23 April 2026
EMADOC-1700519818-3146413
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Skyrizi

International non-proprietary name: risankizumab

Procedure No. EMA/X/0000296763

Note

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

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List of abbreviations

ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	Adverse event of special interest
AI	autoinjector
ALT	alanine aminotransferase
AO	As Observed
AS	active substance
AST	aspartate aminotransferase
BSA	Body surface area
CCI	container closure integrity
CCS	container closure system
CD	Crohn's disease
CDLQI	Children's Dermatology of Life Quality Index
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMC	Chemistry, Manufacturing, and Controls
COVID-19	coronavirus disease - 2019
CPP	critical process parameter
CQA	critical quality attribute(s)
CSR	Clinical Study Report
CWRES	Conditional Weighted Residuals
DMC	Data monitoring committee
DS	drug substance
ePPND	Enhanced pre- and postnatal development
EAER	Exposure-adjusted event rate
EAIR	Exposure adjusted incidence rate
ECG	Electrocardiogram
ECL	Electrochemiluminescence
EMA	European Medicines Agency
ERA	Environmental risk assessment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDLQI	Family Dermatology Life Quality Index
FP	finished product
GCP	Good Clinical Practice

GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GOF	Goodness-of-fit
HB	Hepatitis B
HBV	Hepatitis B virus
HCV	hepatitis C virus
HIV	Human immunodeficiency virus
ICE	Intercurrent event
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IgG1	immunoglobulin G1
IL	interleukin
IPC	in-process controls
IRB	Institutional review board
ITT	intent-to-treat
LOCF	Last Observation Carried Forward
MAA	marketing authorisation application
MAH	Marketing authorisation holder
MASLD	Metabolic Dysfunction–Associated Steatotic Liver Disease
MRA	Mutual recognition agreement
MTX	methotrexate
NAb	neutralising antibody
NBOp	notified body opinion
NMSC	nonmelanoma skin cancer
NOR	normal operating ranges
NRI	Non-Responder Imputation
NRS	Numeric Rating Scale
NSP	needle stick protection device
OLE	open-label extension
PAR	proven acceptable range(s)
PASI	Psoriasis Area Severity Index
PASI 75/90/100	75%/90%/100% improvement in Psoriasis Area and Severity Index
PCS	potentially clinically significant
PD	Pharmacodynamics
PDCO	Paediatric committee
PFS	pre-filled syringe
PhV	Pharmacovigilance
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics

popPK	Population Pharmacokinetics
PPQ	process performance qualification
PsA	psoriatic arthritis
PsO	psoriasis
PT	Preferred term
PY	patient-year
q12w	every 12 weeks
QoL	quality of life
QTPP	quality target product profile
RCTC	Rheumatology Common Toxicity Criteria
RZB	risankizumab
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SIB	suicidal ideation and behavior
SmPC	Summary of product characteristics
SMQ	standardized MedDRA query
SOC	System organ class
sPGA	static Physician Global Assessment
TB	tuberculosis
TDAR	T-cell dependent antibody response
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UC	ulcerative colitis
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VPC	Visual Predictive Check

1. Administrative/regulatory information and recommendations on the procedure

1.1. Submission of the dossier

On 15 September 2025, Abbvie Deutschland GmbH & Co. KG submitted a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

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

Extension application to introduce a new strength (55 mg) of solution for injection in pre-filled syringe grouped with a type II variation C.I.6.a to include the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy for Skyrizi, based on final results from study M19-977 and interim results from study M19-973. Study M19-977 is a phase 3, randomised, active-controlled, efficacy assessor-blinded study to evaluate pharmacokinetics, safety, and efficacy of risankizumab in patients from 6 to less than 18 years of age with moderate to severe plaque psoriasis; Study M19-973 is a phase 3, single-arm, open-label extension study to assess the safety, tolerability, and efficacy of risankizumab in subjects with moderate to severe plaque psoriasis who have completed participation in study M19-977. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2, of the SmPC for Skyrizi 150 mg solution for injection in pre-filled pen, Skyrizi 150 mg solution for injection in pre-filled syringe and Skyrizi 75 mg solution for injection in pre-filled syringe are updated. The Package Leaflet and Labelling are updated in accordance. Version 7.0 of the RMP has also been submitted.

1.2. Legal basis

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations.

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Scientific advice and protocol assistance

Not applicable.

1.4. Information on paediatrics

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA decision P/0497/2022 on the acceptance of a modification of an agreed paediatric investigation plan (PIP) for the treatment of psoriasis.

At the time of submission of the application, PIP P/0497/2022 had been completed.

The Paediatric Committee (PDCO) issued on 12 September 2025 a positive opinion on compliance for

PIP P/0497/2022 (EMA/PE/0000285122).

All studies/measures contained in the PIP were checked for compliance:

Agreed studies (study identifier)	Description
Study 1 (1311.PD.QUAL)	Development of an age-appropriate paediatric formulation for parenteral use
Study 2 (M19-977 (1311.PED))	Randomized, active-controlled, evaluator blinded trial to evaluate PK, safety and efficacy of risankizumab in patients from 6 years to less than 18 years of age with moderate to severe plaque psoriasis

1.5. Information on orphan market exclusivity

1.5.1. Similarity with authorised orphan medicinal products

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

1.6. Patient experience data

Table 1: Patient experience data relevant to the application

Patient experience data submitted with this application				Section where discussed (if applicable)
☒	Patient experience data submitted by the MAH:			
	☒	Clinical outcome assessments (COAs) such as		
		☒	Patient-reported outcomes (PRO)	Section 5.3.2.4.4.
		☐	Other	
	☐	Patient preference studies		
	☐	Observational studies/RWD designed to capture patient experience data		
	☐	Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc)		
	☐	Other (please specify)		
☐	Other patient experience data not submitted by the MAH but considered in this evaluation:			
	☐	Input informed from participation in meetings or public hearings with patient stakeholders		
	☐	CHMP early dialogue with patient organisations		
	☐	Third party interventions from patients and patient groups		

Patient experience data submitted with this application			Section where discussed (if applicable)
	☐	Other (such as medical literature, summaries/analysis from patient engagement activities - please specify)	

1.7. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur:	Finbarr Leacy

The application was received by the EMA on	15 September 2025
The procedure started on	2 October 2025
The CHMP Rapporteur's first Assessment Report was received on	19 December 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	06 January 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	15 January 2026
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	29 January 2026
The MAH submitted the responses to the CHMP consolidated List of Questions on	20 February 2026
The CHMP Rapporteur circulated the Report on the responses to the List of Questions to all CHMP and PRAC members on	24 March 2026
The PRAC Rapporteur circulated the Report on the responses to the List of Questions to all CHMP and PRAC members on	30 March 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 April 2026
The CHMP Rapporteur circulated the Joint CHMP and PRAC Report on the responses to the List of Questions to all CHMP and PRAC members on	16 Apri 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Skyrizi on	23 April 2026

1.8. CHMP outcome

1.8.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.4. of this report.

In this procedure, the CHMP reviewed the available paediatric data from the clinical study conducted in accordance with the agreed PIP P/0497/2022, namely study M19-977. The results of this study are reflected in Sections 4.8, 5.1 and 5.2 of the Summary of Product characteristics (SmPC). Further, these results were pivotal in supporting the new indication of treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

In addition, in this procedure, the CHMP assessed the quality measure required under the agreed PIP P/0497/2022 to develop an age-appropriate paediatric formulation for parenteral use.

On this basis, the CHMP recommends a positive opinion for the age-appropriate paediatric formulation (55 mg solution for injection in pre-filled syringe) and for the new paediatric indication described above.

1.8.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.5. of this report.

1.8.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of the new strength of 55 mg of Skyrizi is favourable in the following indication:

Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

The CHMP therefore recommends the extension of the marketing authorisation for Skyrizi, subject to the conditions described in the following sections.

In addition, the CHMP does recommend the variation to the terms of the marketing authorisation concerning the following changes:

Variation(s) adopted		Type
C.I.6.a	C.I.6 Change(s) to therapeutic indication(s) - C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension application to introduce a new strength (55 mg) for the solution for injection in pre-filled syringe grouped with a type II variation C.I.6.a to include the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy for Skyrizi 150 mg solution for injection in pre-filled pen, Skyrizi 150 mg solution for injection in pre-filled syringe and Skyrizi 75 mg solution for injection in pre-filled syringe based on final results from study M19-977 and interim results from study M19-973. Study M19-977 is a phase 3, randomised, active-controlled, efficacy assessor-blinded study to evaluate pharmacokinetics, safety, and efficacy of risankizumab in patients from 6 to less than 18 years of age with moderate to severe plaque psoriasis. Study M19-973 is a phase 3, single-arm, open-label extension study to assess the safety, tolerability, and efficacy of risankizumab in subjects with moderate to severe plaque psoriasis who have completed participation in study M19-977. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC for Skyrizi 150 mg solution for injection in pre-filled pen, Skyrizi 150 mg solution for injection in pre-filled syringe and Skyrizi 75 mg solution for injection in pre-filled syringe are updated. In addition, editorial changes are implemented in the product information.

The Package Leaflet and Labelling are updated in accordance.

Version 7.2 of the RMP is agreed.

1.8.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

1.8.5. Other conditions and requirements of the marketing authorisation

1.8.5.1. Periodic safety update reports

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

1.8.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.8.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.8.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

2. Introduction

Therapeutic Context

Psoriasis (PsO) is a chronic, systemic, immune-mediated inflammatory disease characterised by erythematous papules that merge to create well-demarcated plaques with irregular borders, covered by a silvery-white scale. Signs and symptoms of PsO develop in about one-third of affected adults before the age of 20 years. Compared to adults, children with PsO have more facial and flexural lesions with more involvement in the anogenital areas; the plaques are smaller and thinner, and more pruritic. Clinical features are the same between adolescents and adults with PsO.

PsO has a global prevalence of 2 to 3%, with approximately one-third occurring during the pediatric years. PsO affects approximately 1% of people under the age of 18. Chronic plaque PsO is the most common type of PsO in children (75% of children with PsO). In a United States (US) population-based study, the incidence of PsO in children < 18 years old has increased dramatically over time from 29.6 per 100,000 individuals between 1970 and 1974 to 62.7 per 100,000 between 1995 and 1999. For adolescents, the annual incidence of PsO across the time period from 1970-1999 was 52.2 per 100,000 patients 11-13 years old and 53.1 per 100,000 patients 14-17 years old.

In addition to cosmetic manifestations, PsO is associated with comorbidities in children that impact disease severity and quality of life (QoL): obesity, psoriatic arthritis (PsA), hyperlipidemia, hypertension, diabetes mellitus, rheumatoid arthritis (juvenile idiopathic arthritis), Crohn's disease (CD), and metabolic syndrome. PsO also imposes a significant psychosocial burden on children and their caregivers. The frequent stigmatisation of patients by their peers can induce depression, anxiety, and changes in behaviour. Additionally, the association between PsO and obesity heightens the risk of social isolation, withdrawal, depression, and anxiety.

PsO therapy depends on several factors such as patient age, type of PsO, affected sites, and the extent of disease. Therapeutic options include topical medications including corticosteroids, phototherapy, and systemic therapies (e.g., methotrexate (MTX), acitretin, cyclosporine, and apremilast), but use may be limited by known toxicity profiles. Potential side effects of these treatment options include: striae and adrenal suppression with corticosteroids; cutaneous carcinogenesis with phototherapy; bone marrow suppression and hepatic and pulmonary toxicity with MTX; nephrotoxicity with cyclosporine; and diarrhoea, nausea, and vomiting with apremilast. In addition, some of these systemic therapies require blood draws for laboratory monitoring. Apremilast requires close monitoring of weight in paediatric patients. Biologic therapies which offer targeted therapy are becoming more frequently used in paediatric patients (e.g., etanercept and adalimumab [tumor necrosis factor (TNF) inhibitors], ustekinumab [interleukin (IL)-12/23 inhibitor], and ixekizumab and secukinumab [both IL-17A inhibitors]). Guselkumab (IL-23 inhibitor) has recently been approved in the EU for the treatment of paediatric PsO.

There is still a clinical unmet need for increased efficacy for the 10% to 20% of paediatric patients with PsO who present with moderate to severe PsO. Twenty-five percent of paediatric patients with PsO experience inadequate response to topical therapy; use of systemic therapies remains low (approximately 11%), with biologics mainly reserved for later use.

2.1. Aspects of development

The risankizumab paediatric plaque PsO clinical development programme designed to support the proposed indication included 2 pivotal Phase 3 studies, Study M19-977 and Study M19-973 (open label extension to Study M19-977).

2.2. Description of the product

Skyrizi (risankizumab) is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of human IL-23 cytokine without binding to IL-12 and inhibits its interaction with the IL-23 receptor complex. IL-23 is a cytokine that is involved in inflammatory and immune responses. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.

In the EU, Skyrizi was approved for treatment of plaque PsO in in 2019. Risankizumab has since been approved in the EU for treatment of psoriatic arthritis (PsA), CD, ulcerative colitis (UC).

Risankizumab was initially approved for the treatment of PsO as a 90 mg/mL formulation in a prefilled syringe (PFS) with a needle stick protection device (NSP) device to be self-administered subcutaneous (SC) in 2 injections per dose (2 × 75 mg/0.83 mL PFS NSP) for a total dose of 150 mg risankizumab administered at Week 0, Week 4, and q12w thereafter. A new strength and formulation of 150 mg/mL risankizumab in PFS with NSP and autoinjector (AI) to administer the 150 mg risankizumab dose in a single injection (150 mg/1.0 mL PFS NSP or AI) have been approved in the EU.

Additional dosage forms and strengths are available for treatment of CD and UC.

Proposed Indication and Dosing Recommendation

The applied indication was *for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy*.

The proposed dose for paediatric patients was based on body weight (**Table** 2) and administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.

Table *2*: Recommended dose for paediatric patients 6 to less than 18 years of age with plaque psoriasis

Body weight at time of dosing	Recommended dose
<40 kg	55 mg
≥40 kg	150 mg

3. Quality aspects

3.1. Introduction

This is an extension application to introduce the new additional 55 mg (also referred to as 55 mg/0.37 mL in this report) strength of Skyrizi. The additional strength of the finished product (FP) is presented as a solution for injection in pre-filled syringe (PFS) containing 55 mg of risankizumab (in 0.37 mL solution) as active substance.

Other ingredients are: sodium acetate trihydrate, acetic acid, trehalose dihydrate, polysorbate 20 and water for injections.

The product is available in a pre-filled glass syringe with a fixed needle and needle cover, assembled in an automatic needle guard.

Skyrizi 55 mg is available in packs containing one pre-filled syringe.

3.2. Active substance

There are no updates to the active substance information in the section 3.2.S. of the dossier, therefore no section 3.2.S has been submitted for this line extension. The same risankizumab 150 mg/mL active substance (AS) formulation used for the 55 mg pre-filled syringe is already approved for manufacture of Skyrizi 150 mg pre-filled syringe (EU/1/19/1361/003) for adult psoriasis and psoriatic arthritis indication and no changes have been made to active substance information.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

Skyrizi 55 mg/0.37 mL PFS is supplied as a 150 mg/mL sterile solution for subcutaneous administration. It is supplied in a 1 mL single-use syringe (Type 1 glass, 27 G stainless steel needle fitted with a rigid needle shield and fluoropolymer coated stopper). The composition of Skyrizi finished product (FP) is provided.

The quality target product profile (QTPP) and the critical quality attributes (CQAs) for the finished product are considered acceptable as they are aligned with the approved 150 mg/1.0 mL PFS.

The finished product CQAs cover all relevant aspects of purity, potency and safety and are controlled by in-process controls (IPCs) during the manufacturing process or in the specifications at FP release and stability testing. The only difference between both products is the syringe fill volume and process characterisation studies are presented for process parameters and IPCs effected by the different fill volume (discussed further below), hence it can be agreed the overall control strategy, which is identical to the approved product, is suitable.

The FP composition is identical to the AS composition, and all excipients are compendial grade. There are no novel excipients in the formulation. A summary of the different formulations and container closures used during non-clinical and clinical development is provided in the dossier and was assessed previously. The overall approach to commercial formulation development is systematic and is adequately justified.

For this line extension to introduce a new 55 mg strength, the MAH is leveraging their process understanding of the approved Skyrizi process. Reference is made to the 150 mg/1.0 mL dossier for process characterisation studies used to confirm the process controls for thawing, AS homogenization, sterile filtration, visual inspection and hold time. Given the differences in the process (filling volume, split fill and plunger stopper position) this approach is agreeable.

New characterisation studies are presented for the proven acceptable ranges (PARs) for the process parameters and the IPCs for the Skyrizi 55 mg/0.37 mL PFS filling and stopper position step. The studies conducted are adequate and support the proposed ranges for the process parameters and IPCs. These parameter ranges were verified during the process performance qualification (PPQ) runs.

Process development history is summarised, and comparative process description tables/summaries of process changes have been provided allowing ease of assessment. The same formulation of Skyrizi 55 mg/0.37 mL PFS has been used in clinical trials, however trials were conducted with batches manufactured with the previous process, and the PFS differed in trials to the proposed commercial presentation as the rigid needle shield was not present (discussed in the container closure section below). This approach is agreeable based on a previous submission (EMEA/H/C/004759/II/0052/G). Analytical comparability between Skyrizi 0.55 mg/0.37 mL manufacturing processes is presented and the 55 mg/ 0.37 mL PFS to the approved 150 mg/ 1.0 mL PFS is presented. A total of 6 batches, 3 from clinical and 3 from the proposed commercial Skyrizi 55 mg/0.37 mL PFS, and 106 batches of Skyrizi 150 mg/1.0 mL PFS were used across release and stability in the comparability studies.

For the release comparability testing, the MAH set the criteria to meeting the specifications from historical batches of 150 mg/1.0 mL PFS batches. This approach is acceptable. For all attributes tested, the release specifications are provided. This approach is endorsed as compliance with specifications alone is not considered sufficient evidence upon which to demonstrate comparability. For all attributes tested, the release specifications are provided. Based on the data presented it is agreed that the Skyrizi 0.55 mg/0.37 mL manufactured using both manufacturing processes are comparable and, overall, the 55 mg/ 0.37 mL PFS is comparable to the approved 150 mg/ 1.0 mL PFS.

As the same container closure is used, the vast majority of supportive data for the suitability of the container closure system (CCS) is leveraged from the 150 mg/0.37 mL dossier. This is agreeable as the processes are largely aligned and any difference due to the fill volume that may impact the suitability of the CCS have been adequately addressed and show functionality, compatibility and Container closure integrity (CCI) is ensured for the 55 mg/0.37 mL PFS. Dose accuracy for the 55 mg/0.37 mL PFS was confirmed by extractable volume testing at release (results are presented in section P.5.4 of the dossier). The CCI test used for the 150 mg/0.37 mL is used at release and to further characterise container integrity the results of helium leakage tests are presented, which support the difference in plunger stopper setting between the 150 mg/1.0 mL and 55 mg/0.37 mL processes. Transportation studies were conducted, which covers the intended shipping routes, applying a bracketing approach using the 150 mg/ mL PFS with three different fill volumes, and differing stopper positions. Data provided demonstrate that no additional safety risk for the actual 0.37 mL fill volume paediatric dose. Extractable studies are leveraged from the 150 mg/ mL PFS which is acceptable given product contact materials are the same for the two manufacturing processes. A leachable study using three batches of 55 mg/ 0.37 mL PFS batches is provided and shows the leachable compounds identified pose negligible risk to the patients.

Regarding the combination product (needle stick protection device (NSP)-PFS), development of the NSP-PFS system is based on a platform approach. The verification and validation activities were completed taking into account the features packaging, labelling and manufacturing processes. Safety and device functionality was confirmed using 55 mg/0.37 mL NSP-PFS in the verification studies,

showing that the Skyrizi 55 mg/0.37 mL NSP-PFS performs similarly to the previous products (i.e., Skyrizi 150 mg/1.0 mL PFS). Given that the same device is used for Skyrizi 150 mg/1.0 mL NSP-PFS this approach is agreeable. An adequate description of the integral medicinal product, its critical functional parts and its operation has been provided, including detailed illustrative figures. Details regarding the materials of construction and the function of each component has been provided. NSP components are not made with natural rubber latex, phthalates or any material of animal origin. Summaries of design inputs (user needs and product requirements) and outputs, risk management (as per ICH Q9) and data from verification studies using four different finished product presentations that include two Becton Dickinson (BD) syringe systems to support the platform approach were provided. Detailed summaries of the design verification and performance testing (basis for setting acceptance criteria, test descriptions and results conducted by AbbVie and the device manufacturer (BD)), and shipping data to show the product remains intact after shipment of the NSP-PFS and throughout the product shelf-life are provided (stability data is assessed and discussed later in this report).

The MAH notes that the syringe system used in the clinical studies for Skyrizi 55 mg/0.37 mL PFS differs slightly in the finger flange and plunger rod components, and there was no needle guard/stick prevention (NSP) used in the clinical studies. Given that addition of the NSP component aims to improve patient safety and this difference is not considered to impact device performance, no queries are raised here. Furthermore, design validation and a summary of the human factor studies are also presented confirming the product conforms to the user needs and its intended use.

The primary container closure is a pre-filled syringe (PFS) composed of a glass barrel with staked needle and rigid needle shield. The PFS is received ready to fill from the supplier pre-washed, siliconized, sterile and non-pyrogenic. Similarly, the plunger stopper is received from the supplier ready to use. The glass syringe is compliant with Ph. Eur. 3.2.1, while the needle shield and plunger stopper are compliant with Ph. Eur. 3.2.9. Technical drawings of each component are provided in the dossier. The glass barrel and plunger stopper are siliconized with silicone oil. The quantity of silicone is listed as a test on the supplier certificate of analysis. The dossier states that the silicone is compliant with the USP-NF "Dimethicone" monograph. The MAH has confirmed that the silicone oil is compliant with Ph. Eur. 3.1.8. This is acceptable.

The specifications for the glass syringe and plunger stopper include a check of the supplier certificate of analysis, residual ethylene oxide, sterility, visual examination, endotoxins and material quality. The manufacturers and sites of sterilisation for the glass syringe and plunger stopper are registered in the dossier. New sites for syringe sterilisation (Sterigenics Germany GmbH) and plunger sterilisation (Steris AST, Synergy Health Marseille -SAS) are included.

The PFS is sterilised using ethylene oxide and the specifications include a test for residual ethylene oxide with a limit of <1 µg/ml. As outlined in the EMA Guideline on the sterilisation, a specification for ethylene chlorhydrin (or any other halogenated ethylenehydrine) is required. However, this test is part of the supplier CoA, which is acceptable. The MAH has described the sterilization method in P.3.5 section of the dossier and confirmed that validation is carried out based on practices recommended in ISO 11135. Additionally, valid GMP certificates for the Sterigenics Germany GmbH and BD Medical, France have been located in EudraGMP.

The plunger stoppers are sterilised by gamma irradiation and the dose indicated in the supplier CoA is in the range of 12-25 KGY. The method is described in P.3.5. Plunger stopper sterilisation is performed by gamma irradiation in accordance with ISO 11137 and sufficient certification, and validation data is provided.

Descriptions, technical drawings, manufacturing site, and specifications are registered for the PFS and NSP-PFS. Representative certificates of analysis have been provided as part of procedure number EMEA/H/C/004759/X/0012. The specifications for the NSP-PFS include relevant functional tests such as compression force, plunger activation force, and separation force.

Overall, the level of information provided is considered acceptable.

The dossier contains extensive comprehensive technical information about the device design and development. Notified body opinions (NBOp) according to Article 117 of the MDR for the approved presentations 150 mg PFS and Pen, 75 mg PFS and the new 55 mg PFS have been submitted. The NBOps for the PFS outline the compliance of the devices incorporated into an integral drug-device combination product with Annex I (General Safety and Performance Requirements) of Regulation (EU) 2017/145 on Medical Devices.

3.3.2. Manufacture of the product and process controls

Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

To note, under Article 9 of the EU–US MRA, EU re-testing of the FP is not required when both manufacture and batch release testing of the FP are performed in the US, even if the AS originates, at least in part, from a third country. This is coupled with EU QP certification and batch release of the FP in the EU, in line with EU GMP Annex 16, so is considered acceptable.

The FP manufacturing process is standard, consisting only of sterile filtration and filling. It has been well described including a narrative description and a flow diagram with IPCs. The applicant has clarified that the second bioburden filter will not be used sequentially but that the manufacturing process would allow for the replacement of the bioburden reduction filter during the bioburden reduction filtration step if a low filtration flow rate is experienced or for one re-filtration if pre-defined acceptance criteria are not met. This was validated and approved as part of another procedure for the 150 mg/1.0 mL PFS (EMA/VR/0000307076) and is acceptable. The description of the manufacturing processes remains largely unchanged to the Skyrizi 150 mg/0.37 mL PFS manufacturing process, the only differences are in fill volume and stopper position.

Additionally, a process flow and description of the final assembly and NSP-PFS packaging processes were provided. Detailed figures for each step of the device assembly process are also provided in the dossier. Overall, the finished product manufacturing process is sufficiently detailed, and no issues arise.

The process control strategy for Skyrizi FP manufacture is outlined; IPCs (with action limits or specifications) and critical process parameters (CPPs) are defined for each process step where relevant. Overall, the IPC tests and proposed limits are considered acceptable and are fully aligned with the approved process for all steps except filling and stoppering. The set points and ranges proposed for the filling and stoppering step are suitably justified by pharmaceutical development data.

Adequate descriptions of the IPC methods, (which are identical to those approved for the 150 mg/1.0 mL) have also been provided, no further information on these is required. No critical steps were identified for the final assembly process; this is considered appropriately justified and acceptable.

The MAH has provided details of the process validation study which was performed by manufacturing 3 consecutive batches at the proposed commercial site (ABL). The MAH has extensive process understanding from the 150 mg/1.0 mL PFS validation studies previously conducted. The approach

used is based on performing the process within the normal operating ranges (NORs) for each parameter and measuring the registered CPPs and all in-process test parameters for each step. This approach is considered acceptable and the in-process controls are adequate. Batch release data is provided for the three PPQ batches in the dossier. All results of the process validation FP batches met the pre-defined acceptance criteria and in-process control ranges. The process performance qualification (PPQ) demonstrated that the FP manufacturing process is under control and reproducible within the established process ranges and set points resulting in FP meeting its specifications. The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Some data was leveraged from the 150 mg/1.0 mL dossier such as filter validation (including microbial retention studies). As the filter material is the same for both processes and this step is identical this is acceptable. The Skyrizi 55 mg/0.37 mL PFS is manufactured on the same filling line as Skyrizi 150 mg/1.0 mL PFS which was qualified for the 150 mg/ 1.0 mL. Results from the last three media fill runs are provided and demonstrate that asepsis is maintained during the fill step as the overall duration of the media fill runs support the filling processing time for the 55 mg/0.37 mL PFS commercial process. Hold times applied for the 150mg/1.0 mL process are applicable for the 55mg/0.37 mL process and was verified for the three PPQ batches.

The same shipping lane process from Puerto Rico to Chicago, USA, (air and ground), which was validated for active shipping for 150 mg/1.0 mL PFS process will be used for the 55 mg/0.37 mL PFS hence no new shipping studies were conducted. This is agreeable. Supportive data is provided in section 3.2.R of the dossier assessing one batch of 55 mg/ 0.37 mL NSP-PFS after shipping. Relevant release tests for the FP (appearance, pH, protein content, purity, PS20, CCI, Break-out and Gliding Force, sub visible particles and bioassay) were evaluated before and after NSP-PFS shipping and all results met the acceptance criteria.

Finished product assembled in a device – three PPQ runs were completed for the final assembled 55 mg/0.37 mL PFS-NSP device, and the release testing results presented support reproducibility of the assembly process to produce a safe and reliable functional device. The information provided on the validation of the final assembly process is acceptable.

3.3.3. Product specification

The finished product specifications: appearance – clarity and degree of opalescence (Ph. Eur.), appearance – degree of coloration (Ph. Eur.), appearance – visible particles (Ph. Eur.), sub-visible particles (Ph. Eur.), pH (Ph. Eur.), osmolality (Ph. Eur.), extractable volume (Ph. Eur.), identity (tryptic peptide mapping), heterogeneity (cation exchange chromatography), purity (size exclusion chromatography), purity (capillary gel electrophoresis non-reduced), potency (RGA bioassay), quantity (protein concentration), container closure integrity (in-house), break-out force (in-house), gliding force (ih-house), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), and polysorbate 20 (in house).

The finished product release and shelf-life specifications have been outlined and are generally in compliance with the Ph. Eur. monograph for monoclonal antibodies for human use and ICH Q6B. The specifications are identical to the 150 mg/1.0 mL PFS with the exception of extractable volume which is reflective of the new fill volume.

No additional impurities are present in the finished product other than those described for the active substance. The impurities profile for the active substance has been previously assessed during the line extension for Skyrizi 150 mg/ 1.0 mL PFS AS for the for psoriasis in adults (EMEA/H/C/004759/II/0052/G). The applicant confirmed that PDE values and safety factors calculated

for the adult population are applicable to the paediatric population considering a maximum dose with an additional 6.5-fold safety factor.

Release and shelf-life specifications consisting of appearance and functionality testing have also been established for the NSP-PFS and are acceptable.

Analytical methods

The analytical procedures used to test Skyrizi 55 mg/0.37 mL PFS on release and/or stability are identical to the methods used for Skyrizi 150 mg/1.0 mL PFS. As most of the methods are identical to the approved 150mg/1.0 mL finished product reference is made to the approved dossier for all methods except the compendial methods visible particles and sub-visible particles, extractable volume, sterility, and in-house methods CCI, break out and glide force (BOGF) and polysorbate 20. Brief descriptions were provided of these and are acceptable. The methods for the assembled NSP-PFS device are also described.

No new method validations were provided. This is acceptable as the methods have been previously demonstrated to be fit for purpose for Skyrizi 150 mg/1.0 mL. Verification data is provided for extractable volume, CCI, Break Out Glide Force (BOGF) and NSP-PFS tests (ejection and activation force and override force). These methods are already in place at ABL for other risankizumab presentations.

Batch analysis

Batch analysis data is provided for a total of 6 finished product batches of Skyrizi 55 mg/0.37 mL used for clinical and stability studies. Batches were tested according to the specification in use at time of development. Results for all batches comply with specifications and no unusual trends were observed.

For the combination product, batch analysis data was presented for 3 batches of 55 mg/ 0,37 mL NSP-PFS and all results met acceptance criteria except one batch (1302219) for ejection and activation force. The MAH determined that this was due to a clogged needle, and an additional 125 units were tested and met the acceptance criteria which is acceptable.

3.3.4. Stability of the product

A shelf-life of 24 months at 2 to 8 °C storage is proposed for Skyrizi 55 mg/0.37 mL PFS.

In support of this claim, the MAH has clarified that Skyrizi 55 mg/0.37 mL PFS manufacturing process is similar, except for fill volume and stopper position to the Skyrizi 150 mg/1.0 mL PFS manufacturing process. Additionally, stability data for 36 months has been provided and found to be acceptable.

For most CQAs no trends were noted. During long term storage (2 to 8 °C) a change over time for an excipient was noted, given that this was also previously observed in another procedure, and the development data and justifications on the excipient provided at the time, it can be concluded that the change is not considered to have a negative impact on the quality of the finished product. Excipient levels in Skyrizi 55 mg/0.37 mL are controlled during AS manufacturing and on release testing of FP (not less than 0.15 mg/mL) ensuring appropriate levels at the end of shelf life. This is considered acceptable.

No blue dye incursion was observed for the stability batches when tested. All results remained within specifications for samples kept at recommended storage conditions (2 to 8 °C), the monomer species is considered normal for a monoclonal antibody. This is acceptable.

Stability data for protein concentration over the shelf life of the 55 mg/0.37 mL finished product is not provided. This is justified by stability data previously submitted in stability tables for commercial site supportive batches as well as for the process performance qualification batches during procedure EMEA/H/C/004759/X/0012. Protein concentration changes were not recorded for any of these batches on stability, and it was not impacted by light or temperature as demonstrated during accelerated, stressed and photostability conditions. Since the concentration of 55 mg/ 0.37 mL is the same of the 150 mg/ mL finished product, they are considered comparable and similarly, an impact on protein concentration during stability is not expected. This is considered acceptable.

A temperature cycling study was carried out on 3 PPQ batches and 9 months data is provided to support temperature excursions. 1 PFS and 2 NSP PFS batches were subjected to Photostability testing as per ICH Q1B. Skyrizi 55 mg/0.37 mL PFS is photo unstable and should be protected from light. Secondary packaging offers sufficient protection. This is acceptable.

Up to 24 months stability data has been provided for four batches of NSP-PFS previously as part of procedure EMEA/H/C/004759/X/0012. The tests include several appearance tests, qualitative functional tests (ability to remove needle shield, ability to dispense solution, full activation at the end of injection stroke deployment of the needle guard, lack of leaks), extractable volume, ejection force and container closure integrity. All data have results of "comply". While no numerical data have been provided, considering that numerical limits are registered for the PFS, and the ejection force test has a numerical limit of ≤20 N, the stability data can be accepted to support the claimed shelf life. Additionally, confirmatory stability information for one batch of 55 mg/ 0.37 mL NSP-PF, including accelerated aging testing per ASTM F1980 was conducted. The results were assessed against and met the criteria described in Section 3.2.P.2.4 of the dossier for the 55 mg/ 0.37 mL NSP-PFS and no relevant changes in any of the monitored parameters were observed.

The shelf-life of the NSP-PFS combination product is determined based on the stability of the PFS finished product solution and the assembled NSP-PFS combination product. The shelf-life is defined using the component providing the shortest shelf-life. Based on the totality of data presented for the 150 mg/mL finished product and confirmatory stability data from 3 PPQ and 1 clinical batch of Skyrizi 55 mg/0.37 mL PFS a shelf life of 24 months is considered approvable.

Data on room temperature excursion was also provided. The data support a shelf life of up to 24 months for the NSP-PFS stored at recommended storage condition of 2 to 8°C with an optional storage condition out of the refrigerator (up to a maximum of 25°C) allowance for up to 24 hr in the original carton to protect from light as also indicated in the SmPC and PL.

3.3.5. Adventitious agents

As the active substance manufacturing process is identical to the 150 mg/1.0 mL PFS the information presented for the safety of risankizumab active substance with respect to both non-viral and viral adventitious agents is the same for the new 55 mg/0.37 mL strength. This information was previously assessed, and it was concluded that several manufacturing steps in the process can effectively clear viruses. A comprehensive strategy to minimise the risk of contamination by adventitious agents is in place and no queries are raised.

3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

A notified body opinion (NBOp) is provided for the pre-filled syringe with needle guard confirming compliance with the relevant General Safety and Performance Requirements in Annex I of Regulation (EU) 2017/745.

3.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

4. Non-clinical aspects

Introduction

Risankizumab, currently marketed as 90 mg/mL Skyrizi drug product, was well tolerated in the toxicology studies performed in support of the original marketing application as well as in the overall clinical programme and by post marketing safety data. On this basis, the only additional toxicology study deemed necessary with the 150 mg/mL risankizumab formulation was the local tolerability study, R&D/18/1025 (EMEA/H/C/004759/X/0012); this study was conducted in accordance with the Good Laboratory Practice (GLP) Regulations.

A Paediatric Investigational Plan (PIP) for the clinical development of risankizumab in children above six years of age in Plaque PsO was submitted to the Paediatric Committee (PDCO) and approved, PIP Decision (P/0497/2022). No toxicology data in juvenile animals were requested by the PDCO.

In this application, no dedicated juvenile toxicology studies were conducted for the purpose of paediatric development. The marketing authorisation holder (MAH) used the weight-of-evidence approached as described in ICH S11.

4.1. Pharmacology

No additional pharmacology studies have been conducted with risankizumab. The pharmacology data submitted in the initial marketing authorisation application (MAA) for Skyrizi is applicable to the 55 mg/mL formulation extension.

4.1.1. Pharmacokinetics

No additional pharmacokinetics studies have been conducted with risankizumab. The Pharmacokinetics data submitted in the initial MAA for Skyrizi is applicable to the 55 mg/mL formulation extension.

4.2. Toxicology

No additional toxicology studies have been conducted with risankizumab. The Toxicology data submitted in the MAA for Skyrizi are applicable to the 55 mg/mL formulation extension.

4.2.1. Developmental and reproductive toxicity

No dedicated juvenile toxicology studies were conducted for the purpose of paediatric development. Using the weight-of-evidence approached as described in ICH S11, the existing risankizumab nonclinical data from repeat dose toxicity studies and the enhanced pre- and postnatal development (ePPND) study support administration to adult and paediatric patients ≥ 6 years old. Therefore, the MAH considered that no risankizumab juvenile animal toxicity studies are warranted. A weight-of-evidence assessment was provided as summarised below:

Per ICH S11, the age of the intended patient population is an important factor in determining the utility of a juvenile animal study. There are heightened safety concerns associated with paediatric clinical studies in infants and neonates. However, since risankizumab is being developed to treat children ≥ 6 years of age, there is low cause for concern, since the majority of critical organ systems have

surpassed structural and functional growth by approximately the age 2 (**Table 3** and ICH S11). Based on the pharmacology of risankizumab, the target organ of concern is the immune system. However, using an assessment of the ICH S8 weight of evidence parameters, no unintended immune system toxicity was evident among the clinical signs, haematology data, peripheral blood immunophenotyping data, T-cell dependent antibody response (TDAR) data, or macroscopic and microscopic datasets in the risankizumab nonclinical studies at doses up to 50 mg/kg/week. Furthermore, in the ePPND study in cynomolgus monkeys that investigated specialised immune function endpoints including clinical pathology with peripheral blood lymphocyte subset analysis (via immunophenotyping), a TDAR in F1 animals, and histopathology assessment of lymphoid organs from F1 animals, there were no adverse effects at doses up to 50 mg/kg/week.

Table 3: Timing of Major Postnatal Development in Cynomolgus Monkeys and Relevant Risankizumab Assessment Nonclinical Study Data

Organ System Development	Monkey *	Risankizumab Assessment Nonclinical Study Data
Kidney	By birth	ePPND
Lung	By birth	ePPND
Heart	By birth	ePPND
Bone Appearance of ossification centers	By birth	ePPND
Reproductive System Puberty	3 to 6 years of age	ePPND, 4-week, 26-week
Immune System	By birth	ePPND
CNS Motor development	By 6 months of age	ePPND
* Martin and Weinbauer, 2010		

The existing risankizumab toxicology data also demonstrated that there is no evidence of other on-target or off-target toxicities at 50 mg/kg/week in the completed 4-week and 26-week repeat dose studies, where monkeys were 3.5 to 6 years of age at initiation of dosing, which is developmentally equivalent to 2 to 12 years old in humans.

Studies with juvenile or adult animals, development and reproductive studies, local tolerance or *in vitro* assays (immunosafety and tissue cross-reactivity) demonstrated no adverse toxicities.

In addition, there is an established clinical safety profile for risankizumab in adult patients in the approved indications. There is also no evidence of IL-23 target liability based on disruption of the IL-23 pathway in animals or humans in published literature or other marketed IL-23 products.

4.2.2. Toxicokinetics and exposure margins

The exposure multiples for the cynomolgus monkey 26-week repeat-dose toxicity study were calculated by the MAH and compared to the adult and paediatric exposures in human clinical studies in patients with PsO in **Table 4**.

Table 4: Exposure Multiples with Risankizumab in Cynomolgus Monkey Compared to Human

Cynomolgus Monkey 26-week chronic toxicity study NOAEL: 50 mg/kg/week SC: $AUC_{0\text{-}12\ wk}$ = 43.1 mg•day/mL[a]

Clinical Study	Dose Level	Route	AUC (mg•day/mL)	Multiples
R&D/17/0881 Adult Ph1 to Ph3 Psoriasis (PsO)	150 mg dosed in Weeks 0 and 4 followed by dosing every 12 weeks (Q12W)	SC	Loading phase: 0.622 Steady state: 0.466[b]	Loading phase: 69x Steady state: 93x
R&D/23/2430 Pediatric subjects (PsO)	150 mg dosed in Weeks 0 and 4 followed by Q12W	SC	Weeks 0-4: 0.294 Weeks 4-16: 0.840 Weeks 40-52: 0.644	Weeks 0-4: 147x Weeks 4-16: 51x Weeks 40-52: 67x
R&D/23/2430 Pediatric subjects (PsO)	55 mg dosed in Weeks 0 and 4 followed by Q12W	SC	Weeks 0-4: 0.215 Weeks 4-16: 0.606 Weeks 40-52: 0.461	Weeks 0-4: 200x Weeks 4-16: 71x Weeks 40-52: 93x

a. AUC value at steady state in the monkey study ($AUC_{0\text{-}168hr}$ (1 week)) was multiplied by 12 weeks to provide an $AUC_{0\text{-}12wk}$ value comparable to the human dosing intervals. The units for the AUC values were adjusted to mg•day/mL. The AUC data are from Study R&D/16/1444; NOAEL at 50 mg/kg/week SC; males and females combined.

b. R&D/17/0881: values from the loading phase ($AUC_{4\text{-}16wk}$ = 622 µg•day/mL) and at steady state ($AUC_{40\text{-}52wk}$ = 466 µg•day/mL).

c. R&D/23/2430 (Population Pharmacokinetics and Exposure-Response Analyses for Risankizumab Efficacy and Safety in Pediatric Subjects with Psoriasis: Analyses of Phase 3 Studies M19-977 and M19-973): Mean AUC reported as µg•day/mL). Note that the first interval, Weeks 0-4, is not 12 weeks in duration and is therefore not a direct comparison to the other reported intervals.

4.2.3. Local tolerance

Considering the nature of the previous formulation change, between the 90 mg/ml and the 150 mg/ml solutions, a local tolerance study with the 150 mg/mL formulation was the only new toxicology study conducted (EMEA/H/C/004759/X/0012). No drug-related local intolerance was observed macroscopically or microscopically in this local tolerability study in rabbits.

The new 55 mg/mL formulation, with the same composition as the 150 mg/mL formulation, provides a lower concentration product to facilitate administration of lower doses in paediatric patients.

4.2.4. Ecotoxicity/environmental risk assessment

The MAH has submitted an updated ERA which was conducted in line with the revised guideline: EMEA/CHMP/SWP/4447/00 Rev. 1 - Corr.

Risankizumab is an antibody (specifically a monoclonal immunoglobulin), and as such is a natural substance. Risankizumab is used to treat multiple inflammatory diseases; at this time, the MAH is

seeking approval of risankizumab for the treatment of plaque psoriasis in paediatric patients (6 years to < 18 years) and a 55 mg/0.37 mL pre-filled syringe for subcutaneous administration as an additional dose strength. The new 55 mg/0.37 mL pre-filled syringe supports dosing in paediatric patients < 40 kg bodyweight. The excretion of risankizumab has not specifically been studied, but it is expected that a substantial percentage of the dosed compound will be degraded (to small peptides and amino acids) in the body. Any risankizumab that is excreted would degrade within a wastewater treatment plant or in the environment. The use of risankizumab will not alter the concentration or distribution of these substances (small peptides and amino acids) in the environment. Therefore, environmental fate and effects studies are not warranted as patient use of risankizumab is unlikely to result in any exposure or risk to the environment.

4.3. Overall discussion and conclusions on non-clinical aspects

4.3.1. Discussion

Risankizumab has a safe toxicity profile, providing a significant safety margin above dose levels explored in clinical studies. Exposure multiples in paediatric subjects were similar to those achieved in adult subjects.

As agreed by the PDCO in the PIP for the clinical development of risankizumab in children above six years of age in plaque PsO, no toxicology data in juvenile animals were deemed necessary. The weight of evidence discussion provided by the MAH in line with ICH S11, supported this decision and was found acceptable.

An updated ERA was provided in line with the revised ERA guideline.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, risankizumab is not expected to pose a risk to the environment.

4.3.2. Conclusions

In conclusion, the non-clinical pharmacological and toxicological studies previously performed with risankizumab support the introduction of the 55 mg/mL formulation for use in the treatment of paediatric patients with moderate to severe chronic plaque psoriasis. In addition, there are no non-clinical safety concerns for the treatment of children in the age range of 6 to < 18 years.

5. Clinical aspects

5.1. Introduction

5.1.1. GCP aspects

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

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

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

5.1.2. Tabular overview of clinical trials

Table 5: Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Phase 3 Therapeutic confirmatory					
M19-977	Part 1, 3, 4: Single-arm, open label, 52 weeks Part 2: Randomised, efficacy assessor blinded, parallel group, active-controlled Period A: 16 weeks Period B: up to 36 weeks Period C: 16 weeks Study completed	Risankizumab 55 mg or 150 mg SC based on bodyweight Ustekinumab 0.75 mg/kg, 45 mg, or 90 mg SC based on bodyweight	Subjects from 6 to < 18 years of age with moderate to severe plaque PsO	Safety, PK, and efficacy of Risankizumab Co-primary endpoints: PASI 75, sPGA 0/1	Part 1: 12 Part 2: 82 Part 3: 13 Part 4: 30; 2 additional adolescent subjects (Japan only)
Phase 3 OLE					
M19-973	Single-arm, OLE study, up to 216 weeks Study ongoing	Risankizumab 55 mg or 150 mg SC based on bodyweight, q12w	Subjects from 6 to < 18 years of age with moderate to severe plaque PsO,	Long-term safety, tolerability, and efficacy of Risankizumab in subjects who have completed Study M19-977	129; 2 additional adolescent subjects (Japan only)

OLE =open label extension; PsO =psoriasis; SC = sub-cutaneous; Q12W = every 12 weeks

5.2. Clinical pharmacology

5.2.1. Methods

Sample analysis for risankizumab concentrations in human serum for the pivotal Phase 3 Studies M19-997 and M19-973 was conducted using a bioanalytical method (bridging Electrochemiluminescence

(ECL) assay) that was previously validated and assessed. Incurred sample reanalysis was not performed for either study M19-977 or study M19-973.

A titre-based acid dissociation bridging ECL immunoassay was used to determine Anti-Drug Antibodies (ADA) (Anti-Risankizumab Antibodies) in human serum samples. For this current extension of indication application, a partial revalidation of method ANA22-015 was conducted which determined disease-specific cut-points, sensitivity, precision and selectivity. This method was used to support the two pivotal Phase 3 studies (Study M19-977 and Study M19-973) in paediatric subjects with psoriasis. The statistical analysis applied for determination of cut-points was described in the validation report and included a description of the methodology for exclusion of outliers (Tukey's outlier criteria with box-plots).

No new method validations were provided for the neutralising antibody (NAb) assay. The NAb method used in the initial MAA submission and the Skyrizi 150 mg/mL formulation line extension was previously assessed and found acceptable. The analytical method was performed as per the validated parameters for the sample analysis of clinical studies M19-977 and M19-973.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

To support the registration of risankizumab in paediatric subjects with psoriasis, additional clinical pharmacology assessments were conducted with data from two pivotal Phase 3 studies (Study M19-977 and Study M19-973). Combined data from the Phase 3 studies were utilised in the integrated analyses of population pharmacokinetics and exposure-response relationships for efficacy and safety, as well as in analyses to evaluate the impact of immunogenicity on pharmacokinetics, safety, and efficacy.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population Pharmacokinetics

Population Pharmacokinetics (popPK) and Exposure-Response Analyses for Risankizumab Efficacy and Safety in Paediatric Subjects with Psoriasis: Analyses of Phase 3 Studies M19-977 and M19-973 (R&D/23/2430)

A popPK analysis was performed to characterise the PK of risankizumab in paediatric subjects using the data from the two phase 3 studies. The objective of this analysis was to characterise the popPK of risankizumab in paediatric subjects with psoriasis and to compare paediatric exposures with adult exposures.

The paediatric source data included the two phase 3 studies (M19-977 and M19-973) performed in paediatric subjects aged 6 to <18 years. The source adult data included those data used in the previously developed popPK model that described risankizumab PK in healthy adults and adults with psoriasis.

The previously developed popPK model that described risankizumab PK in healthy adults and adults with psoriasis served as the starting model for the analyses of the combined adult and paediatric data. Additional covariates were investigated for influence on risankizumab:

- CL: baseline age, body weight (time-varying for paediatric subjects), and paediatric subjects versus adults (baseline age < 18 years versus baseline age ≥ 18 years);
- Vc: baseline age, body weight (time-varying for paediatric subjects), and paediatric subjects versus adults (baseline age < 18 years versus baseline age ≥ 18 years);
- Vp: body weight (time-varying for paediatric subjects).

Standard goodness-of-fit (GOF) plots and Visual Predictive Check (VPCs) were used to evaluate the model.

Results

The final popPK model is a two-compartment model with a first-order absorption and elimination, inter-individual variability on CL, Vc, F, and Ka and a proportional error term. Body weight (time-varying for the paediatric studies), albumin, serum creatinine, hs-CRP, ADA titer on CL, body weight (time-varying for the paediatric studies) and age for the paediatric studies on Vc and body weight (time-varying for the paediatric studies) on Vp were significant covariates and added to the model.

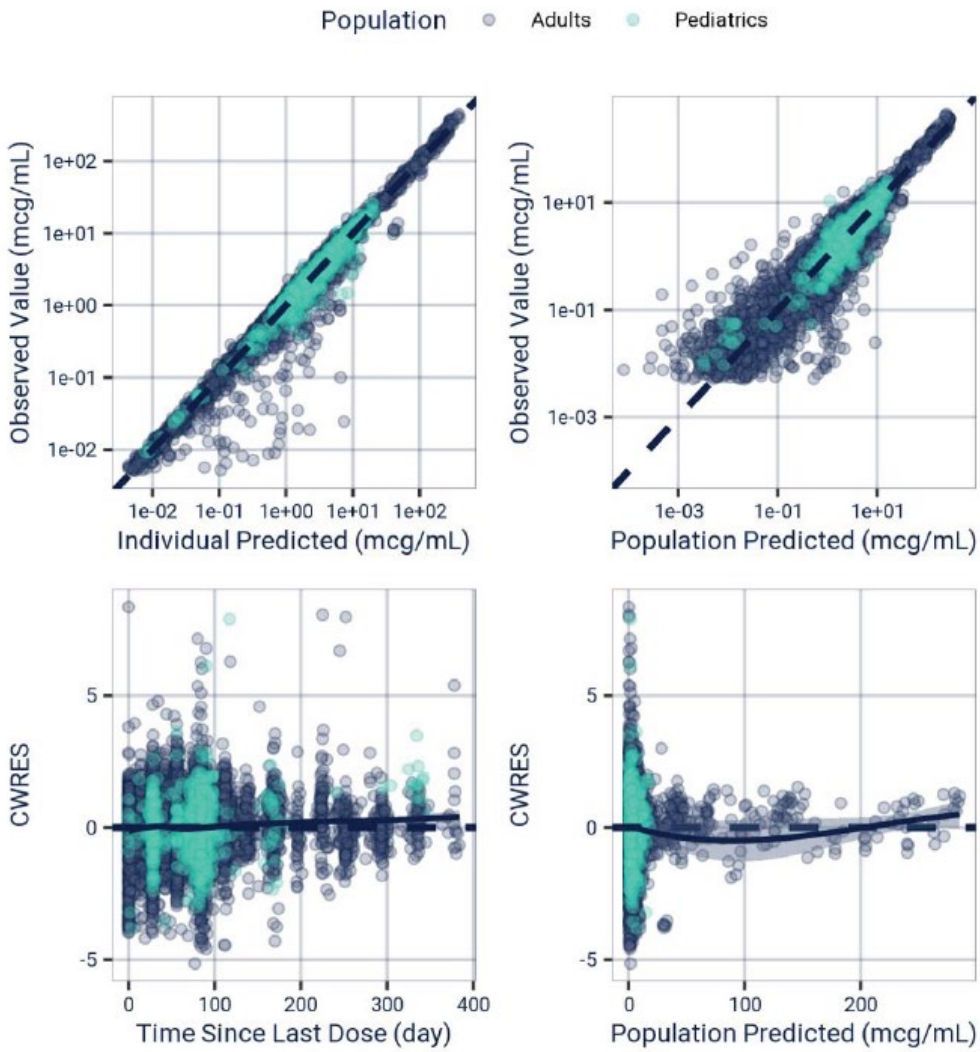
Risankizumab concentrations in paediatric subjects were adequately described by the final popPK model, and the resulting model parameter estimates were all comparable to the parameter estimates from the adult model (**Table 6**). All structural PK parameters in the model were estimated precisely (relative standard error ≤ 27.8%). The shrinkages for risankizumab CL, Vc, F, and Ka were 13.6%, 45.3%, 60.7%, 60.9%, respectively.

Table 6: Fixed and random effects parameter estimates for the final risankizumab population pharmacokinetic model.

Combined Adult and Pediatric Psoriasis Model				Adult Psoriasis Model
Parameter	**Population Estimate**	**%RSE**	**95% Confidence Interval**	**Population Estimate**
CL (L/day)	0.245	1.73	(0.237, 0.253)	0.243
Vc (L)	5.06	3.63	(4.70, 5.42)	4.86
Q (L/day)	0.650	3.87	(0.600, 0.699)	0.656
Vp (L)	4.12	2.11	(3.95, 4.29)	4.25
KA (1/day)	0.226	4.70	(0.205, 0.246)	0.229
F (CMC1)	0.708	2.92	(0.666, 0.747)	0.710
F (CMC2)	0.889	1.69	(0.856, 0.915)	0.890
Body Weight on CL (time-varying for Studies M19-977/M19-973)	0.895	2.71	(0.847, 0.942)	0.933
Body Weight on Vc (time-varying for Studies M19-977/M19-973)	1.02	7.49	(0.873, 1.17)	1.17
Albumin on CL	-0.736	9.79	(-0.878, -0.595)	-0.715
Serum Creatinine on CL	-0.243	9.88	(-0.290, -0.196)	-0.253
Hs-CRP on CL	0.0463	9.41	(0.0378, 0.0549)	0.0437
Body Weight on Vp (time-varying for Studies M19-977/M19-973)	0.524	7.89	(0.443, 0.605)	0.377
ADA Titer on CL	0.428	5.25	(0.384, 0.472)	0.428
Age on Vc for pediatrics	0.572	27.8	(0.260, 0.885)	--
Proportional error	0.0370	0.648	(0.0365, 0.0375)	0.0358
Parameter	**Population Estimate**	**%CV**	**%Shrinkage**	**Population Estimate**
IIV on CL	0.0524	23.2	13.6	0.0539
IIV on Vc	0.113	34.5	45.3	0.110
IIV on F	0.482	78.7	60.7	0.492
IIV on Ka	0.334	62.9	60.9	0.335

%RSE was calculated as the standard error of the estimator divided by the absolute value of the mean of the estimator multiplied by 100. %CV was calculated as SQRT(exp(ω^2)-1)*100).

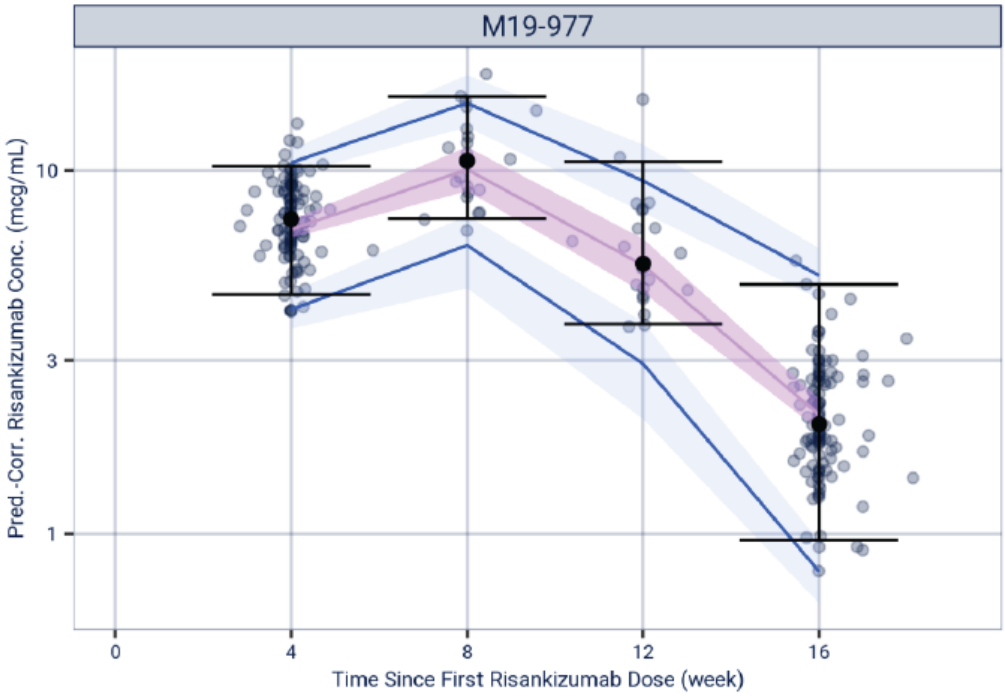
GOF plots of risankizumab PK final model for subjects included in the popPK analysis are presented in Figure 1.



Goodness-of-fit plots for the individual predicted and population predicted versus observed concentrations (top left and right, respectively) and CWRES versus TSLD and population prediction (bottom left and right, respectively) with loess smooth (95% CI).

Figure 1: GOF plots of risankizumab pharmacokinetic final model for subjects included in the population pharmacokinetic analysis.

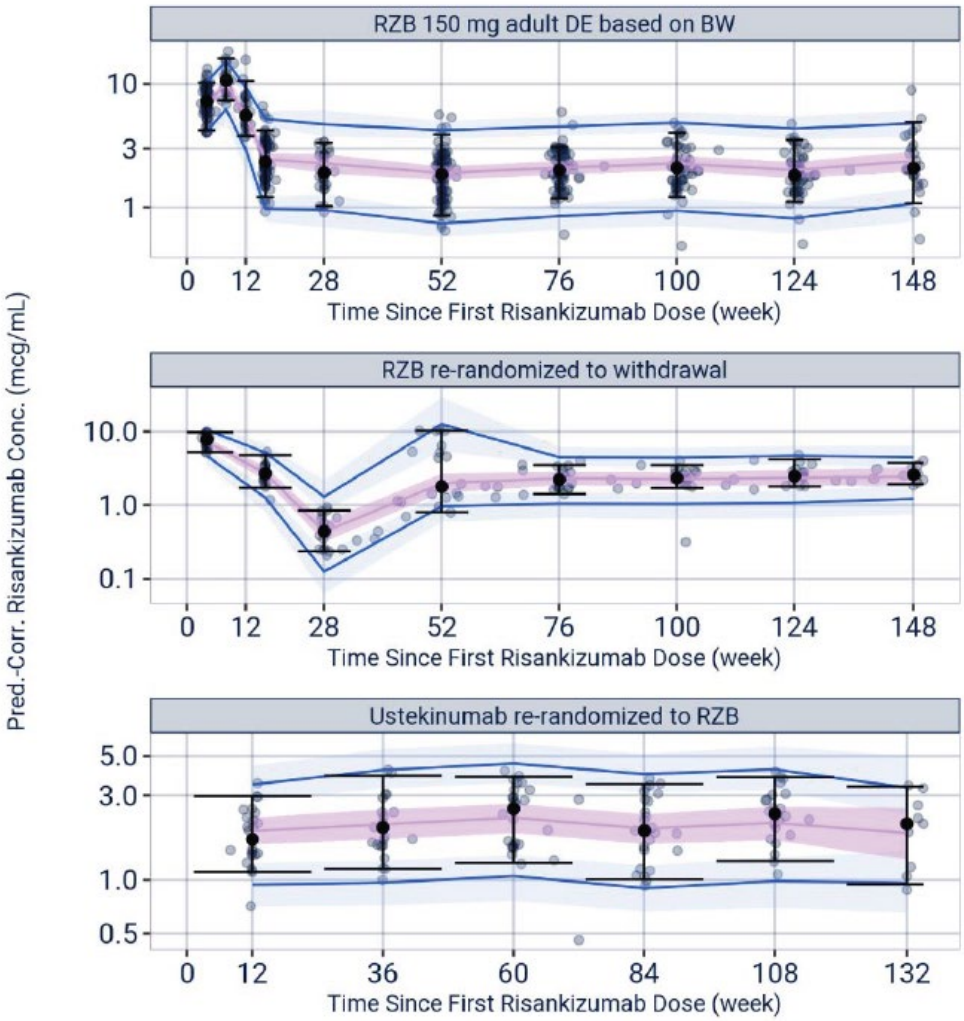
Prediction-corrected VPCs for the risankizumab concentrations in paediatrics with psoriasis are presented in Figure 2 (time points prior to re-randomisation) and Figure 3 (different re-randomisation arms).



The blue lines represent the 90% PI of the model, the shaded blue areas are the associated 90% CIs of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% CI. The black circles and black error bars represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively. Grey circles denote observed concentrations.

Note: Time bins were chosen at 4, 8, 12, and 16 weeks.

Figure *2*: Prediction-corrected visual predictive check of risankizumab concentration in paediatric subjects with psoriasis in Study M19-977 prior to re-randomisation.



The blue lines represent the 90% PI of the model, the shaded blue areas are the associated 90% CIs of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% CI. The black circles and black error bars represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively. Grey circles denote observed concentrations.

Figure 3: Prediction-corrected visual predictive check of risankizumab concentration in paediatric subjects with psoriasis in studies M19-977 and M19-973 stratified by re-randomisation arms.

The estimated median steady-state peak and trough plasma concentrations were 15.7 and 2.3 µg/mL, respectively, in subjects weighing ≥40 kg, and 11.1 and 1.6 µg/mL, respectively, in subjects weighing <40 kg.

5.2.2.2.2. Physiology based pharmacokinetic model

Not applicable for this line extension application.

5.2.2.3. Absorption

Refer to Section 5.2.2.8. on the Pharmacokinetics in the target population.

5.2.2.4. Distribution

Refer to Section 5.2.2.8. on the Pharmacokinetics in the target population..

5.2.2.5. Metabolism

Refer to Section 5.2.2.8. on the Pharmacokinetics in the target population.

5.2.2.6. Elimination

Refer to Section 5.2.2.8. on the Pharmacokinetics in the target population.

5.2.2.7. Dose proportionality and time dependency

Refer to Section 5.2.2.8. on the Pharmacokinetics in the target population.

5.2.2.8. Pharmacokinetics in the target population

Study M19-977 (OptIMMize-1)

This was a randomised, active controlled, efficacy assessor-blinded study to evaluate PK, safety, and efficacy of risankizumab in subjects 6 to less than 18 years of age with moderate to severe plaque PsO. The study consisted of 4 parts, each with distinct patient populations. Study design is presented in Section 5.3.2.2.

Results

A summary of risankizumab serum concentrations in subjects in Study Part 1, Part 2, Part 3 and Part 4 is presented in Table 7, Table 8 and Table 9, Table 10, and Table 11, respectively.

Table 7: Part 1 - Summary of risankizumab serum concentrations (µg/mL) at planned visits for risankizumab 150 mg.

	Geometric Mean (Arithmetic Mean, % CV) [N]				
	Week 4	**Week 8**	**Week 12**	**Week 16**	**Week 52**
RZB 150 mg SC	7.467 (7.938, 38.0) [12]	11.870 (13.032, 46.3) [11]	6.205 (6.591, 38.3) [12]	3.011 (3.185, 33.6) [11]	1.640 (1.947, 67.2) [11]

Table 8: Part 2 - Summary of risankizumab serum concentrations (µg/mL) at planned visits for risankizumab 150 mg.

	Geometric Mean (Arithmetic Mean, % CV) [N]			
Period A	**Week 4**	**Week 16**		
RZB 150 mg SC	6.962 (7.501, 39.1) [49]	2.600 (2.929, 42.8) [48]	--	--
Period B			**Week 28**	**Week 52**
UST to RZB 150 mg SC	NA	NA	1.560 (1.912, 56.0) [23]	1.658 (2.056, 60.0 [21]
RZBnr to RZB 150 mg SC	NA	NA	1.709 (1.945, 51.2) [10]	1.654 (2.051, 68.2) [9]
RZBr to RZB 150 mg SC	NA	NA	2.108 (2.357, 46.2) [20]	1.841 (2.014, 42.8) [21]
Retreatment Period C	**Week 4R**	**Week 16R**		
RZB 150 mg SC	5.108 (5.155, 15.7) [4]	2.179 (2.415, 48.9) [4]	NA	NA

Table 9: Part 2 - Summary of risankizumab serum concentrations (µg/mL) at planned visits for risankizumab 55 mg.

	Geometric Mean (Arithmetic Mean, % CV) [N]			
Period A	**Week 4**	**Week 16**		
RZB 55 mg SC	6.000 (6.000, 0.9) [2]	1.915 (1.930, 17.6) [2]	--	--
Period B			**Week 28**	**Week 52**
UST to RZB 55 mg SC	NA	NA	0.719 (0.719, NC) [1]	0.776 (0.776, NC) [1]
RZBnr to RZB 55 mg SC	NA	NA	NA	NA
RZBr to RZB 55 mg SC	NA	NA	NA	NA
Retreatment Period C	**Week 4R**	**Week 16R**		
RZB 55 mg SC	3.420 (3.420, NC) [1]	1.100 (1.100, NC) [1]	NA	NA

Table *10*: Part 3 - Summary of risankizumab serum concentrations (µg/mL) at planned visits for risankizumab 150 mg and 55 mg.

	Geometric Mean (Arithmetic Mean, % CV) [N]				
	Week 4	Week 8	Week 12	Week 16	Week 52
RZB 150 mg SC	10.515 (11.863, 44.2) [7]	13.372 (14.393, 38.4) [6]	6.685 (8.103, 70.7) [6]	3.065 (3.374, 43.1) [8]	1.760 (2.190, 64.7) [8]
RZB 55 mg SC	6.480 (6.654, 25.9) [5]	9.633 (9.810, 22.6) [5]	5.144 (5.324, 31.1) [5]	2.247 (2.534, 58.5) [5]	1.699 (1.878, 55.6) [5]

Table *11*: Part 4 - Summary of risankizumab serum concentrations (µg/mL) at planned visits for risankizumab 150 mg and 55 mg.

	Geometric Mean (Arithmetic Mean, % CV) [N]		
	Week 4	Week 16	Week 52
RZB 150 mg SC	10.952 (11.332, 27.4) [6]	3.071 (3.212, 33.4) [6]	1.952 (2.026, 31.1) [5]
RZB 55 mg SC	6.691 (6.949, 26.7) [20]	1.860 (2.061, 47.4) [20]	1.329 (1.514, 52.8) [17]

A summary of the immunogenicity results from this study for Part 2, and Part 3 and Part 4 are presented in **Table** 12 and **Table 13**.

Table *12*: Part 2 - Incidence of treatment-emergent ADA and NAb to risankizumab.

	Period A	Period B			Retreatment Period C
Description	RZB	UST to RZB	RZBnr to RZB	RZBr to RZB	RZB
RZB 150 mg by weight					
Evaluable subjects; N	51	27	10	22	7
ADA incidence; n (%)	4 (7.8%)	3 (11.1%)	2 (20%)	3 (13.6%)	1 (14.3%)
NAb incidence; n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
RZB 55 mg by weight					
Evaluable subjects; N	2	1	0	0	1
ADA incidence; n (%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
NAb incidence; n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Note: ADA evaluable: subjects with at least 1 reportable assessment at any time in the study postbaseline. NAb was assessed only when the ADA assessment was positive.

Table *13*: Part 3 and Part 4 - Incidence of treatment-emergent ADA and NAb to risankizumab over 52 weeks.

Description	RZB 150 mg SC	RZB 55 mg SC	RZB Total
Part 3			
Evaluable subjects; N	8	5	13
ADA incidence; n (%)	1 (12.5%)	1 (20%)	2 (15.4%)
NAb Negative; n (%)	1 (12.5%)	0.0%	1 (7.7%)
NAb Positive; n (%)	0.0%	1 (20%)	1 (7.7%)
Part 4			
Evaluable subjects; N	6	23	29
ADA incidence; n (%)	3 (50%)	2 (8.7%)	5 (17.2%)
NAb Negative; n (%)	3 (50%)	1 (4.3%)	4 (13.8%)
NAb Positive; n (%)	0.0%	1 (4.3%)	1 (3.4%)

Note: ADA evaluable: subjects with at least 1 reportable assessment at any time in the study postbaseline. NAb was assessed only when the ADA assessment was positive, at least one positive NAb assessment at any visit.

In the study M19-977, in all subjects who received the 150 mg or 55 mg SC regimen of risankizumab, incidence of ADA and nAb was 14.8% (13/88) and 2.3% (2/88), respectively, over up to 52 weeks of exposure.

Study M19-973 (OptIMMize-2)

This was a Phase 3, multicenter, single-arm, OLE study designed to investigate the long-term safety, tolerability, and efficacy of risankizumab 55 mg or 150 mg by weight (for subjects ≥ 40 kg the risankizumab dose is 150 mg and for subjects < 40 kg the risankizumab dose is 55 mg) q12w in the treatment of moderate to severe plaque PsO in eligible subjects who have completed Study M19-977 and elected to participate in Study M19-973.

Results

A summary of risankizumab serum concentrations in subjects receiving the 150 mg q12w and 55 mg q12w regimens are presented in **Table** 14.

Table *14*: Summary of risankizumab serum concentrations (µg/mL) at planned visits for risankizumab 55 mg and 150 mg.

	Geometric Mean (Arithmetic Mean, %CV) [N]						
Regimen	**Week 24**	**Week 48**	**Week 72**	**Week 96**	**Week 120**	**Week 144**	**Week 168**
RZB 150 mg SC	1.972 (2.262, 51.3) [91]	2.104 (2.407, 50.0) [87]	1.981 (2.267, 51.8) [82]	2.241 (2.513, 51.9) [41]	1.743 (1.955, 57.1) [9]	1.515 (1.571, 70.6) [9]	1.624 (1.773, 39.7) [7]
RZB 55 mg SC	1.358 (1.469, 44.3) [8]	0.897 0.922, 29.8) [3]	1.465 (1.608, 58.3) [2]	1.683 (2.322, 97.4) [2]	--	--	--

A summary of risankizumab immunogenicity results in subjects receiving the 150 mg q12w and 55 mg q12w regimens are presented in **Table 15**.

Table *15*: Incidence of ADAs and NAbs to risankizumab treatment up to Week 168.

Description	RZB 150 mg SC	RZB 55 mg SC	RZB Total
Evaluable subjects; N	**105**	**10**	**115**
Anti-drug antibody incidence (treatment emergent); N (%)	10 (9.5%)	0 (0%)	10 (8.7%)
NAb incidence (treatment emergent); N (%)	0 (0%)	0 (0%)	0 (0%)

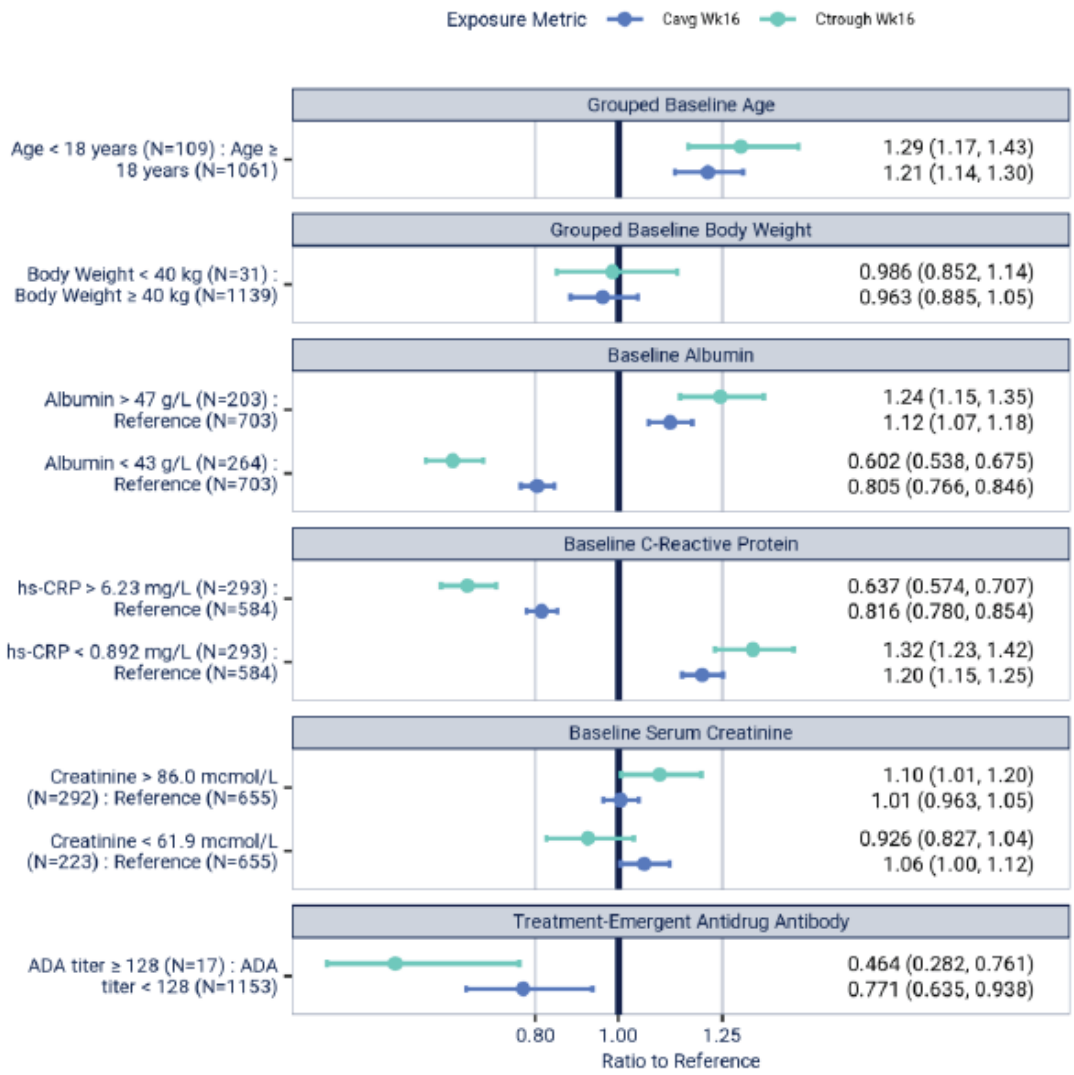
Notes: ADA evaluable: subjects with at least 1 reportable assessment at any time in the study post-Baseline in Study M19-973. NAb was assessed only when the ADA assessment was positive.

R&D/23/2430

Population pharmacokinetic model simulations

Impact of covariates on risankizumab exposures

After identifying the statistically significant covariates on risankizumab PK parameters, simulations were performed to explore the impact of relevant covariate effects on risankizumab Cavg and Ctrough to characterize the effect of these covariates on risankizumab exposures. Model-predicted risankizumab exposures from the simulations in each subset of subjects based on the covariate of interest (test group) were compared to the corresponding reference group by calculating the geometric mean ratio and its 95% CI and summarized graphically using a forest plot. The results of the simulations are presented in Figure 4.



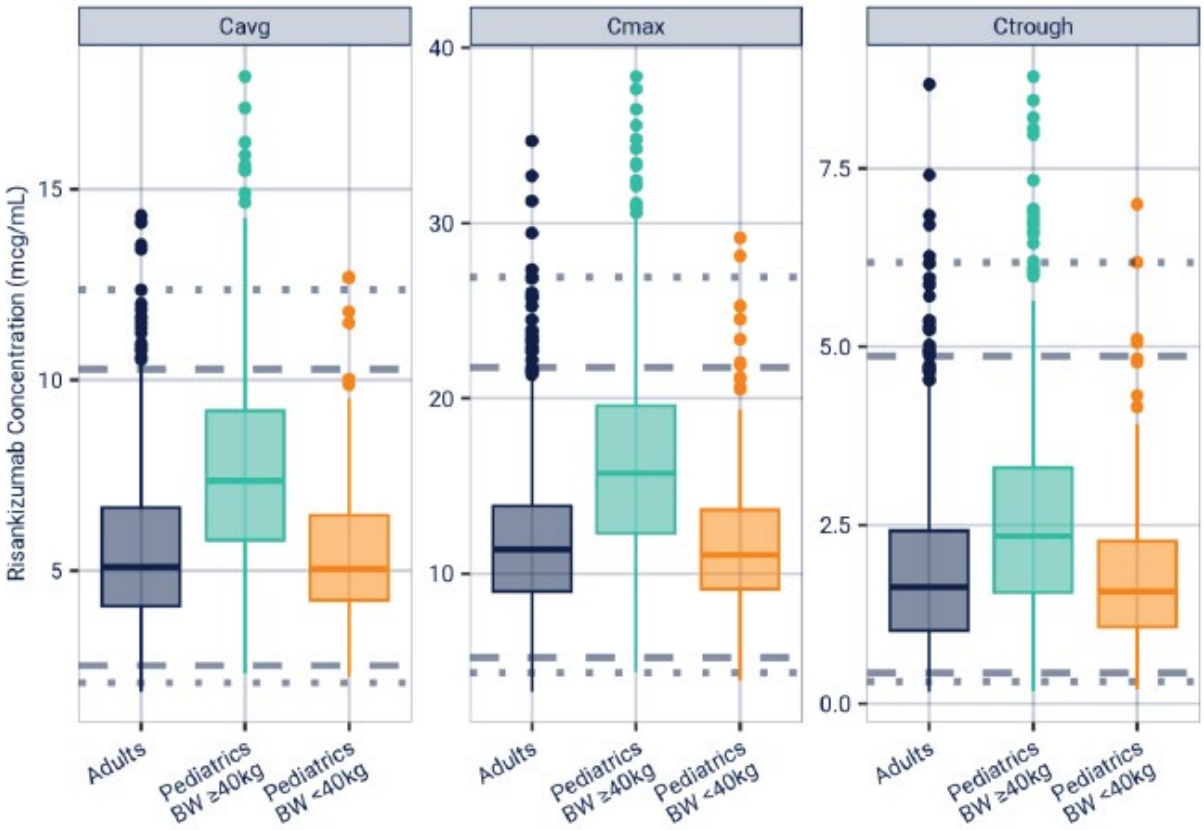
Effect of covariates on risankizumab model-predicted exposures in subjects with psoriasis. The plot includes subjects from the Phase 3 adult psoriasis trials (Studies 1311.03, 1311.04, 1311.28, 1311.30) and the pediatric Study M19-977 who received 150 mg or 55 mg of risankizumab at Weeks 0, 4, and 16. Points represent medians and error bars represent 95% CIs of the normalized exposure ratios. C_{trough} is the model predicted trough concentration at Week 16, and C_{avg} is the model-predicted average concentration over the 16 weeks of initial treatment. For ADA titer stratification, the maximum value of ADA titer for each individual was used with a threshold of 128 for adults and 1280 for pediatric subjects, which accounts for the dilution factor (1:10) used in the ADA titer assay for the pediatric studies.

Figure 4. Forest plot to evaluate the impact of covariates identified in the population pharmacokinetic analyses on risankizumab exposures.

Exposure simulations of risankizumab in paediatric subjects with PsO compared to adults

To compare risankizumab exposures in paediatric subjects with PsO for the body weight based regimen to the adult exposures, exposure metrics in N=1000 paediatric subjects (6 to less than 18 years) with PsO were simulated by sampling covariates with replacement from the risankizumab Studies M19-977 and M19-973 and an adalimumab Study M04-717 (R&D/14/1263) and compared to simulated

exposures in adults (N=1000), sampled from the covariates of adult studies. The results of the simulations are presented in Figure 5.



Horizontal dashed and dotted lines indicate the 95% and 99% CI of the adult exposure, respectively.

Figure 5: Simulated risankizumab exposures in paediatrics with psoriasis compared to adults with psoriasis.

5.2.2.9. Special populations

The paediatric population is the target population for this application. Refer to Section 5.2.2.8. on the Pharmacokinetics in the target population.

5.2.2.10. Pharmacokinetic interaction studies

Not applicable for this line extension application.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

The data submitted in the initial MAA for Skyrizi is applicable for this line extension application, hence, no new information is submitted.

5.2.3.2. Primary and secondary pharmacology

The data submitted in the initial MAA for Skyrizi is applicable for this line extension application, hence, no new information is submitted.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

The data submitted in the initial MAA for Skyrizi is applicable for this line extension application, hence, no new information is submitted.

5.2.3.4. Genetic differences in PD response

The data submitted in the initial MAA for Skyrizi is applicable for this line extension application, hence, no new information is submitted.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Relationship between plasma concentration and effect and safety

R&D/23/2430

An exposure-response analysis was conducted for efficacy and safety in paediatric subjects with psoriasis.

To evaluate the effect of risankizumab exposure on efficacy endpoints, response rates of PASI 75 at Week 16, static Physician Global Assessment (sPGA) clear or almost clear at Week 16, and sPGA clear or almost Clear and ≥ 2 Grade improvement from baseline at Week 16 were plotted against quartiles of risankizumab exposure in Figure 6.

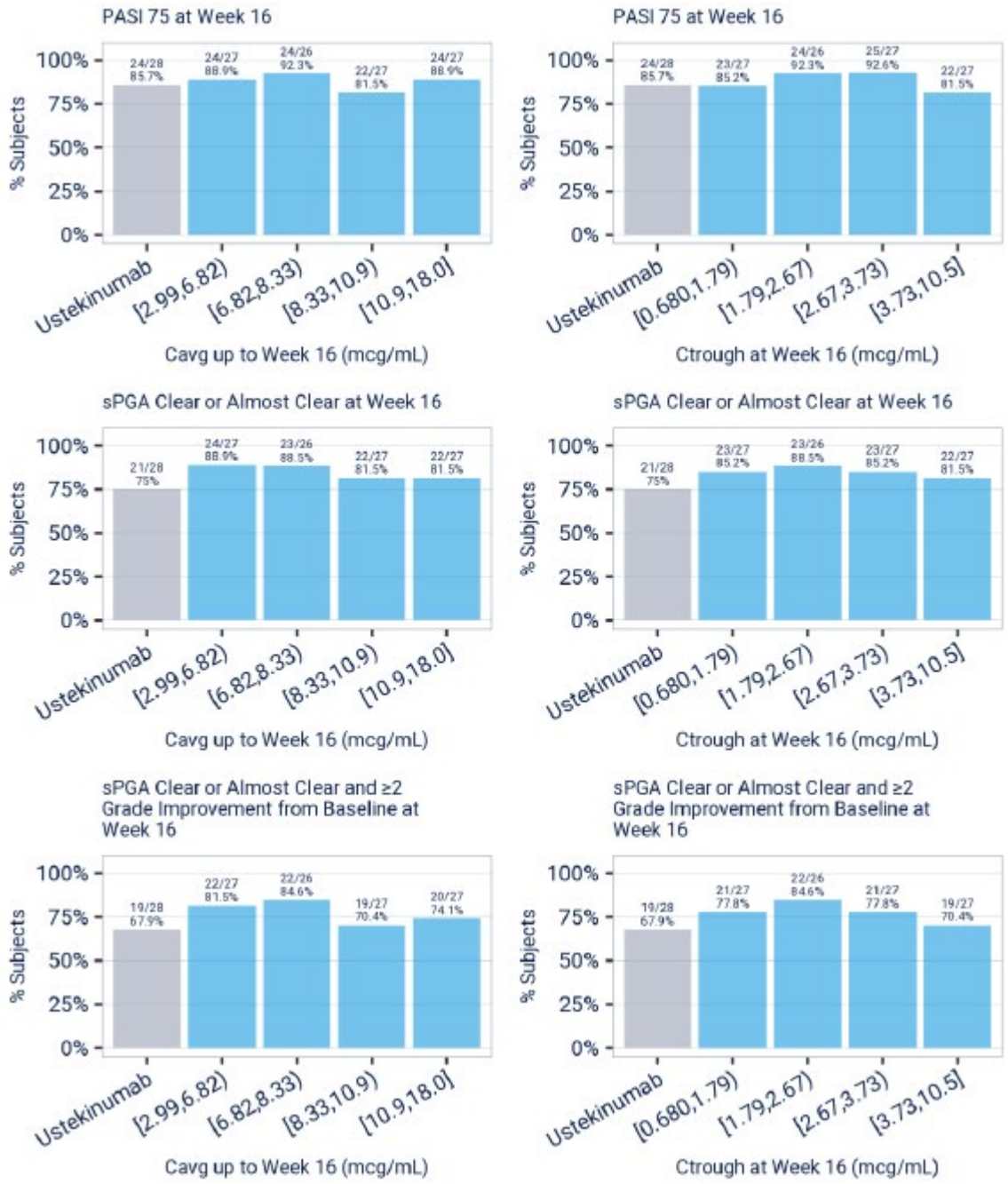


Figure *6*: Graphical assessment of the relationship between risankizumab exposures (Cavg and Ctrough) and efficacy endpoint at Week 16 of treatment.

To evaluate the effect of risankizumab exposure on safety endpoints, response rates of any adverse event, any serious adverse event, and any infection were plotted against quartiles of risankizumab exposure in ***Figure 7***. No occurrences of serious infection were observed in the study and is therefore not shown.

Figure 7: Graphical assessment of the relationship between risankizumab Cavg up to the last dose and safety endpoints in risankizumab.

5.2.5. Dose selection and therapeutic window

Dose justification

The selection of a 40 kg cutoff for dosing in paediatric psoriasis subjects is based on observations from past clinical studies and popPK model predictions.

Historical data from an adalimumab study (Study M04-717) showed that the median body weight of adolescent patients with plaque PsO (ages 12 to < 18 years) was 59 kg, with a range from 38 to 108 kg. This range significantly overlapped with that of adult PsO patients (38.5 to 193 kg) in the risankizumab Phase 3 studies, including Japan Phase 2/3 studies. Consequently, 40 kg was chosen as a potential cutoff, and a previously developed adult popPK model was used to run simulations predicting doses for paediatric subjects weighing ≥ 40 kg and < 40 kg. Based on exposure-matching, the adult therapeutic dose of 150 mg risankizumab was considered appropriate to test in adolescents in Part 1 of Study M19-977. Subsequent predictions with the updated PK model, which incorporated data from Part 1, confirmed the appropriateness of 150 mg SC q12w for subjects weighing ≥ 40 kg and

supported testing 55 mg SC q12w for those weighing < 40 kg in the subsequent parts of Study M19-977.

The totality of data from the Phase 3 paediatric studies and current model simulations show that the proposed weight-based dosing regimens can achieve adult-equivalent exposures in paediatric PsO subjects. Additionally, results of the exposure-response analyses for efficacy showed that the evaluated paediatric dosing regimens resulted in similar efficacy across paediatric subjects. No exposure-dependent safety trends were identified in the paediatric subjects.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Bioanalytical methods

Sample analysis for risankizumab concentrations in human serum for the pivotal Phase 3 Studies M19-997 and M19-973 was conducted using a bioanalytical method (bridging ECL assay) that was previously validated and assessed. Incurred sample reanalysis was not performed for either study M19-977 or M19-973. However, these methods were previously shown to be reproducible in PsO clinical studies. Hence, no concerns were raised. Based on the results presented in the bioanalytical reports, it was agreed that the analytical method was performed in line with the validated parameters. Hence, the results from these studies were considered valid and reliable and the CHMP agreed that revalidation would not be needed for the paediatric indication.

A titre-based acid dissociation bridging ECL immunoassay was used to determine ADA in human serum samples. The validation of this method was previously assessed during the line extension for Skyrizi 150 mg formulation in healthy subjects, psoriasis patients' serum and found suitably validated in line with the relevant EMA guidelines (EMEA/H/C/004759/X/0012). For this current extension of indication application, a partial revalidation of method was conducted which determined disease-specific cut-points, sensitivity, precision and selectivity. This method was used to support the two pivotal Phase 3 studies (Study M19-977 and Study M19-973) in paediatric subjects with psoriasis. In general, the approach taken was acceptable and followed the standard principles outlined in Shankar et al. (2008[1]) and the previous method validations to establish cut-points for psoriasis patients' serum. The analytical method was performed as per the validated parameters for the sample analysis of clinical studies M19-977 and M19-973. Hence, the data were considered valid.

No new method validations were provided for the NAb assay. The NAb method used in the initial MAA submission and the Skyrizi 150 mg/mL formulation line extension (EMEA/H/C/004759/X/0012) was previously assessed. The analytical method was performed as per the validated parameters for the sample analysis of clinical studies M19-977 and M19-973. Hence, the data were considered valid.

Pharmacokinetic data analysis

Data from from the two pivotal Phase 3 studies (Study M19-977 and Study M19-973) were used to inform the popPK model. PopPK analyses were performed to characterise the population pharmacokinetics of risankizumab in paediatric subjects with PsO, to compare paediatric exposures

[1] Shankar, Gopi, et al. "Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products." *Journal of pharmaceutical and biomedical analysis* 48.5 (2008): 1267-1281.

with adult exposures, and to investigate the impact of significant covariates on exposures in paediatrics. Exposure-response analyses were performed to characterise the relationships between risankizumab exposures and efficacy and safety parameters in paediatric subjects with PsO. The findings of the popPK analysis were used to support the dosing justification in paediatric patients aged 6 to <18 years with PsO.

Evaluation and qualification of models – R&D23/2430

Methodology

The studies selected by the MAH for inclusion in the model (paediatric source: Studies M19-977 and M19-973, adult source: data used in the previously developed popPK model) were considered acceptable. The handling of missing data and imputations described in the modelling report were considered acceptable. The inclusion of the data from studies in healthy adults and adults with psoriasis was adequately justified by the exploratory analysis performed in the modelling report. The exploratory analysis demonstrated that, although exposures in paediatric subjects aged 6 – 18 years receiving 150 or 55 mg risankizumab (based on bodyweight) were overall higher than exposures seen in adults, they were still contained within the range of concentrations seen in adults at each time-point. These findings indicated similar PK between the paediatric and adult populations. Additionally, the external validation of the adult popPK model using the paediatric data demonstrated that the adult model could adequately predict the PK exposures from the paediatric clinical studies. The selection of the adult popPK model as a starting point for the development of the paediatric model was considered acceptable. The described model development was considered acceptable and in line with good modelling practices.

Results

The addition of time-varying body weight on CL, Vc, and Vp for the paediatric studies instead of baseline bodyweight was well-justified both from the improvements to model diagnostics and from a physiological perspective. The addition of age on Vc as a covariate was acceptable, and the exclusion of a binary paediatric and adult covariate was well-justified.

For the final popPK model, the PK parameters were identified with high precision for most parameters (RSE <10%) and with acceptable precision for the effect of age on Vc for paediatrics. The shrinkage was acceptable for the IIV on CL and Vc (<50%) and moderately high for F and Ka (~60%). The population estimates for the parameters from the combined adult and paediatric psoriasis model are similar to parameter estimates from the previous adult psoriasis model, indicating that the PK of risankizumab in paediatrics is overall comparable to the PK seen in adults. When adjusted for time-varying body weight in paediatrics, the effects of bodyweight on CL, Vc, and Vp were overall similar to what was estimated in the adult psoriasis model. The effect of age on Vc in paediatrics did demonstrate an ~42% decrease in Vc in paediatrics, which was acceptable.

In the individual predictions plot, there was mild overprediction of the lower values, however, the population predictions plot did not suggest any systematic bias in model predictions compared to the observed data. The CWRES plots did not suggest any model misspecification. The pcVPCs presented in the modelling report demonstrated good prediction of the central tendency at all time-points both prior to and after re-randomisation. The variability in the model was predicted well for the 95th percentile overall and predictions for the 5th percentile were slightly lower than the observed, but overall acceptable. The majority of the observed data was contained within the predictions of the model.

The popPK model predicted the PK exposure data in paediatrics with psoriasis aged 6 to <18 years of age well and was considered fit-for-purpose for the objectives of the model.

Pharmacokinetics in the target population

Study M19-977

In study M19-977 conducted in patients from 6 to less than 18 years of age with moderate to severe plaque PsO, subjects received risankizumab based on body weight. In Part 1, all subjects received 150 mg risankizumab SC. In Parts 2, 3, and 4, risankizumab doses were based on weight; subjects who weighed ≥ 40 kg received 150 mg risankizumab, while subjects who weighed < 40 kg received 55 mg risankizumab.

From the PK perspective, for the 150 mg dosing in adolescent subjects >40 kg aged 12 to <18 years, similar geometric mean risankizumab serum concentrations were seen at Week 4, Week 16, and Week 52 between Part 1 and Part 2 of the study. Slightly higher concentrations were seen in the > 40 kg aged 6 to <12 years at Week 4 in Part 3 and Part 4 of the study, however, similar trough concentrations were seen at Week 16 and Week 52 in these groups. This suggested that the 40 kg weight cut-off for the 150 mg risankizumab dose demonstrated similar PK in paediatrics and adolescents aged 6 to <18 years.

For the 55 mg dosing in adolescents and paediatrics weighing < 40 kg, similar geometric mean risankizumab serum concentrations were seen at Week 4, Week 16, and Week 52 between Part 3 and Part 4. These concentrations were lower than seen with the 150 mg dose in the >40 kg group.

The incidence of ADAs was overall low and the incidence of NAbs in ADA positive subjects was low. Of note, no subject demonstrated an ADA titer > 128, which was identified in the popPK analysis as a relevant cut-off for ADA as a covariate on clearance which could have a significant impact on exposure. The exposure to risankizumab was similar in ADA positive subjects compared to ADA negative subjects which would be expected given the relatively low ADA titers. However, the CHMP acknowledged the limitations of the available data due to the low incidence of ADAs and NAbs.

Study M19-973

In Study M19-973, the open label long term extension for Study M19-977, the trough concentrations measured were overall consistent in the 150 mg risankizumab group from Week 24 to Week 96, with a slight drop in geometric mean for Week 120 to Week 168. However, given the low subject numbers for these time-points, no conclusion was drawn on this finding. The trough concentrations in this study were comparable to what was seen in Study M19-977. The trough concentrations for the 55 mg group were also overall consistent from Week 24 to Week 96 and were comparable to results for the 55 mg groups in Study M19-977. These results indicated that there is no significant accumulation of risankizumab over longer periods of administration for both dosing regimens. Concentrations in the 150 mg risankizumab group were shown to be higher than the 55 mg group, and this was consistent with observations from Study M19-977.

ADA incidence was overall low in this study, with no incidence of NAbs. There was no notable difference in risankizumab exposure between ADA positive and ADA negative subjects.

R&D/23/2430

Impact of covariates on risankizumab exposures in paediatric patients with psoriasis

The simulations performed to demonstrate the impact of the significant covariates of body weight and baseline serum creatinine did not demonstrate a clinically relevant effect on risankizumab

exposures. The lack of effect of body weight was attributed by the MAH to the body weight range-based dosing regimens resulting in similar exposures in paediatrics and adults, and this was supported by the exploratory analysis, where observed paediatric exposures were contained within the range of exposures seen in adult studies. An impact of age <18 years was seen to have a potentially clinically relevant increase in exposure (1.29). This could be expected, as age is included in the model as a covariate on Vc, with age < 18 years reducing Vc. Overall, it was agreed that age, baseline serum creatinine, and body weight are not expected to result in clinically meaningful differences in exposure in the paediatric population.

Lower baseline albumin (< 43 g/L) and higher baseline hs-CRP (> 6.23 mg/L) resulted in a potentially clinically relevant decrease in the Ctrough value. The MAH discussed that for efficacy, the exposure-response exhibited flat trends, indicating no exposure-dependent trends in efficacy in the observed paediatric data. It was also noted that for lower baseline hs-CRP (<0.892 mg/L) there is a potentially clinically relevant increase in risankizumab Ctrough. However, from the safety perspective, in the exposure-response analysis there was no exposure related worsening in safety endpoints. It was accepted that differences in albumin and hs-CRP would not have a clinically meaningful effect in paediatric subjects, and this was in line with results from the adult popPK model analysis.

An ADA titer ≥ 128 demonstrated the most substantial decrease in exposure compared to the reference, with the point estimate for both the Ctrough and Cavg falling below the no effect boundary of 0.8 (0.464 and 0.771 respectively). In studies M19-977 and M19-973, no subject demonstrated ADA titers equivalent to ≥ 128. The MAH discussed that in the subgroup analysis, no difference in efficacy at Week 16 for PASI 75 and sPGA responses was demonstrated between ADA-positive and ADA-negative subjects, although this could be expected as no subject demonstrated ADA titers equivalent to ≥ 128. From the original adult psoriasis popPK report, it was concluded that there would be no clinically meaningful impact on the efficacy even in the patients demonstrating ADA titers ≥ 128. Given that the PK in adults and paediatric patients with psoriasis was overall comparable, the incidence of ADA titers ≥ 128 was low in adults and was not observed in the paediatric studies, and that the exposure-response analysis exhibited flat trends in efficacy with exposure, it was accepted that no clinically meaningful impact of ADA titers ≥ 128 would be expected in the paediatric population.

Exposure simulations of risankizumab in paediatric subjects with psoriasis compared to adults

The simulations demonstrated that paediatric subjects weighting <40 kg receiving 55 mg Q12W demonstrated median exposures similar to adults ≥ 40 kg receiving 150 mg Q12W at steady state. Paediatric subjects weighing ≥ 40 kg receiving 150 mg Q12W demonstrated median exposures higher than in adults. These simulations were overall in line with what was seen in the comparison with the observed data in the exploratory analysis and was considered acceptable overall. These results were considered supportive. Considering the exposure-response analysis, it was agreed that the proposed dosing regimens is expected to achieve adult-equivalent exposures.

Relationship between plasma concentration and effect and safety

Exposure simulations of risankizumab in paediatric subjects with psoriasis compared to adults indicated no exposure-dependent trends for the efficacy endpoints and no exposure-dependent worsening in safety events throughout the observed treatment duration in paediatric subjects.

Dose justification

The MAH has presented two clinical studies in paediatric subjects aged 6 to <18 years (Studies M19-977 and M19-973) and popPK and exposure-response analyses to support the use of risankizumab in paediatric subjects with psoriasis.

The main objective of the PK/PD package was to demonstrate that the proposed dosing regimens would provide exposure matching between paediatric and adult subjects with psoriasis. The sparse PK data from studies M19-977 and M19-973 showed that risankizumab did not demonstrate accumulation in the paediatric population. In the exploratory analysis, as part of the popPK analysis, it was shown that the observed risankizumab exposure in paediatric subjects was higher than in adult subjects, however, were still contained within the range of exposures seen in adults.

The popPK model was considered fit-for-purpose and demonstrated that the PK parameters for risankizumab were comparable between the paediatric subjects with psoriasis and adult populations. The covariate analysis demonstrated that a number of covariates (ADA titers >128, low serum albumin, and high and low hs-CRP) resulted in median exposure parameters outside the no effect limit (0.8 to 1.25). However, these results were in line with the results from the adult popPK model. Simulations comparing the proposed dosing regimen in paediatric subjects with the approved dosing regimen in adults indicated that the 55 mg dosing in paediatrics weighing < 40 kg matched exposures in adults. In paediatric subjects weighing ≥ 40 kg, exposures were overall higher. However, the exposure-response analysis supported that the higher exposures observed in paediatric subjects weighing ≥ 40 kg and the differences in exposure caused by different covariates were unlikely to have a clinically meaningful impact.

It was overall agreed that the totality of the PK/PD evidence supports the use of risankizumab 150 mg SC at Weeks 0, 4, and q12w thereafter for subjects weighing ≥ 40 kg, and 55 mg SC at Weeks 0, 4, and q12w thereafter for subjects weighing < 40 kg, for the treatment of paediatric subjects with psoriasis.

Product information

The MAH simulated risankizumab exposure parameters for the proposed dosing regimens as part of the popPK report. Given that the model was considered robust and fit-for-purpose, it was agreed to include the estimated median steady-state peak and trough plasma concentrations (15.7 and 2.3 µg/mL, respectively, in subjects weighing ≥40 kg, and 11.1 and 1.6 µg/mL, respectively, in subjects weighing <40 kg) in the SmPC Section 5.2 under Special Populations.

5.2.6.2. Conclusions

The clinical pharmacology package provided adequate evidence to support the proposed posology of risankizumab 150 mg SC at Weeks 0, 4, and q12w thereafter for subjects weighing ≥ 40 kg, and 55 mg SC at Weeks 0, 4, and q12w thereafter for subjects weighing < 40 kg, for the treatment of paediatric subjects with plaque PsO.

5.3. Clinical efficacy

5.3.1. Dose response study(ies)

Not applicable.

5.3.2. Main studies – Study #1 (M19-977)

5.3.2.1. Study title

OptIMMize-1: a randomised, active-controlled, efficacy assessor-blinded study to evaluate PK, safety, and efficacy of risankizumab in patients from 6 to less than 18 years of age with moderate to severe plaque PsO.

5.3.2.2. Study design

This was a randomised, active controlled, efficacy assessor-blinded study to evaluate PK, safety, and efficacy of risankizumab in subjects 6 to less than 18 years of age with moderate to severe plaque PsO. Subjects who completed the Week 52 visit in Part 1, Part 2 Period B, Part 3, or Part 4 and those who completed 16 weeks of the retreatment Part 2 Period C had the option to enroll into Study M19-973, the OLE study. A follow-up call took place 20 weeks after the last dose of study drug if the subject did not enroll into the Study M19-973 OLE.

The study consisted of 4 parts, each with distinct patient populations. A 35-day screening period applied to Part 1, 2, 3 and 4. In Part 1, all subjects received risankizumab at Weeks 0, 4, 16, 28, and 40. In Parts 2, 3, and 4, risankizumab was administered at Weeks 0, 4, 16 and then q12w thereafter. In Part 2 Period A, subjects randomised to ustekinumab received ustekinumab at Weeks 0 and 4.

Part 1

Part 1 was a sentinel, open-label cohort of 12 adolescents (aged 12 to less than 18 years) with severe disease (defined as ≥ 20% BSA PsO involvement with sPGA score of 4; or ≥ 10% body surface area (BSA) PsO involvement that includes facial or genital areas with sPGA score of 4; or PASI ≥ 20) with PK sampling for the first 16 weeks.

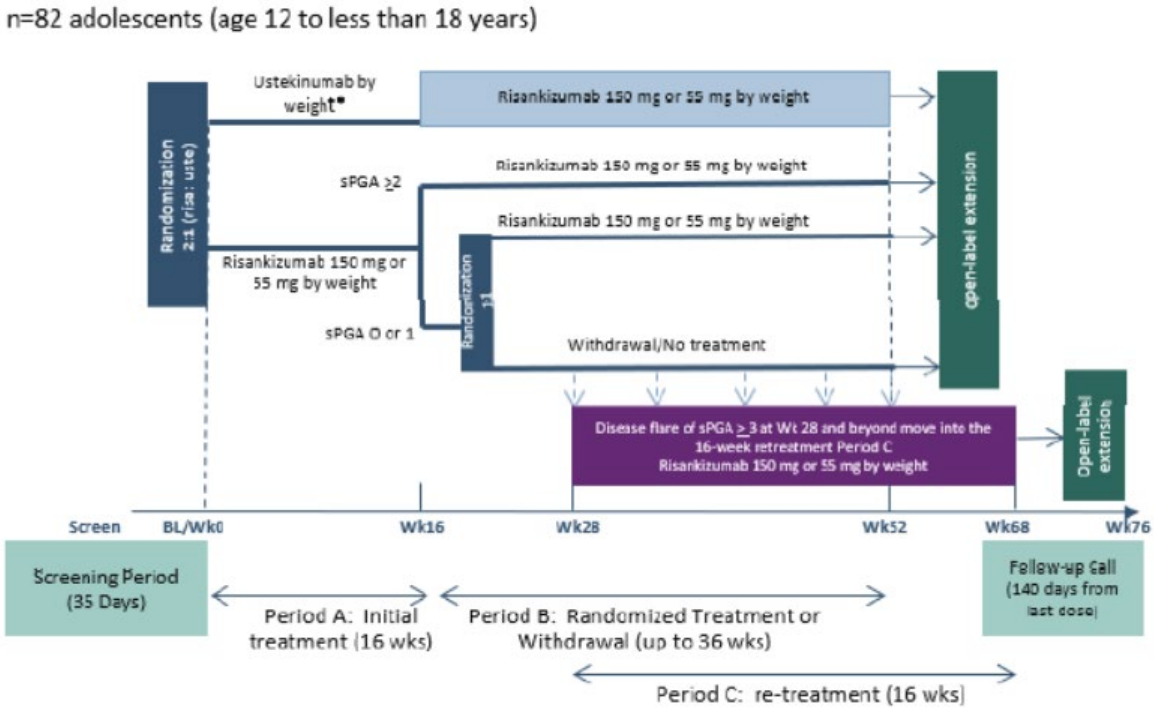
The Part 1 dosing regimen was determined by extrapolation from adult data and Part 1 PK data up to Week 16 informed the dosing regimen for Part 2 in adolescents and triggered the start of enrollment of Part 3 in children 6 to < 12 years of age.

Part 2

Part 2 was a randomised, efficacy assessor-blinded cohort comparing risankizumab with ustekinumab in 82 adolescents (aged 12 to < 18 years) with moderate to severe PsO (defined as ≥ 10% BSA PsO involvement with sPGA score of ≥ 3 or PASI ≥ 12). A 16-week initial treatment period (Period A) was followed by an up to 36-week randomised treatment or withdrawal period (Period B) for risankizumab responders, and then a 16-week retreatment period (Period C) for subjects who experienced a disease flare (defined as sPGA ≥ 3 on or after Week 28). Subjects who were nonresponders to risankizumab at Week 16 or who received ustekinumab in Period A received risankizumab from Week 16 through Week 40 (Period B).

In Period A, subjects were randomised (2:1) to receive risankizumab or ustekinumab SC based on weight at Weeks 0 and 4. At Week 16 of Period A, risankizumab nonresponders (sPGA ≥ 2) and subjects initially randomised to ustekinumab entered Period B and received risankizumab q12w until Week 40. Risankizumab responders (sPGA = 0 or 1) entered Period B and were rerandomised (1:1) to receive either no medication (withdrawal arm) until a disease flare (sPGA ≥ 3 on or after Week 28) or risankizumab q12w until Week 40. Subjects randomised to the withdrawal arm in Period B who experienced a disease flare on or after Week 28 entered Retreatment Period C to receive risankizumab

at Weeks 0 and 4 of the 16-week retreatment period. Randomisation and rerandomisation were not stratified due to the small overall sample size.



* Ustekinumab dose: 0.75 mg/kg for subjects < 60 kg; 45 mg for subjects 60 to < 100 kg; 90 mg for subjects ≥ 100 kg.

Figure 8: Part 2 schematic

Part 3

Part 3 was a sentinel, open-label cohort of 13 children (aged 6 to < 12 years) with severe disease with PK sampling through Week 16. Three subjects aged between 6 to less than 9 years were enrolled to ensure good representation of the lower age range. Subjects received risankizumab based on body weight at Weeks 0, 4, 16, 28, and 40. PK data up to Week 16 informed the dosing regimen for the start of Part 4. Enrolment was triggered by the Week 16 data from Part 1.

Part 4

Part 4 was a 52-week open-label safety cohort of 30 children (aged 6 to < 12 years) with moderate to severe disease with dosing at Weeks 0, 4, 16, 28, and 40. In Japan, 2 adolescents aged 12 to < 18 years were included in the cohort but are not part of the current analysis. Enrollment to Part 4 was triggered by Week 16 data from Part 3.

5.3.2.2.1. Treatment

Study Parts 1, 3, and 4 were open-label, single-arm, and all subjects received risankizumab based on body weight. For Study Part 2, subjects received either risankizumab or ustekinumab based on body weight. At the study visits, risankizumab was dispensed and administered in a PFS and ustekinumab was dispensed in a PFS or vial and administered via PFS.

In Part 1, all subjects received 150 mg risankizumab SC. In Parts 2, 3, and 4, risankizumab doses were based on weight; subjects who weighed ≥ 40 kg received 150 mg risankizumab, while subjects who weighed < 40 kg received 55 mg risankizumab. In Part 2 Period A, subjects randomised to ustekinumab received ustekinumab SC based on weight (0.75 mg/kg for subjects < 60 kg; 45 mg for subjects 60 to < 100 kg; 90 mg for subjects ≥ 100 kg).

Concomitant and rescue therapies

Prohibited medications and therapy were defined as using the following prohibited concomitant PsO treatments within the specified timeframe prior to Baseline Visit and throughout the study:

1. Any systemic biologic therapy (other than the study drug).

2. Systemic non-biologic therapy for PsO, including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, apremilast, and fumaric acid derivatives within 4 weeks.

3. Phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks.

4. Topical PsO treatments, including but not limited to corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, urea, alpha- or beta-hydroxyl acids, and medicated shampoos (for example those that contain > 3% salicylic acid, corticosteroids, coal tar or vitamin D3 analogues) within 2 weeks.

- Exception: Subjects were allowed to use bland (containing no Ps treatment) emollients and shampoos and/or low potency topical corticosteroids (US Class 6 - 7) on the palms, soles, face, inframammary area, and groin only. In areas where available topical corticosteroids are not easily identified by US Class, a list of acceptable low potency topical corticosteroids was provided to sites.

5. Treatment with an experimental non-biologic for PsO within 4 weeks or five half-lives of the drug (whichever was longer).

6. Treatment with an experimental biologic for PsO within 12 weeks or five half-lives of the drug (whichever was longer).

7. Live attenuated vaccines (except non-replicating live vaccines (e.g., Jynneos monkeypox vaccine) were not allowed during the study and including up to 140 days (20 weeks or as guided by local drug label (if approved), whichever was longer) after the last dose of study drug. Examples of live attenuated vaccines include but were not limited to the following:

- Bacille Calmette-Guérin;
- Zoster vaccine live (Zostavax);
- Measles-mumps-rubella or measles mumps rubella varicella;
- Monovalent live attenuated influenza A (intranasal);
- Oral polio vaccine;
- Rotavirus;
- Seasonal trivalent live attenuated influenza (intranasal);
- Smallpox;
- Oral typhoid vaccine;
- Varicella (chicken pox);
- Yellow fever;
- Dengue (Dengvaxia).

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment were judged to exclude the patient from participation, were permissible. Concomitant therapies were not be administered with the intent to treat PsO or have demonstrated efficacy for the treatment of PsO (except for permitted low-potency topical corticosteroids). All concomitant medications were carefully evaluated by the investigator, and the clinical monitor was to be contacted when there were questions regarding concomitant medications.

5.3.2.2.2. Randomisation

Study Parts 1, 3, and 4 were open-label single arms and all subjects received the same dose exposure equivalent based on body weight (Parts 3 and 4) and the same frequency of study drug.

For Part 2, randomisation for Period A was done in a 2:1 ratio of risankizumab vs. ustekinumab. The re-randomisation ratio of continued treatment with risankizumab vs. no treatment for Period B was 1:1. Randomisation and re-randomisation was not stratified due to the small number of subjects.

5.3.2.2.3. Blinding

The blinded efficacy assessor was to be independent from all other study activities. The efficacy assessor was to remain blinded to each subject's treatment, clinical laboratory results, and all subject safety data during the course of the study.

5.3.2.2.4. Patient population

Subjects had to meet all of the following criteria in order to be included in the study:

Consent

1. Subject's parent or legal guardian had to voluntarily sign and date an informed consent, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures. Subject was included in all discussions to obtain verbal or written assent.

Demographic and Laboratory Assessments

2. Subject was judged to be in good general health, as determined by the investigator based upon the results of a medical history, physical examination, laboratory profile, and a 12-lead Electrocardiogram (ECG) performed during the Screening period.

3. Subject was male or female, 6 to < 18 years old:
- Parts 1 and 2: ages included 12 to < 18 years at the time of enrollment;
- Parts 3 and 4: ages included 6 to < 12 years at the time of enrollment.

4. Laboratory values had to meet the following criteria within the screening period prior to the first dose of study drug:
- Serum aspartate transaminase and serum alanine transaminase ≤ 2 × upper limit of normal;
- Serum total bilirubin ≤ 2.0 mg/dL; except for subjects with isolated elevation of indirect bilirubin related to Gilbert syndrome;
- Total white blood cell count ≥ 3,000/µL;
- Absolute neutrophil count ≥ 1,500/µL;
- Platelet count ≥ 100,000/µL;
- Haemoglobin ≥ 10 g/dL.

5. Subject was willing and able to comply with procedures required in this protocol and was not an employee of the sponsor and/or study site or a family member of an employee.

Disease/Condition Activity

6. Diagnosis of chronic plaque PsO for at least 6 months before the Baseline Visit.

7. Subject had to be a candidate for systemic therapy as assessed by the investigator and met the following disease activity criteria at both the Screening and Baseline Visits:

- Part 1: Subject had severe disease defined as ≥ 20% BSA PsO involvement with sPGA score of 4; or ≥ 10% BSA Ps involvement that included facial or genital areas with sPGA score of 4; or PASI ≥ 20;
- Part 2: Subject had moderate to severe disease defined as ≥ 10% BSA Ps involvement with sPGA score of ≥ 3 or PASI ≥ 12;
- Part 3: Subject had severe disease defined as ≥ 20% BSA Ps involvement with sPGA score of 4; or ≥ 10% BSA PsO involvement that included facial or genital areas with sPGA score of 4; OR PASI ≥ 20;
- Part 4: Subject had moderate to severe disease defined as ≥ 10% BSA Ps involvement with sPGA score of ≥ 3 or PASI ≥ 12;

8. Subject had to be a candidate for the treatment with ustekinumab according to local label. For Japan, this included subjects ≥ 15 years old.

- Subjects in Part 2 age < 15 years had to meet the safety requirements of the local label.

Subject History

9. Subject had to not have had a history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months.

10. Subject had to not have had a history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.

11. No history of:

- Erythrodermic Ps, generalized or localized pustular Ps, medication-induced or medication exacerbated Ps, or new onset guttate PsO;
- Active skin disease other than Ps that could interfere with the assessment of PsO;
- Clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months;
- An allergic reaction or hypersensitivity to a biologic agent or its excipients;
- A latex allergy;
- An organ transplant that requires continued immunosuppression;
- Any malignancy except for successfully treated non-melanoma skin cancer or localized carcinoma in situ of the cervix.

12. No evidence of the following medical diseases or disorders:

- Hepatitis B (HB) (hepatitis B virus [HBV]) or hepatitis C (hepatitis C virus [HCV]) infection, defined as
    a. HBV: Hepatitis B surface antigen (HBs antigen) positive (+) test or detected sensitivity on the HBV DNA polymerase chain reaction qualitative test for subjects who are HB core Ab (HB core Ab) positive (+) (and for HB surface Ab [HBs Ab] positive [+] subjects where mandated by local requirements);
    b. HCV: hepatitis C virus RNA detectable in any subject with anti-hepatitis C virus antibody;
- Human immunodeficiency virus (HIV), defined as confirmed positive anti-HIV antibody (HIV Ab) test.
- COVID-19: In subjects who tested positive for COVID-19, at least 5 days have passed since a positive test result in asymptomatic patients. Subjects with mild/ moderate COVID-19

symptoms could be enrolled if fever-free without use of antipyretics for 24 hours and improvement of other symptoms or 5 days had passed since the positive test result (whichever came last). Subjects were rescreened if judged to be in good general health, as determined by the investigator based on medical history and physical examination.
- Active tuberculosis (TB). If presence of latent TB was established, treatment should have been initiated and maintained according to local country guidelines.
- Active systemic infection/clinically important infection during the last 2 weeks prior to Baseline Visit as assessed by the investigator.
- Genetic deficiency in IL-12/IL-23;
- Active or suspected malignancy;
- Recent (within past 6 months) cerebrovascular accident or myocardial infarction (MI);
- Major surgery performed within 12 weeks prior to randomisation or planned during the conduct of the study.

13. Subject did not have concurrent clinically significant medical conditions other than the indication being studied or any other reason that the investigator determines would interfere with the subject's participation in this study, would make the subject an unsuitable candidate to receive study drug, or would put the subject at risk by participating in the study.

14. Subject had an updated immunisation schedule according to local immunisation guidelines

Contraception

15. For all females of child-bearing potential; a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at baseline prior to the first dose of study drug.

16. Female subjects of childbearing potential had to have practiced at least 1 protocol-specified method of birth control, that was effective from Study Day 1 through at least 140 days (20 weeks or as guided by the local drug label, whichever is longer) after the last dose of study drug (local practices may require 2 methods of birth control). Female subjects of non-childbearing potential did not need to use birth control.

17. Female subjects could not be pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 140 days (20 weeks or as guided by the local drug label, whichever is longer) after the last dose of study drug.

Concomitant Medications

18. Subject had to not have received any live viral or bacterial vaccine except non-replicating live vaccines (e.g., JYNNEOS monkeypox vaccine) within 4 weeks prior to the first dose of study drug or expect the need for live vaccination during study participation including at least 140 days (20 weeks or as guided by the local drug label, whichever is longer) after the last dose of study drug.

19. Subject had to not have any previous exposure to risankizumab (all study parts) or ustekinumab (study Part 2).

20. Subject had to not have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or was currently enrolled in another interventional clinical study.

5.3.2.3. Objectives and estimands

5.3.2.3.1. Primary Objective

The primary efficacy objective was to assess the rate of subjects who achieve a) PASI 75 (defined as at least 75% improvement from baseline in PASI) and b) sPGA clear or almost clear (0 or 1) (US only: and ≥ 2 grade improvement from baseline) at Week 16 of initial treatment with study drug based on the Intent-to-Treat (ITT) population.

There were no statistical hypotheses corresponding to the co-primary efficacy objectives as efficacy were assessed descriptively, providing estimates with confidence intervals without performing statistical testing.

5.3.2.3.2. Estimands for the primary objective

Table *16*: Estimands for co-primary objective 1

Population	**Paediatric patients with PsO**
Treatment conditions	Part 1, 3, 4: Assignment to risankizumab without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population Part 2: Assignment to risankizumab compared to assignment to ustekinumab, without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population.
Endpoint (variable)	PASI75 at week 16 of initial treatment
Population-level summary	Part 1, 3 and 4: Percentage of subjects achieving PASI75 at week 16 in the risankizumab group Part 2: Difference in the percentage of subjects achieving PASI75 at week 16 in the risankizumab group in comparison with the ustekinumab group
Intercurrent events and strategy to handle them	
ICE 1 - use of rescue medication	Composite policy
ICE 2 - prematurely discontinue study drug	Treatment policy

Table *17*: Estimands for co-primary objective 2

Population	Paediatric patients with PsO
Treatment conditions	Part 1, 3, 4: Assignment to risankizumab without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population Part 2: Assignment to risankizumab compared to assignment to ustekinumab, without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population.
Endpoint (variable)	sPGA clear or almost clear (0 or 1) at week 16 of initial treatment
Population-level summary	Part 1, 3 and 4: Percentage of subjects achieving sPGA 0/1 at week 16 in the risankizumab group Part 2: Difference in the percentage of subjects achieving sPGA 0/1 at week 16 in the risankizumab group in comparison with the ustekinumab group
Intercurrent events and strategy to handle them	
ICE 1 - use of rescue medication	Composite policy
ICE 2 - prematurely discontinue study drug	Treatment policy

Statistical methods for estimation and sensitivity analysis on primary estimands

Analysis sets

For Part 1, Part 3, and Part 4:

The **ITT Population** in each study part included all enrolled subjects. The ITT Population was used for all efficacy and baseline analyses.

The **Safety Analysis Population** consisted of all subjects who received at least 1 dose of study drug.

For Part 4, the two Japanese adolescents aged 12 to <18 years, were not included in the ITT and Safety Analysis Populations. These 2 subjects are not included in the ITT and the Safety Analysis Populations because they were not from the same age cohort as the population studied in Part 4 (children) but were added to Part 4 for administrative reasons (closure of Part 2 enrolment).

For Part 2:

The **ITT Population** included all randomised subjects. The ITT Population was used for all efficacy and baseline analyses. Subjects were analysed according to treatment as randomised.

The **Safety Analysis Population** in each study part consisted of all subjects who received at least 1 dose of study drug. Subjects were included in the analysis according to the study drug that they received. For Period A, a subject's actual treatment was determined by the first dose of study drug. For subjects rerandomised in Period B, only subjects who received no drug were included in the withdrawal arm, and subjects who received at least 1 dose of study drug were included in the treatment continuation arm.

For analyses by study period in Part 2, only subjects enrolled into the respective study period were included for that period.

Main analysis methods

Primary endpoints

Part 2:

The analysis of the co-primary endpoints, difference in PASI 75 response rates and sPGA score of clear or almost clear response rates between ustekinumab and risankizumab from Baseline at Week 16, were analysed as response rate (%) and 95% confidence interval (CI) over time. NRI was used as the primary approach for the analysis of the co-primary endpoints and ITT Population was used for the efficacy analysis. No statistical testing was performed for analysis of any endpoints. Exact CIs were provided based on the Clopper-Pearson method for proportions. The Miettinen-Nurminen method for differences in proportions was used for comparing response rate differences between the risankizumab and ustekinumab groups.

Part 1, Part 3, and Part 4:

The co-primary endpoints of achievement of PASI 75 at Week 16 of initial treatment and achievement of sPGA clear or almost clear (0 or 1) at Week 16 of initial treatment were analysed similar to Part 2 above excluding a comparator arm. Response rate (%) and 95% CI over time were analysed in the ITT population with NRI. Exact CIs were provided based on the Clopper-Pearson method for proportions.

Intercurrent events handling

As specified in the Statistical Analysis Plan (SAP), for binary endpoints:

- For subjects with the use of rescue medication, values after the start of rescue medication were excluded from analysis and subjects were considered non-responders at all time points after the start of rescue medication.
- Data collected was used regardless of premature discontinuation of study drug.

For continuous endpoints:

- Values after the use of rescue medication was excluded.
- Data collected was used regardless of premature discontinuation of study drug.

Handling of missing data

Missing data was imputed using the following methods for the efficacy analyses:

- Non-Responder Imputation (NRI): the NRI analysis categorised any subject who does not have evaluation during a specific visit window as a non-responder for that visit. NRI was the primary approach in the analyses of categorical variables.
- Last Observation Carried Forward (LOCF): the LOCF analysis imputed a missing value with the last value observed previously. Baseline observations were not carried forward. LOCF was the primary approach in the analyses of continuous variables.
- As Observed (AO): The AO analysis did not impute values for missing evaluations, and thus a subject who did not have an evaluation on a scheduled visit was be excluded from the AO analysis for that visit. AO included all values collected in the study. AO excluded all values collected in the study after the first dose of rescue medication. AO was used as sensitivity analysis in the analyses of categorical and continuous variables.

Sensitivity and supplementary analyses

AO was used as sensitivity analysis for the analyses of the co-primary endpoints and secondary endpoints.

No supplementary analysis was performed.

Subgroup analysis

Due to the small sample sizes and the uncontrolled design of Part 1, Part 3, and Part 4, no efficacy subgroup analyses were planned.

For Part 2, the co-primary endpoints were analysed for the following subgroups, using NRI for imputation of missing data:

- age group (12 to < 15, 15 to < 18 years)
- sex (male, female),
- race (white, non-white)
- weight group (< 40 kg, ≥ 40 kg),
- region (Europe, North America, rest of world),
- baseline PASI (< 20, ≥ 20)
- baseline sPGA (≤ 3, 4)
- baseline BSA (< 20, ≥ 20)
- prior biologic Psoriasis therapy (yes, no)
- prior systemic Psoriasis therapy (yes, no)
- ADA (positive, negative)
- nAb (positive, negative)
- Analyses within subgroups will be conducted providing descriptive statistics and 95% CI as described above.

In Part 3 and Part 4 subgroup analyses by baseline weight category (< 40 kg, ≥ 40 kg) of the co-primary efficacy endpoints using the primary approach for imputation of missing data were performed.

5.3.2.3.3. Secondary objectives

The secondary efficacy objectives were to assess the rate of subjects who achieved the ranked secondary endpoints. There were no statistical hypotheses corresponding to the secondary efficacy objectives as efficacy was assessed descriptively, providing estimates with confidence intervals without performing statistical testing.

Ranked Secondary Endpoints

- Achievement of PASI 90 (defined as at least 90% improvement from baseline in PASI) at Week 16 of initial treatment
- Achievement of PASI 100 (defined as 100% improvement from baseline in PASI) at Week 16 of initial treatment

- Achievement of sPGA clear or almost clear (0 or 1) (US only: and ≥ 2 grade improvement from baseline) at Week 0 and Week 16 of the re-treatment phase in Part 2

Non-ranked Secondary Efficacy Endpoints

- Achievement of PASI 50 (defined as at least 50% improvement from baseline in PASI) at Week 16 of initial treatment
- Achievement of PASI 50 (defined as at least 50% improvement from baseline in PASI) at Week 0 and Week 16 of the re-treatment phase in Part 2
- Achievement of PASI 90 (defined as at least 90% improvement from baseline in PASI) at Week 0 and Week 16 of the re-treatment phase in Part 2
- Achievement of PASI 100 (defined as 100% improvement from baseline in PASI) at Week 0 and Week 16 of the re-treatment phase in Part 2
- Achievement of a PASI 75 (defined as at least 75% improvement from baseline in PASI) at Week 0 and Week 16 of the re-treatment phase in Part 2
- Change in Children's Dermatology Life Quality Index (CDLQI) from Week 0 to Week 16 of initial treatment in Part 2
- Change in CDLQI from Week 0 to Week 16 of re-treatment phase of Part 2
- Change in Family Dermatology Life Quality Index (FDLQI) from Week 0 to Week 16 of initial treatment in Part 2
- Change in FDLQI from Week 0 to Week 16 of re-treatment phase of Part 2
- Change in Itch Numerical Rating Scale (Itch NRS) from Week 0 to Week 16 of initial treatment in Part 2
- Change in Itch NRS from Week 0 to Week 16 of re-treatment phase in Part 2
- Achievement of ≥ 4-point improvement from baseline in the Itch Numerical Rating Scale (in patients with Baseline score ≥ 4) at Week 16 of initial treatment in Part 2.

Other Endpoints

- Achievement of PASI 75 at Week 12 during the treatment or withdrawal period of Part 2.
- Achievement of sPGA clear or almost clear (0 or 1) at Week 12 during the treatment or withdrawal period of Part 2.
- Achievement of PASI 50/75/90/100 at all other visits collected.
- Achievement of sPGA clear (0) at all other visits collected.
- Achievement of sPGA clear or almost clear (0 or 1) at all other visits collected.
- Change in Itch Numerical Rating Scale (Itch NRS) at each study visit from Week 0.
- Achievement of ≥ 4-point improvement from baseline in the Itch Numerical Rating Scale (in patients with baseline score ≥ 4) at each study visit in Part 2.
- Change in CDLQI at each study visit from Week 0.
- Change in FDLQI at each study visit from Week 0.

5.3.2.3.4. Estimands for the secondary objectives

Table *18*: Estimands for ranked secondary objectives

Population	**Paediatric patients with PsO**
Treatment conditions	Part 1, 3, 4: Assignment to risankizumab without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population Part 2: Assignment to risankizumab compared to assignment to ustekinumab, without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population.
Endpoint (variable)	PASI90/100 at week 16 of initial treatment
Population-level summary	Part 1, 3 and 4: Percentage of subjects achieving PASI90/100 at week 16 in the risankizumab group Part 2: Difference in the percentage of subjects achieving PASI90/100 at week 16 in the risankizumab group in comparison with the ustekinumab group
Intercurrent events and strategy to handle them	
ICE 1 - use of rescue medication	Composite policy
ICE 2 - prematurely discontinue study drug	Treatment policy

Table *19*: Estimands for ranked secondary objectives

Population	**Paediatric patients with PsO**
Treatment condition	Assignment to risankizumab without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population
Endpoint (variable)	sPGA clear or almost clear (0 or 1) at week 0 of the retreatment phase in Part 2 sPGA clear or almost clear (0 or 1) at week 16 of the retreatment phase in Part 2
Population-level summary	Percentage of subjects achieving sPGA 0/1 at week 0/16 in the risankizumab group
Intercurrent events and strategy to handle them	
ICE 1 - use of rescue medication	Composite policy
ICE 2 - prematurely discontinue study drug	Treatment policy

Statistical methods for estimation and sensitivity analysis on the secondary estimands

Part 2:

The ranked secondary endpoints of difference in the percentage of subjects achieving PASI 90/100 from Baseline at Week 16 of initial treatment with risankizumab compared to ustekinumab were analysed in the same manner as the co-primary endpoints for Part 2.

The ranked secondary endpoint and sPGA clear or almost clear (0 or 1) at Week 0 and Week 16 of the re-treatment phase was analysed in the same manner as the co-primary endpoints from Part 1, 3, and 4.

Part 1, Part 3, and Part 4:

The ranked secondary endpoints of difference in the percentage of subjects achieving PASI 90/100 at Week 16 of initial treatment were analysed in the same manner as the co-primary endpoints in Part 1, 3, and 4.

For non-ranked secondary endpoints, descriptive statistics including counts and proportions for categorical data, and median, mean, standard deviation, first and third quartiles, and minimum/maximum for continuous data were provided. For continuous endpoints, CIs for means and differences between means, respectively, were based on the Normal distribution. For dichotomous endpoints, exact CIs were provided based on the Clopper-Pearson method for proportions. The Miettinen-Nurminen method for differences in proportions was used in Part 2 for comparing response rate differences between risankizumab and ustekinumab arms.

5.3.2.4. Results

5.3.2.4.1. Participant flow and numbers analysed

First Subject First Visit: 28 July 2020; Last Subject Last Visit: 15 October 2024

A total of 139 subjects were enrolled (12 subjects in Part 1, 82 subjects in Part 2, 13 subjects in Part 3, and 30 subjects (aged 6 to < 12 years) plus 2 adolescent subjects from Japan in Part 4 from 41 sites across 7 countries (Canada, Germany, Japan, Poland, Spain, the United Kingdom, and the US).

54 patients were randomised to risankizumab for period A of Part 2, of these, 1 patient discontinued, 10 patients were non-responders and continued treatment with risankizumab for period B, while 43 patients were responders and re-randomised 1:1 to either continue treatment with risankizumab (n=22) or withdrawal of treatment (n=21) for part B.

28 patients were randomised to ustekinumab for period A of Part 2 and then switched to risankizumab for period B.

In Part 1 and Part 3, no subjects discontinued study drug. In Part 2, 1 subject discontinued study drug during Period A; the primary reason was listed as lost to follow-up. In Part 4, 3 subjects discontinued study drug due to withdrawal of consent, loss to follow-up, and "other reasons," respectively.

In Part 2, of the 21 subjects randomised to withdrawal at the end of the active comparator-controlled Period A, 8 received retreatment after a reported disease flare. For one of the 8 subjects, a flare was reported based on a blinded assessor calculation of sPGA 3 in error at an unscheduled visit and the subject was enrolled in Period C and received risankizumab on the day of the unscheduled visit. This was documented as a protocol deviation noted as "subject received wrong treatment or incorrect dose" because the subject entered retreatment in error despite never experiencing a flare. The safety, physical, or mental integrity of the subject was not affected. Because the subject was incorrectly entered in Period C and did not flare (sPGA = 1), the subject did not receive additional retreatment after the initial incorrect retreatment dose.

5.3.2.4.2. Deviations from study plan

The original protocol (Version 1.0, 18 March 2020, 11 subjects) had 5 global versions, 1 country-specific version (Version 3.1 Japan only), and 2 administrative changes. The versions and number of subjects enrolled under each version were as follows:

- Version 2.0 (06 January 2021, 1 subject)
- Version 3.0 (27 May 2021, 95 subjects); Version 3.1 (Japan only) (25 June 2021, 3 subjects)
- Administrative Change 1 (24 June 2021)
- Version 4.0 (02 February 2023, 27 subjects)
- Administrative Change 2 (23 February 2023)
- Version 5.0 (16 October 2023)

The protocol changes described in the amendments and administrative changes did not affect the interpretation of study results.

Protocol deviations

Protocol deviations were defined in accordance with the ICH guidelines and included but were not limited to: inclusion/exclusion criteria violation (2 subjects [16.7%] in Part 1, 1 subject [1.2%] in Part 2 and 1 subject [3.3%] in Part 4), receipt of wrong treatment or incorrect dose of study drug (1 subject [1.2%] in Part 2), and use of prohibited concomitant medications (2 subjects [2.4%] in Part 2, 1 subject [7.7%] in Part 3, and 2 subjects [6.7%] in Part 4). The subject who received wrong treatment entered the retreatment period in Part 2 in error.

Deviations were assessed for their impact on analyses and data integrity or subject safety. Reported protocol deviations did not have an impact on analysis and data integrity. None of the deviations were considered to have affected the study outcome or interpretation of the study results or conclusions.

Measurements of Treatment Compliance

Mean treatment compliance for subjects in Part 1 and Part 3 was 100%. Mean treatment compliance for subjects in Part 2 Period A, Period B, and Period C was 100%, 98.8% - 100%, and 93.8%, respectively, and 99.3% in Part 4.

5.3.2.4.3. Baseline data

Demographics

In Part 1, Part 2, Part 3, and Part 4, over a third of the subjects were male. Most subjects were white and not Hispanic or Latino, with a mean (SD) age of 14.7 (1.67) years and 9.1 (1.72) years for Parts 1 and 2 combined and Parts 3 and 4 combined, respectively. Regarding weight, n=3 (3.2%) and n=29 (67.4%) of patients weighed < 40kg in parts 1 and 2 combined and parts 3 and 4 combined. Demographic characteristics were generally balanced between ustekinumab and risankizumab arms in Part 2.

Baseline Characteristics Description

Disease History for Parts 1, 2, 3, and 4 is provided in **Table 20**.

Table *20*: Disease History for Parts 1, 2, 3, and 4 (ITT Population)

	12 to < 18 Years				6 to < 12 Years	
	Part 1 Severe	Part 2 Moderate to Severe			Part 3 Severe	Part 4 Moderate to Severe
Characteristic	RZB (N = 12)	UST (N = 28)	RZB (N = 54)	Total (N = 82)	RZB (N = 13)	RZB (N = 30)
History of PsA - n (%)						
Yes	0	0	0	0	1 (7.7)	0
No	12 (100)	28 (100)	54 (100)	82 (100)	12 (92.3)	30 (100)
Duration of Plaque PsO (in Years)						
n	12	28	54	82	13	30
Mean (SD)	6.62 (3.135)	5.20 (3.236)	5.98 (3.666)	5.72 (3.525)	3.39 (2.083)	3.62 (2.355)
Median	7.19	4.30	5.37	5.15	3.22	3.62
Min, Max	1.1, 11.8	0.5, 11.0	0.7, 16.5	0.5, 16.5	0.7, 7.4	0.6, 9.5
Prior Biologic PsO Therapy - n (%)						
Yes	0	1 (3.6)	2 (3.7)	3 (3.7)	0	1 (3.3)
No	12 (100)	27 (96.4)	52 (96.3)	79 (96.3)	13 (100)	29 (96.7)
Prior Systemic PsO Therapy - n (%)						
Yes	0	4 (14.3)	16 (29.6)	20 (24.4)	4 (30.8)	6 (20.0)
No	12 (100)	24 (85.7)	38 (70.4)	62 (75.6)	9 (69.2)	24 (80.0)
PASI						
n	12	28	54	82	13	30
Mean (SD)	21.43 (8.124)	16.55 (7.229)	16.39 (4.909)	16.45 (5.761)	26.21 (9.158)	18.59 (9.211)
Median	20.20	14.70	16.00	15.70	23.40	14.70
Min, Max	13.1, 38.0	7.7, 44.8	6.1, 33.9	6.1, 44.8	17.0, 45.1	8.9, 39.3
BSA						
n	12	28	54	82	13	30
Mean (SD)	21.92 (17.101)	22.44 (15.158)	22.56 (14.546)	22.52 (14.664)	32.15 (18.443)	27.27 (22.069)
Median	16.00	17.50	18.00	18.00	24.00	14.50
Min, Max	13.0, 75.0	10.0, 62.0	10.0, 75.0	10.0, 75.0	10.0, 66.0	10.0, 70.0
sPGA categories - n (%)						
0	0	0	0	0	0	0
1	0	0	0	0	0	0
2	0	2 (7.1)	6 (11.1)	8 (9.8)	0	3 (10.0)
3	0	25 (89.3)	42 (77.8)	67 (81.7)	2 (15.4)	23 (76.7)
4	12 (100)	1 (3.6)	6 (11.1)	7 (8.5)	11 (84.6)	4 (13.3)

CDLQI						
n	NA	27	52	79	NA	NA
Mean (SD)	NA	9.6 (8.04)	10.4 (6.55)	10.1 (7.05)	NA	NA
Median	NA	7.0	9.0	9.0	NA	NA
Min, Max	NA	0, 29	1, 25	0, 29	NA	NA
FDLQI						
n	NA	25	51	76	NA	NA
Mean (SD)	NA	10.3 (6.75)	10.5 (5.80)	10.4 (6.09)	NA	NA
Median	NA	10.0	10.0	10.0	NA	NA
Min, Max	NA	0, 25	0, 26	0, 26	NA	NA
Itch NRS (Continuous)						
n		27	49	76	NA	NA
Mean (SD)	NA	4.7 (3.06)	5.9 (2.91)	5.5 (3.00)	NA	NA
Median	NA	4.0	7.0	6.0	NA	NA
Min, Max	NA	0, 10	0, 10	0, 10	NA	NA
Itch NRS- n (%)						
< 4	NA	13 (48.1)	12 (24.5)	25 (32.9)	NA	NA
≥ 4	NA	14 (51.9)	37 (75.5)	51 (67.1)	NA	NA
Missing	NA	1	5	6	NA	NA

Note: Percentages calculated on nonmissing values.

Prior and Concomitant Medications

In Part 1, Part 2, Part 3, and Part 4 Populations, use of concomitant plaque PsO-related medication (as captured at Baseline) was reported by 58.3%, 72.0%, 76.9%, and 80.0% of subjects, respectively. The most frequently (≥ 15% of subjects) reported concomitant medications were ibuprofen, paracetamol, and vitamins.

Any systemic (oral or parenteral) medication used specifically for the treatment of PsO was considered a rescue medication. Hydroxyzine hydrochloride was the only rescue medication used in Part 2, no other rescue medication was used in Part 1, Part 3, or Part 4.

Extent of Exposure

The mean (SD) duration of study drug exposure was comparable in Parts 1, 3, and 4 with 364.0 (4.20), 363.0 (3.63), and 351.9 (53.07) days, respectively. The mean duration of study drug exposure in Part 2 was comparatively shorter for both ustekinumab and risankizumab with 255.0 (9.50) and 278.1 (111.88) days, respectively.

Switch from 55 mg to 150 mg Risankizumab

Out of the total 32 subjects starting the study on 55 mg risankizumab, 30 subjects did not switch to 150 mg and 2 subjects switched to 150 mg of whom 1 subject remained on 150 mg at last study drug administration and the other subject switched back to 55 mg at last study drug administration due to the variation in weight from 40.5 kg to 39.0 kg.

5.3.2.4.4. Outcomes and estimation

Summary of efficacy results following 16 weeks of initial treatment in Part 2 is presented in **Table 21** and in Part 1, Part 3, and Part 4 are presented in **Table 22**.

Table *21*: Efficacy Following 16 Weeks of Initial Treatment: Co-Primary and Ranked Secondary Endpoints – Study M19-977 Part 2, Period A (NRI, ITT Population)

Assessment	Treatment	N	Within Group Point Estimate [95% CI][a]	Between Group Treatment Difference Point Estimate [95% CI][b]
Co-Primary Endpoints				
PASI 75 (%)	UST	28	85.7 [67.3, 96.0]	
	RZB	54	85.2 [72.9, 93.4]	-0.5 [-15.6, 18.4]
sPGA clear or almost clear (0 or 1) (%) (OUS)	UST	28	75.0 [55.1, 89.3]	
	RZB	54	79.6 [66.5, 89.4]	4.6 [-13.4, 25.4]
Ranked Secondary Endpoints				
PASI 90 (%)	UST	28	60.7 [40.6, 78.5]	
	RZB	54	64.8 [50.6, 77.3]	4.1 [-17.0, 26.2]
PASI 100 (%)	UST	28	17.9 [6.1, 36.9]	
	RZB	54	40.7 [27.6, 55.0]	22.9 [1.4, 40.5]

a. Exact Clopper-Pearson CI for proportions.

b. CI for difference in proportions by Miettinen-Nurminen.

Note: The NRI analysis will categorize any subject who does not have evaluation during a specific post-baseline visit window as a nonresponder for that visit. Values after the start of rescue medication are excluded from analysis and subjects are considered nonresponders at all time points after the start of rescue medication.

Table *22*: Efficacy Following 16 Weeks of Initial Treatment with Risankizumab: Co-Primary and Ranked Secondary Endpoints – Study M19-977 Part 1, Part 3, and Part 4 (NRI, ITT Population)

	Part 1 – Adolescents Severe Disease (N = 12)	Part 3 – Children Severe Disease (N = 13)	Part 4 – Children Moderate to Severe Disease (N = 30)
Assessment	Within Group Point Estimate [95% CI][a]	Within Group Point Estimate [95% CI][a]	Within Group Point Estimate [95% CI][a]
Co-Primary Endpoints			
PASI 75 (%)	83.3 [51.6, 97.9]	92.3 [64.0, 99.8]	86.7 [69.3, 96.2]
sPGA clear or almost clear (0 or 1) (%) (OUS)	83.3 [51.6, 97.9]	84.6 [54.6, 98.1]	90.0 [73.5, 97.9]
Ranked Secondary Endpoints			
PASI 90 (%)	83.3 [51.6, 97.9]	84.6 [54.6, 98.1]	76.7 [57.7, 90.1]
PASI 100 (%)	41.7 [15.2, 72.3]	53.8 [25.1, 80.8]	43.3 [25.5, 62.6]

a. Exact Clopper-Pearson CI for proportions.

Note: The NRI analysis will categorize any subject who does not have evaluation during a specific post-baseline visit window as a nonresponder for that visit. Values after the start of rescue medication are excluded from analysis and subjects are considered nonresponders at all time points after the start of rescue medication.

Non-ranked secondary endpoints

The non-ranked secondary endpoint of PASI 50 at Week 16 demonstrated similarly high rates of improvement for both the risankizumab and ustekinumab arms.

Results for the QoL-related non-ranked secondary endpoints (change in CDLQI, change in FDLQI, and change in Itch NRS from Baseline to Week 16) are provided in **Table 23**.

Table *23*: Efficacy Following 16 Weeks of Initial Treatment in Part 2 Period A: Selected Non-Ranked Secondary Endpoints (ITT Population)

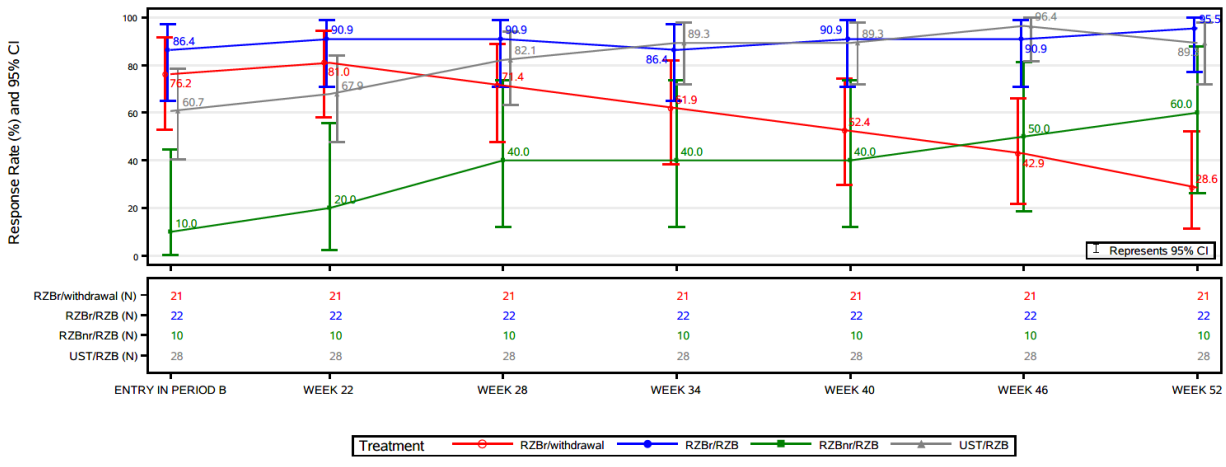
Selected Non-Ranked Secondary Endpoints	Treatment	N	Within Group Change from Baseline LS Mean[c] (95% CI)
Change in Itch NRS from Week 0 to Week 16 (LOCF)	UST	27	-2.9 (-3.89, -1.90)
	RZB	45	-3.8 (-4.52, -2.99)
Change in CDLQI from Week 0 to Week 16 (LOCF)	UST	27	-6.8 (-8.11, -5.48)
	RZB	49	-7.4 (-8.37, -6.42)
Change in FDLQI from Week 0 to Week 16 LOCF)	UST	24	-6.0 (-7.70, -4.33)
	RZB	48	-6.9 (-8.08, -5.70)
			Responder (95% CI)[a]
≥ 4-point improvement from Baseline in Itch NRS at Week 16 (NRI) (%)	UST	14	57.1 (28.9, 82.3)
	RZB	37	64.9 (47.5, 79.8)

Other Endpoints:

During the active-controlled portion of Study M19-977, 40.7% [95% CI 27.6, 55.0] of risankizumab-treated subjects achieved an sPGA of clear (0) following 16 weeks of treatment compared to 17.9% [95% CI 6.1, 36.9] of ustekinumab-treated subjects. In part 4, 43.3% [95% CI 25.5, 62.6] of the subjects achieved an sPGA of clear (0). Similar results were obtained in parts 1 and 3, 41.7% [15.2, 72.3] and 53.8% [25.1, 80.8] respectively.

Efficacy through Week 52

PASI 90, PASI 75 and sPGA 0/1 Response Rates for Part 2, Study Period B are provided in Figure 9, Figure 10, Figure 11, respectively.

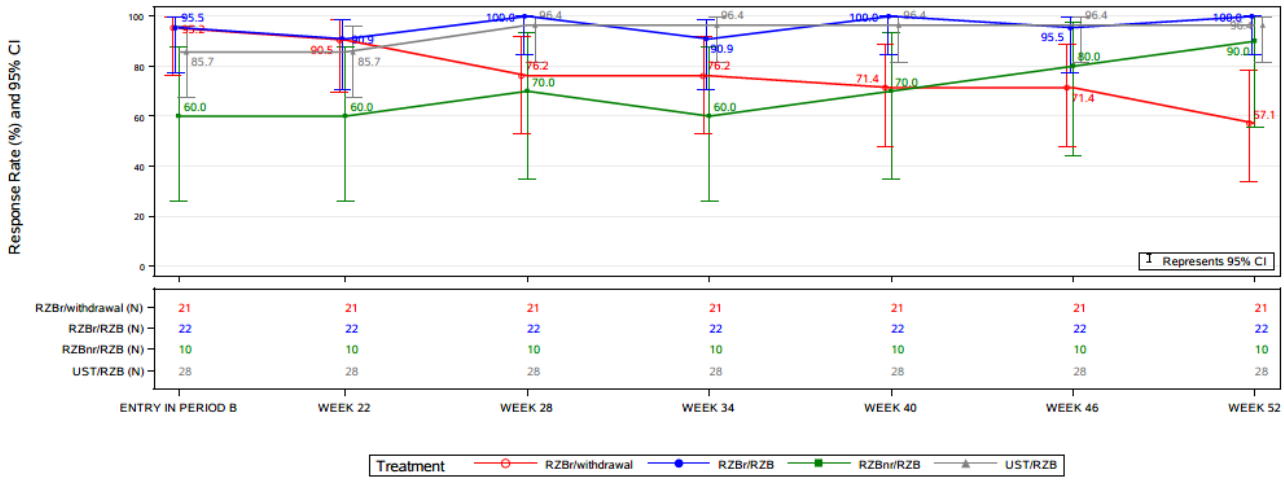


Notes: RZBr/withdrawal = RZB responder randomised to drug withdrawal; RZBr/RZB = RZB responder randomised to risankizumab; RZBnr/RZB = RZB non-responder receiving risankizumab; UST/RZB = UST subjects receiving risankizumab.

The NRI analysis will categorize any subject who does not have evaluation during a specific post-baseline visit window as a nonresponder for that visit. Values after the start of rescue medication are excluded from analysis and subjects are considered nonresponders at all time points after the start of rescue medication.

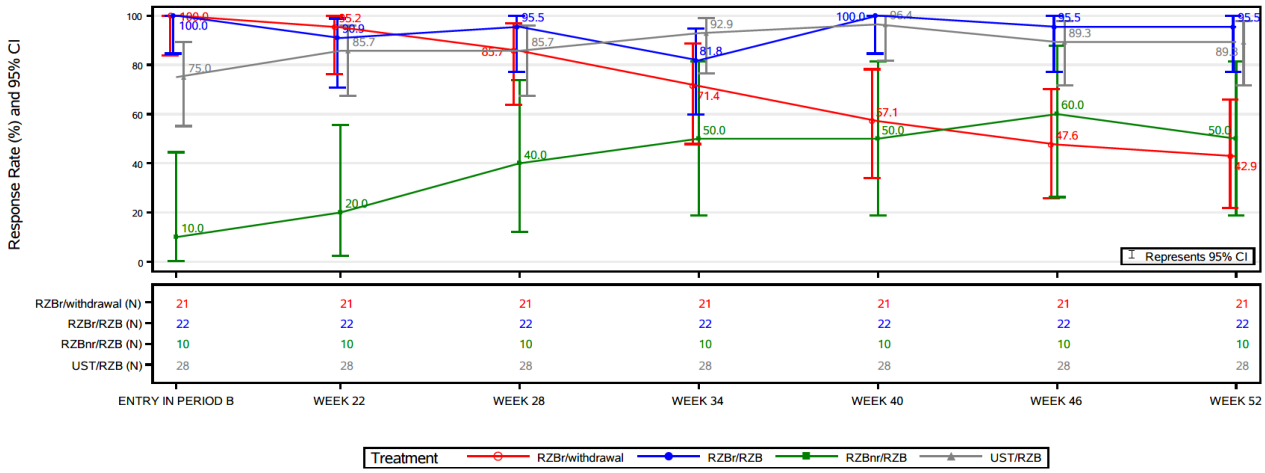
Exact Clopper-Pearson CI for proportions.

Figure 9: PASI 90 Response Rate (NRI) and 95% CI by Visit: Part 2, Study Period B (ITT Population)



Note: The NRI analysis will categorize any subject who does not have evaluation during a specific postbaseline visit window as a nonresponder for that visit. Values after the start of rescue medication are excluded from analysis and subjects are considered nonresponders at all time points after the start of rescue medication.
Exact Clopper-Pearson CI for proportions.

Figure *10*: PASI 75 Response Rate (NRI) and 95% CI by Visit for Part 2 (12 to < 18 Years, Moderate to Severe Disease) Study Period B (ITT Population)



Note: The NRI analysis will categorize any subject who does not have evaluation during a specific postbaseline visit window as a nonresponder for that visit. Values after the start of rescue medication are excluded from analysis and subjects are considered nonresponders at all time points after the start of rescue medication.
Exact Clopper-Pearson CI for proportions.

Figure 11. sPGA Score of Clear or Almost Clear Response Rate (NRI) and 95% CI by Visit for Part 2 (12 to < 18 Years, Moderate to Severe Disease) Study Period B (ITT Population)

In Part 2 Period C, subjects who experienced a symptom flare and entered retreatment regained skin clearance with return to risankizumab treatment as demonstrated by sPGA clear or almost clear after 16 weeks of retreatment. High rates of PASI 75/90 were also observed for these same subjects after 16 weeks of retreatment. For those subjects who experienced a symptom flare and entered retreatment the QoL-related endpoints (change in CDLQI, change in FDLQI and change in Itch NRS from Baseline to Week 16) demonstrated similar outcomes after retreatment.

High rates in PASI 90/100 were observed at Week 16 for subjects in Part 3 and Part 4.

For parts 1, 3 and 4, efficacy results were generally maintained from week 16 to week 52.

5.3.2.4.5. Pre-defined and post hoc important subgroup analyses

Subgroup analyses

Due to the small sample sizes and the uncontrolled design in Part 1, no efficacy subgroup analyses were performed.

In Part 2, efficacy subgroup analyses were performed to evaluate the consistency of risankizumab efficacy for categories of demographic and other baseline characteristics for the co-primary efficacy endpoints using the primary approach for imputation of missing data.

In Part 3 and Part 4 subgroup analyses by baseline weight category (< 40 kg, ≥ 40 kg) of the co-primary efficacy endpoints using the primary approach for imputation of missing data were performed. Due to the small sample sizes and the uncontrolled design of Part 3 and Part 4, no other efficacy subgroup analyses were performed.

Results from subgroup analyses (age group: 12 to <15 yrs, 15 to <18 yrs; sex: male, female; race: white, nonwhite; weight group: <40kg, ≥40kg; region: Europe, North America, Rest of the world; baseline PASI: <20, ≥20; baseline sPGA: ≤3, 4; prior biologic psoriasis therapy: yes, no; prior systemic psoriasis therapy: yes, no) for the co-primary endpoints (Part 2) of proportion of subjects achieving PASI 75, sPGA score of clear or almost clear, and sPGA score of clear or almost clear with a ≥ 2 grade improvement from Baseline (NRI) at Week 16 in the Initial Treatment Period (A), Part 2 were consistent with the results from the overall population. The efficacy of risankizumab by baseline weight group (< 40 kg, ≥ 40 kg) of the co-primary efficacy endpoints was consistent in Part 2, Part 3, and Part 4.

Upon request from the CHMP, the MAH presented PASI 75 and sPGA 0/1 results at week 16 by weight bands of <40 kg or ≥40kg for all patients combined in the studies (regardless of disease severity or age). The percentage of patients that achieved PASI 75 at week 16 was 87.1% [95% CI 70.2, 96.4] and 85.9% [95% CI 76.2, 92.7] in patients <40 kg or ≥40kg, respectively. The percentage of patients that achieved sPGA 0/1 at week 16 was 90.3% [95% CI 74.2, 98.0] and 80.8% [95% CI 70.3, 88.8] in patients <40 kg or ≥40kg, respectively.

Effect of immunogenicity on risankizumab efficacy

Table *24*: Risankizumab Efficacy by Treatment-Emergent ADA and NAb Status at Week 16 from M19-977

	Response to the Primary Clinical Endpoint at Week 16, n (%)			
	ADA Positive (N = 11)	ADA Negative (N = 42)	NAb Positive (N = 0)	NAb Negative (N = 53)
PASI 75	11 (100%)	35 (83.3%)	--	46 (86.8%)
sPGA	10 (90.9%)	33 (78.6%)	--	43 (81.1%)
sPGA and ≥ 2 grade improvement from baseline	8 (72.7%)	29 (69.0%)	--	37 (69.8%)

5.3.3. Main studies - Study #2 (M19-973)

5.3.3.1. Study title

OptIMMize-2: a phase 3 multicenter, single-arm, OLE study to assess the safety, tolerability, and efficacy of risankizumab in subjects with moderate to severe plaque psoriasis who have completed participation in Study M19-977 (OptIMMize-1)

5.3.3.2. Study design

Study M19-973 is an ongoing Phase 3, multicenter, single-arm, OLE study designed to investigate the long-term safety, tolerability, and efficacy of risankizumab 55 mg or 150 mg by weight (for subjects ≥ 40 kg the risankizumab dose is 150 mg and for subjects < 40 kg the risankizumab dose is 55 mg) q12w in the treatment of moderate to severe plaque PsO in eligible subjects who completed Study M19-977 and elected to participate in Study M19-973.

This study will have a duration of up to 224 weeks with the last dose of study drug scheduled at Week 204 and last visit at Week 216, and a follow-up phone call for safety approximately 140 days (20 weeks) after the last dose of study drug.

5.3.3.2.1. Treatment

Risankizumab was administered in the study to all subjects. Subjects who weighed ≥ 40 kg received 150 mg risankizumab, while subjects who weighed < 40 kg received 55 mg risankizumab.

Any subject who entered the study weighing < 40 kg was assigned to receive 55 mg risankizumab. During the conduct of the study, any subject initially assigned to the 55 mg dose of risankizumab who had a recorded weight ≥ 40 kg at a dosing visit was switched to the 150 mg risankizumab dose.

Concomitant and rescue therapies

Concomitant and rescue therapies were the same as per Study #1 M19-977, but without the specified timeline prior to baseline visit.

5.3.3.2.2. Patient population

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

1. Subjects or their legally authorized representative must voluntarily sign and date an informed consent (and assent for minors as required by applicable regulation) approved by an IEC/IRB, prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

2. Subject is judged to be in good health, as determined by the Investigator based on the results of medical history, physical examination, and laboratory testing.

3. Subject is willing and able to comply with procedures required in this protocol and is not an employee of the sponsor and/or study site or a family member of an employee.

Disease/Condition Activity

4. Subjects with a history of moderate to severe plaque psoriasis who have completed participation in Study M19-977 and have not developed any discontinuation criteria as defined in that study.

5. Subjects must be candidates for prolonged risankizumab treatment according to investigator judgment.

Subject History

6. Subject must not have a history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months.

7. Subjects must not have evidence of:

- HIV, HBV, or HCV infection from laboratory testing within the preceding clinical study or any other source.
- Active TB. If presence of latent TB is established, treatment should have been initiated and maintained according to local guidelines.
- Active systemic infection/Clinically important infection during the last 2 weeks prior to Baseline Visit as assessed by the investigator.

8. Subject must not have any of the following medical diseases or disorders:

- Recent (within past 6 months) cerebrovascular accident or myocardial infarction;
- History of an organ transplant which requires continued immunosuppression;
- Active or suspected malignancy during the preceding study, except for successfully treated non-melanoma skin cancer or localized carcinoma *in situ* of the cervix.

9. Subject must not have concurrent clinically significant medical conditions other than the indication being studied or any other reason that the investigator determines would interfere with the subject's participation in this study, would make the subject an unsuitable candidate to receive study drug, or would put the subject at risk by participating in the study.

Contraception

10. For all females of child-bearing potential; a negative urine pregnancy test at Baseline prior to the first dose of study drug is required.

11. Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control, that is effective from Baseline Week 0 through at least 140 days (20 weeks or as guided by the risankizumab label [if approved], whichever is longer) after the last dose of study drug (local practices may require 2 methods of birth control). Female subjects of non-childbearing potential do not need to use birth control.

12. Female subjects may not be pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 140 days (20 weeks or as guided by the local risankizumab label [if approved], whichever is longer) after the last dose of study drug.

Concomitant Medications

13. Subject must not have received any live viral or bacterial vaccine within 4 weeks prior to the first dose of study drug, or expect the need for live vaccination during study participation including at least 140 days (20 weeks or as guided by the local risankizumab label [if approved], whichever is longer) after the last dose of study drug.

14. Subject must not have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of the study drug or is currently enrolled in another clinical study or was previously enrolled in this study.

5.3.3.3. Objectives and estimands

5.3.3.3.1. Objective

The objective of this study is to assess the long-term safety, tolerability, and efficacy of risankizumab in subjects with moderate to severe plaque PsO who had completed participation in the preceding study (Study M19-977).

There was no primary efficacy objective since this was the extension to the preceding Study M19-977 and the efficacy objective was to descriptively assess long term efficacy across a range of different efficacy endpoints.

There were no hypotheses corresponding to the efficacy objectives as efficacy was to be assessed descriptively, without performing comparisons or statistical testing.

5.3.3.3.2. Estimands for the objectives

Table *25*: Estimands for the objective 1

Population	Paediatric patients with PsO
Treatment conditions	Assignment to risankizumab without the use of rescue medication and regardless of premature discontinuation of study drug
Endpoint (variable)	PASI 50/75/90/100 at each study visit
Population-level summary	Percentage of subjects achieving PASI 50/75/90/100 at each study visit
Intercurrent events and strategy to handle them	
ICE 1 - use of rescue medication	Composite policy
ICE 2 - prematurely discontinue study drug	Treatment policy

Table *26*: Estimands for objective 2

Population	Paediatric patients with PsO
Treatment conditions	Assignment to risankizumab without the use of rescue medication and regardless of premature discontinuation of study drug
Endpoint (variable)	sPGA 0, 0/1, 0/1 and ≥ 2 grade improvement from baseline at each study visit
Population-level summary	Percentage of subjects achieving either sPGA 0; sPGA 0 or 1; or achieving sPGA 0 or 1 and ≥ 2 grade improvement from baseline at each study visit in the risankizumab group
Intercurrent events and strategy to handle them	
ICE 1 - use of rescue medication	Composite policy
ICE 2 - prematurely discontinue study drug	Treatment policy

Statistical methods for estimation and sensitivity analysis on estimands

Planned analyses

Analysis sets

Full analysis set (FAS): includes all subjects who received at least 1 dose of study drug in Study M19-973. The FAS Population is used for all efficacy and baseline analyses.

Safety Analysis Set: consists of all subjects who received at least 1 dose of study drug in Study M19-973.

The FAS and the Safety Analysis Set are identical.

The 2 adolescent subjects from Japan who enrolled into Part 4 of Study M19-977 and continued into Study M19-973 were not included in the FAS and the Safety Analysis Populations because they were not from the same age cohort as the population studied in Part 4 (children) but were added to Part 4 for administrative reasons (closure of Part 2 enrolment). Results for these 2 subjects were included in the full data listings and analysed separately outside of the report.

Main analysis methods / Statistical tests and estimation methods

All efficacy analyses were conducted in the FAS Population and presented overall and by the study part the subject was enrolled in during the preceding Study M19-977, unless otherwise specified. No statistical testing was performed. All confidence intervals were two-sided with 95% confidence level. Descriptive statistics included counts and proportions for categorical data, and median, mean, standard deviation, first and third quartiles, and minimum/maximum for continuous data.

Two-sided 95% CIs were reported. For continuous endpoints, CIs for means were based on the normal distribution. For dichotomous endpoints, exact CIs were provided based on the Clopper-Pearson method.

Intercurrent events handling

Binary Endpoints:

- For subjects with the use of rescue medication, values after the start of rescue medication were excluded from analysis and subjects were considered non-responders at all time points after the start of rescue medication.
- Data collected will be used regardless of premature discontinuation of study drug.

Continuous endpoints:

- Values after the use of rescue medication were excluded.
- Data collected were used regardless of premature discontinuation of study drug.

Missing data handling

Missing data was imputed using the following methods for the efficacy analyses:

LOCF: the LOCF analysis imputed a missing value with the last value observed previously. Baseline (i.e., "M19-973 baseline") observations were not carried forward. LOCF was the primary approach in the analyses of categorical and continuous variables.

AO: The AO analysis did not impute values for missing evaluations, and thus a subject who did not have an evaluation on a scheduled visit was excluded from the AO analysis for that visit. AO included all values collected in the study. AO excluded all values collected in the study after the first dose of rescue medication. AO was used as sensitivity analysis in the analyses of categorical and continuous variables.

Sensitivity and supplementary analyses

For dealing with missing data, AO was used as sensitivity analysis for the analyses of the co-primary endpoints. No supplementary analyses were performed.

Planned subgroup analyses

Subgroup analyses for the following endpoints:

- Achievement of PASI 75 at each study visit

- Achievement of the sPGA score of clear or almost clear (0 or 1) at each study visit

were presented for the following subgroups, using LOCF for imputation of missing data:

- age group (6 to < 12, 12 to < 15, 15 to < 18 years at "M19-977 baseline"),
- sex (male, female),
- race (white, non-white),
- weight group (< 40 kg, ≥ 40 kg at "M19-977 baseline"),
- region (Europe, North America, rest of world),
- baseline PASI (< 20, ≥ 20 at "M19-977 baseline"),
- baseline sPGA (≤ 3, 4 at "M19-977 baseline"),
- baseline BSA (< 20, ≥ 20 at "M19-977 baseline"),
- prior biologic Psoriasis therapy (yes, no at "M19-977 baseline"),
- prior systemic Psoriasis therapy (yes, no at "M19-977 baseline"),
- ADA (positive, negative),
- nAb (positive, negative)

Analyses within subgroups were conducted providing descriptive statistics and 95% CI.

5.3.3.4. Results

5.3.3.4.1. Participant flow and numbers analysed

First Subject First Visit: 24 July 2021; Interim Report, Data Cut-off: 01 January 2025

The study population of Study M19-973 consisted of 129 subjects plus the 2 subjects from Japan. Subjects were enrolled from 40 sites across 7 countries (Canada, Germany, Japan, Poland, Spain, the UK, and the US). All but 1 subject each from Study M19-977 Parts 1 and 3 were enrolled in Study M19-973. All but 2 subjects from Study M19-977 Part 2 were enrolled in Study M19-973 (1 subject discontinued in Study M19-977 and 1 subject completed Study M19-977 but did not enter Study M19-973). Twenty-five subjects (out of 30) from Study M19-977 Part 4 plus 2 adolescent subjects from Japan have been enrolled as of the cut-off date (01 January 2025).

In total, 5 subjects discontinued Study M19-973. Three subjects who were enrolled in Part 2 during the preceding Study M19-977 discontinued due to lost to follow-up, lack of efficacy, and "other reasons." Two subjects who were enrolled in Part 1 during the preceding study discontinued due to withdrawal from treatment by subject and "other reasons".

Measurements of Treatment Compliance

Mean overall compliance in Study M19-973 was 97.3%, 98.9%, 100%, and 100% for subjects enrolled in Part 1, Part 2, Part 3, and Part 4 of the preceding Study M19-977, respectively. Mean total compliance for subjects in Study M19-973 was 99.1%.

5.3.3.4.2. Deviations from study plan

The original protocol (Version 1.0, 26 February 2021, 0 subjects) had 3 global amendments, 1 country-specific amendment, and 2 administrative changes. The versions and number of subjects enrolled under each were as follows:

- Version 2.0 (10 June 2021, 12 subjects)
- Administrative Change 1 (24 June 2021, 0 subjects)
- Version 3.0 (17 February 2022, 0 subjects)
- Administrative Change 2 (21 March 2022, 0 subjects)
- Version 4.0 (12 April 2022, 101 subjects)
- Version 4.1 Spain, Germany, and Poland Only (20 June 2022, 18 subjects)

The changes described in the amendments and administrative changes did not affect the interpretation of study results.

Protocol deviations

Protocol deviations were defined in accordance with the ICH guidelines and included, but were not limited to: inclusion/exclusion criteria violation, receipt of wrong treatment or incorrect dose of study drug (2 subjects who originally enrolled in Study M19-977 Part 3), development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications (1 subject originally enrolled in Study M19-977 Part 2). Deviations were assessed for their impact on analyses and data integrity or subject safety. Reported protocol deviations did not have an impact on analysis and data integrity. None of the deviations were considered to have affected the study outcome or interpretation of the study results or conclusions.

5.3.3.4.3. Baseline data

Demographic characteristics

Demographic characteristics of subjects at Baseline of Study M19-973 were similar to those of subjects at Baseline of Study M19-977. The majority of patients were female, white and with a mean age of 14.1 years overall. 21 (16.3%) of patients weighed < 40kg.

Baseline characteristics

Baseline characteristics of subjects at Baseline of Study M19-973 were similar to those of subjects at Baseline of Study M19-977. Median PASI scores were 0.0. 4% of patients had sPGA-3 (moderate) scores, 0% had sPGA-4 (severe) scores. Median baseline scores were 1.0 (CDLQI), 2.0 (FDLQI) and 0.0 (Itch NRS). In Study M19-973, the most frequently reported (> 5.0% of total subjects) medical conditions in subjects' medical history were obesity, seasonal allergy, attention deficit hyperactivity disorder, acne, and asthma.

Prior and Concomitant Medications

Use of concomitant plaque PsO-related medication (as captured at Study M19-973 Baseline) was reported by 66.7%, 77.5%, 75.0%, and 64.0% of subjects enrolled from Part 1, Part 2, Part 3, and Part 4 of M19-977, respectively. The most frequently (≥ 10.0% of subjects) reported concomitant medications in Study M19-973 were paracetamol (15.5%) and ibuprofen (14.7%). One subject enrolled in Part 2 of the preceding Study M19-977 reported use of rescue medication in Study M19-973.

Extent of Exposure

Mean exposure (SD) for subjects who were previously enrolled in Part 1, Part 2, Part 3, and Part 4 during Study M19-977 was 585.3 (276.13) days (**Table 27**).

Table *27*: Extent of exposure

	Enrolled during M19-977 into:						
Variable	Part 1 (N = 12) n (%)	Part 2 (N = 80) n (%)	Combined Parts 1 & 2 (N = 92) n (%)	Part 3 (N = 12) n (%)	Part 4 (N = 25) n (%)	Combined Parts 3 & 4 (N = 37) n (%)	Total (N = 129) n (%)
Duration (day)							
n	12	80	92	12	25	37	129
Mean (SD)	1138.7 (147.97)	621.3 (110.48)	688.8 (209.62)	679.3 (87.14)	159.6 (48.57)	328.1 (254.39)	585.3 (276.13)
Median	1194.0	630.0	664.5	643.5	150.0	205.0	616.0
Min, Max	757, 1258	243, 819	243, 1258	580, 826	80, 247	80, 826	80, 1258

Notes: Duration of treatment = min (Last dose date + 84, cut-off date + 1) - First dose date.

Switch from 55 mg to 150 mg Risankizumab

A summary of subjects who started at 55 mg risankizumab in Study M19-977 and switched from 55 mg to 150 mg risankizumab in Study M19-973 is presented in **Table 28**.

Table *28*: Percentage of subjects who switched from 55 mg Risankizumab to 150 mg Risankizumab in Study M19-973 out of subjects who started on 55 mg Risankizumab in Study M19-977

	Started on Risankizumab 55 mg and Enrolled During Study M19-977 into:				
Category	Part 1 (N = 0) n (%)	Part 2 (N = 3) n (%)	Part 3 (N = 5) n (%)	Part 4 (N = 19) n (%)	Total (N = 27) n (%)
Subjects who started in Study M19-973 on 55 mg	0	2 (66.7)	2 (40.0)	16 (84.2)	20 (74.1)
Subjects who did not switch to 150 mg in Study M19-973	0	1 (33.3)	0	15 (78.9)	16 (59.3)
Subjects who switched to 150 mg in Study M19-973	0	2 (66.7)	5 (100)	4 (21.1)	11 (40.7)
Subjects who switched to 150 mg in Study M19-973 and were on 150 mg at last study drug administration	0	2 (66.7)	4 (80.0)	4 (21.1)	10 (37.0)

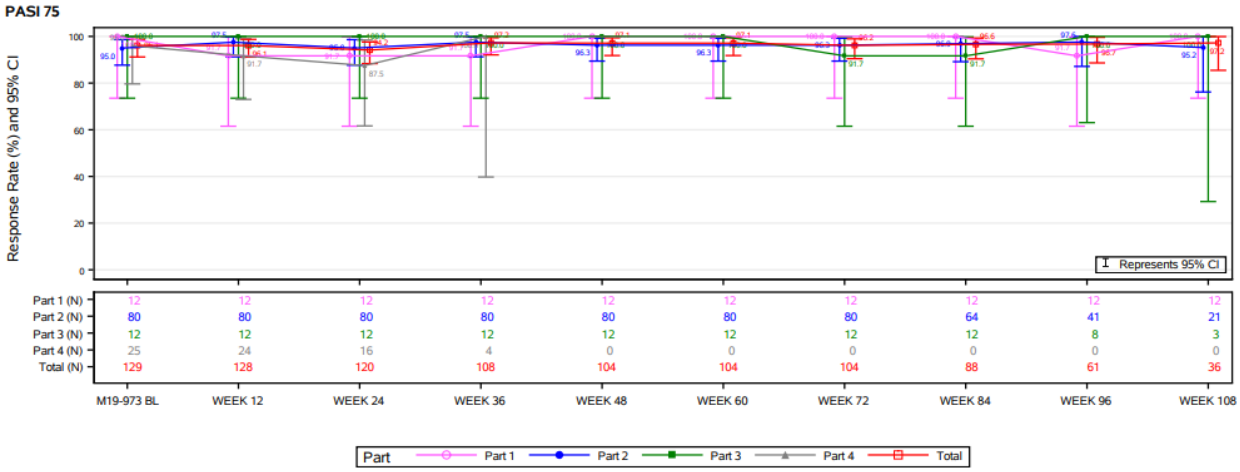
5.3.3.4.4. Outcomes and estimation

There were no primary or secondary efficacy endpoints since this is a single-arm, OLE study providing continued therapy to subjects who completed participation in the preceding Study M19-977.

Efficacy response rates in Study M19-973 as measured by PASI/75/90/100 and sPGA clear or almost clear and sPGA clear or almost clear with ≥ 2-grade improvement from Baseline were generally maintained over the study period up to Week 168 (N=14).

Data up to Week *108 are provided in Figure 12, Figure 13, Figure 14 and Figure 15. Data* beyond Week 108 are not shown due to the small number of observations to improve readability of the figures.

A total of 3.9% of patients discontinued the study during the OLE while the majority of patients had not reached the week 108 timepoint at the time of analysis (82.9%).

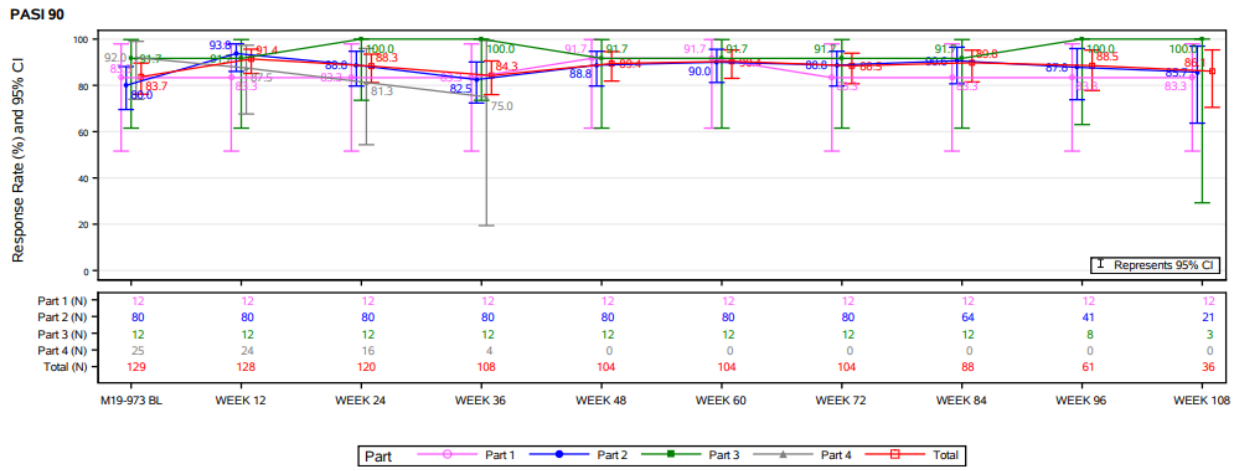


Notes: Study parts of the preceding Study M19-977.

Exact Clopper-Pearson CI for proportions.

Data beyond Week 108 are not shown due to the small number of observations to improve readability of figure.

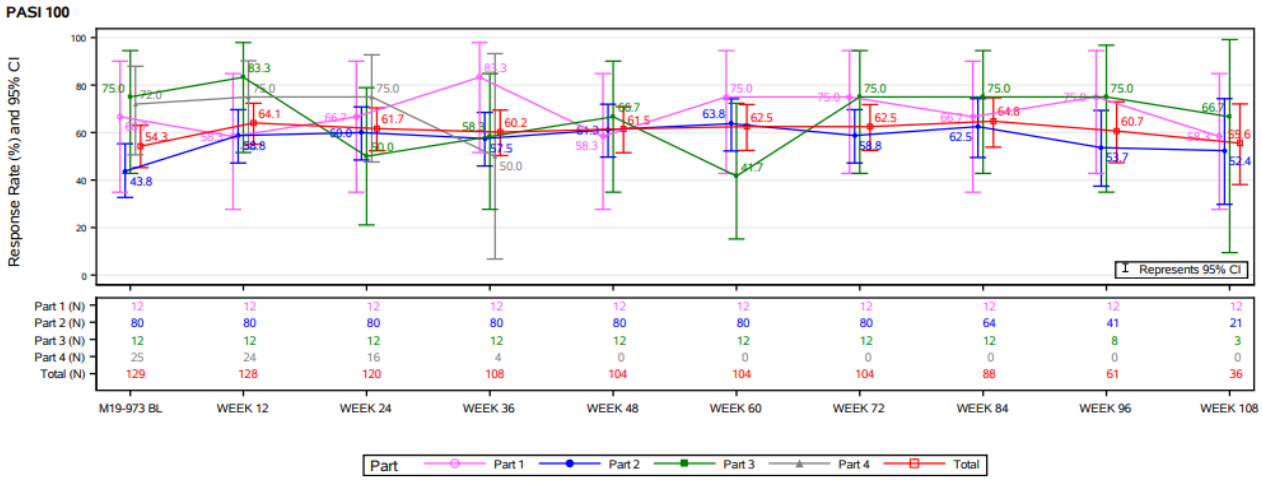
Figure 12: PASI 75 Response Rate (LOCF) and 95% CI by Visit – Study M19-973 (FAS Population)



Notes: Study parts of the preceding Study M19-977.

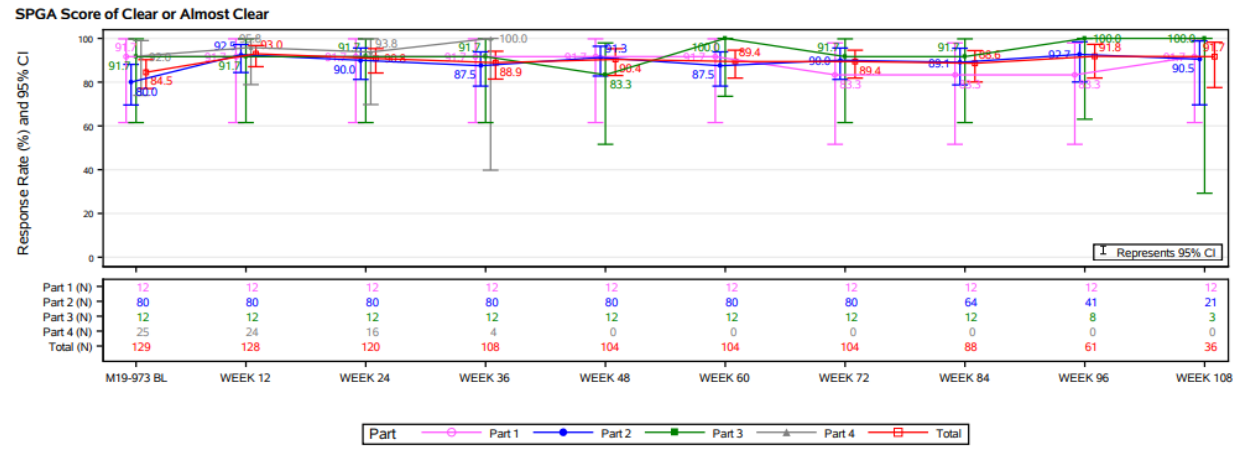
Exact Clopper-Pearson CI for proportions.

Figure *13*: PASI 90 Response Rate (LOCF) and 95% CI by Visit – Study M19-973 (FAS Population)



Notes: Study parts of the preceding Study M19-977.
Exact Clopper-Pearson CI for proportions.

Figure *14*: PASI 100 Response Rate (LOCF) and 95% CI by Visit – Study M19-973 (FAS Population)



Note: Study parts of the preceding Study M19-977.
Exact Clopper-Pearson CI for proportions.

Figure 15: sPGA Score of Clear or Almost Clear Response Rate (LOCF) and 95% CI by Visit – Study M19-973 (FAS Population)

Values in QoL (CDLQI, FDLQI) and Itch NRS assessments were generally maintained throughout Study M19-973. CDLQI scores (max 30) were 4.0 at week 108 for patients that were initially recruited to part 2 and 0.9 at week 24 for patients that were initially recruited to part 4. FDLQI scores (max 30) were 2.4 at week 108 (part 2) and 1.4 at week 24 (part 4). Itch NRS scores (max 30) were 1.7 at week 108 (part 2) and 1.1 at week 24 (part 4).

Upon request from the CHMP, the MAH provided information on the clinical outcomes observed in the OLE study M19-973 for the specified patient treatment groups enrolled in the previous study M19-973, part 2. While patient numbers in the treatment groups were low, the last timepoint in the OLE for which full data (LOCF) was available was week 72.

At week 72, for patients who required retreatment after withdrawal of risankizumab, 75% achieved PASI75 compared to >90% for other treatment groups.

At week 72, for patients who required retreatment after withdrawal of risankizumab and those who were non-responders to risankizumab at week 16, 62.5% and 70% achieved sPGA 0/1 compared to >90% for other subgroups.

5.3.3.4.5. Pre-defined and post hoc important subgroup analyses

PASI and sPGA response rates in Study M19-973 were generally similar across subgroups, and consistent with rates observed in Study M19-977. To evaluate the consistency of the efficacy results, summaries and analyses were performed for certain subgroups across demographic and other baseline characteristics.

PASI 75 was achieved by 85.0% (17/20) of patients weighting <40 kg at week 24 (95% CI 62.1, 96.8), and by 96.9% (31/32) of patients weighing ≥40kg at week 108 (95% CI 83.8, 99.9).

sPGA 0/1 was achieved by 95.0% (19/20) of patients weighting <40 kg at week 24 (95% CI 75.1, 99.9), and by 90.6% (29/32) of patients weighing ≥40kg at week 108 (95% CI 75.0, 98.0).

5.3.4. Clinical studies in special populations

Table *29*: Clinical studies in special populations

	Controlled Trials	Non-controlled trials
Renal impairment* patients (Subjects number /total number)	0/82	0/55
Hepatic impairment** patients (Subjects number /total number)	0/82	0/55
Paediatric patients <18 years (Subjects number /total number)	82/82 (Part 2, M19-977)	55/55 (Part 1, 3, 4, M19-977)
Age 65-74 (Subjects number /total number)	0/82	0/55
Age 75-84 (Subjects number /total number)	0/82	0/55
Age 85+ (Subjects number /total number)	0/82	0/55
Other (Subjects number /total number)	0/82	0/55

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C

5.3.5. Analysis performed across trials (pooled analyses AND meta-analysis)

Not applicable.

5.3.6. Overall discussion and conclusions on clinical efficacy

5.3.6.1. Discussion

Two studies (study M19-977 and study M19-973) were performed to support this extension of indication for the treatment of paediatric patients with plaque PsO. The efficacy of risankizumab in paediatric patients with plaque PsO was further supported by the efficacy established in adult patients with plaque PsO.

Study #1 M19-977

This was a study to evaluate the efficacy, safety and PK of risankizumab in subjects 6 to less than 18 years of age with moderate to severe plaque PsO.

Parts 1, 3 and 4 were open label, single arms, while part 2 was a randomised, actively controlled, efficacy assessor blinded arm.

Parts 1 and 2 recruited patients 12 to <18 years of age. Parts 3 and 4 recruited patients 6 to <12 years of age. As only part 2 was a randomised, active-controlled design, there was no blinded, controlled data for the youngest patients.

Patients in parts 1 and 3 had severe plaque PsO, defined as ≥ 20% BSA PsO involvement with sPGA score of 4; or ≥ 10% BSA PsO involvement that includes facial or genital areas with sPGA score of 4; or PASI ≥ 20. Patients in parts 2 and 4 had moderate to severe plaque PsO, defined as ≥ 10% BSA PsO involvement with sPGA score of ≥ 3 or PASI ≥ 12. Adults recruited to the risankizumab pivotal PsO studies also had moderate to severe plaque PsO, however adult patients had to meet all the above mentioned BSA, sPGA and PASI criteria, compared to the current paediatric study where patients had to have either BSA+sPGA criteria or PASI criteria. Upon request from the CHMP, the MAH discussed the difference between the different criteria used to define moderate to severe plaque PsO between adult and paediatric patients and differences in disease presentation, burden of disease, and outcome measure limitations such as different BSA proportions and greater psychosocial impact for children. The slightly less strict criteria used for paediatric patients aimed to ensure children with meaningful disease were not excluded due to the limitations of one scoring system. This approach was in line with the PIP and was accepted by the CHMP. Further, patients had to be candidates for systemic therapy as assessed by the investigator. Hence, the studied population was in line with the proposed indication *of moderate to severe plaque psoriasis who are candidates for systemic therapy*.

The comparator used in part 2 was ustekinumab which was used in line with its approved posology, s.c. administration based on weight (0.75 mg/kg for subjects <60 kg; 45 mg for subjects 60 to <100 kg; 90 mg for subjects ≥100 kg) at Weeks 0 and 4.

Risankizumab was administered s.c. with a PFS at weeks 0, 4, and every 12 weeks thereafter for up to a year: patients ≥40 kg received 150 mg risankizumab, the approved dose for adults, while subjects who weighed <40 kg received 55 mg risankizumab.

Part 2 of the study included a 16-week initial treatment period (period A), a randomised or withdrawal period for risankizumab responders (period B), and a 16-week retreatment period for subjects who experienced a disease flare (period C). As part 2 only included patients 12 to <18 years of age, there was no withdrawal and retreatment data for the youngest patients.

The study assessments were PASI, sPGA, CDLQI, FDLQI and Itch NRS, all of which are standard assessments for PsO. Overall, the study design was acceptable.

The co-primary endpoints were achievement of PASI 75 and sPGA 0/1 at week 16 of initial treatment. These are standard, widely used and clinically relevant endpoints. PASI 90 and sPGA 0/1 at week 16 were co-primary endpoints in the ULTIMMA-1 and ULTIMMA-2 pivotal adult studies for risankizumab in the PsO indication. It was not clear why PASI 75 over PASI 90 was chosen for the paediatric population, nonetheless, PASI 90 was also a key ranked secondary endpoint. Hence, no concern was raised.

Results were presented descriptively with no formal statistical testing. While this is a limitation of the study, this was accepted due to the small sample size of the study overall, with further smaller numbers in each of the different individual study parts and periods. The specified intercurrent events (ICE) of treatment discontinuation and use of rescue medication were appropriate.

The secondary endpoints were variations of the primary endpoints and were acceptable. Other endpoints included QoL assessments for patients in part 2 only.

The SAP was adequate to support the testing of the PDCO approved PIP. The planned and completed subgroup analyses were acceptable. For Part 2, the lack of sufficient power to test for a significant difference between the risankizumab and ustekinumab groups was compliant with the PDCO approved PIP and acceptable. The study design and sample size determination for Part 1, 3, and 4 were also acceptable. The planned analysis was valid. The changes to the finalised SAP were acceptable and did not detract from the validity of the SAP. The ICE handling and missing data handling strategies for the primary and ranked secondary endpoints were conservative, and the sensitivity analysis added to the interpretability of the study.

Protocol amendments made after the recruitment of the majority of patients (Versions 4 and 5) did not affect the primary endpoints and are not expected to impact on the interpretation of results.

A total of 139 patients were enrolled in the study, this included 2 Japanese patients who were enrolled but not included in any analyses because they were not from the same age cohort as the population studied in Part 4 (children) but were added to Part 4 for administrative reasons (closure of Part 2 enrolment), the ITT data-set therefore included n=137 patients. The number of patients who discontinued treatment was low, n=4. Parts 1, 3 and 4 recruited 12, 13 and 30 patients, respectively. For part 2, a total of 82 patients were recruited and patients were randomised 2:1 to either ustekinumab or risankizumab. 28 patients were randomised to ustekinumab for period A and then switched to risankizumab for period B. 54 patients were randomised to risankizumab for period A, of these 1 patient discontinued, 10 patients were non-responders and continued treatment with risankizumab for period B, while 43 patients were responders and re-randomised 1:1 to either continue treatment with risankizumab (n=22) or withdrawal of treatment (n=21) for part B. Of the 21 patients with withdrawal of treatment, 8 of these had a disease flare and were re-treated with risankizumab in part C.

The overall number of protocol deviations was low: 4 patients had inclusion/exclusion criteria violations, 5 patients received prohibited concomitant medications. One of the patients with a disease flare, did not have a disease flare and was incorrectly re-treated, this was considered a

protocol deviation. No protocol deviations were considered to affect the primary analysis and all patients were therefore included in the analysis.

Treatment compliance was high and a minimum of 94% across all treatment arms.

The majority of patients were female, white and had a mean age of 14.7 years and 9.1 years for parts 1 and 2 combined and parts 3 and 4 combined, respectively. Regarding weight, n=3 (3.2%) and n=29 (67.4%) of patients weighed < 40kg in parts 1 and 2 combined and parts 3 and 4 combined.

For part 2, baseline disease characteristics were similar across both treatment arms. Median PASI scores were 14.7 vs 16.0 for ustekinumab and risankizumab treatment arms; this was comparable though slightly lower than the adult pivotal studies which had a median baseline PASI score of 17.8. For sPGA scores, 89% versus 78% of ustekinumab and risankizumab treated patients had sPGA-3 (moderate) scores, while 4% vs 11% had sPGA-4 (severe) scores, respectively; this was comparable with the adult pivotal studies where 81% and 19% of patients had moderate and severe sPGA scores, respectively. BSA was a median of 17.5% and 18.0% for ustekinumab and risankizumab treatment arms; this was comparable with the adult pivotal studies which had a median BSA of 20.0%. Baseline PASI and sPGA scores were higher for parts 1 and 3 which recruited only severe patients.

More than 96% of patients had never received prior biologic PsO therapy, while 69-100% of patients had never received prior systemic PsO therapy. Only 1 patient had a history of PsA. In the adult pivotal studies, 58% of patients had never received prior biologic therapy, 31% had never received systemic treatment and 10% had a history of PsA.

Overall, 2 out of 32 patients that started on the 55mg dose switched to 150mg during the study.

The co-primary endpoints were PASI 75 and achievement of sPGA clear or almost clear (0 or 1) at week 16. Results from parts 2 and 4 were considered the most important as part 2 was a randomised, controlled, partially blinded design and recruited the most patients compared to the other parts of the study, while parts 2 and 4 had the most relevant population (moderate to severe disease) in relation to the proposed indication, these parts were therefore the main focus of this assessment.

Results demonstrated that the percentage of patients that achieved PASI 75 improvement from baseline at week 16 was comparable across both risankizumab and ustekinumab treated arms in part 2 of the study in patients aged 12 to < 18 years with moderate to severe plaque PsO, 85.2% [95% CI 72.9, 93.4] and 85.7% [95% CI 67.3, 96.0], respectively. Similar results were also obtained for risankizumab in younger patients aged 6 to < 12 years of age with moderate to severe disease in part 4, 86.7% [95% CI 69.3, 96.2].

The percentage of patients that achieved PASI 90 improvement from baseline at week 16 was comparable across both risankizumab and ustekinumab treated arms in part 2 of the study, 64.8% [95% CI 50.6, 77.3] and 60.7% [95% CI 40.6, 78.5], respectively. Similar, though higher response rates were also obtained for risankizumab in younger patients aged 6 to < 12 year of age in part 4, 76.7% [95% CI 57.7, 90.1]. These results were comparable with those obtained in the pivotal adult PsO studies, ULTIMMA-1 and ULTIMMA-2, where 75% of risankizumab treated patients achieved PASI 90 at week 16 in both studies.

The percentage of patients that achieved PASI 100 improvement from baseline at week 16 was higher in risankizumab treated patients compared to ustekinumab patients in part 2 of the study, 40.7% [95% CI 27.6, 55.0] and 17.9% [95% CI 6.1, 36.9], respectively. Similar results were also

obtained for risankizumab in younger patients aged 6 to < 12 year of age in part 4, 43.3% [95% CI 25.5, 62.6]. Again, these results were in line with those obtained in the pivotal adult PsO studies, ULTIMMA-1 and ULTIMMA-2, where 36% and 51% of risankizumab treated patients achieved PASI 100 at week 16.

Similar trends in PASI results were also obtained in patients with severe disease only, parts 1 and 3. For parts 1, 3 and 4, efficacy results were maintained from week 16 to week 52. The non-ranked secondary endpoint of PASI 50 at Week 16 demonstrated similarly high rates of improvement for both the risankizumab and ustekinumab arms.

The percentage of patients that achieved sPGA 0/1 at week 16 was comparable across both risankizumab and ustekinumab treated arms in part 2 of the study, patients aged 12 to < 18 years with moderate to severe PsO, 79.6% [95% CI 66.5, 89.4] and 75.0% [95% CI 55.1, 89.3] respectively. Similar, though higher response rates were also obtained for risankizumab in younger patients aged 6 to < 12 year of age with moderate to severe disease in part 4, 90.0% [95% CI 73.5, 97.9]. Similar results were also obtained in patients with severe disease only, parts 1 and 3. These results were in line with those from the pivotal PsO studies in adults, ULTIMMA-1 and ULTIMMA-2, where 88% and 84% of patients treated risankizumab achieved sPGA 0/1 at week 16.

The percentage of patients that achieved sPGA 0 at week 16 was higher in risankizumab treated patients compared to ustekinumab treated patients in part 2 of the study, 40.7% [95% CI 27.6, 55.0] and 17.9% [95% CI 6.1, 36.9] respectively. Similar results were also obtained for risankizumab in younger patients aged 6 to < 12 year of age with moderate to severe disease in part 4, 43.3% [95% CI 25.5, 62.6]. Similar results were also obtained in patients with severe disease only, parts 1 and 3. These results were in line with those from the pivotal PsO studies in adults, ULTIMMA-1 and ULTIMMA-2, where 37% and 51% of patients treated risankizumab achieved sPGA 0 at week 16.

For parts 1, 3 and 4, efficacy results were generally maintained from week 16 to week 52.

For part 2 period B, of all patients receiving risankizumab (including those initially receiving ustekinumab, those initially who were non-responders to risankizumab, and those who were initially risankizumab responders), >90% achieved PASI 75 at week 52. In contrast however, for the group that were re-randomised to withdrawal treatment, this number dropped to 57.1% of patients achieving PASI 75 at week 52 suggesting the effects of risankizumab wear off over time if treatment is withdrawn. For part 2, period B, of the patients initially receiving ustekinumab and those who were initially risankizumab responders, >89% achieved sPGA 0/1. However, those who were originally non-responders to risankizumab, and those that were re-randomised to withdrawal treatment had lower levels of sPGA 0/1 at week 52, 50% and 43% respectively. Discontinuing treatment in patients who have shown no response after 16 weeks of treatment is referred to in the SmPC, in line with the wording for adults.

For part 2, period C, PASI 75 and sPGA 0/1 results were positive, however, the number of patients (n=8) was too low to draw any conclusions.

The QoL endpoints were change in CDLQI, FDLQI and Itch NRS from baseline to week 16, these were recorded for part 2 only. Comparable results were demonstrated for the changes in CDLQI, FLQI and Itch NRS from Week 0 to Week 16 across risankizumab and ustekinumab arms. These QoL results provided further support for the efficacy of risankizumab in paediatric PsO. The inclusion of the CDLQI and itch NRS endpoints in SmPC Section 5.1 was agreed since this information is considered clinically relevant to the prescriber.

The MAH has not separately discussed the impact on efficacy results for children that switched from 55mg to 150mg, this was accepted as the numbers switching was so low (n=2).

Results were consistent across different subgroups analysed, although small numbers in some subgroups limited interpretation. The number of patients <40 kg or ≥40kg in each part of the clinical study were too small for any meaningful analysis. Upon request from the CHMP, the MAH presented PASI 75 and sPGA 0/1 results at week 16 by weight bands of <40 kg or ≥40kg for all patients combined in the studies (regardless of disease severity or age). Overall, the results demonstrated comparable efficacy in both weight bands.

Subgroup analysis according to ADA status indicated that antibodies to risankizumab were not associated with changes in clinical response. However, the number of patients who were positive for antibodies to risankizumab was too small for definitive conclusions about the impact on efficacy of risankizumab.

Overall, these results demonstrated that risankizumab is efficacious with a treatment effect observed in paediatric patients aged 6 years and older with moderate to severe plaque PsO. Results were in line with those observed in adult patients.

Study #2 M19-973 OLE

Study M19-973 is an OLE to study M19-977 to evaluate the long-term efficacy and safety of risankizumab in subjects 6 to less than 18 years of age with moderate to severe plaque PsO. This study remained ongoing during the procedure, and the data presented were interim data (cut-off date: 01 January 2025). Patients ≥ 40 kg received 150 mg risankizumab, the approved dose for adults, while subjects who weighed < 40 kg received 55 mg risankizumab. Risankizumab was administered s.c. with a PFS every 12 weeks in line with the approved posology for adults, for up to 204 weeks of treatment.

Inclusion/exclusion criteria, prohibited medications, concomitant medications and study assessment were similar to study M19-977. Overall, the study design was acceptable.

The same disease and QoL endpoints were used as for study M19-977, although there were no designated primary/secondary endpoints in this OLE. The estimands and ICE were broadly the same as for study M19-977 taking into consideration the different designs between the two studies.

The SAP was adequate to address the objective of the study. The sample size was dependent on Study M19-977, so lack of power and sample size calculations were acceptable. The planned subgroup analysis was acceptable. The missing data handling and ICE handling strategies were acceptable. The changes to the SAP and protocol were minimal and did not affect the validity of the study.

There were a number of updates to the protocol, the majority of the patients were enrolled under the final global version of the protocol, protocol 4. The amendments during which patients were recruited did not affect inclusion/exclusion criteria or endpoints and were not considered to impact on the interpretation of results.

A total of 131 patients were enrolled in the study, this included 2 Japanese patients who were enrolled to part 4 of the parent study but not included in any analyses, the FAS dataset therefore included n=129 patients. 12/12 (part 1), 80/82 (part 2), 12/13 (part 3), 25/30 (part 4) patients were included from study M19-977. However, the CSR stated that all but 1 subject from study M19-977 part 1 was enrolled in study M19-973, this discrepancy did not affect the benefit risk

assessment of the procedure and was therefore not queried. The number of patients who discontinued the OLE study was low, n=5.

The overall number of protocol deviations was low, n=3. 2 patients received 150 mg dose instead of 55 mg and 1 patient took prohibited concomitants medication. No protocol deviations were considered to affect the primary analysis; all patients were therefore included in the analysis.

Treatment compliance was high and a minimum of 97% across all treatment arms (from study M19-977).

As the majority of patients from study M19-977 were enrolled in the OLE, baseline demographics were similar between the two studies.

The majority of patients were female, white and with a mean age of 14.1 years overall. 21 (16.3%) patients weighed < 40kg.

Median PASI scores were 0.0. 4% of patients had sPGA-3 (moderate) scores, 0% had sPGA-4 (severe) scores. Unlike for study M19-977, CDLQI, FDLQI, and Itch NRS scores were captured for all patients. Median baseline scores were 1.0 (CDLQI), 2.0 (FDLQI) and 0.0 (Itch NRS). These baseline data were reflective of the continued efficacious nature of risankizumab treatment carried over from study M19-977.

As of the interim cut-off date of 01 January 2025, patients from parts 1-4 had a median extent of exposure of 171, 90, 92 and 21 weeks treatment up to week 168.

A larger number of patients switched from 55 mg to 150 mg treatment during the OLE compared to study M19-977 (n=11/27), this was expected due to the longer duration of the OLE and lower weight patients gaining weight as they age.

The outcomes that were the primary endpoints for the initial study, PASI 75 and sPGA 0/1, demonstrated that efficacy results were generally maintained throughout the OLE study.

For patients that were initially recruited to part 2 of study M19-977, patients aged 12 to < 18 years with moderate to severe PsO, PASI 75 was achieved by 95.2% (20/21) of patients at week 108 (LOCF, 95% CI 76.2, 99.9). After this timepoint, numbers were too low to be reliable.

For patients that were initially recruited to part 4 of study M19-977, younger patients aged 6 to < 12 years of age with moderate to severe disease, the extent of exposure was much shorter. PASI 75 was achieved by 87.5% (14/16) of patients at week 24 (LOCF, 95% CI 61.7, 98.4). After this timepoint, numbers were too low to be reliable.

For patients that were initially recruited to part 2 of study M19-977, sPGA 0/1 was achieved by 90.5% (19/21) of patients at week 108 (LOCF, 95% CI 69.6, 98.8). For patients that were initially recruited to part 4 of study M19-977, sPGA 0/1 was achieved by 93.8% (15/16) of patients at week 24 (LOCF, 95% CI 69.8, 99.8).

These results were comparable to the primary endpoint outcomes of study M19-977 at week 16. Similar results were also obtained for patients that were initially recruited to parts 1 and 3. A similar maintenance of results was also obtained for other outcomes including PASI 90/100 and sPGA 0.

The QoL endpoints were change in CDLQI, FDLQI and Itch NRS from baseline, results were generally maintained throughout the OLE study (cut-off date: 01 January 2025) for each QoL parameter.

Upon request from the CHMP, the MAH discussed the impact on efficacy results for children that switched from 55 mg to 150 mg during the OLE study. Overall, a low number of subjects (11

subjects) switched doses from 55 mg to 150 mg and all maintained a response (except for subjects randomised to withdrawal of treatment in Part 2 Period B). These findings were considered reassuring.

Upon request from the CHMP, the MAH provided information on the clinical outcomes (PASI 75, 90 and 100, sPGA of 0/1) observed in the OLE study M19-973 for the specified patient treatment groups enrolled in the previous study M19-973, part 2. While patient numbers in the treatment groups were low, the last timepoint in the OLE for which full data (LOCF) was available was week 72. Results were lower for patients who required retreatment after withdrawal of risankizumab and non-responders to risankizumab at week 16 compared to other part 2 treatment groups. It was agreed that non-responders are likely to be difficult to treat and less likely to show improvement, while patients that discontinue treatment would be more likely to have a loss of response than those who continue treatment. However, while responses may be lower in these two treatment groups, overall responses were still reasonably high.

Results were consistent across different subgroups analysed, including subgroups by weight.

Overall, this OLE study indicated that risankizumab demonstrates long-term efficacy in paediatric patients aged 6 years and older with moderate to severe plaque PsO. Results were in line with the maintenance of response observed in adult patients in the LIMMITLESS study. Further, final results from this study will be submitted for assessment (Category 3 study in the RMP, final report: Q2 2029).

5.3.6.2. Conclusions on the clinical efficacy

Two studies (study M19-977 and study M19-973) were performed to support this extension of indication for the treatment of paediatric patients with PsO. The efficacy of risankizumab in paediatric patients with plaque PsO was further supported by the efficacy established in adult patients with plaque PsO.

The results from Study M19-977 showed that risankizumab is efficacious with a clinically relevant treatment effect in paediatric patients aged 6 years and older with moderate to severe plaque PsO. Results from Study M19-973 showed that the treatment effect was maintained on the long-term. Results were in line with results observed in adult patients.

The agreed therapeutic indication is for *the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy*.

5.4. Clinical safety

Please refer to the table of studies in section 5.1.2.

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in

death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The assessment of safety included the collection of adverse events at all study visits, as well as physical examinations and centrally read laboratory assessments. These assessments took place at screening, baseline, week 4, week 8, week 12, week 16, and every 12 weeks thereafter until the end of either the pivotal study, the OLE study, or discontinuation or withdrawal of the participant. In addition, a safety follow-up telephone call occurred 140 days following the last administered dose of study drug.

The safety evaluation is based on the results from the 2 pivotal Phase 3 studies, Study M19-977 and Phase 3 OLE Study M19-973, up to a cutoff date of 01 January 2025.

For each individual study, an independent external data monitoring committee (DMC) reviewed unblinded safety data at regular intervals during the conduct of the study and recommended whether to continue, modify, or terminate the study after each review. Additionally, serious hypersensitivity reaction events in both studies were identified using a pre-defined search of adverse event (AE) terms and adjudicated using a prespecified definition of anaphylactic reaction by an independent anaphylaxis adjudication committee.

Integration of Safety data

To assess the safety of risankizumab across the PsO development programme, subject data from completed Study M19-977 and Study M19-973 up to a cutoff date of 01 January 2025 were integrated into 4 analysis sets.

The definitions for the Controlled Risankizumab Set, the Short-Term Risankizumab Set, the Long Term Risankizumab Set and the All Risankizumab Set are set out below.

Controlled Risankizumab Set (16 weeks):

This set included all adolescent participants who received at least one dose of study drug in the ustekinumab-controlled 16-week period from Study M19-977 Part 2 Period A. Subjects were assigned to the dose groups based on the starting dose they received. The summarised cohorts and treatment groups included:

- Risankizumab 150 mg - Adolescents
- Risankizumab 55 mg - Adolescents
- Combined Risankizumab - Adolescents
- Ustekinumab - Adolescents

Short-term Risankizumab Set (16 weeks):

This set included all paediatric participants (adolescents and children) who received risankizumab from Study M19-977 Parts 1, 2, 3 and 4. Subjects who received ustekinumab were excluded from this analysis set. Subjects were assigned to the dose groups based on the starting dose they received.

The summarised cohorts and treatment groups included:

- Risankizumab 150 mg - Adolescents
- Risankizumab 55 mg - Adolescents
- Combined Risankizumab - Adolescents
- Risankizumab 150 mg - Children
- Risankizumab 55 mg - Children
- Combined Risankizumab - Children
- Combined Risankizumab 150 mg
- Combined Risankizumab 55 mg
- Combined Risankizumab

Long-term Risankizumab Set (≥ -52 weeks [365 days]):

This set included all paediatric participants (adolescents and children) who received continuous risankizumab from Study M19-977 and/or Study M19-973 for at least 52 weeks (365 days) of exposure. Subjects were assigned to the dose groups based on the first Risankizumab dose in M19-977. Subjects who received ustekinumab in Study M19-977 were excluded from this analysis set. Subjects who received risankizumab who did not have at least 52 weeks (365 days) continuous exposure were excluded from this analysis set and adverse events for these subjects were excluded.

The summarised cohorts and treatment groups included:

- Risankizumab 150 mg - Adolescents
- Risankizumab 55 mg - Adolescents
- Combined Risankizumab - Adolescents
- Risankizumab 150 mg - Children
- Risankizumab 55 mg - Children
- Combined Risankizumab - Children
- Combined Risankizumab 150 mg
- Combined Risankizumab 55 mg
- Combined Risankizumab

All Risankizumab Set (All Exposure):

This set included all paediatric participants (adolescents and children) who received at least one dose of risankizumab from Study M19-977 or Study M19-973. Subject exposure and adverse events were summarised under the starting dose of risankizumab.

The summarised cohorts and treatment groups included:

- Combined Risankizumab 150 mg
- Combined Risankizumab 55 mg
- Combined Risankizumab

Unless otherwise specified, adolescents and children included all subjects from the age cohort regardless of their starting dose.

5.4.2. Patient exposure

Exposure

In the Controlled Risankizumab Set, 82 adolescent subjects received at least 1 dose of risankizumab (N = 54) or ustekinumab (N = 28). The median duration of exposure was 16.00 weeks in the risankizumab arm and 15.93 weeks in the ustekinumab arm.

In the Short-Term Risankizumab Set, median exposure to risankizumab was 16.00 weeks in both adolescents and children. During the short-term period, 111 subjects were treated with risankizumab. This cohort was stratified into two dosing groups: RZB150all (N=78) and RZB55all (N=33).

97.3% of participants completed at least 90 days of treatment. The total patient-years of exposure for the entire short-term set amounted to 34.5 years.

In the Long-Term Risankizumab Set, 106 subjects (66 adolescents and 40 children) received risankizumab for at least 52 weeks. The median length of exposure for adolescents, children, and all subjects was 137.93, 79.36, and 130.57 weeks, representing 184.8, 74.0, and 258.7 PY of exposure, respectively.

In the All Risankizumab Set, the median duration of study drug exposure was 125.43 weeks. The cumulative patient-years of exposure across all risankizumab-treated subjects was 330.5 years in total.

Overall, 137 out of 139 patients (98.6%) had greater than 6 months (≥180 days) exposure, while 135 of 139 patients (97.1%) had greater than 12 months (≥360 days) exposure. In addition, 82.7% of all risankizumab-treated subjects reached at least 18 months of exposure, and 48.9% continued for 30 months or more.

Baseline characteristics

Demographic and baseline disease characteristics were similar between the risankizumab and ustekinumab arms of the Controlled Risankizumab Set. The most frequently reported (≥ 10.0%) conditions in subjects' medical history besides PsO were obesity in the risankizumab arm (13.0%) and obesity and seasonal allergy in the ustekinumab arm (14.3% and 10.7%, respectively).

Use of concomitant medication was reported by 66.7% and 53.6% of subjects in the risankizumab and ustekinumab arms of the Controlled Risankizumab Set, respectively. The most frequently reported (≥ 5.0%) concomitant medications were ibuprofen, paracetamol, glycerol/liquid paraffin/white soft paraffin, and methylphenidate hydrochloride in the risankizumab arm (13.0%, 9.3%, 7.4%, and 5.6% respectively) and paracetamol in the ustekinumab arm (10.7%).

In the Controlled Risankizumab Set, a higher proportion of participants in the risankizumab arm used prior systemic PsO therapies than in the ustekinumab arm (29.6% vs 14.3%).

In the Short-Term Risankizumab Set, a similar proportion of adolescents and children described prior systemic PsO therapies use (23.5% and 23.3%, respectively).

The use of prior biologic therapy for PsO was low in the risankizumab and ustekinumab arms (2/54 (3.7%) and 1/28 (3.6%)), respectively in the Controlled Risankizumab set). In the Short-Term Risankizumab set, 2/68 (2.9%) adolescents and 1/43 (2.3%) received prior biologic therapy for PsO.

In the All Risankizumab Set, the most common medical history conditions were obesity (12 subjects, 8.6%) followed by seasonal allergy (11 subjects, 7.9%). The percentage of subjects with a history of immune system disorders was 13.7%. Use of concomitant medication was reported by 114 subjects

(82.0%). The most frequently reported (≥ 10.0%) concomitant medications were ibuprofen, paracetamol, and amoxicillin in 28.8%, 26.6%, and 10.8% of subjects, respectively.

In the All Risankizumab Set, a greater proportion of adolescents had obesity compared to children (10.3% versus 2.3% respectively).

Table *30*: Patient exposure (cut off: 01 January 2025)

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term (52 continuous weeks)** safety data
Blinded studies (placebo-controlled)	-	-	-	-
Blinded studies (active -controlled)	-	-	-	-
Open studies (all parts combined)	139	139	139	106
Open study -active controlled (M19-977 Part 2) ***	28 UST 54 RZB	28 UST 54 RZB	54 RZB	N/A
Post marketing	-	-	-	-
Compassionate use	-	-	-	-

* Received at least 1 dose of active treatment
** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.
*** 16 week open-label efficacy assessor blinded active controlled part of study in adolescents only

5.4.3. Adverse events

Overall treatment-emergent adverse events (TEAEs)

An overview of TEAEs in Percentage and exposure-adjusted event rate (EAER) per 100 PY in the Controlled Risankizumab Set and Short-Term Risankizumab Set is provided in **Table 31**. In the Controlled Risankizumab Set, there was a higher incidence of nasopharyngitis in the risankizumab group compared to the ustekinumab group (101.8 E/100 PY vs. 46.5 E/100 PY). In the Short-Term Risankizumab set, there was a lower incidence of AEs related to General disorders and administration site conditions in adolescents compared to children, specifically pyrexia (4.8 E/100 PY vs 37.0 E/100 PY respectively). The incidence of nasopharyngitis was higher in adolescents than children (81.0 E/100 PY vs 55.5 E/100 PY respectively).

In the Short-Term Risankizumab Set, the percentage of subjects and event rate of TEAEs were higher in children compared to adolescents (**Table 31**).

The percentage and event rate of TEAEs considered to have a reasonable possibility of being related to study drug was similar in both age cohorts.

Table *31*: Overview of TEAEs in Percentage and EAER per 100 PY (Controlled Risankizumab Set and Short-Term Risankizumab Set)

	Controlled Risankizumab Set (16 Weeks)				**Short-Term Risankizumab Set (16 Weeks)**					
	RZB All - Adolescents (N = 54) (PY = 16.7)		**UST - Adolescents (N = 28) (PY = 8.6)**		**RZB All – Adolescents (N = 68) (PY = 21.0)**		**RZB All – Children (N = 43) (PY = 13.5)**		**RZB All (N = 111) PY = 34.5**	
Subjects with:	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**
All TEAEs	24 (44.4)	54 (323.4)	14 (50.0)	19 (220.9)	30 (44.1)	62 (295.2)	25 (58.1)	54 (400.0)	55 (49.5)	116 (336.2)
TEAEs with reasonable possibility of being related to study drug	7 (13.0)	13 (77.8)	6 (21.4)	6 (69.8)	7 (10.3)	13 (61.9)	6 (14.0)	9 (66.7)	13 (11.7)	22 (63.8)
Severe TEAEs	0	0	1 (3.6)	1 (11.6)	0	0	1 (2.3)	1 (7.4)	1 (0.9)	1 (2.9)
Serious TEAEs	0	0	0	0	0	0	0	0	0	0
TEAEs leading to discontinuation of study drug	0	0	0	0	0	0	0	0	0	0
TEAEs leading to death	0	0	0	0	0	0	0	0	0	0
Subject deaths	0	0	0	0	0	0	0	0	0	0

The most frequent SOCs in which TEAEs with reasonable possibility of being related to study drug were reported were and Infections and infestations 17 (16.0) vs 3 (9.1), General disorders and administration site conditions 7 (6.6%) vs 2 (6.1%), and Gastrointestinal disorders 3 (2.8%) vs 3 (9.1%), respectively. The most frequently reported AE assessed as being possibly drug-related by the investigator was nasopharyngitis in 3/111 subjects (2.7%). None were classified as severe or serious, and none lead to treatment discontinuation.

Table *32*: Overview of TEAEs (Long-Term Risankizumab Set)

	Adolescents			Children			Adolescents + Children		
	RZB 150 mg (N = 63)	**RZB 55 mg (N = 3)**	**RZB All (N = 66)**	**RZB 150 mg (N = 14)**	**RZB 55 mg (N = 26)**	**RZB All (N = 40)**	**RZB 150 mg (N = 77)**	**RZB 55 mg (N = 29)**	**RZB All (N = 106)**
Subjects with:	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
All TEAEs	50 (79.4)	1 (33.3)	51 (77.3)	10 (71.4)	22 (84.6)	32 (80.0)	60 (77.9)	23 (79.3)	83 (78.3)
TEAEs with reasonable possibility of being related to study drug	12 (19.0)	1 (33.3)	13 (19.7)	2 (14.3)	6 (23.1)	8 (20.0)	14 (18.2)	7 (24.1)	21 (19.8)
Severe TEAEs	5 (7.9)	0	5 (7.6)	0	1 (3.8)	1 (2.5)	5 (6.5)	1 (3.4)	6 (5.7)
Serious TEAEs	2 (3.2)	0	2 (3.0)	0	0	0	2 (2.6)	0	2 (1.9)
TEAEs leading to discontinuation of study drug	0	0	0	0	0	0	0	0	0
TEAEs leading to death	0	0	0	0	0	0	0	0	0
Subject deaths	0	0	0	0	0	0	0	0	0

Table *33*: Overview of TEAEs in EAER per 100 PY (Long-Term Risankizumab Set)

	Adolescents			Children			Adolescents + Children		
	RZB 150 mg (N = 63) (PY = 178.9)	**RZB 55 mg (N = 3) (PY = 5.9)**	**RZB All (N = 66) (PY = 184.8)**	**RZB 150 mg (N = 14) (PY = 29.1)**	**RZB 55 mg (N = 26) (PY = 44.9)**	**RZB All (N = 40) (PY = 74.0)**	**RZB 150 mg (N = 77) (PY = 207.9)**	**RZB 55 mg (N = 29) (PY = 50.8)**	**RZB All (N = 106) (PY = 258.7)**
Subjects with:	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**
All TEAEs	307 (171.6)	10 (169.5)	317 (171.5)	26 (89.3)	119 (265.0)	145 (195.9)	333 (160.2)	129 (253.9)	462 (178.6)
TEAEs with reasonable possibility of being related to study drug	62 (34.7)	7 (118.6)	69 (37.3)	2 (6.9)	16 (35.6)	18 (24.3)	64 (30.8)	23 (45.3)	87 (33.6)
Severe TEAEs	5 (2.8)	0	5 (2.7)	0	1 (2.2)	1 (1.4)	5 (2.4)	1 (2.0)	6 (2.3)
Serious TEAEs	3 (1.7)	0	3 (1.6)	0	0	0	3 (1.4)	0	3 (1.2)
TEAEs leading to discontinuation of study drug	0	0	0	0	0	0	0	0	0
TEAEs leading to death	0	0	0	0	0	0	0	0	0
Subject deaths	0	0	0	0	0	0	0	0	0

Table *34*: TEAE Overview in Percentage and EAER per 100 PY (All Risankizumab Set)

	Combined RZB 150 mg (N = 106) (PY = 274.4)		Combined RZB 55 mg (N = 33) (PY = 56.1)		RZB All (N = 139) (PY = 330.5)	
Subjects with:	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**
All TEAEs	84 (79.2)	478 (174.2)	26 (78.8)	138 (246.0)	110 (79.1)	616 (186.4)
TEAEs with reasonable possibility of being related to study drug	22 (20.8)	81 (29.5)	9 (27.3)	27 (48.1)	31 (22.3)	108 (32.7)
Severe TEAEs	8 (7.5)	8 (2.9)	1 (3.0)	1 (1.8)	9 (6.5)	9 (2.7)
Serious TEAEs	5 (4.7)	6 (2.2)	0	0	5 (3.6)	6 (1.8)
TEAEs leading to discontinuation of study drug	0	0	0	0	0	0
TEAEs leading to death	0	0	0	0	0	0
Subject deaths	0	0	0	0	0	0

Re-treatment phase in Study M19-977

In the Part 2 Period C randomised withdrawal part of Study M19-977, 4 subjects had 6 events that occurred after retreatment. These events included Pyrexia (2), chills (1), bacterial vaginosis (1), eczema (1), psoriasis (1). None were reported as serious.

Frequently Reported Adverse Events

An overview of the most frequently reported TEAEs (≥ 5.0%) in the Controlled Risankizumab Set and Short-Term Risankizumab Set is provided in **Table 35**.

In the Controlled Set, the most commonly reported TEAEs in the All Risankizumab and ustekinumab groups respectively were Nasopharyngitis (101.8 E/100 PY vs 46.5 E/100 PY), COVID-19 (29.9 E/100 PY vs 23.3 E/100 PY), and Headache (24.0 E/100 PY vs 34.9 E/100 PY). All other TEAEs were reported as single instances.

In the Short-Term Risankizumab set, the overall EAER-adjusted rate of TEAEs was lower in adolescents than in children (295.2 vs. 400.0 E/100 PY respectively). In the Short-Term Set, the most commonly reported TEAEs (>5%) in adolescents and children respectively were Nasopharyngitis [17 events (81.0 E/100 PY) vs 6 (44.4 E/100 PY)], COVID-19 [6 (28.6 E/100 PY) vs 0], Headache [0 vs 2 (14.8 E/100 PY)], Pyrexia [1 (4.8 E/100 PY) vs 5 (37.0 E/100 PY)], Upper respiratory tract infection [2 (9.5 E/100 PY) vs 4 (29.6 E/100 PY)], and Cough [1 (4.8 E/100 PY) vs 4 (29.6 E/100 PY)].

Table *35*: Most Frequently Reported TEAEs in ⩾ 5.0% of Subjects in Any Treatment Group of the Controlled Risankizumab Set or Short Term Risankizumab Set, in Descending Order by the Risankizumab Arm of the Controlled Risankizumab Set

	Controlled Risankizumab Set (16 Weeks)		Short-Term Risankizumab Set (16 Weeks)		
MedDRA 27.0 PT	RZB_All - Adolescents (N = 54)	UST - Adolescents (N = 28)	RZB All – Adolescents (N = 68)	RZB All – Children (N = 43)	RZB All (N = 111)
Nasopharyngitis	10 (18.5)	4 (14.3)	10 (14.7)	6 (14.0)	16 (14.4)
COVID-19	5 (9.3)	2 (7.1)	6 (8.8)	0	6 (5.4)
Headache	3 (5.6)	3 (10.7)	3 (4.4)	1 (2.3)	4 (3.6)
Cough	1 (1.9)	0	1 (1.5)	4 (9.3)	5 (4.5)
Pyrexia	0	0	1 (1.5)	4 (9.3)	5 (4.5)

An overview of the most frequently reported TEAE (≥ 10.0%) in the Long-Term Risankizumab Set and in the All Risankizumab Set is provided in Table 36.

In the Long-term Set, the EAER-adjusted rate of TEAEs was similar between adolescents and children (77.3 vs 80.0 E/100 PY respectively). In the Long-term Set, the most common TEAEs (>10%) in adolescents and children respectively were Nasopharyngitis [56 events (30.3 E/100 PY) vs 26 (35.1 E/100 PY)], Upper respiratory tract infection [17 (9.2 E/100 PY) vs 5 (6.8 E/100 PY)], Headache [15 (8.1 E/100 PY) vs 4 (5.4 E/100 PY)], Tonsillitis [9 (4.9 E/100 PY) vs 6 (8.1 E/100 PY)], COVID-19 [13 (7.0 E/100 PY) vs 1 (1. E/100 PY)], Cough [7 (3.8 E/100 PY) vs 6 (8.1 E/100 PY)], Pyrexia [5 (2.7 E/100 PY) vs 7 (9.5 E/100 PY)].

Some differences were seen in the incidence and EAER-adjusted rates of TEAEs between the 150 mg and 55 mg dose cohorts, respectively in the All Risankizumab set, as follows: Nasopharyngitis [101 events (36.8 E/100 PY vs 23 events (41.0 E/100 PY)], Headache 31 [(11.3 E/100 PY) vs 4 (7.1 E/100 PY)], Upper respiratory tract infection [21 (7.7) vs 3 (5.3)], Pyrexia [10 (3.6) 10 (17.8) vs 20 (6.1)], Tonsillitis [11 (4.0) 5 (8.9) vs 16 (4.8)], Rhinorrhoea 6 [(2.2) vs 3 (5.3)], Gastroenteritis [4 (1.5) vs 4 (7.1)], Influenza 3 [(1.1) vs 4 (7.1)], and Depression [6 (2.2) vs 0].

Table *36*: Most Frequently Reported in TEAEs in ⩾ 10.0% of Subjects in Any Group of the Long Term Risankizumab Set or All Risankizumab Set in Descending Order by RZB_All Group of the Long-Term Risankizumab Set

	Long-Term Risankizumab Set (≥ 52 Weeks of Continuous Risankizumab Exposure)			All Risankizumab Set (All Exposure)		
	RZB All – Adolescents (N = 66)	RZB All – Children (N = 40)	RZB All (N = 106)	Combined RZB 150 mg (N = 106)	Combined RZB 55 mg (N = 33)	RZB All (N = 139)
Subjects with:	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Nasopharyngitis	21 (31.8)	12 (30.0)	33 (31.1)	37 (34.9)	10 (30.3)	47 (33.8)
Upper respiratory tract infection	12 (18.2)	3 (7.5)	15 (14.2)	16 (15.1)	1 (3.0)	17 (12.2)
COVID-19	13 (19.7)	1 (2.5)	14 (13.2)	14 (13.2)	3 (9.1)	17 (12.2)
Headache	9 (13.6)	3 (7.5)	12 (11.3)	13 (12.3)	3 (9.1)	16 (11.5)
Cough	6 (9.1)	5 (12.5)	11 (10.4)	12 (11.3)	3 (9.1)	15 (10.8)
Pyrexia	4 (6.1)	4 (10.0)	8 (7.5)	5 (4.7)	6 (18.2)	11 (7.9)
Tonsillitis	3 (4.5)	5 (12.5)	8 (7.5)	5 (4.7)	4 (12.1)	9 (6.5)
Gastroenteritis	3 (4.5)	3 (7.5)	6 (5.7)	4 (3.8)	4 (12.1)	8 (5.8)

Safety in Subjects Who Switched Risankizumab Doses

Of all 106 subjects with a starting dose of risankizumab 150 mg in the All Risankizumab Set, no subject switched to a lower dose. Of the 33 subjects with a starting dose of risankizumab 55 mg SC, 13 subjects (39.4%) switched to a higher dose. In the All Risankizumab Set, the EAER-adjusted rate of TEAEs was similar between those patients receiving 150mg and 55mg (79.2 vs 78.8 E/100 PY respectively). A review of TEAEs reported in subjects who switched did not reveal any dose dependent AE or new safety concerns.

Severe AEs

One severe, nonserious AE of hypertriglyceridaemia was reported in an ustekinumab-treated subject within the first 16 weeks of treatment in the Controlled Risankizumab Set.

There was 1 severe, non-serious event of blood potassium increased in a child in the Short Term Risankizumab Set. The event was not considered to be related to study drug and resolved without study drug discontinuation.

In the Long-Term Risankizumab Set, severe TEAEs were reported in 5/66 adolescents (7.6%): fibula fracture, meniscus injury, blood creatine phosphokinase increased, depression, and proteinuria in 1

subject each. One child (2.5%) had a severe AE of blood potassium increased (included above in the Short Term Risankizumab Set).

Overall, 9 subjects (6.5%) in the All Risankizumab Set had severe TEAEs. Compared to the Long-Term Risankizumab Set, additional severe AEs of blood creatine phosphokinase increased, suicidal ideation, and presyncope were reported. None of the severe AEs were considered to have a reasonable possibility of being related to study drug by the investigator.

Adverse drug reactions

The MAH has stated that ADRs identified for risankizumab followed the guidelines described in CIOMS Working Groups III and V 'Guidelines for Preparing Core Clinical-Safety Information on Drugs' (CIOMS Working Groups III and V 1999). TEAEs included in the safety data analysis sets were medically reviewed to determine the ADRs for risankizumab.

The MAH did not propose adding any ADRs to section 4.8 of the SmPC.

In the Controlled Risankizumab Set, 7 participants (13.0%) in the All Risankizumab group were reported to have experienced an ADR, versus 6 (21.4%) in the Ustekinumab group. Nasopharyngitis was the most commonly reported ADR in the ustekinumab and risankizumab groups (5.6% and 7.1% respectively). None of these were classified as severe or serious and none led to treatment discontinuation.

In the Short-term Set, 7 (10.3%) of adolescents and 6 (14.0%) of children were reported as having experienced an ADR. The most frequently reported drug-related AE was nasopharyngitis in adolescents (3 subjects, 4.4%) and cough in children (2 subjects, 4.7%); all other AEs in both age cohorts were reported in 1 subject each. None of these were classified as severe or serious, and none led to discontinuation of treatment.

In the Long-Term Set, 13 (18.7%) of adolescents and 8 (20.0%) of children were reported as having experienced an ADR. None of these were classified as severe or serious, and none led to treatment discontinuation. In the Long-Term Risankizumab Set, the most frequently reported TEAEs assessed by the investigator as having a reasonable possibility of being related to study drug was nasopharyngitis (14 events, 7.6 E/100 PY) in adolescents and cough and headache (3 events each, 4.1 E/100 PY) in children.

In the All Risankizumab Set, 22 (20.8% of participants in the 150mg dose cohort and 9 (27.3%) of participants in the 55mg dose cohort were reported as having experienced an ADR. The most frequent SOCs in which these were reported were and Infections and infestations 17 (16.0) vs 3 (9.1), General disorders and administration site conditions 7 (6.6%) vs 2 (6.1%), and Gastrointestinal disorders 3 (2.8%) vs 3 (9.1%), respectively. The most frequently reported AE assessed as being possibly drug-related by the investigator was nasopharyngitis in 3/111 subjects (2.7%). None were classified as severe or serious, and none lead to treatment discontinuation.

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Adverse Events of Special Interest (AESIs) were prospectively defined by the MAH based on known or potential risks of risankizumab, events anticipated to occur in the study population due to underlying disease, established concerns with injected immunoglobulin products, the immunomodulatory activity of the product, or by regulatory interest.

These AESIs included:

- infections (including serious infections, active TB, opportunistic infections [excluding TB and herpes zoster], and herpes zoster)
- malignancies (including malignant tumours, NMSC, and malignant tumours excluding NMSC)
- hypersensitivity reactions and adjudicated anaphylactic reactions
- hepatic events
- injection site reactions
- Suicidal Ideation and Behaviour (SIB)

Serious hypersensitivity reaction events were identified using a pre-defined search of AE terms and adjudicated using a prespecified definition of anaphylactic reaction by an independent anaphylaxis adjudication committee.

Overall AESIs

An Overview of TEAEs in AESIs in Percentage and EAER per 100 PY (Controlled Risankizumab Set and Short Term Risankizumab Set) is provided in **Table 37**.

Overviews of TEAEs in AESIs in the Long-Term Risankizumab Set in Percentage and EAER per 100 PY are provided in **Table 38** and Table 39, respectively.

An Overview of TEAEs in AESIs in Percentage and EAER per 100 PY (All Risankizumab Set) is provided in **Table 40**.

Table *37*: Overview of TEAEs in AESIs in Percentage and EAER per 100 PY (Controlled Risankizumab Set and Short Term Risankizumab Set)

	Controlled Risankizumab Set (16 Weeks)				**Short-Term Risankizumab Set (16 Weeks)**					
	RZB All - Adolescents (N = 54) (PY = 16.7)		**UST-Adolescents (N = 28) (PY = 8.6)**		**RZB All – Adolescents (N=68) (PY = 21.0)**		**RZB All – Children (N=43) (PY = 13.5)**		**RZB All (N=111) (PY = 34.5)**	
Subjects with:	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**
Serious infections	0	0	0	0	0	0	0	0	0	0
Opportunistic infections	0	0	0	0	0	0	0	0	0	0
Active TB	0	0	0	0	0	0	0	0	0	0
Herpes zoster	0	0	0	0	0	0	0	0	0	0
Malignant tumours	0	0	0	0	0	0	0	0	0	0
Malignant tumours excluding NMSC	0	0	0	0	0	0	0	0	0	0

	Controlled Risankizumab Set (16 Weeks)				Short-Term Risankizumab Set (16 Weeks)					
	RZB All - Adolescents (N = 54) (PY = 16.7)		UST-Adolescents (N = 28) (PY = 8.6)		RZB All – Adolescents (N=68) (PY = 21.0)		RZB All – Children (N=43) (PY = 13.5)		RZB All (N=111) (PY = 34.5)	
Subjects with:	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**
NMSC	0	0	0	0	0	0	0	0	0	0
Hepatic events	0	0	0	0	0	0	0	0	0	0
Hypersensitivity	1 (1.9)	1 (6.0)	0	0	1 (1.5)	1 (4.8)	3 (7.0)	4 (29.6)	4 (3.6)	5 (14.5)
Serious hypersensitivity	0	0	0	0	0	0	0	0	0	0
Injection site reaction	0	0	0	0	0	0	0	0	0	0
Adjudicated anaphylactic reaction	0	0	0	0	0	0	0	0	0	0
SIB	0	0	0	0	0	0	0	0	0	0

Table *38*: Overview of TEAEs in AESIs (Long-Term Risankizumab Set)

	Adolescents			Children			Adolescents + Children	
	RZB 150 mg (N = 63)	**RZB 55 mg (N = 3)**	**RZB All (N = 66)**	**RZB 150 mg (N = 14)**	**RZB 55 mg (N = 26)**	**RZB All (N = 40)**	**RZB 150 mg (N = 77)**	**RZB 55 mg (N = 29)**
Subjects with:	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Serious infections	0	0	0	0	0	0	0	0
Opportunistic infections	0	0	0	0	0	0	0	0
Active TB	0	0	0	0	0	0	0	0
Herpes zoster	0	0	0	0	0	0	0	0
Malignant tumours	0	0	0	0	0	0	0	0

	Adolescents			Children			Adolescents + Children	
	RZB 150 mg (N = 63)	RZB 55 mg (N = 3)	RZB All (N = 66)	RZB 150 mg (N = 14)	RZB 55 mg (N = 26)	RZB All (N = 40)	RZB 150 mg (N = 77)	RZB 55 mg (N = 29)
Subjects with:	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Malignant tumours excluding NMSC	0	0	0	0	0	0	0	0
NMSC	0	0	0	0	0	0	0	0
Hepatic events	5 (7.9)	0	5 (7.6)	0	0	0	5 (6.5)	0
Hypersensitivity	7 (11.1)	0	7 (10.6)	2 (14.3)	5 (19.2)	7 (17.5)	9 (11.7)	5 (17.2)
Serious hypersensitivity	0	0	0	0	0	0	0	0
Injection site reaction	2 (3.2)	0	2 (3.0)	0	0	0	2 (2.6)	0
Adjudicated anaphylactic reaction	0	0	0	0	0	0	0	0
SIB	0	0	0	0	0	0	0	0

Table *39*: Overview of TEAEs in AESIs in EAER per 100 PY (Long-Term Risankizumab Set)

	Adolescents			Children			Adolescents + Children		
	RZB 150 mg (N = 63) (PY = 178.9)	RZB 55 mg (N = 3) (PY = 5.9)	RZB All (N = 66) (PY = 184.8)	RZB 150 mg (N = 14) (PY = 29.1)	RZB 55 mg (N = 26) (PY = 44.9)	RZB All (N = 40) (PY = 74.0)	RZB 150 mg (N = 77) (PY = 207.9)	RZB 55 mg (N = 29) (PY = 50.8)	RZB All (N = 106) (PY = 258.7)
Subjects with:	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**
Serious infections	0	0	0	0	0	0	0	0	0
Opportunistic infections	0	0	0	0	0	0	0	0	0
Active TB	0	0	0	0	0	0	0	0	0
Herpes zoster	0	0	0	0	0	0	0	0	0
Malignant tumours	0	0	0	0	0	0	0	0	0
Malignant tumours excluding NMSC	0	0	0	0	0	0	0	0	0
NMSC	0	0	0	0	0	0	0	0	0
Hepatic events	5 (2.8)	0	5 (2.7)	0	0	0	5 (2.4)	0	5 (1.9)
Hypersensitivity	15 (8.4)	0	15 (8.1)	2 (6.9)	7 (15.6)	9 (12.2)	17 (8.2)	7 (13.8)	24 (9.3)
Serious hypersensitivity	0	0	0	0	0	0	0	0	0
Injection site reaction	2 (1.1)	0	2 (1.1)	0	0	0	2 (1.0)	0	2 (0.8)

	Adolescents			Children			Adolescents + Children		
	RZB 150 mg (N = 63) (PY = 178.9)	**RZB 55 mg (N = 3) (PY = 5.9)**	**RZB All (N = 66) (PY = 184.8)**	**RZB 150 mg (N = 14) (PY = 29.1)**	**RZB 55 mg (N = 26) (PY = 44.9)**	**RZB All (N = 40) (PY = 74.0)**	**RZB 150 mg (N = 77) (PY = 207.9)**	**RZB 55 mg (N = 29) (PY = 50.8)**	**RZB All (N = 106) (PY = 258.7)**
Subjects with:	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**	**Events (E/100 PY)**
Adjudicated anaphylactic reaction	0	0	0	0	0	0	0	0	0
SIB	0	0	0	0	0	0	0	0	0

Table *40*: Overview of TEAEs in AESIs (All Risankizumab Set)

	Combined RZB 150 mg (N = 106) (PY = 274.4)		Combined RZB 55 mg (N = 33) (PY = 56.1)		RZB All (N = 139) (PY = 330.5)	
Subjects with:	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**
Serious infections	0	0	0	0	0	0
Opportunistic infections	0	0	0	0	0	0
Active TB	0	0	0	0	0	0
Herpes zoster	0	0	0	0	0	0
Malignant tumours	0	0	0	0	0	0
Malignant tumours excluding NMSC	0	0	0	0	0	0
NMSC	0	0	0	0	0	0
Hepatic events	8 (7.5)	14 (5.1)	0	0	8 (5.8)	14 (4.2)
Hypersensitivity	9 (8.5)	17 (6.2)	5 (15.2)	7 (12.5)	14 (10.1)	24 (7.3)
Serious hypersensitivity	0	0	0	0	0	0
Injection site reaction	3 (2.8)	3 (1.1)	0	0	3 (2.2)	3 (0.9)

Subjects with:	Combined RZB 150 mg (N = 106) (PY = 274.4)		Combined RZB 55 mg (N = 33) (PY = 56.1)		RZB All (N = 139) (PY = 330.5)	
	n (%)	Events (E/100 PY)	n (%)	Events (E/100 PY)	n (%)	Events (E/100 PY)
Adjudicated anaphylactic reaction	0	0	0	0	0	0
SIB	2 (1.9)	2 (0.7)	0	0	2 (1.4)	2 (0.6)

Infections (Including Serious Infections, Active TB, Opportunistic Infections)

Overall Infections

In the Controlled Risankizumab Set, the percentage of subjects with TEAEs in the SOC of infections and infestations in the risankizumab and ustekinumab arms was 19 subjects [35.2%] and 9 subjects [32.1%], respectively. The most frequently reported infection (> 5.0%) was COVID-19 in both arms (9.3% in the risankizumab arm and 7.1% in the ustekinumab arm).

In the Short-Term Risankizumab Set, the number, percentage and event rates of infection related TEAEs in adolescents and children were 21 subjects (30.9%, 157.1 E/100 PY) and 15 subjects (34.9%, 177.8 E/100 PY), respectively. The most frequently reported infection AE (> 10.0%) in both age cohorts was nasopharyngitis (14.7% of adolescents and 14.0% of children).

In the Long-Term Risankizumab Set, the event rate of TEAEs in the SOC of infections and infestations was lower in adolescents (75.8 E/100 PY) compared to children (104.1 E/100 PY). The most frequently reported infection related AEs (> 10.0%) were nasopharyngitis (31.8%), COVID 19 (19.7%), and upper respiratory tract infection (18.2%) in adolescents, and nasopharyngitis (30.0%) and tonsillitis (12.5%) in children.

In the All Risankizumab Set, 67.6% of subjects had a TEAE in the SOC of infections and infestations, with a corresponding event rate of 85.0 E/100 PY. The most frequently reported infection related AEs (> 10.0% of subjects) were nasopharyngitis, COVID 19, and upper respiratory tract infection in 33.8%, 12.2%, and 12.2% of subjects, respectively. There were no severe or serious infections, and no infection led to study drug discontinuation.

No serious infections, active TB, herpes zoster, or opportunistic infections were reported in Study M19-977 or Study M1-973.

Malignancies, NMSC, and Malignant Tumours Excluding NMSC

There were no malignancies in any subject in Study M19-977 or Study M19-973 up to the data cutoff date.

Hypersensitivity Reactions (Including Serious Hypersensitivity Reactions) and Adjudicated Anaphylactic Reactions

In the Controlled Risankizumab Set, 1 treatment emergent hypersensitivity reaction (conjunctivitis allergic) occurred in a risankizumab-treated subject compared with no subjects in the ustekinumab arm. This was a mild, nonserious event, considered not related to risankizumab by the investigator, and resolved with additional concomitant treatment.

In the Short Term Risankizumab Set, the event rate of treatment emergent hypersensitivity AEs was 4.8 E/100 PY in adolescents compared to 29.6 E/100 PY in children. There was 1 event of conjunctivitis allergic in an adolescent and 4 events (dermatitis allergic, dermatitis contact, eczema, and dermatitis infected) in children contributing to the event rates above. All events were nonserious, mild or moderate in severity, and none led to study discontinuation. With the exception of the AE of eczema, the events were not considered to have a reasonable possibility of being related to study drug by the investigator.

In the Long-Term Risankizumab Set, the event rate of treatment-emergent hypersensitivity AEs was lower in adolescents (8.1 E/100 PY) compared with children (12.2 E/100 PY). The most frequently reported hypersensitivity AE occurred in the SOC of skin and subcutaneous tissue disorders, and the most frequently reported (≥ 1.5 E/100 PY) hypersensitivity AEs were eczema (2.3 E/100 PY) and urticaria (1.5 E/100 PY).

No additional hypersensitivity occurred in the All Risankizumab Set compared to the Long-Term Risankizumab Set.

The incidence of hypersensitivity reactions was compared between ADA positive and ADA negative subjects in the All Risankizumab Set and included all subjects that received at least 1 dose of study drug. Among evaluable paediatric subjects, the incidence of hypersensitivity reactions was numerically higher among treatment-emergent ADA positive (4/21, 19.0%) than the ADA negative (10/116, 8.6%) subjects. All hypersensitivity reactions events in treatment-emergent ADA positive subjects were Grade 1 or 2 in severity, nonserious, and none of these events led to treatment discontinuation.

Across all analysis sets, all hypersensitivity events were mild or moderate in severity, and the majority (22 of 24 events) were not considered to be related to study drug by the investigator. No hypersensitivity event led to study drug discontinuation. There were no serious hypersensitivity events or adjudicated anaphylactic reactions.

Table *41*: Summary of Treatment-Emergent Hypersensitivity Reaction AEs (Long-Term Risankizumab Set and All Risankizumab Set)

	Long-Term Risankizumab Set (≥ 52 Weeks of Continuous Risankizumab Exposure)						**All Risankizumab Set (All Exposure)**	
	RZB All – Adolescents (N = 66) (PY = 184.8)		**RZB All – Children (N = 40) (PY = 74.0)**		**RZB All (N = 106) (PY = 258.7)**		**RZB All (N = 139) (PY = 330.5)**	
SOC MedDRA 27.0 PT	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**
Any AE	7 (10.6)	15 (8.1)	7 (17.5)	9 (12.2)	14 (13.2)	24 (9.3)	14 (10.1)	24 (7.3)
Eye disorders	2 (3.0)	2 (1.1)	1 (2.5)	1 (1.4)	3 (2.8)	3 (1.2)	3 (2.2)	3 (0.9)
Conjunctivitis allergic	2 (3.0)	2 (1.1)	1 (2.5)	1 (1.4)	3 (2.8)	3 (1.2)	3 (2.2)	3 (0.9)

SOC MedDRA 27.0 PT	**Long-Term Risankizumab Set (≥ 52 Weeks of Continuous Risankizumab Exposure)**						**All Risankizumab Set (All Exposure)**	
	RZB All – Adolescents (N = 66) (PY = 184.8)		**RZB All – Children (N = 40) (PY = 74.0)**		**RZB All (N = 106) (PY = 258.7)**		**RZB All (N = 139) (PY = 330.5)**	
	n (%)	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**
Infections and infestations	0	0	1 (2.5)	1 (1.4)	1 (0.9)	1 (0.4)	1 (0.7)	1 (0.3)
Dermatitis infected	0	0	1 (2.5)	1 (1.4)	1 (0.9)	1 (0.4)	1 (0.7)	1 (0.3)
Injury, poisoning and procedural complications	1 (1.5)	1 (0.5)	0	0	1 (0.9)	1 (0.4)	1 (0.7)	1 (0.3)
Injection related reaction	1 (1.5)	1 (0.5)	0	0	1 (0.9)	1 (0.4)	1 (0.7)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (1.5)	1 (0.5)	0	0	1 (0.9)	1 (0.4)	1 (0.7)	1 (0.3)
Bronchospasm	1 (1.5)	1 (0.5)	0	0	1 (0.9)	1 (0.4)	1 (0.7)	1 (0.3)
Skin and subcutaneous tissue disorders	5 (7.6)	11 (6.0)	6 (15.0)	7 (9.5)	11 (10.4)	18 (7.0)	11 (7.9)	18 (5.4)
Dermatitis	0	0	1 (2.5)	1 (1.4)	1 (0.9)	1 (0.4)	1 (0.7)	1 (0.3)
Dermatitis allergic	0	0	1 (2.5)	1 (1.4)	1 (0.9)	1 (0.4)	1 (0.7)	1 (0.3)
Dermatitis atopic	1 (1.5)	2 (1.1)	0	0	1 (0.9)	2 (0.8)	1 (0.7)	2 (0.6)
Dermatitis contact	1 (1.5)	1 (0.5)	1 (2.5)	2 (2.7)	2 (1.9)	3 (1.2)	2 (1.4)	3 (0.9)
Eczema	3 (4.5)	5 (2.7)	1 (2.5)	1 (1.4)	4 (3.8)	6 (2.3)	4 (2.9)	6 (1.8)
Hand dermatitis	1 (1.5)	1 (0.5)	0	0	1 (0.9)	1 (0.4)	1 (0.7)	1 (0.3)

	Long-Term Risankizumab Set (≥ 52 Weeks of Continuous Risankizumab Exposure)						All Risankizumab Set (All Exposure)	
	RZB All – Adolescents (N = 66) (PY = 184.8)		RZB All – Children (N = 40) (PY = 74.0)		RZB All (N = 106) (PY = 258.7)		RZB All (N = 139) (PY = 330.5)	
SOC MedDRA 27.0 PT	n (%)	Events (E/100 PY)	n (%)	Events (E/100 PY)	n (%)	Events (E/100 PY)	n (%)	Events (E/100 PY)
Urticaria	2 (3.0)	2 (1.1)	2 (5.0)	2 (2.7)	4 (3.8)	4 (1.5)	4 (2.9)	4 (1.2)

Treatment-emergent adverse events (TEAEs) are defined as events occurring after the first dose of risankizumab during M19-977 and/or M19-973 (excluding the time off treatment during the withdrawal period of M19-977 Period B) and within 140 days of after the last dose of risankizumab or database cutoff, whichever occurs first.

Hepatic Disorders

No treatment-emergent hepatic events were reported in the Controlled Set or in the Short-Term Set.

The percentages and event rates of treatment emergent hepatic events in the Long-Term Set and the All Risankizumab Set are provided in **Table 42**.

Table *42*: Treatment-Emergent Hepatic AEs (Long-Term Risankizumab Set and All Risankizumab Set)

	Long-Term Risankizumab Set (≥ 52 Weeks of Continuous Risankizumab Exposure)						All Risankizumab Set (All Exposure)	
	RZB All – Adolescents (N = 66) (PY = 184.8)		RZB All – Children (N = 40) (PY = 74.0)		RZB All (N = 106) (PY = 258.7)		RZB All (N = 139) (PY = 330.5)	
SOC MedDRA 27.0 PT	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**	**n (%)**	**Events (E/100 PY)**
Any AE	5 (7.6)	5 (2.7)	0	0	5 (4.7)	5 (1.9)	8 (5.8)	14 (4.2)
Hepatobiliary disorders	2 (3.0)	2 (1.1)	0	0	2 (1.9)	2 (0.8)	3 (2.2)	3 (0.9)
Hepatic steatosis	0	0	0	0	0	0	1 (0.7)	1 (0.3)

SOC MedDRA 27.0 PT	Long-Term Risankizumab Set (≥ 52 Weeks of Continuous Risankizumab Exposure)						All Risankizumab Set (All Exposure)	
	RZB All – Adolescents (N = 66) (PY = 184.8)		RZB All – Children (N = 40) (PY = 74.0)		RZB All (N = 106) (PY = 258.7)		RZB All (N = 139) (PY = 330.5)	
	n (%)	Events (E/100 PY)	n (%)	Events (E/100 PY)	n (%)	Events (E/100 PY)	n (%)	Events (E/100 PY)
Hypertransaminasaemia	2 (3.0)	2 (1.1)	0	0	2 (1.9)	2 (0.8)	2 (1.4)	2 (0.6)
Investigations	3 (4.5)	3 (1.6)	0	0	3 (2.8)	3 (1.2)	6 (4.3)	11 (3.3)
Alanine aminotransferase increased	0	0	0	0	0	0	3 (2.2)	7 (2.1)
Aspartate aminotransferase increased	2 (3.0)	2 (1.1)	0	0	2 (1.9)	2 (0.8)	3 (2.2)	3 (0.9)
Hepatic enzyme increased	1 (1.5)	1 (0.5)	0	0	1 (0.9)	1 (0.4)	1 (0.7)	1 (0.3)

In the Long-Term Set, there were 5 subjects with 5 treatment emergent hepatic events, all in adolescents: hypertransaminasemia in 2 subjects, aspartate aminotransferase (AST) increased in 2 subjects, and hepatic enzyme increased in 1 subject each. All hepatic events were Grade 1 or 2, nonserious, and did not result in study drug discontinuation. Apart from the AE of hepatic enzyme increased, all AEs were considered as not being related to study drug by the investigator.

Three of 5 hepatic events were in the SOC of investigations and are described below:

- One subject with a medical history of being overweight. The subject experienced a mild AE of AST increased on Day 86 which resolved 13 days later while on risankizumab. The subject also had a mild AE of blood creatine phosphokinase increased on the same day. The events were considered nonserious and unrelated to risankizumab.
- One subject with a medical history of acne who experienced a moderate AE of AST increased on Day 369. The event was nonserious, not related, and resolved. The subject had started isotretinoin for acne 3 months prior to the event. On the same day, the subject had a concomitant AE of blood creatine phosphokinase increased (Grade 4 elevation).
- One subject with a medical history of being overweight. At Baseline, the subject had a Grade 1 alanine aminotransferase (ALT) elevation and a Grade 1 AST elevation of AST. The subject experienced a mild AE of hepatic enzyme increased which resolved 88 days later. The event was nonserious and considered related to the study drug.

More details about the 2 subjects with AEs of hypertransaminasemia are provided below.

- One subject with medical history of acne and obesity (BMI 32.1 kg/m2). Concomitant medications included oral contraceptives. The subject had a baseline Grade 1 elevation of ALT. The subject developed a nonserious, mild AE of hypertransaminasemia on Day 118 which resolved on Day 127. The subject had a concurrent urinary tract infection on Day 118. The event was considered not related to risankizumab and did not lead to study drug discontinuation.
- One subject who experienced a mild AE of hypertransaminasemia on Day 362. The subject had a potentially clinically significant (PCS) AST value > 5.0 × ULN concurrent with elevated ALT. At the same visit, the subject had a Grade 4 creatine kinase elevation associated with a nonserious, mild AE of blood creatine phosphokinase increased. The investigator considered the laboratory findings to be attributable to rigorous exercise and unrelated to risankizumab. Subsequent blood samples were taken and laboratory values normalised with ongoing risankizumab.

An additional 3 adolescents had 9 treatment emergent hepatic events in the All Risankizumab Set, for a total of 8 adolescents with 14 treatment emergent hepatic events.

Details of the 3 additional subjects appear below.

- An adolescent subject with a medical history of elevated ALT and hypertriglyceridemia from Part 2 of Study M19-977 experienced 4 nonserious treatment emergent hepatic events: an AE of ALT increased on Day 172 which resolved 116 days later while continuing risankizumab (in Study M19 977), and 3 AEs in Study M19-973: ALT increased, AST increased, and ALT increased on Days 365, 394, and 876, respectively. All 4 events were mild or moderate in severity and considered to have no reasonable possibility of being related to study drug by the investigator. The subject had ALT levels > 3.0 × Upper Limit of Normal (ULN) observed on Days 365, 394, 871, and 1043, respectively. All hepatic events resolved with ongoing risankizumab, except for the AE of ALT increased on Day 876, which was ongoing at the time of database lock. Per investigator, the hepatic events were attributed to diet and fatty liver disease and dietary changes were implemented.
- A subject with a medical history of being overweight and baseline elevation of ALT had 3 treatment emergent, nonserious hepatic events: 2 AEs of ALT increased of mild severity on Days 114 and 197 (in Study M19-977) and 1 AE of ALT increased of moderate severity on Day 697 (in Study M19-973). On Day 697, AST and TBIL were elevated (< 3.0× ULN and < 1.5 × ULN, respectively) and ALT was > 3.0 × ULN. On Day 715, ALT remained at > 3.0 × ULN with an elevated AST value (< 3.0× ULN). One event of ALT increased was considered ongoing at database lock. Risankizumab was not discontinued and all events were considered to have no reasonable possibility of being related to study drug by the investigator. A baseline high ALT in a subject with a history of being overweight suggests underlying Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) as the cause of elevated liver enzymes. The waxing and waning pattern further corroborate this.
- A subject with a medical history of obesity had an ALT elevation (< 3.0× ULN) on Day 30, occurring while on ustekinumab, prior to switching to risankizumab in the UST/RZB arm of the study. The subject developed 2 nonserious, treatment emergent hepatic events that were mild in severity: 1 AE of ALT increased on Day 112 and 1 AE of hepatic steatosis on Day 597 (concurrent with a moderate SAE of obesity). The AE of ALT increased resolved on Day 372. Abdominal ultrasound showed enlarged liver and features of fatty liver. All hepatic events were considered to have no reasonable possibility of being related to study drug by the investigator.

Analysis of Hepatic Laboratory Data

No subject had PCS liver-related laboratory elevations or met biochemical Hy's law criteria (ALT or AST > 3 × ULN and TBL > 2 × ULN) in the Controlled Set or the Short-Term Set.

In the Long-Term Set, the majority of liver-related elevations occurred in adolescents. No child had an ALT or AST elevation > 3.0× ULN. The percentages of adolescents with ALT or AST elevations > 3.0× ULN were 6.1% and 4.5%, respectively. None were determined by the investigator as being related to study drug.

In one subject, an ALT elevation > 5.0× ULN was reported at 1 visit:

- A subject developed an ALT (> 5.0× ULN) and AST (> 3.0× ULN) on Day 297 (Day 57 of retreatment after being randomised to the withdrawal arm of Study M19-977). Both ALT and AST improved by Day 311 and returned to normal while continuing risankizumab and prior to entering Study M19 973. The abnormal liver test values were attributed to oral metronidazole administered to treat a mild TEAE of bacterial vaginosis (which occurred on Day 284).

Overall, the proportions of subjects in the All Risankizumab Set who had liver test elevations that met criteria of PCS were low (≤ 4.4%), with all occurring in adolescents. Six subjects met criteria for Temple's corollary for ALT (maximum ALT > 3 × ULN and maximum TBL ≤ 2 × ULN) and 3 subjects met criteria for Temple's corollary for AST (maximum AST > 3 × ULN and maximum TBL ≤ 2 × ULN). Of these 9 subjects, 1 subject met criteria for Temple's corollary for both ALT and AST. No subject met biochemical Hy's law criteria in the All Risankizumab Set.

Table *43*: Summary of Subjects with Elevated Liver Tests (Long-Term Risankizumab Set and All Risankizumab Set)

	Long-Term Risankizumab Set (≥ 52 Weeks of Continuous Risankizumab Exposure)			**All Risankizumab Set (All Exposure)**
Criteria	**RZB All – Adolescents (N = 66) n/N_OBS (%)**	**RZB All – Children (N = 40) n/N_OBS (%)**	**RZB All (N = 106) n/N_OBS (%)**	**RZB All (N = 139) n/N_OBS (%)**
ALT > 3.0 × ULN	4/66 (6.1)	0/40	4/106 (3.8)	6/137 (4.4)
ALT > 5.0 × ULN	1/66 (1.5)	0/40	1/106 (0.9)	1/137 (0.7)
ALT > 10.0 × ULN	0/66	0/40	0/106	0/137
ALT > 20.0 × ULN	0/66	0/40	0/106	0/137
AST > 3.0 × ULN	3/66 (4.5)	0/40	3/106 (2.8)	3/137 (2.2)
AST > 5.0 × ULN	1/66 (1.5)	0/40	1/106 (0.9)	1/137 (0.7)
AST > 10.0 × ULN	0/66	0/40	0/106	0/137
AST > 20.0 × ULN	0/66	0/40	0/106	0/137
TBL > 1.5 × ULN	1/66 (1.5)	2/40 (5.0)	3/106 (2.8)	5/137 (3.6)
TBL > 2.0 × ULN	0/66	0/40	0/106	0/137

Criteria	Long-Term Risankizumab Set (≥ 52 Weeks of Continuous Risankizumab Exposure)			All Risankizumab Set (All Exposure)
	RZB All – Adolescents (N = 66) n/N_OBS (%)	RZB All – Children (N = 40) n/N_OBS (%)	RZB All (N = 106) n/N_OBS (%)	RZB All (N = 139) n/N_OBS (%)
Alkaline phosphatase > 1.5 × ULN	1/66 (1.5)	1/40 (2.5)	2/106 (1.9)	4/137 (2.9)
Alkaline phosphatase > 2.0 × ULN	1/66 (1.5)	0/40	1/106 (0.9)	1/137 (0.7)
ALT and/or AST > 3.0 × ULN and TBL > 1.5 × ULN	0/66	0/40	0/106	0/137
ALT and/or AST > 3.0 × ULN and TBL > 2.0 × ULN	0/66	0/40	0/106	0/137
ALT > 3.0 × ULN and TBL > 1.5 × ULN	0/66	0/40	0/106	0/137
ALT > 3.0 × ULN and TBL > 2.0 × ULN	0/66	0/40	0/106	0/137

Note: The denominator N_OBS is defined as the number of subjects with at least one post-baseline value for the respective parameter.

Injection Site Reactions

No treatment-emergent injection site reactions were reported in the Controlled Set or in the Short-Term Set.

In the Long-Term Set, 2 treatment-emergent injection site reactions were reported in 2 out of 106 subjects (1.9%, 0.8 E/100 PY); both of whom were adolescents): an AE of injection site pain and injection site hematoma in 1 subject each. Both events were mild, nonserious, and did not lead to study drug discontinuation.

In the All Risankizumab Set, the event rate of treatment-emergent injection site reactions was 0.9 E/100 PY. In addition to the 2 injection site reactions reported in the Long-Term Set, 1 adolescent reported a mild, nonserious AE of injection site erythema.

Suicidal Ideation and Behaviour (SIB)

There were no SIB events for subjects in the Controlled Set, the Short-Term Set, or the Long-Term Set.

Two events of SIB were reported in the All Risankizumab Set, both in adolescents.

A severe SAE of suicidal ideation was reported in an adolescent with a history of suicidal thoughts and aggravated depression who switched from ustekinumab to risankizumab on Day 105. The event occurred on Day 150, after the subject had discontinued fluoxetine on Day 119. The event was assessed by the investigator as having no reasonable possibility of being related to study drug.

A moderate SAE of suicidal ideation was reported on Day 384 (while in Study M19-973) in an adolescent with a previously undisclosed history of suicidal thoughts. The investigator initially considered it a reasonable possibility the event was related to study drug, and this assessment was reflected in the data submitted.

At the time of this disclosure, the participant stated that the suicidal thoughts began while the patient was enrolled in Study M19-977. The participant received 2 doses of ustekinumab at Weeks 0 and 4 in the study and was later switched to risankizumab, receiving the first dose on Day 114 (Week 16). As the participant was already enrolled in Study M19-977, this event was reported as a TEAE. However, as the participant reported that the first onset of this TEAE was coincidental with the receipt of ustekinumab, and the investigator-reported cause of the worsening suicidal thoughts at Day 384 is major depressive disorder and anxiety, this TEAE was not considered related to risankizumab.

Deaths

No deaths occurred in Study M19-977 or Study M19-973.

5.4.5. Discontinuation due to adverse events

No participants reported discontinuing the study medication as a result of an adverse event.

In the 16-week randomised treatment period of Study M19-977 (part 2), 1 subject discontinued study drug during Period A; the primary reason was listed as lost to follow-up. In Part 4, 3 subjects discontinued study drug due to withdrawal of consent, loss to follow-up, and "other reasons", respectively. No patient discontinued treatment as a result of an adverse event.

Overall, a total of 9 participants have discontinued from the development to date. Specific reasons given included "Lost to follow-up" (3), "Withdrew consent" (2), "Lack of efficacy" (1), and "" Other" (3).

5.4.6. Safety in special populations

Table *44*: AEs by age range

	Active (risankizumab)				Comparator (ustekinumab)	
MedDRA Terms	6-<12 yr* n (%) (16 weeks-controlled data set) N=0	12-<18 yr n (%) (Part 2 16 weeks-controlled data set) N=54	ALL RZB short term data set (16 weeks) N=111	ALL RZB long term data set (at least 52 weeks continuous exposure) N=106	6-<12 yr* n (%) N=0	12-<18 yr n (%) (16 weeks) N=28
Total AEs	N/A	24(44.4)	55(49.5)	83(78.3)	N/A	14 (50)
Serious AEs – Total	-	0	0	2(1.9)	-	0
- Fatal	-	N/A	N/A	0	-	N/A
- Hospitalization/ prolong existing hospitalization	-	N/A	N/A	2	-	N/A
- Life-threatening	-	N/A	N/A	0	-	N/A
- Disability/ incapacity	-	N/A	N/A	0	-	N/A
- Other (medically significant)	-	N/A	N/A	0	-	N/A
AE leading to drop-out	-	0	0	0	-	0
Psychiatric disorders	-	0	0	6(5.7)	-	0
Nervous system disorders	-	3(5.6)	4(3.6)	13(12.3)	-	3(10.7)
Injury, Poisoning and procedural complications	-	3(5.6)	5(4.5)	13(12.3)	-	0
Cardiac disorders	-	0	0	0	-	0
Vascular disorders	-	0	1(0.9)	2(1.9)	-	0
Cerebrovascular disorders	-	0	0	0	-	0
Infections and infestations	-	19(35.2)	36(32.4)	73(68.9)	-	9(32.1)

*Controlled data set does not apply to the 6-<12-year age group for risankizumab and ustekinumab

Renal or hepatic impairment

No information is available from the clinical development programme on the safety of risankizumab in paediatric patients with renal or hepatic impairment as these participants were not represented in the clinical studies.

Pregnancy

There were no pregnant subjects in either study M19-977 or study M19-973.

Prior biologic or systemic therapy

Two subgroup categories (prior biologic therapy and prior systemic therapy) were analysed to assess whether there was any impact on the overall safety profile of risankizumab. Among all 139 subjects included in the All Risankizumab Set, only 4 subjects were biologic therapy experienced. Of these, 3 participants received risankizumab 150 mg and 1 received risankizumab 55 mg. No TEAEs were reported in these participants.

In the Controlled Set, 16 participants in the risankizumab group and 4 participants in the ustekinumab group were systemic therapy experienced. There were 16 (320.0 E/100 PY) TEAEs in the risankizumab group and 1 (83.3 E/100 PY) in the ustekinumab group. None were severe or serious, and none were AESIs.

There were 38 participants in the risankizumab group and 24 participants in the Ustekinumab group who were systemic treatment naïve. Of these, there were 38 (324.8 E/100 PY) and 18 (243.2 E/100.PY) TEAEs respectively.

In the Short term Set, 16 adolescents and 10 children were systemic therapy experienced. There were 16 (320.0 E/100 PY) TEAEs in adolescents and 3 (96.8 E/100 PY) in children. None were reported as being serious or severe.

There were 52 adolescents and 33 children who were treatment naïve. Of these, there were 46 (287.5 E/100 PY) and 51 (485.7 E/100 PY) TEAEs in the respective groups.

In the Long term set, 15 adolescents and 10 children were systemic therapy experienced. There were 88 (221.1E/100 PY) and 12 (165.6 E/100 PY) TEAEs reported in adolescents and children respectively. 2 TEAEs in adolescents were reported as being serious and severe. Ther were no AESIs in children.

Ther were 51 adolescents and 30 children who were treatment naïve. Of these, there were 29 (157.9 E/100 PY) and 33 (238.8 E/100 PY) TEAEs in the respective groups.

There was 1 AESI (injection site reaction) in a treatment experienced adolescent participant, and 6 AESIs (5 hepatic events and 1injection sire reaction) in treatment naïve adolescent participants.

In the All Risankizumab set, 22 participants in the 150 mg risankizumab group and 8 in the 55 mg group were systemic therapy experienced. There were 112 (206.3 E/100 PY) TEAEs in the 150 mg group and 123 (177.0 E/100 PY) in the 55mg group.

There were 84 and 25 treatment naïve participants inth 150 mg and 55 mg groups respectively. Of these, there were 366 (155.4 E/100 PY) and 127 (310.6 E/100 PY) TEAEs reported respectively.

5.4.7. Immunological events

The incidence of hypersensitivity reactions was compared between ADA positive and ADA negative subjects in the All Risankizumab Set. The incidence of hypersensitivity reactions was numerically higher among treatment-emergent ADA positive (4/21, 19.0%) than the ADA negative (10/116, 8.6%)

subjects. All hypersensitivity reactions events in treatment-emergent ADA positive subjects were Grade 1 or 2 in severity, nonserious, and none of these events led to treatment discontinuation.

In the All Risankizumab Set, there were no injection site TEAEs in ADA positive antibody participants, 3 events in ADA negative participants in the 150mg dose cohorts, and none in the 55mg dosing cohort. No neutralising antibody positive participant had an injection site reaction, while 3 NAb–negative participants in the 150mg dose cohort had an injection site reaction. No anti-drug antibody positive participants had an injection site reaction, while 3 participants in the 150mg dosing cohort had an injection site reaction.

Upon request from the CHMP, the MAH presented comparative data illustrating the rates of ADA-associated hypersensitivity in children and adults seen in the overall clinical development:

Table *45*: Comparison of Hypersensitivity Reactions by ADA Status in Adult (All Risankizumab Psoriasis Analysis Set) and Paediatric (All-Risankizumab Safety Analysis Set) Psoriasis Subjects

	Paediatric Subjects (150 mg or 55 mg SC Dose) (N=137)		Adult Subjects (150 mg SC Dose) (N=1590)		Adult Subjects (All Risankizumab Doses) (N=1807)	
	ADA Positive (N = 21)	ADA Negative (N = 116)	ADA Positive (N = 377)	ADA Negative (N = 1213)	ADA Positive (N = 420)	ADA Negative (N = 1387)
hypersensitivity reaction (per SMQ), n (%)	4 (19.0%)	10 (8.6%)	31 (8.2%)	78 (6.4%)	32 (7.6%)	97 (7.0%)

5.4.8. Safety related to drug-drug interactions and other interactions

The potential for drug-drug interactions between risankizumab and CYP450 enzyme activity, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A using their probe substrates was assessed in the Phase 1 Study M16-007 (1311.36) in adult subjects with plaque PsO which was included and reviewed previously in the risankizumab submission for PsO. Based on the results of this study, no dose adjustments are required for the drugs that are substrates of these cytochrome P450 enzymes during co-administration with risankizumab. Given the underlying disease pathophysiology of plaque PsO is similar between adults and paediatric subjects, the results of Study M16-007 are pertinent and applicable to paediatric subjects with PsO.

5.4.9. Vital signs and laboratory findings

Haematology

No subject had a haematology value that met PCS (Grade 3 or 4) criteria in the Controlled Set or the Short Term Set.

In the Long-Term Set, no Grade 3 or 4 haematology values were reported in children. The percentages of subjects who had Grade 3 haematology values were low (≤ 1.5% for each parameter) in

adolescents, with no Grade 4 values reported. Grade 3 values in haemoglobin and platelets were observed in 1 subject each, and none of the values were associated with a TEAE.

In the All Risankizumab Set, no additional Grade 3 haematology values were reported beyond those from the Long-Term Risankizumab Set.

Clinical Chemistry Except Liver Tests

In the Controlled Set, no subject had clinical chemistry (except liver test) values that met Grade 3 or 4 criteria in the risankizumab or ustekinumab arms except for 1 ustekinumab-treated subject (3.6%) with a Grade 3 value in triglycerides that was associated with a severe, nonserious TEAE of hypertriglyceridaemia.

In the Short-Term Set, the percentage of subjects with PCS clinical chemistry abnormalities was low in adolescents (≤ 1.5%) and children (≤ 2.4%).

One child had a Grade 3 PCS value in potassium (hyper) associated with a severe, nonserious TEAE of blood potassium increased which resolved without study drug interruption. One adolescent with PCS creatine kinase reported a Grade 4 value at a single visit, which resolved and was not associated with a TEAE.

In the Long-Term Set, the percentage of subjects with PCS clinical chemistry (except liver test) abnormalities was low in adolescents (≤ 4.5%) and children (≤ 2.5%). Most abnormal chemistry values were observed at a single visit and subsequently resolved. In adolescents, all PCS Grade 3 and 4 values were observed in creatine kinase.

The percentage of subjects with PCS clinical chemistry abnormalities in the All Risankizumab Set was low (≤ 3.6%), and the abnormalities observed were consistent with those in the Long-Term Set. Some subjects had PCS clinical abnormalities associated with TEAEs. One adolescent had a Grade 3 creatine kinase elevation on Day 453 that was associated with a severe, nonserious TEAE of blood creatine phosphokinase increased; this subject had previously had a Grade 3 value in triglycerides on Day 372. In another adolescent, a Grade 4 creatine kinase measurement was observed on Day 369 and was associated with a TEAE of blood creatine phosphokinase increased and a moderate, nonserious AE of AST increased on the same day.

Across the safety analysis sets, there were no PCS abnormalities in GGT, alkaline phosphatase, creatinine, calcium, sodium, glucose, albumin, or cholesterol.

Vital Signs, Physical Findings, and Other Observations Related to Safety

In the Controlled Set, mean changes in vital sign parameters during risankizumab administration were not considered to be clinically meaningful and were comparable to changes observed in the ustekinumab arm. The proportion of subjects treated with risankizumab who experienced PCS vital sign abnormalities was low (≤ 3.8% for each parameter).

In the Short-Term Set, 4 of 43 children (9.3%) exhibited diastolic blood pressure values ≤ lower limit (based on age) and ≥ 10 mmHg decrease from Baseline compared to no subjects in the adolescent cohort. Small proportions of subjects experienced other PCS vital sign abnormalities.

In the Long-Term Set, 5 of 40 children (12.5%) exhibited diastolic blood pressure values ≤ lower limit (based on age) and ≥ 10 mmHg decrease from Baseline compared to 3 of 66 adolescents (4.5%). Small proportions of subjects experienced other PCS vital sign abnormalities.

In the All Risankizumab Set, there were no clinically meaningful mean changes from Baseline in vital sign parameters overall. The most frequently reported PCS vital sign abnormalities were diastolic blood

pressure values ≤ lower limit (based on age) and ≥ 10 mmHg decrease from Baseline (13/138 subjects, 9.4%) followed by systolic blood pressure values ≤ lower limit (based on age) and ≥ 20 mmHg decrease from Baseline (8/138 subjects, 5.8%). Small proportions of subjects experienced other PCS vital sign abnormalities (≤ 2.9%).

Height Analysis

In the Controlled Set, mean changes in height during risankizumab administration were comparable to changes observed in the ustekinumab arm.

The MAH stated that no meaningful conclusions regarding height analysis can be drawn using the Short Term Set, the Long Term Set, or the All Risankizumab Set due to the lack of a comparator and the use of risankizumab in paediatric subjects who are actively growing in height.

5.4.10. Post marketing experience

As risankizumab is not approved for the paediatric population, AEs other than PT off-label use were presented. The most frequently reported MedDRA SOC was General disorders and administration site conditions; the AEs reported within this SOC comprised 21.7% of all events. The top PTs within this SOC were drug ineffective (13.8%), fatigue (7.2%), and injection site pain (6.6%).

Among all 924 paediatric reports, the most frequent AEs (serious and nonserious) reported included PTs of drug ineffective (3.0%), PsO (2.9%), and device issue (2.5%). Device issues were most frequently seen with the on-body injector (used for CD or UC indications); no specific pattern or trend was identified.

The most frequently reported SAE PTs were CD, intestinal obstruction, and hospitalization (0.3% of each), and the remaining SAEs were reported in less than 0.3% of the retrieved reports. There were no fatal reports.

Among the 924 post marketing cases described above, 199 reports were for the PsO indication (21.5%). Most of these reports (193 reports, 97.0%) were nonserious reports, and 6 reports were serious. Overall, the most frequently reported MedDRA SOC was skin and subcutaneous tissue disorders (21.3%) with the PT of PsO the most frequently reported within the SOC. Among all the reports for the PsO indication, the 3 most frequent AEs reported included PTs of PsO (9.2%), headache (3.4%) and drug ineffective (3.4%).

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

5.4.11.1.1. Overall assessment of available safety data

The MAH presented a pooled analysis of the safety data generated from the pivotal Study M19-977 and the subsequent OLE Study M19-973. This was acceptable, given the transition of participants from the pivotal study to the OLE study, the similarity in safety assessments in both studies, and the timing of those assessments.

4 analysis sets were created from the pooled data:

- The Controlled Set included all participants who were randomised to receive either risankizumab or ustekinumab. This set allowed a direct comparison of the safety profiles of risankizumab and ustekinumab in adolescent participants over 16 weeks.
- The short-term set comprised of all adolescents and children who received risankizumab for 16 weeks. This set allowed an assessment of the short-term safety profile of risankizumab.
- The long-term set comprised of all adolescents and children who received risankizumab for 52 weeks. This set allowed an assessment of the longer-term safety profile of risankizumab.
- The All Risankizumab set comprised of all adolescents and children who received at least 1 dose of risankizumab.

Taken together, the analysis sets allowed for a comprehensive assessment of the safety profile compared to an established comparator as well as over an extended period of exposure. This was acceptable.

The CHMP noted that the design of the study was such that only the assessments in the ustekinumab-controlled part of the study were blinded and that participants and assessors were aware of the treatment allocation at all other times. However, upon request from the CHMP, the MAH clarified that appropriate measures (including objective outcome measures, independent blinded assessors for key efficacy endpoints, and centralised blinded adjudication of certain AE outcomes) were included in the clinical development to mitigate the risk of bias as a result of the open-label nature of the assessments. This was acceptable.

Disposition

The overall retention rate of >90% in the development was high.

Exposure

A total of 139 patients were exposed to risankizumab over the course of the clinical development and, of these, 135 patients had a duration of exposure greater than one year which was considered adequate for this extension of indication application.

The cumulative patient-years of exposure across all risankizumab-treated subjects was 330.5 years in total.

Long-term safety is listed as missing information in the RMP of risankizumab. Long-term safety in the paediatric population will be further characterised with the provision of the final results of the OLE study M19-973 (Category 3 study in the RMP, final report: Q2 2029).

Demographics and Baseline characteristics

The analysis sets included patients with moderate to severe plaque PsO and were similar with respect to baseline disease severity.

A majority of participants described prior medication use, with topical dermatological agents representing the majority of prior medicine use. A similar proportion of adolescents and children described prior systemic medication use. It was noted that a higher proportion of participants in the risankizumab arm reported prior systemic therapy than those in the ustekinumab arm (30% vs 14%); however, no significant differences were seen in the incidence of TEAEs between the groups.

Very few (4) patients reported prior use of biological therapies. The background medicines were appropriate for the treatment of PsO and, in general, were unlikely to represent a confounding factor in the analysis of safety.

It was noted that, in the All Risankizumab Set, a greater proportion of adolescents had obesity compared to children (10.3% versus 2.3% respectively). Given the known association between PsO and metabolic dysfunction (Cho et al, 20212), this was not unexpected.

As discussed in the pharmacology section, the exploratory analysis for the popPK showed that the observed concentrations were higher in paediatric subjects weighing >40 kg receiving the 150 mg dose of risankizumab than in adults, however, these exposures were contained within the range of exposures seen in adults. Paediatric subjects receiving 55 mg risankizumab showed comparable exposures to adults. Although the exposure in the 150 mg paediatric group was slightly higher than in adults, the exposure-response for the observed data from both studies demonstrated that there was no exposure-dependent worsening in safety events (any adverse event, any infection, or any serious event). As such, the difference seen between the populations was not clinically significant.

Overall, there were no differences in demographics or baseline disease characteristics across the groups considered likely to be a confounding factor in the analysis of safety.

Adverse events

Overall TEAEs

In the Controlled Risankizumab set, the EAER-adjusted rate of overall AEs was higher in patients taking risankizumab than in those taking ustekinumab (323.4 E/100 PY vs. 220.9 E/100 PY, respectively). This difference was associated with a higher incidence of nasopharyngitis in the risankizumab group (101.8 E/100 PY vs. 46.5 E/100 PY). Upper respiratory infections (including nasopharyngitis) is listed in section 4.8 of risankizumab SmPC as "very common" and nasopharyngitis is listed in the ustekinumab SmPC as "common". The difference in the reported incidences in the paediatric population was considered unlikely to be of clinical significance, hence, no concern was raised.

In the Short-Term Risankizumab set, the overall EAER-adjusted rate of TEAEs was lower in adolescents than in children (295.2 vs. 400.0 E/100 PY respectively). This difference was associated with a higher incidence of AEs related to General disorders and administration site conditions, specifically pyrexia (4.8 E/100 PY vs 37.0 E/100 PY respectively) in children. The incidence of nasopharyngitis was higher in adolescents than children (81.0 E/100 PY vs 55.5 E/100 PY respectively). These differences were considered unlikely to be clinically significant, hence, no concern was raised.

In the Long-term Set, the EAER-adjusted rate of TEAEs was similar between adolescents and children (171.5 vs 195.9 E/100 PY respectively).

In the All Risankizumab Set, the EAER-adjusted rate of TEAEs was similar between those patients receiving 150mg and 55mg (174.2 vs 246.0 E/100 PY respectively).

The similarity between the EAER-adjusted rates between adolescents and children in the longer-term exposure sets suggested that the difference seen in the short-term set was incidental. Hence, no concern was raised.

[2] Cho, Soo Ick, Ye Eun Kim, and Seong Jin Jo. "Association of metabolic comorbidities with pediatric psoriasis: a systematic review and meta-analysis." *Annals of Dermatology* 33.3 (2021): 203.

Re-treatment phase in Study M19-977

In the Period C randomised withdrawal part of Study M19-977, 4 subjects had 6 events that occurred after retreatment. These events included pyrexia (2), chills (1), bacterial vaginosis (1), eczema (1), psoriasis (1). None were reported as serious.

Common TEAEs

In the Controlled Set, the most commonly reported TEAEs (≥ 5.0%) in the All Risankizumab and ustekinumab groups respectively were Nasopharyngitis (101.8 E/100 PY vs 46.5 E/100 PY), COVID-19 (29.9 E/100 PY vs 23.3 E/100 PY), and Headache (24.0 E/100 PY vs 34.9 E/100 PY). All other TEAEs were reported as single instances.

In the Short-Term Set, the most commonly reported TEAEs (>5%) in adolescents and children respectively were Nasopharyngitis (81.0 E/100 PY vs 44.4 E/100 PY), COVID-19 (28.6 E/100 PY vs 0), Headache (0 vs 14.8 E/100 PY), Pyrexia (4.8 E/100 PY vs 37.0 E/100 PY), Upper respiratory tract infection (9.5 E/100 PY vs 29.6 E/100 PY), and Cough (4.8 E/100 PY vs 29.6 E/100 PY). As noted above, the main differences between the groups related to nasopharyngitis and pyrexia. As pyrexia is a common symptom in young children, this finding was not unexpected. Hence, no concern was raised

In the Long-term Set, the most common TEAEs (>10%) in adolescents and children respectively were Nasopharyngitis (30.3 E/100 PY vs 35.1 E/100 PY), Upper respiratory tract infection (9.2 E/100 PY vs 6.8 E/100 PY), Headache (8.1 E/100 PY vs 5.4 E/100 PY), Tonsillitis (4.9 E/100 PY vs 8.1 E/100 PY), COVID-19 (7.0 E/100 PY vs 1. E/100 PY), Cough (3.8 E/100 PY vs 8.1 E/100 PY), Pyrexia (2.7 E/100 PY vs 9.5 E/100 PY). There were no significant differences between the incidences of TEAEs between the groups in the long-term set.

Some minor differences were seen in the incidence and EAER-adjusted rates of TEAEs between the 150 mg and 55 mg dose cohorts, respectively in the All Risankizumab set. These differences were unlikely to be of clinical significance. Depression was reported at a higher frequency in the 150 mg dose cohort compared to the 55 mg dose cohort (2.2 vs 0). While the incidence of depression was low, the CHMP noted that there is increasing awareness of the association of depression with PsO. This aspect is further discussed in the AESI sub-section.

The most common AEs reported following risankizumab use in adults include, URTIs (very common), headache (common), and fatigue and injection site reactions (both common). The most common TEAEs seen in children were similar to those seen in adults.

Safety in Subjects Who Switched Risankizumab Doses

Of all 106 subjects with a starting dose of risankizumab 150 mg in the All Risankizumab Set, no subject switched to a lower dose. Of the 33 subjects with a starting dose of risankizumab 55 mg SC, 13 subjects (39.4%) switched to a higher dose. A review of TEAEs reported in subjects who switched did not reveal any dose dependent AE or new safety concerns.

Severe AEs

One severe, non-serious AE of hypertriglyceridaemia was reported in an ustekinumab treated subject within the first 16 weeks of treatment in the Controlled Risankizumab Set.

There was 1 severe, non-serious event of blood potassium increased in a child in the Short Term Risankizumab Set. The event was not considered to be related to study drug and resolved without study drug discontinuation.

In the Long-Term Risankizumab Set, severe TEAEs were reported in 7.6% adolescents, all events were reported in 1 subject each. One child (2.5%) had a severe AE of blood potassium increased (included above in the Short Term Risankizumab Set).

Overall, 6.5% subjects in the All Risankizumab Set had severe TEAEs. Compared to the Long-Term Risankizumab Set, additional severe AEs of blood creatine phosphokinase increased, suicidal ideation, and presyncope were reported in the RZB_All group of the All Risankizumab Set. None of the severe AEs were considered to have a reasonable possibility of being related to study drug by the investigator. Hence, no concern was raised.

Serious AEs

In the Controlled Set, there were no serious TEAEs for all Risankizumab and ustekinumab cohorts. Similarly, there were no serious TEAEs in the Short-Term Set. In the long-term Set, the incidence of serious TEAEs for adolescents and children respectively were 1.6 E/100 PY vs 0. There was 1 event of fibular fracture and 1 event of depression, the latter is discussed further below.

In the All Risankizumab Set, the incidence of serious TEAEs for the 150mg and 55mg cohorts respectively was 2.2 E/100 PY vs 0. Of these, 2 events related to suicidal ideation and 1 to depression. These are discussed further below under AESIs.

AESIs

The list of AESIs included hypersensitivity reactions, serious and opportunistic infections, malignancies, liver dysfunction, injection site reactions and SIB.

Upon request from the CHMP, the MAH explained that it was not needed to specifically list major adverse cardiac events (MACE) as AESI since MACE events are rare in the paediatric population. This was accepted. MACE is an important potential risk for risankizumab and will be further characterised in the paediatric population with the provision of the final results of the OLE study M19-973 (Category 3 study in the RMP, final report: Q2 2029).

An adjudication committee was instituted only for suspected hypersensitivity reactions because these events are clinically complex, can be difficult to diagnose or distinguish from other conditions, and can have safety implications. This was acceptable.

Serious and opportunistic infections

No serious infections, active TB, herpes zoster or opportunistic infections were reported in the clinical development in paediatric patients with PsO. All infections that occurred were mild or moderate and have been described in the previous sections.

Serious infections is an important potential risk for risankizumab and will be further characterised in the paediatric population with the provision of the final results of the OLE study M19-973 (Category 3 study in the RMP, final report: Q2 2029).

Malignancies, NMSC, and Malignant Tumours

No malignancies were reported in the clinical development in paediatric patients with PsO up to the data cut-off date.

Malignancies is an important potential risk for risankizumab and will be further characterised in the paediatric population with the provision of the final results of the OLE study M19-973 (Category 3 study in the RMP, final report: Q2 2029).

Hypersensitivity

In the Controlled Set, 1 TEAE for hypersensitivity (conjunctivitis allergic) occurred in a risankizumab treated subject compared with no subjects in the ustekinumab arm. This was described as a mild, non-serious event, was considered as not related by the investigator, and resolved with additional concomitant treatment.

In the Short-Term Set, the EAER-adjusted incidence of hypersensitivity TEAEs was 4.8 E/100 PY in adolescents compared to 29.6 E/100 PY in children. These rates correspond to 1 event of conjunctivitis allergic in an adolescent and 4 events (dermatitis allergic, dermatitis contact, eczema, and dermatitis infected) in children. Only the eczema AE was reported to be related to study drug. It was agreed with the MAH that the other hypersensitivity events that occurred during the development were in general unrelated to the exposure to the study drug.

In the Long-Term Risankizumab Set, the event rate of treatment-emergent hypersensitivity reaction was lower in adolescents (8.1 E/100 PY) compared with children (12.2 E/100 PY), with the most frequently reported hypersensitivity reactions in adolescents being eczema (2.3 E/100 PY) and urticaria (1.5 E/100 PY). No additional hypersensitivity occurred in the All Risankizumab Set compared to the Long-Term Risankizumab Set. The CHMP noted that there was a slightly higher exposure adjusted incidence of hypersensitivity reactions in adolescents versus children in the Long-Term set. However, the difference in the incidences was smaller than those seen in the Short-term set. Hence, no concern was raised.

Across all analysis sets, all hypersensitivity events were mild or moderate in severity, and the majority (22 of 24 events) were not considered to be related to study drug by the investigator. No hypersensitivity event led to study drug discontinuation. There were no serious hypersensitivity events or adjudicated anaphylactic reactions. Serious hypersensitivity is an important identified risk for risankizumab and a warning regarding hypersensitivity is implemented in the product information of risankizumab. The risk of serious hypersensitivity reactions in the paediatric population will be further characterised with the provision of the final results of the OLE study M19-973 (Category 3 study in the RMP, final report: Q2 2029).

Safety related to Immunogenicity

The incidence of hypersensitivity reactions was compared between ADA positive and ADA negative subjects in the All Risankizumab Set. The incidence of hypersensitivity reactions was numerically higher among treatment-emergent ADA positive (4/21, 19.0%) than the ADA negative (10/116, 8.6%) subjects.

Rates of ADA-associated hypersensitivity in children were compared to the rates observed in adults; the data suggested that the rates were overall similar between the different age groups. The CHMP acknowledged the limitations of the provided data in view of the low numbers of events observed in children and the potential impact of each event on the observed incidence of hypersensitivity. Considering that these events were mild/moderate in nature, the CHMP agreed with the MAH's conclusion that these events are not clinically significant.

For hypersensitivity and immunogenicity, it was accepted that the patterns of these AESIs were similar between adults, adolescents, and children. However, it was acknowledged that the small number of participants who were positive for antibodies to risankizumab prevented any definitive conclusion being made on the effect of immunogenicity on the safety of risankizumab.

Hepatic Disorders

No treatment-emergent hepatic events were reported in the Controlled Set or in the Short-Term Set.

5 events were seen in the long-Term Set, 3 of which related to laboratory values only. None of these events were described as serious, and all resolved spontaneously. A review of the cases indicated that these events were associated with possibly confounding factors such as concomitant medications or conditions such as Fatty Liver Disease secondary to obesity, or exercise induced liver function test elevations. This was accepted and no concern was raised.

Liver Function laboratory evaluations

No subject had PCS liver-related laboratory elevations or met biochemical Hy's law criteria (ALT or AST > 3 × ULN and TBL > 2 × ULN) in the Risankizumab Controlled Set or the Short Term Risankizumab Set.

In the Long-Term Set, the majority of liver-related elevations occurred in adolescents. No child had an ALT or AST elevation > 3.0× ULN. The percentages of adolescents with ALT or AST elevations > 3.0× ULN were 6.1% and 4.5%, respectively, but none were determined by the investigator as being related to study drug.

In 1 subject, an ALT elevation > 5.0× ULN was reported at 1 visit, after which ALT returned to normal levels. The patient presented also AST elevation (> 3.0× ULN). The transient liver function test elevation was attributed to the concomitant use of metronidazole for bacterial vaginosis and resolved without treatment discontinuation of risankizumab.

Overall, the data available did not show any significant liver function test elevations.

Injection Site Reactions

No treatment-emergent injection site reactions were reported in the Controlled Set or in the Short-Term Set.

In the Long-Term Risankizumab Set, 2 treatment-emergent injection site reactions were reported in 2 out of 106 subjects. Both events were mild, nonserious, and did not lead to study drug discontinuation. In the All Risankizumab Set, 1 additional mild, nonserious AE of injection site erythema was reported in 1 adolescent.

In the All Risankizumab Set, there were no injection site TEAEs in ADA positive antibody participants, 3 events in ADA negative participants in the 150mg dose cohorts, and none in the 55mg dosing cohort. No neutralising antibody positive participant had an injection site reaction, while 3 NAb – negative participants in the 150mg dose cohort had an injection site reaction. No anti-drug antibody positive participants had an injection site reaction, while 3 participants in the 150mg dosing cohort had an injection site reaction. No concern was raised.

Suicidal Ideation and Behaviour (SIB)

There were no SIB events for subjects in the Controlled Set, the Short-Term Set, or the Long-Term Set.

Two events of SIB were reported in the All Risankizumab Set, both in adolescents. One was reported as moderate and the other as severe. Both were reported as serious. Neither event was assessed to have a reasonable possibility of being related to study drug and this was accepted.

Depression was reported in 2 adolescent participants in the Long-Term set; there was history of pre-existing depressive conditions in both cases.

While SIB was designated as an AESI, depression was not. Given that there is a relationship between depression and SIB, that depression was listed as an AESI in the development plans for the adult indications, and that mental health concerns in children with PsO are increasingly being reported (Del Valle Martín et al, 20253), the MAH agreed to add depression as an AESI for the final CSR for Study M19-973. These events will also be monitored through routine pharmacovigilance activities (eg. PSUR).

Deaths

No deaths occurred in Study M19-977 or Study M19-973.

Discontinuation

No participant reported discontinuing treatment as a result of an adverse event. Only 1 subject who discontinued from the study gave a specific reason (" Lack of efficacy") for their decision to discontinue. The remaining 8 participants' reasons could not be assessed in this regard. Upon request from the CHMP, the MAH provided additional information regarding the AEs that were reported by participants who discontinued from the development programme. The information provided by the MAH showed that, while AEs were reported by many of these participants, the time between the reporting of these events and the decision of the participant to withdraw from the study was sufficiently long to support the MAH's contention that there is no relationship between the events.

Special populations

Renal or hepatic impairment

No information was available from the clinical development on the safety of risankizumab in paediatric patients with renal or hepatic impairment as these participants were not represented in the clinical studies.

Prior biologic or systemic therapy

Only 4 participants in total had a history of receiving prior biologic therapy in the All Risankizumab set, so no conclusions could be made based on this small number.

There were no clear patterns or meaningful differences seen between the treatment arms of the Controlled Set based on prior systemic therapy.

In the Short-Term Risankizumab Set, numerically lower event rates of TEAEs were observed in children who had previously received systemic therapy compared to systemic therapy naïve children. However, given the small number of participants in this group, no meaningful conclusions could be made.

In the Long-Term Risankizumab Set, numerically higher event rates of TEAEs were observed in adolescents who had previously received systemic therapy compared to systemic therapy naïve adolescents, while the opposite trend was observed in children.

There were no clear patterns or meaningful differences between the 150 mg and 55 mg groups of the All Risankizumab Set based on receipt of prior systemic therapy.

Overall, children experienced fewer TEAEs with prior systemic therapy before receiving risankizumab, while the opposite trend was seen for adolescents. However, these results should be

[3] Martín, M. Del Valle, D. Velilla Antolin, and N. Román Avezuela. "Mental health in children and young people with psoriasis. A comorbidity to consider." *European Psychiatry* 68.S1 (2025): S547-S548.

interpreted with caution due to the small number of participants in each group and so this issue was not pursued.

Drug-drug interactions

No additional drug-drug interaction studies specific to the paediatric population were included as part of this application. The MAH stated that the existing information on drug-drug interactions that has already been generated is equally applicable to the paediatric PsO population. No dose adjustments are required for the medicinal products that are substrates of cytochrome P450 enzymes during co-administration with risankizumab. This was accepted.

Laboratory investigations

Apart from the liver function test AEs discussed above, no significant laboratory abnormalities were seen in the clinical development in paediatric patients with PsO.

Post-marketing experience

While there is post-marketing experience of risankizumab in other conditions for which it has been approved, these conditions are limited to the adult population. No paediatric post-marketing experience is available for the currently approved indications.

924 reports of AEs associated with off-label paediatric use were received by the MAH. Within these reports, the most frequent AEs (serious and nonserious) reported included PTs of drug ineffective (3.0%), PsO (2.9%), and device issue (2.5%).

The most frequently reported SAE PTs were Crohn's Disease, intestinal obstruction, and hospitalization (0.3% of each), with all others being less than 0.3% of the retrieved reports. There were no fatal reports.

It was agreed with the MAH that the review of the paediatric post-marketing reports did not identify any new safety risks for risankizumab.

5.4.11.1.2. Adverse drug reactions in the SmPC

The decision to consider an AE as an ADR was based on the totality and levels of evidence including disproportionality, biological plausibility, and case details. This was accepted.

In the Controlled Risankizumab Set, the incidence of ADRs was higher with ustekinumab than with risankizumab (21.4% vs 13.0%), while nasopharyngitis was the most commonly reported ADR in the ustekinumab and risankizumab groups (5.6% and 7.1% respectively). However, no concern was raised since the observed difference was likely due to the small number of participants reporting ADRs. None of these events was reported as being severe or serious.

In the Short-term set, 10.3% of adolescents and 14.0% of children had ADRs, the most frequently reported were nasopharyngitis in adolescents (4.4%) and cough in children (4.7%). Overall, the number of participants reported as having an ADR was low in all cohorts.

For the long-term set, the most frequently reported ADR was nasopharyngitis in adolescents (7.6 E/100 PY) and both cough and headache in children (4.1 E/100 PY). The absolute numbers of these events were low. None of these events was reported as being severe or serious. Hence, no concern was raised.

No additional ADRs were proposed for inclusion in Section 4.8 of the SmPC. This was accepted.

The MAH stated that the ADR profile observed in child and adolescent subjects treated with risankizumab in the Short-Term Set was consistent with the ADR profile observed in adult subjects with PsO with the exception of upper respiratory tract infection, which was numerically higher in paediatric subjects. However, this finding could be expected, given that upper respiratory tract infections are common in the paediatric population in general. Overall, it was accepted that the incidence of other adverse events seen in the development in paediatric patients was similar to that seen in adults.

Table *46*: ADRs identified in children with PsO by Grouped Term (Controlled Risankizumab Set and Short Term Risankizumab Set) Compared to Data from the Adult Risankizumab PsO Programme

	Short-Term Risankizumab Set (16 Weeks)			**Adult PsO (16 Weeks)[a]**
	RZB All – Adol. (N = 68)	**RZB All – Children (N = 43)**	**RZB All (N = 111)**	**RZB 150 mg (N = 1306)**
ADR Grouping	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Upper respiratory tract infections	12 (17.6)	11 (25.6)	23 (20.7)	170 (13.0)
Headache	3 (4.4)	1 (2.3)	4 (3.6)	46 (3.5)
Fatigue	1 (1.5)	0	1 (0.9)	33 (2.5)
Injection site reactions	0	0	0	19 (1.5)
Tinea infections	1 (1.5)	0	1 (0.9)	15 (1.1)

The following addition to the Description of selected adverse reactions of the SmPC Section 4.8 were agreed:

- Immunogenicity in the paediatric population:

For paediatric subjects 6 to less than 18 years of age treated with risankizumab at the recommended clinical dose for up to 52 weeks in the psoriasis clinical trial, treatment-emergent anti-drug antibodies and neutralising antibodies were detected in 14.8% (13/88) and 2.3% (2/88) of evaluated subjects, respectively. Antibodies to risankizumab were not associated with changes in clinical response or safety; however, the number of patients who were positive for antibodies to risankizumab is too small for definitive conclusions about the impact of efficacy and safety of risankizumab.

- Paediatric population

The safety of risankizumab was assessed in a four-part trial of paediatric subjects with moderate to severe plaque psoriasis that evaluated safety for up to 52 weeks in 137 paediatric subjects 6 to less than 18 years of age. Overall, the safety profile observed in paediatric subjects with plaque psoriasis treated with risankizumab was generally consistent with the safety profile observed in adult subjects with plaque psoriasis.

5.4.11.2. Conclusions on clinical safety

The MAH provided an integrated safety analysis of risankizumab in paediatric patients with moderate to severe plaque PsO, pooling data from pivotal Study M19-977 and its open-label extension Study M19-973.

TEAEs were generally consistent with adult data, with upper respiratory tract infections, nasopharyngitis, and headache being most frequent. Severe TEAEs were rare and mostly unrelated to the study drug. Isolated and unrelated cases of depression and suicidal ideation were reported. No serious opportunistic infections, malignancies, or anaphylactic reactions occurred, and hypersensitivity events were mild and infrequent. Serious hypersensitivity is an important identified risk for risankizumab and a warning regarding hypersensitivity is implemented in the product information of risankizumab. The risk of serious hypersensitivity reactions in the paediatric population will be further characterised with the provision of the final results of the OLE study M19-973 (Category 3 study in the RMP, final report: Q2 2029). The important potential risks of malignancies, serious infections and MACE will also be further characterised in the paediatric population with the provision of the final results of the OLE study M19-973.

Laboratory findings were largely unremarkable, with no Hy's law cases and only transient liver enzyme elevations linked to confounding factors. Injection site reactions were rare and mild. For hypersensitivity and immunogenicity, it was accepted that the patterns of these AESIs were similar between adults, adolescents, and children.

Antibodies to risankizumab were not associated with changes in safety.

Discontinuations were minimal and unrelated to adverse events. Post-marketing data from off-label paediatric use did not reveal new safety concerns, and no deaths occurred during clinical development.

In conclusion, risankizumab was well tolerated in the paediatric population, with a safety profile consistent with adult experience.

Long-term safety is listed as missing information in the RMP of risankizumab. Long-term safety in the paediatric population will be further characterised with the provision of the final results of the OLE study M19-973.

6. Risk management plan

The assessment of the RMP version 7.2 (with date of sign-off 8 April 2026) submitted during the procedure is provided hereafter.

6.1. Safety specification

6.1.1. Proposed safety specification

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

The epidemiology for the proposed paediatric plaque psoriasis (6 to < 18 years) indication was added.

Module SII – Non-Clinical Part of the Safety Specification

No changes.

Module SIII – Clinical Trial Exposure

Most recent clinical trial cumulative exposure data was added.

Module SIV – Populations Not Studied in Clinical Trials

No new exclusion criteria in pivotal studies within the development programme were added.

Exposure of pregnant or nursing women, and exposure of subjects ≥ 75 years of age while in a risankizumab study in the development programme was updated.

Module SV – Post-Authorization Experience

This module has been updated by the MAH with updated information about post-authorisation exposure, including post-authorisation exposure by dose and indication.

Module SVI – Additional EU Requirements for the Safety Specification

No changes.

Module SVII – Identified and Potential Risks

No changes.

Module SVIII – Summary of the Safety Concerns

No changes of the safety specification were proposed compared to currently approved RMP.

Table *47*: Summary of safety concerns in the proposed RMP (version 7.2)

Summary of safety concerns	
Important identified risks	• Serious hypersensitivity reactions
Important potential risks	• MACE • Serious Infections • Malignancies
Missing information	• Use during pregnancy and lactation • Long-term safety

6.1.2. Discussion on proposed safety specification

The proposed updates to the RMP Product Overview including the addition of the new strength of 55 mg solution for injection and the newly proposed paediatric plaque PsO (6 to < 18 years) indication, which were considered acceptable.

The changes made to Modules SI-SVI (Part II of the RMP) reflected the data that have become available for the proposed paediatric plaque PsO (6 to < 18 years) indication as well as the post-marketing experience so far. These changes were considered acceptable.

Updated Module SVII was considered acceptable.

The MAH did not propose new safety concerns specific for the paediatric indication, which was acceptable.

The potential for off-label use in the paediatric population was already covered in the RMP and so no additional text was necessary in this regard.

The proposed safety specification, including the summary of safety concerns, in RMP version 7.2 was considered acceptable.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

The MAH proposed the following changes of the additional pharmacovigilance activities (new text **underlined and in bold**, deleted text ~~strike through)~~ to RMP Part III.3:

Table *48*: Planned additional pharmacovigilance activities (RMP version 7.2)

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 – Required additional pharmacovigilance activities				
P19-633: Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting/Ongoing	Estimate the risks of the following events in individuals with psoriasis exposed to risankizumab relative to individuals with psoriasis (including patients with arthropathic psoriasis [PsA]) exposed to other systemic psoriasis treatments: i) TNF-α inhibitors; ii) other IL inhibitors; and iii) non-biological systemic treatments: • overall malignancy excluding NMSC • NMSC • MACE (defined as a composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death) • serious infections (incl. opportunistic infections) • serious hypersensitivity reactions	Risks of serious hypersensitivity reactions, malignancies, MACE, and serious infections among moderate to severe plaque psoriasis patients exposed to risankizumab and comparators. Missing information: long-term safety	~~Start of data collection (incl. data up to December 2019) : January 2020~~ ~~-~~ Study Progress report~~: Q3 2023~~	~~Final study report: December 2034~~ ~~(Protocol v1.6 for psoriasis and psoriatic arthritis accepted by EMA Pharmacovigilance Risk Assessment Committee (PRAC) as of January 2023).~~**Q3 2023**
			1st Interim report of study results (incl. data up to December 2024) ~~: December 2026~~	**December 2026**
			2nd Interim report of study results (incl. data up to December 2028) ~~: December 2030~~	**December 2030**
			~~End of data collection (incl. data up to December 2032): December 2033~~ Final **study** report~~ of study results: December 2034~~	**December 2034**

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
P16-751: Pregnancy Exposures and Outcomes in Women with Psoriasis Treated with Risankizumab: A Cohort Study Utilizing Large Electronic Healthcare Databases with Mother-Baby Linkage in the United States/Ongoing	The specific objectives of this study are to: - Evaluate the rate of major congenital malformations in infants born to women exposed to risankizumab during pregnancy compared to those exposed to other systemic treatments (primary outcome for sample size estimation). - Evaluate and compare pregnancy outcomes (i.e., live birth, spontaneous abortion, elective abortion, stillbirth) among women exposed to risankizumab versus comparators during pregnancy - Assess and compare infant outcomes (neonatal deaths, serious infections up to 1 year of age) among infants born to women exposed to risankizumab during pregnancy compared to those exposed to other biologic treatments.	Missing information on the use during pregnancy.	~~- Estimated start of data collection (when Q2 2019 data become available): Q1 2021~~ - Study progress **report**~~: Q3 2024~~ ~~- End of data collection: Q3 2029~~	~~Final study report: Q3 2030~~ ~~(Protocol v1.4 for psoriasis accepted by EMA PRAC as of April 2022).~~**Q3 2024** **Q3 2027**
			–Final study report~~: Q3 2030~~	**Q3 2030**

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
P23-653: Pregnancy Exposure and Outcomes for Women with Inflammatory Bowel Disease Treated with Risankizumab/ Ongoing	The clinical trial programs did not assess the safety of risankizumab use during pregnancy. In addition to the study of risankizumab exposure in psoriasis patients, a study of pregnancy outcomes in patients with IBD (Crohn's disease and ulcerative colitis) who are exposed to risankizumab, compared to alternative biologic treatments, will be conducted. A comparative cohort study will be conducted to describe risankizumab exposure in pregnant patients with IBD, and compare pregnancy and infant outcomes to pregnant patients with IBD who were treated with alternative therapies (e.g., biologics). In addition, descriptive analyses of pregnancy outcomes in patients with IBD without exposure to any treatments under investigation will also be conducted.	Missing information: use during pregnancy.	~~– Start data collection period: Q3 2025~~ –Progress report~~: Q3 2028~~ ~~– End data collection period: Q2 2032~~	~~Final report: Q2 2033~~**Q3 2028**
			–Final report~~: Q2 2033~~	**Q2 2033**
P23-654: Long-Term Comparative Cohort Study in Patients with Ulcerative Colitis and Crohn's Disease in a Real World Setting/ Planned	The clinical trial program was not able to fully characterize the safety profile of risankizumab in the ulcerative colitis and Crohn's disease populations. Additional	Risks of serious hypersensitivity reactions, malignancies, serious infections, and MACE. Missing	~~– Start data collection period: Q1 2025~~ –Interim report~~: Q4 2029~~ ~~– End data collection period Q1 2034~~	~~Final report:~~ **Q4** ~~2034~~**2029**

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	long-term data are needed from the real-world experience of patients with ulcerative colitis and Crohn's disease treated with risankizumab to assess product potential risks. A comparative cohort study will be conducted to estimate rates of malignancy (malignancy excluding NMSC, NMSC), serious infections, serious hypersensitivity reactions, and MACE in risankizumab treated patients with ulcerative colitis or Crohn's disease, relative to alternative systemic therapies (e.g., biologics).	information: long-term safety	~~–~~Final report~~:~~ ~~Q4 2034~~	**Q4 2034**
M16-011: A Phase 3, Randomized, Double-Blind, Study Comparing Risankizumab to Placebo in Subjects with Active Psoriatic Arthritis (PsA) Who Have a History of Inadequate Response to or Intolerance to at Least One Disease Modifying Anti-Rheumatic Drug (DMARD) Therapy (KEEPsAKE 1)/ Ongoing	The primary objective of the open-label Period 2 of Study M16-011 is to evaluate the long-term safety, tolerability and efficacy of risankizumab 150 mg in subjects with psoriatic arthritis who have completed the double-blind period.	Risks of serious hypersensitivity reactions, malignancies, MACE, and serious infections Missing information: long-term safety	Final report ~~Q1 2027~~	~~Final report~~ Q1 2027
M15-998: A Phase 3, Randomized, Double-Blind Study Comparing Risankizumab to Placebo in Subjects with Active Psoriatic Arthritis Including Those Who Have a History of Inadequate Response or Intolerance to Biologic Therapy(ies) (KEEPsAKE 2)/Ongoing	The primary objective of the open-label Period 2 of Study M15-998 is to evaluate the long-term safety, tolerability and efficacy of risankizumab 150 mg in subjects with psoriatic arthritis who have completed the double-blind period.	Risks of serious hypersensitivity reactions, malignancies, MACE, and serious infections Missing information: long-term safety	Final report ~~Q4 2026~~	~~Final report~~ Q4 2026

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
M19-973: OptIMMize-2: A Phase 3 multicenter, single-arm, open-label extension study to assess the safety, tolerability, and efficacy of risankizumab in subjects with moderate to severe plaque psoriasis who have completed participation in Study M19-977 (OptIMMize-1)/Ongoing	**The objective of this study is to assess the long-term safety, tolerability, and efficacy of risankizumab in pediatric subjects with moderate to severe plaque psoriasis who have completed participation in the preceding study (Study M19-977).**	**Risks of serious hypersensitivity reactions, malignancies, MACE, and serious infections** **Missing information: long-term safety**	**Final report**	**Q2 2029**

6.2.2. Discussion on the Pharmacovigilance Plan

6.2.2.1. Routine pharmacovigilance activities

No changes to the routine pharmacovigilance activities were proposed, this was considered acceptable by the PRAC.

No changes to the already existing follow-up questionnaires for pregnancy were proposed, this was acceptable by the PRAC.

6.2.2.2. Additional pharmacovigilance activities

Additional pharmacovigilance studies were proposed to evaluate safety risks including malignancies, MACE, serious infections, serious hypersensitivity reactions, use in pregnancy, and long-term safety.

Regarding the newly sought indication of paediatric plaque PsO (6 to < 18 years), the MAH proposed the addition of the ongoing OLE Study M19-973 to the pharmacovigilance (PhV) plan in order to further characterize the risks of serious hypersensitivity reactions, malignancies, MACE and serious infections as well as long-term safety (missing information).

The PRAC agreed that additional PhV activities are required to further characterise safety concerns associated with risankizumab for the indication of paediatric plaque PsO (6 to < 18 years). At the moment, safety data in paediatric patients rely on a total of 135 patients who have >12 months exposure. Since the available safety data for risankizumab in the paediatric population did appear similar to those in the adult population, the MAH's proposal to further characterise the safety of risankizumab in the paediatric population with OLE study M19-973 (and routine PhV activities) was considered acceptable. Final report is expected in Q2 2029. In addition, there is an existing ongoing long-term PASS study (study P19-633) in patients with PsO. This study will also further contribute to the characterisation of the safety profile, and these data are also considered relevant for children and adolescents considering that the safety specification is similar between this population and adult patients with PsO.

The MAH also updated the status and milestones of existing studies of the PhV plan, which was also considered acceptable.

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

6.3. Plans for post-authorisation efficacy studies

There are no post-authorisation efficacy studies in place for risankizumab.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

No changes of the routine risk minimisation measures activities were proposed compared to currently approved RMP.

Table *49*: Planned routine risk minimisation measures (RMP version 7.2)

Safety Concern	Routine Risk Minimization Activities
Serious hypersensitivity reactions	Routine risk communication: SmPC Section 4.3 indicates contraindication if known hypersensitivity to the active substance or to any of the excipients listed in SmPC Section 6.1. SmPC Section 4.4 specifies that serious hypersensitivity reactions, including anaphylaxis, have been reported with use of risankizumab. SmPC Section 4.8 includes anaphylactic reactions as an ADR. Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4 states if a serious hypersensitivity reaction occurs, administration of risankizumab should be discontinued immediately and appropriate therapy initiated. Other routine risk minimization measures: Prescription-only medicine
MACE	Routine risk communication: No specific measures are required for patients receiving risankizumab; standard of care is adequate. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures: Prescription-only medicine
Serious infections	Routine risk communication: Summary of Product Characteristics (SmPC) Section 4.3 indicates contraindication for clinically important active infections such as active TB. SmPC Section 4.4 includes language that risankizumab may increase the risk of infections, that prescribers should consider the risks and benefits in patients with a chronic infection, a history of recurrent infection, known risk factors for infection, and language specific to TB. Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4 includes language regarding: • Treatment with risankizumab should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

Safety Concern	Routine Risk Minimization Activities
	• Patient instructions to seek medical advice for signs or symptoms suggestive of clinically important chronic or acute infection. • Closely monitor a patient who develops an infection or is not responding to standard treatment for the infection • Interrupt risankizumab until infection resolves • Evaluate patients for TB infection prior to treatment • Monitor patients for TB infection during treatment • Consider anti-TB therapy for patients with a past history of latent or active TB which was not adequately treated. Other routine risk minimization measures: Prescription-only medicine
Malignancies	Routine risk communication: No specific measures are required for patients receiving risankizumab; standard of care is adequate. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures: Prescription-only medicine
Use during pregnancy and lactation	Routine risk communication: SmPC Section 4.6 states there are limited data from the use of risankizumab in pregnant women. As a precautionary measure, it is preferable to avoid the use of risankizumab during pregnancy. Women of childbearing potential should use an effective method of contraception during treatment and for at least 21 weeks after treatment. It is unknown whether risankizumab is excreted in human milk and a decision should be made to discontinue or abstain from risankizumab therapy. The effect of risankizumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility. SmPC Section 5.3 states animal studies do not indicate direct or indirect harmful effects with respect to pre- and post-developmental toxicity. Routine risk minimization activities recommending specific clinical measures to address the risk: Product labeling will be determined based on local regulatory requirements. Other routine risk minimization measures: Prescription-only medicine
Long-term safety	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures: Prescription-only medicine

The MAH did not propose any changes of the additional risk minimisation measures.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The proposed routine risk minimisation measures were considered sufficient to minimise the risks of the product in the paediatric plaque PsO (6 to < 18 years) indication.

6.4.2.2. Additional risk minimisation measures

The MAH did not propose new additional risk minimisation measures with the introduction of a new strength of 55 mg solution for injection and a new indication of paediatric plaque PsO (6 to < 18 years). It was agreed that no new safety concerns could be identified that would require additional risk minimisation measures.

6.5. RMP Summary and RMP Annexes overall conclusion

The summary of the RMP for risankizumab has been updated in line with the updated Part I-III and Part V of the RMP. RMP Part VI was acceptable.

6.6. Overall conclusion on the Risk Management Plan

☒ The PRAC consider that the updated risk management plan version 7.2 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic Safety Update Reports submission requirements

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

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The approved indication is aligned with the population studied in the pivotal clinical study.

8.2. Labelling

8.2.1. User consultation

8.2.1.1. Conclusion from the checklist for the review of user consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Skyrizi 75 mg PFS. The bridging report submitted by the MAH has been found acceptable.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

PsO is a chronic, systemic, immune-mediated inflammatory disease characterised by erythematous papules that merge to create well-demarcated plaques with irregular borders, covered by a silvery-white scale. Signs and symptoms of PsO develop in about one-third of affected adults before the age of 20 years. Compared to adults, children with PsO have more facial and flexural lesions with more involvement in the anogenital areas; the plaques are smaller and thinner, and more pruritic. Clinical features are the same between adolescents and adults with PsO.

In addition to cosmetic manifestations, PsO is associated with comorbidities in children that impact disease severity and QoL: obesity, PsA, hyperlipidemia, hypertension, diabetes mellitus, rheumatoid arthritis (juvenile idiopathic arthritis), CD, and metabolic syndrome. PsO also imposes a significant psychosocial burden on children and their caregivers. The frequent stigmatisation of patients by their peers can induce depression, anxiety, and changes in behaviour. Additionally, the association between PsO and obesity heightens the risk of social isolation, withdrawal, depression, and anxiety.

9.1.2. Available therapies and unmet medical need

PsO therapy depends on several factors such as patient age, type of PsO, affected sites, and the extent of disease. Therapeutic options include topical medications including corticosteroids, phototherapy, and systemic therapies (e.g., MTX, acitretin, cyclosporine, and apremilast), but the use may be limited by known toxicity profiles. Biologic therapies which offer targeted therapy are becoming more frequently used in paediatric patients (e.g., etanercept and adalimumab [TNF inhibitors], ustekinumab [IL-12/23 inhibitor], and ixekizumab and secukinumab [both IL-17A inhibitors]). Guselkumab (IL-23 inhibitor) has recently been approved in the EU for the treatment of paediatric PsO.

There is still a clinical unmet need for increased efficacy for the 10% to 20% of paediatric patients with PsO who present with moderate to severe PsO. Twenty-five percent of paediatric patients with PsO experience inadequate response to topical therapy; use of systemic therapies remains low (approximately 11%), with biologics mainly reserved for later use.

9.2. Main clinical studies

Two studies were performed to support this extension of indication for the treatment of moderate to severe plaque PsO in children and adolescents from the age of 6 years who are candidates for systemic therapy:

- a pivotal phase 3 efficacy and safety study (M19-977) of risankizumab in patients from 6 to < 18 years of age with moderate to severe plaque PsO who had to be a candidate for systemic therapy. The study was completed. The study consisted of 4 parts, each with distinct patient populations.

  Parts 1 and 3 were sentinel, open-label cohorts in patients with severe plaque PsO.

Parts 2 and 4 were cohorts in patients with moderate to severe disease, hence, considered the most relevant population in relation to the proposed indication. Further, part 2 was a randomised, controlled, partially (efficacy assessor) blinded design. Part 2 and part 4 recruited the most patients compared to the other parts of the study. Hence, part 2 and part 4 were considered the most important parts to support this extension of indication application.

In Part 2, 82 paediatric subjects 12 to less than 18 years of age were enrolled. Subjects were randomised to receive risankizumab (N=54) or ustekinumab (N=28). Subjects randomised to ustekinumab received 0.75 mg/kg for subjects <60 kg; 45 mg for subjects 60 to <100 kg; 90 mg for subjects ≥100 kg, at week 0 and week 4. At week 16, ustekinumab subjects were switched to receive risankizumab every 12 weeks thereafter. The duration of treatment was up to 68 weeks.

Part 4 was a single-arm, open-label cohort that enrolled 30 paediatric subjects 6 to less than 12 years of age. All subjects received risankizumab. The duration of treatment was 52 weeks.

In this study, subjects weighing ≥40 kg received risankizumab 150 mg and subjects weighing <40 kg received risankizumab 55 mg at week 0, week 4, and every 12 weeks thereafter.

- a supportive open label extension study (M19-973) of eligible subjects who completed study M19-977. The study was ongoing during this procedure. Results were available for 129 paediatric subjects 6 to less than 18 years of age.

This application was also supported by popPK simulations from the observed data in paediatric subjects (studies M19-977 and M19-973) compared to adult subjects (data taken from popPK model that described risankizumab pharmacokinetics in healthy adults and adults with PsO).

The analysis of the unfavourable effects was based on the pooled safety analysis sets from studies M16-977 and M16-973. The safety analysis sets comprised:

- the Controlled Risankizumab Set (comparing risankizumab versus ustekinumab in adolescents over 16 weeks): 82 adolescent subjects received at least 1 dose of risankizumab (N = 54) or ustekinumab (N = 28). The median duration of exposure was 16.00 weeks in the risankizumab arm and 15.93 weeks in the ustekinumab arm.
- the Short-Term Set (including all participants who received risankizumab for 16 weeks): median exposure to risankizumab was 16.00 weeks in both adolescents and children. During the short-term period, 111 subjects were treated with risankizumab.
- the Long-Term set (exposure for 52 weeks): 106 subjects (66 adolescents and 40 children) received risankizumab for at least 52 weeks. The median length of exposure for adolescents, children, and all subjects was 137.93, 79.36, and 130.57 weeks, respectively.
- the All risankizumab set all participants who received at least 1 dose of Risankizumab: the median duration of study drug exposure was 125.43 weeks. The cumulative patient-years of exposure across all risankizumab-treated subjects was 330.5 years in total.

Overall, 137 out of 139 patients (98.6%) had greater than 6 months exposure, while 135 of 139 patients (97.1%) had greater than 12 months exposure. In addition, 82.7% of all risankizumab-treated subjects reached at least 18 months of exposure, and 48.9% continued for 30 months or more.

9.3. Favourable effects

The popPK model adequately predicted the observed data from paediatric studies M19-977 and M19-973 and demonstrated that the PK of risankizumab is comparable in paediatric subjects aged 6 to <18 years with PsO and adult subjects with PsO. Simulations indicated that the proposed dosing regimens of 55 mg in paediatric subjects weighing < 40 kg and 150 mg in paediatric subjects weighing ≥ 40 kg adequately matched risankizumab exposures seen in adult subjects with PsO. The exposure-response analysis supported that the slightly higher exposures in paediatric subjects weighing ≥ 40 kg receiving 150 mg risankizumab and the differences in exposure caused by different covariates in paediatric subjects are unlikely to have a clinically meaningful impact in practice.

In the pivotal phase 3 study M19-977, the co-primary endpoints were achievement of PASI 75 and sPGA 0/1. These are standard, widely used and clinically relevant endpoints. In part 2 of the study, the percentage of patients that achieved PASI 75 improvement from baseline at week 16 was comparable across both risankizumab and ustekinumab treated arms, (85.2% [95% CI 72.9, 93.4] and 85.7% [95% CI 67.3, 96.0], respectively). Further, the percentage of patients that achieved sPGA 0/1 at week 16 was also comparable across both risankizumab and ustekinumab treated arms (79.6% [95% CI 66.5, 89.4] and 75.0% [95% CI 55.1, 89.3], respectively). Similar results were obtained for risankizumab in parts 1, 3 and 4. These results were generally in line with those from the pivotal adult PsO studies.

For PASI 90, comparable improvements from baseline at week 16 were reached across both risankizumab and ustekinumab treated arms in part 2 of the study. Comparable response rates were also obtained for risankizumab in younger patients aged 6 to < 12 year of age in part 4 of the study. These results were comparable with those obtained in the pivotal adult PsO studies.

For other outcomes, PASI 100 and sPGA 0, improvements from baseline at week 16 were overall lower than for the co-primary endpoints, however, response rates were higher in risankizumab treated patients compared to ustekinumab patients in part 2 of the study. Comparable response rates were obtained for risankizumab in younger patients aged 6 to < 12 year of age in part 4. These results were comparable with those obtained in the pivotal adult PsO studies.

The QoL endpoints were change in CDLQI, FDLQI and Itch NRS from baseline to week 16 and were recorded for part 2 only. Comparable QoL results were demonstrated across both treatment arms and provided further support for the efficacy of risankizumab in paediatric psoriasis.

Results of study M19-977 were generally consistent across the different subgroups analysed and considered in line with those observed in adult patients.

Results from study M19-973, demonstrated that efficacy results were generally maintained throughout the OLE study with a comparable percentage of patients achieving PASI 75 and sPGA 0/1 throughout the OLE as for the primary endpoint outcomes of study M19-977 at week 16. Results were consistent across different subgroups analysed, including subgroups by weight (<40 kg/≥40kg). Results were in line with the maintenance of response observed in adult patients.

9.3.1. Uncertainties and limitations about favourable effects

Data for the youngest patients (6 to < 12 years of age) were limited since no there was no comparator, no withdrawal and no retreatment in part 4 of study M19-977. However, these limitations were found acceptable considering the supportive efficacy data of risankizumab in adolescents and adults with plaque PsO.

The sample size was limited for both studies (studies M19-973 and M19-977) in patients with paediatric plaque PsO, particularly for any subgroup analyses including the number of patients weighing < 40 kg, which limited interpretation of results. However, these limitations were overall acceptable since results in these studies showed a clinically relevant effect in paediatric patients with plaque PsO. The efficacy of risankizumab in paediatric patients with plaque PsO was further supported by the efficacy established in adult patients with plaque PsO.

While the objective of the supportive open label study M19-973 was to evaluate the long-term safety and efficacy of risankizumab in paediatric patients, only interim data were presented and the extent of exposure varied amongst patient groups. This impacted the robustness of conclusions in some patient groups, in particular in Part 4 where the number of patients with data available after week 24 was too low for interpretation. However, the CHMP considered it acceptable that the final results from this study will be submitted for assessment in the post-authorisation setting (Category 3 study in the RMP, final report: Q2 2029).

9.4. Unfavourable effects

In the Long-term Set, the most common TEAEs (>10%) in adolescents and children respectively were nasopharyngitis, upper respiratory tract infection, headache, tonsillitis, COVID-19, cough and pyrexia. The most common TEAEs seen in children were similar to those seen in adults.

The key unfavourable effects observed in the paediatric psoriasis programme were hypersensitivity events. In the Short-Term Set, the number and EAER-adjusted incidence of hypersensitivity TEAEs was 1 (4.8 E/100 PY) in adolescents compared to 4 (29.6 E/100 PY) in children. The event rate differences are likely due to low numbers rather than a physiological reason. All hypersensitivity events were mild or moderate in severity, and the majority (22 of 24 events) were not considered to be related to study drug by the investigator. There were no serious hypersensitivity events or adjudicated anaphylactic reactions. Serious hypersensitivity is an important identified risk for risankizumab and a warning regarding hypersensitivity is implemented in the product information of risankizumab. The risk of serious hypersensitivity reactions in the paediatric population will be further characterised with the provision of the final results of the OLE study M19-973 (Category 3 study in the RMP, final report: Q2 2029).

Overall, risankizumab appeared generally well tolerated in the paediatric population, with a safety profile consistent with adult experience.

9.4.1. Uncertainties and limitations about unfavourable effects

Despite a sufficient number of paediatric participants enrolled in the study for at least 1 year, there remains a lack of long-term safety data that would allow the characterisation of known safety concerns that are recognised as being potentially associated with medicines in this class such as malignancies. Long term safety is listed as missing information in the RMP. Long-term safety in the paediatric population will be further characterised with the provision of the final results of the OLE study M19-973 (Category 3 study in the RMP, final report: Q2 2029). The important potential risks of malignancies, serious infections and MACE will also be further characterised in the paediatric population with the provision of the final results of the OLE study M19-973.

Suicidal ideation or behaviour was listed as an AESI in the development in paediatric plaque PsO. In the Long-Term Set, 6 events (2.2 E/100 PY) were reported in adolescents, while none were reported in children. In the All Risankizumab set, 2 adolescents reported SIB. None of the TEAEs had a reasonable possibility of being related to risankizumab exposure. There is increasing awareness of

the association between PsO and mental health disorders, and as such the reporting of both depression and SIB in this small population was noted. It was further noted that depression will be included as an AESI in the final analysis of Study M19-973. These events will also be monitored through routine pharmacovigilance activities (e.g. PSUR).

9.5. Effects Table

Table *50*: Effects Table for Skyrizi in paediatric psoriasis (1/1/2025).

Effect (short description)	Treatment		Control	Uncertainties/ Strength of evidence	Ref
Favourable Effects					
	Risankizumab 150mg ≥40kg or 55mg <40kg		Ustekinumab		
sPGA 0/1 at week 16, n (%)	43 (79.6)		21 (75.0)	**Unc:** Assessed descriptively, no statistical testing performed	Study M19-977, Part 2, patients aged 12 to < 18 years with moderate to severe PsO
PASI 75 at week 16, n (%)	46 (85.2)		24 (85.7)		
PASI 90 at week 16, n (%)	35 (64.8)		17 (60.7)		
PASI 100 at week 16, n (%)	22 (40.7)		5 (17.9)		
sPGA 0/1 at week 16, n (%)	27 (90.0)		N/A	**Unc:** Assessed descriptively, no statistical testing performed	Study M19-977, Part 4, patients aged 6 to < 12 years with moderate to severe PsO
PASI 75 at week 16, n (%)	26 (86.7)		N/A		
PASI 90 at week 16, n (%)	23 (76.7)		N/A		
PASI 100 at week 16, n (%)	13 (43.3)		N/A		
Unfavourable Effects					
	Risankizumab (adolescents)	Risankizumab (children)	Ustekinumab (adolescents)		
Nasopharyngitis TEAEs (n (EAER))	56 (30.3 E/100 PY)	26 (35.1 E/100 PY)	N/A	**SoE:** Representative. Balanced groups **Unc:** Single arm design	Long-Term set, Integrated analysis of M16-977 and M16-973
Upper respiratory tract infection TEAEs (n (EAER))	17 (9.2 E/100 PY)	5 (6.8 E/100 PY)	N/A		

Effect (short description)	Treatment		Control	Uncertainties/ Strength of evidence	Ref
Headache TEAEs (n (EAER))	15 (8.1 E/100 PY)	4 (5.4 E/100 PY	N/A		
Tonsillitis TEAEs (n (EAER))	9 (4.9 E/100 PY)	6 (8.1 E/100 PY)	N/A		
COVID-19 TEAEs (n (EAER))	13 (7.0 E/100 PY)	1 (1. E/100 PY)	N/A		
Cough TEAEs (n (EAER))	7 (3.8 E/100 PY)	6 (8.1 E/100 PY)	N/A		
Pyrexia TEAEs (n (EAER))	5 (2.7 E/100 PY)	7 (9.5 E/100 PY)	N/A		
Hypersensitivity TEAEs (n (EAER))	1 (4.8 E/100 PY)	4 (29.6 E/100 PY)	N/A	**SoE:** Representative. Balanced groups **Unc:** Single arm design	Short-Term set, Integrated analysis of M16-977 and M16-973

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; EAER: Exposure adjusted event Rates; N/A: Not applicable; TEAE – treatment emergent adverse event

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

In the pivotal study M19-973, risankizumab was efficacious with a clinically relevant treatment effect in paediatric patients aged 6 years and older with moderate to severe plaque PsO. The OLE study M19-973 showed long-term efficacy of risankizumab in paediatric patients aged 6 years and older with moderate to severe plaque PsO. Results were in line with those observed in adult patients. There is an unmet need for increased efficacy for the 10% to 20% of paediatric patients with PsO who present with moderate to severe plaque PsO and the 25% of patients who experience inadequate response to topical therapy. The main limitations of the paediatric clinical studies included the small sample size, the lack of blinded, controlled data available for the youngest patients (6 to < 12 years of age), and the lack of statistical testing of the efficacy results. However, since a clinically relevant effect was observed in all subsets of the studied paediatric patients and considering the established efficacy in adult patients with PsO, it was concluded that the efficacy of risankizumab in the treatment of paediatric patients aged 6 years and older with moderate to severe plaque PsO was shown. This conclusion was further supported by the simulations indicating risankizumab exposures at the proposed posology in paediatric patients with PsO adequately matching exposures seen in adult patients with PsO.

From a safety perspective, risankizumab was well-tolerated in both adolescents and children, with no discontinuations reported as a result of adverse events. The safety profile seen in children and adolescents with plaque PsO was similar to that seen in adults being treated with risankizumab in this condition. The most common adverse events related to infections. Serious infections is an important

potential risk for risankizumab and will be further characterised in the paediatric population with the provision of the final results of the OLE study M19-973 (Category 3 study in the RMP, final report: Q2 2029), as agreed by the CHMP. There were no serious hypersensitivity events or adjudicated anaphylactic reactions in paediatric patients. Serious hypersensitivity is an important identified risk for risankizumab that will be further characterised in the paediatric population with the provision of the final results of the OLE study M19-973. The existing warning on hypersensitivity remains adequate. Long-term safety, MACE, and malignancies, which are safety concerns of risankizumab, will also be further characterised in the paediatric population through the provision of the final results of the OLE study M19-973.

9.6.2. Balance of benefits and risks

Results of one pivotal study and a supportive long-term open label extension study demonstrated that risankizumab is efficacious with a large, clinically relevant treatment effect in paediatric patients aged 6 years and older with moderate to severe plaque PsO who are candidates for systemic therapy. Efficacy results in children were in line with the efficacy results observed in adult patients with plaque PsO. In terms of safety, risankizumab was well-tolerated in the paediatric population, with a safety profile consistent with adult experience.

Overall, the benefits of risankizumab outweigh the risks for the treatment of moderate to severe plaque PsO in children and adolescents from the age of 6 years who are candidates for systemic therapy.

9.7. Benefit-risk conclusions

9.7.1. At Day 180 – CHMP conclusions

The benefit/risk of risankizumab is positive for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.