia were more frequent in the 50 mg and/or 30 mg dose groups compared to the 10 mg group.

Infections and infestations (SOC) occurred in 38% of patients in the combined 50 mg group, 37% in the 30 mg group, 32% in the 10 mg group and in 31% of the placebo group; this proportion was higher in the 200/50 mg group (41%) as compared to the 50/50 mg group (33%). **Herpes zoster** was infrequent but occurred in 2 patients (1.5%) of the 50/50 mg group and in 2 patients (0.8%)

of the 30 mg group, but not in the 10 mg group or the placebo group. In the one-year exposure data, infections and infestations (SOC) were more frequent in the 50 mg group (51%), as compared to the 30 mg (47%) and the 10 mg (40%) groups, most commonly nasopharyngitis (14% and 16% versus 9.7%) and upper respiratory tract infections (11% and 11% versus 3.2%).

Serious adverse events and deaths

In the All-exposure pool, there were 2 **deaths** (breast cancer, acute respiratory failure and cardiorespiratory arrest) and 1 death (severe myocardial infarction) in the clinical study programme for Ulcerative Colitis. The three events were considered unrelated to the study medication.

In the placebo-controlled AA pool, there were 4 (1.9%) participants with at least one **SAE** in the 200/50 mg group, none in the 50/50 mg group, 1 (0.4%) in the 30 mg group, 2 (3.2%) in the 10 mg group, and 4 (1.9%) in the placebo group. The SAEs in the 200/50 mg group were: three instances of serious infections (appendicitis, empyema, and sepsis), a case of breast carcinoma, and a spontaneous abortion. After 48 weeks of treatment, the 6 SAEs that had occurred in the combined 50 mg group were: appendicitis, empyema, sepsis, breast cancer and invasive lobular breast cancer, spontaneous abortion, and pulmonary embolism.

Adverse events of special interest

In safety study 037, the PD safety outcomes (BAEP, axonal swelling) did not show differences between the ritlecitinib (200/50 mg) group and the placebo group over 9 months. In the placebo-controlled AA pool, **paraesthesia and dysaesthesia** occurred in 1.7% of the combined 50 mg group, 1.5% of the 30 mg group, not in the 10 mg group, and 0.9% of the placebo group. The occurrence was highest (1.9%) in the 200/50 mg group. Most cases were mild and resolved while being on treatment. Treatment-emergent **tinnitus** was most frequent in the 200/50 mg group (2.5%), less frequent in the 50/50 mg group (0.5%), and overall as frequent in the 50 mg group (1.5%) as in the placebo group (1.4%). Adjudicated sensorineural **hearing loss** occurred in 1 patient each in the ritlecitinib 50 mg, 30 mg and 10 mg groups. In the one-year exposure pool of the pivotal AA trial, adjudicated sensorineural hearing loss was still infrequent but occurred only in the highest dose groups: 1% (n=3) in the 50 mg group, 0.8% (n=2) in the 30 mg and 0 in the 10 mg group.

In the placebo-controlled AA pool and in the one-year follow-up data, few cases of **MACE, serious infections, malignancies** and **NMSC** occurred in patients treated with ritlecitinib, there was one case of PE. The occurrences (IR) were lower than those in the reference cohorts from US and Denmark.

Special populations

The proportion of **elderly** participants >65 years (n=30; 2%) experiencing severe AEs, SAEs, and AEs leading to permanent discontinuations was higher than adults. Urinary tract infections decreased lymphocyte count, and arthralgia were more common in elderly patients as compared to adults <65 years. No events were adjudicated as OI, TB, MACE, or ATE.

In the placebo-controlled AA pool, with **adolescents** (n=105; 15%), in the combined 50 mg group (n=38), the proportion of adolescents with at least 1 TEAE was 79% (71% in adults), SAEs did not occur (1.3% in adults), there were 2.6% (2.3% in adults) adolescents who permanently discontinued study drug due to an AE, and 7.9% of adolescents temporary discontinued (9.4% in adults) due to an AE. There were no reports of HZ, HS, or adjudicated events of OI, TB, MACE, malignancy, ATE, or audiologic events of interest in adolescents. Measurements of height and weight in adolescents in studies 015 and 032, standardised to the US, did not suggest deviations from normal growth.

3.5. Uncertainties and limitations about unfavourable effects

As ritlecitinib-mediated axonal dystrophies in dogs were already observed at low safety margins (6.0x and 7.4x in terms of Cmax and AUC24, respectively) in respect to clinical exposure, and as cumulative exposure appeared to be the relevant determinant of neurotoxicity in study 20099163, a risk to patients cannot be excluded. Therefore, a warning was added to the SmPC section 4.4. Moreover, neurotoxicity will be followed-up post approval (see RMP).

Data on the elderly were scarce, which aligns with the target population encountered in clinical practice. It, however, limits the interpretation of the safety profile in this population. The lack of safety data on the elderly is however reflected in a warning in the SmPC section 4.4.

Adverse events considered class effects of oral JAKis (MACE, VTE, malignancies, NMSC, serious infections) did occur in patients treated with ritlecitinib 50 mg, albeit at low frequencies. Occurrences were not higher than those in the US and Danish AA reference cohorts. However, the clinical studies were relatively short in duration, and the AA and vitiligo study populations are relatively young and without a strong accumulation of other risk factors for MACE, as compared to, e.g. the average population with other auto-immune diseases, such as rheumatoid arthritis. Nevertheless, appropriate warnings were included in the SmPC and those adverse events will also be followed-up post-approval (see RMP).

Considering the safety profile of ritlecitinib, the exposure should be limited where possible. At the CHMP's request, section 4.2 of the SmPC was updated to include the following guidance: '*The benefit-risk of treatment should be re-assessed at regular intervals on an individual basis.'*

As long-term clinical safety data are still limited, long-term safety in adolescent patients will be followed-up post-approval (see RMP).

Given that use of ritlecitinib 50 mg in the clinical programme (maternal and partner exposure) was very limited and that other JAKis authorised in the treatment of chronic inflammatory disorders are contraindicated for use during pregnancy, pregnancy and lactation were included in the SmPC as contra-indications. In addition, the applicant also provided a recommendation for a sufficiently long ritlecitinib-free period prior to pregnancy initiation. In addition, embryofoetal toxicity following exposure in utero will be followed-up post approval (see RMP).

3.6. Effects Table

Table 37: Effects Table for Litfulo for the treatment of adolescents and adults with severe AA (data cut-off: 30 May 2022)

Effect	Short Description	Unit	Ritl 200/50 mg	Ritl 50 /50mg	Placebo	Uncertainties/ Strength of evidence
Favourable Effects						
		n=	132	130	131	
SALT10	≤10% scalp hair loss	%	21	13	1.5	**SoE:** The mean difference (95%CI) with placebo was 12% (5% - 18%) for the 50 mg group; p <0.005 while controlled for multiplicity. Supported by eyebrow (EBA) and eyelash (ELA) regrowth, and SALT20
PGI-C	Patient response	%	52	49	9	**SoE:** The mean difference (95%CI) with placebo was 40% (29% - 51%) for the 50 mg group; p <0.005 while controlled for multiplicity. Supported by patient assessed AAPPO
SALT20*	≤20% scalp hair loss	%	30	23	1.5	**SoE**: The mean difference (95%CI) with placebo was 21% (13% – 29%) for the 50 mg group; p<0.0001 while controlled for multiplicity. *supportive; SALT20 is perceived by patients with severe AA as clinically relevant
Unfavourable Effects						
		n=	215	130	213	
Nerve effects -Hearing loss -Tinnitus -Par/dysaeasthesia	sensorineural	%	0 2.8 1.9	0.8 0 1.5	0 0.9 0.9	**Unc:** Strong non-clinical evidence for the mechanism, safety margins relatively low. Tendency to accumulate in tissues, including CNS, should resolve on discontinuation. No clinical PD effects on BAEP and peripheral axonal dystrophy or swelling in 9 month study 037. Usually resolved on treatment. Long term effects in humans unknown.
Serious infections		%	0.9	0	0	**Unc:** 0.8% and IR 0.7/100PY on prolonged exposure; lower than reference cohort
Infections		%	41	33	31	**SoE:** Dose-response (50 mg vs 30 mg vs 10 mg) in 0-48 week data. Difference mostly due to upper respiratory tract infections.

Abbreviations: Ritl: Ritlecitinib; SoE:strength of evidence; Unc: uncertainty
Notes: the time point of the presented favourable effects of study 015 is 24 weeks.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Ritlecitinib has been shown to be effective in the treatment of AA, including adolescents and patients with more severe disease. The treatment effects are maintained over time, although time to response takes longer than inflammatory diseases such as rheumatoid arthritis and psoriasis. This can be expected based on the pathophysiology of AA. Although the responses in SALT10 as a primary outcome appear numerically small, it is considered a clinically relevant treatment effect. Indeed, SALT10 is a rather stringent measure ('near remission'), and 24 weeks is relatively short for treatment effects in AA. In addition, the larger treatment effect supports the clinical relevance in SALT20 and PGI-C.

In line with the time to respond, it takes at least 36 weeks of treatment before it can be concluded that treatment should be stopped in case of insufficient response. There are no data to support stopping treatment in case of prolonged good response, however, the limited data available showed that loss of response is likely after 6 weeks of interruption.

The selected study population was representative of the target population as reflected in the approved indication and aligns with a population eligible for systemic treatment. Even if there is no universally adopted definition of 'severe AA' (SALT>50), this was also agreed for the AA indication of Olumiant.

The application is based on a single pivotal study that included adults and adolescents. This is considered acceptable, and in line with the single pivotal study guideline (CPMP/EWP/2330/99). There is a well-grounded pharmacologic rationale for the plausibility of ritlecitinib's efficacy in AA and sufficient internal and external validity (demonstrated by, e.g. adequate blinding of all parties, randomisation of participants, well-justified inclusion and exclusion criteria). The effect-sizes of primary and secondary outcomes are statistically significant at an adequate level for a single pivotal trial.

The safety profile of ritlecitinib is favourable in the short term but comes with several uncertainties regarding long term exposure, neurosafety, class effects of other JAKis approved for the treatment of chronic inflammatory disorders; and use in adolescents. These uncertainties however were adequately addressed in the SmPC and will be followed-up post approval.

The main apparent safety concern is the occurrence of infections, most notable upper respiratory tract infections which was included as an ADR in section 4.8 of the SmPC. This is in line with the immunomodulating effect of ritlecitinib. The occurrence of infections is considered manageable. Active serious infections are a contra-indication.

Although neurotoxic events were evident in the non-clinical dog studies, neurological events such as par-/dysaesthesias and neurosensory deafness were infrequent in the clinical data and there was no evidence in the clinical data relating these causally to ritlecitinib. However, neurotoxicity for patients cannot be totally ruled out, the residual uncertainty is addressed with a warning in section 4.4 of the SmPC and will also be followed-up post-approval (see RMP). In addition, the applicant will closely monitor neurological and audiological events in future PSURs.

SAEs considered class effects of oral JAKis approved in the chronic treatment of inflammatory disorders did occur in patients exposed to ritlecitinib in the proposed dose of 50 mg QD (MACE, VTE, malignancy, serious infections), albeit at a low frequency. It is unknown whether the class effects of JAKis do apply to ritlecitinib,

however, this cannot be fully discarded. Hence warnings were included in section 4.4 of the SmPC. In addition, thromboembolic events (which include MI, VTE, and MACE) and malignancies (including NMSC) will be followed-up post-approval (see RMP).

The safety data in adolescents (>100 followed for >12 months) on growth (height, weight), AEs (fractures), and development (Tanner scale, neuropsychological development) of adolescents did not point to a safety risk. This is supported by the non-clinical data that became available during the assessment. However, as long-term clinical safety data are limited, growth and bone effects will be followed-up post-marketing (See RMP).

Given the high value patients with severe AA placed on scalp hair regrowth in the patient preference studies in adults and adolescents, the net B/R for ritlecitinib 50 mg, compared to no treatment, is considered positive from the patient's perspective.

3.7.2. Balance of benefits and risks

The primary endpoint was met, which was supported by key secondary endpoints. Primary and secondary outcomes support the clinical relevance of the treatment effect. The long-term efficacy of ritlecitinib until week 48 data has been demonstrated.

The treatment is effective in the proposed dose of 50 mg once daily, including adolescents and patients with more severe disease.

Dosing recommendations for stopping in case of non-response were included in the SmPC at the CHMP's request.

The safety profile of ritlecitinib is overall acceptable and considered manageable.

The balance of benefits and risks of Litfulo for the treatment of severe alopecia areata in adults and adolescents 12 years and older is positive in the following indication:

'Litfulo is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older (see section 5.1).'

3.8. Conclusions

The overall benefit/risk balance of Litfulo is positive, subject to the conditions stated in section 'Recommendations'.

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 Litfulo is favourable in the following indication:

Litfulo is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older (see section 5.1).

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 ritlecitinib 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, specifically in regard to infections (including herpes zoster and serious infections and opportunistic infections), thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis, MACE, malignancy, neurotoxicity and embryo-fetal toxicity following exposure *in utero*.

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

The physician educational material should contain:

- The Summary of Product Characteristics
- Package leaflet
- Healthcare Professional Guide

- Patient Card (PC)

The healthcare professional guide shall contain the following key elements:

- Language for healthcare providers (HCPs) to inform patients of the importance of the PC.
- *Potential risk of infections (including herpes zoster and serious infections or opportunistic infections)*
    - Describe that Litfulo must not be used in patients with an active, serious infection.
    - Language on the risk of infections during treatment with Litfulo.
    - Language recommending that risk factors for infections should be considered when prescribing ritlecitinib including elderly age and diabetes.
    - Details on how to reduce the risk of infection with specific clinical measures (what laboratory parameters should be used to initiate Litfulo, screening for TB, and screening for viral hepatitis and temporary interruption of Litfulo if an infection is not responding to appropriate therapy until the infection is controlled).
    - Language stating the use of live, attenuated vaccines should be avoided during or immediately prior to treatment along with examples of live, attenuated vaccines.
- *Potential risk of thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis*
    - Language describing that events of venous and arterial thromboembolism, including MACE, have been observed in studies in Litfulo.
    - Details of how to reduce the potential risk: Litfulo should be used with caution in patients with known risk factors for thromboembolism. In patients with a suspected thromboembolic event, discontinuation of Litfulo and prompt re-evaluation is recommended. The risks and benefits of treatment should be considered prior to initiating Litfulo therapy in patients.
- *Potential risk of malignancy*
    - Language describing that malignancies, including non-melanoma skin cancer, have been observed in studies with Litfulo.
    - Details of how to reduce the potential risk with specific clinical measures (that the risks and benefits of Litfulo treatment should be considered prior to initiating in patients with a known malignancy or when considering continuing Litfulo therapy in patients who develop a malignancy, and that periodic skin examination is recommended for patients who are at increased risk for skin cancer).
- *Potential risk of neurotoxicity*
    - Language describing that ritlecitinib-related axonal dystrophy has been observed in chronic Beagle dog toxicity studies at systemic exposures of at least 7.4-times the expected exposure in patients treated with 50 mg per day. At a systemic exposure that was 33-times above the expected exposure in patients treated with 50 mg per day, axonal dystrophy was associated with neurological hearing loss. While these findings proved to reverse after dosing cessation of ritlecitinib in dogs, a risk to patients at a chronic dosing regimen cannot be fully excluded. Available clinical data has not indicated an effect on neurological or audiological outcomes.

- Details on how to reduce the risk Neurotoxicity, treatment with Litfulo should be discontinued in case unexplained neurological symptoms occur.

- *Potential risk of embryo-foetal toxicity following exposure in utero*
  - Language describing there are no or limited data on the use of Litfulo in pregnant women.
  - Details on how to reduce the risk of exposure during pregnancy for women of childbearing potential based on the following: Litfulo is contraindicated during pregnancy, women of childbearing potential should be advised to use effective contraception both during treatment and for 1 month following cessation of Litfulo, 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:
  - Language describing Litfulo (i.e. what it is and what it is used for).
  - Contact details of the Litfulo 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- Litfulo 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 Litfulo therapy with examples of live vaccines.
  - Reminder of the risk of cancer. Regarding skin cancer reminder to let their doctor know if they notice any new growth on the skin.
  - Description of signs/symptoms of thromboembolic events including blood clots in the veins (deep vein thrombosis) or in the lungs (pulmonary embolism) and blood clots in an artery (arterial thrombosis), in the heart (heart attack), in the brain (stroke) or in the eye (profound vision loss in one eye) which the patient needs to be aware of, so that they can seek immediate attention from an HCP.
  - Language that treatment with Litfulo should be discontinued in case unexplained neurological symptoms occur.
  - Language that there are no or limited data on the use of Litfulo in pregnant women.
  - Language describing on how to reduce the risk of exposure during pregnancy for women of childbearing potential based on the following:
    - Litfulo is contraindicated during pregnancy, women of childbearing potential should be advised to use effective contraception both during treatment and for 1 month following cessation of Litfulo, and to advise patients to inform their HCP immediately if they think they could be pregnant or if pregnancy is confirmed.

- A reminder to use contraception, that Litfulo is contraindicated during pregnancy, and to notify their HCPs if they become pregnant while taking Litfulo.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that ritlecitinib 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.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0147/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.