LITFULO (RITLECITINIB) RISK MANAGEMENT PLAN

RMP Version number: 2.0

Data lock point for this RMP: 25 June 2024

Date of final sign off: 22 October 2024

Rationale for submitting an updated RMP: Submission of the long-term efficacy and safety data upon availability of the PCD CSR for the long-term Study B7981032 by the end of November 2024 is a Category 3 Pharmacovigilance Activity listed in the RMP PART III. This RMP accompanies a Type II Variation for fulfilment of this commitment and includes an update the RMP with currently available clinical safety data integrated within the AEP (All-exposure Pool) safety pool, through to the safety data cut-off date of 25 June 2024.

Summary of significant changes in this RMP:

- Part I was updated: The following were moved from "Proposed" to "Current" following ritlecitinib's authorisation on 15 September 2024
    - Indication (s) in the EEA
    - Dosage in the EEA
    - Pharmaceutical form (s) and strengths
- Part II (Module SIII) was updated with clinical trial exposure data from All-Exposure Pool
- Part II (Module SV.1) was updated with post-authorisation exposure data
- Part II (Module SVII) was updated with clinical trial exposure data from All-Exposure Pool
- PART III.2 and PART III.3 were updated to align details for the following studies with the final protocols. It was agreed with the EMA that these updates can be incorporated within the scope of this Type II Variation as protocols for these studies have already been formally assessed and agreed in principle within the relevant PAM procedures:
    - B7981101 (final protocol agreed within procedure EMEA/H/C/006025/MEA/001, 27 June 2024)

- B7981102 (final protocol agreed within procedure EMEA/H/C/006025/MEA/003, 27 June 2024)
- B7981092 (final protocol agreed within procedure EMEA/H/C/006025/MEA/002.1, 17 October 2024)
- In addition to the above, a typographical error in the LSLV date for B7981032 PCD was corrected as previously communicated with the EMA

- PART V was updated to add study identifiers next to the description of Studies B7981101, B7981102 and B7981092
- PART VI was updated to accurately reflect the RMP summary taking in account the updates listed above
- Modifications to Annexes 2, 3 and 8

Other RMP versions under evaluation: Not Applicable

RMP Version number*:* Not Applicable

Submitted on: Not Applicable

Procedure number: Not Applicable

Details of the currently approved RMP: Not Applicable

Version number: Not Applicable

Approved with procedure: Not Applicable

Date of approval (opinion date): Not Applicable

QPPV name: Barbara De Bernardi, MD

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

LIST OF ABBREVIATIONS

AA	Alopecia Areata
AAD	American Academy of Dermatology
ACE	Alopecia Areata Consensus of Experts
ADR	Adverse Drug Reaction
AER	Adverse Event Report
aHR	Adjusted Hazard Ratio
aOR	Adjusted Odds Ratio
AT	Alopecia Totalis
AU	Alopecia Universalis
AUC	Area Under Curve
BAD	British Association of Dermatology
BAEP	Brainstem Auditory Evoked Potential
CI	Confidence Interval
C_{max}	Maximum Observed Concentration
CNS	Central Nervous System
C-SSRS	Columbia Suicide Severity Rating Scale
CSP	Core Safety Profile
CSR	Clinical Safety report
CV	cardiovascular
DPCP	Diphenylcyclopropenone
DLP	Data-Lock Point
EFD	Embryofoetal Development
EMA	European Medicines Agency
FDA	(US) Food and Drug Administration
HA	Health Authority
HCP	Healthcare Provider
hERG	human Ether-a-go-go-related Gene
HLT	High Level Term
HPV	Human Papillomavirus
IBD	International Birth Date
IENF	Intraepidermal Nerve Fiber
ILCS	Intralesional Corticosteroids
IRR	Incidence Rate Ratio
JAK	Janus Kinase
LLT	Lowest Level Term
LSLV	Last Subject Last Visit
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NHS	Nurses' Health Study
NICE	National Institute for Health and Care Excellence

NK	Natural Killer
NOAEL	No Observed Adverse Event Level
OR	Odds Ratio
PCD	Primary Completion Date
PHO	Patient Health Organisation
PND	Postnatal Day
PNS	Peripheral Nervous System
PT	Preferred Term
QD	Once Daily
RBC	Red Blood Cell
RSI	Reference Safety Information
SAE	Serious Adverse Event
SALT	Severity of Alopecia Tool
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
UK	United Kingdom
US	United States
WBC	White Blood Cell

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Ritlecitinib
Pharmacotherapeutic group(s) (ATC Code)	Janus-associated kinase (JAK) inhibitors: L04AF08
Marketing Authorisation Applicant	Pfizer Europe MA EEIG Boulevard De La Plaine 17 Brussels 1050 Belgium
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Litfulo
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class Janus kinase (JAK) 3 and tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family inhibitor.
	Summary of mode 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.
	Important information about its composition: Excipient-Lactose monohydrate Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Hyperlink to the Product Information:	Module 1.3.1 SmPC

Indication(s) in the EEA	Current: Litfulo is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older.
	Proposed: Not Applicable
Dosage in the EEA	Current: The recommended dose is 50 mg once daily.
	Proposed (if applicable): Not Applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Each hard capsule contains ritlecitinib tosylate equivalent to 50 mg ritlecitinib. Opaque hard capsules, yellow body and blue cap approximately 16 mm long and 6 mm wide, of which the body is printed with “RCB 50” and the cap is printed with “Pfizer” in black
	Proposed: Not Applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

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

Litfulo is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older. Alopecia areata is an autoimmune disease that has an underlying immuno-inflammatory pathogenesis and is characterised by nonscarring hair loss ranging from small patches to complete scalp, face, and/or body hair loss.[1]

Epidemiological Literature Search Strategy

The United States (US) National Library of Medicine PubMed database was searched for literature reporting the incidence, prevalence, and demographic profile of AA from 1 January 2011 through 18 October 2021. Article titles were restricted to human populations, observational data, and the English language. Potentially relevant abstracts were reviewed by epidemiologists, and articles were excluded if they reported exclusively on clinical trial participants or were case reports.

Incidence:

Europe

A meta-analysis including articles published up to 01 September 2018 calculated the overall pooled incidence of AA in Europe as 4.92% (95% Confidence interval [CI] 2.41-8.25%).[2] In a separate study in the United Kingdom (UK), the incidence rate of AA was reported to be 2.6 per 10,000 person-years.[3]

US

A meta-analysis including articles published up to 01 September 2018 calculated the overall pooled incidence of AA in North America as 0.54% (95% CI 0.27-0.91%).[2] In the US, a 2014 study reported the age- and sex-adjusted incidence rate of AA as 2.1 per 10,000 person-years, and the cumulative lifetime incidence as 2.1%.[4] A study in the Nurses' Health Study (NHS) and NHS II reported the lifetime incidence of AA to be 0.76%.[5]

China

No China specific data was found on the incidence of AA.

RoW

A meta-analysis including articles published up to September 1, 2018 calculated the overall pooled incidence of AA in Asia as 1.92% (95% CI 0.66-3.83%).[2] Population-based data from Korea showed that between 2006 and 2015 the incidence rate of AA ranged between 19.3 and 20.6 per 10,000 person-years.[6] A separate study in South Korea found that the incidence rate in persons without a family history of AA was 10.0 per 10,000 person-years.[7]

SI.1. Prevalence

Europe

The pooled prevalence of AA was estimated at 0.58% (95% CI 0.49-0.66%) in Europe.[2] In France, a population-based study using a representative sample of the French general population over 15 years old reported an age and sex-standardised overall point prevalence of AA of 1.05% (95% CI 0.92-1.20%).[8] In the UK, a population-based cohort study of 4.16 million adults and children reported an AA point prevalence of 0.58%.[3]

US

In the US, the overall prevalence of AA has been estimated as 2.47% (95% CI 2.05-2.94%).[2] An online, cross-sectional survey with a representative sample of the US population reported that the clinician-adjudicated point prevalence of AA was 0.21% (95% CI 0.17-0.25%) overall, 0.12% (95% CI 0.09-0.15%) for "mild" disease (≤50% Severity of Alopecia Tool [SALT] score), 0.09% (95% CI 0.06-0.11%) for "moderate to severe" disease (>50% SALT score), and 0.04% (95% CI 0.02-0.06%) for patients with alopecia totalis (AT)/alopecia universalis (AU).[9] Self-reported lifetime prevalence in that study was 2.51% (95% CI: 2.37-2.65%) overall.[9]

China

No China specific data was found on the incidence of AA.

RoW

In Asia, the pooled prevalence of AA was reported as 1.46% (95% CI 1.17-1.79%).[2] A population-based study in South Korea estimated the point prevalence as 0.37% in 2015.[6]

SI.2. Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age and age of onset: Patients with AA are relatively young, with an average age of onset reported between 22 and 40 years.[4,10,11,12,13,14] However, diagnosis can occur at any age.[15] 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 and subsequently decreased with age.[3] A population-based study conducted between 1973-2011 in the Faroe Islands reported age- and sex-specific incidence rates of AA (Table 1).[15] In that study, the incidence rate of AA diagnosis was 0.8 per 10,000 person-years in the youngest age category (0-9 years), increased to 1.1 per 10,000 person-years in patients 10-19 years, and peaked at 1.5 per 10,000 person-years in patients 20-29 years, before declining in subsequent age categories.[15] A US study conducted among residents of Olmsted County, Minnesota, reported a similar trend in age-specific incidence rates (Table 2).[4] In that study, incidence rate of AA was 1.6 per 10,000 person-years in the youngest age category (0-9 years), increased to 1.7 per 10,000 person-years in patients 10-19 years, and peaked at 3.0 per 10,000 person-years in patients 20-39 years, before declining in subsequent age categories.[4]

Gender: Studies have reported conflicting findings regarding whether there is a gender predominance in patients with AA.[4,11,15,16,17,18,19]

Table 1. Age and sex specific distribution and incidence of AA in Europe[15]

	Female			Male			Total	
Age (years)	Incidence rate*	Age group distribution	Gender group distribution	Incidence rate*	Age group distribution	Gender group distribution	Incidence rate*	Age group distribution
0-9	0.6	9%	35%	1.0	17%	65%	0.8	13%
10-19	1.0	15%	45%	1.1	20%	55%	1.1	17%
20-29	1.8	21%	54%	1.2	19%	46%	1.5	20%
30-39	1.1	13%	39%	1.5	22%	61%	1.3	17%
40-49	1.4	15%	58%	0.9	12%	42%	1.1	13%
50-59	2.0	18%	81%	0.4	5%	19%	1.2	12%
≥60	0.5	9%	62%	0.4	6%	38%	0.4	7%
Total	1.1	100%	52%	0.9	100%	48%	1.0	100%

*per 10,000 person-years

Table 2. Age and sex specific distribution and incidence of AA in the US[4]

	Female			Male			Total	
Age (years)	Incidence rate*	Age group distribution	Gender group distribution	Incidence rate*	Age group distribution	Gender group distribution	Incidence rate*	Age group distribution
0-9	1.5	10%	46%	1.7	12%	54%	1.6	11%
10-19	1.9	12%	56%	1.5	10%	44%	1.7	11%
20-29	2.7	18%	46%	3.3	22%	54%	3.0	20%
30-39	2.3	17%	38%	3.7	28%	62%	3.0	22%
40-49	2.7	19%	59%	1.9	14%	41%	2.3	17%
50-59	2.5	13%	59%	1.8	9%	41%	2.2	11%
≥60	1.4	11%	75%	0.6	4%	25%	1.1	8%
Total	2.1	100%	51%	2.0	100%	49%	2.1	100%

*per 10,000 person-years

Race and ethnicity: A UK study reported that the incidence rate ratio (IRR) of AA was higher in Asian (IRR: 3.32, 95% CI 3.11-3.55), black (IRR 1.54; 95% CI 1.36-1.75), and mixed ethnicity (IRR 2.15; 95% CI 1.82, 2.54) patient populations, as compared to white patients.[3] Similarly, in the US, a study in the NHS reported that the lifetime incidence of AA was higher in black females (1.66-4.07%) compared to white females (0.64-0.78%) and, in age-adjusted analyses, black, as compared with white women, had a greater lifetime incidence of AA (NHS: odds ratio [OR]: 2.72; 1.61-4.61; NHS II: OR: 5.48; 4.10-7.32).[5] Confirming the findings from the NHS, a cross-sectional study of both men and women in the US from the National Alopecia Areata Registry, reported that the odds of AA was greater

in African Americans as compared to white Americans, after adjusting for age, gender, and comorbidities (adjusted OR [aOR] 1.77; 95% CI 1.37-2.28).[20]

Risk Factors: Family history may be a risk factor for developing AA. Indeed, a Korean study found that the incidence rate of AA in patients without a family history of AA was 10.0 per 10,000 person-years vs 19.7 per 10,000 person-years in patients with a family history (IRR 1.98 [95% CI: 1.96-2.00]).[7] Rates increasingly grew higher as the genetic similarity among first degree relatives increased (affected father vs. no family history [IRR: 1.77 (95% CI: 1.74-1.81)]; affected twin vs. no family history [IRR: 5.08 (95% CI: 4.52-5.70)]) and among patients with more than one affected first degree relative (IRR: 3.43 [95% CI: 3.29-3.57]). [7] However, at least one other study did not identify a trend of higher rates of AA in first-degree family members as compared to second- and third-degree relatives.[15]

Risk of AA has been reported to increase after exposure to viral infections. For example, in a Taiwanese study, history of HPV infection was associated with the development of subsequent AA (adjusted hazard ratio [aHR] 2.55; 95% CI 1.88–3.47) after adjusting for sex, age, and comorbidities.[21]

AA often co-occurs with other autoimmune diseases and psychiatric disorders. For example, the relationship between AA and major depressive disorder (MDD) was found to be bidirectional, with MDD increasing the risk of subsequently developing AA by 90% (aHR 1.90, 95% CI 1.67-2.15) and AA increasing the risk of developing MDD by 34% (aHR 1.34; 95% CI 1.23-1.46).[22]

Deficiency of micronutrients have been linked to AA. For example, a small cross-sectional study in Israel found that serum vitamin D levels <30 ng/ml were significantly associated with AA (aOR 2.3, 95% CI 2.2-3.1).[23] This finding has been replicated in other studies.[24,25,26,27,28,29,30]

In a 2017 review of the literature, serum vitamin D, zinc, and folate were found to be generally lower in patients with AA than in patients without AA.[31] However, there were conflicting findings for iron, vitamin B12, copper, magnesium, and selenium.[31]

Lifestyle factors, such as smoking and alcohol consumption, are associated with AA. Indeed, current smokers had a 1.86 to 2.25-fold increased risk of AA, depending on the smoking habits, in a recent (2020) study from Taiwan.[32]

AA incidence may also be associated with other environmental factors, such as social deprivation (IRR most vs least deprived quintile 1.47; 95% CI 1.37-1.59) and urban living (IRR 1.23; 95% CI 1.14-1.32).[3] Further, a US study has suggested a possible seasonal pattern, with a greater frequency of flares in the winter.[33]

SI.3. Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The three main variants of AA are patchy AA (localised hairless areas), AT (entire scalp affected), and AU (affecting all body surface area).[1] Other AA subtypes include ophiasis,

sisaipho, alopecia incognita, and Marie Antoinette syndrome.[1] AA severity can be divided into mild (≤3 patches), moderate (≥3 patches without AT or AU), severe (AT, AU), and ophiasis (Snake-shaped plaques extending to the scalp border or loss of hair in the shape of a wave at the circumference of the head).[34,35] The SALT score is often used to report the overall percentage of the extent of hair loss on the scalp.[36]

Single centre studies have generally found that studied patients (including adults and paediatric patients) tend to most often have the patchy sub-type[12,35,37,38] and be of mild-to moderate severity.[35,38] A cross-sectional study of approximately 45,000 participants in the US aged 11 years and older reported the clinician-adjudicated point prevalence of "moderate to severe" (>50% SALT score) AA was 0.09% and the clinician-adjudicated point prevalence for the subset of AA with AT/AU was 0.04%.[9] Generally, earlier disease onset is associated with a higher likelihood of severe alopecia.[11,12,37] For example, one study reported full or significant re-growth of hair after the first episode in 74% of childhood-onset patients, as compared to 94% of adult-onset patients.[38]

Paediatric Onset

The severity of the first visit has been associated with more severe long-term prognosis;[39,40] however this trend was not apparent in patients with childhood-onset disease in at least one study.[39] Another 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.[38] In that study, both the duration of first AA episode and the duration of the disease-free interval after the first episode tended to be shorter in younger patients.[38]

Mortality

A large population-based study in Korea did not find an association between AA and increased risk of all-cause mortality.[41] However, an increased risk of mortality associated with intentional self-harm/psychiatric diseases was found in patients with AA compared to controls (HR 1.21; 95% CI 1.04-1.41), and this risk was even greater among adult patients aged 35 years or younger (HR 1.68; 95% CI 1.32-2.12) and patients with AT/AU (HR 1.85; 95% CI 1.25-2.75).[41] Mortality associated with lung cancer was greater in patients with AT/AU (HR, 2.16; 95% CI, 1.41-3.33) and the risk of mortality associated with diabetes mellitus was significantly lower in AA patients (HR 0.53; 95% CI 0.36-0.79).[41]

SI.4. The main existing treatment options:

At the time of the preparation of the original submission dossier, there were no approved treatments for AA by the EU or MHRA, although baricitinib (a JAK inhibitor with preferential selectivity towards JAK1/2) had received a positive CHMP opinion in May 2022 for the treatment of severe AA. Since the original submission, baricitinib has received marketing authorization in the EU and UK for the treatment of adult patients with severe AA. Review of the expert recommendations including the AAD, BAD guidelines, Italian guidelines, ACE, and NICE Clinical Knowledge Summary indicate a number of off-label

therapies, including injectables, topicals, and systemics, that are frequently used after assessing factors such as the age of the patient, disease extent and disease duration.

There is no therapy which reliably produces long-term remissions of disease off drug nor is there a therapy convincingly demonstrated to have the efficacy and safety appropriate for long-term management required to maintain hair re-growth.[42,43,44,45,46]A large proportion of patients are dissatisfied with treatment options in AA. A survey conducted in 2016 in the US showed that 78.1% of AA patients were very or somewhat unsatisfied, compared to 7.7% who were very or somewhat satisfied with the current medical treatments for AA.[47] Additionally, in the ACE, a panel of 50 hair experts achieved only 33% consensus for treatment specific questions and concluded that there is a need for robust research in AA therapeutics to support clinical decision making.[48]

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 and no established standard of care for ≥50% scalp hair loss. Treatment recommendations vary between guidelines and expert consensus statements, but generally distinguish between “acute” or “active” vs “chronic” AA.[42,48,49]

The AAD, BAD, Italian guidelines, and international recommendations summarize evidence based on expert opinion (dermatologist experience), clinical study data and RWE[48,49,50,51,52] The evidence for efficacy of any of the off-label treatments reviewed is variable and limited, and a standard of care in AA has not been established.[42,46,48]

Corticosteroids

ILCS are commonly used for limited AA [42,44,49] and can be used as adjunctive therapy to systemic treatment in those with extensive disease (SALT >50).[53] Response defined as >50% improvement is poorer in extensive AA (25-50% after 6 months) in comparison to limited AA even with longer duration of therapy (82.1% after 12 weeks).[53] Treatments require frequent office visits as they are repeated every 4 to 6 weeks. Adverse effects can include pain, atrophy of the skin and hair follicles, telangiectasia, and hypo/depigmentation.[54] Skin atrophy and telangiectasia may inhibit hair regrowth; therefore, this risk should be minimised by use of smaller volumes and number of injections per site.[52] Additionally, there can be a risk for cataract and raised intraocular pressure if ILCS are used close to the eye when treating eyebrows.[42,54] Pain may limit the practicality of this treatment modality, especially for children and patients with extensive scalp involvement.

TCS can be used in limited AA and children under 10 years of age may prefer this treatment due to intolerance of painful ILCS injections.[53] However, monotherapy use may be ineffective.[42,44,45,46,55] Data suggest limited benefit with topical compared to injectable corticosteroids.[53] A small randomised controlled trial (n=54) showed ILCS to be significantly better than topical corticosteroids in achieving complete hair regrowth (P=0.03).[56] Side effects associated with topical corticosteroids include folliculitis, itching and burning of the skin, acne, stretch marks, and skin atrophy. [53,57] It is recommended to wash the skin after 12 hours of application to minimize the risk for folliculitis and limit use to 5 times a week to prevent the onset of skin atrophy.[51]

SC are recommended in patients 13 years of age and above with acute AA and SALT >30. Use is not recommended in adolescents with chronic AA with SALT >50 due to the potential toxicity associated with the likely requirement for prolonged treatment.[48] Studies report response rates based on >75% scalp coverage or regrowth of affected area to range from 28.6-63.3% and have shown that ophiasis and AT/AU are far less responsive than patchy or recent-onset AA.[58,59] Long-term use is limited by side effects such as weight gain, osteoporosis, cataract formation, hypertension, peptic ulceration, metabolic abnormalities, gastrointestinal irritation, and suppression of the hypothalamic-pituitary-adrenal axis (HPA axis) along with high relapse rates (22-100%).[49,60,61]

Contact Immunotherapy

In adults and children >10 years of age presenting with SALT ≥50, AAD recommends contact immunotherapy with DPCP or SADBE.[44] The BAD and Japanese guidelines also recommend contact immunotherapy as first-line therapy.[42,52] Reported response rates defined as >75% scalp hair coverage are 88.1% and 17.4% for patients with 50-74% and 100% scalp involvement at baseline, respectively, suggesting poorer response with more extensive disease.[62] DPCP requires a sensitization process with the concentration of the sensitizing agent increased weekly until a low-grade erythema and mild pruritus is achieved on the treated area for 24 to 36 hours after application. The solution should be applied weekly and left on the scalp for 48 hours before being washed off. Exposure to the sun should be avoided during this time. This process may be time-consuming and burdensome to patients as well as to HCPs who have to apply it and avoid occupational sensitization. Side effects include severe eczema, vesicular or bullous reactions, facial and scalp edema, and occipital and/or cervical lymphadenopathy. Over the long-term, approximately one third of responders may eventually stop responding.[63]

Immunomodulators/suppressors

The AAD and BAD guidelines mention that broad immunomodulators or immunosuppressants (including sulfasalazine, methotrexate, cyclosporine, psoralen plus ultraviolet A, and calcineurin inhibitors) may be used in treatment refractory patients.[42,53] These treatments can be included in dermatologist's armamentarium based on experience in uncontrolled studies; however, limited evidence in AA patients is available.[48,63] Due to weak evidence from case reports or small uncontrolled retrospective studies,[50] demonstrating varying efficacy, high relapse rates, and systemic side effects (including but not limited to hypertension, malignancies, bone marrow suppression, hepatotoxicity, nephrotoxicity, and pancytopenia) these treatments are not commonly recommended or appropriate for long-term treatment.[42,44]

Minoxidil

Topical minoxidil is approved for treatment of androgenetic alopecia, but it is also used off-label (topical and oral) for other hair loss conditions. Minoxidil's mode of action for stimulation of hair regrowth is not fully understood (vasodilation and angiogenesis are among the mechanisms that have been postulated), but it does not have a direct immunomodulatory effect and thus is not expected to alter the course of AA or induce

remission. However, both oral and topical minoxidil are sometimes used (off-label) as adjunctive therapy to oral or topical steroids to stimulate hair growth in AA, although evidence is scarce and histologic studies on its effect on perifollicular lymphocytic infiltration in AA are inconsistent.[53,59,64,65] Its use is less common in extensive disease due to limited efficacy and unsatisfactory results when used as monotherapy.[57] Topical minoxidil is not expected to be effective in AT/AU.[50] Side effects with oral minoxidil may include hypertrichosis and postural hypotension, while topical minoxidil may cause itching and dermatitis.[59]

Treatment In Refractory Patients

It should be noted that extensive AA can become less responsive or refractory to treatment if it has been active for a substantial period of time before effective treatment commences. Studies with oral corticosteroids and topical immunotherapy have shown that early initiation of treatment within 3 months to 1 year of disease onset may be more effective and disease may be less likely to relapse in comparison to patients who start treatment later.[66,67,68] It has also been suggested that patients with AA may be more refractory to the benefit of JAK inhibition when episodes of hair loss have lasted 10 years or longer.[69] Thus, it is important to offer patients effective treatment early.[53]

SI.5. Important co-morbidities Found in the Target Population

Table 3 presents a subset of comorbidities reported in the literature to be common (>5%) and/or significantly increased in patients with AA as compared to patients without AA.

Table 3. Comorbidities Among Persons with AA

	Comorbidities
Autoimmune	Any autoimmune disease[70,71]
	Atopy / atopic disease[29,71,72,73]
	Allergic rhinitis[14,29,70,71,74]
	Asthma[13,14,29,70,71,74]
	Atopic dermatitis[14,29,30,35,70,71,74]
	Lupus erythematosus[14,29]
Cardiovascular	Diabetes mellitus[13,14,35,75,76,77]
	Hyperinsulinemia[78]
	Hyperlipidemia[13,75,76]
	Hypertension[13,75,76]
	Metabolic syndrome[29,78]
	Obesity[13,30,77]
Gastrointestinal	Helicobacter pylori infection[29,79]
Hematologic	Anemia[29,30,35,74]
	Iron deficiency anemia[29,35,74]
Thyroid	Thyroid dysfunction or disease[13,14,29,35,74,80]
	Hashimoto thyroiditis[81]
	Graves' disease[81]
	Subclinical hypothyroidism[29,82,83]
	Subclinical hyperthyroidism[29,83]
	Thyroid cancer[29,81]

Table 3. Comorbidities Among Persons with AA

	Comorbidities
Psychiatric	Any psychiatric disease[29,84,85]
	Alexithymia[29]
	Anxiety[29,72,73,77,80,84,86,87,88]
	Depression[29,30,72,73,80,84,86,87]
	Obsessive-compulsive disorder[84]
Other	Audiologic abnormality[29,89]
	Lens change[29,85,90,91]
	Retinal change[29,85,90,91]
	Vitamin D deficiency[23,24,25,26,27,28,29,30,74]

Module SII. Non-Clinical Part of the Safety Specification

Ritlecitinib has undergone a comprehensive toxicological evaluation in dogs, rats, rabbits, and mice in studies up to 2 years in duration. Safety pharmacology studies were conducted in vitro and in vivo (rats and dogs) to assess potential effects on cardiovascular, pulmonary, or neurofunctional endpoints. In vitro and in vivo genetic toxicity studies were conducted to assess the genotoxic potential of ritlecitinib. Chronic toxicity assessment was conducted in rats and dogs. Fertility and pre- and postnatal development studies were conducted in rats, and embryo-foetal development studies were conducted in rats and rabbits. Carcinogenicity was assessed in a 6-month rasH2 transgenic mouse study and a 2-year rat carcinogenicity study. The above comprehensive nonclinical data package supports using ritlecitinib in participants 12 years of age and above. The ages of rats (approximately 7 weeks at dose initiation) and dogs (approximately 9-12 months at dose initiation) used in the chronic toxicity studies are comparable to adolescent human age (≥12 years).

Table 4 provides a summary of key safety findings from ritlecitinib nonclinical studies.

Table 4. Key Safety Findings and Relevance to Human Usage

Key Safety Findings from Non-clinical Studies	Relevance to Human Usage
Toxicity	
Central and Peripheral Nervous System	
Chronic administration of ritlecitinib to dogs led to the occurrence of axonal dystrophy (swelling) in the CNS or PNS at systemic exposures at least 7.4-times the expected exposure in patients treated with 50 mg per day (based on unbound AUC_{24}). Axonal dystrophy is presumably related to binding to off-target neuronal proteins. The finding was not associated with microscopic evidence of a degenerative process or impact on myelination or synapses. It is not known if axonal dystrophy occurred in dogs at lower systemic exposures. At 33-times the expected exposure in patients treated with 50 mg per day (based on unbound AUC_{24}), axonal dystrophy was associated with neurological hearing loss. Axonal dystrophy and hearing loss reversed after dosing cessation of ritlecitinib in dogs. .	The clinical relevance of ritlecitinib-related axonal dystrophy was evaluated in the ritlecitinib clinical program. Overall, events evaluated by independent external adjudication as potential neurological and/or audiological safety events of interest did not demonstrate evidence suggestive of neurotoxicity or ototoxicity with ritlecitinib treatment. Clinical safety study B7981037 demonstrated no effect on axonal swelling in IENFs or IENF density and no notable mean changes from baseline in BAEP I-V interwave latency or Wave V amplitude at 80dB nHL following 9 months of administration of the proposed chronic therapeutic dose of ritlecitinib compared to placebo. Neurotoxicity is an important potential risk for ritlecitinib.
Immune and haematolymphopoietic system	
Effects on the immune and haematolymphopoietic systems were consistent with the intended pharmacologic activity of ritlecitinib (inhibition of JAK3 and TEC kinases). Effects in animals were reversible and associated with over-immunosuppression leading to opportunistic infections at exposures ≥14 times the unbound AUC_{24} at the 50 mg human dose.	Ritlecitinib, due to pharmacologic inhibition of JAK3 and TEC kinases, may be associated with immunosuppression; opportunistic and/or serious infections should be considered an important potential risk to humans.

Table 4. Key Safety Findings and Relevance to Human Usage

Key Safety Findings from Non-clinical Studies	Relevance to Human Usage
Lower circulating WBC, lymphocytes, monocytes, eosinophils, and/or basophils were observed in rats. Similarly, lower circulating lymphocytes were noted in dogs. Decreases in circulating lymphocytes correlated with decreased cellularity of lymphoid tissues.	In placebo-controlled clinical trials, ritlecitinib treatment was associated with decreases in lymphocyte counts. The incidence of discontinuations from clinical studies due to decreased lymphocyte counts was low. There was no association between lower lymphocyte counts and the rate of serious infection or herpes zoster. Age appeared to be a risk factor for lower ALC in participants ≥65 years of age. The clinical data are sufficient to conclude that Lymphocyte count decreased is an ADR.
Immunophenotyping conducted in the 8-week and 9-month studies in dogs showed decreases in total T cells, T helper cells, cytotoxic T cells, and NK cells. Decreases in B cells were also observed at 45 mg/kg/day in the 8-week study and at all doses in the first 9-month toxicity study only.	In AA clinical trials, treatment with ritlecitinib was associated with dose-dependent early decreases in T-lymphocytes (CD3) and T lymphocyte subsets (CD4 and CD8). After the initial decrease, levels partially recovered and remained stable throughout the remainder of the clinical trial period. There was no change in B lymphocytes (CD19) in any treatment group. There was a dose-dependent early decreased in NK cells (CD16/56) which remained stable throughout the remainder of the clinical trial period. The clinical relevance of decreases in lymphocyte subsets (circulating T cell lymphocytes and NK cells) is defined under Lymphocyte count decreased.
Dose-dependent and fully reversible decreases in RBC parameters (haemoglobin, hematocrit, and reticulocytes) and increases in platelets and fibrinogen were observed in rats or dogs without adverse macroscopic or microscopic findings indicative of hematologic dysfunction or systemic infection.	Haemoglobin: In clinical trials there was a slight median decrease from baseline (BL) in haemoglobin (Hgb) up to 4 weeks after initiation of ritlecitinib; Hgb remained stable and near BL to Week 24 with a slight median decrease from BL observed at Week 48 in the All-Exposure Pool (50 mg). Less than 0.1% of patients met protocol-specified discontinuation criteria for change in Hgb (< 0.9 g/dL) or a decrease of > 30% (confirmed with a retest) from BL. No participant had confirmed Hgb < 8g/dL. Platelets: In the placebo-controlled clinical trials for up to 24 weeks, treatment with ritlecitinib was associated with a decrease in platelet count. Maximum effect on platelets were observed within 4 weeks after which platelet counts remained stable at a lower level with continued therapy. Across all clinical trials with ritlecitinib, < 0.1% of patients treated with ritlecitinib 50 mg or higher had a confirmed platelet count < 100 $x10^3/mm^3$. No patient had a confirmed platelet count of < 75 x $10^3/mm^3$. There were no bleeding events associated with changes in platelets.

Table 4. Key Safety Findings and Relevance to Human Usage

Key Safety Findings from Non-clinical Studies	Relevance to Human Usage
	The clinical data are sufficient to conclude that Platelet count decreased is an ADR.
Kidney	
Reversible hyaline droplet accumulation in proximal tubular epithelial cells (primarily lipofuscin in the medulla and alpha2μ-globulin in the cortex) was observed in the chronic rat toxicity study only and did not progress with longer dose administration, as demonstrated by data from the 2-year rat carcinogenicity study.	These findings are not relevant to human usage. Lipofuscin and alpha2μ globulin are findings noted in normal rats and have limited or no renal functional or clinical significance. There was no evidence of effects on the kidney in clinical trials with ritlecitinib; there were no clinically meaningful changes in serum creatinine over time in any ritlecitinib treatment group or placebo.
Liver	
Hepatocyte vacuolation or centrilobular hypertrophy were observed only in shorter (≤8-week) rat toxicity studies. Non-neoplastic increases in multinucleated hepatocytes (relative to controls) were observed in female rats in the 2-year carcinogenicity study. No microscopic evidence of hepatocyte degeneration, necrosis, or inflammation was noted.	These findings are not relevant to human usage. Multinucleated hepatocytes are considered an adaptive response and not an indication of potential carcinogenicity. Multinucleated hepatocytes can occur spontaneously in aged rats; therefore, the increased prominence of these findings in rats was considered a ritlecitinib-related exacerbation of background findings in rats without relevance to humans.
Adrenal Gland	
Transient, dose-related findings not associated with degenerative changes in the adrenal gland were noted in short-duration toxicity studies in rats and dogs. Lower adrenal weights (males) and increased adrenal cortical vacuolation were observed in rats and an increase in the incidence and/or severity of cortical cell vacuolation was observed in the zona glomerulosa in male dogs.	Effects on the adrenal gland or adrenal gland function are not anticipated in humans based on known pharmacology of JAK or TEC inhibitors. There was no evidence of effects on the adrenal gland in clinical trials with ritlecitinib.
Abnormal feces	
Abnormal feces (soft, watery, mucoid, red-tinged) were observed in dogs without macroscopic or microscopic findings in the gastrointestinal tract.	Based upon the clinical trial data, diarrhea is an ADR for ritlecitinib.
Reproductive/developmental toxicity	
Fertility	
Ritlecitinib did not affect female rat fertility at exposures up to 55 times the unbound AUC_{24} at the 50 mg human dose. Male rat fertility was affected at 55 times the unbound AUC_{24} at the 50 mg human dose. There was a higher number of preimplantation losses resulting in a lower number of implantation sites and corresponding lower litter size in naïve females mated with ritlecitinib dosed males.	Results from the rat fertility toxicity study are not relevant to human usage at clinically relevant exposures.

Table 4. Key Safety Findings and Relevance to Human Usage

Key Safety Findings from Non-clinical Studies	Relevance to Human Usage
Reproductive/developmental	
Developmental effects observed when pregnant rats and rabbits were administered ritlecitinib included skeletal malformations and variations and lower foetal body weights in both species, and higher incidences of visceral malformations (kidney malformation) and higher postimplantation loss in rabbits. The lowest NOAEL from the EFD studies was in rabbits with an exposure margin of 12 times the unbound AUC_{24} at the 50 mg human dose. In a pre- and postnatal development study in rats, adverse ritlecitinib-related effects were observed at the highest dose in the F1 male and female offspring, at 41 times the unbound AUC_{24} at the 50 mg human dose. This dose included lower mean postnatal survival, lower body weights, and lower body weight gains during the preweaning and postweaning periods, effects on sexual maturation (considered secondary to the lower body weights), and effects on reproduction in F1 females (lower mean number of corpora lutea, implantation sites, and viable embryos). The exposure margins at the NOAEL of 75 mg/kg/day for developmental toxicity was 14 times the unbound AUC_{24} at the 50 mg human dose. A juvenile toxicity study was conducted to determine the potential effects of oral administration of ritlecitinib on postnatal growth and development, including effects on the skeletal and nervous systems and neurobehavior, in juvenile male and female Wistar Han rats when administered by oral gavage from postnatal day (PND) 10 through PND 60. These ages correspond to a human age range of approximately 3 months to adolescence. There were no ritlecitinib-related effects on bone growth or the CNS/PNS, synaptogenesis, myelination, or neurobehavioral endpoints at exposures up to 19 times the unbound AUC_{24} at the 50 mg human dose. Delayed attainment of balanopreputial separation and shorter femur length (relative to control) were observed secondary to the lower body weight and body weight gain in males at 100 mg/kg/day, findings which are observed secondary to lower body weights. The NOAEL was 50 mg/kg/day for males based on the adverse effects on body weight/body weight gain at 100 mg/kg/day, and as 100 mg/kg/day for females, based on the lack of adverse effects at any dose (7-and 19 times, respectively, the unbound AUC_{24} at the 50 mg human dose).	Results from rat and rabbit EFD toxicity studies are potentially relevant to human usage. The foetal skeletal findings in pregnant animals are not relevant to usage in adults and adolescents >12 years of age. Pregnancy is contraindicated and Embryofoetal toxicity following exposure in utero is an important potential risk for ritlecitinib.

Table 4. Key Safety Findings and Relevance to Human Usage

Key Safety Findings from Non-clinical Studies	Relevance to Human Usage
Genotoxicity	
Ritlecitinib was negative in the bacterial reverse mutation assay. Ritlecitinib was not aneugenic or clastogenic at exposures equal to 130 times the unbound AUC_{24} at the 50 mg human dose based on the results of the in vivo rat bone marrow micronucleus assay.	Not relevant to human usage.
Carcinogenicity	
In a 2-year rat carcinogenicity study in Wistar Han rats, a higher incidence of benign thymomas in female rats and benign thyroid follicular cell adenomas in male rats were noted following ritlecitinib administration at exposures equal to 29 times the unbound AUC_{24} at the 50 mg human dose. At this ritlecitinib exposure, a higher incidence of malignant thymomas in female rats cannot be excluded. No ritlecitinib-related thymomas or thyroid follicular adenomas were observed at exposures ≤6.3 times the unbound AUC_{24} at the 50 mg human dose. No evidence of tumourigenicity was observed in the 6-month Tg.rasH2 mice administered ritlecitinib at exposures equal to 11 times the unbound AUC_{24} at the 50 mg human dose.	Not relevant to human usage. The mechanism by which ritlecitinib leads to increased thymoma and benign thyroid follicular adenoma incidence in rats is likely related to a non-genotoxic mechanism as ritlecitinib is not genotoxic. Furthermore, there is evidence that thymoma and benign thyroid follicular adenomas are rat specific. Female Wistar rats exhibit strain-specific differences in thymus biology, and thymomas in these rats form spontaneously with age at a high incidence relative to other rat strains. This effect has been demonstrated to be exacerbated following administration of other immunosuppressive drugs. Male Wistar Han rats are particularly susceptible to spontaneous thyroid adenomas as they age, and published literature suggests there is limited translation of rodent thyroid tumours to humans. No events of benign or malignant thymoma have been reported in ritlecitinib clinical studies. Malignancy is an important potential risk for ritlecitinib.
Safety Pharmacology	
Cardiovascular system There was no ritlecitinib-related QTc prolongation after administration of ritlecitinib in any safety pharmacology CV or effects on the CV system in the repeat-dose toxicity study in dogs. The IC50 value for the inhibitory effect of ritlecitinib on the hERG potassium current was >273 times the unbound C_{max} at the 50 mg human dose. Low magnitude and inconsistent changes in heart rate and blood pressure were observed in safety pharmacology and toxicity studies. There were no microscopic changes in the heart in any toxicity study and no evidence of ritlecitinib-related thrombi, emboli, or changes in coagulation parameters in rats or dogs in repeat-dose toxicity studies up to 6 or 9 months in duration, respectively.	Not relevant to human usage. There were no clinically meaningful changes in ECG measurements in participants in ritlecitinib treatment or placebo in clinical trials. There were no clinically meaningful changes in baseline median QTcF interval over time across the treatment groups up to week 48. In a concentration/QTc analysis to characterize potential of ritlecitinib to prolong QTc interval, no evidence of any relevant QTc interval prolongation was observed. There were no clinically meaningful changes across ritlecitinib treatment groups in blood pressure and pulse rate in clinical trials.

Table 4. Key Safety Findings and Relevance to Human Usage

Key Safety Findings from Non-clinical Studies	Relevance to Human Usage
Nervous system There were no ritlecitinib-related effects on neurofunctional endpoints (body temperature, quantitative locomotor activity, or functional observation assessment) in rats. *Respiratory system* There were no ritlecitinib-related effects on respiratory endpoints (respiratory rate, tidal or minute volumes) in rats.	
Drug interactions	
The metabolism of ritlecitinib is mediated by multiple isoforms of Glutathione S-transferase (GST) (cytosolic GST A1/3, M1/3/5, P1, S1, T2, Z1 and microsomal MAPEG1/2/3) and CYP enzymes (CYP3A, CYP2C8, CYP1A2, and CYP2C9), with no single clearance route contributing more than 25%. Hence, drugs inhibiting a selective metabolic pathway are unlikely to impact the systemic exposures of ritlecitinib. Specific inhibitors of transporters are unlikely to result in clinically relevant changes in the bioavailability of ritlecitinib.	Based on itraconazole and rifampin DDI studies, no clinically significant changes in AUCinf were observed. Dose adjustment is not required when ritlecitinib is administered with CYP3A inhibitors or CYP enzyme inducers.
Ritlecitinib is a moderate inhibitor of CYP3A.	Multiple doses of 200 mg once daily ritlecitinib increased the AUC_{inf} and C_{max} of midazolam a CYP3A4 substrate, by approximately 2.7 fold and 1.8 fold, respectively. Ritlecitinib is a moderate inhibitor of CYP3A. Caution should be exercised with concomitant use of ritlecitinib with CYP3A substrates (e.g., quinidine, cyclosporine, dihydroergotamine, ergotamine, pimozide) where moderate concentration changes may lead to serious adverse reactions, and dose adjustment recommendations for the CYP3A substrate (e.g., colchicine, everolimus, tacrolimus, sirolimus) should be considered.
Ritlecitinib is a moderate inhibitor of CYP1A2.	Multiple doses of 200 mg once daily ritlecitinib increased the AUC_{inf} and C_{max} of caffeine, a CYP1A2 substrate, by approximately 2.7-fold and 1.1- fold, respectively. Caution should be exercised with concomitant use of ritlecitinib with other CYP1A2 substrates (e.g., tizanidine) where moderate concentration changes may lead to serious adverse reactions, and dose adjustment recommendations for the CYP1A2 substrate (e.g., theophylline, pirfenidone) should be considered.
Ritlecitinib and OCT1 substrates	The coadministration of a single 400 mg dose of ritlecitinib increased the AUC_{inf} of sumatriptan (an OCT1 substrate) by approximately 1.3 to 1.5 fold relative to sumatriptan dose given alone. The

Table 4. Key Safety Findings and Relevance to Human Usage

Key Safety Findings from Non-clinical Studies	Relevance to Human Usage
	increase in sumatriptan exposure is not considered clinically relevant. Caution should be exercised with concomitant use of ritlecitinib with OCT1 substrates where small concentration changes may lead to serious adverse reactions. Ritlecitinib did not produce clinically significant changes in the exposures of oral contraceptives (e.g., ethinyl oestradiol or levonorgestrel), CYP2B6 substrates (e.g., efavirenz), CYP2C substrates (e.g., tolbutamide), or substrates of organic anion transporter (OAT)P1B1, breast cancer resistant protein (BCRP), and OAT3 (e.g., rosuvastatin).
Other toxicity-related information or data	
Lactation Ritlecitinib was excreted in milk of lactating rats.	There are no data on the presence of ritlecitinib in human milk, effects on the breast-fed infant, or effects on milk production. A risk to newborns/infants cannot be excluded and ritlecitinib is contraindicated during breastfeeding.

Module SIII. Clinical Trial Exposure

The ritlecitinib clinical trial program includes 21 Phase 1 studies, 2 completed studies of participants with AA (1 Phase 2a study and 1 Phase 2b/3 study), 2 ongoing studies of participants with AA (1 Phase 2a study and 1 Phase 3 long-term study).

Additional safety data from 5 clinical studies in other indications is also included: vitiligo (1 completed Phase 2b study), UC (1 completed Phase 2b study), Crohn's disease (1 ongoing Phase 2a study), and RA (1 completed Phase 2a study and 1 ongoing Phase 2 study).

The clinical trial exposure data is provided for 2 safety pools, the Placebo-Controlled AA Pool and the All-Exposure Pool (AA + Vitiligo). The Placebo-Controlled AA Pool (PCPAA) includes studies (B7931005, B7981015, B7981037) with a placebo comparator, of similar duration (24 weeks), similar doses of ritlecitinib, similar patient populations and comparable safety outcome assessments. The treatment groups summarised in this pool are participants who received ritlecitinib 200/50 mg (200 mg for 4 weeks, followed by 50 mg); 50/50 mg, All 50 mg (combined 200/50 mg and 50/50 mg), All 30 mg (combined 200/30 mg and 30/30 mg) and 10 mg, with placebo as a comparator. The studies in this pool allow for comparison of adolescent and adult data as Study B7981015 includes both adolescents and adults and Studies B7931005 and B7981037 include adults. Cumulatively through 04 January 2022, there were 345 participants exposed to ritlecitinib All 50 mg in the PCPAA, totaling 154.4 patient-years of exposure to ritlecitinib 50 mg or higher (Table 5).

The All-Exposure Pool includes the same studies (B79831005, B7981015, B7981037) included in the placebo-controlled pool, the long-term, open-label study (B7981032), and a

Phase 2b study in vitiligo (B7981019). Study B7981019 in vitiligo is relevant for the evaluation of safety in AA due to similarities between AA and vitiligo populations (including disease pathophysiology, age distribution and comorbidities), similar dosing regimens to those in the AA studies, and similar safety monitoring. All participants who received ritlecitinib, from the start of their first dose of ritlecitinib in studies B7931005, B7981015, B7981019 and B7981037, as well as the long-term, open-label study B7981032 are included in this pool. The treatment groups summarised in this pool are ritlecitinib All 50 mg (200/50 mg, 100/50 mg, and 50/50 mg) and Any Ritlecitinib (participants who received any dose of ritlecitinib) from all studies. Cumulatively through 25 June 2024, there were 1523 patients exposed to ritlecitinib All 50 mg in the All-Exposure Pool, totaling 3429 patient-years of exposure to ritlecitinib 50 mg or higher (Table 9).

Clinical Trial Exposure for ritlecitinib is provided in Table 5-Table 12.

Table 5. Ritlecitinib Summary of Clinical Safety Clinical Trial Exposure to Ritlecitinib by Duration Placebo-Controlled AA Pool

	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)	
Duration of Exposure Category[a]	n (%)	PY[b]	n (%)	PY[b]	n (%)	PY[b]	n (%)	PY[b]	n (%)	PY[b]	n (%)	PY[b]
< 4 weeks	4 (1.9)	0.18	2 (1.5)	0.10	6 (1.7)	0.28	8 (3.1)	0.21	1 (1.6)	0.00	3 (1.4)	0.09
≥4 weeks to < 8 weeks	2 (0.9)	0.26	2 (1.5)	0.21	4 (1.2)	0.47	5 (1.9)	0.65	1 (1.6)	0.08	2 (0.9)	0.21
≥8 weeks to < 12 weeks	2 (0.9)	0.39	1 (0.8)	0.19	3 (0.9)	0.58	5 (1.9)	0.92	0		3 (1.4)	0.64
≥12 weeks to < 16 weeks	2 (0.9)	0.49	3 (2.3)	0.81	5 (1.4)	1.30	1 (0.4)	0.30	1 (1.6)	0.26	2 (0.9)	0.47
≥16 weeks to ≤24 weeks	55 (25.6)	24.54	36 (27.7)	16.21	91 (26.4)	40.75	87 (33.3)	39.26	19 (30.6)	8.59	57 (26.8)	25.07
>24 weeks	150 (69.8)	70.13	86 (66.2)	40.64	236 (68.4)	110.77	155 (59.4)	73.20	40 (64.5)	18.71	146 (68.5)	68.33
Total	215 (100.0)	95.99	130 (100.0)	58.16	345 (100.0)	154.15	261 (100.0)	114.54	62 (100.0)	27.64	213 (100.0)	94.81

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.
a. Number of days from first to and including last day of each study treatment (Last Dosing Date - First Dosing Date + 1).
b. Total Patient-years: Total follow up time calculated up to 35 days after the last dose in the corresponding treatment group /365.25.
B7981037 data cutoff date: 04JAN2022.
[redacted] Source Data: adex Source Dataset Creation: 23MAR2022 (22:02) Table Generation: 31MAR2022 (08:48)
Output File: ./aa_scs_nda/PCPAA/adex_s001_rmp_1b

Table 6. Ritlecitinib Summary of Clinical Safety Clinical Trial Exposure to Ritlecitinib by Age Group and Gender Placebo-Controlled AA Pool

	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)			
	Male		Female		Male		Female		Male		Female		Male		Female		Male		Female		Male		Female	
Age Group	n (%)	PY[a]	n (%)	PY[a]	n (%)	PY[a]	n (%)	PY[a]	n (%)	PY[a]	n (%)	PY[a]	n (%)	PY[a]	n (%)	PY[a]	n (%)	PY[a]	n (%)	PY[a]	n (%)	PY[a]	n (%)	PY[a]
Adolescent (12-<18)	13 (6.0)	6.00	7 (3.3)	3.28	12 (9.2)	5.18	6 (4.6)	2.79	25 (7.2)	11.18	13 (3.8)	6.07	16 (6.1)	7.42	23 (8.8)	10.77	3 (4.8)	1.39	6 (9.7)	2.74	7 (3.3)	3.27	12 (5.6)	5.57
Adult (≥18)	60 (27.9)	26.90	135 (62.8)	59.81	47 (36.2)	20.65	65 (50.0)	29.54	107 (31.0)	47.55	200 (58.0)	89.35	80 (30.7)	36.30	142 (54.4)	60.05	17 (27.4)	7.47	36 (58.1)	16.04	66 (31.0)	29.40	128 (60.1)	56.57
Adult (18-<50)	49 (22.8)	22.12	111 (51.6)	49.31	45 (34.6)	19.71	52 (40.0)	24.10	94 (27.2)	41.83	163 (47.2)	73.41	72 (27.6)	32.50	112 (42.9)	47.25	16 (25.8)	7.01	25 (40.3)	10.95	55 (25.8)	24.69	104 (48.8)	46.24
Adult (≥50)	11 (5.1)	4.78	24 (11.2)	10.50	2 (1.5)	0.94	13 (10.0)	5.44	13 (3.8)	5.72	37 (10.7)	15.94	8 (3.1)	3.80	30 (11.5)	12.80	1 (1.6)	0.46	11 (17.7)	5.09	11 (5.2)	4.71	24 (11.3)	10.33
Adult (≥65)	1 (0.5)	0.46	4 (1.9)	1.83	0		3 (2.3)	1.42	1 (0.3)	0.46	7 (2.0)	3.25	1 (0.4)	0.45	7 (2.7)	2.46	0		0		0		6 (2.8)	2.73
Total	73 (34.0)	32.90	142 (66.0)	63.09	59 (45.4)	25.83	71 (54.6)	32.33	132 (38.3)	58.73	213 (61.7)	95.42	96 (36.8)	43.72	165 (63.2)	70.82	20 (32.3)	8.86	42 (67.7)	18.78	73 (34.3)	32.67	140 (65.7)	62.14

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.
a. Total Patient-years: Total follow up time calculated up to 35 days after the last dose in the corresponding treatment group /365.25.
B7981037 data cutoff date: 04JAN2022.
[redacted] Source Data: adex Source Dataset Creation: 23MAR2022 (22:02) Table Generation: 31MAR2022 (08:48)
Output File: ./aa_scs_nda/PCPAA/adex_s001_rmp_2b

Table 7. Ritlecitinib Summary of Clinical Safety Clinical Trial Exposure to Ritlecitinib by Ethnic Origin Placebo-Controlled AA Pool

	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)	
Ethnicity	**n (%)**	**PY[a]**	**n (%)**	**PY[a]**	**n (%)**	**PY[a]**	**n (%)**	**PY[a]**	**n (%)**	**PY[a]**	**n (%)**	**PY[a]**
Hispanic or Latino	24 (11.2)	11.00	11 (8.5)	5.10	35 (10.1)	16.10	39 (14.9)	17.63	8 (12.9)	3.26	18 (8.5)	8.03
Not Hispanic or Latino	190 (88.4)	84.53	116 (89.2)	51.62	306 (88.7)	136.15	222 (85.1)	96.91	54 (87.1)	24.38	194 (91.1)	86.32
Not Reported	1 (0.5)	0.46	3 (2.3)	1.44	4 (1.2)	1.90	0		0		1 (0.5)	0.46
Total	215 (100.0)	95.99	130 (100.0)	58.16	345 (100.0)	154.15	261 (100.0)	114.54	62 (100.0)	27.64	213 (100.0)	94.81

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.
a. Total Patient-years: Total follow up time calculated up to 35 days after the last dose in the corresponding treatment group /365.25.
B7981037 data cutoff date: 04JAN2022.
[redacted] Source Data: adex Source Dataset Creation: 23MAR2022 (22:02) Table Generation: 31MAR2022 (08:48)
Output File: ./aa_scs_nda/PCPAA/adex_s001_rmp_3b

Table 8. Ritlecitinib Summary of Clinical Safety Clinical Trial Exposure to Ritlecitinib by Race Placebo-Controlled AA Pool

	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)	
Race	**n (%)**	**PY[a]**	**n (%)**	**PY[a]**	**n (%)**	**PY[a]**	**n (%)**	**PY[a]**	**n (%)**	**PY[a]**	**n (%)**	**PY[a]**
White	155 (72.1)	70.10	79 (60.8)	35.36	234 (67.8)	105.46	181 (69.3)	78.03	41 (66.1)	18.28	167 (78.4)	74.36
Black	17 (7.9)	6.67	5 (3.8)	2.22	22 (6.4)	8.89	9 (3.4)	3.90	2 (3.2)	0.87	8 (3.8)	3.35
Asian	39 (18.1)	17.59	43 (33.1)	19.18	82 (23.8)	36.77	62 (23.8)	28.75	17 (27.4)	7.57	33 (15.5)	14.76
Other	3 (1.4)	1.17	1 (0.8)	0.44	4 (1.2)	1.61	8 (3.1)	3.40	1 (1.6)	0.46	4 (1.9)	1.88
Not Reported	1 (0.5)	0.46	2 (1.5)	0.96	3 (0.9)	1.42	1 (0.4)	0.46	1 (1.6)	0.46	1 (0.5)	0.46
Total	215 (100.0)	95.99	130 (100.0)	58.16	345 (100.0)	154.15	261 (100.0)	114.54	62 (100.0)	27.64	213 (100.0)	94.81

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.
a. Total Patient-years: Total follow up time calculated up to 35 days after the last dose in the corresponding treatment group /365.25.
B7981037 data cutoff date: 04JAN2022.
[redacted] Source Data: adex Source Dataset Creation: 23MAR2022 (22:02) Table Generation: 31MAR2022 (08:48)
Output File: ./aa_scs_nda/PCPAA/adex_s001_rmp_4b

Table 9. Ritlecitinib Summary of Clinical Safety Clinical Trial Exposure to Ritlecitinib by Duration All-Exposure Pool

Duration of Exposure[a]	Ritlecitinib 50 mg (N=1523) n (%)	Ritlecitinib 50 mg (N=1523) PY[b]	Any Ritlecitinib (N=1630) n (%)	Any Ritlecitinib (N=1630) PY[b]
<6 months	159 (10.4)	40.00	164 (10.1)	39.86
≥6 months to <12 months	288 (18.9)	159.06	266 (16.3)	153.87
≥12 months to <18 months	179 (11.8)	184.71	255 (15.6)	258.55
≥18 months to <24 months	62 (4.1)	98.49	81 (5.0)	127.02
≥24 months to <30 months	65 (4.3)	136.39	77 (4.7)	160.19
≥30 months to <36 months	49 (3.2)	124.23	54 (3.3)	135.93
≥36 months to <42 months	73 (4.8)	218.12	51 (3.1)	152.64
≥42 months to <48 months	320 (21.0)	1110.57	219 (13.4)	767.45
≥48 months to <54 months	168 (11.0)	654.18	171 (10.5)	665.18
≥54 months to <60 months	136 (8.9)	586.51	240 (14.7)	1036.95
≥60 months to <66 months	22 (1.4)	106.62	48 (2.9)	232.28
≥66 months to <72 months	2 (0.1)	10.24	4 (0.2)	20.58
≥72 months	0	0.00	0	0.00
Total	1523 (100.0)	3429.12	1630 (100.0)	3750.50

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.
a. Number of days from first to and including last day of each study treatment (Last Dosing Date - First Dosing Date + 1).
b. Total Patient-years: Total follow up time calculated up to 35 days after the last dose in the corresponding treatment group /365.25.
As a convention 1 month is equivalent to 4 weeks, 12 months is equivalent to 48 weeks.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25June2024.
[redacted] Source Data: adex Source Dataset Creation: 19AUG2024 (01:23 Table Generation: 23AUG2024 (13:17)
Output File: ./aa scs nda/AEP SU/adex s001 rmp 1b

Table 10. Ritlecitinib Summary of Clinical Safety Clinical Trial Exposure to Ritlecitinib by Age Group and Gender All-Exposure Pool

	Ritlecitinib 50 mg (N=1523)				Any Ritlecitinib (N=1630)			
	Male		Female		Male		Female	
Age Group	n (%)	PY[a]	n (%)	PY[a]	n (%)	PY[a]	n (%)	PY[a]
Adolescent (12-<18)	80 (5.3)	187.87	92 (6.0)	239.34	83 (5.1)	205.29	98 (6.0)	265.71
Adult (≥ 18)	503 (33.0)	1040.94	848 (55.7)	1960.97	549 (33.7)	1144.57	900 (55.2)	2134.93
Adult (18-<50)	405 (26.6)	872.67	648 (42.5)	1552.84	441 (27.1)	960.11	686 (42.1)	1682.97
Adult (≥ 50)	98 (6.4)	168.27	200 (13.1)	408.13	108 (6.6)	184.46	214 (13.1)	451.96
Adult (≥ 65)	4 (0.3)	6.78	26 (1.7)	60.37	4 (0.2)	7.71	29 (1.8)	66.16
Total	583 (38.3)	1228.81	940 (61.7)	2200.31	632 (38.8)	1349.86	998 (61.2)	2400.64

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.
a. Total Patient-years: Total follow up time calculated up to 35 days after the last dose in the corresponding treatment group /365.25.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25June2024.
[redacted] Source Data: adex Source Dataset Creation: 19AUG2024 (01:23) Table Generation: 23AUG2024 (13:17)
Output File: ./aa scs nda/AEP SU/adex s001 rmp 2b

Table 11. Ritlecitinib Summary of Clinical Safety Clinical Trial Exposure to Ritlecitinib by Ethnic Origin All-Exposure Pool

	Ritlecitinib 50 mg (N=1523)		Any Ritlecitinib (N=1630)	
Ethnicity	**n (%)**	**PY[a]**	**n (%)**	**PY[a]**
Hispanic or Latino	189 (12.4)	423.36	206 (12.6)	472.81
Not Hispanic or Latino	1315 (86.3)	2949.35	1405 (86.2)	3220.80
Not reported	19 (1.2)	56.41	19 (1.2)	56.89
Total	1523 (100.0)	3429.12	1630 (100.0)	3750.50

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.
a. Total Patient-years: Total follow up time calculated up to 35 days after the last dose in the corresponding treatment group /365.25.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adex Source Dataset Creation: 19AUG2024 (01:23) Table Generation: 23AUG2024 (13:17) Output File: ./aa scs nda/AEP SU/adex s001 rmp 3b

Table 12. Ritlecitinib Summary of Clinical Safety Clinical Trial Exposure to Ritlecitinib by Race All-Exposure Pool

Race	Ritlecitinib 50 mg (N=1523) n (%)	Ritlecitinib 50 mg (N=1523) PY[a]	Any Ritlecitinib (N=1630) n (%)	Any Ritlecitinib (N=1630) PY[a]
White	1063 (69.8)	2397.79	1135 (69.6)	2617.43
Black	57 (3.7)	87.64	63 (3.9)	98.09
Asian	344 (22.6)	829.47	366 (22.5)	908.44
Other	31 (2.0)	65.31	35 (2.1)	74.16
Not Reported	28 (1.8)	48.91	31 (1.9)	52.38
Total	1523 (100.0)	3429.12	1630 (100.0)	3750.50

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.
a. Total Patient-years: Total follow up time calculated up to 35 days after the last dose in the corresponding treatment group /365.25.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adex Source Dataset Creation: 19AUG2024 (01:23) Table Generation: 23AUG2024 (13:17) Output File: ./aa scs nda/AEP SU/adex s001 rmp 4b

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Detailed descriptions of all inclusion and exclusion criteria for clinical studies are provided in the individual CSRs.

Table 13. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
Exclusion criteria with respect to psychiatric conditions	Any psychiatric condition including recent or active suicidal ideation or behavior that meets any of the following criteria: • Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the Columbia suicide severity rating scale (C-SSRS); • Previous history of suicidal behaviors in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS; • Any lifetime history of serious or recurrent suicidal behavior; • Clinically significant depression: patient health questionnaire – 8 items (PHQ8) total score ≥15; • The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria.	Patients with AA have a higher incidence of SIB than the general population and, as such, to ensure patient safety, compliance with the protocol and interpretability of study results, it was important not to initiate patients with profound SIB in trials of an experimental drug.	Not considered missing information. Distribution of ritlecitinib to the brain is limited (brain:plasma AUC ratio <0.05). Analysis of participants with evidence of depression and anxiety[a] at baseline (of Study B7981015) showed improvement in patients treated with ritlecitinib in the depression and anxiety subscales through week 48. Across all patients treated with ritlecitinib 50 mg in the All Exposure Pool, there was 1 adolescent with a serious event of suicidal ideation, which was considered not related to study intervention by the investigator.
Exclusion criteria with respect to hematology parameters	Baseline values of • Absolute neutrophil count of <1.2 x 10^9/L (<1200/mm^3) • Hemoglobin <11.0 g/dL or hematocrit <33% • Platelet count of <150 x 10^9/L (<150,000/mm^3) • Absolute lymphocyte count of <0.80 x 10^9/L (<800/mm^3).	These criteria were included to mitigate the risk of the potential impact of JAK and TEC kinase inhibition on hematologic parameters. Although ritlecitinib selectivity for JAK3 and the TEC kinase family may spare adverse effects associated with other JAK signaling, such as neutropenia, thrombocytopenia and anemia associated with JAK2 cytokine signaling,	Not considered missing information. The clinical data are sufficient to determine that decreased lymphocyte count and decreased platelet counts (but not anemia or neutropenia), are ADRs. The SmPC states in Section 4.2 posology and method of administration that Treatment with ritlecitinib should not be initiated in patients with an absolute lymphocyte count (ALC) < 0.5 × 10^3/mm^3 or a platelet count < 100 × 10^3/mm^3.

Table 13. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
		this had not been tested in large populations.	
Exclusion criteria with respect to vaccinations	Vaccinated or exposed to a live or attenuated vaccine within the 6 weeks prior to the first dose of investigational product or is expected to be vaccinated or to have household exposure to these vaccines during treatment or during the 6 weeks following discontinuation of investigational product. Adolescent participants 12 to <18 years old without documented evidence of having received varicella vaccination (2 doses) or those who do not have evidence of prior exposure to varicella zoster virus (VZV) based on serological testing (i.e., varicella zoster virus immunoglobulin G antibody [VZV IgG Ab]) at screening.	This exclusion criterion was included due to the risk of infection associated with the use of live vaccines in participants receiving drugs with immunosuppressive activity. Immunosuppressive effects of ritlecitinib based on mechanism of action may affect lymphocyte function and viral reactivation, therefore vaccination criteria were included to minimize the participant's risk of infection.	Use of live/attenuated vaccines is not considered missing information. The SmPC states in Section 4.4 Special warnings and precautions for use that use of live attenuated vaccines should be avoided during or immediately prior to ritlecitinib treatment. In addition, the SmPC states that prior to initiating ritlecitinib, it is recommended that patients be brought up to date with all immunisations, including prophylactic herpes zoster vaccinations, in agreement with current immunisation guidelines.
Exclusion criteria with respect to infection history	• Have a history of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to day 1 . • Have active chronic or acute infection requiring treatment with oral antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to Baseline, or superficial skin infections within 1 week prior to day 1.	It may be complicated to interpret safety data from studies which enrolled participants with a history of active or recurrent infection. . In addition, participants with active TB, serious infections such as sepsis, or opportunistic infections (OIs) may be at risk for prolonged or more complicated illness.	Not considered missing information. Serious and opportunistic infections is an important potential risk. The SmPC states in Section 4.4 Special warnings and precautions for use that treatment with ritlecitinib should be avoided in patients with an active, serious infection.

Table 13. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
	• A subject known to be infected with HIV, Hepatitis B or Hepatitis C. • Have a history (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localised, dermatomal herpes zoster. • Have evidence of untreated or inadequately treated active or latent Mycobacterium tuberculosis (TB) infection.	Participants with recurrent or complicated HZ, active Hepatitis B or Hepatitis C may be at increased risk for reactivation.	In addition, the SmPC recommends that patients be screened for TB before starting therapy with ritlecitinib. Ritlecitinib should not be given to patients with active TB. Anti-TB therapy should be started prior to initiating therapy with ritlecitinib in patients with a new diagnosis of latent TB or previously untreated latent TB. Screening for viral hepatitis should be performed in accordance with local guidelines before starting therapy with ritlecitinib. The SmPC also states that the risks and benefits of treatment with ritlecitinib should be carefully considered for patients: • with chronic or recurrent infection • who have been exposed to TB • with a history of a serious or an opportunistic infection • who have resided or travelled in areas of endemic TB or endemic mycoses; or • with underlying conditions that may predispose them to infection
Exclusion criteria with respect to renal function and renal disease	Estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 based on the age appropriate calculation. Current or recent history of clinically significant severe, progressive, or uncontrolled renal disease (including but	This exclusion criterion was applied to clinical studies to protect participant safety while the effects of ritlecitinib on renal	Not considered missing information. A study to evaluate PK in subjects with severe renal impairment provides dosing recommendations such that no clinically significant difference in safety profile is

Table 13. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
	not limited to active renal disease or recent kidney stones)"	parameters were further explored and understood.	anticipated in patients with mild, moderate or severe renal impairment.
Exclusion criteria with respect to hepatic impairment and transaminase increase	Current or recent history of clinically significant, severe, progressive or uncontrolled disease hepatic disease. • AST or ALT values >2 times the ULN; • Total bilirubin ≥1.5 times the ULN; participants with a history of Gilbert's syndrome would be eligible provided the direct bilirubin is ≤ ULN.	These exclusion criteria were applied to clinical studies to protect participant safety while the effects of ritlecitinib on hepatic parameters were further explored and understood.	Use in patients with mild, moderate and severe hepatic impairment or with transaminase increase is not considered missing information. Based on studies to evaluate PK in subjects with mild and moderate hepatic impairment, no dosing adjustment is required in patients with mild and moderate hepatic impairment. As such, no difference in safety profile is anticipated for patients with mild or moderate hepatic impairment. Ritlecitinib is contraindicated in patients with severe hepatic impairment (Child Pugh C).

Table 13. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
Exclusion with respect to other immunosuppressive agents	Have received any of the following treatment regimens specified in the timeframes prior to the first dose of study intervention as outlined below: • Any prior treatment with non-B cell selective lymphocyte depleting agents. • B-cell-depleting agents within 6 months or 5 half-lives (if known), or until lymphocyte count returns to normal, whichever is longer. • Other immunomodulatory biologic agents within 12 weeks or 5 half-lives (if known), whichever is longer. • Use of systemic immunosuppressants within 8 weeks or 5 half-lives (if known), whichever is longer. • Prior treatment with any JAK inhibitors (Permitted in Study B7981032).	Concurrent use of these drugs may have compromised interpretation of efficacy endpoints and safety data as well as patient safety.	Not considered missing information. Serious and opportunistic infections are considered an important potential risk for ritlecitinib.
Exclusion criteria with respect to history of malignancy and lymphoproliferative disorders	Have a history of any lymphoproliferative disorder such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, history of lymphoma, history of leukemia, or signs and symptoms suggestive of current lymphatic or lymphoid disease. Have any present malignancies or have a history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.	Drugs with immunosuppressive activity may have the potential to affect host defense against malignancies. Thus, exclusion of participants with known previous malignancy was prudent while data were generated on the incidence and type of malignancies observed in patients treated with ritlecitinib.	Not considered missing information. The SmPC states in Section 4.4 Special warnings and precautions for use that the risks and benefits of ritlecitinib treatment should be considered prior to initiating or continuing therapy in patients with a known malignancy other than a successfully treated NMSC or cervical cancer. Malignancy is an important potential risk.

Table 13. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
Exclusion due to know immunodeficiency disorder or with respect to family history of hereditary immunodeficiency	Have a known immunodeficiency disorder or a first-degree relative with a hereditary immunodeficiency.	Patients with an immunodeficiency disorder could affect patient safety and would confound interpretation of safety data.	Not considered missing information. This exclusion criteria addresses a rare condition. Prescribers will be able to assess risk without specific risk minimization measures.
Exclusion criteria with respect to hearing loss	Have hearing loss with progression over the previous 5 years, or sudden hearing loss, or middle or inner ear disease such as otitis media, cholesteatoma, Meniere's disease, labyrinthitis, or other auditory condition that is considered acute, fluctuating or progressive.	Patients with certain hearing conditions would confound interpretation of safety data.	Not considered missing information. Evaluation of the potential for hearing loss in the clinical program did not demonstrate evidence suggestive of ototoxicity.

a. HADS anxiety subscale score of > 7 for adults and >8 for adolescents is indicative of anxiety; a HADS depression subscale score of >7 for adults and >6 for adolescents is indicative of depression. "

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme, given its sample size and duration of follow-up at the time of submission, is unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency (eg, malignancies and cardiovascular events). The long-term safety data will continuously be collected via routine and additional pharmacovigilance activities.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

There has been limited exposure to ritlecitinib in special populations and no epidemiologic studies have been conducted in pregnant/lactating women.

Table 14. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women and Breastfeeding women	There are no adequate and well-controlled studies on the use of ritlecitinib in pregnant or breast-feeding women. Pregnant and breastfeeding women were not included in the clinical development program. Ritlecitinib use during pregnancy and breastfeeding is contraindicated.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Participants were excluded with: • Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2x ULN • Total bilirubin >1.5 times the ULN; participants with a history of Gilbert's syndrome would be eligible provided the direct bilirubin was ≤ULN. • Current or recent history of clinically significant severe, progressive, or uncontrolled hepatic disease. Study B7981016 evaluated the pharmacokinetics, safety and tolerability of ritlecitinib in participants with hepatic impairment and in healthy participants with normal hepatic function. 10 participants with moderate hepatic impairment and 8 participants with normal hepatic function were enrolled. No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Ritlecitinib is not recommended in patients with severe hepatic impairment (Child Pugh C).
• Patients with renal impairment	Participants were excluded with: • Estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 based on the age-appropriate calculation. • Current or recent history of clinically significant severe, progressive, or uncontrolled renal disease (including but not limited to active renal disease or recent kidney stones). Study B7981020 evaluated the pharmacokinetics, safety and tolerability of ritlecitinib in participants with renal impairment and in healthy participants with normal renal function. Eight participants with severe renal impairment were enrolled. No dose adjustment is required in patients with mild, moderate or severe renal impairment. Ritlecitinib was not studied in patients with end stage renal disease (ESRD) or in patients with a renal transplant.

Table 14. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
• Patients with cardiovascular disease	There are no adequate and well-controlled studies on the use of ritlecitinib in this patient population. Across all participants exposed to ritlecitinib 50 mg (N=1521), 63 participants (4.3%) reported current or ongoing medical history in the cardiac disorders SOC.
• Immunocompromised patients	Not included in the clinical development program.
• Patients with a disease severity different from inclusion criteria in clinical trials	The proposed indication will be for Litfulo is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older. Participants who were not candidates for systemic therapy were excluded from the clinical studies.
Population with relevant different ethnic origin	Across all participants exposed to ritlecitinib 50 mg (N=1521), there was more overall exposure in the White (1061 participants, 1230.75 PY) and Asian (344 participants, 418.97 PY) subgroups relative to the Black (57 participants, 53.79 PY) and Other/not reported (59 participants, 59.82 PY) subgroups. There were 189 participants in the Hispanic/Latino subgroup (208.84 PY) and 1313 participants in the Not Hispanic/Latino subgroup (1528.59 PY). No unique risks were identified by race or ethnicity.
Subpopulations carrying relevant genetic polymorphisms	Evaluation of genetic polymorphisms was not included in the clinical development program.

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

SV.1.1. Method Used to Calculate Exposure

SV.1.2. Exposure

The estimated cumulative patient exposure was obtained from the most recent PSUR (23 December 2023 through 22 June 2024).

The cumulative exposure to ritlecitinib since the product was first approved and became commercially available until the Data Lock Point (DLP) of this PSUR is estimated to be 1139 patient-years.

The cumulative estimated patient exposure is based on worldwide sales of 20,798,250 mg. Assuming that patients are taking a dose of 50 mg per day, the estimated exposure is 415,965 patient-days. As such, the patient-years is estimated to be 1139 patient-years by dividing the patient-days by 365.25.

Cumulative estimated exposure by indication and gender based on data provided by IQVIA Health Prescribing Insights Medical for the period from IBD (23 June 2023) through the 1st quarter of 2024 and extrapolated by taking the daily average KG sales of the 1st quarter of 2024 through 22 June 2024, are summarised in Table 15.

Table 15. Cumulative Exposure for Ritlecitinib (IBD to 22 June 2024)

Indications	Gender		Age (years)		
	Male	Female	0 - 16	17 - 65	> 65
Alopecia areata[a]	639	500	389	713	37

a. Form, region and dosage splits have not been calculated since only one category was present.

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

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

Module SVII. Identified and Potential Risks

The safety concerns for this Initial RMP for ritlecitinib are described in the relevant sections below

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

Table 16. Summary of Safety Concerns

Important identified risks	Herpes zoster

Table 16. Summary of Safety Concerns

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.

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

- Lymphocyte count decreased
- Platelet count decreased
- Blood CPK increased
- Acne,
- Rash,
- Urticaria
- Diarrhoea
- Dizziness
- Folliculitis
- Upper respiratory tract infection
- Alanine aminotransferase increased > 3 × ULN
- Aspartate aminotransferase increased > 3 × ULN

Reason for not including an identified or potential risk in the list of safety concerns in the RMP: The above risks described in the proposed Summary of Product Characteristics (SmPC) and package leaflet (PL) require no further characterisation and are followed via routine pharmacovigilance namely through signal detection and adverse reaction reporting.

The risk minimisation messages in the product information are to be adhered to by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised).

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

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

Table 17. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks and Missing Information	Risk-Benefit Impact
Important Identified Risks	
Herpes zoster	Herpes zoster has the potential to impact the risk-benefit profile for ritlecitinib as this event, though infrequent, may be serious or life-threatening. Additional pharmacovigilance and additional risk minimisation measures are planned.
Important Potential Risks	
Serious and opportunistic infections	Serious and opportunistic infections have the potential to impact the risk-benefit profile for ritlecitinib as these events, though infrequent, may be serious or life-threatening. Additional pharmacovigilance and additional risk minimization measures are planned.
Malignancy	Malignancies have the potential to impact the risk-benefit profile for ritlecitinib as these events, though infrequent, may be serious or life-threatening. Additional pharmacovigilance and additional risk minimization measures are planned.
Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis	Thromboembolic events have the potential to impact the risk-benefit profile for ritlecitinib as these events, though infrequent, may be serious or life-threatening. Additional pharmacovigilance and additional risk minimisation measures are planned.
Embryofoetal toxicity following exposure in utero	Given the non-clinical data regarding embryofoetal toxicity with ritlecitinib, ritlecitinib is contraindicated during pregnancy. Additional pharmacovigilance and additional risk minimisation measures are planned.
MACE	Major adverse cardiovascular events have the potential to impact the risk-benefit profile for ritlecitinib as these events, although infrequent, may be serious or life threatening. Additional pharmacovigilance measures are planned.
Neurotoxicity	Neurotoxic events have the potential to impact the risk-benefit profile for ritlecitinib as these events, though infrequent, may be serious or life threatening. Additional pharmacovigilance measures are planned.
Missing Information	
Long-term safety	There were limited long-term data in clinical studies.
Long-term safety in adolescent patients including growth and bone development, and maturation and pubertal development.	There were limited long-term data in clinical studies

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

Not Applicable for this initial RMP.

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

Herpes zoster is an important Identified risk for ritlecitinib. The important potential risks include Serious and Opportunistic infections, Malignancy, Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis and Embryofoetal toxicity following exposure in utero. The missing information includes Long-term safety and long-term safety in adolescent patients including growth and bone development, and maturation and pubertal development These risks were determined using data from the following clinical trials: PCPAA and AEP.

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

SVII.3.1.1. Important Identified Risk: Herpes zoster

Potential Mechanisms

Ritlecitinib's pharmacology of inhibition of JAK3 and TEC family of kinases may result in modulation of multiple aspects of the immune response.[92, 93] Viral reactivation, including herpes zoster infections, have been associated with the use of immunomodulators.

Evidence Source and Strength of Evidence

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

Characterisation of the Risk

Frequency of Herpes zoster

The frequencies for herpes zoster and adjudicated opportunistic herpes zoster are provided in Table 17. Adjudicated opportunistic herpes zoster events are a subset of all herpes zoster. There were 2 events confirmed as opportunistic infections; both were multi-dermatomal herpes zoster and neither was disseminated. In the placebo-controlled AA pool, there was 1 adjudicated event of multi-dermatomal herpes zoster (PT of Varicella zoster virus infection) in the ritlecitinib 200/50 mg group. In the All Exposure Pool, there was 1 additional event of multi-dermatomal herpes zoster (PT of Herpes zoster) in the all 50 mg group.

Table 18. Proportion and Incidence Rates of Subjects for Treatment-Emergent Herpes Zoster - Placebo-Controlled AA Pool

	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)
Opportunistic Infections						
	Number of Subjects with Event n (%) Total Drug exposure (PY)[a] Incidence rates (95% CI)[b]					
Adjudicated Opportunistic Herpes Zoster	1 (0.5) 101.19 0.50 (0.02, 4.62)	0 59.16 0.00 (0.00, 4.05)	1 (0.3) 160.34 0.50 (0.02, 2.85)	0 116.77 0.00 (0.00, 2.06)	0 28.03 0.00 (0.00, 8.56)	0 99.85 0.00 (0.00, 3.98)
All Herpes Zoster Infections (CMQ)	1 (0.5) 101.19 0.50 (0.02, 4.62)	2 (1.5) 58.49 2.74 (0.45, 9.05)	3 (0.9) 159.68 1.85 (0.46, 5.15)	2 (0.8) 116.61 1.37 (0.23, 4.55)	0 28.03 0.00 (0.00, 8.56)	0 99.85 0.00 (0.00, 3.98)

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.
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].
N: Number of participants in pool. N: Number of participants with event.
a. 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.
b. Study-size adjusted results per 100 PY and mid-p gamma intervals.
B7981037 data cutoff date: 04JAN2022.
[redacted] Source Data: adae Source Dataset Creation: 24MAR2022 (08:52) Table Generation: 09JUN2022 (08:46)
Output File: ./aa_scs_nda/PCPAA/sum_ae_out

Seriousness/Outcomes
All opportunistic infections in the PCPAA pool resolved.

Table 19. Summary of Treatment Emergent Herpes Zoster by PTs/Seriousness – Placebo-Controlled AA Pool

	Total		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)	
	S	NS	S	NS	S	NS	S	NS	S	NS	S	NS	S	NS
Herpes zoster	0	6	0	0	0	2 (100.0)	0	2 (100.0)	0	2 (100.0)	0	0	0	0
Varicella zoster virus infection	0	2	0	1[a] (100.0)	0	0	0	1[a] (100.0)	0	0	0	0	0	0
Total	0	8	0	1 (12.5)	0	2 (25.0)	0	3 (37.5)	0	2 (25.0)	0	0	0	0

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 only counted once per treatment in each row.
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].
N: Number of participants in pool. %: Based on Total AE.
a. There was 1 adjudicated opportunistic infection of a multidermatomal herpes zoster.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
B7981037 data cutoff date: 04JAN2022.
Abbreviations: S – serious, NS – Non-serious
[redacted] Source Data: adae Source Dataset Creation: 24MAR2022 (08:52) Table Generation: 10JUN2022 (17:04)
Output File: ./aa_scs_nda/PCPAA/sum_ae_ser_oph

Maximum Severity

The maximum severity of each event type in the PCAAP are provided in Table 20.

Table 20. Summary of Treatment Emergent Herpes Zoster (PTs) by Severity – Placebo-controlled AA Pool

	Total		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)	
	Mild	Moderate	Mild	Moderate	Mild	Moderate	Mild	Moderate	Mild	Moderate	Moderate	Severe	Moderate	Severe
Herpes zoster	2	4	0	0	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	0	2 (100.0)	0	0	0	0
Varicella zoster virus infection	2	0	1[a] (100.0)	0	0	0	1[a] (100.0)	0	0	0	0	0	0	0
Total	4	4	1 (25.0)	0	1 (25.0)	1 (25.0)	2 (50.0)	1	0	2 (50.0)	0	0	0	0

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 only counted once per treatment in each row.
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].
N: Number of participants in pool. %: Based on Total AE.
a. There was 1 adjudicated opportunistic infection of a multidermatomal herpes zoster.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
B7981037 data cutoff date: 04JAN2022.
[redacted] Source Data: adae Source Dataset Creation: 24MAR2022 (08:52) Table Generation: 10JUN2022 (17:05)
Output File: ./aa_scs_nda/PCPAA/sum_ae_sev_oph

All Exposure Pool

Table 21. Proportion and Incidence Rates of Subjects for Herpes Zoster - AEP

	Ritlecitinib 50 mg	Any Ritlecitinib
Opportunistic Infections		
	Number of Subjects with Event n (%) **Total Drug exposure (PY)[a]** **Incidence rates (95% CI)[b]**	
Adjudicated Herpes zoster	4 (0.3) 3563.74 0.12 (0.03, 0.29)	4 (0.2) 3895.34 0.10 (0.03, 0.25)
All Herpes zoster Infections (CMQ)	36 (2.4) 3507.93 1.05 (0.75, 1.45)	38 (2.3) 3834.86 0.99 (0.71, 1.35)

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.
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].
n (%): Number of participants with event
a. 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.
b. Study-size adjusted results per 100 PY and mid-p gamma intervals

MedDRA v27.0 coding dictionary applied for updated AEP-2024 data.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (10:15)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_out

Seriousness/Outcomes

All events of Herpes zoster, including adjudicated opportunistic herpes zoster, were non-serious.
The outcomes for opportunistic infections and all Herpes zoster in the AEP pool are provided in Table 22 and Table 23.

Table 22. Summary of Treatment Emergent Herpes Zoster events by Outcomes and Preferred Term in the Ritlecitinib 50 mg Arm - AEP

Ritlecitinib 50 mg (N=1523)						
Latest Outcome						
Preferred Term	**Total**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Herpes zoster	33	1 (3.03)	32 (96.97)	0	0	0
Herpes zoster infection neurological	1	0	1 (100.0)	0	0	0
Post herpetic neuralgia	2	0	2 (100.0)	0	0	0
Varicella zoster virus infection	2	0	2 (100.0)	0	0	0
Total	38	1 (2.63)	37 (97.37)	0	0	0

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in pool. %: Based on Total AE.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/ae_sum_out_pt_hz

Table 23. Summary of Treatment Emergent Herpes Zoster events by Outcomes and Preferred Term in Any Ritlecitinib - AEP

Any Ritlecitinib (N=1630)						
Latest Outcome						
Preferred Term	**Total**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Herpes zoster	35	1 (2.86)	34 (97.14)	0	0	0
Herpes zoster infection neurological	1	0	1 (100.0)	0	0	0

Table 23. Summary of Treatment Emergent Herpes Zoster events by Outcomes and Preferred Term in Any Ritlecitinib - AEP

Any Ritlecitinib (N=1630)						
Latest Outcome						
Preferred Term	Total	Still Present	Resolved	Resolved with sequelae	Unknown	Death
Post herpetic neuralgia	2	0	2 (100.0)	0	0	0
Varicella zoster virus infection	2	0	2 (100.0)	0	0	0
Total	40	1 (2.50)	39 (97.50)	0	0	0

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in pool. %: Based on Total AE.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/ae_sum_out_pt_hz

Maximum Severity

The maximum severity of each event type in the AEP are provided in Table 24 and Table 25.

Table 24. Summary of Treatment Emergent Herpes Zoster events by Maximum Severity and Preferred Term in Any Ritlecitinib - AEP

Ritlecitinib 50 mg (N=1523)				
Maximum Severity				
Preferred Term	Total	Mild	Moderate	Severe
Herpes zoster	33	15 (45.45)	18 (54.55)	0
Herpes zoster infection neurological	1	1 (100.0)	0	0
Post herpetic neuralgia	2	2 (100.0)	0	0

Table 24. Summary of Treatment Emergent Herpes Zoster events by Maximum Severity and Preferred Term in Any Ritlecitinib - AEP

Ritlecitinib 50 mg (N=1523)				
Maximum Severity				
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Varicella zoster virus infection	2	2 (100.0)	0	0
Total	38	20 (52.63)	18 (47.37)	0

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in pool. %: Based on Total AE.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_sev_hz

Table 25. Summary of Treatment Emergent Herpes Zoster events by Maximum Severity and Preferred Term in Any Ritlecitinib - AEP

Any Ritlecitinib (N=1630)				
Maximum Severity				
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Herpes zoster	35	15 (42.86)	20 (57.14)	0
Herpes zoster infection neurological	1	1 (100.0)	0	0
Post herpetic neuralgia	2	2 (100.0)	0	0
Varicella zoster virus infection	2	2 (100.0)	0	0
Total	40	20 (50.0)	20 (50.0)	0

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.

Table 25. Summary of Treatment Emergent Herpes Zoster events by Maximum Severity and Preferred Term in Any Ritlecitinib - AEP

Any Ritlecitinib (N=1630)				
Maximum Severity				
Preferred Term	Total	Mild	Moderate	Severe

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in pool. %: Based on Total AE.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_sev_hz

SVII.3.1.1.1. Risk Factors and Risk Groups

For all herpes zoster events (regardless of adjudication as opportunistic), age (≥65 years) was identified as a statistically significant covariate on the baseline incidence of herpes zoster infections. In addition, while not identified in the covariate analysis, the IR for herpes zoster was higher in women than men.

SVII.3.1.1.2. Preventability

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

Routine risk minimisation measures in the SmPC include a contraindication for patients with active serious infections. Special warnings and precautions for use include consideration of the risk and benefits of treatment in patients with chronic or recurrent infection. Finally, the SmPC recommends that immunization be up to date prior to initiating. Health care provider and patient educational materials will include the risk for infections, including herpes zoster (see Section VI).

SVII.3.1.1.3. Impact on the Risk-Benefit Balance of the Product

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

SVII.3.1.1.4. Public Health Impact

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

SVII.3.1.2. Important Potential Risks:

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

Potential Mechanisms

Serious and opportunistic infections have been associated with the use of immunomodulators including JAK inhibitors and TEC kinase family inhibitors.

Evidence Source and Strength of Evidence

Ritlecitinib's mechanism of action includes effects on the immune system, therefore, serious infections and adjudicated opportunistic infections were assessed in the ritlecitinib development program.

Characterisation of the Risk

Frequency of Serious Infections

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

Placebo-Controlled AA Pool

Table 26. Proportion and Incidence Rates of Subjects for Treatment-Emergent Serious Infections - Placebo-Controlled AA Pool

	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)
Serious Infections						
Number of Subjects with Event n (%)	2 (0.9)	0 (0.0)	2 (0.6)	1 (0.4)	0 (0.0)	0 (0.0)
Total Drug exposure (PY)[a]	101.46	59.16	160.62	116.46	28.03	99.85
Incidence rates (95% CI)[b]	2.66 (0.44, 8.80)	0.00 (0.00, 4.05)	1.34 (0.22, 4.44)	0.69 (0.03, 3.40)	0.00 (0.00, 8.55)	0.00 (0.00, 3.98)

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.
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].
n: Number of participants with event
N: Number of participants in pool.

Table 26. Proportion and Incidence Rates of Subjects for Treatment-Emergent Serious Infections - Placebo-Controlled AA Pool

	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)
Serious Infections						

a.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.
b.Study-size adjusted results per 100 PY and mid-p gamma intervals.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
B7981037 data cutoff date: 04JAN2022.
[redacted] Source Data: adae Source Dataset Creation: 24MAR2022 (08:52) Table Generation: 09JUN2022 (16:08)
Output File: ./aa_scs_nda/PCPAA/sum_ae_

Seriousness/Outcomes

All the serious infections in the PCPAA pool were serious and each event resolved.

Table 27. Summary of Treatment Emergent Serious Infections by PTs - Placebo-Controlled AA Pool

	Total	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)
Appendicitis	2	1 (50.0)	0	1 (50.0)	0	0	0
Diverticulitis	1	0	0	0	1 (100.0)	0	0
Empyema	2	1 (50.0)	0	1 (50.0)	0	0	0
Sepsis	2	1 (50.0)	0	1 (50.0)	0	0	0
Total	7	3 (42.9)	0	3 (42.9)	1 (14.3)	0	0

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 only counted once per treatment in each row.
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].
N: Number of participants in pool. %: Based on Total AE.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
B7981037 data cutoff date: 04JAN2022.
[redacted] Source Data: adae Source Dataset Creation: 24MAR2022 (08:52) Table Generation: 10JUN2022 (10:12)
Output File: ./aa_scs_nda/PCPAA/sum_ae-out

Maximum Severity

Table 28. Summary of Severity of Treatment Emergent Serious Infections by PTs - Placebo-Controlled AA Pool

	Total		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)	
	Moderate	Severe	Moderate	Severe	Moderate	Severe	Moderate	Severe	Moderate	Severe	Moderate	Severe	Moderate	Severe
Appendicitis	2 (28.6)	0	1 (100.0)	0	0	0	1 (100.0)	0	0	0	0	0	0	0
Diverticulitis	1 (14.3)	0	0	0	0	0	0	0	1 (100.0)	0	0	0	0	0
Empyema	2 (28.6)	0	0	1 (100.0)	0	0	0	1 (100.0)	0	0	0	0	0	0
Sepsis	2 (28.6)	0	0	1 (100.0)	0	0	0	1 (100.0)	0	0	0	0	0	0
Total	7	0	1 (33.3)	2 (66.7)	0	0	1 (33.3)	2 (66.7)	1 (100.0)	0	0	0	0	0

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 only counted once per treatment in each row.
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].
N: Number of participants in pool. %: Based on Total AE.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
B7981037 data cutoff date: 04JAN2022.
[redacted] Source Data: adae Source Dataset Creation: 24MAR2022 (08:52) Table Generation: 10JUN2022 (17:03)
Output File: ./aa_scs_nda/PCPAA/sum_ae_sev_inf

Opportunistic Infections

There is an important potential risk for other opportunistic infections considering the immunomodulatory effects of ritlecitinib.

Table 29. Proportion and Incidence Rates of Subjects for Treatment-Emergent Opportunistic Infections - Placebo-Controlled AA Pool

	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)
Opportunistic Infections						
	Number of Subjects with Event n (%) Total Drug exposure (PY)[a] Incidence rates (95% CI)[b]					
Adjudicated Opportunistic Infections (excluding Herpes Zoster and Tuberculosis)	0 101.57 0.00 (0.00, 3.98)	0 59.16 0.00 (0.00, 4.05)	0 160.73 0.00 (0.00, 2.01)	0 116.77 0.00 (0.00, 2.05)	0 28.03 0.00 (0.00, 8.55)	0 99.85 0.00 (0.00, 3.98)
Adjudicated Tuberculosis	0 101.57 0.00 (0.00,3.98)	0 59.16 0.00 (0.00, 4.05)	0 160.73 0.00 (0.00, 2.01)	0 116.77 0.00 (0.00, 2.05)	0 28.03 0.00 (0.00, 8.55)	0 99.85 0.00 (0.00, 3.98)

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.
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].
N: Number of participants in pool. N: Number of participants with event.
a.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.
b.Study-size adjusted results per 100 PY and mid-p gamma intervals.
B7981037 data cutoff date: 04JAN2022.
[redacted] Source Data: adae Source Dataset Creation: 24MAR2022 (08:52) Table Generation: 09JUN2022 (08:46)
Output File: ./aa_scs_nda/PCPAA/sum_ae_out

All Exposure Pool

Table 30. Proportion and Incidence Rates of Subjects for Treatment-Emergent Serious Infections - AEP

	50 mg	Any Ritlecitinib
Serious Infections		
Number of Subjects with Event n (%)	20 (1.3)	22 (1.3)
Total Drug exposure (PY)[a]	3551.20	3875.34
Incidence rates (95% CI)[b]	0.57 (0.36, 0.87)	0.57 (0.36, 0.85)

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.
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].
n: Number of participants with event
a. 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.
b. Study-size adjusted results per 100 PY and mid-p gamma intervals.
MedDRA v27.0 coding dictionary applied for updated AEP-2024 data.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (10:15)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_out

Seriousness/Outcomes

All of the serious infections in the AEP pool met the criteria to be considered as serious. The outcomes of each event type in the AEP are provided in Table 31 and Table 32.

Table 31. Summary of Treatment Emergent Serious Infections by Outcomes and Preferred Term in the Ritlecitinib 50 mg - AEP

Ritlecitinib 50 mg (N=1523)						
		Latest Outcome				
Preferred Term	**Total**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Appendicitis	6	0	6 (100)	0	0	0
Covid-19	2	0	2 (100)	0	0	0
Covid-19 Pneumonia	2	0	2 (100)	0	0	0
Cellulitis	1	0	1 (100)	0	0	0
Diverticulitis	0	0	0	0	0	0
Empyema	1	0	1 (100.0)	0	0	0
Gingivitis	1	0	1 (100.0)	0	0	0
Latent tuberculosis	1	0	1 (100.0)	0	0	0

Table 31. Summary of Treatment Emergent Serious Infections by Outcomes and Preferred Term in the Ritlecitinib 50 mg - AEP

Ritlecitinib 50 mg (N=1523)						
Latest Outcome						
Preferred Term	**Total**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Osteomyelitis	1	0	1 (100.0)	0	0	0
Pelvic abscess	1	0	1 (100.0)	0	0	0
Peritonsillar abscess	1	0	1 (100.0)	0	0	0
Pyelonephritis	1	0	1(100.0)	0	0	0
Sepsis	1	0	1(100.0)	0	0	0
Septic Shock	1	0	1(100.0)	0	0	0
Staphylococcal Sepsis	1	0	1(100.0)	0	0	0
Urinary tract infection	1	0	1 (100.0)	0	0	0
Vulval Abscess	1	0	1(100.0)	0	0	0
Total	23	0	23 (100.0)	0	0	0

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in pool. %: Based on Total AE.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/ae_sum_out_pt_rmp

Table 32. Summary of Treatment Emergent Serious Infections by Outcomes and Preferred Term in the Any Ritlecitinib - AEP

Any Ritlecitinib (N=1630)						
Latest Outcome						
Preferred Term	**Total**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Appendicitis	7	0	7 (100.0)	0	0	0
Covid-19	2	0	2 (100.0)	0	0	0
Covid-19 Pneumonia	2	0	2 (100.0)	0	0	0
Cellulitis	1	0	1 (100.0)	0	0	0
Diverticulitis	1	0	1 (100.0)	0	0	0

Table 32. Summary of Treatment Emergent Serious Infections by Outcomes and Preferred Term in the Any Ritlecitinib - AEP

Any Ritlecitinib (N=1630)						
Latest Outcome						
Preferred Term	**Total**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Empyema	1	0	1 (100.0)	0	0	0
Gingivitis	1	0	1 (100.0)	0	0	0
Latent tuberculosis	1	0	1 (100.0)	0	0	0
Osteomyelitis	1	0	1 (100.0)	0	0	0
Pelvic abscess	1	0	1 (100.0)	0	0	0
Peritonsillar abscess	1	0	1 (100.0)	0	0	0
Pyelonephritis	1	0	1 (100.0)	0	0	0
Sepsis	1	0	1 (100.0)	0	0	0
Septic Shock	1	0	1 (100.0)	0	0	0
Staphylococcal Sepsis	1	0	1 (100.0)	0	0	0
Urinary tract infection	1	0	1 (100.0)	0	0	0
Vulval Abscess	1	0	1 (100.0)	0	0	0
Total	25	0	25 (100)	0	0	0

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.
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].
N: Number of participants in pool. %: Based on Total AE.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/ae_sum_out_pt_rmp

Maximum Severity

The maximum severity of each event type in the AEP are provided in Table 33 and Table 34.

Table 33. Summary of Treatment Emergent Serious Infections by Maximum Severity and Preferred Term in the Ritlecitinib 50 mg - AEP

Ritlecitinib 50 mg (N=1523)				
	Maximum Severity			
Preferred Term	Total	Mild	Moderate	Severe
Appendicitis	6	0	3 (50.0)	3 (50.0)
Covid-19	2	0	0	2 (100.0)
Covid-19 Pneumonia	2	0	0	2 (100.0)
Cellulitis	1	0	0	1 (100.0)
Diverticulitis	0	0	0	0
Empyema	1	0	0	1 (100.0)
Gingivitis	1	0	0	1 (100.0)
Latent tuberculosis	1	1 (100.0)	0	0
Osteomyelitis	1	0	0	1 (100.0)
Pelvic abscess	1	0	0	1 (100.0)
Peritonsillar abscess	1	0	0	1 (100.0)
Pyelonephritis	1	0	0	1 (100.0)
Sepsis	1	0	0	1 (100.0)
Septic Shock	1	0	0	1 (100.0)
Staphylococcal Sepsis	1	0	0	1 (100.0)
Urinary tract infection	1	0	0	1 (100.0)
Vulval Abscess	1	1 (100.0)	0	0
Total	23	2 (8.70)	3 (13.04)	18 (78.26)

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in pool. %: Based on Total AE.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_sev_inf

Table 34. Summary of Treatment Emergent Serious Infections by Maximum Severity and Preferred Term in the Any Ritlecitinib - AEP

Any Ritlecitinib (N=1630)				
	Maximum Severity			
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Appendicitis	7	0	3 (42.86)	4 (57.14)
Covid-19	2	0	0	2 (100.0)
Covid-19 Pneumonia	2	0	0	2 (100.0)
Cellulitis	1	0	0	1 (100.0)
Diverticulitis	1	0	1 (100.0)	0
Empyema	1	0	0	1 (100.0)
Gingivitis	1	0	0	1 (100.0)
Latent tuberculosis	1	1 (100.0)	0	0
Osteomyelitis	1	0	0	1 (100.0)
Pelvic abscess	1	0	0	1 (100.0)
Peritonsillar abscess	1	0	0	1 (100.0)
Pyelonephritis	1	0	0	1 (100.0)
Sepsis	1	0	0	1 (100.0)
Septic Shock	1	0	0	1 (100.0)
Staphylococcal Sepsis	1	0	0	1 (100.0)
Urinary tract infection	1	0	0	1 (100.0)
Vulval Abscess	1	1 (100.0)	0	0
Total	25	2 (8.0)	4 (16.0)	19 (76.0)

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in pool. %: Based on Total AE.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_sev_inf

Opportunistic Infections

There is an important potential risk for other opportunistic infections considering the immunomodulatory effects of ritlecitinib.

Table 35. Proportion and Incidence Rates of Subjects for Treatment-Emergent Opportunistic Infections - AEP

	Ritlecitinib 50 mg	Any Ritlecitinib
Opportunistic Infections		
	Number of Subjects with Event n (%) **Total Drug exposure (PY)[a]** **Incidence rates (95% CI)[b]**	
Adjudicated Opportunistic Infections (excluding Herpes zoster and Tuberculosis)	0 3568.61 0.00 (0.00, 0.10)	0 3900.21 0.00 (0.00, 0.08)
Adjudicated Tuberculosis	0 3568.61 0.00 (0.00, 0.10)	0 3900.21 0.00 (0.00, 0.08)

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.
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].
n (%): Number of participants with event
a.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.
b.Study-size adjusted results per 100 PY and mid-p gamma intervals
MedDRA v27.0 coding dictionary applied for updated AEP-2024 data.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (10:15)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_out

Risk Factors and Risk Groups

Risk factors for serious infections include elderly age, certain medical conditions such as diabetes, patients that use drugs along with ritlecitinib that suppress the immune system (including corticosteroids), patients with low absolute lymphocyte counts and people with weakened immune systems.

Preventability

Serious infections and opportunistic infections (including herpes zoster) can have significant impact on individual patients. Therefore, routine and additional RMMs have been proposed to mitigate the risk.

Routine risk minimisation measures in the special warnings and precautions for use section of the product label include the benefits and risks of treatment in patients with chronic or recurrent infection, patients who have been exposed to tuberculosis (TB) or who have a history of serious infection or opportunistic infection. Patients should be screened for TB

before starting therapy; screening for viral hepatitis should be performed in accordance with clinical guidelines prior to starting therapy with ritlecitinib.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ritlecitinib. Treatment should be interrupted if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with ritlecitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Health care provider and patient educational materials (non-routine risk minimisation measures) will include the risk for serious and opportunistic infections.

Impact on the Risk-Benefit Balance of the Product

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

Routine risk minimisation measures in prescribing information include instruction that patients should be monitored for infection, promptly evaluated and treated for infection and that therapy should be interrupted if the patient develops a serious or opportunistic infection. Health care provider and patient educational materials will include the risk for serious and opportunistic infections. Further, prescribing information includes specific cautionary language with respect to elderly and use in the diabetic population in general, as there is a higher incidence of infections in these populations.

Public Health Impact

Serious infection is a common cause of morbidity and mortality. The impact of these infections on public health is significant both in terms of lost time at work and increased burden on medical care. Reports of an association between AA and infections, including Helicobacter pylori infection,[29,94] cytomegalovirus,[95] Epstein-Barr virus,[96] human immunodeficiency virus (HIV),[97,98] coronavirus disease,[99,100] and others,[101,102,103] have been reported in some small studies and case reports. However, not all studies have found this association.[104,105,106] Studies reporting the overall risk of infections in AA patients have not been found.

- In the general population, the incidence rate of serious infections ranged between 78.5 and 107 per 10,000 population.[107,108 ,109]

- In the general population, the rate of opportunistic infections including herpes zoster, opportunistic infections excluding herpes zoster, and herpes zoster was 1.2,[108] 2.1,[107] and 54.4[107] per 10,000 person-years, respectively.

SVII.3.2. Important Potential Risk: Malignancy

Potential Mechanisms

Malignancy events are of special interest for agents such as ritlecitinib that have an immunomodulatory mechanism of action due to potential decreased immune surveillance. The immune system is thought to function as a tumour suppressor through the effect of cytokines or cell types (e.g., NK cells) that may be affected by a JAK3 and TEC family kinase inhibitor and other immunomodulators.[110] When cancers developing in subjects with extreme immunosuppression (HIV infection or renal transplantation) are analysed, cancers related to infections with viruses and bacteria are overrepresented whereas the incidence of epithelial cancers (for example ovary and prostate) are not increased relative to age-matched controls.[111]

Evidence Source and Strength of Evidence

Clinical study data and understanding of immunomodulatory effects based on the data from the JAK class. Adjudicated malignancy events were assessed in the ritlecitinib development program.

Characterisation of the Risk

PCPAA

Table 36. Proportion and Incidence Rates for Treatment-Emergent Malignancies - Placebo-Controlled AA Pool

	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)
Number of Subjects with Event n (%) Total Drug exposure (PY)[a] Incidence rates (95% CI)[b]						
Adjudicated Malignancies, excluding NMSC	1 (0.5) 101.47 1.33 (0.06, 6.57)	0 59.16 0.00 (0.00, 4.05)	1 (0.3) 160.63 0.67 (0.03, 3.32)	0 116.77 0 (0.00, 2.05)	0 28.03 0 (0.00, 8.55)	0 99.85 0 (0.00, 3.98)
Adjudicated NMSC	0 101.57 0.00 (0.00, 3.98)	0 59.16 0.00 (0.00, 4.05)	0 160.73 0 (0.00, 2.01)	0 116.77 0 (0.00, 2.05)	0 28.03 0 (0.00, 8.55)	0 99.85 0 (0.00, 3.98)

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.
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].
n (%): Number of participants with the event.
N:Number of participants in pool

Table 36. Proportion and Incidence Rates for Treatment-Emergent Malignancies - Placebo-Controlled AA Pool

	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)
Number of Subjects with Event n (%) Total Drug exposure (PY)[a] Incidence rates (95% CI)[b]						

a. 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.
b. Study-size adjusted results per 100 PY and mid-p gamma intervals.
B7981037 data cutoff date: 04JAN2022.
[redacted] Source Data: adae Source Dataset Creation: 24MAR2022 (08:52) Table Generation: 09JUN2022 (08:56)
Output File: ./aa_scs_nda/PCPAA/sum_ae_

Seriousness/Outcomes

There was 1 malignancy event of invasive lobular breast cancer in the PCPAA pool. This event was in the ritlecitinib 200/50 mg treatment arm (also in 50 mg treatment arm). The event was considered serious and was still present at the time of reporting.

Maximum Severity

The event of invasive lobular breast cancer in the PCPAA pool was considered severe.

AEP

Table 37. Proportion and Incidence Rates of Subjects for Treatment-Emergent Malignant Events AEP

	Ritlecitinib 50 mg	Any Ritlecitinib
	Number of Subjects with Event n (%) Total Drug exposure (PY)[a] Incidence rates (95% CI)[b]	
Adjudicated Malignancies excluding NMSC	9 (0.6) 3565.70 0.25 (0.11, 0.47)	10 (0.6) 3895.01 0.26 (0.12, 0.46)
Adjudicated NMSC	11 (0.7) 3557.62 0.31 (0.15, 0.55)	11 (0.7) 3889.21 0.28 (0.14, 0.50)

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.
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].
n (%): Number of participants with the event.

Table 37. Proportion and Incidence Rates of Subjects for Treatment-Emergent Malignant Events AEP

	Ritlecitinib 50 mg	Any Ritlecitinib

a. 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.
b. Study-size adjusted results per 100 PY and mid-p gamma intervals.
MedDRA v27.0 coding dictionary applied for updated AEP-2024 data.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (10:15)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_out_

Seriousness/Outcomes

The seriousness/outcomes of each event type in the AEP are provided in Table 38 and Table 39.

Table 38. Summary of Seriousness and Latest Outcome for Treatment Emergent Malignancies by Preferred Terms in Ritlecitinib 50 mg - AEP

Ritlecitinib 50 mg (N=1523)							
			Latest Outcome				
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Basal cell carcinoma	8	2	0	8 (100.0)	0	0	0
Bowen's disease	1	0	0	1 (100.0)	0	0	0
Breast cancer	3	3	2 (66.7)	0	0	0	1 (33.3)
Cervical dysplasia	1	0	0	1 (100.0)	0	0	0
Intraductal proliferative breast lesion	1	1	0	0	0	1 (100.0)	0
Invasive lobular breast carcinoma	1	1	1 (100.0)	0	0	0	0
Malignant melanoma	1	1	1 (100.0)	0	0	0	0
Papillary thyroid cancer	1	1	1 (100.0)	0	0	0	0
Squamous cell carcinoma	1	0	0	1 (100.0)	0	0	0
Squamous cell carcinoma of skin	1	0	0	1 (100.0)	0	0	0
Testis cancer	1	1	0	1 (100.0)	0	0	0
Total	20	10	5 (25.0)	13 (65.0)	0	1 (5.0)	1 (5.0)

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.

Table 38. Summary of Seriousness and Latest Outcome for Treatment Emergent Malignancies by Preferred Terms in Ritlecitinib 50 mg - AEP

Ritlecitinib 50 mg (N=1523)							
			Latest Outcome				
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**

Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in the pool. %: Based on Total number of events.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/ae_sum_out_pt_malig

Table 39. Summary of Seriousness and Latest Outcome for Treatment Emergent Malignancies by Preferred Terms in any Ritlecitinib - AEP

Any Ritlecitinib (N=1630)							
			Latest Outcome				
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Basal cell carcinoma	8	2	0	8 (100.0)	0	0	0
Bowen's disease	1	0	0	1 (100.0)	0	0	0
Breast cancer	3	3	2 (66.7)	0	0	0	1 (33.33)
Cervical dysplasia	2	0	0	2 (100.0)	0	0	0

Table 39. Summary of Seriousness and Latest Outcome for Treatment Emergent Malignancies by Preferred Terms in any Ritlecitinib - AEP

Any Ritlecitinib (N=1630)							
			Latest Outcome				
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Intraductal proliferative breast lesion	1	1	0	0	0	1 (100.0)	0
Invasive lobular breast carcinoma	1	1	1 (100.0)	0	0	0	0
Malignant melanoma	1	1	1 (100.0)	0	0	0	0
Papillary thyroid cancer	1	1	1 (100.0)	0	0	0	0
Squamous cell carcinoma	1	0	0	1 (100.0)	0	0	0
Squamous cell carcinoma of skin	1	0	0	1 (100.0)	0	0	0
Testis cancer	1	1	0	1 (100.0)	0	0	0
Total	21	10	5 (23.81)	14 (66.67)	0	1 (4.76)	1 (4.76)

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in the pool. %: Based on Total number of events.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/ae_sum_out_pt_malig

Maximum Severity

The maximum severity of each event type in the AEP are provided in Table 40 and Table 41.

Table 40. Summary of Maximum Severity for Treatment Emergent Malignancies by Preferred Terms in Ritlecitinib 50 mg - AEP

Ritlecitinib 50 mg (N=1523)				
Maximum Severity				
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Basal cell carcinoma	8	4 (50.0)	3 (37.50)	1 (12.50)
Bowen's disease	1	0	1 (100.0)	0
Breast cancer	3	0	1 (33.3)	2 (66.7)
Cervical dysplasia	1	0	1 (100.0)	0
Intraductal proliferative breast lesion	1	1 (100.0)	0	0
Invasive lobular breast carcinoma	1	0	0	1 (100.0)
Malignant melanoma	1	0	1 (100.0)	0
Papillary thyroid cancer	1	0	0	1 (100.0)
Squamous cell carcinoma	1	0	1 (100.0)	0
Squamous cell carcinoma of skin	1	1 (100.0)	0	0
Testis cancer	1	0	0	1 (100.0)
Total	20	6 (30.0)	8 (40.0)	6 (30.0)

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.

Table 40. Summary of Maximum Severity for Treatment Emergent Malignancies by Preferred Terms in Ritlecitinib 50 mg - AEP

Ritlecitinib 50 mg (N=1523)				
		Maximum Severity		
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**

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].
N: Number of participants in the pool. %: Based on Total number of events.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_sev_malig

Table 41. Summary of Maximum Severity for Treatment Emergent Malignancies by Preferred Terms in Any Ritlecitinib - AEP Pool

Any Ritlecitinib (N=1630)				
		Maximum Severity		
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Basal cell carcinoma	8	4 (50.0)	3 (37.50)	1 (12.50)
Bowen’s disease	1	0	1 (100.0)	0
Breast cancer	3	0	1 (33.3)	2 (66.7)
Cervical dysplasia	2	0	2 (100.0)	0
Intraductal proliferative breast lesion	1	1 (100.0)	0	0
Invasive lobular breast carcinoma	1	0	0	1 (100.0)
Malignant melanoma	1	0	1 (100.0)	0
Papillary thyroid cancer	1	0	0	1 (100.0)

Table 41. Summary of Maximum Severity for Treatment Emergent Malignancies by Preferred Terms in Any Ritlecitinib - AEP Pool

Any Ritlecitinib (N=1630)				
		Maximum Severity		
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Squamous cell carcinoma	1	0	1 (100.0)	0
Squamous cell carcinoma of skin	1	1 (100.0)	0	0
Testis cancer	1	0	0	1 (100.0)
Total	21	6 (28.57)	9 (42.86)	6 (28.57)

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in the pool. %: Based on Total number of events.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_sev_malig

Risk Factors and Risk Groups

Malignancies were observed in clinical studies of ritlecitinib. However, there were an insufficient number of events for risk factor or subgroup analysis. The risks and benefits of ritlecitinib treatment should be considered prior to initiating or continuing therapy in patients with a known malignancy (other than a successfully treated non-melanoma skin cancer (NMSC) or cervical cancer).

Preventability

Health care provider educational materials will include the risk of malignancy. In addition, periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Impact on the Risk-Benefit Balance of the Product

Malignancy can severely impact a patient's quality of life. While specific potential effects on an individual patient depend upon a variety of factors including site of malignancy, tolerability of therapy, and degree of social and emotional support, malignancy can cause psychological distress due to the gravity of the diagnosis and fear about its effects and possible recurrence. In addition, it can directly impact a patient's physical functioning and lifespan. Skin cancer is the most common type of cancer in fair-skinned individuals around the world. Although NMSC is rarely fatal, it can cause significant morbidity. As such, both routine and non-routine risk minimisation measures are proposed.

Public Health Impact

Malignancy is a major public health problem. It is among the leading causes of morbidity and mortality worldwide.[112] There is conflicting evidence regarding the cancer risk associated with AA. For example, one large population-based study in Taiwan reported a significantly reduced risk of malignancy in male patients with AA as compared to the general population (standardised incidence ratio [SIR] 0.89, 95% CI 0.85-0.93), and no increased risk in females (SIR 1.02, 95% CI 0.97-1.06).[113] However, another large population-based study reported a slightly higher overall cancer risk in AA patients as compared to age- and sex-matched comparators (HR 1.043; 95% CI 1.022-1.065).[114] Risk of malignancy may vary by cancer subtype. Indeed, studies have generally reported decreased risks for gastric,[29,81,114]colorectal,[29,81,114] and uterine[113,114] cancers in AA patients, and a decreased or no increased risk of nonmelanoma skin,[113] lung,[29,81,113,114] and liver[81,113,114] cancer. Patients with AA may be at an increased risk for thyroid cancer,[29,81,114] prostate cancer,[114] lymphoma,[113] and kidney and urinary bladder cancer [113,114] however findings are not consistent across studies.[29,113,114] The incidence rate of overall cancer in patients with AA was reported as 37.3 per 10,000 person-years.[114]

The incidence rate of a selection of cancer subtypes in patients with AA is reported below:[114]

- Thyroid 1.10 per 10,000 person-years

- Breast 0.96 per 10,000 person-years
- Colorectal 0.55 per 10,000 person-years
- Stomach 0.44 per 10,000 person-years
- Prostate 0.31 per 10,000 person-years
- Liver 0.25 per 10,000 person-years
- Lung 0.25 per 10,000 person-years
- Cervix 0.22 per 10,000 person-years
- Ovary 0.18 per 10,000 person-years
- Pancreas 0.17 per 10,000 person-years
- Uterus 0.11 per 10,000 person-years
- Kidney 0.08 per 10,000 person-years
- Bladder 0.08 per 10,000 person-years
- Lymphoma 0.08 per 10,000 person-years
- Biliary tract 0.06 per 10,000 person-years
- Nerve 0.06 per 10,000 person-years
- Oral cavity 0.05 per 10,000 person-years
- Leukaemia 0.05 per 10,000 person-years
- Esophagus 0.02 per 10,000 person-years
- Multiple myeloma 0.02 per 10,000 person-years
- Testis 0.02 per 10,000 person-years
- Larynx 0.02 per 10,000 person-years
- Skin 0.01 per 10,000 person-years

SVII.3.3. Important Potential Risk: Thromboembolic Events including deep vein thrombosis, pulmonary embolism and arterial thrombosis

Potential Mechanisms

The mechanism is unknown.

Evidence Source and Strength of Evidence

Thromboembolic events have been reported in the ritlecitinib development program.

Characterisation of the Risk

PCPAA

No events were reported in the PCPAA pool for the risk of Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis.

AEP

Table 42. Proportion and Incidence Rates for Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis - AEP

	50 mg	Any Ritlecitinib
	Number of Subjects with Event n (%) Total Drug exposure (PY)[a] Incidence rates (95% CI)[b]	
Adjudicated Thromboembolism	1 (<0.1) 3568.51 0.03 (0.00, 0.15)	1 (<0.1) 3900.11 0.03 (0.00, 0.13)
Adjudicated Pulmonary embolism	1 (<0.1) 3568.51 0.03 (0.00, 0.15)	1 (<0.1) 3900.11 0.03 (0.00, 0.13)
Adjudicated Deep vein thrombosis	0 3568.51 0.00 (0.00, 0.10)	0 3900.21 0.00 (0.00, 0.08)
Arterial thrombotic events (CMQ)	5 (0.3) 3567.77 0.13 (0.04, 0.30)	5 (0.3) 3899.37 0.13 (0.04, 0.29)

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.
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].
n: Number of participants with the event.
a.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.
b.Study-size adjusted results per 100 PY and mid-p gamma intervals.
MedDRA v27.0 coding dictionary applied for updated AEP-2024 data.

Table 42. Proportion and Incidence Rates for Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis - AEP

	50 mg	Any Ritlecitinib

Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (10:15)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_out

Seriousness/Outcomes

The seriousness/outcomes of each event type in the AEP are provided in Table 43 and Table 44.

Table 43. Summary of Treatment Emergent Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis by Seriousness/Outcomes and Preferred Term in Ritlecitinib 50 mg Arm - AEP

Ritlecitinib 50 mg (N=1523)							
			Latest Outcome				
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Adjudicated Thromboembolic Events							
Pulmonary embolism	1	1	0	1 (100.0)	0	0	0
Arterial Thrombotic Events (CMQ)							
Acute myocardial infarction	3	3	0	3 (100.0)	0	0	0
Myocardial infarction	1	1	0	0	1 (100.0)	0	0
Retinal artery occlusion	1	1	0	0	1 (100.0)	0	0
Total	6	6	0	4 (66.7)	2 (33.3)	0	0

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in the pool. %: Based on Total AE.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/ae_sum_out_pt_te

Table 44. Summary of Treatment Emergent Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis by Seriousness/Outcomes and Preferred Term in Any Ritlecitinib - AEP

Any Ritlecitinib (N=1630)							
			Latest Outcome				
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Adjudicated Thromboembolic Events							
Pulmonary embolism	1	1	0	1 (100.0)	0	0	0
Arterial Thrombotic Events (CMQ)							
Acute myocardial infarction	3	3	0	3 (100.0)	0	0	0
Myocardial infarction	1	1	0	0	1 (100.0)	0	0
Retinal artery occlusion	1	1	0	0	1 (100.0)	0	0
Total	6	6	0	4 (66.7)	2 (33.3)	0	0

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in the pool. %: Based on Total AE.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/ae_sum_out_pt_te

Maximum Severity

The maximum severity of each event type in the AEP are provided in Table 45 and Table 46.

Table 45. Summary of Treatment Emergent Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis by Maximum Severity and Preferred Term in Ritlecitinib 50 mg - AEP

Ritlecitinib 50 mg (N=1523)				
Maximum Severity				
Adjudicated Thromboembolic Events				
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Pulmonary embolism	1	0	1 (100.0)	0
Arterial Thrombotic Events (CMQ)				
Acute myocardial infarction	3	0	0	3 (100.0)
Myocardial infarction	1	0	0	1 (100.0)
Retinal artery occlusion	1	0	1 (100.0)	0
Total	6	0	2 (33.3)	4 (66.7)

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in pool %: Based on Total AE.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_sev_te

Table 46. Summary of Treatment Emergent Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis by Maximum Severity and Preferred Term in Any Ritlecitinib - AEP

Any Ritlecitinib (N=1630)				
	Maximum Severity			
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Pulmonary embolism	1	0	1 (100.0)	0
Arterial Thrombotic Events (CMQ)				
Acute myocardial infarction	3	0	0	3 (100.0)
Myocardial infarction	1	0	0	1 (100.0)
Retinal artery occlusion	1	0	1 (100.0)	0
Total	6	0	2 (33.3)	4 (66.7)

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in the pool. %: Based on Total AE.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_sev_te

Risk Factors and Risk Groups

There was an insufficient number of cases to analyze risk factors from the ritlecitinib clinical trial data. Risk factors for thromboembolic events in the general population also apply to patients with AA including older age, obesity, a medical history of thromboembolism, prothrombotic disorder, use of combined hormonal contraceptives or hormone replacement therapy, patients undergoing major surgery, or prolonged immobilization.

Preventability

Ritlecitinib should be used with caution in patients with risk factors for thromboembolic events. Patients with signs and symptoms of a thromboembolic event should be urgently evaluated. Healthcare provider and patient educational materials will include information on the risk of a thromboembolic event.

Impact on the Risk-Benefit Balance of the Product

Thromboembolic events, including deep vein thrombosis, pulmonary embolism and arterial thrombosis can have an impact on individual patients and may lead to significant morbidity or mortality.

Public Health Impact

Venous Thromboembolic Events

Venous thromboembolic events, comprised of DVT and PE, represents a global health concern. A large commercial claims database study in the US reported that the incidence rate of venous thromboembolism (VTE) in patients with AA was 9.4 per 10,000 person-years and was not significantly increased compared to propensity-score matched patients without chronic inflammatory skin diseases (HR: 0.97 [95% CI 0.65-1.46]).[115]

- In the general population, the incidence rate of VTE ranges from 10 to 20 per 10,000 person-years.[116,117]

- In the general population, the incidence rate of pulmonary embolism (PE; with or without deep vein thrombosis) ranges from 2.9 to 7.8 per 10,000 person-years.[117]

- In the general population, the incidence rate of deep vein thrombosis alone (without PE) ranges from 4.5 to 1.17 per 10,000 person-years.[117]

Arterial Thromboembolic Events

Ischaemic heart disease and ischaemic stroke are the most common forms of arterial thromboembolism.[118] A study based in Taiwan reported an incidence rate of ischaemic stroke in patients with AA of 28.9 per 10,000 person-years (95% CI: 18.9-42.3).[76] In that study, rate of ischemia stroke was significantly greater in patients with AA than comparator patients, even after adjusting for monthly income, geographic region, hyperlipidemia, and coronary heart disease (adjusted HR: 1.58 [95% CI: 1.00-2.45]).[76] In contrast, a study in the US

reported a significantly decreased risk of ischaemic stroke (OR: 0.39 [95% CI: 0.18-0.87]) and no increased risk of myocardial infarction (OR: 0.91 [95% CI: 0.59-1.39]) in AA patients as compared to propensity matched controls.[75] Differences in racial distribution of study populations, validation of AA diagnosis, and accounting for the key confounder of smoking in the latter study have been proposed as potential explanations for the difference in ischaemic stroke rates.[75]

- In the general population, the Global Burden of Disease project estimated an age-standardised incidence rate of ischaemic heart disease of 151.9 per 10,000 person-years.[119]

- In the general population, the Global Burden of Disease project estimated an age-standardised incidence rate of ischaemic stroke of 11.4 per 10,000 person-years.[119] However, a wide range of incidence rates has been reported in the literature depending on region of study and patient risk factors (0.07 to 54.5 per 10,000 person-years).[118]

SVII.3.4. Important Potential Risk: Embryofoetal toxicity following exposure in utero

Potential Mechanisms

The potential mechanism is unknown.

Evidence Source and Strength of Evidence

There are limited data from the use of ritlecitinib in human pregnancy. Studies in animals have shown developmental toxicity with no effects at clinically relevant exposures. In an embryofoetal development study in pregnant rats, oral administration of ritlecitinib from gestation days 6 to 17 resulted in foetal skeletal malformations and variations and lower foetal body weights at exposures greater than or equal to 49 times the unbound AUC at the MRHD. There were no effects on embryo-foetal development at exposures equal to 16 times the unbound AUC at the MRHD.

In an embryo-foetal development study in pregnant rabbits, oral administration of ritlecitinib from gestation days 7 to 19 resulted in lower mean foetal body weights and higher incidences of visceral malformations, skeletal malformations, and skeletal variations at exposures equal to 55 times the unbound AUC at the MRHD. There were no effects on embryo-foetal development at exposures equal to 12 times the unbound AUC at the MRHD.

In a rat pre- and postnatal development study, oral administration of ritlecitinib from gestation day 6 through lactation day 20 resulted in developmental toxicity that included lower postnatal survival, lower offspring body weights, and secondary developmental delays at exposure equal to 41 times the unbound AUC at the MRHD. Bred females in the F1 generation exhibited lower mean numbers of corpora lutea at exposures equal to 41 times the unbound AUC at the MRHD. There were no effects on pre and postnatal development at exposures equal to 14 times the unbound AUC at the MRHD.

Characterisation of the Risk

Frequency of Embryofoetal toxicity following exposure in utero

No events were reported.

Seriousness/Outcomes

Not applicable

Maximum Severity

Not applicable.

Risk Factors and Risk Groups

Risk of foetal malformation pertains only to women of childbearing potential who become pregnant while receiving ritlecitinib.

Preventability

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

Impact on the Risk-Benefit Balance of the Product

Embryofoetal toxicity effects could range from minor (minimal clinical implications) or major (having medical or social implications).

Public Health Impact

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

SVII.3.5. MACE

Potential Mechanisms
The potential mechanism is unknown.

Evidence Source and Strength of Evidence
It is not known whether selective JAK3 inhibition may be associated with adverse reactions of JAK inhibition predominantly involving JAK1 and JAK2. In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in RA patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of MACE, defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, and a dose dependent higher rate of venous thromboembolism including DVT and PE were observed

with tofacitinib compared to TNF inhibitors. Long-term safety evaluations for ritlecitinib are ongoing.

Characterisation of the Risk

PCPAA

No events were reported in the PCPAA pool for the risk of MACE.

AEP

Frequency of Events of MACE

Table 47. Proportion and Incidence Rates for Events of MACE - AEP

	50 mg	Any Ritlecitinib
	Number of Subjects with Event n (%) Total Drug exposure (PY)[a] Incidence rates (95% CI)[b]	
Adjudicated MACE events	7 (0.5) 3566.03 0.19 (0.08, 0.39)	7 (0.4) 3897.63 0.18 (0.07, 0.36)

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.
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].
n: Number of participants with the event.
a. 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.
b. Study-size adjusted results per 100 PY and mid-p gamma intervals.
MedDRA v27.0 coding dictionary applied for updated AEP-2024 data.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (10:15)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_out

Seriousness/Outcomes

The seriousness/outcomes of each event type in the AEP are provided in Table 48 and Table 49.

Table 48. Summary of Treatment Emergent Events of MACE by Seriousness/Outcomes and Preferred Term in Ritlecitinib 50 mg Arm - AEP

Ritlecitinib 50 mg (N=1523)							
			Latest Outcome				
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Acute MI	3	3	0	3 (100.0)	0	0	0
Acute Respiratory failure	1	1	0	0	0	0	1 (100.0)
Antiphospholipid Syndrome	1	0	1 (100.0)	0	0	0	0
Cardio-respiratory Arrest	1	1	0	0	0	0	1 (100.0)
Cerebrovascular accident	1	1	0	0	1 (100.0)	0	0
Myocardial infarction	1	1	0	0	1 (100.0)	0	0
Retinal Artery Occlusion	1	1	0	0	1 (100.0)	0	0
Total	9	8 (88.89)	1 (11.11)	3 (33.33)	3 (33.33)	0	2 (22.22)

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in the pool. %: Based on Total AE
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/ae_sum_out_pt_mace

Table 49. Summary of Treatment Emergent Events of MACE by Seriousness/Outcomes and Preferred Term in any Ritlecitinib - AEP

Any Ritlecitinib (N=1630)							
Latest Outcome							
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Acute MI	3	3	0	3 (100.0)	0	0	0
Acute Respiratory failure	1	1	0	0	0	0	1 (100.0)
Antiphospholipid Syndrome	1	0	1 (100.0)	0	0	0	0
Cardio-respiratory Arrest	1	1	0	0	0	0	1 (100.0)
Cerebrovascular accident	1	1	0	0	1 (100.0)	0	0
Myocardial infarction	1	1	0	0	1 (100.0)	0	0
Renal Artery Occlusion	1	1	0	0	1 (100.0)	0	0
Total	9	8 (88.89)	1 (11.11)	3 (33.33)	3 (33.33)	0	2 (22.22)

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in the pool. %: Based on Total n.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/ae_sum_out_pt_mace

Maximum Severity

The maximum severity of each event type in the AEP are provided in Table 50 and Table 51.

Table 50. Summary of Treatment Emergent Events of MACE by Maximum Severity and Preferred Term in Ritlecitinib 50 mg - AEP

Ritlecitinib 50 mg (N=1523)				
Maximum Severity				
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Acute MI	3	0	0	3 (100.0)
Acute Respiratory failure	1	0	0	1 (100.0)
Antiphospholipid Syndrome	1	0	1 (100.0)	0
Cardio-respiratory Arrest	1	0	0	1 (100.0)
Cerebrovascular accident	1	0	1 (100.0)	0
Myocardial infarction	1	0	0	1 (100.0)
Retinal Artery Occlusion	1	0	1 (100.0)	0
Total	9	0	3 (33.33)	6 (66.67)

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in pool %: Based on Total n.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_sev_mace

Table 51. Summary of Treatment Emergent Events of MACE by Maximum Severity and Preferred Term in any Ritlecitinib - AEP

Any Ritlecitinib (N=1630)				
Maximum Severity				
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Acute MI	3	0	0	3 (100.0)
Acute Respiratory failure	1	0	0	1 (100.0)

Table 51. Summary of Treatment Emergent Events of MACE by Maximum Severity and Preferred Term in any Ritlecitinib - AEP

Any Ritlecitinib (N=1630)				
	Maximum Severity			
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Antiphospholipid Syndrome	1	0	1 (100.0)	0
Cardio-respiratory Arrest	1	0	0	1 (100.0)
Cerebrovascular accident	1	0	1 (100.0)	0
Myocardial infarction	1	0	0	1 (100.0)
Retinal Artery Occlusion	1	0	1 (100.0)	0
Total	9	0	3 (33.33)	6 (66.67)

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in pool %: Based on Total n.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_sev_mace

Risk Factors and Risk Groups

There was an insufficient number of events in the ritlecitinib development program for formal risk factor or subgroup analysis and there are limited data in patients ≥ 65 years of age. Age ≥65 years, current or past smoking history, a history of atherosclerotic disease and other cardiovascular risk factors are all considered risk factors for MACE in patients treated with JAK class inhibitors.

Preventability

Risks and benefits of ritlecitinib treatment should be considered prior to initiating therapy in patients with known risk factors for cardiovascular disease.

Impact on the Risk-Benefit Balance of the Product

Cardiovascular disease can have a significant impact on individual patients and may lead to significant morbidity and mortality.

Public health impact

Cardiovascular disease is associated with significant morbidity and is currently the top cause of death worldwide[120]. While some autoimmune diseases are associated with a higher risk of cardiovascular disease, such as rheumatoid arthritis[121] and systemic lupus erythematous[122], no differences in cardiovascular risk have been identified in patients with AA compared to the general population[123].

SVII.3.6. Neurotoxicity

Potential Mechanisms

The potential mechanism is unknown.

Evidence Source and Strength of Evidence

Chronic nonclinical toxicity study in Beagle dogs showed the presence of axonal dystrophy in the CNS and PNS which was associated with a functional effect of BAEP waveform change at 33-times the human dose of 50 mg. Clinical data does not indicate an effect on neurological or audiological outcomes.

Characterisation of the Risk

PCAAP

Frequency of Events of Neurotoxicity

Table 52. Proportion and Incidence Rates for Treatment-Emergent Event of Neurotoxicity - Placebo-Controlled AA Pool

	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)
Number of Subjects with Event n (%) Total Drug exposure (PY)[a] Incidence rates (95% CI)[b]						
Neurotoxicity	6 (2.8) 100.02 3.82 (1.39, 9.46)	3 (2.3) 58.71 4.10 (1.03, 11.15)	9 (2.6) 158.72 5.19 (2.52, 9.69)	13 (5.0) 113.64 9.17 (5.09, 15.29)	4 (6.5) 26.95 11.90 (3.77, 28.70)	9 (4.2) 97.48 7.98 (3.59, 15.89)

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.
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].
n (%): Number of participants with the event.
N:Number of participants in pool

Table 52. Proportion and Incidence Rates for Treatment-Emergent Event of Neurotoxicity - Placebo-Controlled AA Pool

	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)
Number of Subjects with Event n (%) **Total Drug exposure (PY)[a]** **Incidence rates (95% CI)[b]**						

a. 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.
b. Study-size adjusted results per 100 PY and mid-p gamma intervals.
B7981037 data cutoff date: 04JAN2022.
[redacted] Source Data: adae Source Dataset Creation: 24MAR2022 (08:52) Table Generation: 19May2023 (17:21)
Output File: ./aa_scs_nda/PCPAA/sum_ae_out_

Seriousness/Outcomes

All the events in the PCPAA pool were non-serious. The outcomes of each event type in the AEP are provided in Table 53.

Table 53. Summary of the Latest Outcome for Treatment Emergent Events of Neurotoxicity by Preferred Terms in Placebo-controlled AA Pool

	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)	
	Still Present	Resolved	Still Present	Resolved	Still Present	Resolved	Still Present	Resolved	Still Present	Resolved	Still Present	Resolved
Deafness Neurosensory	0	0	0	1 (100.0)	0	1 (100.0)	1 (100.0)	0	0	0	0	0
Dizziness	0	0	0	0	0	0	0	1 (100.0)	0	1 (100.0)	0	0
Headache	0	1 (100.0)	0	0	0	1 (100.0)	0	4 (100.0)	0	0	0	2 (100.0)
Hyperaesthesia	0	2 (100.0)	0	0	0	2 (100.0)	0	0	0	0	0	0
Hypoaesthesia	1 (100.0)	0	0	2 (100.0)	1 (33.3)	2 (66.7)	1 (25.0)	3 (75.0)	0	0	1 (50.0)	1 (50.0)
Lethargy	0	0	0	0	0	0	0	1 (100.0)	0	0	0	0
Orthostatic Hypotension	0	0	0	0	0	0	0	1 (100.0)	0	0	0	0
Paraesthesia	0	1 (100.0)	0	0	0	1 (100.0)	1 (100.0)	0	0	0	0	1 (100.0)
Restlessness	0	0	0	0	0	0	0	0	0	0	0	1 (100.0)
Somnolence	0	0	0	0	0	0	0	0	0	1 (100.0)	1 (100.0)	0
Syncope	0	1 (100.0)	0	0	0	1 (100.0)	0	0	0	1 (100.0)	0	3 (100.0)

Table 53. Summary of the Latest Outcome for Treatment Emergent Events of Neurotoxicity by Preferred Terms in Placebo-controlled AA Pool

	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)	
Vertigo Positional	0	0	0	0	0	0	0	1 (100.0)	0	1 (100.0)	0	0
Visual Impairment	0	0	0	0	0	0	0	0	0	1 (100.0)	0	0
Total	1 (16.7)	5 (83.3)	0 (0.0)	3 (100.0)	1 (14.3)	6 (85.7)	3 (21.4)	11 (78.6)	0 (0.0)	5 (100.0)	2 (2-0.0)	8 (80.0)

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 only counted once per treatment in each row.
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].
N: Number of participants in pool. N: Number of participants with event.
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present
B7981037 data cutoff date: 04JAN2022.
[redacted] Source Data: adae Source Dataset Creation: 24MAR2022 (08:52) Table Generation: 09JUN2022 (08:46)
Output File: ./aa_scs_nda/scsb7980062a_PCPAA_RMP/ae_sum_out_PT_neuro

Maximum Severity

The maximum severity of each event type in the PCAAP are provided in Table 54.

Table 54. Summary of the Maximum Severity for Treatment Emergent Events of Neurotoxicity by Preferred Terms in Placebo-controlled AA Pool

	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)	
	Mild	Moderate	Mild	Severe	Mild	Moderate	Severe	Mild	Moderate	Mild	Moderate	Severe	Mild	Moderate
Deafness Neuro-	0	0	1 (100.0)	0	1	0	0	0	1 (100.0)	0	0	0	0	0

Table 54. Summary of the Maximum Severity for Treatment Emergent Events of Neurotoxicity by Preferred Terms in Placebo-controlled AA Pool

	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)	
sensory														
Dizziness	0	0	0	0	0	0	0	0	1 (100.0)	0	1 (100.0)	0	0	0
Headache	0	1 (100.0)	0	0	0	1 (100.0)		0	4 (100.0)	0	0	0	0	2 (100.0)
Hyper-aesthesia	2 (100.0)	0	1 (50.0)	1 (50.0)	2 (100.0)	0	0	0	0	0	0	0	0	0
Hypo-aesthesia	1 (100.0)	0	0	0	2 (66.7)	0	1 (33.3)	3 (75.0)	2 (25.0)	0	0	0	2 (100.0)	0
Lethargy	0	0	0	0	0	0	0	1 (100.0)	0	0	0	0	0	0
Orthostatic Hypo-tension	0	0	0	0	0	0	0	1 (100.0)	0	0	0	0	0	0
Paraesthesia	1 (100.0)	0	0	0	1 (100.0)	0	0	1 (100.0)	0	0	0	0	1 (100.0)	0
Restlessness	0	0	0	0	0	0	0	0	0	0	0	0	1 (100.0)	0
Somnolence	0	0	0	0	0	0	0	0	0	1 (100.0)	0	0	0	1 (100.0)
Syncope	1 (100.0)	0	0	0	1 (100.0)	0	0	0	0	1 (100.0)	0	0	1 (33.3)	2 (66.7)
Vertigo Positional	0	0	0	0	0	0	0	1 (100.0)	0	0	0	1 (100.0)	0	0
Visual Impairment	0	0	0	0	0	0	0	0	0	1	0	0	0	0

Table 54. Summary of the Maximum Severity for Treatment Emergent Events of Neurotoxicity by Preferred Terms in Placebo-controlled AA Pool

	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)	
										(100.0)				
Total	5 (83.3)	1 (16.7)	2 (66.7)	1 (33.3)	7 (77.8)	1 (11.1)	1 (11.1)	7 (50.0)	7 (50.0)	3 (60.0)	1 (20.0)	1 (20.0)	5 (50.0)	5 (50.0)

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 only counted once per treatment in each row.
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].
n: Number of participants with the event. %: Based on Total n.
MedDRA v24.1 coding dictionary applied.
B7981037 data cutoff date: 04JAN2022.
[redacted] Source Data: adae1 Source Dataset Creation: 24MAR2022 (09:03) Table Generation: 16MAY2023 (15:29)
Output File: ./aa_scs_nda/scsb7980062a_PCPAA_RMP/sum_ae_sev_neuro

AEP

Frequency of Events of Neurotoxicity

Table 55. Proportion and Incidence Rates of Subjects for Events of Neurotoxicity AEP

	Ritlecitinib 50 mg	Any Ritlecitinib
	Number of Subjects with Event n (%) Total Drug exposure (PY)[a] Incidence rates (95% CI)[b]	
Adjudicated Neurotoxicity	119 (7.8) 3356.57 3.58 (2.98, 4.29)	142 (8.7) 3638.12 3.90 (3.30, 4.59)

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.

Table 55. Proportion and Incidence Rates of Subjects for Events of Neurotoxicity AEP

	Ritlecitinib 50 mg	Any 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.
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].
n (%): Number of participants with the event.
a. 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.
b. Study-size adjusted results per 100 PY and mid-p gamma intervals.
MedDRA v27.0 coding dictionary applied for updated AEP-2024 data. Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (10:15)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_out

Seriousness/Outcomes

The seriousness/outcomes of each event type in the AEP are provided Table 56 and Table 57

Table 56. Summary of Treatment Emergent Events of Neurotoxity by Seriousness/Outcomes and Preferred Term in Ritlecitinib 50 mg Arm - AEP

Ritlecitinib 50 mg (N=1523)							
			Latest Outcome				
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Agitation	1	0	0	1 (100.0)	0	0	0
Anisocoria	1	0	1 (100.0)	0	0	0	0
Areflexia	1	0	0	1 (100.0)	0	0	0
Asthenia	1	0	0	1 (100.0)	0	0	0
Attention deficit hyperactivity disorder	2	0	2 (100.0)	0	0	0	0

Table 56. Summary of Treatment Emergent Events of Neurotoxity by Seriousness/Outcomes and Preferred Term in Ritlecitinib 50 mg Arm - AEP

Ritlecitinib 50 mg (N=1523)							
			Latest Outcome				
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Audiogram abnormal	1	0	1 (100.0)	0	0	0	0
Bell's palsy	1	1	1 (100.0)	0	0	0	0
Blindness	1	1	0	0	1 (100.0)	0	0
Burning sensation	1	0	0	1 (100.0)	0	0	0
Carpal tunnel syndrome	7	0	5 (71.43)	2 (28.57)	0	0	0
Cervical radiculopathy	1	0	0	0	1 (100.0)	0	0
Deafness	3	0	2 (66.67)	1 (33.33)	0	0	0
Deafness neurosensory	13	0	8 (61.54)	5 (38.46)	0	0	0
Deafness unilateral	1	0	0	1 (100.0)	0	0	0
Delirium	1	1	0	1 (100.0)	0	0	0
Diplopia	1	0	1 (100.0)	0	0	0	0
Disturbance in attention	2	0	0	2 (100.0)	0	0	0
Dizziness	1	0	0	1 (100.0)	0	0	0
Dysaesthesia	2	0	2 (100.0)	0	0	0	0
Dysgeusia	3	0	0	3 (100.0)	0	0	0
Dyskinesia	2	0	2 (100.0)	0	0	0	0
Eyelid myokymia	1	0	0	1 (100.0)	0	0	0
Eyelid ptosis	1	0	0	1 (100.0)	0	0	0
Gait disturbance	0	0	0	0	0	0	0
Headache	14	0	4 (28.57)	9 (64.29)	0	1 (7.14)	0

Table 56. Summary of Treatment Emergent Events of Neurotoxity by Seriousness/Outcomes and Preferred Term in Ritlecitinib 50 mg Arm - AEP

Ritlecitinib 50 mg (N=1523)							
			Latest Outcome				
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Hyperaesthesia	1	0	0	1 (100.0)	0	0	0
Hyperreflexia	1	0	1 (100.0)	0	0	0	0
Hypoacusis	3	0	2 (66.67)	1 (33.33)	0	0	0
Hypoaesthesia	13	0	2 (15.38)	11 (84.62)	0	0	0
Lethargy	4	0	0	4 (100.0)	0	0	0
Mental impairment	1	0	1 (100.0)	0	0	0	0
Migraine	8	1	4 (50.00)	4 (50.00)	0	0	0
Muscular weakness	1	0	0	1 (100.0)	0	0	0
Myoclonus	1	0	0	1 (100.0)	0	0	0
Neuropathy peripheral	2	0	2 (100.0)	0	0	0	0
Orthostatic hypotension	3	0	1 (33.33)	2 (66.67)	0	0	0
Paraesthesia	18	0	3 (16.67)	15 (83.33)	0	0	0
Parkinson's disease	1	0	1 (100.0)	0	0	0	0
Peroneal nerve palsy	1	0	0	1 (100.0)	0	0	0
Polyneuropathy	1	0	1 (100.0)	0	0	0	0
Post concussion syndrome	1	0	1 (100.0)	0	0	0	0
Presyncope	1	0	0	1 (100.0)	0	0	0
Restless legs syndrome	0	0	0	0	0	0	0
Restlessness	1	0	0	1 (100.0)	0	0	0

Table 56. Summary of Treatment Emergent Events of Neurotoxity by Seriousness/Outcomes and Preferred Term in Ritlecitinib 50 mg Arm - AEP

Ritlecitinib 50 mg (N=1523)							
			Latest Outcome				
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Sciatica	5	0	2 (40.00)	3 (60.00)	0	0	0
Sensitive skin	1	0	0	1 (100.0)	0	0	0
Somnolence	3	0	0	3 (100.0)	0	0	0
Syncope	7	1	0	7 (100.0)	0	0	0
Taste disorder	2	0	0	2 (100.0)	0	0	0
Tinnitus	2	0	2 (100.0)	0	0	0	0
Vertigo positional	4	0	0	4 (100.0)	0	0	0
Vision blurred	1	0	1 (100.0)	0	0	0	0
Visual acuity reduced	1	0	1 (100.0)	0	0	0	0
Visual impairment	0	0	0	0	0	0	0
Total	151	5	54 (35.76)	94 (62.25)	2 (1.32)	1 (0.66)	0

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in the pool. %: Based on Total AE
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/ae_sum_out_pt_ns

Table 57. Summary of Treatment Emergent Events of Neurotoxity by Seriousness/Outcomes and Preferred Term in any Ritlecitinib Arm - AEP

Any Ritlecitinib (N=1630)							
			Latest Outcome				
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Agitation	1	0	0	1 (100.0)	0	0	0
Anisocoria	1	0	1 (100.0)	0	0	0	0
Areflexia	1	0	0	1 (100.0)	0	0	0
Asthenia	1	0	0	1 (100.0)	0	0	0
Attention deficit hyperactivity disorder	2	0	2 (100.0)	0	0	0	0
Audiogram abnormal	1	0	1 (100.0)	0	0	0	0
Bell's palsy	1	1	1 (100.0)	0	0	0	0
Blindness	1	1	0	0	1 (100.0)	0	0
Burning sensation	1	0	0	1 (100.0)	0	0	0
Carpal tunnel syndrome	7	0	5 (71.43)	2 (28.57)	0	0	0
Cervical radiculopathy	1	0	0	0	1 (100.0)	0	0
Deafness	3	0	2 (66.67)	1 (33.33)	0	0	0
Deafness neurosensory	16	0	10 (62.50)	6 (37.50)	0	0	0
Deafness unilateral	1	0	0	1 (100.0)	0	0	0
Delirium	1	1	0	1 (100.0)	0	0	0
Diplopia	1	0	1 (100.0)	0	0	0	0
Disturbance in attention	2	0	0	2 (100.0)	0	0	0

Table 57. Summary of Treatment Emergent Events of Neurotoxity by Seriousness/Outcomes and Preferred Term in any Ritlecitinib Arm - AEP

Any Ritlecitinib (N=1630)							
Latest Outcome							
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Dizziness	5	0	0	5 (100.0)	0	0	0
Dysaesthesia	2	0	2 (100.0)	0	0	0	0
Dysgeusia	3	0	0	3 (100.0)	0	0	0
Dyskinesia	2	0	2 (100.0)	0	0	0	0
Eyelid myokymia	1	0	0	1 (100.0)	0	0	0
Eyelid ptosis	1	0	0	1 (100.0)	0	0	0
Gait disturbance	1	0	0	1 (100.0)	0	0	0
Headache	18	0	4 (22.22)	13 (72.22)	0	1 (5.56)	0
Hyperaesthesia	1	0	0	1 (100.0)	0	0	0
Hyperreflexia	1	0	1 (100.0)	0	0	0	0
Hypoacusis	3	0	2 (66.67)	1 (33.33)	0	0	0
Hypoaesthesia	18	0	3 (16.67)	15 (83.33)	0	0	0
Lethargy	5	0	0	5 (100.0)	0	0	0
Mental impairment	1	0	1 (100.0)	0	0	0	0
Migraine	9	2	4 (44.44)	5 (55.6)	0	0	0
Muscular weakness	1	0	0	1 (100.0)	0	0	0
Myoclonus	1	0	0	1 (100.0)	0	0	0
Neuropathy peripheral	2	0	2 (100.0)	0	0	0	0
Orthostatic hypotension	4	0	1 (25.0)	3 (75.0)	0	0	0
Paraesthesia	19	0	4 (21.05)	15 (78.95)	0	0	0
Parkinson's disease	1	0	1 (100.0)	0	0	0	0

Table 57. Summary of Treatment Emergent Events of Neurotoxity by Seriousness/Outcomes and Preferred Term in any Ritlecitinib Arm - AEP

Any Ritlecitinib (N=1630)							
			Latest Outcome				
Preferred Term	**Total number of events**	**# of serious events**	**Still Present**	**Resolved**	**Resolved with sequelae**	**Unknown**	**Death**
Peroneal nerve palsy	1	0	0	1 (100.0)	0	0	0
Polyneuropathy	1	0	1 (100.0)	0	0	0	0
Post concussion syndrome	1	0	1 (100.0)	0	0	0	0
Presyncope	1	0	0	1 (100.0)	0	0	0
Restless legs syndrome	1	0	0	1 (100.0)	0	0	0
Restlessness	1	0	0	1 (100.0)	0	0	0
Sciatica	5	0	2 (40.0)	3 (60.0)	0	0	0
Sensitive skin	1	0	0	1 (100.0)	0	0	0
Somnolence	4	0	0	4 (100.0)	0	0	0
Syncope	8	1	0	8 (100.0)	0	0	0
Taste disorder	2	0	0	2 (100.0)	0	0	0
Tinnitus	2	0	2 (100.0)	0	0	0	0
Vertigo positional	6	0	0	6 (100.0)	0	0	0
Vision blurred	1	0	1 (100.0)	0	0	0	0
Visual acuity reduced	1	0	1 (100.0)	0	0	0	0
Visual impairment	1	0	0	1 (100.0)	0	0	0
Total	178	6	58 (32.58)	117 (65.73)	2 (1.12)	1 (0.56)	0

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.

Table 57. Summary of Treatment Emergent Events of Neurotoxity by Seriousness/Outcomes and Preferred Term in any Ritlecitinib Arm - AEP

Any Ritlecitinib (N=1630)							
Latest Outcome							
Preferred Term	Total number of events	# of serious events	Still Present	Resolved	Resolved with sequelae	Unknown	Death

Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in the pool. %: Based on Total AE
For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/ae_sum_out_pt_ns

Maximum Severity

The maximum severity of each event type in the AEP are provided in Table 58 and Table 59.

Table 58. Summary of Treatment Emergent events of Neurotoxicity by Maximum Severity and Preferred Terms in Ritlecitinib 50 mg - AEP

Ritlecitinib 50 mg (N=1523)				
Maximum Severity				
Preferred Term	Total	Mild	Moderate	Severe
Agitation	1	1 (100.0)	0	0
Anisocoria	1	0	1 (100.0)	0
Areflexia	1	1 (100.0)	0	0
Asthenia	1	1 (100.0)	0	0
Attention deficit hyperactivity disorder	2	2 (100.0)	0	0

Table 58. Summary of Treatment Emergent events of Neurotoxicity by Maximum Severity and Preferred Terms in Ritlecitinib 50 mg - AEP

Ritlecitinib 50 mg (N=1523)				
Maximum Severity				
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Audiogram abnormal	1	1 (100.0)	0	0
Bell's palsy	1	0	0	1 (100)
Blindness	1	0	1 (100.0)	0
Burning sensation	1	1 (100.0)	0	0
Carpal tunnel syndrome	7	6 (85.71)	1 (14.29)	0
Cervical radiculopathy	1	1 (100.0)	0	0
Deafness	3	3 (100.0)	0	0
Deafness neurosensory	13	12 (92.31)	1 (7.69)	0
Deafness unilateral	1	1 (100.0)	0	0
Delirium	1	0	0	1 (100)
Diplopia	1	1 (100.0)	0	0
Disturbance in attention	2	2 (100.0)	0	0
Dizziness	1	0	1 (100.0)	0
Dysaesthesia	2	1 (50.0)	1 (50.0)	0
Dysgeusia	3	3 (100.0)	0	0
Dyskinesia	2	2 (100.0)	0	0
Eyelid myokymia	1	1 (100.0)	0	0
Eyelid ptosis	1	1 (100.0)	0	0
Gait disturbance	0	0	0	0
Headache	14	0	13 (92.86)	1 (7.14)
Hyperaesthesia	1	1 (100.0)	0	0
Hyperreflexia	1	1 (100.0)	0	0
Hypoacusis	3	3 (100.0)	0	0

Table 58. Summary of Treatment Emergent events of Neurotoxicity by Maximum Severity and Preferred Terms in Ritlecitinib 50 mg - AEP

Ritlecitinib 50 mg (N=1523)				
	Maximum Severity			
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Hypoaesthesia	13	11 (84.62)	1 (7.69)	1 (7.69)
Lethargy	4	4 (100.0)	0	0
Mental impairment	1	1 (100.0)	0	0
Migraine	8	0	5 (62.50)	3 (37.50)
Muscular weakness	1	1 (100.0)	0	0
Myoclonus	1	1 (100.0)	0	0
Neuropathy peripheral	2	0	2 (100.0)	0
Orthostatic hypotension	3	3 (100.0)	0	0
Paraesthesia	18	17 (94.44)	1 (5.56)	0
Parkinson's disease	1	1 (100.0)	0	0
Peroneal nerve palsy	1	1 (100.0)	0	0
Polyneuropathy	1	0	1 (100.0)	0
Post concussion syndrome	1	0	1 (100.0)	0
Presyncope	1	0	1 (100.0)	0
Restless legs syndrome	0	0	0	0
Restlessness	1	1 (100.0)	0	0
Sciatica	5	2 (40.0)	2 (40.0)	1 (20.0)
Sensitive skin	1	1 (100.0)	0	0
Somnolence	3	3 (100.0)	0	0
Syncope	7	3 (42.86)	4 (57.14)	0
Taste disorder	2	2 (100.0)	0	0
Tinnitus	2	1 (50.0)	0	1 (50.0)
Vertigo positional	4	3 (75.0)	1 (25.0)	0

Table 58. Summary of Treatment Emergent events of Neurotoxicity by Maximum Severity and Preferred Terms in Ritlecitinib 50 mg - AEP

Ritlecitinib 50 mg (N=1523)				
Maximum Severity				
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Vision blurred	1	0	1 (100.0)	0
Visual acuity reduced	1	1 (100.0)	0	0
Visual impairment	0	0	0	0
Total	151	103 (68.21)	39 (25.83)	9 (5.96)

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in the pool. %: Based on Total number of events.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_sev_ns

Table 59. Summary of Treatment Emergent events of Neurotoxicity by Maximum Severity and Preferred Terms in in any Ritlecitinib Arm - AEP

Any Ritlecitinib (N=1630)				
Maximum Severity				
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Agitation	1	1 (100.0)	0	0
Anisocoria	1	0	1 (100.0)	0
Areflexia	1	1 (100.0)	0	0

Table 59. Summary of Treatment Emergent events of Neurotoxicity by Maximum Severity and Preferred Terms in in any Ritlecitinib Arm - AEP

Any Ritlecitinib (N=1630)				
Maximum Severity				
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Asthenia	1	1 (100.0)	0	0
Attention deficit hyperactivity disorder	2	2 (100.0)	0	0
Audiogram abnormal	1	1 (100.0)	0	0
Bell's palsy	1	0	0	1 (100.0)
Blindness	1	0	1 (100.0)	0
Burning sensation	1	1 (100.0)	0	0
Carpal tunnel syndrome	7	6 (85.71)	1 (14.29)	0
Cervical radiculopathy	1	1 (100.0)	0	0
Deafness	3	3 (100.0)	0	0
Deafness neurosensory	16	14 (87.50)	2 (12.50)	0
Deafness unilateral	1	1 (100.0)	0	0
Delirium	1	0	0	1 (100.0)
Diplopia	1	1 (100.0)	0	0
Disturbance in attention	2	2 (100.0)	0	0
Dizziness	5	0	4 (80.0)	1 (20.0)
Dysaesthesia	2	1 (50.0)	1 (50.0)	0
Dysgeusia	3	3 (100.0)	0	0
Dyskinesia	2	2 (100.0)	0	0
Eyelid myokymia	1	1 (100.0)	0	0
Eyelid ptosis	1	1 (100.0)	0	0
Gait disturbance	1	0	1 (100.0)	0
Headache	18	0	17 (94.44)	1 (5.56)
Hyperaesthesia	1	1 (100.0)	0	0

Table 59. Summary of Treatment Emergent events of Neurotoxicity by Maximum Severity and Preferred Terms in in any Ritlecitinib Arm - AEP

Any Ritlecitinib (N=1630)				
Maximum Severity				
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Hyperreflexia	1	1 (100.0)	0	0
Hypoacusis	3	3 (100.0)	0	0
Hypoaesthesia	18	15 (83.33)	2 (11.11)	1 (5.56)
Lethargy	5	5 (100.0)	0	0
Mental impairment	1	1 (100.0)	0	0
Migraine	9	0	5 (55.56)	4 (44.44)
Muscular weakness	1	1 (100.0)	0	0
Myoclonus	1	1 (100.0)	0	0
Neuropathy peripheral	2	0	2 (100.0)	0
Orthostatic hypotension	4	4 (100.0)	0	0
Paraesthesia	19	18 (94.74)	1 (5.26)	0
Parkinson's disease	1	1 (100.0)	0	0
Peroneal nerve palsy	1	1 (100.0)	0	0
Polyneuropathy	1	0	1 (100.0)	0
Post concussion syndrome	1	0	1 (100.0)	0
Presyncope	1	0	1 (100.0)	0
Restless legs syndrome	1	0	1 (100.0)	0
Restlessness	1	1 (100.0)	0	0
Sciatica	5	2 (40.0)	2 (40.0)	1 (20.0)
Sensitive skin	1	1 (100.0)	0	0
Somnolence	4	4 (100.0)	0	0
Syncope	8	4 (50.0)	4 (50.0)	0
Taste disorder	2	2 (100.0)	0	0

Table 59. Summary of Treatment Emergent events of Neurotoxicity by Maximum Severity and Preferred Terms in in any Ritlecitinib Arm - AEP

Any Ritlecitinib (N=1630)				
Maximum Severity				
Preferred Term	**Total**	**Mild**	**Moderate**	**Severe**
Tinnitus	2	1 (50.0)	0	1 (50.0)
Vertigo positional	6	4 (66.67)	1 (16.67)	1 (16.67)
Vision blurred	1	0	1 (100.0)	0
Visual acuity reduced	1	1 (100.0)	0	0
Visual impairment	1	1 (100.0)	0	0
Total	178	116 (65.17)	50 (28.09)	12 (6.74)

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.
Except for the Number of Adverse Events, participants are only counted once per treatment in each row.
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].
N: Number of participants in the pool. %: Based on Total number of events.
MedDRA v27.0 coding dictionary applied.
Updated AEP-2024 includes data from updated AEP, plus the additional follow-up data from studies B7981037 and B7981032. Study B7981032 with cutoff date of 25JUN2024.
[redacted] Source Data: adae Source Dataset Creation: 13SEP2024 (11:34) Table Generation: 16SEP2024 (12:13)
Output File: ./aa_scs_nda/AEP_SU/sum_ae_sev_ns

Risk Factors and Risk Groups

Risk factors in the general population include extremes in age, prior neurological disease, chronic illness and renal impairment.

Preventability

Treatment with ritlecitinib should be discontinued in case unexplained neurological symptoms occur.

Impact on the Risk-Benefit Balance of the Product

Neurotoxicity can have an impact on individual patients and may lead to significant morbidity or mortality.

Public health impact

Neurotoxicity potentially includes a broad group of nervous system diseases such as peripheral neuropathy, neurological hearing loss, and seizures, some more common than others and each with varying levels of severity. No differences in neurological risk have been identified in patients with AA compared to the general population[124].

SVII.3.7. Presentation of the Missing Information

Table 60. Missing Information: Long - Term Safety

Evidence source There are limited long-term safety data from ritlecitinib clinical studies. Anticipated risk/consequence of the missing information The risk of longer latency events such as malignancy or cardiovascular disease may not be fully captured in the clinical development program. Long-term safety will be monitored using routine pharmacovigilance and additional PV measures.

Table 61. Missing Information: Long-Term safety in adolescent patients including growth and bone development, and maturation and pubertal development.

Evidence source There are limited long-term safety data from ritlecitinib clinical studies. Anticipated risk/consequence of the missing information The risk of longer latency events in adolescents may not be fully captured in the clinical development program. Long-term safety will be monitored using routine pharmacovigilance and additional PV measures

Module SVIII. Summary of Safety Concerns

Table 62. Summary of 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
	Embryofoetal 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.

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

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance for the lifecycle of a product is a critical component to the detection, assessment, understanding and mitigation of AEs. Objectives of routine pharmacovigilance includes having processes in place to assure the ongoing and timely collection, processing, follow-up, and analysis of individual AE reports and aggregate data globally, following global safety Standard Operating Procedures and regulatory guidance.

Pfizer monitors the safety profile of its products, evaluates issues potentially impacting product benefit-risk profiles in a timely manner, and ensures that appropriate communication of relevant safety information is conveyed in a timely manner to regulatory authorities and other interested parties as appropriate and in accordance with international principles and prevailing regulations.

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

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

None.

III.2. Additional Pharmacovigilance Activities

B7981101: Active Safety Surveillance Study in Secondary Databases Summary

Study short name and title:

Study B7981101: An Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Patients with Alopecia Areata in Denmark, France, and Sweden (See RMP Part VII Annex 3 for protocol).

Rationale and study objectives:

The study will be an active safety surveillance study to assess safety endpoints of interest associated with ritlecitinib in the post-approval setting.

The primary objective is to estimate the incidence rates (IRs) of safety events of interest among patients with AA initiating ritlecitinib and patients with AA initiating baricitinib or other approved systemic treatments for AA in a real-world setting. The following are the primary safety events of interest:

- Thromboembolic events (including venous thromboembolism (VTE) and arterial thrombosis)

- Herpes zoster;
- Serious infections;
- Opportunistic infections;
- Malignancy;
    - Malignancy excluding nonmelanoma skin cancer (NMSC); and
    - NMSC.
- Major adverse cardiovascular events (MACE);
- Neurological events of interest
    - Peripheral neuropathy
    - Sensorineural hearing loss
    - Migraine
    - Seizures and seizure disorders
    - Demyelinating disorders including multiple sclerosis
    - Neurodegenerative disorders
- Bone fractures
- Growth metrics in adolescents (height and weight, conditional on sufficient data available beyond age 12 years; Denmark only)

Exploratory objective: to compare incidence rates of the safety events of interest among patients with AA initiating ritlecitinib and patients with AA initiating baricitinib or other approved systemic treatments for AA, if study size permits.

Study design:

The study population will include patients with AA initiating ritlecitinib, baricitinib or another approved systemic AA treatment as recorded in the participating data sources in Denmark, France, and Sweden during the cohort accrual period.

Safety Assessments

This study will assess the following safety outcomes in existing electronic healthcare data: thromboembolic events, herpes zoster, serious infections, opportunistic infections, malignancy, MACE, neurological events of interest, bone fractures, and growth metrics in adolescents (Denmark only). The data include diagnosis and procedure codes, dispensed prescription medications, and administered medications.

Milestones:

Milestone	Planned Date[a]	Comments
Registration in the EU PAS register	August 2027	Prior to initiating data collection
Draft protocol submission	March 2024	Within 6 months from approval of ritlecitinib in the European Union (EU).
Start of data collection[b]	September 2027	Within 4 years from approval of ritlecitinib in the EU.
End of data collection[c]	September 2035	Within 2 years after the end of study period, considering the lag in data availability in the respective data sources
Interim analysis reports[d]	September 2028 September 2030 September 2032 September 2034	The 1st interim report is planned to be submitted within 5 years of approval of ritlecitinib in the EU, considering the lag in data availability in the respective data sources. Subsequent interim reports are planned every 2 years thereafter over 6 years (4 interim reports total).
Final study reports[d]	March 2036	Final study report is planned for submission within 6 months from the end of data collection.

a EU approval 15 September 2023.
b Defined as the date from which data extraction starts for the first interim report.
c Defined as the date from which the analytical dataset is completely available for the final study report. The analytical dataset is the dataset that contains clean and coded data from all participating countries/databases.
d Interim reports will contain analyses addressing the primary objectives. The final study report will be inclusive of all objectives, conditional on feasibility of the exploratory objective.

B7981102: Drug Utilization Study Summary

Study short name and title:

Study B7981102: A Drug Utilization Study to Evaluate Indicators of Adherence to the Risk Minimization Measures for Ritlecitinib Using Electronic Healthcare Data in Denmark, France, and Sweden (See RMP Part VII Annex 3 for protocol)

Rationale and study objectives:

To mitigate the risks associated with ritlecitinib use, required routine risk minimization measures (RMMs), including the Summary of Product Characteristics (SmPC) and package leaflet, are being employed. In addition to the routine RMMs, the Applicant has agreed to implement additional risk minimization measures (aRMMs) following ritlecitinib approval in EU including an educational program intended to enhance the communication of the risks

and risk minimization practices to healthcare professionals (HCPs) via an “HCP Guide” and to patients via a “Patient Card”.

An evaluation of the database-measurable indicators of adherence of HCPs with the RMMs will help understand whether the program objectives have been met and if further amendments to the program may be needed. Therefore, the Applicant aims to evaluate indicators of adherence to the routine and additional RMMs for ritlecitinib in three EU countries: Denmark, France, and Sweden.

The research question is: To what extent do routinely collected data indicate HCPs adherence to the recommendations for the use of ritlecitinib described in the SmPC, HCP guide, and Patient card?

The study objectives are to:

1. Evaluate, to the extent measurable in the available routinely collected data, indicators of HCPs adherence to the RMMs in accordance with the ritlecitinib SmPC and HCP guide, and Patient Card, specifically:
    - Performing laboratory tests of lymphocyte count, platelet count, hepatitis B/C, and tuberculosis (TB) screening prior to initiation of ritlecitinib treatment
    - Performing laboratory tests of lymphocyte count and platelet count at week 4 (± 2 weeks) from initiation of ritlecitinib treatment
    - Avoiding live attenuated vaccines shortly before and during treatment with ritlecitinib
    - No use during pregnancy
    - No use in patients aged < 12 years
    - No use during serious infections
2. Describe the characteristics of patients before initiation of ritlecitinib treatment, in terms of:
    - Risk factors for thromboembolic events (including DVT, PE, and arterial thrombosis)
    - Risk factors for malignancy
    - Risk factors for CV disease

Study design:

This is a descriptive drug utilization study using secondary data from healthcare databases in Denmark, France, and Sweden.

Study population:

The study population will include patients identified in each data source with a record of treatment with ritlecitinib from 15 September 2023 through 14 September 2028. Patients will not be required to have a recorded diagnosis of AA.

Safety Assessments

This study will analyse existing electronic healthcare data to assess indicators of HCP adherence to RMMs such whether laboratory tests were performed according to the recommended schedule and whether live vaccines were administered during ritlecitinib treatment. The data include dispensed prescription medications, administered medications, laboratory tests, and diagnosis and procedure codes.

Milestones:

Milestone	Planned Date [a]	Comments
Registration in the EU PAS register	August 2027	Prior to initiating the data collection
Draft protocol submission	March 2024	Within 6 months from approval of ritlecitinib in the European Union (EU).
Start of data collection[b]	September 2027	Within 4 years from approval of ritlecitinib in the EU.
End of data collection[c]	September 2030	Within 2 years after the end of study period, considering the lag in data availability in the respective data sources
Interim Report	September 2028	Interim study report planned for submission within 5 years of approval of ritlecitinib in the EU, considering the lag in data availability in the respective data sources.
Final study report	March 2031	Final study report planned for submission within 6 months from the end of data collection.

a EU approval 15 September 2023.
b Defined as the date from which data extraction starts.
c Defined as the date from which the analytical dataset is completely available, i.e., clean and coded data from all participating countries/databases

B7981092: Active Safety Surveillance Study in Adolescents Summary

Study short name and title:

Study B7981092: A Prospective Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Adolescents with Alopecia Areata

Rationale and study objectives:

The available nonclinical data for ritlecitinib do not suggest a risk associated with growth and development in patients ≥12 years old. However, the potential impact of the long-term use of ritlecitinib on growth and bone development, and maturation and pubertal development. is considered missing information. Neurotoxicity is an important potential risk. Therefore, at

the Pharmacovigilance Risk Assessment Committee's (PRAC's) request, a long-term follow-up study will be conducted to actively monitor growth and development (including bone fractures), maturation and pubertal development, and neurotoxicity (as evaluated via neurological events of interest) associated with exposure to ritlecitinib in adolescents aged 12-17 years in the post-approval setting. This study is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the EMA.

The primary objectives are:

- Among adolescent participants with AA who are treated with ritlecitinib and, separately, among adolescent participants in the comparator cohort, including those exposed to other medications for the treatment of AA in adolescents, to:
    - Estimate growth and bone development metrics;
    - Estimate maturation and pubertal development metrics;
    - Estimate the incidence of bone fractures; and
    - Estimate the incidence of neurotoxicity events.

The exploratory objectives are:

- Among adolescent participants with AA who are treated with ritlecitinib and adolescent participants in the comparator cohort, including those exposed to other medications for the treatment of AA in adolescents, to:
    - Compare growth and bone development metrics;
    - Compare maturation and pubertal development metrics;
    - Compare the incidence of bone fractures; and
    - Compare the incidence of neurotoxicity events.

Study design:

This will be a prospective observational cohort study of adolescents with severe AA who receive ritlecitinib and those in the comparator cohort, including those exposed to other medications for the treatment of AA in adolescents.

Study population:

The study will include adolescents (aged 12-17 years) with AA receiving ritlecitinib and adolescents with AA who are unexposed to ritlecitinib, including those exposed to other approved systemic treatments for AA.

Safety Assessments

This PASS will use the CorEvitas International Adolescent AA Registry, which collects a range of clinical and participant-reported variables. Growth and bone development outcomes include change over follow-up in height standard deviation scores (SDS) and weight SDS, as well as the incidence of bone fractures. Maturation and pubertal development is measured by Tanner staging and age at peak height velocity (PHV), a measure of timing of somatic maturity. Additionally, neurotoxicity is measured via capture of pre-specified neurological adverse events using registry questionnaires. Registry questionnaires (including Provider Follow-up, Targeted Adverse Event Questionnaires, and/or Subject Exit questionnaires) are used to assess risk for bone fractures and potential neurotoxicity. Additional medical records are collected and submitted to the registry to support validation of physician-reported adverse events.

Milestone	Planned date
Registration in EU PAS register	Pending (prior to the start of data collection)
Start of data collection	31 March 2026[a]
Interim analysis report #1	30 September 2026
Interim analysis report #2	30 September 2028
Interim analysis report #3	30 September 2030
Interim analysis report #4	30 September 2032
Interim analysis report #5	30 September 2034
End of data collection	30 September 2036
Final study report	31 March 2037

a First participant enrolled in the underlying registry remains planned for September 2024. Given secondary dataset design, start of data collection has been defined as "the date from which data extraction starts" from the registry for the first interim analysis report.

B7981032: Long-term study

Study short name and title:

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. (See RMP Part VII Annex 3 for protocol amendment 6)

Rationale and Study Objectives

This study is specifically designed to evaluate the long-term safety, tolerability and efficacy of ritlecitinib in adults and adolescents.

The primary objectives are:

- 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.

Study Design

This is a Phase 3, open label, multi center, long-term study designed to evaluate the safety and efficacy of ritlecitinib (PF 06651600) in adults and adolescents ≥12 years of age with AA over a maximum duration of approximately 62 months, with participants continuing after the Month 36 visit for a maximum of 24 months or until availability of commercial product in their country, or until the sponsor terminates the study in that country, whichever occurs first. Eligible participants from the index studies B7931005 and B7981015 are given the opportunity to enroll, as well as approximately 450 de novo participants (ie, those who have not previously received study intervention in Study B7931005 or B7981015). Participants enrolling from the index studies receive open label 50 mg QD ritlecitinib for up to 60 months and de novo participants receive open label 200 mg ritlecitinib QD for 4 weeks followed by open-label 50 mg QD ritlecitinib for up to 59 months.

Study Population

All participants (in adults and adolescents ≥12) in this study, including those who participated in a qualifying index study and de novo participants, must have met protocol eligibility criteria.

Safety Assessments

Safety will be assessed by the spontaneous reporting of AEs, physical examinations, audiological evaluations and clinical laboratory results in all subjects who receive at least one dose of the study intervention. This study will collect safety data for the safety concerns (as outlined in Table 62), including safety events of interest such as serious infections, opportunistic infections, herpes zoster, malignancy, thromboembolic events (including deep vein thrombosis, pulmonary embolism and arterial thrombosis) cardiovascular events, neurological and audiological events and pregnancy outcomes.

Milestones

LSLV for PCD - (28 days after the Month 36 visit) – 25 June 2024.

CSR for PCD – November 2024.

LSLV for the study - July 2025 or until market availability of ritlecitinib in all countries in which the study is being conducted, whichever occurs first.

III.3. Summary Table of Additional Pharmacovigilance Activities

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

Table 63. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
B7981101: An Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Patients with Alopecia Areata in Denmark, France, and Sweden (Secondary Databases) Planned	Primary objective: to estimate the incidence rates (IRs) of safety events of interest among patients with alopecia areata (AA) initiating ritlecitinib and patients with AA initiating baricitinib or other approved systemic treatments for AA in a real-world setting. The following are the primary safety events of interest: • Thromboembolic events (including venous thromboembolism (VTE) and arterial thrombosis [AT]) • Herpes zoster • Serious infections • Opportunistic infections; • Malignancy o Malignancy excluding nonmelanoma skin cancer (NMSC) o NMSC	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

Table 63. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates

	• Major adverse cardiovascular events (MACE)
	• Neurological events of interest;
	  ○ Peripheral neuropathy
	  ○ Sensorineural hearing loss
	  ○ Migraine
	  ○ Seizures and seizure disorders
	  ○ Demyelinating disorders including multiple sclerosis
	  ○ Neurodegenerative disorders
	• Bone fractures
	• Growth metrics in adolescents (Denmark only)			

B7981092: A Prospective Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Adolescents with Alopecia Areata
 	
Planned
	The primary objectives are to:
	
	• Among adolescent participants with AA who are treated with ritlecitinib and, separately, among adolescent participants in the comparator cohort, including those exposed to other medications for the treatment of AA in adolescents, to:
	
	  ○ Estimate growth and bone development metrics;
	
	  ○ Estimate maturation and pubertal development metrics;
		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

Table 63. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	○ Estimate the incidence of bone fractures; and ○ Estimate the incidence of neurotoxicity events. The exploratory objectives are: • Among adolescent participants with AA who are treated with ritlecitinib and adolescent participants in the comparator cohort, including those exposed to other medications for the treatment of AA in adolescents, to: ○ Compare growth and bone development metrics; ○ Compare maturation and pubertal development metrics; ○ Compare the incidence of bone fractures; and ○ Compare the incidence of neurotoxicity events.			
B7981102: A Drug Utilization Study to Evaluate Indicators of Adherence to the Risk Minimizatio	The study objectives are to: 1) 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),	The following are the safety concerns addressed: • Herpes zoster; • Serious and opportunistic infections; • Malignancy;	Draft protocol submission	March 2024
			Interim report	Septe mber 2028
			Final report	March 2031

Table 63. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
n Measures for Ritlecitinib Using Electronic Healthcare Data in Denmark, France, and Sweden Planned	HCP guide and patient card, specifically: • Performing laboratory tests of lymphocyte count, platelet count, hepatitis B/C, and tuberculosis (TB) screening prior to initiation of ritlecitinib treatment • Performing laboratory tests of lymphocyte count and platelet count at week 4 (± 2 weeks) from initiation of ritlecitinib treatment • Avoiding live attenuated vaccines shortly prior to and during treatment with ritlecitinib • No use during pregnancy • No use in patients aged < 12 years • No use during serious infections 2) Describe the characteristics of patients before initiation of ritlecitinib treatment, in terms of: • Risk factors for thromboembolic events (including deep vein thrombosis, pulmonary embolism, and arterial thrombosis); • Risk factors for malignancy • Risk factors for cardiovascular (CV) disease.	• Thromboembolic events (including DVT, PE, AT); and • Embryofoetal toxicity following exposure in utero.		
B7981032: A Phase 3 Open-Label Multi-Center Long-Term study investigating the Safety and Efficacy of ritlecitinib in Adult and Adolescent Participants with	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.	This study will collect safety data for • Serious infections, • Opportunistic infections, • Herpes zoster, • Malignancy,	LSLV for PCD PCD CSR	(28 days after the Month 36 visit) - 25 June 2024

Table 63. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Alopecia Areata. On-going	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.	• 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 the study	November 2024 July 2025 or until market availability of ritlecinib in all countries in which the study is being conducted, whichever occurs first.

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

Not Applicable.

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

RISK MINIMISATION PLAN

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Table 64. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Important Identified risks	
Herpes Zoster	Routine risk communication: SmPC Section 4.4 Special Warnings and Precautions for use SmPC Section 4.8 Undesirable Effects Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 states: Viral reactivations, including cases of herpes virus reactivation (e.g., herpes zoster), have been reported. If a patient develops herpes zoster, temporary interruption of treatment may be considered until the episode resolves. Other routine risk minimisation measures beyond the Product Information: None
Important Potential risks	
Serious and Opportunistic infections	Routine risk communication: SmPC Section 4.2 Posology and method of administration. SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use. SmPC Section 4.8 Undesirable effects Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2 states: if a patient develops serious infection or opportunistic infection, ritlecitinib should be interrupted until the infection is controlled. SmPC Section 4.3 Contraindications include: Active serious infections, including tuberculosis (TB) SmPC Section 4.4 states: Serious infections have been reported in patients receiving ritlecitinib. The most frequent serious infections

Table 64. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	have been appendicitis, COVID-19 infection (including pneumonia), and sepsis. Treatment with ritlecitinib should be avoided in patients with an active, serious infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ritlecitinib. Treatment should be interrupted if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with ritlecitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored. Prescribers should evaluate whether interrupting treatment for alopecia areata is the best course of action for an individual patient. Ritlecitinib may be resumed once the infection is controlled. As there is a higher incidence of infections in elderly and in the diabetic population in general, caution should be exercised when treating the elderly and patients with diabetes, and particular attention paid with respect to occurrence of infections. Patients should be screened for tuberculosis and viral hepatitis before starting therapy. Use of live attenuated vaccines should be avoided during or immediately prior to ritlecitinib therapy. Prior to initiating ritlecitinib, it is recommended that patients be brought up to date with all immunisations, including prophylactic herpes zoster vaccinations, in agreement with current immunisation guidelines. <u>Other routine risk minimisation measures beyond the Product Information:</u> None
Malignancy	<u>Routine risk communication:</u> SmPC Section 4.4 Special warnings and precautions for use. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> SmPC Section 4.4 states: Malignancies, including non-melanoma skin cancer (NMSC) have been reported in patients receiving ritlecitinib. The risks and benefits of ritlecitinib treatment should be considered prior to initiating or continuing therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or cervical cancer. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. <u>Other routine risk minimisation measures beyond the Product Information:</u> None

Table 64. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 states: Events of venous and arterial thromboembolism have been reported in patients receiving ritlecitinib. The risks and benefits should be considered before initiating ritlecitinib in patients at high risk for thromboembolic events. Other routine risk minimisation measures beyond the Product Information: None
Embryofoetal toxicity following exposure in utero	Routine risk communication SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, pregnancy and lactation Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.3 contraindications include: Pregnancy and breast-feeding. SmPC Section 4.6 states: There are no or limited data from the use of ritlecitinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Ritlecitinib was teratogenic in rats and rabbits at high doses. Litfulo is contraindicated during pregnancy. Other routine risk minimisation measures beyond the Product Information: None
MACE	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 states: Events of venous and arterial thromboembolism, including MACE, have been reported in patients receiving ritlecitinib. The risks and benefits of ritlecitinib treatment should be considered prior to initiating therapy in patients. Other routine risk minimisation measures beyond the Product Information: None

Table 64. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Neurotoxicity	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use. SmPC Section 5.3 Pre-clinical Safety Data Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 states: Treatment with ritlecitinib should be discontinued in case unexplained neurological symptoms occur. SmPC Section 5.3 describes the nonclinical finding of axonal dystrophy in Beagle dogs Other routine risk minimisation measures beyond the Product Information: None
Missing Information	
Long - Term Safety	Routine risk communication None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Long-term safety in adolescent patients including growth and bone development, and maturation and pubertal development.	Routine risk communication None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None

V.2. Additional Risk Minimisation Measures

Patient card

Objectives:

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

- Herpes Zoster
- Serious and opportunistic Infections
- Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis
- Embryofoetal toxicity exposure in utero
- Neurotoxicity
- MACE

Rationale for the additional risk minimisation activity:

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

Target audience and planned distribution path:

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

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

A drug utilization study (B7981102) is planned to evaluate the effectiveness of RMMs for ritlecitinib in the EU using electronic healthcare data. The criteria for success will include indicators of adherence to the recommended risk minimisation measures in accordance with the ritlecitinib SmPC, HCP guide and Patient Card. The relevant details are included in the full protocol (See RMP Part VII Annex 3 for protocol).

Healthcare Professional Guide

Objectives:

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

To accomplish the objective, the Healthcare Professional Guide was developed to inform prescribers about the risks and missing information and to provide recommendations on how to mitigate the risk through appropriate monitoring and management.

- Serious and opportunistic infections (including Herpes Zoster)
- Malignancy
- Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis
- Embryofoetal toxicity following exposure in utero
- Neurotoxicity
- MACE

Rationale for the additional risk minimisation activity:

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

Target audience and planned distribution path:

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

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

A drug utilization study is planned to evaluate the effectiveness of RMMs for ritlecitinib in the EU using electronic healthcare data. The criteria for success will include indicators of adherence to the recommended risk minimisation measures in accordance with the ritlecitinib SmPC, HCP guide, and Patient Card. The relevant details will be included in the full protocol.

V.3. Summary of Risk Minimisation Measures

Table 65. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

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:** B7981101: Active surveillance study in secondary databases Final study report: March 2036 B7981102: Drug utilization 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:** B7981101: Active surveillance study in secondary databases Final study report: March 2036 B7981102: Drug utilization study Final study report: March 2031 B7981032: Long-term study

Table 65. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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:** B7981101: Active surveillance study in secondary databases Final study report: March 2036 B7981102: Drug utilization 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 **Additional risk minimisation measures.** Healthcare Professional Guide Patient Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** B7981101: Active surveillance study in secondary databases Final study report: March 2036 B7981102: Drug utilization study Final study report: March 2031 B7981032: Long-term study

Table 65. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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:** B7981102: Drug utilization 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:** B7981101: 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:** B7981101: Active surveillance study in secondary databases Final study report: March 2036 B7981092: Active surveillance study in adolescents Final study report: Mar 2037 B7981032: Long-term study
Missing Information		

Table 65. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Long-Term Safety	**Routine risk minimization measures:** None **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** B7981101: Active surveillance study in secondary databases Final study report: March 2036 B7981092: Active surveillance study in adolescents 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:** B7981101: Active surveillance study in secondary databases Final study report: March 2036 B7981092: Active surveillance study in adolescents Final study report: Mar 2037 B7981032: Long-term study

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Litfulo

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

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

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

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

I. The Medicine and What It Is Used For

Litfulo is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older. It contains ritlecitinib as the active substance and it is given by oral of administration.

Further information about the evaluation of Litfulo’s benefits can be found in Litfulo’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage link to the EPAR summary landing page.

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

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

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

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals

- Important advice on the medicine’s packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

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

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

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

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

II.A List of Important Risks and Missing Information

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

Table 66. Summary of Safety Concerns

Summary of 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
	Embryofoetal 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.

II.B Summary of Important Risks

Table 67. Important Identified Risk: Herpes Zoster

Evidence for linking the risk to the medicine	Clinical study data of ritlecitinib and understanding of effects of immunomodulatory mechanisms. Herpes zoster infections were assessed in the ritlecitinib development program.
Risk factors and risk groups	Risk factors for Herpes zoster infections include patients that use drugs along with ritlecitinib that suppress the immune system (including corticosteroids), patients with low absolute lymphocyte counts and people with weakened immune systems.
Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.4 Special warnings and precautions for use.

Table 67. Important Identified Risk: Herpes Zoster

	SmPC Section 4.8 Undesirable Effects Additional risk minimisation measures Healthcare Professional Guide Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: B7981101: Active surveillance study in secondary databases B7981102: Drug utilization study B7981032: Long-term study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 68. Important Potential Risk: Serious and Opportunistic infections

Evidence for linking the risk to the medicine	Clinical study data of ritlecitinib and understanding of immunomodulatory mechanisms. Serious infections and adjudicated opportunistic infections were assessed in the ritlecitinib development program.
Risk factors and risk groups	Risk factors for serious infections include elderly age, certain medical conditions such as diabetes, patients that use drugs along with ritlecitinib that suppress the immune system (including corticosteroids), patients with low absolute lymphocyte counts and people with weakened immune systems.
Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.2 Posology and method of administration. SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use. SmPC Section 4.8 Undesirable effects Additional risk minimisation measures Healthcare Professional Guide Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: B7981101: Active surveillance study in secondary databases B7981102: Drug utilization study B7981032: Long-term study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 69. Important Potential Risk: Malignancy

Evidence for linking the risk to the medicine	Clinical study data and understanding of immunomodulatory mechanisms based on the data from the JAK class. Adjudicated malignancy events were assessed in the ritlecitinib development program.
Risk factors and risk groups	Malignancies were observed in clinical studies of ritlecitinib. However, there were an insufficient number of events for risk factor or subgroup analysis. The risks and benefits of ritlecitinib treatment should be considered prior to initiating or continuing therapy in patients with a known malignancy (other than a successfully treated non-melanoma skin cancer (NMSC) or cervical cancer).
Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.4 Special Warnings and Precautions for use Additional risk minimisation measures Healthcare Professional Guide Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: B7981101: Active surveillance study in secondary databases B7981102: Drug utilization study B7981032: Long-term study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 70. Important Potential Risk: Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis

Evidence for linking the risk to the medicine	Thrombotic events have been reported in patients receiving ritlecitinib in clinical studies. Adjudicated thromboembolic events (venous and arterial) were assessed in the ritlecitinib development program.
Risk factors and risk groups	There were an insufficient number of cases to analyze risk factors from the ritlecitinib clinical trial data. Risk factors for thromboembolic events in the general population also apply to patients with AA including older age, obesity, a medical history of thromboembolism, prothrombotic disorder, use of combined hormonal contraceptives or hormone replacement therapy, patients undergoing major surgery, or prolonged immobilization.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 Special Warnings and Precautions for use Additional risk minimisation measures Healthcare Professional Guide Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: B7981101: Active surveillance study in secondary databases B7981102: Drug utilization study B7981032: Long-term study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 71. Important Potential Risk: Embryofoetal toxicity following exposure in utero

Evidence for linking the risk to the medicine	There are limited data from the use of ritlecitinib in human pregnancy. Studies in animals have shown developmental toxicity with no effects at clinically relevant exposures. In an embryo-foetal development study in pregnant rats, oral administration of ritlecitinib from gestation days 6 to 17 resulted in foetal skeletal malformations and variations and lower foetal body weights at exposures greater than or equal to 49 times the unbound AUC at the MRHD. There were no effects on embryo-foetal development at exposures equal to 16 times the unbound AUC at the MRHD. In an embryo-foetal development study in pregnant rabbits, oral administration of ritlecitinib from gestation days 7 to 19 resulted in lower mean foetal body weights and higher incidences of visceral malformations, skeletal malformations, and skeletal variations at exposures equal to 55 times the unbound AUC at the MRHD. There were no effects on embryo-foetal development at exposures equal to 12 times the unbound AUC at the MRHD. In a rat pre- and postnatal development study, oral administration of ritlecitinib from gestation day 6 through lactation day 20 resulted in developmental toxicity that included lower postnatal survival, lower offspring body weights, and secondary developmental delays at exposure equal to 41 times the unbound AUC at the MRHD. Bred females in the F1 generation exhibited lower mean numbers of corpora lutea at exposures equal to 41 times the unbound AUC at the MRHD. There were no effects on pre- and postnatal development at exposures equal to 14 times the unbound AUC at the MRHD.
Risk factors and risk groups	Risk of foetal malformation pertains only to women of childbearing potential who become pregnant while receiving ritlecitinib. There were no cases reported of Embryofoetal toxicity.
Risk minimisation measures	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
Additional pharmacovigilance activities	Additional pharmacovigilance activities: B7981102: Drug utilization study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 72. Important Potential Risk: MACE

Evidence for linking the risk to the medicine	Events of venous and arterial thromboembolism-including MACE, have been reported in patients receiving ritlecitinib. It is not known whether JAK3 inhibition may be associated with all adverse reactions of non-selective JAK inhibition. In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in RA patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of MACE, defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, and a dose dependent higher rate of venous thromboembolism including DVT and PE were observed with a JAK inhibitor compared to TNF inhibitors.
Risk factors and risk groups	There was an insufficient number of events in the ritlecitinib development program for formal risk factor or subgroup analysis. Age ≥65 years, current or past smoking history, and a history of atherosclerotic disease are risk factors for MACE in patients treated with JAK class inhibitors.
Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.4 Special Warnings and Precautions for use Additional risk minimisation measures Healthcare Professional Guide Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: B7981101: Active surveillance study in secondary databases B7981032: Long-term study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 73. Important Potential Risk: Neurotoxicity

Evidence for linking the risk to the medicine	Ritlecitinib-related axonal dystrophy has been observed in chronic Beagle dog toxicity studies (see section 5.3). Treatment with ritlecitinib should be discontinued in case unexplained neurological symptoms occur.
Risk factors and risk groups	Risk factors in the general population include extremes in age, prior neurological disease, chronic illness and renal impairment.
Risk minimisation measures	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 measure Healthcare Professional Guide Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: B7981101: Active surveillance study in secondary databases B7981092: Active surveillance study in adolescents B7981032: Long-term study

Table 73. Important Potential Risk: Neurotoxicity

	See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 74. Missing Information: Long-Term Safety

Evidence for linking the risk to the medicine	There are limited long-term safety data from ritlecitinib clinical studies.
Risk Minimisation Measures	Routine risk minimisation measures: None Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: B7981101: Active surveillance study in secondary databases B7981092: Active surveillance study in adolescents B7981032: Long-term study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 75. Missing Information: Long-Term safety in adolescent patients including growth and bone development, and maturation and pubertal development.

Evidence for linking the risk to the medicine	There were limited long-term data in adolescent participants in clinical studies to fully characterize any potential effect on growth and bone development, and maturation and pubertal development.
Risk Minimisation Measures	Routine risk minimisation measures: None Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: B7981101: Active surveillance study in secondary databases B7981092: Active surveillance study in adolescents B7981032: Long-term study See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

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

The following studies are conditions of the marketing authorisation:

None.

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

Study short name

B7981101: An Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Patients with Alopecia Areata in Denmark, France, and Sweden (Secondary Databases) (See RMP Part VII Annex 3 for protocol)**.**

Purpose of the study: The primary objective is to estimate the incidence rates (IRs) of safety events of interest among patients with AA initiating ritlecitinib and patients with AA initiating baricitinib or other approved systemic treatments for AA in a real-world setting. The following are the primary safety events of interest:

- Thromboembolic events (including venous thromboembolism (VTE) and arterial thrombosis);
- Herpes zoster
- Serious infections
- Opportunistic infections
- Malignancy
    - Malignancy excluding nonmelanoma skin cancer (NMSC)
    - NMSC
- Major adverse cardiovascular events (MACE)
- Neurological events of interest
    - Peripheral neuropathy
    - Sensorineural hearing loss
    - Migraine
    - Seizures and seizure disorders
    - Demyelinating disorders including multiple sclerosis
    - Neurodegenerative disorders
- Bone fractures
- Growth metrics in adolescents (Denmark only)

Exploratory objective: to compare incidence rates of the safety events of interest among patients with AA initiating ritlecitinib and patients with AA initiating baricitinib or other approved systemic treatments for AA, if study size permits.

Study short name

B7981102: A Drug Utilization Study to Evaluate Indicators of Adherence to the Risk Minimization Measures for Ritlecitinib Using Electronic Healthcare Data in Denmark, France, and Sweden (See RMP Part VII Annex 3 for protocol).

Purpose of the study:

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.

Describe the characteristics of patients prior to initiation of ritlecitinib treatment.

Study short name

B7981092: A Prospective Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Adolescents with Alopecia Areata (See RMP Part VII Annex 3 for protocol).

Purpose of the study:

The primary objectives are:

- Among adolescent participants with AA who are treated with ritlecitinib and, separately, among adolescent participants in the comparator cohort, including those exposed to other medications for the treatment of AA in adolescents, to:
    - Estimate growth and bone development metrics;
    - Estimate maturation and pubertal development metrics;
    - Estimate the incidence of bone fractures; and
    - Estimate the incidence of neurotoxicity events.

The exploratory objectives are:

- Among adolescent participants with AA who are treated with ritlecitinib and adolescent participants in the comparator cohort, including those exposed to other medications for the treatment of AA in adolescents, to:
    - Compare growth and bone development metrics;
    - Compare maturation and pubertal development metrics;
    - Compare the incidence of bone fractures; and

- Compare the incidence of neurotoxicity events.

B7981032 Long-term study

Study short name:

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 (See RMP Part VII Annex 3 for protocol amendment 6).

Rationale and Study Objectives

This study is specifically designed to evaluate the long-term safety, tolerability and efficacy of ritlecitinib in adults and adolescents.

The primary objectives are:

- To evaluate the long-term safety and tolerability of ritlecitinib in adult and adolescent participants with AA.

The secondary objectives are:

- To evaluate the effect of ritlecitinib on participant-centered outcomes and payer relevant measures to assess treatment benefit from the participant perspective and to demonstrate value.

- To evaluate the long-term efficacy of ritlecitinib in adult and adolescent participants with AA.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

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

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

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

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

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

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

REFERENCES

1 Pratt CH, King LE, Jr., Messenger AG, et.al. Alopecia areata. Nat Rev Dis Primers. 2017;3:17011.

2 Lee HH, Gwillim E, Patel KR, et al. Epidemiology of alopecia areata, ophiasis, totalis, and universalis: A systematic review and meta-analysis. J Am Acad Dermatol 2020;82(3):675-682.

3 Harries M, Macbeth AE, Holmes S, et al. The epidemiology of alopecia areata: a population-based cohort study in UK primary care. Br J Dermatol.

4 Mirzoyev SA, Schrum AG, Davis MDP, et al. Lifetime incidence risk of alopecia areata estimated at 2.1% by Rochester Epidemiology Project, 1990-2009. The Journal of investigative dermatology. 2014;134(4):1141-2.

5 Thompson JM, Park MK, Qureshi AA, et al. Race and Alopecia Areata amongst US Women. The journal of investigative dermatology Symposium proceedings. 2018;19(1):S47-s50.

6 Lee JH, Kim HJ, Han KD, et al. Incidence and prevalence of alopecia areata according to subtype: a nationwide, population-based study in South Korea (2006-2015). Br J Dermatol 2019;181(5):1092-1093.

7 Kim HJ, Kazmi SZ, Kang T, et al. Familial risk and incidence of alopecia areata among first degree relatives-A nationwide population-based study in Korea. J Am Acad Dermatol. 2021;85(5):1360-2.

8 Richard MA, Corgibet F, Beylot-Barry M, et al. Sex- and age-adjusted prevalence estimates of five chronic inflammatory skin diseases in France: results of the « OBJECTIFS PEAU » study. J Eur Acad Dermatol Venereol 2018;32(11):1967-1971.

9 Benigno M, Anastassopoulos KP, Mostaghimi A, et al. A Large Cross-Sectional Survey Study of the Prevalence of Alopecia Areata in the United States. Clinical, cosmetic and investigational dermatology. 2020;13:259-66.

10 Tan E, Tay YK, Goh CL, et al. The pattern and profile of alopecia areata in Singapore--a study of 219 Asians. International journal of dermatology. 2002;41(11):748-53.

11 Yang S, Yang J, Liu JB, et al. The genetic epidemiology of alopecia areata in China. Br J Dermatol 2004;151(1):16-23.

12 Goh C, Finkel M, Christos PJ, et al. Profile of 513 patients with alopecia areata: associations of disease subtypes with atopy, autoimmune disease and positive family history. J Eur Acad Dermatol Venereol 2006;20(9):1055-60.

13 Senna M, Ko J, Tosti A, et al. Alopecia Areata Treatment Patterns, Healthcare Resource Utilization, and Comorbidities in the US Population Using Insurance Claims. Adv Ther 2021;38(9):4646-4658.

14 Chu SY, Chen YJ, Tseng WC, et al. Comorbidity profiles among patients with alopecia areata: the importance of onset age, a nationwide population-based study. J Am Acad Dermatol 2011;65(5):949-56.

15 Jacobsen EW, Pedersen OB, Andorsdóttir G, et al. Family recurrence risk of alopecia areata in the Faroe Islands. Clin Exp Dermatol 2019;44(7):e224-e229.

16 Safavi KH, Muller SA, Suman VJ, et al. Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989. Mayo Clin Proc. 1995;70(7):628-33.

17 Nanda A, Al-Fouzan AS, Al-Hasawi F. Alopecia areata in children: a clinical profile. Pediatric dermatology. 2002;19(6):482-5.

18 Sharma VK, Dawn G, Kumar B. Profile of alopecia areata in Northern India. International journal of dermatology. 1996;35(1):22-7.

19 Guzman-Sanchez DA, Villanueva-Quintero GD, Alfaro N, et al. A clinical study of alopecia areata in Mexico. International journal of dermatology. 2007;46(12):1308-10.

20 Lee H, Jung SJ, Patel AB, et al. Racial characteristics of alopecia areata in the United States. J Am Acad Dermatol 2020;83(4):1064-1070.

21 Tu TY, Chang R, Lai JN, Tseng CC, et al. Human papillomavirus symptomatic infection associated with increased risk of new-onset alopecia areata: A nationwide population-based cohort study. Journal of autoimmunity. 2021;119:102618.

22 Vallerand IA, Lewinson RT, Parsons LM, et al. Assessment of a Bidirectional Association Between Major Depressive Disorder and Alopecia Areata. JAMA Dermatol 2019;155(4):475-479.

23 Mahamid M, Abu-Elhija O, Samamra M, et al. Association between vitamin D levels and alopecia areata. Isr Med Assoc J 2014;16(6):367-70.

24 Daroach M, Narang T, Saikia UN, et al. Correlation of vitamin D and vitamin D receptor expression in patients with alopecia areata: a clinical paradigm. Int J Dermatol 2018;57(2):217-222.

25 Bhat YJ, Latif I, Malik R, et al. Vitamin D Level in Alopecia Areata. Indian J Dermatol 2017;62(4):407-410.

26 Bakry OA, El Farargy SM, El Shafiee MK, Soliman A. Serum Vitamin D in patients with alopecia areata. Indian Dermatol Online J 2016;7(5):371-377.

27 Aksu Cerman A, Sarikaya Solak S, Kivanc Altunay I. Vitamin D deficiency in alopecia areata. Br J Dermatol 2014;170(6):1299-304.

28 d'Ovidio R, Vessio M, d'Ovidio FD. Reduced level of 25-hydroxyvitamin D in chronic/relapsing Alopecia Areata. Dermatoendocrinol 2013;5(2):271-3.

29 Lee S, Lee H, Lee CH, et al. Comorbidities in alopecia areata: A systematic review and meta-analysis. J Am Acad Dermatol 2019;80(2):466-477.e16.

30 Conic RZ, Tamashunas NL, Damiani G, et al. Comorbidities in pediatric alopecia areata. J Eur Acad Dermatol Venereol 2020;34(12):2898-2901.

31 Thompson JM, Mirza MA, Park MK, et al. The Role of Micronutrients in Alopecia Areata: A Review. Am J Clin Dermatol 2017;18(5):663-679.

32 Dai YX, Yeh FY, Shen YJ, et al. Cigarette Smoking, Alcohol Consumption, and Risk of Alopecia Areata: A Population-Based Cohort Study in Taiwan. Am J Clin Dermatol 2020;21(6):901-911.

33 Putterman E, Castelo-Soccio L. Seasonal patterns in alopecia areata, totalis, and universalis. J Am Acad Dermatol 2018;79(5):974-975.

34 Kavak A, Baykal C, Ozarmagan G, et al. HLA in alopecia areata. International journal of dermatology. 2000;39(8):589-92.

35 Thomas EA, Kadyan RS. Alopecia areata and autoimmunity: a clinical study. Indian J Dermatol 2008;53(2):70-4.

36 Olsen EA, Hordinsky MK, Price VH, Roberts JL, et al; National Alopecia Areata Foundation. Alopecia areata investigational assessment guidelines--Part II. National Alopecia Areata Foundation. J Am Acad Dermatol 2004;51(3):440-7.

37 Alshahrani AA, Al-Tuwaijri R, Abuoliat ZA, et al. Prevalence and Clinical Characteristics of Alopecia Areata at a Tertiary Care Center in Saudi Arabia. Dermatology research and practice. 2020;2020:7194270.

38 Lyakhovitsky A, Aronovich A, Gilboa S, et al. Alopecia areata: a long-term follow-up study of 104 patients. J Eur Acad Dermatol Venereol 2019;33(8):1602-1609.

39 Tosti A, Bellavista S, Iorizzo M. Alopecia areata: a long term follow-up study of 191 patients. J Am Acad Dermatol. 2006;55(3):438-41.

40 Jang YH, Eun DH, Kim DW. Long-Term Prognosis of Alopecia Areata in Children and Adolescents. Annals of dermatology. 2019;31(2):231-4.

41 Lee S, Lee YB, Kim BJ, et al. All-Cause and Cause-Specific Mortality Risks Associated With Alopecia Areata: A Korean Nationwide Population-Based Study. JAMA Dermatol 2019;155(8):922-928.

42 Messenger A, McKillop J, Farrant P, et al. British Association of Dermatologists' guidelines for the management of alopecia areata 2012. Br J Dermatol. 2012;166(5):916-26

43 Hordinsky M, Junqueira A. Alopecia areata update. Semin Cutan Med Surg. 2015;34(2):72-5.

44 Alkhalifah A, Alsantali A, Wang E, et al. Alopecia areata update: part II. Treatment. J Am Acad Dermatol. 2010;62(2):191-202, quiz 03-4.

45 Delamere F, Sladden M, Dobbins H, et al. Interventions for alopecia areata. The Cochrane database of systematic reviews. 2008;10.1002/14651858.CD004413.pub2(2):Cd004413.

46 Hordinsky M, Donati A. Alopecia areata: an evidence-based treatment update. American journal of clinical dermatology. 2014;15(3):231-46.

47 Hussain ST, Mostaghimi A, Barr PJ, et al. Utilization of Mental Health Resources and Complementary and Alternative Therapies for Alopecia Areata: A U.S. Survey. Int J Trichology. 2017;9(4):160-64.

48 Meah N, Wall D, York K, et al. The Alopecia Areata Consensus of Experts (ACE) study: Results of an international expert opinion on treatments for alopecia areata. J Am Acad Dermatol. 2020;83(1):123-30.

49 Rossi A, Muscianese M, Piraccini BM, et al. Italian Guidelines in diagnosis and treatment of alopecia areata. G Ital Dermatol Venereol. 2019;154(6):609-23.

50 Cranwell WC, Lai VW, Photiou L, et al. Treatment of alopecia areata: An Australian expert consensus statement. Australas J Dermatol. 2019;60(2):163-70.

51 Abbade LPF, Frade MAC, Pegas JRP, et al. Consensus on the diagnosis and management of chronic leg ulcers - Brazilian Society of Dermatology. An Bras Dermatol. 2020;95 Suppl 1:1-18.

52 Ito T. Advances in the management of alopecia areata. J Dermatol. 2012;39(1):11-7.

53 Strazzulla L, Wang E, Avila L, et al. Alopecia areata: An appraisal of new treatment approaches and overview of current therapies. J Am Acad Dermatol. 2018;78(1):15-24.

54 Kumaresan M. Intralesional steroids for alopecia areata. Int J Trichology. 2010;2(1):63-5.

55 Alkhalifah A. Alopecia areata update. Dermatologic clinics. 2013;31(1):93-108.

56 Charuwichitratana S, Wattanakrai P, Tanrattanakorn S. Randomized double-blind placebo-controlled trial in the treatment of alopecia areata with 0.25% desoximetasone cream. Arch Dermatol. 2000;136(10):1276-7.

57 Ramos PM, Anzai A, Duque-Estrada B, et al. Consensus on the treatment of alopecia areata - Brazilian Society of Dermatology. An Bras Dermatol. 2020;95 Suppl 1:39-52.

58 Kar BR, Handa S, Dogra S, et al. Placebo-controlled oral pulse prednisolone therapy in alopecia areata. J Am Acad Dermatol. 2005;52(2):287-90.

59 Sharma VK, Gupta S. Twice weekly 5 mg dexamethasone oral pulse in the treatment of extensive alopecia areata. J Dermatol. 1999;26(9):562-5.

60 Lester RS, Knowles SR, Shear NH. The risks of systemic corticosteroid use. Dermatologic clinics. 1998;16(2):277-88.

61 Kurosawa M, Nakagawa S, Mizuashi M, et al. A Comparison of the Efficacy, Relapse Rate and Side Effects among Three Modalities of Systemic Corticosteroid Therapy for Alopecia Areata. Dermatology. 2006;212(4):361-65.

62 Wiseman MC, Shapiro J, MacDonald N, et al. Predictive model for immunotherapy of alopecia areata with diphencyprone. Arch Dermatol. 2001;137(8):1063-8.

63 Madani S, Shapiro J. Alopecia areata update. J Am Acad Dermatol. 2000;42(4):549-66; quiz 67-70.

64 Ranchoff RE, Bergfeld WF, Steck WD, et al. Extensive alopecia areata. Results of treatment with 3% topical minoxidil. Cleve Clin J Med. 1989;56(2):149-54.

65 Randolph M, Tosti A. Oral minoxidil treatment for hair loss: A review of efficacy and safety. J Am Acad Dermatol. 2021;84(3):737-46.

66 Yang CC, Lee CT, Hsu CK, et al. Early intervention with high-dose steroid pulse therapy prolongs disease-free interval of severe alopecia areata: a retrospective study. Ann Dermatol. 2013;25(4):471-4.

67 Im M, Lee SS, Lee Y, et al. Prognostic factors in methylprednisolone pulse therapy for alopecia areata. J Dermatol. 2011;38(8):767-72.

68 Chiang KS, Mesinkovska NA, Piliang MP, et al. Clinical Efficacy of Diphenylcyclopropenone in Alopecia Areata: Retrospective Data Analysis of 50 Patients. J Investig Dermatol Symp Proc. 2015;17(2):50-5.

69 Liu L, Craiglow B, Dai F, et al. Tofacitinib for the treatment of severe alopecia areata and variants: A study of 90 patients. J Am Acad Dermatol. 2017;76(1):22-28.

70 Ali NS, Tollefson MM, Lohse CM, et al. Incidence and comorbidities of pediatric alopecia areata: A retrospective matched cohort study using the Rochester Epidemiology Project. J Am Acad Dermatol 2021:S0190-9622(21)02395-1.

71 Barahmani N, Schabath MB, Duvic M; National Alopecia Areata Registry. History of atopy or autoimmunity increases risk of alopecia areata. J Am Acad Dermatol 2009;61(4):581-91.

72 Ataseven A, Saral Y, Godekmerdan A. Serum cytokine levels and anxiety and depression rates in patients with alopecia areata. Eurasian J Med 2011;43(2):99-102.

73 Aghaei S, Saki N, Daneshmand E, et al. Prevalence of psychological disorders in patients with alopecia areata in comparison with normal subjects. ISRN Dermatol 2014;2014:304370.

74 Conic RZ, Miller R, Piliang M, et al. Comorbidities in patients with alopecia areata. J AmAcad Dermatol 2017;76(4):755-757.

75 Huang KP, Joyce CJ, Topaz M, et al. Cardiovascular risk in patients with alopecia areata (AA): A propensity-matched retrospective analysis. J Am Acad Dermatol 2016;75(1):151-4.

76 Kang JH, Lin HC, Kao S, et al. Alopecia Areata Increases the Risk of Stroke: a 3-year Follow-Up Study. Sci Rep 2015;5:11718.

77 Tzur Bitan D, Berzin D, Kridin K, et al. The association between alopecia areata and anxiety, depression, schizophrenia, and bipolar disorder: a population-based study. Arch Dermatol Res 2021.

78 Karadag AS, Ertugrul DT, Bilgili SG, et al. Insulin resistance is increased in alopecia areata patients. Cutan Ocul Toxicol 2013;32(2):102-6.

79 Behrangi E, Mansouri P, Agah S, et al. Association between Helicobacter Pylori Infection and Alopecia Areata: A Study in Iranian Population. Middle East J Dig Dis 2017;9(2):107-110.

80 Villasante Fricke AC, Miteva M. Epidemiology and burden of alopecia areata: a systematic review. Clin Cosmet Investig Dermatol 2015;8:397-403.

81 Seo HM, Han SS, Kim JS. Cancer risks among patients with alopecia areata: A population-based case-control study in Korea. J Am Acad Dermatol 2018;78(1):209-211.

82 Bin Saif GA. Severe subtype of alopecia areata is highly associated with thyroid autoimmunity. Saudi Med J 2016;37(6):656-61.

83 Díaz-Angulo S, López-Hoyos M, Muñoz-Cacho P, et al. High prevalence of thyroid autoimmunity in patients with alopecia areata and vitiligo: a controlled study. Australas J Dermatol 2015;56(2):142-3.

84 Chu SY, Chen YJ, Tseng WC, et al. Psychiatric comorbidities in patients with alopecia areata in Taiwan: a case-control study. Br J Dermatol 2012;166(3):525-31.

85 Recupero SM, Abdolrahimzadeh S, De Dominicis M, et al. Ocular alterations in alopecia areata. Eye (Lond) 1999;13 (Pt 5):643-6.

86 Sellami R, Masmoudi J, Ouali U, et al. The relationship between alopecia areata and alexithymia, anxiety and depression: a case-control study. Indian J Dermatol 2014;59(4):421.

87 Bilgiç Ö, Bilgiç A, Bahalı K, et al. Psychiatric symptomatology and health-related quality of life in children and adolescents with alopecia areata. J Eur Acad Dermatol Venereol 2014;28(11):1463-8.

88 Baghestani S, Zare S, Seddigh SH. Severity of Depression and Anxiety in Patients with Alopecia Areata in Bandar Abbas, Iran. Dermatol Reports 2015;7(3):6063.

89 Ucak H, Soylu E, Ozturk S, et al. Audiological abnormalities in patients with alopecia areata. J Eur Acad Dermatol Venereol 2014;28(8):1045-8.

90 Ergin C, Acar M, Kaya Akış H, et al. Ocular findings in alopecia areata. Int J Dermatol 2015;54(11):1315-8.

91 Pandhi D, Singal A, Gupta R, et al. Ocular alterations in patients of alopecia areata. J Dermatol 2009;36(5):262-8.

92 Hua Xu M, Jesson MI, Seneviratne UI, et al. PF-06651600, a Dual JAK3/TEC Family Kinase Inhibitor. ACS Chem Biol. 2019;14(6):1235-42.

93 Winthrop K, 2017. The emerging safety profile of JAK inhibitors in rheumatic disease. Nature Reviews Rheumatology, 13, pp 234-243.

94 Campuzano-Maya G. Cure of alopecia areata after eradication of Helicobacter pylori: a new association? World J Gastroenterol 2011;17(26):3165-70.

95 Skinner RB Jr, Light WH, Bale GF, et al. Alopecia areata and presence of cytomegalovirus DNA. JAMA 1995;273(18):1419-20.

96 Rodriguez TA, Duvic M; National Alopecia Areata Registry. Onset of alopecia areata after Epstein-Barr virus infectious mononucleosis. J Am Acad Dermatol 2008;59(1):137-9.

97 Cho M, Cohen PR, Duvic M. Vitiligo and alopecia areata in patients with human immunodeficiency virus infection. South Med J 1995 ;88(4):489-91.

98 Stewart MI, Smoller BR. Alopecia universalis in an HIV-positive patient: possible insight into pathogenesis. J Cutan Pathol 1993 ;20(2):180-3.

99 Rossi A, Magri F, Michelini S, et al. New onset of alopecia areata in a patient with SARS-CoV-2 infection: Possible pathogenetic correlations? J Cosmet Dermatol 2021;20(7):2004-2005.

100 Flvenson D. COVID-19: association with rapidly progressive forms of alopecia areata. Int J Dermatol 2021;60(1):127.

101 Bhardwaj EK, Trüeb RM. Acute diffuse and total alopecia of the female scalp associated with borrelia-infection. Int J Trichology 2015;7(1):26-8.

102 Gil Montoya JA, Cutando Soriano A, Jimenez Prat J. Alopecia areata of dental origin. Med Oral 2002;7(4):303-8.

103 Ito T, Tokura Y. Alopecia areata triggered or exacerbated by swine flu virus infection. J Dermatol 2012;39(10):863-4.

104 Jackow C, Puffer N, Hordinsky M, et al. Alopecia areata and cytomegalovirus infection in twins: genes versus environment? J Am Acad Dermatol 1998;38(3):418-25.

105 Offidani A, Amerio P, Bernardini ML, et al. Role of cytomegalovirus replication in alopecia areata pathogenesis. J Cutan Med Surg 2000;4(2):63-5.

106 Rigopoulos D, Katsambas A, Karalexis A, et al. No increased prevalence of Helicobacter pylori in patients with alopecia areata. J Am Acad Dermatol 2002;46(1):141.

107 Takeshita J, Shin DB, Ogdie A, et al. Risk of Serious Infection, Opportunistic Infection, and Herpes Zoster among Patients with Psoriasis in the United Kingdom. J Invest Dermatol 2018;138(8):1726-1735.

108 Simard JF, Rossides M, Gunnarsson I, et al. Infection hospitalisation in systemic lupus in Sweden. Lupus Sci Med 2021;8(1):e000510.

109 Ludvigsson JF, Holmgren J, Grip O, et al. Adult-onset inflammatory bowel disease and rate of serious infections compared to the general population: a nationwide register-based cohort study 2002-2017. Scand J Gastroenterol 2021;56(10):1152-1162.

110 Winthrop K, 2017. The emerging safety profile of JAK inhibitors in rheumatic disease. Nature Reviews Rheumatology, 13, pp 234-243.

111 Grulich AE, van Leeuwen MT, Falster MO, et al. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: A meta-analysis. Lancet 2007; 370(9581):59-67.

112 World Health Organization. Cancer. Fact sheet No 297. Updated February 2015. http://www.who.int/mediacentre/factsheets/fs297/en/

113 Chen CC, Chang YT, Liu HN, et al. Cancer risk in patients with alopecia areata: a nationwide population-based matched cohort study. Cancer Med 2018;7(5):2153-2159.

114 Lee JH, Song Y, Do Han K, et al. Cancer risk by the subtype of alopecia. Sci Re. 2018;8(1):9748.

115 Schneeweiss MC, Kim SC, Wyss R, et al. Incidence of Venous Thromboembolism in Patients With Dermatologist-Diagnosed Chronic Inflammatory Skin Diseases. JAMA Dermatol. 2021 Jul 1;157(7):805-816.

116 Kearon C. Epidemiology of venous thromboembolism. Semin Vasc Med 2001;1(1):7-26.

117 Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol 2015;12(8):464-74.

118 Wendelboe AM, Raskob GE. Global Burden of Thrombosis: Epidemiologic Aspects. Circ Res 2016 118(9):1340-7.

119 Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386(9995):743-800.

120 World Health Organization. The top 10 causes of death. 9 December 2020. Accessed 25 May 2023. Available at: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.

121 England RB, Thiele GM, Anderson DR, et al. Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. BMJ 2018; 361:k1036

122 Giannelou M, Mavragani CP. Cardiovascular disease in systemic lupus erythematosus: a comprehensive update. Journal of Autoimmunity 2017; 82:1012.

123 Strazzulla LC, Wang EHC, Avila L, et al. Alopecia areata: disease characteristics, clinical evaluation, and new perspectives on pathogenesis. Journal of the American Academy of Dermatology 2018; 78(1):1-12.

124 Lee S, Lee C, Lee CH, et al. Comorbidities in alopecia areata: a systematic review and meta-analysis. Journal of the American Academy of Dermatology 2019; 80(2):466-477.

ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not Applicable.

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Draft key messages of the 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-foetal 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 Litfulo 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.