14 October 2021
EMA/639007/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Skyrizi

International non-proprietary name: risankizumab

Procedure No. EMEA/H/C/004759/II/0014

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

Ab	Antibody
ACR	American College of Rheumatology
ACR/NAPF	American College of Rheumatology/National Psoriasis Foundation
ACR20	American College of Rheumatology 20% improvement criteria
ACR50	American College of Rheumatology 50% improvement criteria
ACR70	American College of Rheumatology 70% improvement criteria
ADAs	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
AI	Autoinjector
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AO	As Observed
AS	ankylosing spondylitis
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASIs	adverse events of safety interest
AST	aspartate aminotransferase
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	biologic disease-modifying antirheumatic drug
Bio-IR	inadequate response to 1 or 2 biologic therapies or intolerance
BL	Baseline
BMI	body mass index
BSA	body surface area
BSA-PsO	body surface area - psoriasis
CASPAR	ClASsification criteria for Psoriatic ARthritis
CD	Crohn's disease
CFB	change from Baseline
CFR	Code of Federal Regulations
CHMP	Committee for Human Medicinal Products
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
csDMARD-IR	inadequate response to at least 1 csDMARD or intolerance
csDMARDs	conventional synthetic disease-modifying anti-rheumatic drugs
CSR	clinical study report
CSS	Clinical Summary of Safety
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DAS28	Disease Activity Score 28
DAS28-hsCRP	Disease Activity Score 28 using hsCRP
DMARD	disease-modifying antirheumatic drug
DMARD-IR	disease-modifying antirheumatic drug-intolerant or inadequate responder

EAERs	exposure-adjusted event rates
EU	European Union
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy - Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire - Disability Index
HS	hidradenitis suppurativa
hsCRP	high sensitivity C-reactive protein
IBD	inflammatory bowel disease
IC_{50}	concentration producing 50% inhibition
ICH	International Council for Harmonisation
IE	Intercurrent events
IgG1	immunoglobulin G1
IL	Interleukin
IR	incidence ratio
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
JAK	Janus kinase
JSN	joint space narrowing
K_d	dissociation constant
LDI	Leeds Dactylitis Index
LEF	Leflunomide
LEI	Leeds Enthesitis Index
LS	least square
mAb	monoclonal antibody
MACE	Major Adverse Cardiovascular Event
MCS	Mental Component Summary
MDA	minimal disease activity
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	Mixed-Effect Model Repeated Measures
mNAPSI	Modified Nail Psoriasis Severity Index
MRI	magnetic resonance imaging
mTSS	modified Total Sharp Score
MTX	Methotrexate
NAb	neutralizing antibody
NCI	National Cancer Institute
NMSC	non-melanoma skin cancer
NRI	Non-Responder Imputation

NSAID	nonsteroidal anti-inflammatory drug
NSP	needle stick protection device
PASI	Psoriasis Area Severity Index
PASI 90	90% improvement in Psoriasis Area and Severity Index
PASI 100	100% improvement in Psoriasis Area and Severity Index
PBO	Placebo
PCS	Physical Component Summary
PFS	prefilled syringe
PGA	Physician's Global Assessment
PGA-F	Physician Global Assessment of Fingernail Psoriasis
pM	Picomolar
PRO	patient-reported outcome
PsA	Psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
PSOLAR	Psoriasis Longitudinal Assessment and Registry
PT	Preferred Term
PUVA	psoralen and ultraviolet A radiation
PY	patient-year
q12w	every 12 weeks
QoL	quality of life
R&D	research and development
RCT	randomized clinical trial
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SF-36	36-Item Short Form Health Survey
SIR	standardized incidence ratio
SJC	swollen joint count
SMR	standard mortality ratio
SOC	System Organ Class
SpA	Spondyloarthritis
SSA	study size adjusted
SSZ	Sulfasalazine
TB	Tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNF	tumor necrosis factor
UC	ulcerative colitis
US	United States
vs.	Versus
W	Week
WPAI	Work Productivity and Activity Impairment

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 26 March 2021 an application for a variation.

The following variation was requested:

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

Extension of indication for the treatment of active psoriatic arthritis in adults. Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 to the SmPC have been updated. The Package leaflet is updated accordingly. Additionally, Annex II is also updated.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) n P/0039/2021 on the granting of a PIP.

At the time of submission of the application, the PIP P/0039/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did seek Scientific Advice at the CHMP relating to the Phase 3 clinical development program in the psoriatic arthritis indication was obtained in October 2015 (EMEA/H/SA/3171/1/2015/III and EMEA/H/SA/3171/2/2015/II) and October 2017 (EMEA/H/SA/3171/2/FU/1/2017/II).

1.2. Steps taken for the assessment of the product

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

Rapporteur: Peter Kiely Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	26 March 2021
Start of procedure:	24 April 2021
CHMP Co-Rapporteur Assessment Report	18 June 2021
CHMP Rapporteur Assessment Report	18 June 2021
PRAC Rapporteur Assessment Report	18 June 2021
PRAC members comments	30 June 2021
Updated PRAC Rapporteur Assessment Report	2 July 2021
PRAC Outcome	8 July 2021
CHMP members comments	12 July 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 July 2021
Request for supplementary information (RSI)	22 July 2021
CHMP Rapporteur Assessment Report	14 September 2021
PRAC Rapporteur Assessment Report	17 September 2021
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	30 September 2021
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	07 October 2021
Opinion	14 October 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Risankizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that is directed against interleukin (IL)-23 p19. The framework of the risankizumab antibody (Ab) has been engineered with 2 mutations in the Fc region to reduce Fcγ receptor and complement binding. Binding of risankizumab to IL-23 p19 inhibits the action of IL-23 to induce and sustain T helper 17 type cells, innate lymphoid cells, γδT cells, and natural killer cells responsible for tissue inflammation, destruction, and aberrant tissue repair.

Psoriatic arthritis (PsA) is a chronic systemic inflammatory disease classified as a sub-type of spondyloarthritis (SpA) and characterized by the hallmark features of arthritis and psoriasis. The estimated prevalence of PsA in the general population varies from 0.02% to 1.0% across the world; in patients with psoriasis, the prevalence of PsA ranges from 6% to 42%. The course of PsA is usually one of flares and remissions with varying combinations of disease manifestations affecting the synovium, tendons, entheses, skin, and bone. Under current clinical guidelines, the primary goal of treatment is to maximize long-term health-related quality of life and treatment should be aimed at the target of remission, or low disease activity, by regular disease activity and appropriate adjustment of therapy

(Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis. 2020;79(6):700-12).

Initial treatment of musculoskeletal symptoms is with nonsteroidal anti-inflammatory drugs (NSAIDs) and local corticosteroid injections. Topical therapies are used for the initial treatment of psoriasis. In case of toxicity or lack of efficacy with these measures, clinical guidelines recommend systemic therapy with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (methotrexate [MTX], leflunomide [LEF], sulfasalazine [SSZ], or ciclosporin A), followed by biologic therapy (tumor necrosis factor [TNF], IL-17, or IL-12/23 inhibitors) in those who do not respond adequately to csDMARDs.

Primary or secondary non-response or intolerance to adverse effects of available therapies leaves patients with an unmet medical need. The development of other target-specific biologic therapies (e.g., IL-23 inhibitors) or targeted synthetic DMARDs (such as Janus kinase [JAK] inhibitors) provides additional therapy options.

Risankizumab is authorised in the European Union (EU) for the treatment of moderate to severe plaque psoriasis in aduts at the same dose and posology as that proposed for treatment of PsA under this variation (Skyrizi; EU/1/19/1361/001-3).

The claimed therapeutic indication is:

Skyrizi, alone or in combination with non-biologic disease-modifying antirheumatic drugs (csDMARDs), is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more DMARDs.

The dose proposed is risankizumab 150 mg subcutaneously (sc) at Week 0, Week 4 and every 12 weeks thereafter.

In support of this application, the risankizumab clinical development program for PsA includes one Phase 2 dose ranging study (Study M16-002), one Phase 2 open-label extension study (Study M16-244) and two pivotal Phase 3 studies (Studies M15-998 and M16-011) designed to evaluate safety and efficacy of risankizumab as monotherapy and as combination therapy (with background csDMARDs) by enrolling adult subjects who had an inadequate response or intolerance to one or 2 biologic therapies (Bio-IR) and subjects who had an inadequate response or intolerance to at least one csDMARD (csDMARD IR). The complete Week 52 dataset for the Phase 3 trials is expected to be available in the third quarter of 2021.

An integrated safety analyses of long-term data from studies of risankizumab in subjects with moderate to severe psoriasis (All Risankizumab PsO Analysis Set, which primarily examined the same dosing regimen as the psoriatic arthritis clinical studies) are provided to support the safety assessment of risankizumab for the treatment of subjects with PsA.

2.1.2. About the product

Risankizumab is authorised in the European Union (EU) for the treatment of moderate to severe plaque psoriasis in adults at the same dose and posology as that proposed for treatment of PsA under this variation (Skyrizi; EU/1/19/1361/001-3).

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

The Phase 3 program for psoriatic arthritis is largely consistent with the advice on the Phase 3 development program received from the CHMP (October 2015 (EMEA/H/SA/3171/1/2015/III and

EMEA/H/SA/3171/2/2015/II) and October 2017 (EMEA/H/SA/3171/2/FU/1/2017/II) for the treatment of psoriatic arthritis in adult subjects.

The same 90 mg/mL risankizumab formulation in PFS (75 mg/0.83 mL) approved for the treatment of psoriasis was evaluated in the clinical development program for PsA including the two pivotal Phase 3 studies (Studies M15-998 and M16-011). Applications for a new strength and formulation of 150 mg/mL risankizumab in prefilled syringe with needle stick protection and autoinjector (AI) to administer the 150 mg risankizumab dose in a single injection are currently under review in the US, EU, and other countries. Following approval of the new 150 mg/mL PFS and AI, these presentations will also be proposed for use in psoriatic arthritis.

2.1.4. General comments on compliance with GCP

The MAH states all clinical studies in support of this application have been conducted in accordance with the International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and relevant regulatory requirements. Subjects were accorded all rights granted by the Declaration of Helsinki.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, its use 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.

2.2.2. Discussion on non-clinical aspects

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of risankizumab.

Considering the above data, risankizumab is not expected to pose a risk to the environment.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of risankizumab.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 2 Safety	M16-244	5.3.5.2	Assess the safety and tolerability of risankizumab in PsA subjects who have completed all doses of study drug and Wk 24 visit of Study M16-002 (1311.5)	Single-arm, open-label extension	RZB: 150 mg q12w with an optional 150 mg dose at Wk 4 for subjects who have not achieved response	145	Adult subjects with PsA who completed Study M16-002 (1311.5)	36 weeks	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3 Efficacy and Safety	M15-998	5.3.5.1	Primary, Period 1 Compare the efficacy of RZB 150 mg vs. PBO for the treatment of signs and symptoms of PsA Secondary, Period 1 Compare the safety and tolerability of RZB 150 mg vs. PBO Secondary, Period 2 Evaluate the long-term safety, tolerability, and efficacy of RZB 150 mg in subjects who have completed Period 1	Period 1: Randomized, DB, parallel-group, PBO-controlled Period 2: Long-term, open-label extension	Period 1: RZB arm: RZB 150 mg SC at BL and Wks 4 and 16 PBO arm: Matching PBO SC at BL and Wks 4 and 16 Period 2: RZB to RZB arm: PBO at Wk 24, then RZB 150 mg SC at Wk 28 and q12w thereafter PBO to RZB arm: RZB 150 mg SC at Wks 24, 28, and q12w thereafter	RZB to RZB arm: 224 PBO to RZB arm: 220	Adult subjects with moderately to severely active PsA with either 1) inadequate response or intolerance to 1 or 2 biologic therapies or 2) inadequate response to ≥ 1 csDMARD or an intolerance or contraindication to csDMARDs	Period 1: 24 weeks; Period 2: Up to 208 weeks	Ongoing; Interim Full CSR (up to Wk 24)

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 2 Efficacy and Safety	M16-002 (1311.5)	5.3.5.1	Provide proof-of-concept and dose-ranging data of RZB in subjects with active PsA	Randomized, DB, PBO-controlled, multiple-doses, parallel-design, dose-ranging	RZB: Arm 1: 150 mg SC at Wks 0, 4, 8, 12, 16 Arm 2: 150 mg SC at Wks 0, 4, 16 (PBO at Wks 8, 12) Arm 3: 150 mg SC at Wks 0, 12 (PBO at Wks 4, 8, 16) Arm 4: 75 mg SC at Wk 0 (PBO at Wks 4, 8, 12, 16) PBO: Arm 5: SC at Wks 0, 4, 8, 12, 16	RZB Arm 1: 42 Arm 2: 42 Arm 3: 39 Arm 4: 20 PBO Arm 5: 42	Adult subjects with active PsA	16 weeks	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3 Efficacy and Safety	M16-011	5.3.5.1	Primary, Period 1 Compare the efficacy of RZB 150 mg vs. PBO for the treatment of signs and symptoms of PsA Secondary, Period 1 Compare the efficacy of RZB 150 mg vs. PBO for the inhibition of progression of structural damage and to compare the safety and tolerability of RZB 150 mg vs. PBO Secondary, Period 2 Evaluate the long-term safety, tolerability, and efficacy of RZB 150 mg in subjects who have completed Period 1	Period 1: Randomized, DB, parallel-group, PBO-controlled Period 2: Long-term, open-label extension	Period 1: RZB arm: RZB 150 mg SC at BL and Wks 4 and 16 PBO arm: Matching PBO SC at BL and Wks 4 and 16 Period 2: RZB to RZB arm: PBO at Wk 24, then RZB 150 mg SC at Wk 28 and q12w thereafter PBO to RZB arm: RZB 150 mg SC at Wks 24, 28, and q12w thereafter	RZB to RZB arm: 483 PBO to RZB arm: 481	Adult subjects with moderately to severely active PsA with inadequate response to ≥ 1 csDMARD or an intolerance or contraindication to csDMARDs	Period 1: 24 weeks; Period 2: Up to 208 weeks	Ongoing; Interim Full CSR (up to Wk 24)

2.3.2. Pharmacokinetics

The pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and exposure-response relationships for efficacy and safety of risankizumab have been well characterized in healthy subjects and subjects with moderate to severe plaque psoriasis, for which the medicinal product is already authorised.

To support the registration in active PsA, additional clinical pharmacology assessments were conducted in two Phase 2 studies (Studies M16-002 and M16-244) and two Phase 3 studies (Studies M15-998 and M16-011).

Integrated analyses of population pharmacokinetics (PoP PK) and exposure-response for efficacy and safety, as well as analyses on the impact of immunogenicity on PK, safety, and efficacy were performed using combined data from these studies to further characterize risankizumab clinical pharmacology in subjects with active PsA.

PK data for risankizumab across the Phase 2 and 3 studies indicated linear and time-independent PK consistent with typical IgG1 mAbs and the known risankizumab PK profiles in healthy subjects and subjects with plaque psoriasis. A summary of risankizumab trough concentrations across the Phase 2 and Phase 3 studies after administration of 150 mg SC at Week 0, 4 and then q12w thereafter in subjects with PsA is presented in Table 1.

Table 1: Summary of Risankizumab Trough Concentrations (100 µg/mL) in Subjects with Active Psoriatic Arthritis Across Phase 2 and Phase 3 Studies

Regimen: Risankizumab 150 mg SC at Weeks 0, 4, 16	Geometric Mean (Mean, %CV) [N]						
	Week 4	Week 12	Week 16	Week 24	Week 28	Week 36	Week 48
Phase 2 Study M16-002	6.88 (7.20, 29) [42]	--	2.70 (3.01, 52) [41]	--	2.41 (2.97, 79) [8]	--	--
Phase 2 Study M16-244	--	2.95 (3.47, 68) [28]	--	2.28 (2.46, 40) [23]	--	2.63 (3.24, 79) [31]	1.96 (2.14, 42) [22]
Phase 3 Study M15-998	--	--	--	--	1.51 (1.91, 70) [199]	--	--
Phase 3 Study M16-011	--	--	--		1.46 (1.81, 67) [437]	--	--

Risankizumab exposures approximated steady-state exposures by Week 16 in the Phase 2 dose-ranging study based on similar trough concentrations at Week 16 and Week 28 in Study M16-002.

The slightly higher exposures observed at Week 28 in Phase 2 Study M16-002 as compared to both Phase 3 studies was attributed to the smaller sample size and larger variability at Week 28 in Study M16-002.

Bioanalytical methods

Determination of Risankizumab Concentrations in Human Serum

The samples from the Phase 2 psoriatic arthritis Studies M16-002 and M16-244 were analysed for risankizumab concentrations using ligand binding assays previously validated and submitted for the psoriasis application. For the pivotal psoriatic arthritis studies M15-998 and M16-011, a bridging electrochemiluminescence (ECL) assay was employed to determine risankizumab concentrations in human serum samples. While this assay is based on the same ligand binding assay principles as the previous risankizumab assay used for the Phase 2 studies, it uses serum instead of plasma for sample matrix as well as new critical reagents compared to the previous assay.

The defined assay performance specifications and the method validation carried out are, in general, in line with the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 rev.1 corr.2).

Determination of Anti-Drug Antibodies (ADAs) in Human Serum

For the pivotal psoriatic arthritis studies, a titer-based acid dissociation bridging electrochemiluminescence (ECL) immunoassay was developed. It uses the same principle as the previous assay used in the original psoriasis submission (and in the phase 2 studies for psoriatic arthritis), with the main differences being the sample matrix (serum instead of plasma), the different critical reagents, and the way the titers are being reported.

Determination of Risankizumab Neutralizing Antibodies (NAb) in Human Serum

A cell based NAb assay was developed to determine NAbs in human serum samples and a psoriatic arthritis specific cut point was established. The method is based on the same cell assay principle and critical reagents as the previous risankizumab NAb assay used in the psoriatic arthritis Phase 2 studies and the psoriasis Phase 3 studies.

Determination of Serum Biomarkers IL-6, IL-17A, IL-17F, IL-22 and TNF-α

IL-17A, IL-17F and IL-22 were determined in serum using a quantitative fluorescent sandwich immunoassay (SMC™ Human High Sensitivity Immunoassay Kits; EMD Millipore). IL-6 and TNF-α were determined in serum using a three-step digital immunoassay on the Simoa HD-1 or HD-X Analyzer and Single Molecule Array technology (Simoa™ Assay Kit; Quanterix).

Phase 2 Studies in Subjects with Psoriatic Arthritis

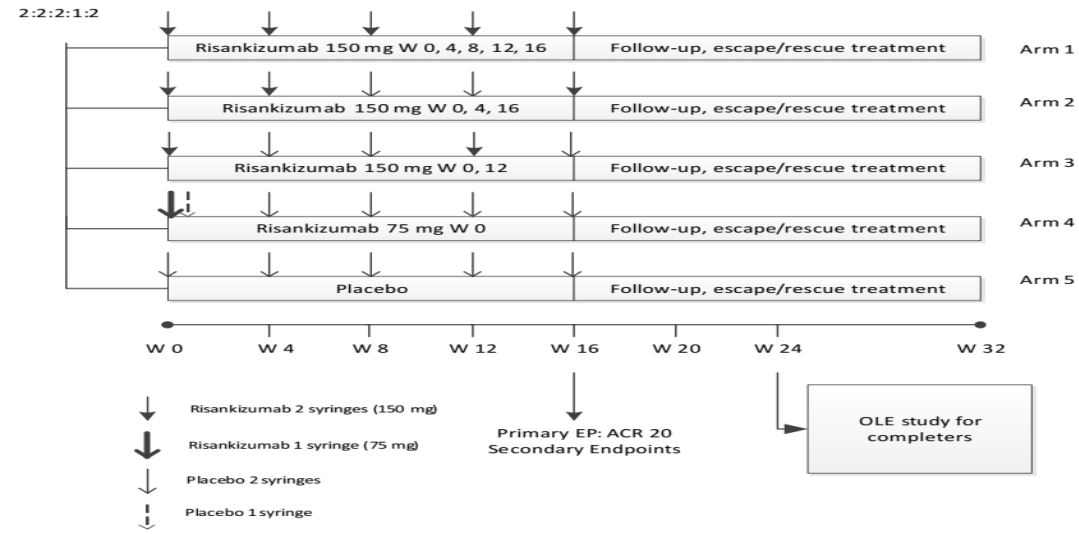
Study M16-002

Study M16-002 was a Phase 2, multi-center, randomized, placebo-controlled double-blind study to evaluate risankizumab in patients with moderate to severe active psoriatic arthritis. A total of 185 subjects with active psoriatic arthritis were randomized in a 2:2:2:1:2 ratio to the following dosing groups:

- Arm 1: Risankizumab 150 mg SC at Weeks 0, 4, 8, 12, 16
- Arm 2: Risankizumab 150 mg SC at Weeks 0, 4, 16
- Arm 3: Risankizumab 150 mg SC at Weeks 0, 12
- Arm 4: Risankizumab 75 mg SC at Week 0
- Arm 5: Placebo

A schematic of the study is presented in **Figure 1.**

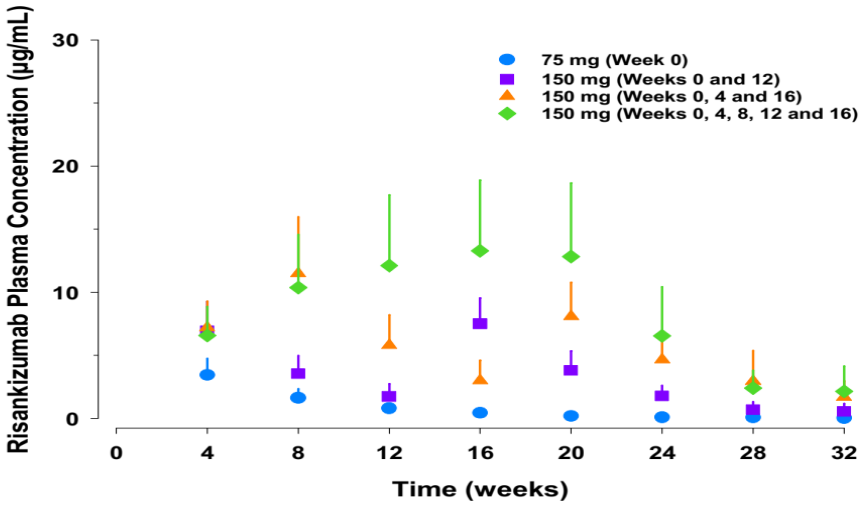
Figure 1: Study design Schematic



ACR = American College of Rheumatology; EP = endpoint; OLE = open-label extension; W = week

Summary of risankizumab trough concentrations (Ctrough) in subjects with active psoriatic arthritis from this study is presented in

Figure 2: Risankizumab Plasma Concentration (µg/mL) Versus Time by Dose Regimen



A dose- and dosing-frequency-dependent increase in risankizumab plasma concentrations was observed across the different regimens evaluated in the study.

Immunogenicity

In subjects who received at least 1 dose of risankizumab in the study, no regimen dependent trend in the incidence of risankizumab anti-drug antibodies was observed. Anti-drug antibody incidence (treatment emergent) to risankizumab over the entire study duration (32 weeks) was approximately 12% in evaluable subjects (17/140) and none of them were positive for NAb. Treatment-emergent ADA incidence (TEADA) to risankizumab over the entire study duration (32 weeks) is presented in Table 2.

Table 2: Incidence of Anti-Drug Antibodies and Neutralizing Antibodies to Risankizumab Over 32 Weeks of Study Duration

		Risankizumab				
Week 0 to Week 32	**Placebo**	**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**	**Total**
Evaluable subjects; N	42	40	42	39	19	140
Anti-drug Antibody Incidence (Treatment Emergent); N (%)	0 (0%)	3 (7.5%)	9 (21.4%)	2 (5.1%)	3 (15.8%)	17 (12.1%)
NAb Incidence (Treatment Emergent); N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

NAb = Neutralizing Antibody; Anti-drug antibody evaluable: subjects with at least 1 reportable assessment at any time in the study post Baseline

Arm 1: risankizumab 150 mg every 4 weeks, Arm 2: risankizumab 150 mg Weeks 0, 4, and 16.

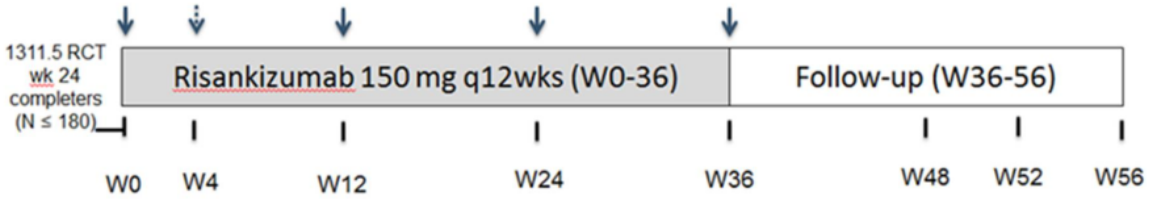
Arm 3: risankizumab 150 mg Weeks 0 and 12, and Arm 4: risankizumab 75 mg Week 0.

Development of anti-drug antibodies did not appear to have an impact on risankizumab plasma exposures in this study.

Study M16-244

Study M16-244 was a Phase 2, single-arm, multicenter, open-label extension (OLE) study to assess the safety, tolerability, and efficacy of risankizumab in psoriatic arthritis subjects who had completed all doses of study drug and the Week 24 visit of Study M16-002. A schematic of the study is presented in Figure 3. A total of 145 subjects with active psoriatic arthritis received risankizumab SC at Week 0 of Study M16-244 and q12w thereafter.

Figure 3: Study M16-244 Study Schematic



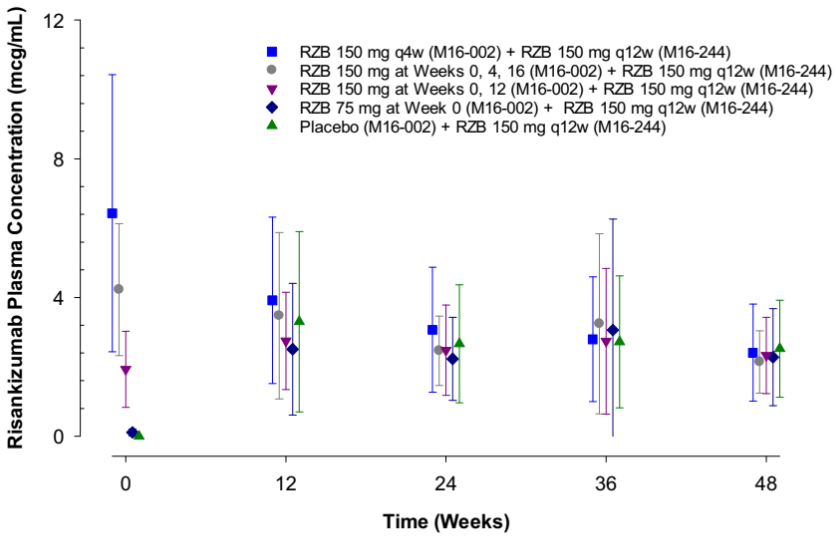
RCT = randomized controlled trial; SC = subcutaneous; SJC = swollen joint count; TJC = tender joint count; W/Wk = week

↓ Risankizumab: 2 × 75 mg SC.

⇣ Risankizumab: Additional 2 × 75 mg SC for subjects with < 20% improvement in TJC or SJC.

Summary of risankizumab trough concentrations (Ctrough) in subjects with active psoriatic arthritis from this study is presented in graphically in **Figure 4,** numerically in Table 3.

Figure 4: Risankizumab Trough Concentrations (µg/mL) in Study M16-002 The trough concentrations numerically are presented in Table 3.



RZB = risankizumab; q4w = every 4 weeks; q12w = every 12 weeks

Note: All subjects in this OLE study received risankizumab 150 mg SC q12w.

Table 3: Summary of Risankizumab Trough Concentrations (µg/mL) in this OLE study Stratified by Treatment Received in the Randomized Control Study M16-002

	Geometric Mean (Arithmetic Mean, %CV) [N]				
Treatment Group	**Week 0[a]**	**Week 12**	**Week 24**	**Week 36**	**Week 48**
Risankizumab (RZB) 150 mg q4w/ RZB 150 mg q12w	5.24 (6.43, 62) [33]	3.17 (3.92, 61) [29]	2.49 (3.07, 60) [27]	2.27 (2.80, 63) [33]	1.97 (2.41, 60) [27]
RZB 150 mg at Weeks 0, 4, 16/ RZB 150 mg q12w	3.75 (4.23, 45) [33]	2.95 (3.47, 68) [28]	2.28 (2.46, 40) [23]	2.63 (3.24, 79) [31]	1.96 (2.14, 42) [22]
RZB 150 mg at Weeks 0, 12/ RZB 150 mg q12w	1.71 (1.93, 57) [30]	2.47 (2.75, 50) [29]	2.23 (2.48, 51) [25]	2.25 (2.74, 77) [29]	1.96 (2.33, 48) [22]
RZB 75 mg at Week 0/ RZB 150 mg q12w	0.98 (0.110, 87) [15]	1.82 (2.51, 77) [15]	1.75 (2.23, 55) [15]	2.05 (3.06, 105) [15]	1.61 (2.28, 60) [14]
Placebo/ RZB 150 mg q12w	--	2.33 (3.30, 79) [31]	2.22 (2.67, 64) [25]	2.17 (2.72, 71) [31]	2.16 (2.52, 54) [22]
All Subjects	2.17 (2.86, 116) [144]	2.58 (3.26, 68) [132]	2.23 (2.62, 56) [115]	2.30 (2.90, 77) [139]	1.95 (2.35, 53) [107]

%CV = coefficient of variation; q12w = every 12 weeks; q4w = every 4 weeks; RZB = risankizumab

a. Procedure was completed at Week 24 or a later visit (up to Week 32) in Study M16-002 and results served as Week 0 for Study M16-244.

Note: Some subjects (N = 35) received an additional dose of 150 mg SC at Week 4.

Immunogenicity

Immunogenicity of risankizumab was assessed using a 3-tiered approach. In this tiered approach, all ADA samples were first analyzed in a screening assay (Tier 1). The samples that were screened positive were confirmed in the confirmatory assay (Tier 2), followed by the titer determination step (Tier 3). The confirmed positive samples were also evaluated in the neutralizing antibody (NAb) assay to detect the presence of NAb. The summary of ADA incidence is presented in Table 4.

Table 4: Summary of Incidence of Anti-Drug Antibodies (Anti-Risankizumab Antibodies) and Neutralizing Antibodies to Risankizumab Over 0 to 52 Weeks Treatment Duration.

	Risankizumab Treatment Group					
	RZB 150 mg q4w/ RZB 150 mg q12w	RZB 150 mg at Weeks 0, 4, 16/ RZB 150 mg q12w	RZB 150 mg at Weeks 0, 12/ RZB 150 mg q12w	RZB 75 mg at Week 0/ RZB 150 mg q12w	Placebo/ RZB 150 mg q12w	All Subjects
Evaluable subjects; N	33	33	30	15	34	145
ADA incidence (treatment-emergent); N (%)	5 (15.2)	10 (30.3)	5 (16.7)	4 (26.7)	8 (23.5)	32 (22.1)
NAb incidence (treatment-emergent); N (%)	0	1 (3.0)	0	0	1 (2.9)	2 (1.4)

ADA = anti-drug antibody; NAb = neutralizing antibody; q12w = every 12 weeks; q4w = every 4 weeks; RZB = risankizumab

Notes: ADA evaluable: subjects with at least one reportable assessment at any time post-Baseline in Study M16-244.
NAb was assessed only when the ADA assessment was positive.

Phase 3 Studies in Subjects with Active Psoriatic Arthritis

Study M16-011 (KEEPsAKE 1)

Study M16-011 was a Phase 3, randomized, double-blind, placebo-controlled study in subjects with active psoriatic arthritis who had an inadequate response or intolerance to at least 1 csDMARD (csDMARD-IR). The study evaluated the efficacy and safety of risankizumab 150 mg SC at Weeks 0, 4, and q12w thereafter versus placebo. A total of 964 subjects were randomized to risankizumab or placebo in a ratio of 1:1 through Week 24:

-Risankizumab: 150 mg dose SC at Weeks 0, 4 and 16, blinded placebo at Week 24, then open-label risankizumab at Week 28 and q12w thereafter

-Placebo: SC at Weeks 0, 4, and 16; blinded Risankizumab at Weeks 24, then open-label risankizumab 28 and q12w thereafter

Blood samples for risankizumab assay were taken at Week 28. Risankizumab serum trough concentrations in subjects with active psoriatic arthritis are presented in Table 5.

Table 5: Summary of Risankizumab Serum Trough Concentrations (µg/mL) at Planned Visits in Subjects with Active Psoriatic Arthritis

	Geometric Mean (Arithmetic Mean, %CV) [N] Week 28
Risankizumab arm 150 mg SC	1.46 (1.81, 67) 437
Placebo to Risankizumab 150 mg SC at Week 24	5.40 (5.77, 38) 445

CV = coefficient of variation; SC = subcutaneous

For subjects who received risankizumab treatment from the beginning, following administration of risankizumab 150 mg SC dose at Weeks 0, 4, and then q12w, geometric mean risankizumab trough serum concentration was 1.46 µg/mL at Week 28. For subjects who received placebo during the double-blind

period and later switched to risankizumab, their geometric mean risankizumab serum concentration at Week 28 (4 weeks after their first risankizumab dose at Week 24) was 5.40 µg/mL.

Immunogenicity

At Baseline (prior to the first risankizumab dose), pre-existing ADAs and pre-existing NAbs were detected in 2.4% (21/863) and 0% (0/863) of the subjects who received at least 1 dose of risankizumab in the study. Across the study duration by the interim CSR data cutoff date of 20 January 2021 (Weeks 0 to 28), the incidence of ADAs to risankizumab (amongst the 446 evaluable subjects, defined earlier) in subjects who received at-least 150 mg dose of risankizumab at Weeks 0, 4, and q12w thereafter, is summarized below:

- ADA incidence (treatment emergent) was approximately 12% (52/446) of evaluable subjects
- None of the 52 subjects who developed ADAs to risankizumab had positive NAb results
- The ADA titer values ranged from 10 to 4050 across study visits.

Risankizumab serum exposures in subjects at Week 28 by ADA status are presented in Table 6.

Table 6: Summary of Risankizumab Trough Serum Concentrations (µg/mL) by ADA Status in Subjects with Active Psoriatic Arthritis.

	Geometric Mean (Arithmetic Mean, %CV) [N]	
	ADA positive[a]	ADA negative[a]
Risankizumab 150 mg SC	1.19 (1.49, 62) [53]	1.50 (1.86, 67) [381]
Placebo to Risankizumab 150 mg SC	5.19 (5.74, 43) [30]	5.41 (5.76, 38) [411]

ADA = anti-drug antibody; CV = coefficient of variation; SC = subcutaneous

a. Subjects who had both risankizumab concentration and ADA assessment at each visit are included in this summary.

Study M15-998 (KEEPsAKE 2)

Study M15-998 was a Phase 3, randomized, double-blind, placebo-controlled study in subjects with active psoriatic arthritis. The study was designed to evaluate the efficacy and safety of risankizumab 150 mg SC at Weeks 0, 4, and every 12 weeks thereafter versus placebo. A total of 444 subjects were randomized to receive blinded risankizumab or placebo in 1:1 ratio through Week 24:

- Risankizumab: 150 mg dose SC at Weeks 0, 4 and 16, blinded placebo at Week 24, then open-label risankizumab at Week 28 and q12w thereafter

- Placebo: SC at Weeks 0, 4, and 16; blinded risankizumab at Weeks 24, then open-label risankizumab at Week 28 and q12w thereafter.

A single blood sample for analysis of risankizumab serum concentration was collected pre-dose at Week 28. The summary of the trough concentrations are presented in Table 7.

Table 7: Summary of Risankizumab Serum Trough Concentrations (µg/mL) at Planned Visits in Subjects with Active Psoriatic Arthritis

	Geometric Mean (Arithmetic Mean, %CV) [N]
	Week 28
Risankizumab 150 mg SC	1.51 (1.91, 70) [199]
Placebo to Risankizumab 150 mg SC at Week 24	4.97 (5.46, 48) [181]

CV = coefficient of variation; N = sample size; SC = subcutaneous

Immunogenicity

The summary of treatment-emergent ADAs and NAbs to risankizumab in subjects who received at least 1 dose of risankizumab is presented in Table 8.

Table 8: Summary of Incidence of Anti-Drug Antibodies and Neutralizing Antibodies to Risankizumab Over Study Duration 0 to 28 Weeks.

	Risankizumab 150 mg SC	Placebo to Risankizumab 150 mg SC at Week 24	Risankizumab Total Subjects
Evaluable subjects; N	206	186	392
Anti-drug antibody incidence (treatment emergent); N (%)	27 (13%)	14 (8%)	41 (11%)
NAb incidence (treatment emergent); N (%)	0 (0%)	0 (0%)	0 (0%)

N = sample size; NAb = neutralizing antibody; SC = subcutaneous

Notes: Anti-drug antibody evaluable: subjects with at least 1 reportable immunogenicity assessment for at least one sampling time during the study post Baseline. NAb was assessed only when the anti-drug antibody assessment was positive.

A single blood sample for analysis of risankizumab serum concentration was collected pre-dose at Week 28. Risankizumab serum exposures in subjects at Week 28 by ADA status are presented in Table 9.

Table 9: Summary of Risankizumab Trough Serum Concentrations (µg/mL) by ADA Status in Subjects with Active Psoriatic Arthritis at Week 28

	Geometric Mean (Arithmetic Mean, %CV) [N]	
	ADA positive[a]	ADA negative[a]
Risankizumab 150 mg SC	1.30 (1.59, 72) [28]	1.54 (1.97, 69) [169]
Placebo to Risankizumab 150 mg SC at Week 24	4.23 (5.19, 71) [13]	5.07 (5.51, 46) [167]

ADA = anti-drug antibodies; CV = coefficient of variation; N = sample size; SC = subcutaneous

a. Subjects who had both risankizumab concentration and ADA assessment at each visit are included in this summary.

Absorption

Risankizumab absolute SC bioavailability was estimated to be 83.5%.

Distribution

Based on population pharmacokinetic analyses, risankizumab central volume of distribution (V2), peripheral volume of distribution (V3), and volume of distribution at steady state (Vss) were estimated to be 6.8 L, 4.3 L, and 11.1 L, respectively, for a typical 90 kg subject.

Elimination

Risankizumab is not expected to undergo metabolism by hepatic metabolic enzymes or renal elimination. Therefore, no dedicated studies were conducted to evaluate risankizumab pharmacokinetics in patients with hepatic or renal impairment. Based on population pharmacokinetic analyses, risankizumab plasma clearance (CL) was estimated to be 0.31 L/day for a typical 90 kg subject. The typical value for risankizumab terminal phase elimination half-life was approximately 26.3 days.

Dose proportionality and time dependencies

Risankizumab exhibited linear and time-independent pharmacokinetic characteristics in subjects with active psoriatic arthritis, similar to those in healthy subjects and subjects with plaque psoriasis.

Special populations

Psoriatic Arthritis Disease: Based on the cross-study population pharmacokinetic analyses, risankizumab pharmacokinetic parameters were similar in heathy subjects and subjects with active psoriatic arthritis regardless of disease-related characteristics including presence of axial spondylitis, baseline DAS28 score, baseline HAQ-DI score, baseline PASI score, duration of disease, etc.

Age: Based on the cross-study population pharmacokinetic analyses, age (range 20 to 85 years) had no clinically meaningful impact on risankizumab exposure.

Race and Sex: Based on the cross-study population pharmacokinetic analyses, risankizumab pharmacokinetic parameters were not impacted by race or sex.

Body Weight: Similar to other IgG1 mAbs, and consistent with the psoriasis population pharmacokinetics model, risankizumab clearance and volume of distribution increase as body weight increases, resulting in modest changes of exposure. However, differences in exposures as a result of differences in body weight were deemed to be clinically irrelevant.

Pharmacokinetic interaction studies

The cross-study population pharmacokinetic analyses indicated that methotrexate, which was a common concomitantly administered medication in psoriatic arthritis patients during risankizumab Phase 3 clinical trials, did not significantly affect risankizumab clearance.

Pharmacokinetics using human biomaterials

The completed therapeutic protein-drug interaction study (Study M16-007) included in the psoriasis submission) using cytochrome P450 substrate cocktail approach in subjects with psoriasis (with or without psoriatic arthritis) demonstrated that repeated administration of risankizumab 150 mg SC at Weeks 0, 4, 8, and 12 had no effect on the exposures of probe substrates of CYP1A2 (caffeine 100 mg), CYP2C9 (warfarin 10 mg), CYP2C19 (omeprazole 20 mg), CYP2D6 (metoprolol 50 mg), and CYP3A (midazolam 2 mg) in subjects with plaque psoriasis.

2.3.3. Pharmacodynamics

Mechanism of action

No new data presented.

Primary and secondary pharmacology

Study M15-998 Biomerker Report, R&D/21/0058

To assess the PD effect of treatment with risankizumab 150 mg sc at Week 0, Week 4, and every 12 weeks (q12w) thereafter on serum protein biomarkers downstream of the IL-23 pathway (IL-17A, IL-17F and IL-22) and on protein biomarkers independent of the IL-23 pathway (IL-6 and TNF-alpha), the change in baseline in the levels of these biomarkers was assessed in 100 randomly selected subjects with PsA enrolled in M15-998 (phase 3). Key parameters of these assays are shown in **Table 10.**

Table 10:

Analyte	IL-17A	IL-17F	IL-22	IL-6	TNF-α
Test Method Number	PCDSTM-15-012	PCDSTM-15-009	PCDSTM-15-010	PCDSTM-17-006	PCDSTM-17-009
Quantitation range (in assay well)	0.05-10 pg/mL	0.25–50 pg/mL	0.5-75 pg/mL	0.1–25 pg/mL	0.05-50 pg/mL
Average recovery of standards in the quantitative range	96.0%–107.6%	93.0%-111.4%	93.6%–110.7%	97.8%–103.2%	97.7%–104.6%
Standard curve concentrations (pg/mL)	0.03, 0.07, 0.14, 0.28, 0.56, 1.11, 2.22, 6.67, 20	0.1, 0.2, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50, 100	0.1, 0.2, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50, 100	0.04, 0.12, 0.37, 1.11, 3.33, 10, 30	0.02, 0.07, 0.21, 0.62, 1.85, 5.56, 16.67, 50
QC conc. (low, mid, high) (pg/mL)	0.2, 1, 7.5	1, 5, 40	2, 10, 50	0.8, 2, 10	1, 5, 40
Sample handling during testing	<2 hours at RT				
Freeze-thaw cycles during testing	1 except for retest samples				2 except for retest samples
Parallelism in pre-study validation	Demonstrated up to 1:16 in individuals with higher endogenous levels		Demonstrated up to 1:8 in individuals with higher endogenous levels		Demonstrated up to 1:16 in individuals with higher endogenous levels
Sample dilution (MRD)	1:4	1:2	1:2	1:4	1:2
Specificity (evaluated prior to sample testing)	No interference by ABBV-066 observed				

Baseline characteristics of this substudy population (n=100) are summarised in Table 11.

Table 11: Biomarker Subjects Sub-Population Baseline Characteristics

mean or n (%)	PBO N=50	RZB (150mg SC) N=50	Total N=100
Male (%)	24 (48)	25 (50)	49 (49)
Age (years)	52.90	52.66	52.78
Disease duration (years)	7.25	9.27	8.25
BMI (kg/m^2)	31.07	29.31	30.19
Baseline CRP (mg/L)	5.42	7.13	6.28
csDMARD-IR (%)	29 (58)	25 (50)	54 (54)
Bio-IR (%)	21 (42)	25 (50)	46 (46)

PBO (placebo); RZB (risankizumab)

Treatment with risankizumab 150 mg SC at Week 0, Week 4 and 12 weekly thereafter resulted in a statistically significant decrease in the levels of IL-17A, IL-17F and IL-22 compared to baseline; IL-6 and TNF-alpha levels were not significantly altered.

During the course of the study the M15-998, interleukins (Figure 5) and TNF-α (Figure 6) concentration profiles showed distinctively different time profiles.

Figure 5: Relative changes in interleukin levels during the course of Study M15-998 (means +/- SE).

Placebo: ●; Risankizumab 150 mg SC: ▲

Figure 1. Change from Baseline in IL-17A at Week 4 and 24

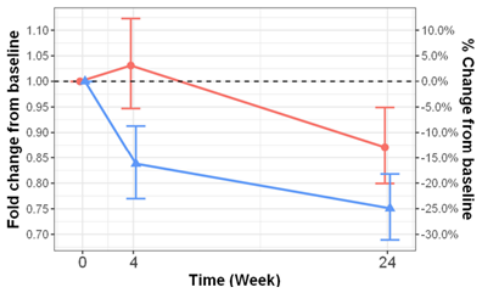


Figure 2. Change from Baseline in IL-17F at Week 4 and 24

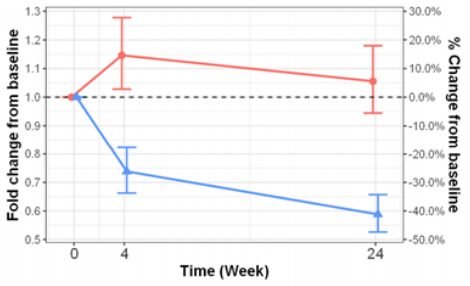


Figure 3. Change from Baseline in IL-22 at Week 4 and 24

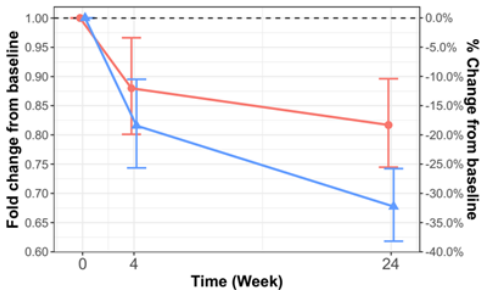


Figure 4. Change from Baseline in IL-6 at Week 4 and 24

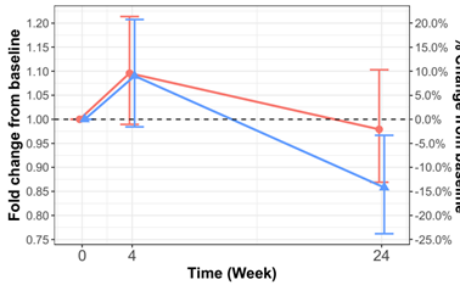
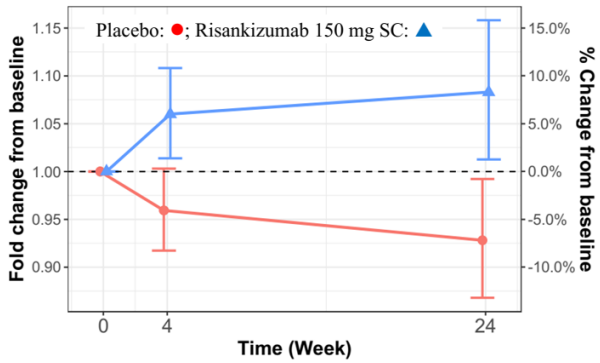


Figure 6: Change from Baseline in TNF-alpha at Week 4 and 24 (means +/- SE).



Compared to baseline IL-17A, IL-17F and IL-22; IL-6 decreased significantly at Week 24 while the TNF-alpha levels were not significantly altered. Compared to placebo, risankizumab resulted in a significantly greater decrease in IL-17F levels and in numerically greater decrease in IL-17A and IL-22 levels.

2.3.4. PK/PD modelling

Population PK & Exposure Response Report, R&D/20/1395

The population pharmacokinetics of risankizumab in subjects with psoriatic arthritis was characterized using data from one Phase 1 study in healthy volunteer subjects, two Phase 2 and two Phase 3 studies in subjects with psoriatic arthritis. Data from subjects with active psoriatic arthritis (N = 1459) and healthy volunteers (N = 67) who received risankizumab and had at least one post-treatment measurable concentration were included in the population pharmacokinetic analyses.

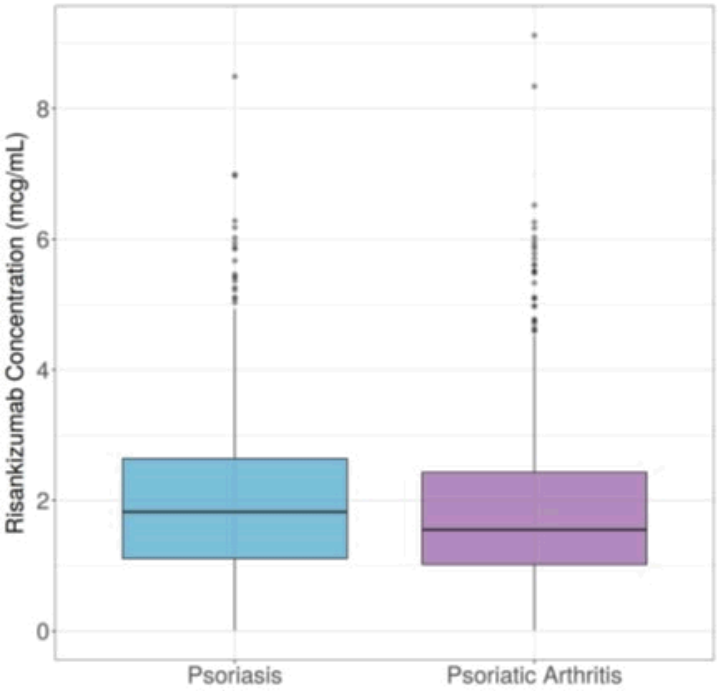
Table 12: Summary of Studies and Data Included in the Population Pharmacokinetic Analyses and Exposure-Response Analyses.

Study (N = Treated/Total)	Phase/Population	Risankizumab Doses	Study Design and Pharmacokinetic Sampling	Data for Exposure-Response Analyses Efficacy and Safety
M16-513 (Stage 1: N = 49/65, Stage 2: N = 18/24)	Phase 1/Healthy male Japanese, Chinese and Caucasian subjects	Stage 1: Placebo, 18 mg SC; 90 mg SC; 300 mg SC Stage 2: Placebo, 200 mg IV; 600 mg IV; 1200 mg IV	Single ascending dose, placebo-controlled; Stage 1: Day 1 0 hour (pre-dose) and Days 2, 3, 4, 8, 15, 29, 57, 85, and 137 Stage 2: Day 1: 0 hour (pre-dose) and at 0.3, 1.5, 2, 4, 8, and 12 hours post-dose; Days 2, 3, 4, 8, 15, 29, 57, 85, and 137	Efficacy: N/A Safety: N/A
M16-002 (N = 143/185)	Phase 2/Subjects with active PsA who are naïve to or were previously treated with anti-TNF therapy	Placebo; 75 mg SC Week 0; 150 mg SC Weeks 0 and 12; 150 mg SC Weeks 0, 4, and 16; 150 mg SC Weeks 0, 4, 8, 12, and 16	Multiple doses, placebo-controlled, parallel-group; pre-dose PK samples at Weeks 0, 4, 8, 12, 16, 20, 24, 28 and 32	Efficacy: ACR20/50/70 responses, HAQ-DI, PASI 90/100 responses, MDA
M16-244 [Extension study of M16-002] (N = 145/145)	Phase 2/Subjects with active PsA who had completed all doses of study drug and the Week 24 visit of Study M16-002	150 mg SC Weeks 4 (for subjects with < 20% improvement in TJC or SJC only), 12, 24, and 36	Single-arm, open-label extension study; pre-dose PK samples at Weeks 4, 12, 24, and 36, and post-dose PK samples at Weeks 48 and 52	Efficacy: N/A Safety: N/A
M15-998 (N = 224/443)	Phase 3/Subjects with active PsA, ≤ 50% Bio-IR and rest csDMARD-IR subjects	Placebo; 150 mg SC at Weeks 0, 4, and 16 and q12w thereafter	Placebo-controlled; pre-dose PK sample drawn at Week 28	Efficacy: ACR20/50/70 responses, HAQ-DI, PASI 90/100 responses, MDA Safety: AE, SAE, Infection, Serious Infection
M16-011 (N = 483/964)	Phase 3/Subjects with active PsA, csDMARD-IR subjects	Placebo; 150 mg SC at Weeks 0, 4, and 16 and q12w thereafter	Placebo-controlled; pre-dose PK sample drawn at Week 28	Efficacy: ACR20/50/70 responses, HAQ-DI, PASI 90/100 responses, MDA Safety: AE, SAE, Infection, Serious Infection

ACR20/50/70 = At least 20%/50%/70% improvement in American College of Rheumatology response criteria; AE = adverse event; Bio-IR = inadequate response to one or two biologic therapies or intolerance; csDMARD-IR = inadequate response to at least one conventional synthetic disease-modifying anti-rheumatic drug or intolerance; HAQ-DI = Health Assessment Questionnaire-Disability Index; IV = intravenous; MDA = minimal disease activity; N/A= not applicable; PASI 90/100 = At least 90%/100% improvement in Psoriasis Area and Severity Index relative to Baseline; PK = pharmacokinetic; PsA = psoriatic arthritis; q12w = every 12 weeks; SAE = serious adverse event; SC = subcutaneous; SJC = swollen joint count; TJC = tender joint count; TNF = tumor necrosis factor

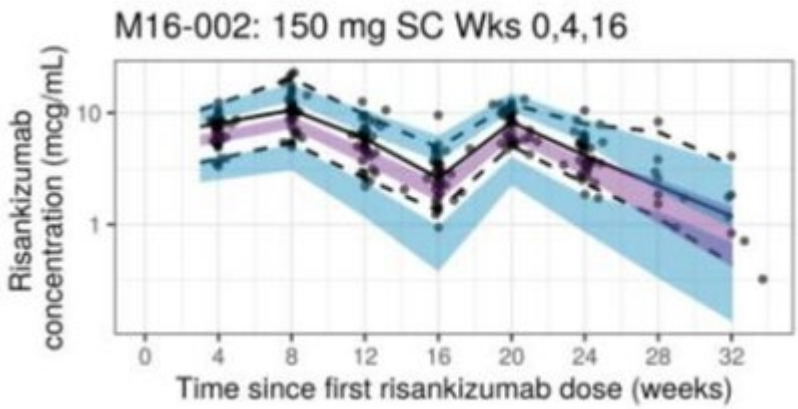
While patients with psoriasis were not included into the analysis, a graphical comparison demonstrated the similarity of risankizumab exposure levels between psoriasis and psoriatic arthritis patient populations for the clinical regimen of 150 mg SC at Weeks 0, 4, and q12w thereafter (A schematic of the study is presented in Figure 1.

Figure 7: Comparison of Week 28 Predose Observed Risankizumab Concentrations in Subjects with Psoriatic Arthritis and Psoriasis.



The similarity between psoriasis and PsA populations was also confirmed by conducting visual predictive check using the previous POP-PK model parameters developed for psoriasis patients with PsA data from study M16-002.

Figure 8: Comparison of Simulated 150 mg SC Risankizumab Concentrations Using Psoriasis Population Pharmacokinetic Model and Observed Concentrations in Psoriatic Arthritis Studies



The population pharmacokinetic model that had been previously developed to support the registration of risankizumab for moderate to severe plaque psoriasis was used. Notably a two-compartment model with first-order absorption for SC administration, and first-order elimination was used.

The POP-PK parameter estimates are shown in Table 13 while the covariate effects in **Figure 9.**

Table 13: Fixed and Random Effects Parameter Estimates for Final Risankizumab Population Pharmacokinetic Models.

Parameter	Psoriatic Arthritis Model			Psoriasis Model
	Population Estimate	%RSE[a]	95% Confidence Interval	Population Estimate (%RSE[a])
Clearance (CL; L/day)	0.248	6.2	0.218, 0.278	0.243 (1.8)
Central Volume of Distribution (V_2; L)	4.71	12.7	3.54, 5.88	4.86 (3.8)
Inter-Compartmental Clearance (Q; L/day)	0.839	8.2	0.705, 0.973	0.656 (3.7)
Peripheral Volume of Distribution (V_3; L)	4.26	5.9	3.77, 4.75	4.25 (2.0)
Absorption Rate Constant (K_a; Day -1)	0.218	10.4	0.174, 0.262	0.229 (4.8)
Absolute SC Bioavailability (F)	0.835	6.3	0.732, 0.938	0.890 (7.2)
Exponent for the Effect of Body Weight on Risankizumab Clearance (CL)	0.869	5.1	0.781, 0.957	0.933 (3.3)
Exponent for the Effect of Body Weight on Risankizumab Central Volume of Distribution (V_2)	1.46	9.7	1.18, 1.74	1.17 (7.2)
Exponent for the Effect of Serum Albumin on Risankizumab Clearance (CL)	-0.703	17.2	-0.940, -0.466	–0.715 (10.6)
Exponent for the Effect of Serum Creatinine on Risankizumab Clearance (CL)	-0.201	18.3	-0.273, -0.129	–0.253 (10.2)
Exponent for the Effect of C-Reactive Protein on Risankizumab Clearance (CL)	0.0471	12.9	0.0352, 0.0590	0.044 (10.5)
Age on Risankizumab Clearance (CL)	-0.138	21.2	-0.195, -0.0808	--
Variance of Inter-Individual Variability on CL, %CV[b]	0.0943, 31.4	5.8	0.0835, 0.105	0.054 (3.6)
Variance of Inter-Individual Variability on V_2, %CV[b]	0.171, 43.2	18.9	0.107, 0.235	0.110 (6.6)
Variance of Inter-Individual Variability on K_a, %CV[b]	0.164, 42.2	29.3	0.0699, 0.258	0.335 (5.5)
Covariance between Inter-Individual Variability on CL and V_2, %correlation[c]	0.0836, 65.8	12.0	0.0640, 0.103	0.030 (8.1)
Variance of Proportional Residual Error	0.0382	1.4	0.0372, 0.0392	0.036 (0.68)

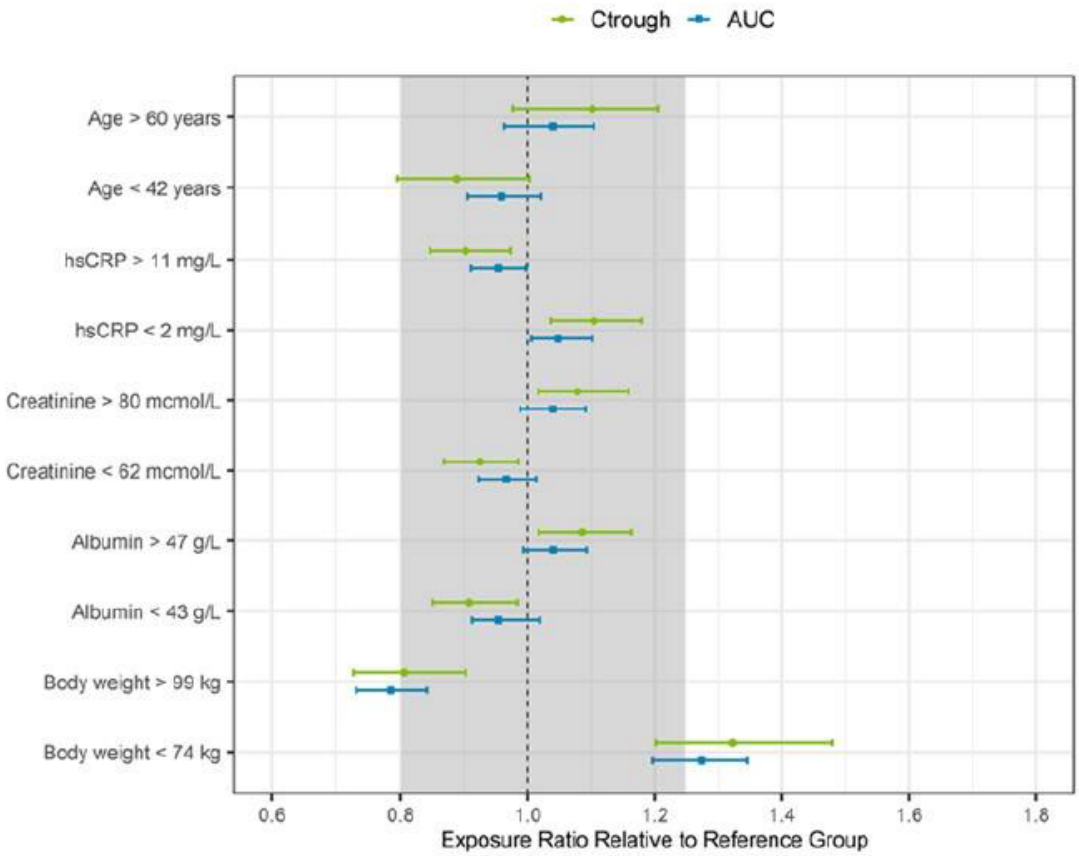
RSE = relative standard error

a. % Relative standard error (%RSE) was estimated as the standard error of the estimate divided by the population estimate multiplied by 100.

b. %CV = SQRT[exp(ω2)-1]*100.

c. %correlation = $100*(\omega_{CL,V2}/(\omega_{CL} * \omega_{V2}))$.

Figure 9: Forest Plot to Demonstrate the Impact of Statistically Significant Covariates Identified in the Population Pharmacokinetic Analyses on Risankizumab Exposures

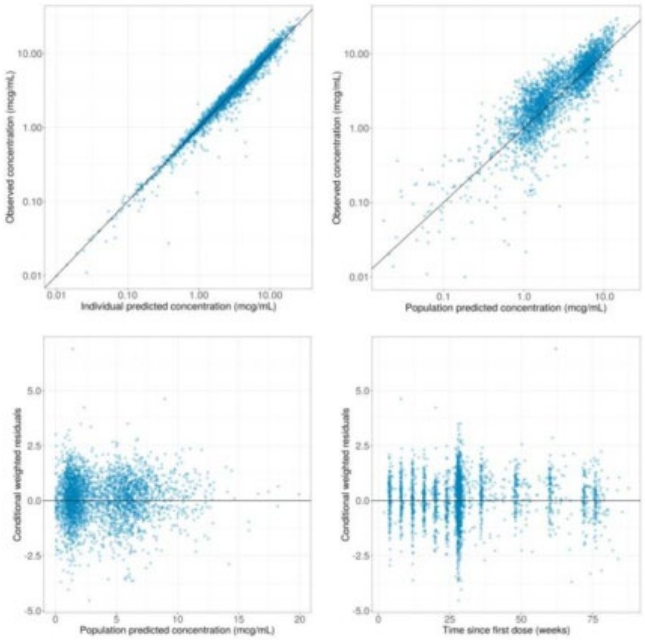


AUC = area under the concentration-time curve between Weeks 16 and 28 (AUC_{tau}); C_{trough} = concentration after a dosing interval at Week 28; hsCRP = high-sensitivity C-reactive protein

Effect of covariates on risankizumab simulated exposures in subjects with psoriatic arthritis. Points represent medians and error bars represent 95% confidence intervals of the normalized exposure ratios across 200 simulation replicates.

Goodness-of-Fit Plots for Risankizumab Population Pharmacokinetic Model in Psoriatic Arthritis. The goodness-of-fit for the final model, based on data from the four psoriatic arthritis Phase 2 and 3 studies, was evaluated graphically (**Figure 10**).

Figure 10: Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model

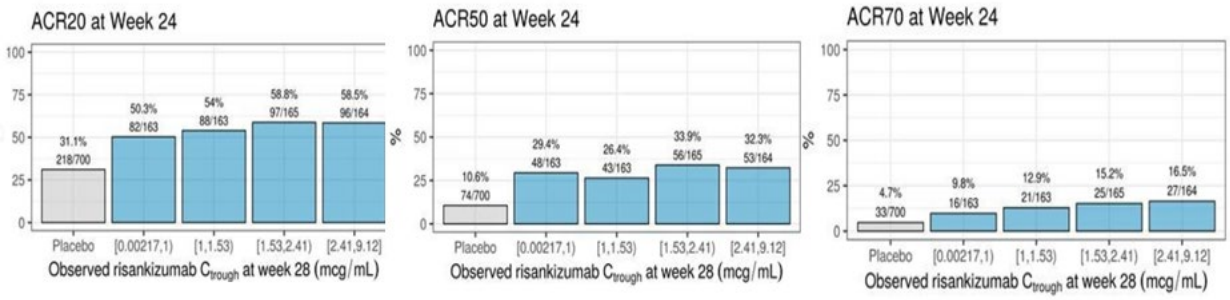


Risankizumab Exposure-Response Analyses for Efficacy

ACR

Exposure-response quartile plots for ACR20, ACR50, and ACR70 responses at Week 24 for Phase 3 Studies M15-998 and M16-011 are presented in **Figure 11.**

Figure 11: ACR20/50/70 Response Dependence on Ctrough-s (Phase III studies data)

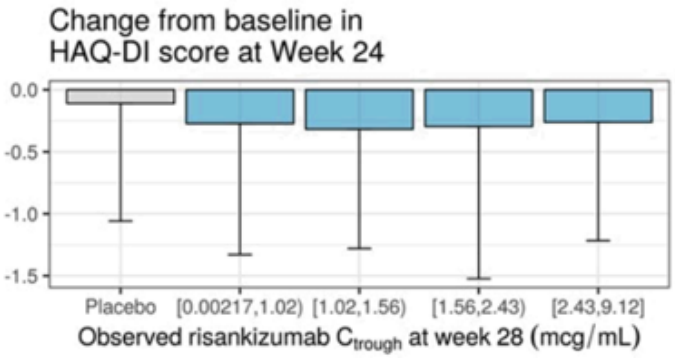


Logistic regression analyses that accounted for study stratification factors for ACR20, ACR50, and ACR70 at Week 24 revealed a statistically significant treatment effect ($p < 0.01$) but no statistically significant exposure-response relationship.

HAQ-DI

Exposure-response quartile plot to evaluate the relationship between observed risankizumab exposure at Week 28 and change in HAQ-DI score from baseline at Week 24 is presented in **Figure 12.**

Figure 12: Exposure-Response Analysis for Change from Baseline in HAQ-DI Score from Phase 3 Studies M15-998 and M16-011 at Week 24.



C_{trough} = concentration at the end of a dosing interval; HAQ-DI = Health Assessment Questionnaire-Disability Index
Values on x-axis represent range of the observed Studies M15-998 and M16-011 risankizumab C_{trough} at Week 28 for each quartile. HAQ-DI at Week 24 was evaluated for a total of 1213 subjects from Phase 3 Studies M15-998 and M16-011. Plot shows mean change in HAQ-DI score from baseline and the error bar shows the lower 95% confidence interval around the mean for subjects in each exposure quartile. N = 28 subjects from Phase 3 Studies M15-998 and M16-011 that had missing C_{trough} at Week 28 are excluded from these plots. These subjects showed a mean change of -0.478 with the lower 95% confidence interval at -1.51 at Week 24.

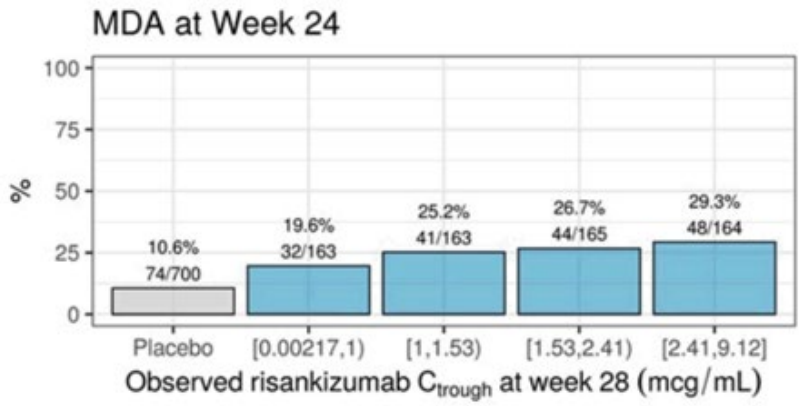
Subjects treated with risankizumab showed a higher magnitude of change in HAQ-DI score from baseline than the placebo subjects. However, the mean change in HAQ-DI from baseline across all risankizumab exposure quartiles was comparable, showing an efficacy plateau has been reached.

MDA

Exposure-response quartile plot exploring impact of observed risankizumab exposure at Week 28 on MDA response at Week 24 (

Figure 13) showed numerically higher response rates with increasing risankizumab exposure.

Figure 13: Figure 5.4.3.6 Exposure-Response Analysis for MDA Response from Phase 3 Studies M15-998 and M16-011 at Week 24.



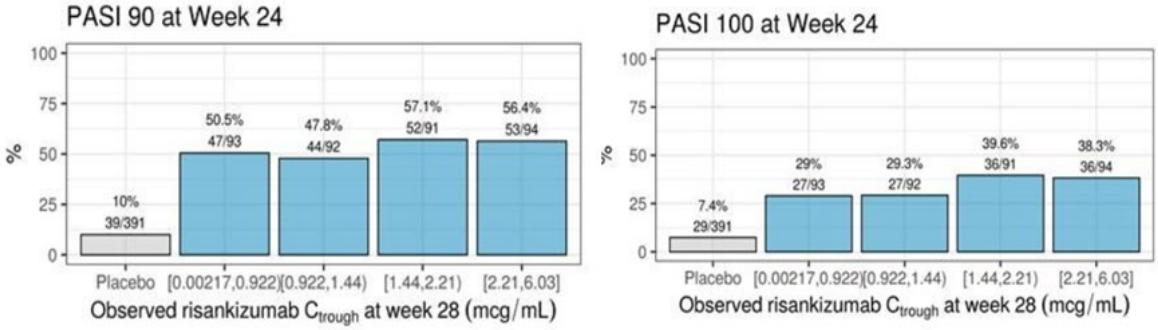
C_{trough} = concentration at the end of a dosing interval; MDA = minimal disease activity

Values on x-axis represent range of the observed Studies M15-998 and M16-011 risankizumab C_{trough} at Week 28 for each quartile. Plots show %response (using non-responder imputation) and n/N, where n represents number of responders and N represents total number of subjects in each exposure quartile bin. N = 52 subjects from Phase 3 Studies M15-998 and M16-011 that had missing C_{trough} at Week 28 are excluded from these plots. Of these 52 subjects, 14 (26.9%) were MDA responders at Week 24.

PASI

The PASI 90 and PASI 100 responses were only evaluated for subjects with psoriasis surface area ≥ 3% of BSA at baseline. Exposure-response quartile plots for PASI 90 and PASI 100 responses at Week 24 are presented in **Figure 14.**

Figure 14: Exposure-Response Quartile Analyses for PASI 90/100 Responses from Phase 3 Studies



M15-998 and M16-011 at Week 24. Values on x-axis represent range of the observed Studies M15-998 and M16-011 risankizumab Ctrough at Week 28 for each quartile. Plots show % response (using non-responder imputation) and n/N, where n represents number of responders and N represents total number of subjects in each exposure quartile bin. N = 26 subjects from Phase 3 Studies M15-998 and M16-011 that had missing Ctrough at Week 28 are excluded from these plots. Of these 26 subjects, 11 (42.3%) and 9 (34.6%) were PASI 90 and PASI 100 responders, respectively, at Week 24.

Like ACR responses, logistic regression analyses with models that accounted for study stratification factors for PASI 90 and PASI 100 at Week 24 identified a statistically significant treatment effect for risankizumab, but with no statistically significant exposure-response relationships.

2.3.5. Discussion on clinical pharmacology

PK data of risankizumab across the Phase 2 and 3 studies in subjects indicated linear and time-independent PK consistent with typical IgG1 mAbs and the known risankizumab PK profiles from studies in healthy subjects and subjects with plaque psoriasis.

The PK assay has been appropriately validated in accordance with the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2. The ADA assay, and neutralising antibody (NAb) assay have been validated in accordance with the EMA Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010).

Results from the biomarker subset study from M15-998 showed an inhibitory effect of risankizumab on pathways downstream of IL-23 (IL-17 and IL-22) in subjects with PsA.

Descriptive and POP-PK analysis did not reveal difference regarding PK between psoriasis and PsA patients. Two specific aspects however are noted which require further clarifications.

Up to week 28 in both studies, of 376 evaluable subjects in M15-09881 and of 863 evaluable subjects in M16-011, 1.3% (5/376) and 2.4% (21/863) respectively had pre-exisiting ADA positivity. In the risankizumab arms 13% (27/206) in M15-988 and 12% (52/442) developed ADA positivity and none developed NAb positivity. It is unknown what percentage of patients will develop ADA over time with chronic treatment and at what titre it would become clinically significant for patients. However, no impact of ADAs on risankizumab exposures was observed. Overall, the ADA formation rate by MTX co-treatment was found to be decreased by 24.4 %. The effect is moderate and corresponds to expectations.

While a dose-response relationship was not been clearly demonstrated clinically, and a lack of correlation between risankizumab trough concentrations and the IL17F levels, additional evidence showed that therapeutic risankizumab concentrations were however on the plateau of the concentration-response curve.

2.3.6. Conclusions on clinical pharmacology

Overall, the clinical pharmacology properties of risankizumab are considered sufficiently characterised.

2.4. Clinical efficacy

2.4.1. Dose response study

Study M16-002: A Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Dose-Ranging Study of BI 655066/ABBV-066/Risankizumab in Patients with Active Psoriatic Arthritis

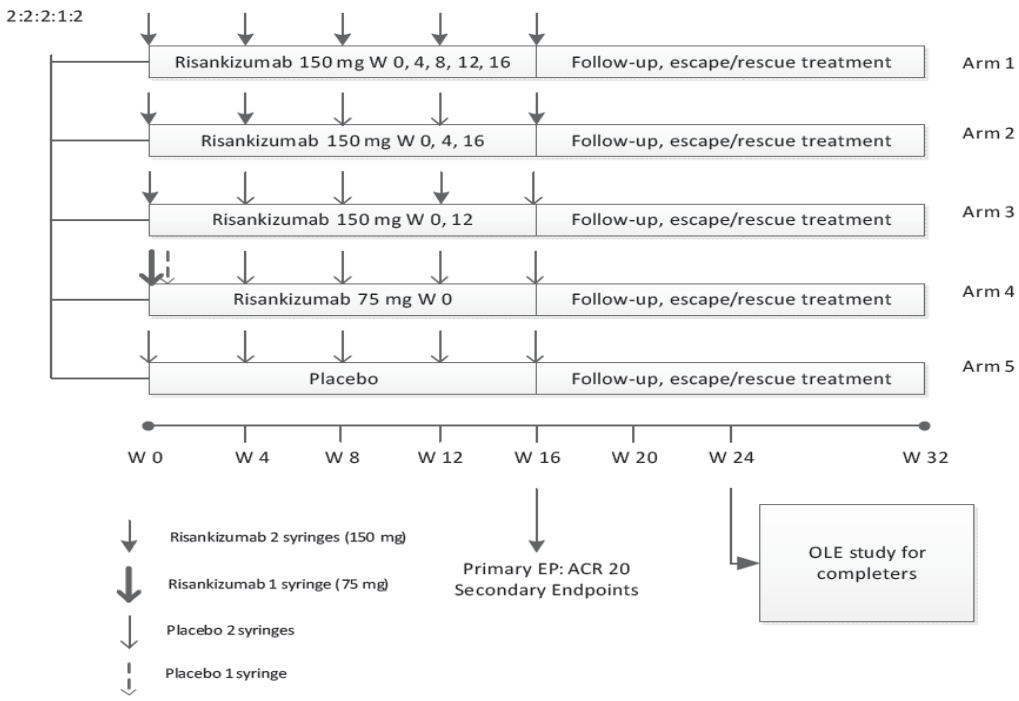
Methods

This phase 2 study was a multinational, double blinded randomised, parallel design, dose-ranging placebo contolled study in adult patients with active psoriatic arthritis, with a 16 week treatment duration and an additional follow up period of 16 weeks.

Study design

Approximately 180 eligible subjects with active psoriatic arthritis were to be randomized at a 2:2:2:1:2 ratio, stratified based on prior TNFi use and concurrent MTX use into 5 treatment arms shown in **Figure 15.** Enrollment of subjects with prior TNFi experience was capped at approximately 70%.

Figure 15: Study Design Schematic



ACR = American College of Rheumatology; EP = endpoint; OLE = open-label extension; W = week

Study participants

Key inclusion criteria included:

- a history of psoriatic arthritis (PSA) symptoms for ≥ 6 months prior to screening as assessed by the investigator;

- meet the classification criteria for PSA (CASPAR) with peripheral symptoms at screening visit; have ≥ tender joints and ≥ 5 swollen joints at screening;
- at least 1 documented PSO lesion or documented history of PSO at screening;
- be on a stable dose of PSA treatments if on concurrent PSA treatment;
- active PSA inadequately controlled by standard NSAID doses administered for 4 weeks or more, traditional DMARDS administered for 3 months or more, TNFI agents, or be intolerant to any of these medications as assessed by the investigator;
- stable doses of concurrent MTX, corticosteroids, NSAIDS or paracetamol/acetaminophen were allowed (as needed) for the treatment of psoriatic arthritis.

Exclusion criteria included:

- major chronic inflammatory or connective tissue diseases other than PSA; history of receipt of directly targeted IL-12/13 (including ustekinumab),
- IL-23 or IL-17 (including secukinumab) therapies;
- prior use of more than two different TNFI agents; previous treatment with any cell-depleting therapies;
- participation in another trial within 4 to 12 weeks depending on the investigational agent.

Treatments

Risankizumab and matching placebo were to be administered in the study. Risankizumab 150 mg for subcutaneous (SC) administration was to be provided in 2 pre-filled syringes (PFS) of 75 mg each. Placebo was also to be administered subcutaneously via a PFS.

Objectives

The primary objective of the study was to provide proof of concept for the efficacy of risankizumab as a treatment for psoriatic arthritis.

Secondary objectives were to provide further support of efficacy, establish safety, and provide dose-ranging data of risankizumab in patients with active psoriatic arthritis. In addition, risankizumab pharmacokinetics (PK) exposure was assessed to provide data for subsequent PK-PD modelling**.**

Outcomes/endpoints

The primary endpoint was the ACR 20 response at Week 16.

Secondary endpoints assessed at Week 16 included: ACR 50 and ACR 70 responses; Change intender joint count compared to baseline; change in swollen joint count compared to baseline; change in HAQ-DI compared to baseline; change in SF-36 compared to baseline; for patients with dactylitis at baseline, change in dactylitis count compared to baseline; for those with enthesitis at baseline, change in SPARCC enthesitis index compared to baseline; in patients with nail psoriasis at baseline, change in mNAPSI compared to baseline and; PASI 90 response assessed in patients with a ≥ 3% baseline psoriasis BSA.

Sample size

The sample size was determined on the basis of a one-sided comparison between the average rate of ACR 20 response at Week 16 of Arm 1 and Arm 2 versus placebo with the assumed Week 16 ACR 20 response rate of 38% in the combined arms (Arm 1 and Arm 2) and of 15% in the placebo arm, 40 participants each for Arm 1, Arm 2 and placebo will provide 85% power to detect a 23% difference in proportion

(combination of Arm 1 and Arm 2 versus placebo) using a one-sided test of 0.05 significance (equivalent to two sided test of 0.1 significance).

Although not included in the hypothesis testing strategy, Arm 3 will have about 40 participants. In addition, we plan to enrol 20 participants into Arm 4 dose response modelling. The total sample size for this study was therefore 180 participants.

This study was not powered to detect statistically significant differences between the different risankizumab treatment arms.

Randomisation

Eligible patients were randomised to five parallel groups, Arm 1 – Arm 5, in a 2:2:2:1:2 ratio, respectively. Randomisation was stratified with respect to naïve or experienced to TNFi therapy and concurrent MTX (yes or no) use as determined at baseline. The randomisation system used by the MAH has not been described.

Subjects were randomized at a 2:2:2:1:2 ratio into 1 of the following treatment arms:

● Arm 1: risankizumab 150 mg every 4 weeks

● Arm 2: risankizumab 150 mg Weeks 0, 4, and 16

● Arm 3: risankizumab 150 mg Weeks 0 and 12

● Arm 4: risankizumab 75 mg Week 0

● Arm 5: placebo

Statistical methods

The efficacy analyses were based on the Full Analysis Set (FAS). The FAS consists of all randomized subjects who received at least 1 dose of study medication. The subjects were grouped by the treatment group assigned at the time of randomization regardless of the actual treatment they received during the study. The treatment effect was evaluated based on a 2-sided significance level of 0.1. The primary efficacy analysis was to be performed once all subjects completed Week 16 visits based on the interim locked database.

The SAP for Study M16-002, dated 12 May 2017, was approved before the Week 16 database lock and was used for the analysis of efficacy performed once all subjects completed Week 16 visits The SAP revisions, dated 16 October 2017, were used for all efficacy and safety analyses after final database lock.

Results

Participant flow

Overall 185 patients were randomised. Completion rates were high overall with the highest rates in the placebo arm (97.6%), followed by Arm 3 (94.9%); Arm 2 (92.9%); Arm 1 (90.4%) and Arm 4 (90%)

Baseline data

Demographic characteristics were balanced between the placebo and risankizumab groups and were similar to subject populations in other studies of biologic treatments for psoriatic arthritis (Table 14 and Table 14.1)

Table 14: Demographic Characteristics of Subjects – Categorical Variables (FAS)

VARIABLE	Placebo (N = 42) n (%)	Risankizumab Arms 1 + 2 (N = 84) n (%)	Arm 1 (N = 42) n (%)	Arm 2 (N = 42) n (%)	Arm 3 (N = 39) n (%)	Arm 4 (N = 20) n (%)	Total (N = 143) n (%)
Sex							
Female	18 (42.9)	35 (41.7)	21 (50.0)	14 (33.3)	17 (43.6)	10 (50.0)	62 (43.4)
Male	24 (57.1)	49 (58.3)	21 (50.0)	28 (66.7)	22 (56.4)	10 (50.0)	81 (56.6)
Race							
White	36 (85.7)	72 (88.9)	35 (85.4)	37 (92.5)	34 (89.5)	15 (78.9)	121 (87.7)
Black or African American	0	0	0	0	0	0	0
Asian	5 (11.9)	9 (11.1)	6 (14.6)	3 (7.5)	4 (10.5)	4 (21.1)	17 (12.3)
American Indian or Alaska Native	1 (2.4)	0	0	0	0	0	0
Missing	0	3	1	2	1	1	5
Ethnicity							
Hispanic or Latino	2 (4.8)	1 (1.2)	0	1 (2.5)	0	0	1 (0.7)
Not Hispanic or Latino	40 (95.2)	80 (98.8)	41 (100)	39 (97.5)	38 (100)	19 (100)	137 (99.3)
Missing	0	3	1	2	1	1	5
Age (years)							
< 65	39 (92.9)	71 (84.5)	34 (81.0)	37 (88.1)	34 (87.2)	16 (80.0)	121 (84.6)
≥ 65	3 (7.1)	13 (15.5)	8 (19.0)	5 (11.9)	5 (12.8)	4 (20.0)	22 (15.4)
Weight (kg)							
< 100	33 (78.6)	67 (79.8)	32 (76.2)	35 (83.3)	32 (82.1)	18 (90.0)	117 (81.8)
≥ 100	9 (21.4)	17 (20.2)	10 (23.8)	7 (16.7)	7 (17.9)	2 (10.0)	26 (18.2)
BMI (kg/m^2)							
< 30	25 (59.5)	53 (63.1)	26 (61.9)	27 (64.3)	24 (61.5)	10 (50.0)	87 (60.8)
≥ 30	17 (40.5)	31 (36.9)	16 (38.1)	15 (35.7)	15 (38.5)	10 (50.0)	56 (39.2)

BMI = body mass index; FAS = Full Analysis Set

Table 15: M16-002 Baseline Disease Characteristics (FAS)

VARIABLE	PLACEBO (N=42) n (%)	ARMS 1+2 (N=84) n (%)	ARMS 2+3 (N=81) n (%)	RISA ARM 1 (N=42) n (%)	RISA ARM 2 (N=42) n (%)	RISA ARM 3 (N=39) n (%)	RISA ARM 4 (N=20) n (%)	RISA TOTAL (N=143) n (%)	OVERALL TOTAL (N=185) n (%)	P-VALUE@
MDA FOR PSA										
NO	41 (97.6)	81 (96.4)	77 (95.1)	41 (97.6)	40 (95.2)	37 (94.9)	19 (95.0)	137 (95.8)	178 (96.2)	1.000
YES	1 (2.4)	3 (3.6)	4 (4.9)	1 (2.4)	2 (4.8)	2 (5.1)	1 (5.0)	6 (4.2)	7 (3.8)	
MISSING	0	0	0	0	0	0	0	0	0	
BODY SURFACE AREA (BSA) OF PSORIATIC PLAQUES										
< 3%	21 (50.0)	44 (55.0)	37 (46.3)	23 (59.0)	21 (51.2)	16 (41.0)	10 (52.6)	70 (50.7)	91 (50.6)	1.000
>= 3%	21 (50.0)	36 (45.0)	43 (53.8)	16 (41.0)	20 (48.8)	23 (59.0)	9 (47.4)	68 (49.3)	89 (49.4)	
MISSING	0	4	1	3	1	0	1	5	5	
sPGA ASSESSED IN SUBJECTS WITH >=3% BSA OF PSORIATIC PLAQUES										
CLEAR	0	0	0	0	0	0	0	0	0	0.422
ALMOST CLEAR	6 (28.6)	7 (19.4)	6 (14.0)	3 (18.8)	4 (20.0)	2 (8.7)	1 (11.1)	10 (14.7)	16 (18.0)	

VARIABLE	PLACEBO (N=42) n (%)	ARMS 1+2 (N=84) n (%)	ARMS 2+3 (N=81) n (%)	ARM 1 (N=42) n (%)	ARM 2 (N=42) n (%)	ARM 3 (N=39) n (%)	ARM 4 (N=20) n (%)	RISA----- TOTAL (N=143) n (%)	OVERALL TOTAL (N=185) n %)	P-VALUE@
MILD	9 (42.9)	12 (33.3)	20 (46.5)	5 (31.3)	7 (35.0)	13 (56.5)	3 (33.3)	28 (41.2)	37 (41.6)	
MODERATE	6 (28.6)	15 (41.7)	15 (34.9)	7 (43.8)	8 (40.0)	7 (30.4)	5 (55.6)	27 (39.7)	33 (37.1)	
SEVERE	0	2 (5.6)	2 (4.7)	1 (6.3)	1 (5.0)	1 (4.3)	0	3 (4.4)	3 (3.4)	
sPGA RESPONSE										
RESPONDERS	6 (28.6)	7 (19.4)	6 (14.0)	3 (18.8)	4 (20.0)	2 (8.7)	1 (11.1)	10 (14.7)	16 (18.0)	0.193
NON-RESPONDERS	15 (71.4)	29 (80.6)	37 (86.0)	13 (81.3)	16 (80.0)	21 (91.3)	8 (88.9)	58 (85.3)	73 (82.0)	
PRESENCE OF DACTYLITIS										
NO	33 (78.6)	59 (71.1)	58 (71.6)	29 (70.7)	30 (71.4)	28 (71.8)	15 (75.0)	102 (71.8)	135 (73.4)	0.433
YES	9 (21.4)	24 (28.9)	23 (28.4)	12 (29.3)	12 (28.6)	11 (28.2)	5 (25.0)	40 (28.2)	49 (26.6)	
MISSING	0	1	0	1	0	0	0	1	1	
PRESENCE OF ENTHESITIS BASED ON LEI										
NO	21 (50.0)	42 (50.6)	38 (46.9)	20 (48.8)	22 (52.4)	16 (41.0)	9 (45.0)	67 (47.2)	88 (47.8)	0.861
YES	21 (50.0)	41 (49.4)	43 (53.1)	21 (51.2)	20 (47.6)	23 (59.0)	11 (55.0)	75 (52.8)	96 (52.2)	
MISSING	0	1	0	1	0	0	0	1	1	
PRESENCE OF ENTHESITIS BASED ON LEI AND SPARCC										
NO	15 (35.7)	29 (34.9)	30 (37.0)	12 (29.3)	17 (40.5)	13 (33.3)	7 (35.0)	49 (34.5)	64 (34.8)	1.000
YES	27 (64.3)	54 (65.1)	51 (63.0)	29 (70.7)	25 (59.5)	26 (66.7)	13 (65.0)	93 (65.5)	120 (65.2)	
MISSING	0	1	0	1	0	0	0	1	1	
PRESENCE OF NAIL PSORIASIS BASED ON MNAPSI										
NO	12 (28.6)	35(42.2)	29 (35.8)	19 (46.3)	16 (38.1)	13 (33.3)	9 (45.0)	57 (40.1)	69 (37.5)	0.206
YES	30(71.4)	48(57.8)	52 (64.2)	22 (53.7)	26 (61.9)	26 (66.7)	11 (55.0)	85 (59.9)	115 (62.5)	
MISSING	0	1	0	1	0	0	0	1	1	
PRIOR EXPOSURE TO TNF ANTAGONISTS										
TNF EXPERIENCED	10 (23.8)	22 (26.2)	20 (24.7)	11 (26.2)	11 (26.2)	9 (23.1)	4 (20.0)	35 (24.5)	45 (24.3)	1.000
TNF NAÏVE	32 (76.2)	62 (73.8)	61 (75.3)	31 (73.8)	31 (73.8)	30 (76.9)	16 (80.0)	108 (75.5)	140 (75.7)	
MISSING	0	0	0	0	0	0	0	0	0	

NOTE: DACTYLITIS IS DEFINED AS A FINGER OR TOE BEING AFFECTED, TENDER, AND HAVING A CIRCUMFERENCE 10% GREATER THAN
THAT OF ITS CONTRALATERAL DIGIT OR, IF THAT IS NOT APPLICABLE, A REFERENCE VALUE.
BASELINE WAS DEFINED AS THE LAST NON-MISSING VALUE PRIOR TO THE FIRST DOSE OF STUDY DRUG.
PERCENTAGES CALCULATED ON NON-MISSING VALUES.
THE sPGA IS DICHOTOMIZED INTO RESPONDERS, 0 (CLEAR) AND 1 (ALMOST CLEAR) IN ONE CATEGORY, AND NON-RESPONDERS,
>=2 IN THE OTHER.
@ P-VALUE TO COMPARE TREATMENT GROUPS IS BASED ON FISHER'S EXACT TEST FROM PLACEBO VERSUS RISA TOTAL.
TREATMENT ARMS:
ARM 1: RISANKIZUMAB 150 MG Q4W
ARM 2: RISANKIZUMAB 150 MG W0_4_16
ARM 3: RISANKIZUMAB 150 MG W0_12
ARM 4: RISANKIZUMAB 75 MG W0

Outcomes and estimation

Primary endpoint

All baseline and efficacy analyses were based on the FAS with non-responder imputation. The primary efficacy endpoint was ACR 20 response rate at Week 16.

Subjects with psoriatic arthritis who received risankizumab 150 mg at Weeks 0, 4, 8, 12, and 16 (Arm 1) or Weeks 0, 4, and 16 (Arm 2) experienced improvement in signs and symptoms of psoriatic arthritis, as demonstrated by statistically significant differences in the proportion of subjects who achieved ACR 20 at Week 16 in comparisons of the combined Arm 1 + Arm 2 risankizumab group and the placebo arm. Statistically significant differences between all risankizumab treatment arms and the placebo arm were observed at Week 16.

Table 15: ACR 20 Response Rate at Week 16 (NRI, FAS)

		Responder	Response rate	Response Rate Difference (Risankizumab – Placebo)	
Treatment	N	n (%)	90% CI	Estimate (90% CI)	*P* value
Placebo	42	15 (35.7)	(23.5, 49.5)		
Arms 1 + 2	84	50 (59.5)	(50.0, 68.6)	24.0 (9.3, 38.7)	0.007
Arm 1	42	24 (57.1)	(43.3, 70.2)	21.8 (4.6, 39.1)	0.038
Arm 2	42	26 (61.9)	(48.0, 74.4)	26.4 (9.8, 43.0)	0.009
Arm 3	39	23 (59.0)	(44.6, 72.3)	23.1 (5.7, 40.4)	0.029
Arm 4	20	13 (65.0)	(44.2, 82.3)	28.5 (7.7, 49.4)	0.024
RZB Total	143	86 (60.1)	(52.9, 67.0)	24.4 (10.7, 38.0)	0.003

ACR = American College of Rheumatology; CI = confidence interval; FAS = Full Analysis Set; NRI = non responder imputation; RZB = risankizumab

Secondary endpoints

Analysis of secondary endpoints demonstrated that subjects who received risankizumab 150 mg at Weeks 0, 4, 8, 12, and 16 (Arm 1) or Weeks 0, 4, and 16 (Arm 2) experienced clinical improvement in signs and symptoms of psoriatic arthritis, as demonstrated by statistically significant differences between the combined Arm 1 + Arm 2 risankizumab groups and placebo in the proportion of subjects who achieved ACR 70 at Week 16

At Week 16, subjects who received risankizumab did not show significant improvement in tender joints, swollen joints, dactylitis, enthesitis, or nail psoriasis compared with subjects who received placebo.

No significant improvement in SF-36 (Physical Component Summary (PCS) or HAQ-DI was observed at Week 16.

Table 16: Summary of ACR50 response rate

SUMMARY OF ACR50 RESPONSE RATE AT WEEK 16 (FULL ANALYSIS SET)NRI					
Treatment	N	Responder N (%)	Response rate 90% CI	Response rate diff RZB – placebo	
				Estimate 90% CI	P
Placebo	42	5 (11.9%)	4.8, 23.4%		
Arms 1 +2	84	20 (23.8%)	16.4, 32.7%	12 (1.0, 23)	0.074
Arm 1	42	10 (23.8%)	13.5, 37%	12.2 (-1.0, 25.4)	0.128
Arm 2	42	10 (23.8%)	13.5, 37%	12 (-1.2, 25.3)	0.135
Arm 3	39	15 (38.5%)	25.4, 52.9%	26.7 (11.9, 41.4)	0.003
Arm 4	20	5 (25%)	10.4, 45.6%	13.1 (-4.3, 30.5)	0.215
Rzb total	143	40 (28%)	21.8, 34.8%	16 (5.9, 26.1)	0.009

Table 17: Summary of ACR 70 response rates

SUMMARY OF ACR70 RESPONSE RATE AT WEEK 16 (FULL ANALYSIS SET)NRI					
Treatment	N	Responder N (%)	Response rate 90% CI	Response rate diff RZB – placebo	
				Estimate 90% CI	P

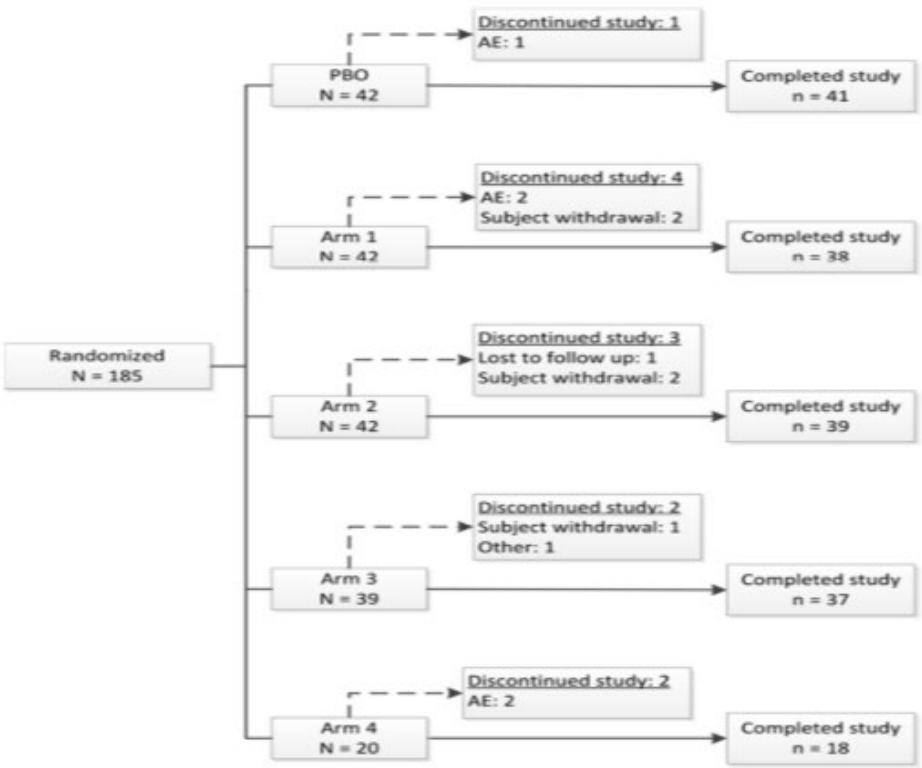
Placebo	42	0	0.0, 6.9		
Arms 1 +2	84	9 (10.7)	5.7, 18.0	10.3 (4.1, 16.4)	0.006
Arm 1	42	6 (14.3)	6.4, 26.3	14.3 (5.1, 23.5)	0.010
Arm 2	42	3 (7.1)	2.0, 17.4	6.9 (-0.0, 13.8)	0.100
Arm 3	39	10 (25.6)	14.6, 39.6	25.4 (14.0, 36.9)	<0.001
Arm 4	20	3 (15)	4.2, 34.4	15.5 (2.7, 28.4)	0.047
Rzb total	143	22 (15.4)	10.7, 21.2	14.8 (9.3, 20.4)	<0.001

Ancillary analyses

A number of subgroup analyses were performed. There was no difference between the TNF experienced and TNF naïve subgroups, and both groups showed statistically significant differences in ACR 20 response rate at Week 16 with risankizumab treatment (Arm 1 + Arm 2) compared to placebo .

In the concurrent MTX subgroup analysis, the group of subjects who did use MTX concurrently showed statistically significantly higher ACR 20 response rates with risankizumab treatment compared to placebo treatment, while the group with subjects who did not use MTX concurrently showed improvements that were not statistically significant.

Figure 16: Subject Disposition Through Week 16



Arm 1 = risankizumab 150 mg every 4 weeks; Arm 2 = risankizumab 150 mg Weeks 0, 4, and 16; Arm 3 = risankizumab 150 mg Weeks 0 and 12; Arm 4 = risankizumab 75 mg Week 0; PBO = placebo.

2.4.2. Main studies

The efficacy data presented for the two phase III trials are interim data with a primary database lock (DBL) cut-off date of 02 November 2020. This includes data from all subjects through the primary efficacy endpoint at Week 24 for both studies.

Table 18:

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3 Efficacy and Safety	M15-998	5.3.5.1	Primary, Period 1 Compare the efficacy of RZB 150 mg vs. PBO for the treatment of signs and symptoms of PsA Secondary, Period 1 Compare the safety and tolerability of RZB 150 mg vs. PBO Secondary, Period 2 Evaluate the long-term safety, tolerability, and efficacy of RZB 150 mg in subjects who have completed Period 1	Period 1: Randomized, DB, parallel-group, PBO-controlled Period 2: Long-term, open-label extension	Period 1: RZB arm: RZB 150 mg SC at BL and Wks 4 and 16 PBO arm: Matching PBO SC at BL and Wks 4 and 16 Period 2: RZB to RZB arm: PBO at Wk 24, then RZB 150 mg SC at Wk 28 and q12w thereafter PBO to RZB arm: RZB 150 mg SC at Wks 24, 28, and q12w thereafter	RZB to RZB arm: 224 PBO to RZB arm: 220	Adult subjects with moderately to severely active PsA with either 1) inadequate response or intolerance to 1 or 2 biologic therapies or 2) inadequate response to ≥ 1 csDMARD or an intolerance or contraindication to csDMARDs	Period 1: 24 weeks; Period 2: Up to 208 weeks	Ongoing; Interim Full CSR (up to Wk 24)

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3 Efficacy and Safety	M16-011	5.3.5.1	Primary, Period 1 Compare the efficacy of RZB 150 mg vs. PBO for the treatment of signs and symptoms of PsA Secondary, Period 1 Compare the efficacy of RZB 150 mg vs. PBO for the inhibition of progression of structural damage and to compare the safety and tolerability of RZB 150 mg vs. PBO Secondary, Period 2 Evaluate the long-term safety, tolerability, and efficacy of RZB 150 mg in subjects who have completed Period 1	Period 1: Randomized, DB, parallel-group, PBO-controlled Period 2: Long-term, open-label extension	Period 1: RZB arm: RZB 150 mg SC at BL and Wks 4 and 16 PBO arm: Matching PBO SC at BL and Wks 4 and 16 Period 2: RZB to RZB arm: PBO at Wk 24, then RZB 150 mg SC at Wk 28 and q12w thereafter PBO to RZB arm: RZB 150 mg SC at Wks 24, 28, and q12w thereafter	RZB to RZB arm: 483 PBO to RZB arm: 481	Adult subjects with moderately to severely active PsA with inadequate response to ≥ 1 csDMARD or an intolerance or contraindication to csDMARDs	Period 1: 24 weeks; Period 2: Up to 208 weeks	Ongoing; Interim Full CSR (up to Wk 24)

2.4.2.1. Study M15–998

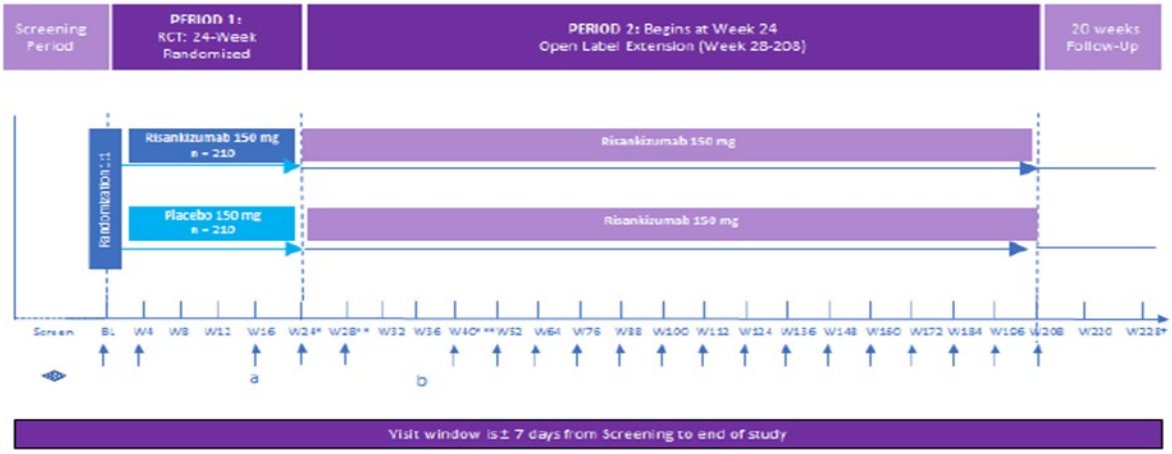
Study title : A Phase 3, Randomized, Double-Blind Study Comparing Risankizumab to Placebo in Subjects with Active Psoriatic Arthritis Including Those Who Have a History of Inadequate Response or Intolerance to Biologic Therapy(ies)

Methods

The study consisted of a Screening Period (~35 days), Period 1, Period 2, and a 20-week follow-up period after last dose at Week 208 i.e. a total of 228 weeks' study duration. The first subject first visit was on 07 March 2019 and last subject last visit (Week 24 DLP) on 22 June 2020.

The study design is detailed in the following **Figure 17.**

Figure 17: Study Design Schematic



BL = Baseline; RCT = randomized clinical trial; W = Week

* At Week 24, subjects randomized to placebo in Period 1 receive a blinded dose of risankizumab. Subjects randomized to risankizumab treatment in Period 1 receive a blinded dose of placebo.

** At Week 28, subjects randomized to placebo in Period 1 receive a 2nd dose of risankizumab. Subjects randomized to risankizumab in Period 1 receive risankizumab (scheduled dose).

*** From Week 40 to Week 208 Visits, doses were to occur q12w.

† Follow up phone call.

Dosing.

Bilateral radiographs of hands and feet.

a. At Week 16, subjects classified as non-responders (defined as not achieving at least a 20% improvement in either or both tender joint count [TJC] and swollen joint count [SJC] at both Week 12 and Week 16) compared to Baseline were to add or modify rescue concomitant medications/therapy. Rescue therapy qualification was to occur only at Week 16 Visit.

b. Starting at Week 36, subjects classified as non-responders are to be discontinued from study drug.

Study participants

This multi-centre study evaluated subjects with moderately to severely active PsA.

Key eligibility criteria

Subjects enrolled were adults, ≥ 18 years of age, with a clinical diagnosis of PsA and:

- symptom onset at least 6 months prior to the Screening Visit
- fulfilment of the Classification Criteria for Psoriatic Arthritis (CASPAR) at Screening Visit
- active disease, defined as ≥ 5 tender joints (based on 68 joint counts) and ≥ 5 swollen joints (based on 66 joint counts) at both the Screening Visit and Baseline
- active plaque psoriasis with at least one psoriatic plaque of ≥ 2 cm diameter *or*
- nail changes consistent with psoriasis at Screening Visit.

- inadequate response (lack of efficacy at maximally tolerated dose after a minimum 12-week duration of therapy) or intolerance to 1 or 2 biologic therapies (Bio-IR), or
- inadequate response (lack of efficacy at maximally tolerated dose after a minimum 12-week duration of therapy) or
- intolerance to at least 1 csDMARD (csDMARD-IR)

'csDMARD-IR' means at least one of methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), apremilast, bucillamine and iguratimod, or ciclosprin A, and without any prior exposure to a biologic agent for PsA. MTX – IR was defined as an inadequate response at the following doses ranges: ≥ 15 mg/week, or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week after complete titration (in some countries ≥ 7.5 mg/week or as required per local authorities).

Concomitant medications

For Bio-IR subjects, timeframes for discontinuation of biologic therapy prior to first dose of study drug were specified in the protocol.

Subjects were not required to be receiving csDMARD therapy to participate in the clinical trial. Concomitant csDMARDs allowed at study entry were ≤2 of the following, for ≥ 12 weeks and at stable dose from ≥ 4 weeks prior to the Baseline Visit up to Week 36 of the study, at the following doses

MTX (≤ 25 mg/week) (+folic acid);	SSZ (≤ 3000 mg/day);
LEF (≤ 20 mg/day);	apremilast (≤ 60 mg/day);
hydroxychloroquine (HCQ) (≤ 400 mg/day);	bucillamine (≤ 300 mg/day);
iguratimod (≤ 50 mg/day)	ciclosporin A (≤ 5 mg/kg/day)

Other csDMARDS and the combination of MTX and LEF was exclusionary. The protocol specified discontinuation and/or dose reduction requirements before Baseline Visit for allowable csDMARDS and pain relief medications. The time frames for discontinuation of concomitant psoriasis treatments (

Treatments

Subjects were assigned to one of two blinded treatment arms, risankizumab 150 mg sc or placebo. Risankizumab was administered as an injection solution at a concentration of 90 mg/mL in a prefilled syringe (PFS) for subcutaneous (SC) injection. The study dose of risankizumab 150 mg was provided in 2 PFS of 75 mg/0.83 mL each. Placebo was similarly administered subcutaneously via a PFS.

Risankizumab arm: blinded risankizumab 150 mg sc at Week 0, Week 4, Week 16, placebo Week 24, open label risankizumab week 28 and 12 weekly thereafter.

Placebo arm: blinded placebo at Week 0, Week 4, Week 16, risankizumab 150 mg sc Weeek 24, open label risankizumab Week 28 and 12 weekly thereafter.

Allowed concomitant medications/therapy

Subjects could be enrolled on 0, 1 or 2 csDMARDs as per eligibility criteria, alone or along with NSAIDS, acetaminophen/paracetamol, low potency opioids, oral corticosteroids (~prednisolone ≤10 mg/day), to continue stable until week 36. Subjects could start any of the above treatments during the trial only per protocol or could reduce doses or substitute from the same class as needed. After Week 24 assessments, subjects could use any topical therapy for PsO per investigator judgment.

Rescue Treatment

At Week 16, subjects classified as non-responders (i.e. not achieving at least a 20% improvement in either/both TJC and SJC vs. Baseline at both Week 12 and Week 16) could:

- Add or modify doses of NSAIDs, acetaminophen/paracetamol, low potency opioid medications (tramadol, codeine, or hydrocodone, alone or in combination with acetaminophen);

OR

- Receive 1 intra articular, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroid injection for 1 peripheral joint or 1 enthesis (avoided within 21 days prior to the next scheduled study visit, such injected joints or enthesitis sites considered trial "not assessable" for 90 days from the time of the injection;

OR

- Titrate current background csDMARD or add an additional csDMARD, as allowed by eligibility criteria. Adding a biologic therapy was not permitted and maximum 2 csDMARDs were permitted.

Objectives

Primary objective : To compare the efficacy of risankizumab 150 mg versus placebo for the treatment of signs and symptoms of PsA in the study population during the double-blind Period 1.

Secondary objectives :

Period 1 Double-Blind: To compare the safety and tolerability of risankizumab 150 mg versus placebo in the study population.

Period 2 Open-Label: To evaluate the long-term safety, tolerability, and efficacy of risankizumab 150 mg in subjects who completed Period 1.

e.g. oral retinoids; fumarates; PUVA; UVA and UVB; topical treatments) were also specified.

Outcomes/endpoints

Primary endpoint : The proportion of subjects in each arm achieving American College of Rheumatology (ACR) 20 Response (ACR20) at Week 24.

Ranked secondary endpoints with multiplicity adjustment

1. Change from Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24;
2. Proportion of subjects achieving Psoriasis Area Severity Index (PASI) 90 response at Week 24 (in the subset of subjects with a body surface area (BSA) ≥ 3% at Baseline);
3. Proportion of subjects achieving ACR20 at Week 16;
4. Proportion of subjects achieving Minimal Disease Activity (MDA) at Week 24;
5. Change from Baseline in 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) at Week 24;
6. Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue) Questionnaire at Week 24.

Other secondary endpoints without multiplicity adjustment

1. Proportion of subjects achieving ACR50 response at Week 24;
2. Proportion of subjects achieving ACR70 response at Week 24;
3. Proportion of subjects with resolution of enthesitis (LEI = 0) at Week 24 in subjects with enthesitis at Baseline;
4. Proportion of subjects with resolution of dactylitis (LDI = 0) at Week 24 in subjects with dactylitis at Baseline.

Pharmacokinetics:

Serum risankizumab concentrations, anti-drug antibodies (ADA), and neutralizing antibodies (NAb) were determined at study visits.

According to the submission, the original protocol (v1.0 26 July 2018) was amended on 4 occasions.

Amendment 4 (v4.0, 17 March 2020) incorporated clarification of secondary vs. additional endpoints, modification of resolution of enthesitis and dactylitis endpoints, and addition of ACR50 and ACR70 as secondary endpoints.

With Amendment 5 (v5.0, 10 September 2020) ACR20 at Week 16 was added as a ranked secondary endpoint, resolution of enthesitis and dactylitis were modified to unranked additional secondary endpoints without multiplicity adjustment and changes due to the COVID-19 pandemic were incorporated. Mitigation strategies put in place to minimize the impact of COVID-19 logistical restrictions on missing data and on the ability of subjects to complete study visits included at-home visits, partial assessment completion at study sites, virtual visits, and out-of-window (OOW) study visits.

Sample size

A sample of 420 subjects were to be randomized to risankizumab 150 mg or placebo in a ratio of 1:1 in order to have 90% power to detect a 20% treatment difference in ACR20 at Week 24, with assumed placebo response rate of 35%, using a two-sided test at a 0.05 significance level and accounting for a 10% dropout rate *and* to detect a difference in HAQ-DI mean change from baseline of 0.24 (the difference between risankizumab 150 mg mean change from baseline of –0.37 and placebo mean change from baseline of –0.13) assuming a common standard deviation of 0.72 using a two-group Satterthwaite t-test with a two-sided significance level of 0.05.

Randomisation

The MAH states that enrolled subjects were assigned a unique identification number by interactive response technology (IRT) at the Screening Visit and randomized 1:1 ratio to one of two treatment groups:

- Group 1: Risankizumab 150 mg (target N = 210)
- Group 2: Placebo (target N = 210)

Randomization was stratified at Baseline by:

- current use of csDMARD (0 vs ≥ 1),
- number of prior biologic therapies (0 vs ≥ 1), and
- extent of psoriasis (≥ 3% BSA or < 3% BSA).

Blinding (masking)

To maintain the blind during Period 1, the risankizumab pre-filled syringe (PFS) and placebo PFS were identical in appearance. At Week 24 those in the risankizumab arm received placebo and those in the placebo arm received risankizumab. The Investigator, study site personnel, and subject were to remain blinded to treatment administered in Period 1 until study end. During the study, the Investigator could access the IRT if an urgent therapeutic intervention was necessary that warranted breaking the blind.

Statistical methods

For efficacy analysis, a fixed sequence testing procedure was used to control the overall type I error rate at 2-sided alpha = 0.05 for the primary endpoint and ranked secondary endpoints.

Comparisons between risankizumab and placebo treatment groups for the primary efficacy endpoint (ACR20 at Week 24) were performed using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline stratification factors (concurrent use of csDMARD (0 vs. ≥1), number of prior biologic therapies (0 vs. ≥1), extent of psoriasis (≥3% BSA or <3% BSA)).

Continuous efficacy endpoints: treatment comparisons were conducted using a Mixed-Effect Model Repeated Measures (MMRM) method as primary inference purpose. Results for radiographic continuous endpoints were based on an ANCOVA model.

Categorical efficacy variables: analyzed using the CMH test to control for stratification variables.

Non-Responder Imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C) was used for missing data imputation. The As Observed (AO) analysis does not impute values for missing evaluations.

Long-term efficacy by time point was summarized using descriptive statistics.

PK data was summarised using descriptive statistics (risankizumab concentrations, ADA titre, NAb titre).

Results

An interim report for Study M15-998 with a data cut-off date of 02 November 2020 has been provided.

Participant flow

Overall, 443 subjects were enrolled into Period 1 (placebo n=219; risankizumab n=224).

In Period 1 the rate of discontinuation was low: risankizumab (4.0%; n=9), placebo (9.1%; n=20); no subjects discontinued due to COVID-19; 1 discontinued due to COVID-19 logistical restrictions. Overall, 414 subjects (93.5%) completed Period 1. Overall, treatment compliance was greater than 99% across treatment arms.

Period 2 is ongoing.

Table 19: Subject Disposition in Study M15-998 (FAS)

	Placebo[a] (N = 219) n (%)	Risankizumab 150 mg (N = 224) n (%)	Total (N = 443) n (%)
Completed Period 1 Study Participation	199 (90.9)	215 (96.0)	414 (93.5)
Discontinuation from the study during Period 1 due to (Primary Reason)	20 (9.1)	9 (4.0)	29 (6.5)
Adverse Event	3 (1.4)	2 (0.9)	5 (1.1)
Withdrew Consent	8 (3.7)	2 (0.9)	10 (2.3)
Lost to Follow-up	1 (0.5)	2 (0.9)	3 (0.7)
Lack of Efficacy	7 (3.2)	2 (0.9)	9 (2.0)
COVID-19 Infection	0	0	0
COVID-19 Logistical Restrictions	0	1 (0.4)	1 (0.2)
Other	1 (0.5)	0	1 (0.2)
Entered Period 2 Study Participation	199 (90.9)	215 (96.0)	414 (93.5)
Ongoing in Period 2	183 (83.6)	199 (88.8)	382 (86.2)
Discontinuation from the study in Period 2 due to (Primary Reason)	16 (7.3)	16 (7.1)	32 (7.2)
Adverse Event	0	0	0
Withdrew Consent	4 (1.8)	6 (2.7)	10 (2.3)
Lost to Follow-up	3 (1.4)	1 (0.4)	4 (0.9)
<20% Improvement in TJC/SJC Compared to Baseline	2 (0.9)	4 (1.8)	6 (1.4)
Lack of Efficacy	2 (0.9)	4 (1.8)	6 (1.4)
COVID-19 Infection	0	0	0
COVID-19 Logistical Restrictions	2 (0.9)	0	2 (0.5)
Other	3 (1.4)	1 (0.4)	4 (0.9)
Completed Period 1 and Period 2 Study Participation	0	0	0

Recruitment

A total of 444 subjects were recruited (target: 420). One subject discontinued during the randomisation visit due to failure to draw requisite blood samples (n=443; placebo n=291; risankizumab n=224). Over-recruitment arose in the context of the Covid-19 pandemic rather than due to a formal sample size re-estimation during the trial. Subjects were recruited from 99 sites across Europe (Belgium, Denmark, Estonia, France, Germany, Greece, Hungary, Italy, Poland, Portugal, Spain, Sweden, UK), Israel, South Africa, Argentina, Brazil, Australia, New Zealand, Canada and USA + Puerto Rico.

Conduct of the study

The CSR states 'This study was conducted in compliance with the protocol, Good Clinical Practice and other applicable regulatory requirements including the archiving of essential documents'. An independent ethics committee (IEC)/institutional review board (IRB) approved the study and there is an external, independent data monitoring committee (IDMC).

Baseline data

Demographic characteristics were balanced between treatment groups and overall. Overall, there were slightly more female subjects, mean age was 52.9 years (range 23-84 years), the vast majority were classified as 'white', and 20.1% were ≥65 years.

Table 20: Demographic Characteristics (FAS)

	Placebo (N = 219) n (%)	Risankizumab 150 mg (N = 224) n (%)	Total (N = 443) n (%)
Sex			
Female	120 (54.8)	124 (55.4)	244 (55.1)
Male	99 (45.2)	100 (44.6)	199 (44.9)
Age (years)			
n	219	224	443
Mean (SD)	52.7 (12.64)	53.1 (12.53)	52.9 (12.57)
Median	52.0	53.0	53.0
Min, Max	24, 83	23, 84	23, 84
Age (years)			
< 65	176 (80.4)	178 (79.5)	354 (79.9)
≥ 65	43 (19.6)	46 (20.5)	89 (20.1)
≥ 65 - < 75	34 (15.5)	39 (17.4)	73 (16.5)
≥ 75	9 (4.1)	7 (3.1)	16 (3.6)
Race			
White	210 (95.9)	218 (97.3)	428 (96.6)
Black or African American	3 (1.4)	2 (0.9)	5 (1.1)
Asian	3 (1.4)	2 (0.9)	5 (1.1)
Multiple	3 (1.4)	2 (0.9)	5 (1.1)

Table 21: Demographic Characteristics (FAS) (Continued)

	Placebo (N = 219) n (%)	Risankizumab 150 mg (N = 224) n (%)	Total (N = 443) n (%)
Ethnicity			
Hispanic or Latino	43 (19.6)	42 (18.8)	85 (19.2)
Not Hispanic or Latino	176 (80.4)	182 (81.3)	358 (80.8)
Weight (kg)			
n	219	224	443
Mean (SD)	89.21 (21.583)	88.86 (21.475)	89.03 (21.505)
Median	85.64	87.95	86.73
Min, Max	37.2, 156.9	28.6, 168.4	28.6, 168.4
Weight (kg)			
< 100	154 (70.3)	164 (73.2)	318 (71.8)
≥ 100	65 (29.7)	60 (26.8)	125 (28.2)
Body Mass Index (kg/m^2)			
n	219	224	443
Mean (SD)	31.2 (6.81)	31.5 (7.98)	31.4 (7.42)
Median	30.2	30.4	30.4
Min, Max	16.0, 53.0	10.4, 87.2	10.4, 87.2
Body Mass Index (kg/m^2)			
< 25	38 (17.4)	38 (17.0)	76 (17.2)
≥ 25 - < 30	68 (31.1)	68 (30.4)	136 (30.7)
≥ 30	113 (51.6)	118 (52.7)	231 (52.1)

FAS = Full Analysis Set; Max = maximum; Min = minimum; SD = standard deviation

PsA disease characteristics were balanced between treatment groups (M15-998 CSR, Table 7). A selection of Baseline disease characteristics are presented here.

Less than 3% had MDA for PsA in either arm and overall. Median Total dactylitis count was similar across arms, with a higher median LDI score in the placebo vs. risankizumab arm (54.75 v 39.74). Median total enthesitis count, LEI score, CASPAR total score, BSA-PsO and HAQ-DI score (1.13) were also similar across arms. Almost half of subjects in either arm had a diagnosis of PsA for ≤5 years, with approximately a quarter in either arm diagnosed between 5-10 years or >10 years (median duration 5.5 years in both arms).

Table 22:

Presence of:	Placebo (n=219) %	Risankizumab (n=224) %	Total (n=443) %
Dactylitis (LDI>0)	26.3	17.9	22.0
Enthesitis (LEI >0)	72.1	65.6	68.8
BSA of Psoriatic Plaques ≥3%	54.3	54.9	45.4
Spondylitis	17.8	21.4	19.6

Median of:	Units	Units	Units
PASI (BSA≥3%)	5.50	5.80	5.60
DAS28-hsCRP	4.88	4.91	4.90
TCJ68	20.0	18.0	19.0
SJC66	10.0	10.0	10.0
hsCRP (mg/L)	3.22	3.16	3.19
HAQ-DI	1.13	1.13	1.13

Prior use of DMARDs was balanced across arms. Overall, 94.8% of subjects had prior use of at least one csDMARD (1 prior: 38.1%; 2 prior: 27.1%; ≥3 prior: 29.6%).

Prior use of biologics and TNF antagonists was balanced across arms. Overall, 46.5% of subjects had prior use of at least one biologic therapy (1 prior failed: 30.7%; ≥2 prior failed: 8.6%); 45.8% had prior exposure to at least one TNF antagonist.

Medication use at Baseline was similar in both arms. Overall: csDMARDs 60.9%; NSAIDS 64.6%; oral corticosteroids 11.3%; MTX 47.2%; csDMARD other than MTX (sulfasalazine, leflunomide, apremilast) 13.8%.

Overall, 39.1% of subjects were not on a concomitant DMARD at baseline.

Table 23: Baseline Characteristics (FAS) (Continued)

	Placebo (N = 219) n (%)	Risankizumab 150 mg (N = 224) n (%)	Total (N = 443) n (%)
Number of Prior csDMARDs			
0	11 (5.0)	12 (5.4)	23 (5.2)
1	81 (37.0)	88 (39.3)	169 (38.1)
2	60 (27.4)	60 (26.8)	120 (27.1)
≥ 3	67 (30.6)	64 (28.6)	131 (29.6)
Number of Prior Biologics			
0	118 (53.9)	119 (53.1)	237 (53.5)
≥ 1	101 (46.1)	105 (46.9)	206 (46.5)
Number of Prior Failed Biologics			
0	132 (60.3)	137 (61.2)	269 (60.7)
1	64 (29.2)	72 (32.1)	136 (30.7)
≥ 2	23 (10.5)	15 (6.7)	38 (8.6)
Prior Exposure to TNF Antagonists			
0	119 (54.3)	121 (54.0)	240 (54.2)
≥ 1	100 (45.7)	103 (46.0)	203 (45.8)
NSAID Use at Baseline			
Yes	145 (66.2)	141 (62.9)	286 (64.6)
No	74 (33.8)	83 (37.1)	157 (35.4)
Oral Corticosteroid Use at Baseline			
Yes	22 (10.0)	28 (12.5)	50 (11.3)
No	197 (90.0)	196 (87.5)	393 (88.7)
Concomitant MTX Use at Baseline			
Yes	99 (45.2)	110 (49.1)	209 (47.2)
No	120 (54.8)	114 (50.9)	234 (52.8)
Concomitant csDMARD at Baseline			
Any csDMARD	129 (58.9)	141 (62.9)	270 (60.9)
Any MTX	99 (45.2)	110 (49.1)	209 (47.2)
MTX alone	89 (40.6)	102 (45.5)	191 (43.1)
MTX and other csDMARD	10 (4.6)	8 (3.6)	18 (4.1)
csDMARD other than MTX	30 (13.7)	31 (13.8)	61 (13.8)
Any sulfasalazine, without MTX	9 (4.1)	9 (4.0)	18 (4.1)
Any leflunomide, without MTX	15 (6.8)	12 (5.4)	27 (6.1)
Any apremilast, without MTX	5 (2.3)	9 (4.0)	14 (3.2)
None	90 (41.1)	83 (37.1)	173 (39.1)

Numbers analysed

All baseline and efficacy analyses were based on the FAS (n=443; placebo n=219; risankizumab n=224), with additional primary endpoint analysis conducted based on the Per Protocol Analysis (PPA) set (n=417), a subset of FAS containing subjects who did not have any major protocol deviations that were

deemed to have a potential impact on primary efficacy endpoint up to Week 24 in Period 1. Final criteria and exclusion of subjects from the PPA were identified before primary analysis DBL.

Protocol deviations

Table 24: Protocol Deviations (All Randomized Subjects)

Criteria Category	Placebo (N = 220) n (%)	Risankizumab 150 mg (N = 224) n (%)	Total (N = 444) n (%)
Subjects who had at least one protocol deviation	38 (17.3)	41 (18.3)	79 (17.8)
Subject entered into the study even though she/he did not satisfy entry criteria	7 (3.2)	6 (2.7)	13 (2.9)
Eligibility criterion #10	2 (0.9)	0	2 (0.5)
Eligibility criterion #11	0	1 (0.4)	1 (0.2)
Eligibility criterion #23	2 (0.9)	2 (0.9)	4 (0.9)
Eligibility criterion #24	1 (0.5)	0	1 (0.2)
Eligibility criterion #27	0	1 (0.4)	1 (0.2)
Eligibility criterion #28	1 (0.5)	0	1 (0.2)
Eligibility criterion #29	1 (0.5)	0	1 (0.2)
Eligibility criterion #33	1 (0.5)	2 (0.9)	3 (0.7)
Subject received wrong treatment or incorrect dose	1 (0.5)	2 (0.9)	3 (0.7)
Subject received excluded concomitant treatment	31 (14.1)	37 (16.5)	68 (15.3)

Six (6) subjects had an incorrect eligibility criterion selected in the eCRF, identified on DBL and to be corrected in the final CSR. In addition, 38 subjects (8.6% 38/444) received medication not permitted during the study phase. Due to the COVID-19 pandemic restrictions 5 subjects did not have the Week 24 visit performed; 11 subjects had Week 24 laboratory testing performed at a local laboratory; 3 subjects did not have Week 24 central laboratory results; 6 subjects had partial targeted source data verification (SDV) at the time of database lock (more than 99.9% of overall targeted SDV was complete).

Outcomes and estimation

Efficacy analyses are based on the FAS i.e. all randomised subjects who received at least 1 dose of study medication, grouped by treatment assignment at randomisation regardless of the actual treatment received on study. The primary endpoint was the proportion of subjects in each arm achieving ACR20 Response at Week 24.

Analyses for the ranked secondary endpoints of resolution of enthesitis and resolution of dactylitis at Week 24 used pooled data from Studies M15-998 and M16-011 following.

- Primary efficacy endpoint

Table 25: ACR20 Response at Week24 (NRI-C, FAS)

Treatment	Responder n (%)	Responder 95% CI[a]	Response Rate Diff Compared to Placebo Diff (%)[b]	Response Rate Diff Compared to Placebo 95% CI[b]	Response Rate Diff Compared to Placebo *P*-value[b]	Missing Due to COVID-19 (n)
Placebo (N = 219)	58 (26.5)	(20.7, 32.4)				3
Risankizumab 150 mg (N = 224)	115 (51.3)	(44.8, 57.9)	24.5	(15.9, 33.0)	< 0.001***,$	4

The primary endpoint was reached. The response rate in ACR20 with risankizumab at Week 24 was 51.3% (95% CI 44.8, 57.9%) versus placebo 26.5% (95% CI 20.7 – 32.4%). The treatment difference between risankizumab and placebo arms, 24.5%, was statistically significant at p<0.001.

The impact of inter-current events on the primary endpoint was assessed i.e. subjects who:

- did not meet ACR20 response criteria (risankizumab 83; placebo 110)
- took rescue medication at Week 16 (risankizumab 15; placebo 28)
- took concomitant medications that could impact efficacy (risankizumab 2; placebo 4)
- with missing data due to COVID-19 (risankizumab 1; placebo 2)
- with missing data due to reasons other than COVID-19 (risankizumab 8; placebo 17).

As observed (AO) analysis, AO with imputation, tipping point analysis for ACR20 response at Week 24 and PPA proved consistent with the primary analysis.

- Ranked secondary efficacy endpoints

All ranked secondary endpoints were achieved, summarised in Table 10 following.

Table 26: Summary of Ranked Secondary Endpoints (NRI-C, MMRM, FAS)

Endpoint[a] Treatment	Within Group Mean Estimate (95% CI)	Between Group Difference (Risankizumab 150 mg - Placebo) Mean Estimate (95% CI)	*P*-value	Multiplicity Adjusted Results	Missing Due to COVID-19 n
Change from Baseline in HAQ-DI Score at Week 24					
Placebo (N = 219)	-0.05 (-0.12, 0.02)				3
Risankizumab 150 mg (N = 224)	-0.22 (-0.28, -0.15)	-0.16 (-0.26, -0.07)	<0.001***,$	Significant	2
PASI 90 Response at Week 24 (For Subjects with BSA >= 3% at Baseline)					
Placebo (N= 119)	10.2 (4.7, 15.6)				1
Risankizumab 150 mg (N = 123)	55.0 (46.2, 63.9)	44.3 (33.9, 54.6)	<0.001***,$	Significant	1
ACR20 Response at Week 16					
Placebo (N = 219)	25.3 (19.4, 31.2)				5
Risankizumab 150 mg (N = 224)	48.3 (41.7, 54.8)	22.6 (13.9, 31.2)	<0.001***,$	Significant	2
MDA at Week 24					
Placebo (N = 219)	11.4 (7.2, 15.6)				0
Risankizumab 150 mg (N = 224)	25.6 (19.9, 31.4)	14.0 (7.0, 21.0)	<0.001***,$	Significant	2
Change from Baseline in SF-36 PCS Score at Week 24					
Placebo (N = 219)	2.01 (0.94, 3.08)				2
Risankizumab 150 mg (N = 224)	5.87 (4.86, 6.88)	3.86 (2.41, 5.31)	<0.001***,$	Significant	2
Change from Baseline in FACIT-Fatigue Score at Week 24					
Placebo (N = 219)	2.6 (1.4, 3.9)				2
Risankizumab 150 mg (N = 224)	4.9 (3.7, 6.0)	2.2 (0.6, 3.9)	0.009**,$	Significant	2

***,**,*. *P*-value ≤ 0.001, ≤ 0.01, and ≤ 0.05 respectively.

Compared to the placebo arm, subjects in the risankizumab arm had a statistically significantly:
-greater decrease from Baseline in HAQ-DI (mean estimate -0.16 [-0.26, -0.07])
-greater response in PASI 90 for those with BSA ≥3% (mean estimate 44.3 [33.9, 54.6])
-higher percentage achieving ACR20, Week 16 (mean estimate 22.6 [13.9, 31.2])
-higher percentage achieving MDA (mean estimate 14.0 [7.0, 21.0])
-greater change from Baseline in SF-36 PCS (mean estimate 3.86 [2.41, 5.31])
-greater change from Baseline in FACIT-Fatigue (mean estimate 2.2 [0.6, 3.9])

As Observed (AO) analysis and AO with imputation analysis proved consistent with the primary analysis for ranked secondary endpoints.

Similar response regardless of prior therapy was observed in the risankizumab arm vs. placebo arm for the subgroup analyses in the DMARD-IR and the Bio-IR population for all ranked secondary endpoints, summarised in Table 27 and Table 28 following.

Table 27: Continuous Ranked Secondary Endpoints by Number of Prior Biologic Therapies (MMRM, FAS)

					Change from Baseline			
							Between Group Comparison (Risankizumab 150 mg - Placebo)	
	N		Missing Due to COVID-19 n		Within Group LS Mean (95% CI)[a]		LS Mean Diff (95% CI)[a]	
Endpoints Treatment	csDMARD-IR[b]	Bio-IR[c]	csDMARD-IR[b]	Bio-IR[c]	csDMARD-IR[b]	Bio-IR[c]	csDMARD-IR[b]	Bio-IR[c]
Change from Baseline in HAQ-DI Score at Week 24								
Placebo	118	101	3	0	-0.12 (-0.21, -0.03)	0.04 (-0.07, 0.14)		
Risankizumab 150 mg	119	105	2	0	-0.24 (-0.33, -0.15)	-0.19 (-0.29, -0.09)	-0.12 (-0.25, 0.01)	-0.22 (-0.37, -0.08)
Change from Baseline in SF-36 PCS Score at Week 24								
Placebo	118	101	2	0	3.04 (1.58, 4.50)	0.51 (-1.08, 2.10)		
Risankizumab 150 mg	119	105	2	0	6.09 (4.66, 7.52)	5.58 (4.14, 7.03)	3.05 (1.07, 5.03)	5.07 (2.93, 7.21)
Change from Baseline in FACIT-Fatigue Score at Week 24								
Placebo	118	101	2	0	4.1 (2.4, 5.8)	1.0 (-0.8, 2.9)		
Risankizumab 150 mg	119	105	2	0	5.8 (4.2, 7.4)	4.1 (2.4, 5.8)	1.7 (-0.6, 4.0)	3.1 (0.6, 5.6)

Table 28: Binary Ranked Secondary Endpoints by Number of Prior Biologic Therapies (NRI-C, FAS)

					Responder				Response Rate Diff Compared to Placebo			
	N		Missing Due to COVID-19 n		n (%)		(95% CI)[a]		Diff (%)[b]		(95% CI)[b]	
Endpoint Treatment	csDMARD-IR[c]	Bio-IR[d]	csDMARD-IR[c]	Bio-IR[d]	csDMARD-IR[c]	Bio-IR[d]	csDMARD-IR[c]	Bio-IR[d]	csDMARD-IR[c]	Bio-IR[d]	csDMARD-IR[c]	Bio-IR[d]
PASI 90 Response at Week 24												
Placebo	62	57	1	0	7 (11.5)	5 (8.8)	(3.5, 19.4)	(1.4, 16.1)				
Risankizumab 150 mg	65	58	1	0	37 (56.5)	31 (53.4)	(44.3, 68.6)	(40.6, 66.3)	43.9	44.6	(29.3, 58.5)	(29.9, 59.4)
ACR20 Response at Week 16												
Placebo	118	101	3	2	32 (27.1)	23 (23.1)	(18.9, 35.3)	(14.8, 31.4)				
Risankizumab 150 mg	119	105	1	1	65 (54.7)	43 (41.0)	(45.7, 63.6)	(31.6, 50.5)	26.9	17.6	(14.9, 38.9)	(5.3, 30.0)
MDA at Week 24												
Placebo	118	101	0	0	19 (16.1)	6 (5.9)	(9.5, 22.7)	(1.3, 10.6)				
Risankizumab 150 mg	119	105	2	0	37 (31.4)	20 (19.0)	(23.0, 39.8)	(11.5, 26.6)	14.9	13.0	(4.3, 25.4)	(4.3, 21.8)

- Other secondary efficacy variables

A greater percentage of subjects in the risankizumab arm achieved ACR50 and ACR70 responses at Week 24 compared with placebo (Table 13).

Among subjects with enthesitis and/or dactylitis at Baseline, a larger percentage of subjects in the risankizumab arm achieved resolution of enthesitis (LEI = 0) and/or dactylitis (LDI=0) at Week 24 compared with placebo. Data for the resolution of enthesitis (LEI) and dactylitis (LDI) was pooled with and analysed under the multiplicity control of Study M16-011 following.

Table 29: Summary of Other Secondary Efficacy Endpoints (NRI-C, FAS)

Endpoint[a] Treatment	Within Group Mean Estimate (95% CI)	Between Group Difference (Risankizumab 150 mg - Placebo)		Missing Due to COVID-19 n
		Mean Estimate (95% CI)	*P*-value	
ACR50 Response at Week 24				
Placebo (N = 219)	9.3 (5.4, 13.2)			3
Risankizumab 150 mg (N = 224)	26.3 (20.3, 32.3)	16.6 (9.7, 23.6)	<0.001***	5
ACR70 Response at Week 24				
Placebo (N = 219)	5.9 (2.7, 9.0)			3
Risankizumab 150 mg (N = 224)	12.0 (7.7, 16.3)	6.0 (0.8, 11.3)	0.024*	3
Resolution of Enthesitis (LEI = 0) at Week 24 (For Subjects with Baseline Presence of Enthesitis [LEI > 0])	_			
Placebo (N = 158)	30.4 (23.2, 37.6)			1
Risankizumab 150 mg (N = 147)	42.9 (34.9, 50.9)	13.8 (3.5, 24.2)	0.009**	1
Resolution of Dactylitis (LDI = 0) at Week 24 (For Subjects with Baseline Presence of Dactylitis [LDI > 0])				
Placebo (N = 57)	42.1 (29.3, 54.9)			0
Risankizumab 150 mg (N = 40)	72.5 (58.7, 86.3)	38.8 (22.9, 54.8)	<0.001***	0

***,**,*. *P*-value ≤ 0.001, ≤ 0.01, and ≤ 0.05 respectively.

Regarding available Period 2 data up to Week 52 (full data set awaited), positive trends for efficacy of risankizumab over placebo are found for:

- an ACR20 response beginning at Week 4 compared with subjects in the placebo arm after a single dose of risankizumab through Week 24, with an increase in the percentage of subjects achieving ACR20 response from Week 24 to Week 52.
- an increasing percentage of subjects achieving ACR50 and ACR70 responses from Week 24 to Week 52.

A rapid onset of action in subjects was found in the placebo arm beginning 4 weeks after first risankizumab treatment (i.e., Week 28), similar to the percentage of subjects who achieved ACR20 response after a single dose of risankizumab at Week 4 in the risankizumab arm**.**

- ACR components & HAQ-DI by visit

There was a statistically significant improvement from Baseline in HAQ-DI in the risankizumab arm versus placebo at Week 24, supported by consistent, greater improvement in ACR individual components versus placebo (TJC68, SJC66, PGA, PtGA, Patient's Assessment of Pain, and hsCRP [all nominal p-value ≤ 0.001]).

In the subset of subjects with ≥ 0.35 HAQ-DI at Baseline, a greater percentage of subjects in the risankizumab arm achieved a clinically significant improvement in HAQ-DI (i.e., change from Baseline in HAQ-DI ≤ −0.35) compared with subjects in the placebo arm at Week 24.

- Spondylitis

Overall, 87 subjects (19.6%) had spondylitis at Baseline based upon clinical assessment (including on radiography or MRI confirmation). For this subset, response rates were higher for the risankizumab arm in all BASDAI and ASDAS assessments versus placebo.

- PASI 90 and PASI 100 response by visit

For the subset of subjects with BSA ≥ 3% at Baseline, there was a statistically significant difference in achieving PASI 90 response in the risankizumab arm over placebo. A greater proportion of subjects on risankizumab achieved PASI 100 response at Week 24 versus placebo.

For the subset of subjects with BSA ≥ 3% at Baseline, the proportion of subjects in the risankizumab arm who achieved PASI 90 and PASI 100 responses increased through Week 52. Subjects in the placebo arm who switched from placebo to risankizumab treatment at Week 24 achieved similar PASI 90 responses following risankizumab treatment at Week 52 as subjects in the risankizumab arm at Week 24. Similar results were seen for PASI 100 response.

- MDA by visit

A statistically significantly higher percentage of subjects achieved MDA in the risankizumab arm compared to placebo at Week 24. The percentage of subjects who achieved MDA in the risankizumab arm increased between Weeks 24 and 52. The percentage of subjects in the placebo arm who achieved MDA at Week 52 was similar to the percentage in the risankizumab arm at Week 24.

- SF-36 and FACIT-Fatigue by visit

At Week 24, there were statistically significantly greater improvements in change from Baseline in SF-36 PCS and FACIT-Fatigue. In the risankizumab arm, there were greater improvements in changes from Baseline in 7 underlying domains of SF-36: vitality scale, physical functioning scale, bodily pain scale, general health scale, role physical scale, social functioning scale, and mental health scale.

Improvements in FACIT-Fatigue and SF-36 PCS in subjects in the risankizumab arm increased between Week 24 and Week 52. Of the 8 underlying domains of SF- 36, improvements in role physical scale, physical functioning scale, bodily pain scale, and vitality scale in the risankizumab arm subjects increased between Week 24 and Week 52.

- EuroQol-5D-5L & WPAI

There was improvement from Baseline at Week 24 in EuroQol-5D-5L Index Score and VAS Score and in WPAI components (presenteeism, overall work impairment, and activity impairment) in the risankizumab arm over placebo, numerically increasing between Weeks 24 and 52. Subjects in the placebo arm achieved similar improvements at Week 52 as subjects in the risankizumab arm at Week 24.

- DAPSA & PASDAS

Subjects in the risankizumab arm demonstrated greater improvements from Baseline in Disease Activity in Psoriatic Arthritis (DAPSA) scores and Psoriatic Arthritis Disease Activity Score (PASDAS) compared with subjects in the placebo arm at Week 24, with improvements increasing the risankizumab arm up to Week 52. Changes from Baseline in DAPSA and PASDAS improved for the placebo arm on risankizumab treatment from Week 24 at Week 52. At Week 52, results for both arms were similar.

- DAS28-hsCRP

There were greater improvements from Baseline in DAS28 using hsCRP (DAS28-hsCRP) at Week 24 in the risankizumab arm compared to placebo, increasing in the risankizumab arm up to Week 52. In the placebo arm similar improvement was seen on commencing risankisumab up to Week 52, which compared with the risankizumab arm results at Week 24.

- PsARC

A higher percentages of subjects achieved modified PsARC responses at Week 24 on risankizumab compared to placebo, the percentage increasing up to Week 52. For placebo subjects, on switching to risankizumab at Week 24, the percentage achieving PsARC responses at Week 52 was similar to that of the risankizumab arm at Week 24.

Ancillary analyses

Subgroups for efficacy analysis

Table 30: Subgroups for Efficacy Analysis

Subgroup Factor	Categories
Age	< 65 years, ≥ 65 years, ≥ 65 - < 75 years, ≥ 75 years
Sex	Male vs Female
BMI	< 25, ≥ 25 and < 30, ≥ 30 kg/m^2
Race	White vs Non-white
Geographic Region	North America, South/Central America, Western Europe, Eastern Europe, Asia, Other
Number of prior csDMARDs	≤ 1 vs > 1
Number of prior biologic therapies	0 vs ≥ 1
Number of prior anti-TNFs	0 vs ≥ 1
hsCRP at Baseline	< 3 vs ≥ 3 mg/L
Extent of psoriasis at Baseline	≥ 3% BSA vs < 3% BSA
Duration of PsA	≤ 5, > 5 and ≤ 10, > 10 years

Concomitant csDMARD at baseline	Any csDMARD
	• Any MTX
	  ○ MTX alone
	  ○ MTX and other csDMARD
	• csDMARD other than MTX
	None

Subgroup efficacy analyses were all positive numerically in favour of risankizumab apart from the subgroup 'Non-white' (16/443; treatment difference -21%). A consistent response was seen in the BIO-IR and csDMARD-IR subjects at Week 24 and ACR20 response rates were higher in the risankizumab arm regardless of the use of concomitant csDMARDs or monotherapy.

Table 31: ACR20 Response at Week 24 by Number of Prior Biologic Therapies and Concomitant csDMARDs (NRI-C, FAS)

Subgroup Category Treatment	Responder n (%)	Responder 95% CI[a]	Response Rate Diff Compared to Placebo Diff (%)[b]	Response Rate Diff Compared to Placebo 95% CI[b]	Missing Due to COVID-19 (n)
Number of prior biologic therapies					
0 (csDMARD-IR)					
Placebo (N = 118)	43 (36.6)	[27.8, 45.3]			3
Risankizumab 150 mg (N = 119)	67 (56.3)	[47.3, 65.3]	19.0	(6.6, 31.4)	4
≥ 1 (Bio-IR)					
Placebo (N = 101)	15 (14.9)	[7.9, 21.8]			0
Risankizumab 150 mg (N = 105)	48 (45.7)	[36.2, 55.2]	30.7	(19.2, 42.3)	0
Number of concomitant csDMARD at Baseline					
Any csDMARD					
Placebo (N = 129)	44 (33.9)	[25.7, 42.1]			2
Risankizumab 150 mg (N = 141)	71 (50.4)	[42.0, 58.7]	16.0	[4.6, 27.5]	4
None					
Placebo (N = 90)	14 (16.0)	[8.3, 23.6]			1
Risankizumab 150 mg (N = 83)	44 (53.0)	[42.3, 63.7]	37.7	[25.0, 50.4]	0

2.4.2.1. Study M16–011

Study title : 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 (KEEPsAKE1).

Methods

Trial Design

This was a multi-centre, 2-arm study of risankizumab in subjects with moderately to severely active PsA who were biologic naïve and who had an inadequate response or intolerance to at least 1 csDMARD (csDMARD-IR; e.g. list). An 'inadequate response' was defined as lack of efficacy after a minimum 12-week duration of therapy.

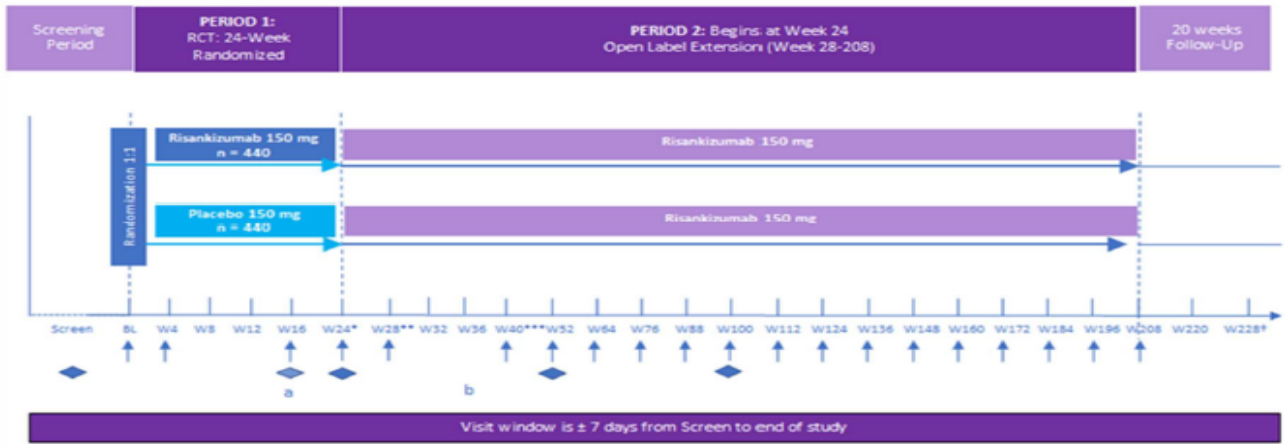
The study consisted of a Screening period (~35 days), Period 1, Period 2 and a 20-week follow-up period after last dose at Week 208, allowing for a toal of 228 weeks; stud duration. Subjects were assigned to one of two blinded treatment arms, risankizumab or placebo. At Week 24, those in the placebo arm were given risankizumab and those in the risankizumab arm were given placebo. From Week 28 onwards, subjects in both arms received open label risankizumab. Consequent to this design, all subjects ultimately received the active, risankizumab, according to a dosing interval of week 0, week 4 and 12 weekly thereafter.

Rescue therapy was allowed for non-responders identified at Week 16. Non-response was defined as those not achieving at least a 20% improvement in either or both tender joint count (TCJ) and swollen joint count (SJC) at both Week 12 and Week 16 compared to baseline.

The study design is detailed in the following

Figure 18 (M16-011 CSR).

Figure 18: Study Design Schematic



BL = Baseline; RCT = randomized clinical trial; W = Week

* At Week 24, subjects randomized to placebo in Period 1 were to receive a blinded dose of risankizumab. Subjects randomized to risankizumab treatment in Period 1 were to receive a blinded dose of placebo.

** At Week 28, subjects randomized to placebo in Period 1 were to receive a 2nd dose of risankizumab. Subjects randomized to risankizumab in Period 1 were to receive risankizumab (scheduled dose).

*** From Week 40 to Week 208 Visits, doses were to occur q12w.

† Follow up phone call.

↑ Dosing.

Bilateral radiographs of hands and feet.

a. At Week 16, subjects classified as non-responders (defined as not achieving at least a 20% improvement in either or both tender joint count [TJC] and swollen joint count [SJC] at both Week 12 and Week 16) compared to Baseline had the option to add or modify rescue concomitant medications/therapy. Rescue therapy qualification was to occur only at Week 16 Visit.

b. Starting at Week 36, subjects classified as non-responders are to be discontinued from study drug.

Study participants

Key eligibility criteria

Subjects enrolled were adults, ≥ 18 years of age, with a clinical diagnosis of psoriatic arthritis and:

- symptom onset at least 6 months prior to the Screening Visit
- fulfilment of the Classification Criteria for PsA (CASPAR) at Screening Visit
- active disease defined as ≥ 5 tender joints (based on 68 joint counts) and ≥ 5 swollen joints (based on 66 joint counts) at both the Screening Visit and Baseline
- active plaque psoriasis, with at least one psoriatic plaque of ≥ 2 cm diameter
  or
  nail changes consistent with psoriasis at the Screening Visit.
- Presence Screening of:
  ≥ 1 erosion on radiograph as determined by central imaging review
  or
  hs-CRP ≥ 3.0 mg/L
- inadequate response to previous or current treatment with at least 1 csDMARD at maximally tolerated dose
  or
  an intolerance to or contraindication for csDMARD (csDMARD-IR).

csDMARD-IR represented at least one of methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), apremilast, bucillamine and iguratimod, or ciclosprin A, and without any prior exposure to a biologic agent for PsA. MTX – IR was defined as an inadequate response (lack of efficacy after minimum 12 weeks

duration of therapy) at the following doses ranges: ≥ 15 mg/week, or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week after complete titration (in some countries ≥ 7.5 mg/week or as required per local authorities).

- **Concomitant medications**

Subjects were not required to be receiving csDMARD therapy at Baseline. Concomitant csDMARDs allowed at study entry were ≤2 of the following, for ≥ 12 weeks and at stable dose for ≥ 4 weeks prior to the Baseline Visit up to Week 36 of the study, at the following doses:

MTX (≤ 25 mg/week);	SSZ (≤ 3000 mg/day);
LEF (≤ 20 mg/day);	apremilast (≤ 60 mg/day);
hydroxychloroquine (HCQ) (≤ 400 mg/day);	bucillamine (≤ 300 mg/day);
iguratimod (≤ 50 mg/day)	ciclosporin A (≤ 5 mg/kg/day)

Prior exposure to biologics, other csDMARDS and the combination of MTX and LEF were exclusionary. Subjects on MTX were to be taking folic acid also. The protocol specified discontinuation and/or dose reduction requirements before Baseline Visit and allowable: non biologic csDMARDS to meet local requirements; pain relief medications; the time frame for discontinuation of concomitant psoriasis treatments (e.g. oral retinoids; fumarates; PUVA; UVA and UVB; topical treatments).

Treatments

Risankizumab was administered as an injection solution at a concentration of 90 mg/mL in a prefilled syringe (PFS) for subcutaneous (SC) injection. The study dose of risankizumab 150 mg was provided in 2 PFS of 75 mg/0.83 mL each. Placebo was similarly administered subcutaneously via a PFS.

Risankizumab arm: blinded risankizumab 150 mg sc at Week 0, Week 4, Week 16, placebo Week 24, open label risankizumab week 28 and 12 weekly thereafter.

Placebo arm: blinded placebo at Week 0, Week 4, Week 16, risankizumab 150 mg sc Weeek 24, open label risankizumab Week 28 and 12 weekly thereafter.

Allowed concomitant medications/therapy

Subjects could be enrolled on 0, 1 or 2 csDMARDs as per eligibility criteria alone or along with NSAIDS, acetaminophen/paracetamol, low potency opioids, oral corticosteroids (~prednisolone ≤10 mg/day), to continue stable until week 36. Subjects were permitted to start any of the above during the trial only per protocol but could reduce doses or substitute from the same class as needed. After Week 24 assessments, subjects could use any topical therapy for PsO per investigator judgment.

Rescue Treatment

At Week 16, subjects classified as non-responders (i.e. not achieving at least a 20% improvement in either/both TJC and SJC vs. Baseline at both Week 12 and Week 16) could:

• Add or modify doses of NSAIDs, acetaminophen/ paracetamol, low potency opioid medications (tramadol, codeine, or hydrocodone, alone or in combination with acetaminophen);

OR

• Receive 1 intra articular, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroid injection for 1 peripheral joint or 1 enthesis (avoided within 21 days prior to the next scheduled study visit, such injected joints or enthesitis sites considered trial "not assessable" for 90 days from the time of the injection;

OR

• Titrate current background csDMARD or add an additional csDMARD, as allowed by eligibility criteria. Adding a biologic therapy was not permitted and maximum 2 csDMARDs were permitted.

Objectives

The primary objective was to compare the efficacy of risankizumab 150 mg versus placebo for the treatment of signs and symptoms of PsA in the study population during the double-blind Period 1 (24 weeks).

The secondary objectives were:

Period 1 Double-Blind

- to compare the efficacy of risankizumab 150 mg versus placebo for the inhibition of progression of structural damage as assessed by radiographs in the study population.
- To compare the safety and tolerability of risankizumab 150 mg versus placebo in the study population.

Period 2 Open-Label:

- To evaluate the long-term safety, tolerability and efficacy of risankizumab 150 mg in subjects who completed Period 1.

Outcomes/endpoints

Primary endpoint: The proportion of subjects achieving American College of Rheumatology 20 Response (ACR20) at Week 24.

Ranked secondary endpoints with multiplicity adjustment:

1. Change from Baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 24;
2. Proportion of subjects achieving Psoriasis Area Severity Index (PASI) 90 response at Week 24 (in the subset of subjects with a body surface area (BSA) ≥ 3% at Baseline);
3. Proportion of subjects achieving ACR20 at Week 16;
4. Proportion of subjects achieving Minimal Disease Activity (MDA) at Week 24;
5. Change from Baseline in modified Nail Psoriasis Severity Index (mNAPSI) at Week 24 in the subset of subjects with psoriatic nail disease at Baseline;
6. Change from Baseline in Physician Global Assessment of Fingernail Psoriasis (PGA-F) at Week 24 in the subset of subjects with psoriatic nail disease at Baseline;
7. Proportion of subjects with resolution of enthesitis (LEI = 0) at Week 24 in subjects with enthesitis at Baseline;
8. Proportion of subjects with resolution of dactylitis (LDI = 0) at Week 24 in subjects with dactylitis at Baseline;
9. Change from Baseline in modified Total Sharp Score (mTSS) at Week 24;
10. Change from Baseline in 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) at Week 24;

11. Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue) Questionnaire at Week 24.

Other secondary endpoints without multiplicity adjustment

1. Proportion of subjects achieving ACR50 response at Week 24;

2. Proportion of subjects achieving ACR70 response at Week 24.

Pharmacokinetics

Serum risankizumab concentrations, anti-drug antibodies (ADA), and neutralizing antibodies (NAb) were determined at study visits.

According to the submission the original protocol (v1.0 26 July 2018) was amended on 3 occasions. Version 3 (v3.0, 13 March 2020) modified secondary endpoints for resolution of enthesitis and dactylitis endpoints. In Version 4 (v4.0, 10 September 2020) ACR20 at Week 16 was added as a ranked secondary endpoint, separated the endpoint of mNAPSI and PGA-F in to 2 individual endpoints, the ranking of mTSS in the secondary ranked endpoints was adjusted and changes due to the COVID-19 pandemic were incorporated. Mitigation strategies to minimize the impact of COVID-19 logistical restrictions on missing data and on the ability of subjects to complete study visits included at-home visits, partial assessment completion at study sites, virtual visits, and out-of-window (OOW) study visits.

Sample Size

A sample of 880 subjects were to be randomized to risankizumab 150 mg or placebo in a ratio of 1:1 (440 subjects/treatment group) to provide at least 90% power to detect at least 25% difference in ACR20 response rate at Week 24 (assuming a placebo ACR20 response rate of 35%) and to provide approximately 80% power to detect a standardized effect size of 0.20 for mTSS change from Baseline for risankizumab versus placebo group at Week 24. Power and sample size were calculated based on at two-sided significance level of 0.05 and accounting for a 10% dropout rate.

Randomisation

Enrolled subjects were assigned a unique identification number by interactive response technology (IRT) at the Screening Visit and randomized 1:1 ratio to one of two treatment groups:

- Group 1: Risankizumab 150 mg (target N = 440)
- Group 2: Placebo (target N = 440)

Randomization was stratified at Baseline by:

- extent of psoriasis (≥ 3% BSA or < 3% BSA),
- current use of at least 1 csDMARD (0 vs ≥ 1),
- presence of dacylitis (yes vs. no),
- presence of enthesitis (yes vs. no).

Blinding (Masking)

To maintain the blind during Period 1, the risankizumab PFS and placebo PFS were identical in appearance. Subjects in the risankizumab arm had placebo at Week 24 and subject in the placebo arm had risankizumab. The Investigator, study site personnel, and subject were to remain blinded to treatment administered in Period 1 until study end. During the study, the Investigator could access the IRT if an urgent therapeutic intervention was necessary that warranted breaking the blind.

Statistical methods

A fixed sequence testing procedure was used to control the overall type I error rate at 2-sided alpha=0.05 for the primary endpoint and ranked secondary endpoints.

The comparisons between the risankizumab and placebo treatment groups for the primary efficacy endpoint (ACR20 at Week 24) was performed using the Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors.

For continuous efficacy endpoints, the treatment comparisons were conducted using a Mixed-Effect Model Repeated Measures (MMRM) method as primary inference purpose.

Categorical efficacy variables are analyzed using the CMH test controlling for stratification variables.

Non-Responder Imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C) was used for missing data imputation. The As Observed (AO) analysis did not impute values for missing evaluations.

Long-term efficacy by time point was summarized using descriptive statistics.

Data for the analyses of the resolution of enthesitis and of dactylitis were pooled from Studies M15-998 with M16-011 and evaluated under the multiplicity control of M16-011, adjusting for common stratification factors (extent of psoriasis and concomitant use of csDMARDs).

Pharmacokinetics data : Serum risankizumab concentrations were summarized at the sampling time point using descriptive statistics. ADA titers were tabulated for each ADA positive subject at the respective study visits. The number and percentage of subjects with ADA and NAb were calculated.

Results

Participant flow

Overall, 964 subjects were enrolled into Period 1 (placebo, n=481, risankizumab, n=483).

In Period 1 the rate of discontinuation was low: rizankisumab (2.1%; n=10), placebo (2.9%; n=14); no subjects discontinued due to COVID-19; 3 discontinued due to COVID-19 logistical restrictions.

Overall, 940 subjects completed Period 1. Overall, treatment compliance was greater than 99% across treatment arms.

The period 2 is ongoing.

Table 32: Subject Disposition in Study M16-011(FAS)

	Placebo (N = 481) n (%)	Risankizumab 150 mg (N = 483) n (%)	Total (N = 964) n (%)
Completed study in Period 1	467 (97.1)	473 (97.9)	940 (97.5)
Discontinuation from the study during Period 1 due to (Primary Reason)	14 (2.9)	10 (2.1)	24 (2.5)
Adverse event	3 (0.6)	2 (0.4)	5 (0.5)
Withdrew consent	6 (1.2)	4 (0.8)	10 (1.0)
Lost to Follow-up	3 (0.6)	0	3 (0.3)
Lack of efficacy	1 (0.2)	1 (0.2)	2 (0.2)
COVID-19 infection	0	0	0
COVID-19 logistical restrictions	1 (0.2)	2 (0.4)	3 (0.3)
Other	0	1 (0.2)	1 (0.1)
Entered Period 2 study participation	467 (97.1)	473 (97.9)	940 (97.5)
Ongoing in Period 2	453 (94.2)	460 (95.2)	913 (94.7)
Discontinuation during Period 1 due to (all reasons)[a]	14 (2.9)	10 (2.1)	24 (2.5)
Adverse event	3 (0.6)	2 (0.4)	5 (0.5)
Withdrew consent	8 (1.7)	4 (0.8)	12 (1.2)
Lost to follow-up	3 (0.6)	0	3 (0.3)
Lack of efficacy	1 (0.2)	1 (0.2)	2 (0.2)
COVID-19 infection	0	0	0
COVID-19 logistical restrictions	1 (0.2)	2 (0.4)	3 (0.3)
Other	0	1 (0.2)	1 (0.1)

Conduct of the study

An independent ethics committee (IEC)/institutional review board (IRB) approved the study and there is an external, independent data monitoring committee (IDMC) data monitoring committee.

Baseline data

Demographic characteristics were balanced between treatment groups and overall. Overall, there were slightly more male subjects, mean age was 51.3 years (range 20-85 years), the vast majority were classified as 'white', and 14.7% were ≥65 years.

Table 33: Demographic Characteristics (FAS)

	Placebo (N = 481) n (%)	Risankizumab 150 mg (N = 483) n (%)	Total (N = 964) n (%)
Sex			
Female	247 (51.4)	231 (47.8)	478 (49.6)
Male	234 (48.6)	252 (52.2)	486 (50.4)
Age (years)			
n	481	483	964
Mean (SD)	51.2 (12.10)	51.3 (12.21)	51.3 (12.15)
Median	52.0	52.0	52.0
Min, Max	22, 79	20, 85	20, 85
Age (years)			
< 65	408 (84.8)	414 (85.7)	822 (85.3)
≥ 65	73 (15.2)	69 (14.3)	142 (14.7)
≥ 65 - < 75	66 (13.7)	60 (12.4)	126 (13.1)
≥ 75	7 (1.5)	9 (1.9)	16 (1.7)
Race			
White	451 (93.8)	454 (94.0)	905 (93.9)
Black or African American	2 (0.4)	4 (0.8)	6 (0.6)
Asian	22 (4.6)	13 (2.7)	35 (3.6)
Native Hawaiian or Other Pacific Islander	1 (0.2)	3 (0.6)	4 (0.4)
American Indian or Alaska Native	0	1 (0.2)	1 (0.1)
Multiple	5 (1.0)	8 (1.7)	13 (1.3)
Ethnicity			
Hispanic or Latino	92 (19.1)	93 (19.3)	185 (19.2)
Not Hispanic or Latino	389 (80.9)	390 (80.7)	779 (80.8)
Weight (kg)			
n	481	483	964
Mean (SD)	86.40 (18.993)	88.33 (19.252)	87.37 (19.138)
Median	84.20	87.00	85.50
Min, Max	45.0, 152.0	40.5, 186.0	40.5, 186.0
Weight (kg)			
< 100	371 (77.1)	363 (75.2)	734 (76.1)
≥ 100	110 (22.9)	120 (24.8)	230 (23.9)
Body Mass Index (kg/m^2)			
n	481	483	964
Mean (SD)	30.3 (6.21)	30.7 (6.43)	30.5 (6.32)
Median	29.3	29.8	29.5
Min, Max	15.5, 59.2	15.6, 64.4	15.5, 64.4
Body Mass Index (kg/m^2)			

< 25	89 (18.5)	82 (17.0)	171 (17.7)
≥ 25 - < 30	178 (37.0)	167 (34.6)	345 (35.8)
≥ 30	214 (44.5)	234 (48.4)	448 (46.5)

FAS = Full Analysis Set; Max = maximum; Min = minimum; SD = standard deviation
Note: Percentages calculated on non-missing values.
Cross reference: Table 14.1__2

A selection of Baseline disease characteristics are presented here.

Less than 1.3% had MDA for PsA in either arm and overall. Median total dactylitis count was similar across arms, with a higher median LDI score in the placebo vs. risankizumab arm (53.48 v 49.36). Median total enthesitis count, LEI score, CASPAR total score, BSA-PsO were similar across arms. HAQ-DI score was higher in the placebo arm versus risanikizumab (1.25 v 1.13).

Just over half of subjects in either arm had a diagnosis of PsA for ≤5 years, with approximately a quarter in either arm diagnosed between 5-10 years or >10 years (median duration similar in both arms and overall 4.66 year).

Table 34:

Presence of:	Placebo (n=481) %	Risankizumab (n=483) %	Total (n=964) %
Dactylitis (LDI>0)	30.6	30.6	30.6
Enthesitis (LEI >0)	60.3	61.5	60.9
SPARCC >0	68.0	70.4	69.2
Psoriasis nail disease	70.6	64.0	67.3
BSA of Psoriatic Plaques ≥3%	43.5	43.5	43.5
Spondylitis	19.8	19.5	19.6
Median of:	Units	Units	Units
PASI (BSA≥3%)	6.30	7.20	6.80
mTSS	1.5	1.5	1.5
mNAPSI	10.00	13.00	12.00
DAS28-hsCRP	4.86	4.89	4.89
TCJ68	17.0	17.0	17.0
SJC66	9.0	9.0	9.0
hsCRP (mg/L)	6.64	6.89	6.80
HAQ-DI	1.25	1.13	1.13

Prior use of DMARDs was balanced across arms. Overall, 99.6% of subjects had prior use of at least one csDMARD (1 prior: 67.3.1%; 2 prior: 25.0%; ≥3 prior: 7.3%). The most frequently reported prior csDMARDs overall were methotrexate (MTX) (89.9%), sulfasalazine (21.5%), and leflunomide (12.8%); the rest were used by < 10% of subjects.

Medication use at Baseline was similar in both arms. Overall: any csDMARD 75.7%; NSAIDS 63.3%; oral corticosteroids 19.5%; MTX 60.2%; csDMARD other than MTX (sulfasalazine, leflunomide, apremilast) 10.5%. Overall, 24.3% of subjects were not on a concomitant csDMARD at baseline.

Table 35: Baseline Disease Characteristics (FAS)

	Placebo (N = 481) n (%)	Risankizumab 150 mg (N = 483) n (%)	Total (N = 964) n (%)
Number of Prior csDMARDs			
0	2 (0.4)	2 (0.4)	4 (0.4)
1	311 (64.7)	338 (70.0)	649 (67.3)
2	136 (28.3)	105 (21.7)	241 (25.0)
≥ 3	32 (6.7)	38 (7.9)	70 (7.3)
NSAID use at Baseline - n (%)			
Yes	314 (65.3)	296 (61.3)	610 (63.3)
No	167 (34.7)	187 (38.7)	354 (36.7)
Oral corticosteroid use at Baseline			
Yes	87 (18.1)	101 (20.9)	188 (19.5)
No	394 (81.9)	382 (79.1)	776 (80.5)
Concomitant MTX use at Baseline			
Yes	315 (65.5)	314 (65.0)	629 (65.2)
No	166 (34.5)	169 (35.0)	335 (34.8)
Concomitant csDMARD at Baseline			
Any csDMARD	364 (75.7)	366 (75.8)	730 (75.7)
Any MTX	315 (65.5)	314 (65.0)	629 (65.2)
MTX alone	286 (59.5)	294 (60.9)	580 (60.2)
MTX and other csDMARD	29 (6.0)	20 (4.1)	49 (5.1)
csDMARD other than MTX	49 (10.2)	52 (10.8)	101 (10.5)
Any sulfasalazine, without MTX	22 (4.6)	20 (4.1)	42 (4.4)
Any leflunomide, without MTX	19 (4.0)	28 (5.8)	47 (4.9)
Any apremilast, without MTX	8 (1.7)	4 (0.8)	12 (1.2)
None	117 (24.3)	117 (24.2)	234 (24.3)

Numbers analysed

All baseline and efficacy analyses were based on the FAS (n=964; placebo n=481; risankizumab n=483), with additional primary endpoint analysis conducted based on the Per Protocol Analysis set (n=927), a subset of FAS containing subjects who did not have any major protocol deviations that were deemed to have a potential impact on primary efficacy endpoint up to Week 24 in Period 1. Final criteria and exclusion of subjects from the PPA were identified before primary analysis DBL.

Protocol deviations

Table 36: Protocol Deviations (All Randomized Subjects)

Category	Placebo (N = 481) n (%)	Risankizumab 150 mg (N = 483) n (%)	Total (N = 964) n (%)
Subjects who had at least one protocol deviation	39 (8.1)	53 (11.0)	92 (9.5)
Subject entered into the study even though s/he did not satisfy entry criteria	8 (1.7)	14 (2.9)	22 (2.3)
Eligibility criterion #5	1 (0.2)	0	1 (0.1)
Eligibility criterion #8	0	1 (0.2)	1 (0.1)
Eligibility criterion #10	0	2 (0.4)	2 (0.2)
Eligibility criterion #18	0	1 (0.2)	1 (0.1)
Eligibility criterion #21	0	1 (0.2)	1 (0.1)
Eligibility criterion #22	1 (0.2)	0	1 (0.1)
Eligibility criterion #24	2 (0.4)	2 (0.4)	4 (0.4)
Eligibility criterion #25	1 (0.2)	1 (0.2)	2 (0.2)
Eligibility criterion #27	0	1 (0.2)	1 (0.1)
Eligibility criterion #28	0	1 (0.2)	1 (0.1)
Eligibility criterion #31	2 (0.4)	4 (0.8)	6 (0.6)
Eligibility criterion #32	1 (0.2)	0	1 (0.1)
Subject developed withdrawal criteria during the study and was not withdrawn	1 (0.2)	0	1 (0.1)
Subject received wrong treatment or incorrect dose	1 (0.2)	0	1 (0.1)
Subject received excluded concomitant treatment	29 (6.0)	39 (8.1)	68 (7.1)

The assigned treatment allocation for 43 subjects was potentially viewable in the interactive response technology (IRT) system to 12 blinded users. Of 12 potentially unblinded users, one was a study coordinator at a site where a single subject was enrolled at the time. This was considered a major protocol deviation and that subject was excluded from the PPA Set.

For the remaining 42 subjects, no site personnel were potentially unblinded and these were not categorized as major deviations. For these 42 subjects, the MAH reports a sensitivity analysis excluding these 42 subjects was performed for the primary endpoint and the first ranked secondary endpoint. The sensitivity analysis result is comparable with that of the full analysis set.

Four (4) subjects had an incorrect eligibility criterion selected in the eCRF. In addition, 56 subjects (56/964; 5.8%) received a medication not permitted during the study phase.

Due to COVID-19 pandemic and site logistics/limitations 18 subjects did not have the Week 24 visit performed; 4 subjects at Baseline and 56 at Week 24 visits had laboratory testing performed at a local laboratory; 2 subjects at Baseline and 5 at Week 24 did not have central laboratory results reported and 16 subjects had partial targeted source data verification (SDV) at the time of database lock (99.71% of targeted SDV was complete).

The MAH states all deviations were assessed for their impact on analyses and data integrity and were not considered to have affected overall efficacy results.

Outcomes and estimation

Efficacy analyses are based on the FAS i.e. all randomised subjects who received at least 1 dose of study medication, grouped by treatment assignment at randomisation regardless of the actual treatment received on study with the primary endpoint when all subjects complete at Week 24.

Analyses for the ranked secondary endpoints of resolution of enthesitis and resolution of dactylitis at Week 24 used pooled data from Studies M15-998 and M16-011. The SAP was approved before DBL.

- **Primary efficacy endpoint**

Table 37: ACR20 Response at Week24 (NRI-C, FAS)

	Responder		Response Rate Diff Compared to Placebo			Missing Due to COVID-19
Treatment	n (%)	95% CI[a]	Diff (%)[b]	95% CI[b]	P-value[b]	(n)
Placebo (N = 481)	161 (33.5)	(29.3, 37.8)				10
Risankizumab 150 mg (N = 483)	277 (57.3)	(52.9, 61.8)	24.0	(18.0, 30.0)	< 0.001***,$	7

The primary endpoint was reached. The response rate in ACR20 with risankizumab was 57.3% (95% CI 52.9, 61.8%) versus placebo 33.5% (95% CI 29.3.7, 3.8%). The treatment difference between risankizumab and placebo arms, 24.0%, was statistically significant at p<0.001.

The impact of inter-current events on the primary endpoint was assessed i.e. subjects who:

- did not meet ACR20 response criteria (risankizumab 163; placebo 256)
- took rescue medication at Week 16 (risankizumab 25; placebo 35)
- took concomitant medications that could impact efficacy (risankizumab 1; placebo 5)
- with missing data due to COVID-19 (risankizumab 2; placebo 6)
- with missing data due to reasons other than COVID-19 (risankizumab 15; placebo 18).

As observed (AO) analysis, AO with imputation, tipping point analysis for ACR20 response at Week 24 and PPA proved consistent with the primary analysis. The sensitivity analysis results of the ACR20 response excluding the 42 subjects whose treatment allocation was potentially unblended from FAS were consistent with the primary analysis results.

- **Ranked secondary endpoints**

Of 11 ranked secondary endpoints, the first 8 were achieved, summarised in Table 38 following.

Table 38: Summary of Ranked Secondary Endpoints (FAS)

Endpoint[a] Treatment	Within Group Mean Estimate (95% CI)	Between Group Difference (Risankizumab 150 mg - Placebo) Mean Estimate (95% CI)	*P*-value	Multiplicity Adjusted Results	Missing Due to COVID-19 n
Change from Baseline in HAQ-DI Score at Week 24					
Placebo (N = 479)	-0.11 (-0.16, -0.06)				7
Risankizumab 150 mg (N = 482)	-0.31 (-0.36, -0.27)	-0.20 (-0.26, -0.14)	< 0.001***,$	Significant	7
PASI 90 Response rate at Week 24 (For Subjects with BSA ≥ 3% at Baseline)					
Placebo (N= 272)	9.9 (6.4, 13.5)				6
Risankizumab 150 mg (N = 273)	52.3 (46.4, 58.3)	42.5 (35.6, 49.3)	< 0.001***,$	Significant	7
ACR20 Response at Week 16					
Placebo (N = 481)	33.4 (28.9, 37.9)				10
Risankizumab 150 mg (N = 483)	56.3 (51.7, 60.8)	23.1 (16.8, 29.4)	<0.001***,$	Significant	6
MDA Response at Week 24					
Placebo (N = 481)	10.2 (7.5, 12.9)				3
Risankizumab 150 mg (N = 483)	25.0 (21.2, 28.9)	14.8 (10.2, 19.4)	< 0.001***,$	Significant	4
Change from Baseline in mNAPSI Score at Week 24 (For Subjects with psoriatic nail disease at Baseline)					
Placebo (N = 338)	-5.57 (-6.70, -4.44)				5
Risankizumab 150 mg (N = 309)	-9.76 (-10.95, -8.58)	-4.19 (-5.70, -2.68)	<0.001***,$	Significant	7
Change from Baseline in PGA-F Score at Week 24 (For Subjects with psoriatic nail disease at Baseline)					
Placebo (N = 338)	-0.4 (-0.5, -0.3)				5
Risankizumab 150 mg (N = 309)	-0.8 (-1.0, -0.7)	-0.4 (-0.6, -0.3)	< 0.001***,$	Significant	7
Resolution of enthesitis defined as LEI = 0 at Week 24 (for subjects with Baseline presence of enthesitis [LEI > 0][b])					
Placebo (N = 448)	34.8 (30.4, 39.2)				7
Risankizumab 150 mg (N = 444)	48.4 (43.8, 53.1)	13.9 (7.6, 20.2)	<0.001***,$	Significant	5
Resolution of dactylitis defined as LDI = 0 at Week 24 (for subjects with Baseline presence of dactylitis [LDI > 0][b]					
Placebo (N = 204)	51.0 (44.1, 57.8)				1
Risankizumab 150 mg (N = 188)	68.1 (61.4, 74.7)	16.9 (7.5, 26.4)	<0.001***,$	Significant	2
Change from Baseline in modified Total Sharp Score (mTSS) at Week 24					
Placebo (N = 457)	0.32 (0.11, 0.53)				6
Risankizumab 150 mg (N = 458)	0.23 (0.02, 0.44)	-0.09 (-0.36, 0.17)	0.496	Not Significant	7
Change from Baseline in 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) Scores at Week 24					
Placebo (N = 477)	3.20 (2.50, 3.89)				7
Risankizumab 150 mg (N = 482)	6.52 (5.83, 7.20)	3.32 (2.42, 4.22)	<0.001	Not Significant	8
Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Scores at Week 24					
Placebo (N = 477)	3.9 (3.1, 4.7)				7
Risankizumab 150 mg (N = 482)	6.5 (5.6, 7.3)	2.6 (1.5, 3.7)	<0.001	Not Significant	8

***,**,*. *P*-value ≤ 0.001, ≤ 0.01, and ≤ 0.05 respectively.

HAQ-DI at Week 24

Subjects in the risankizumab arm a statistically significantly greater decrease from Baseline in HAQ-DI at Week 24 compared to placebo. Sensitivity analysis results for change from Baseline in HAQ-DI at Week 24 excluding the 42 subjects whose treatment allocation was potentially unblinded from FAS showed similar results. Tipping point analysis for HAQ-DI at Week 24 showed that the analysis was robust to missing data assumptions.

PASI 90 at Week 24

In subjects with BSA ≥ 3% at Baseline, there was a statistically significant difference in favour of risankizumab vs. placebo in the percentage of subjects who achieved PASI 90 response at Week 24.

ACR20 at week 16

At Week 16, a statistically significantly greater percentage of subjects achieved ACR20 response in the risankizumab arm compared with subjects in the placebo arm.

MDA at week 24

At Week 24, a statistically significantly higher percentage of subjects achieved MDA in the risankizumab arm compared with subjects in the placebo arm.

mNAPSI & PGA-F at week 24

Among the subset of subjects with psoriatic nail disease at Baseline, subjects in the risankizumab arm experienced statistically significant improvements from Baseline in mNAPSI and PGA-F at Week 24 compared with the placebo arm.

Resolution of enthesitis at week 24 – LEI

Data for the analyses of the resolution of enthesitis was pooled from Studies M15-998 and M16-011 and were evaluated under the multiplicity control of Study M16-011.

Among subjects with enthesitis at Baseline, in the risankizumab arm there was a statistically significantly higher percentage of subjects with resolution of enthesitis (LEI =0) at Week 24 compared with placebo.

Resolution of dactylitys at week 24 – LDI

Data for the analyses of the resolution of enthesitis was pooled from Studies M15-998 and M16-011 and were evaluated under the multiplicity control of Study M16-011.

Among subjects with dactylitis at Baseline, those in the risankizumab arm showed a statistically significantly higher percentage of subjects with resolution of dactylitis (LDI = 0) at Week 24 compared with subjects in the placebo arm (results of resolution of enthesitis and resolution of dactylitis from Study M16-011 only, CSR Table 14.2__4.19.1 and Table 14.2__4.17.1, respectively).

mTSS at Week 24

The change in mTSS for risankizumab was not statistically significant as per the pre-specified statistical significance level (α=0.05) compared to placebo. While numerically better efficacy in the risankizumab arm vs. placebo arm was demonstrated, final 52-week data is awaited to complete assessment.

SF-36 & FACIT-Fatigue at Week 24

These 2 ranked secondary endpoints did not undergo statistical testing as the prior ranked secondary endpoint, mTSS at week 24, did not reach statistical significance (both had a nominal p value < 0.001).

AO analysis and AO with imputation analysis proved consistent with the primary analysis for ranked secondary endpoints.

- **Other secondary efficacy variables**

A greater percentage of subjects in the risankizumab arm achieved ACR50 and ACR70 responses at Week 24 compared with placebo (**Table 39**).

Similar results were observed for ACR50 & ACR70 response rates using the AO and AO with imputation analyses.

Table 39: **Summary of Other Secondary Efficacy Endpoints (NRI-C, FAS)**

Endpoint[a] Treatment	Within Group Mean Estimate (95% CI)	Between Group Difference (Risankizumab 150 mg - Placebo)		Missing Due to COVID-19 n
		Mean Estimate (95% CI)	*P*-value	
ACR50 Response at Week 24				
Placebo (N = 219)	9.3 (5.4, 13.2)			3
Risankizumab 150 mg (N = 224)	26.3 (20.3, 32.3)	16.6 (9.7, 23.6)	<0.001***	5
ACR70 Response at Week 24				
Placebo (N = 219)	5.9 (2.7, 9.0)			3
Risankizumab 150 mg (N = 224)	12.0 (7.7, 16.3)	6.0 (0.8, 11.3)	0.024*	3
Resolution of Enthesitis (LEI = 0) at Week 24 (For Subjects with Baseline Presence of Enthesitis [LEI > 0])				
Placebo (N = 158)	30.4 (23.2, 37.6)			1
Risankizumab 150 mg (N = 147)	42.9 (34.9, 50.9)	13.8 (3.5, 24.2)	0.009**	1
Resolution of Dactylitis (LDI = 0) at Week 24 (For Subjects with Baseline Presence of Dactylitis [LDI > 0])				
Placebo (N = 57)	42.1 (29.3, 54.9)			0
Risankizumab 150 mg (N = 40)	72.5 (58.7, 86.3)	38.8 (22.9, 54.8)	<0.001***	0

***,**,*. *P*-value ≤ 0.001, ≤ 0.01, and ≤ 0.05 respectively.

Additional efficacy variables

A greater percentage of subjects in the risankizumab arm achieved an ACR20 response beginning at Week 4 versus placebo after a single dose of risankizumab through Week 24. Through available Week 52 data there was an increase in the percentage of subjects achieving ACR20, ACR50 and ACR70 response from Week 24**.**

Risankizumab onset of action in subjects in the placebo arm was evident at 4 weeks after risankizumab treatment (i.e., Week 28) with a similar percentage achieving ACR20 response after a single dose of risankizumab as those at Week 4 in the risankizumab arm.

There was a clinically relevant and greater improvement from Baseline in all remaining individual components of the ACR response (TJC68, SJC66, PGA, PtGA, Patient's Assessment of Pain, and hsCRP [all nominal p-value ≤ 0.001]) at Week 24 for subjects in the risankizumab arm compared to placebo.

Spondylitis

Overall, 189 subjects (19.6%) had spondylitis at Baseline based upon clinical assessment (including radiography or MRI). There was greater clinical improvement in the risankizumab arm compared to placebo at Week 24, with in changes from Baseline in the BASDAI score, modified BASDAI score, morning stiffness score (mean of BASDAI Questions 5 and 6), and ASDAS.

A greater percentage of risankizumab versus placebo-treated subjects achieved BASDAI50 response and ASDAS clinically important improvement at Week 24, consistent with the efficacy observed in the overall population with spondylitis.

PASI90 and PASI100 response by visit

Among subjects with BSA ≥ 3% at Baseline, those in the risankizumab arm demonstrated by a statistically significant difference in favour of risankizumab versus placebo in the percentage of subjects who achieved PASI 90 response. A greater proportion of subjects achieved PASI 100 response at Week 24, with the the proportion of subjects in the risankizumab arm achieving PASI 90 and PASI 100 responses increasing through Week 52.

Placebo arm subjects who switched to risankizumab treatment at Week 24 achieved similar PASI 90 responses at Week 52 as those in the risankizumab arm at Week 24. Similar results were seen for PASI 100 response.

MDA by visit

At Week 24 a statistically significantly higher percentage of subjects achieved MDA in the risankizumab arm versus placebo. The percentage of subjects achieving MDA in the risankizumab arm increased up to Week 52. Placebo arm subjects who switched to risankizumab and achieved MDA at Week 52 was similar to those in the risankizumab arm at Week 24.

SF-36 and FACIT-Fatigue by visit

At Week 24, subjects in the risankizumab arm vs. placebo demonstrated greater improvements in change from Baseline in FACIT-Fatigue and SF-36 PCS. These improvements increased from Week 24 to Week 52 for FACIT-Fatigue, SF-36 PCS, SF-36 MCS, and all 8 underlying domains.

Placebo arm subjects who switched to risankizumab treatment at Week 24 showed similar improvements in FACIT-Fatigue, SF-36 PCS, SF-36 MCS, and all 8 underlying components of the SF-36 following risankizumab treatment at Week 52 as subjects in the risankizumab arm at Week 24.

EuroQol-5D-5L & WPAI

There was improvement from Baseline at Week 24 in EuroQol-5D-5L Index Score and VAS Score and in WPAI components (presenteeism, overall work impairment, and activity impairment) in the risankizumab arm compared to placebo, numerically increasing between Weeks 24 and 52. Subjects in the placebo arm achieved similar improvements at Week 52 as subjects in the risankizumab arm at Week 24.

DAPSA & PASDAS

Subjects in the risankizumab arm demonstrated greater improvements from Baseline in Disease Activity in Psoriatic Arthritis (DAPSA) scores and Psoriatic Arthritis Disease Activity Score (PASDAS) compared with subjects in the placebo arm at Week 24, with improvements increasing the risankizumab arm up to Week 52. Changes from Baseline in DAPSA and PASDAS improved for the placebo arm on risankizumab treatment from Week 24 at Week 52. At Week 52, results for both arms were similar.

DAS28-hsCRP

There were greater improvements from Baseline in DAS28 using hsCRP (DAS28-hsCRP) at Week 24 in the risankizumab arm compared to placebo, increasing in the risankizumab arm up to Week 52. In the placebo arm similar improvement was seen on commencing risankizumab up to Week 52, which compared with the risankizumab arm results at Week 24.

PsARC

A higher percentage of subjects achieved modified PsARC responses at Week 24 on risankizumab compared to placebo, the percentage increasing up to Week 52. For placebo subjects, on switching to risankizumab at Week 24, the percentage achieving PsARC responses at Week 52 was similar to that of the risankizumab arm at Week 24.

Ancillary analyses

Subgroups for efficacy analysis

Table 40: Subgroups for Efficacy Analysis

Subgroup Factor	Categories
Age	<65, ≥ 65 years, ≥ 65 years and < 75, ≥ 75 years
Sex	Male vs. Female
BMI	< 25, ≥ 25 and 30, ≥ 30 kg/m^2
Race	White vs. Non-white
Geographic Region	North America, South/Central America, Western Europe, Eastern Europe, Asia, Other
Number of prior csDMARDs	≤ 1 vs. > 1
Presence of enthesitis at Baseline based on LEI	yes vs. no
Presence of dactylitis at Baseline based on LDI	yes vs. no
hsCRP at Baseline	< 3 vs. ≥ 3 mg/L
Extent of psoriasis at Baseline	≥ 3% BSA vs. < 3% BSA
Duration of Psoriatic Arthritis	≤ 5, > 5 and ≤ 10, > 10 years
Concomitant csDMARD at baseline	Any csDMARD • Any MTX ○ MTX alone ○ MTX and other csDMARD • csDMARD other than MTX None

BMI = body mass index; BSA = Body Surface Area; csDMARDs = conventional synthetic disease modifying anti-rheumatic drugs; hsCRP = high-sensitivity C reactive protein; LDI = Leeds Dactylitis Index; LEI = Leeds Enthesitis Index; MTX = methotrexate; vs. = versus

Subgroup efficacy analyses were all positive in favour of risankizumab for higher ACR response rates at Week 24 compared to placebo.

ACR20 response rates were higher in the risankizumab arm regardless of the number of prior csDMARDs (≤ 1 vs. > 1) or the use of concomitant csDMARDs (Table 41).

Table 41: ACR20 Response at Week 24 by Subgroups (NRI-C, FAS)

Subgroup Category Treatment	Responder		Response Rate Diff Compared to Placebo		Missing Due to COVID-19 (n)
	n (%)	95% CI[a]	Diff (%)[b]	95% CI[b]	
Number of prior csDMARDs					
≤ 1 csDMARD					
Placebo (N = 313)	113 (36.2)	(30.8, 41.5)			6
Risankizumab 150 mg (N = 340)	186 (54.6)	(49.3, 60.0)	18.6	(11.2, 25.9)	3
> 1 csDMARDs					
Placebo (N = 168)	48 (28.6)	(21.7, 35.5)			4
Risankizumab 150 mg (N = 143)	91 (63.7)	(55.7, 71.6)	36.2	(26.4, 46.1)	4
Concomitant csDMARD at Baseline					
Any csDMARD					
Placebo (N = 364)	131 (35.9)	(30.9, 40.8)			6
Risankizumab 150 mg (N = 366)	212 (57.9)	(52.8, 63.0)	22.0	(15.0, 29.0)	6
No csDMARD					
Placebo (N = 117)	31 (26.2)	(18.2, 34.3)			4
Risankizumab 150 mg (N = 117)	65 (55.5)	(46.4, 64.5)	30.2	(18.6, 41.7)	1

Summary of main studies

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

Table 42: Summary of Efficacy for trial M15-998, KEEPsAKE 2

Title: 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)			
Study identifier	M15-998		
Design	The study consists of a Screening Period (approximately 35 days), Period 1, Period 2, and 20-week Follow-up Period. **Period 1** is a 24-week randomized, double-blind, placebo-controlled, parallel-group period. Eligible subjects were randomized to risankizumab 150 mg (RZB) or placebo (PBO) in 1:1 ratio through Week 24 and dosing in period 1 were at Week 0, Week 4, and Week 16. **Period 2** is the long-term period and starts at Week 24. At Week 24, subjects randomized to PBO receive blinded RZB, and subjects randomized to RZB receive blinded PBO. Starting from Week 28 to Week 208, all subjects receive open-label RZB q12w.		
	Duration of main phase:		24 weeks (Period 1: double-blind period) 184 weeks (Period 2: open-label period)
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority of RZB vs. PBO at Week 24		
Treatment groups	Period 1	RZB	RZB at Week 0, 4 and 16
		PBO	PBO at Week 0, 4 and 16
	Period 2	RZB to RZB	PBO at Week 24 and RZB q12w starting from Week 28 to Week 208
		PBO to RZB	RZB at Week 24 and RZB q12w starting from Week 28 to Week 208
Endpoints and definitions	Primary	ACR20 at Week 24	Achievement of ACR20 response at Week 24
	Ranked Secondary	HAQ-DI at Week 24	Change from baseline in HAQ-DI score at Week 24
		PASI 90 at Week 24	Achievement of PASI 90 response at Week 24
		ACR20 at Week 16	Achievement of ACR20 response at Week 16
		MDA at Week 24	Achievement of Minimal Disease Activity (MDA) response at Week 24

		SF-36 PCS at Week 24	Change from baseline in SF-36 physical component summary (PCS) at Week 24
		FACIT-Fatigue at Week 24	Change from baseline in FACIT-Fatigue score at Week 24
	Other Secondary	ACR50 at Week 24	Achievement of ACR50 response at Week 24
		ACR70 at Week 24	Achievement of ACR70 response at Week 24
		Resolution of Enthesitis at Week 24	Achievement of resolution of enthesitis response at Week 24
		Resolution of Dactylitis at Week 24	Achievement of resolution of dactylitis response at Week 24
Database lock	21 November 2020		
Analysis population and time point description	The Full Analysis Set (FAS) included all randomized subjects who received at least one dose of study drug. The FAS was used for all efficacy analysis. Subjects were included in the analysis according to the treatment groups that they were randomized to.		
Results and Analysis			
Analysis description	**Primary and Secondary Analysis**		
Descriptive statistics and estimate variability	Treatment group	Risankizumab 150 mg (RZB)	Placebo (PBO)
	Number of Subjects	224	219
	ACR20 at Week 24 (NRI-C), n/N (%)	115/224 (51.3%)	58/219 (26.5%)
	HAQ-DI at Week 24 (MMRM), LS-Mean Change from Baseline [95% CI]	−0.22 [−0.28, −0.15]	−0.05 [−0.12, 0.02]
	PASI 90 at Week 24 (NRI-C)[a], n/N (%)	68/123 (55.0%)	12/119 (10.2%)
	ACR20 at Week 16 (NRI-C), n/N (%)	108/224 (48.3%)	55/219 (25.3%)
	MDA at Week 24 (NRI-C), n/N (%)	57/224 (25.6%)	25/219 (11.4%)
	SF-36 PCS at Week 24 (MMRM), LS-Mean Change from Baseline [95% CI]	5.87 [4.86, 6.88]	2.01 [0.94, 3.08]
	FACIT-Fatigue at Week 24 (MMRM), LS-Mean Change from Baseline [95% CI]	4.9 [3.7, 6.0]	2.6 [1.4, 3.9]
	ACR50 at Week 24 (NRI-C), n/N (%)	59/224 (26.3%)	20/219 (9.3%)
	ACR70 at Week 24 (NRI-C), n/N (%)	27/224 (12.0%)	13/219 (5.9%)
	Resolution of Enthesitis at Week 24 (NRI-C)[b], n/N (%)	63/147 (42.9%)	48/158 (30.4%)
	Resolution of Dactylitis at Week 24 (NRI-C)[c], n/N (%)	29/40 (72.5%)	24/57 (42.1%)

Effect estimate per comparison	ACR20 at Week 24 (NRI-C)	Comparison groups	RZB vs PBO
		Difference	24.5%
		95% CI	[15.9%, 33.0%]
		P-value	< 0.001
	HAQ-DI at Week 24 (MMRM)	Comparison groups	RZB vs PBO
		Difference	−0.16
		95% CI	[−0.26, −0.07]
		P-value	< 0.001
	PASI 90 at Week 24 (NRI-C)[a]	Comparison groups	RZB vs PBO
		Difference	44.3%
		95% CI	[33.9%, 54.6%]
		P-value	< 0.001
	ACR20 at Week 16 (NRI-C)	Comparison groups	RZB vs PBO
		Difference	22.6%
		95% CI	[13.9%, 31.2%]
		P-value	< 0.001
	MDA at Week 24 (NRI-C)	Comparison groups	RZB vs PBO
		Difference	14.0%
		95% CI	[7.0%, 21.0%]
		P-value	< 0.001
	SF-36 PCS at Week 24 (MMRM)	Comparison groups	RZB vs PBO
		Difference	3.86
		95% CI	[2.41, 5.31]
		P-value	< 0.001
	FACIT-Fatigue at Week 24 (MMRM)	Comparison groups	RZB vs PBO
		Difference	2.2
		95% CI	[0.6, 3.9]
		P-value	0.009
	ACR50 at Week 24 (NRI-C)	Comparison groups	RZB vs PBO
		Difference	16.6%
		95% CI	[9.7%, 23.6%]

		P-value	< 0.001
	ACR70 at Week 24 (NRI-C)	Comparison groups	RZB vs PBO
		Difference	6.0%
		95% CI	[0.8%, 11.3%]
		P-value	0.024
	Resolution of Enthesitis at Week 24 (NRI-C)[b]	Comparison groups	RZB vs PBO
		Difference	13.8%
		95% CI	[3.5%, 24.2%]
		P-value	0.009
	Resolution of Dactylitis at Week 24 (NRI-C)[c]	Comparison groups	RZB vs PBO
		Difference	38.8%
		95% CI	[22.9%, 54.8%]
		P-value	< 0.001
Notes	Treatment differences presented above were adjusted for the stratification factors of current use of csDMARD (0 vs ≥ 1), number of prior biologic therapies (0 vs ≥ 1), and extent of psoriasis (≥ 3% BSA vs < 3% BSA) at baseline. a. For subjects with Baseline BSA ≥ 3% only. b. For subjects with Baseline LEI > 0 only. c. For subjects with Baseline LDI > 0 only.		

Table 43: Summary of Efficacy for Trial M16-011, KEEPsAKE 1

Title: A Phase 3, Randomized, Double-Blind Study Comparing Risankizumab to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to or Intolerance to at Least One Disease Modifying Anti-Rheumatic Drug (DMARD) Therapy (KEEPsAKE 1)			
Study identifier	M16-011		
Design	The study consists of a Screening Period (approximately 35 days), Period 1, Period 2, and 20-week Follow-up Period. **Period 1** is a 24-week randomized, double-blind, placebo-controlled, parallel-group period. Eligible subjects were randomized to risankizumab 150 mg (RZB) or placebo (PBO) in 1:1 ratio through Week 24 and dosing in period 1 were at Week 0, Week 4, and Week 16. **Period 2** is the long-term period and starts at Week 24. At Week 24, subjects randomized to PBO receive blinded RZB, and subjects randomized to RZB receive blinded BPO. Starting from Week 28 to Week 208, all subjects receive open-label RZB q12w.		
	Duration of main phase:		24 weeks (Period 1: double-blind period) 184 weeks (Period 2: open-label period)
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority of RZB vs. PBO at Week 24		
Treatment groups	Period 1	RZB	RZB at Week 0, 4 and 16
		PBO	PBO at Week 0, 4 and 16
	Period 2	RZB to RZB	PBO at Week 24 and RZB q12w starting from Week 28 to Week 208
		PBO to RZB	RZB at Week 24 and RZB q12w starting from Week 28 to Week 208
Endpoints and definitions	Primary	ACR20 at Week 24	Achievement of ACR20 response at Week 24
	Ranked Secondary	HAQ-DI at Week 24	Change from baseline in HAQ-DI score at Week 24
		PASI 90 at Week 24	Achievement of PASI 90 response at Week 24
		ACR20 at Week 16	Achievement of ACR20 response at Week 16
		MDA at Week 24	Achievement of Minimal Disease Activity (MDA) response at Week 24
		mNAPSI at Week 24	Change from baseline in mNAPSI score at Week 24
		PGA-F at Week 24	Change from baseline in PGA-F at Week 24
		Resolution of Enthesitis at Week 24	Achievement of resolution of enthesitis response at Week 24 (pooled from M15-998 and M16-011)

		Resolution of Dactylitis at Week 24	Achievement of resolution of dactylitis response at Week 24 (pooled from M15-998 and M16-011)
		mTSS at Week 24	Change from Baseline in modified Total Sharp Score (mTSS) at Week 24
		SF-36 PCS at Week 24	Change from baseline in SF-36 physical component summary (PCS) at Week 24
		FACIT-Fatigue at Week 24	Change from baseline in FACIT-Fatigue score at Week 24
	Other Secondary	ACR50 at Week 24	Achievement of ACR50 response at Week 24
		ACR70 at Week 24	Achievement of ACR70 response at Week 24
	Additional Efficacy	Resolution of Enthesitis at Week 24	Achievement of resolution of enthesitis response at Week 24
		Resolution of Dactylitis at Week 24	Achievement of resolution of dactylitis response at Week 24
Database lock	06 December 2020		
Analysis population and time point description	The Full Analysis Set (FAS) included all randomized subjects who received at least one dose of study drug. The FAS was used for all efficacy analysis. Subjects were included in the analysis according to the treatment groups that they were randomized to.		
Results and Analysis			
Analysis description	**Primary and Secondary Analysis**		
Descriptive statistics and estimate variability	Treatment group	Risankizumab 150 mg (RZB)	Placebo (PBO)
	Number of Subjects	483	481
	ACR20 at Week 24 (NRI-C), n/N (%)	277/483 (57.3%)	161/481 (33.5%)
	HAQ-DI at Week 24 (MMRM), LS-Mean Change from Baseline [95% CI]	−0.31 [−0.36, −0.27]	−0.11 [−0.16, −0.06]
	PASI 90 at Week 24 (NRI-C)[a], n/N (%)	143/273 (52.3%)	27/272 (9.9%)
	ACR20 at Week 16 (NRI-C), n/N (%)	272/483 (56.3%)	161/481 (33.4%)
	MDA at Week 24 (NRI-C), n/N (%)	121/483 (25.0%)	49/4sn81 (10.2%)
	mNAPSI at Week 24 (MMRM), LS-Mean Change from Baseline [95% CI]	−9.76 [−10.95, −8.58]	−5.57 [−6.70, −4.44]
	PGA-F at Week 24 (MMRM), LS-Mean Change from Baseline [95% CI]	−0.8 [−1.0, −0.7]	−0.4 [−0.5, −0.3]
	Resolution of Enthesitis at Week 24 (NRI-C, pooled M15-998 and M16-011)[b], n/N (%)	215/444 (48.4%)	156/448 (34.8%)

	Resolution of Dactylitis at Week 24 (NRI-C, pooled M15-998 and M16-011)[c], n/N (%)	128/188 (68.1%)	104/204 (51.0%)
	mTSS at Week 24 (Linear Extrapolation and ANCOVA), LS-Mean Change from Baseline [95% CI]	0.23 [0.02, 0.44]	0.32 [0.11, 0.53]
	SF-36 PCS at Week 24 (MMRM), LS-Mean Change from Baseline [95% CI]	6.52 [5.83, 7.20]	3.20 [2.50, 3.89]
	FACIT-Fatigue at Week 24 (MMRM), LS-Mean Change from Baseline [95% CI]	6.5 [5.6, 7.3]	3.9 [3.1, 4.7]
	ACR50 at Week 24 (NRI-C), n/N (%)	162/483 (33.4%)	54/481 (11.3%)
	ACR70 at Week 24 (NRI-C), n/N (%)	74/483 (15.3%)	23/481 (4.7%)
	Resolution of Enthesitis at Week 24 (NRI-C)[b], n/N (%)	152/297 (51.2%)	108/290 (37.2%)
	Resolution of Dactylitis at Week 24 (NRI-C)[c], n/N (%)	99/148 (66.9%)	80/147 (54.4%)

Effect estimate per comparison	ACR20 at Week 24 (NRI-C)	Comparison groups	RZB vs PBO
		Difference	24.0%
		95% CI	[18.0%, 30.0%]
		P-value	< 0.001
	HAQ-DI at Week 24 (MMRM)	Comparison groups	RZB vs PBO
		Difference	−0.20
		95% CI	[−0.26, −0.14]
		P-value	< 0.001
	PASI 90 at Week 24 (NRI-C)[a]	Comparison groups	RZB vs PBO
		Difference	42.5%
		95% CI	[35.6%, 49.3%]
		P-value	< 0.001
	ACR20 at Week 16 (NRI-C)	Comparison groups	RZB vs PBO
		Difference	23.1%
		95% CI	[16.8%, 29.4%]
		P-value	< 0.001
	MDA at Week 24 (NRI-C)	Comparison groups	RZB vs PBO
		Difference	14.8%
		95% CI	[10.2%, 19.4%]
		P-value	< 0.001
	mNAPSI at Week 24 (MMRM)	Comparison groups	RZB vs PBO
		Difference	−4.19
		95% CI	[−5.70, −2.68]
		P-value	< 0.001
	PGA-F at Week 24 (MMRM)	Comparison groups	RZB vs PBO
		Difference	−0.4
		95% CI	[−0.6, −0.3]
		P-value	< 0.001
	Resolution of Enthesitis at Week 24 (NRI-C, pooled M15-998 and M16-011)[b]	Comparison groups	RZB vs PBO
		Difference	13.9%
		95% CI	[7.6%, 20.2%]

		P-value	< 0.001
	Resolution of Dactylitis at Week 24 (NRI-C, pooled M15-998 and M16-011)[c]	Comparison groups	RZB vs PBO
		Difference	16.9%
		95% CI	[7.5%, 26.4%]
		P-value	< 0.001
	mTSS at Week 24 (Linear Extrapolation and ANCOVA)	Comparison groups	RZB vs PBO
		Difference	−0.09
		95% CI	[−0.36, 0.17]
		P-value	0.496
	SF-36 PCS at Week 24 (MMRM)	Comparison groups	RZB vs PBO
		Difference	3.32
		95% CI	[2.42, 4.22]
		P-value	< 0.001
	FACIT-Fatigue at Week 24 (MMRM)	Comparison groups	RZB vs PBO
		Difference	2.6
		95% CI	[1.5, 3.7]
		P-value	< 0.001
	ACR50 at Week 24 (NRI-C)	Comparison groups	RZB vs PBO
		Difference	22.2%
		95% CI	[17.3%, 27.2%]
		P-value	< 0.001
	ACR70 at Week 24 (NRI-C)	Comparison groups	RZB vs PBO
		Difference	10.5%
		95% CI	[6.9%, 14.2%]
		P-value	< 0.001
	Resolution of Enthesitis at Week 24 (NRI-C)[b]	Comparison groups	RZB vs PBO
		Difference	13.9%
		95% CI	[6.2%, 21.7%]
		P-value	< 0.001
	Resolution of Dactylitis at Week 24 (NRI-C)[c]	Comparison groups	RZB vs PBO

		Difference	11.9%
		95% CI	[0.9%, 22.9%]
		P-value	0.034
Notes	Treatment differences presented above were adjusted for the stratification factors of current use of csDMARD (0 vs ≥ 1), presence of dactylitis (yes vs no), presence of enthesitis (yes vs no) and extent of psoriasis (≥ 3% BSA or < 3% BSA) at baseline. a. For subjects with Baseline BSA ≥ 3% only. b. For subjects with Baseline LEI > 0 only. c. For subjects with Baseline LDI > 0 only.		

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

Pooled Data for Resolution of Enthesitis and Resolution of Dactylitis

To test treatment effect with appropriate power, the MAH, by way of protocol amendments, pooled dactylitis and enthesitis data from Studies M15-998 and M16-011 for analysis under the multiplicity control of M16-011 as ranked secondary endpoints.

As a ranked secondary endpoint, the treatment difference for resolution of dactylitis at Week 24 (NRI-C) for risankizumab vs placebo was statistically significant at 16.9% (95% CI 7.5-26.4%; p<0.001).

As a ranked secondary endpoint, the treatment difference for resolution of enthesitis at Week 24 (NRI-C) for risankizumab vs. placebo was statistically significant at 13.9% (95% CI 7.6-20.2%; p<0.001).

Pending the availability of Week 52 data and final CSRs, the MAH presented integrated efficacy analyses across the two Phase III trials based on cumulative data up to a DBL cut off of 14 December 2020. By this date 634 subjects (placebo: 310; risankizumab: 324) i.e. 45.1% of subjects randomised across both trials (634/1407), had completed the week 52 visit.

Clinical studies in special populations

No efficacy data has been presented for special populations or paediatric subjects. Subjects could be enrolled in Phase 3 trials from 18 years of age; 16.4% (231/1407 across both trials) were greater than 65 years of age (placebo 16.6% [116]; risankizumab 16.3% [115]) and the oldest subject was 85 years old. *arthritis*

2.4.3. Discussion on clinical efficacy

The MAH seeks the following indication: *Skyrizi, alone or in combination with non-biologic disease-modifying antirheumatic drugs (DMARDs), is indicated for the treatment of active psoriatic in adults who have had an inadequate response or who have been intolerant to one or more DMARDs.*

This application is based on interim data presented for the two phase 3 clinical trials, M15-988 and M16-011, which includes the findings at the primary endpoint at Week 24, indicates that risankizumab 150 mg at Week 0, Week 4, and 12 weekly thereafter, improved signs and symptoms of psoriatic arthritis, including skin, peripheral joint, enthesitis, and dactylitis signs and symptoms.

Study design

The design and conduct of both studies were similar. Subjects were recruited according to CASPAR criteria and with the same baseline disease activity parameters. M15-998 recruited up to 50% subjects who were intolerant to or lacked response to at least one biologic treatment, otherwise subjects across both studies were intolerant to or lacked efficacy with at least 1 csDMARD. M16-011 assessed the effect of treatment on nail psoriasis; enthesitis and dactylitis in both studies were assessed under hierarchical statistical control in M16-011, to allow power to detect a risankizumab treatment on these endpoints.

The proportion of subjects with dactylitis and enthesitis were 22% and 68.8% in M15-998 (n=443) versus 30.6% and 60.9% in M16-011 (n= 964). The presence of psoriatic spondylitis was overall 19.6% in both trials.

Mean duration of PsA in years was 8.2 years for M15-998 (median 5.5 years) and 7.1 years for M16-011 (median 4.7 years). Baseline proportion with BSA involvement ≥ 3% was similar across trials (54.6% M15-988; 56.5% M16-011); mean PASI for those with BSA ≥ 3% was higher in biologic naïve subjects in M16-011 at 6.8 overall versus 5.6 overall in M15-998.

The dosing regimen for both studies was that of the licenced posology for risankizumab in the treatment of psoriasis i.e. risankizumab 150 mg sc at week 0, week 4 and 12 weekly thereafter. The selection of this dose and dosing regimen were based on the clinical development programme to date and the phase 2 study M16-002. An active comparator arm was not used and is not mandated by the current guidelines.

For both studies, the primary endpoint was American College of Rheumatology (ACR) 20 response at Week 24, which is in line with previous product authorisations and with current EMA guidelines.

Secondary endpoints included HAQ-DI, ACR50, ACR70, IGA, DAS 28 (CRP), effects on BASDAI, dactylitis, enthesitis and quality of life scores.

Study results

The primary and all ranked secondary endpoints were reached in M15-988 (n=443), in which subjects were either csDMARD-IR or Bio-IR.

For M16-011, (n=964) in which subjects were csDMARD experienced but biologic naïve, the primary and first 8 ranked secondary endpoints were statistically significant when compared with the placebo arm. For the 9th ranked secondary endpoint, mTSS, while a greater percentage of subjects receiving risankizumab showed no radiographic progression, the treatment difference result did not reach the pre-specified statistical significance level. Statistical testing was thus not conducted for the subsequent, sequenced ranked secondary endpoints, SF-36 PCS at Week 24 and FACIT-Fatigue.

It is noted that there was a strong placebo effect for biologic naïve subjects on csDMARDs at baseline in M15-998, compared to those who were on no csDMARD at baseline or to those BIO-IR subjects who had failed ≥1 prior biologic therapy (Table 9, M15-998 CSR).

More or less remarkable placebo effects were observed in Study M16-011 for some clinical efficacy endpoints including ACR responses, changes from BL in HAQ-DI scores, SF-36 PCS scores, FACIT-Fatigue scores and mTSS scores. While discussing 24-week hsCRP and HAQ-DI changes from BL results, the MAH stated that the population in study M16-011 might have had more severe PsA according to the inclusion criterion of presence of one or more joint erosion(s). Most Baseline Disease characteristics showed numerically higher values, which also might have been indicative for a more severe PsA of patients in M16-011, although confidence intervals of all baseline disease characteristics in question were overlapping while compared the corresponding values from Study M15-998 and M-16-011. The MAH is asked to provide some explanation of the increased placebo effect observed in Study M16-011.

Recommendations of the EMA clinical guidance for psoriatic arthritis (2007 Guideline on clinical investigation of medicinal products indicated for the treatment of psoriatic arthritis, CHMP/EWP/438/04) have been taken into account in the clinical development programme.

Updated EULAR guidelines (Gossec et al, 2019) advise a treat to target approach to achieve remission (abrogation of inflammation) or low disease activity. In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a biological DMARD should be commenced, considering an IL-17 or IL-12/23 inhibitor if there is relevant skin involvement i.e. where risankizumab could fit into the PsA treatment paradigm.

In summary, the week 52 data efficacy analysis is consistent with the week-24 primary analysis and supports maintenance of effect and inhibition of progression of structural joint damage through 24 and 52 weeks of treatment with RZB.

The MAH applied for a broad indication regarding csDMARDs, however significant proportions of the populations studied in M15-988 and M16-011 were on comcomitant MTX at baseline when compared to baseline rates for sulfasalazine, leflunomide and apremilast without MTX.

Therefore, the recommendation that Skyrizi could be potentially combined with all cDMARDs was considered insufficiently justified given that the majority of patients treated with concomitant cDMARDs received MTX and the proposed indication was amended consequently

Skyrizi, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).

2.4.4. Conclusions on the clinical efficacy

The primary endpoint was met at Week 24 for both phase 3 trials, with risankizumab 150 mg at Week 0, Week 4 and 12 weekly thereafter proving more effective against signs and symptoms of PsA than placebo in the cohorts studied.

In M15-998, clinically relevant, statistically significant results were demonstrated for risankizumab versus placebo in the ranked secondary endpoint for signs and symptoms, physical function and health related quality of life scores. Additional secondary endpoint results supported these findings. These effects were consistent in the Bio-IR and csDMARD-IR subjects at Week 24. Results were also consistent for subjects with concomitant csDMARDs or monotherapy. Trends in available data for these efficacy effects generally increased through Week 52.

In M16-011, clinically relevant, statistically significant results were demonstrated for 8 of the 11 ranked secondary endpoints (mTSS not statistically significant, thus SF-36 and Facit-FATIGUE not analysed) with similar consistency in additional secondary endpoints and trends in available data for efficacy effects through Week 52.

The recommendation that Skyrizi could be potentially combined with all cDMARDs was considered insufficiently justified given that the majority of patients treated with concomitant cDMARDs received MTX and the proposed indication was amended consequently

Skyrizi, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).

2.5. Clinical safety

Introduction

Risankizumab received marketing approval in the European Union in April 2019 for the treatment of adult patients with moderate to severe plaque psoriasis (PsO). The psoriatic arthritis program includes two pivotal Phase 3 studies M16-011 KEEPsAKE 1 and M15-998 KEEPsAKE2.

The psoriatic arthritis program also included Study M16-002: A Phase 2b dose ranging study **,** Study M16-244: A Phase 2 open-label extension study.

Data from the studies outlined above were integrated into 3 integrated analysis sets that are the primary focus of the safety review as follows:

- Phase 3 PsA PBO-Controlled Analysis Set
- Phase 3 PsA Long-term Analysis Set,
- All Risankizumab PsA Analysis Set

Data from the All Risankizumab PsO Analysis Set also forms part of the safety assessment. This supportive analysis set includes studies that primarily examined the same dosing regimen (risankizumab 150 mg administered by SC injection at Week 0, Week 4, and q12w thereafter), as the psoriatic arthritis studies. The All Risankizumab PsO Analysis Set includes all subjects who received risankizumab from the psoriasis studies included in original psoriasis Marketing Authorization Application submission (9 studies) and 8 additional completed psoriasis studies, including Studies M15-999 (150 mg new formulation/PFS) and M16-005 150 mg new formulation/auto injector) through a data cutoff of 20 October 2020.

The Safety data packages in PsA and PsO are presented separately, not integrated as a single analysis set, due to differing study designs, patient exposures, and patient populations.

Safety was evaluated by monitoring of AEs, including serious AEs (SAEs); evaluation of clinical laboratory values (hematology and clinical chemistry) and physical examination, including vital signs. Real world data sets and long-term clinical trial safety data with non-TNF biologics used in psoriatic arthritis have been presented as reference benchmarks to contextualize the long-term event rates of ASIs that are uncommon or rare and of longer latency such as Major Adverse Cardiovascular Event (MACE) and malignancies. An independent adjudication committee adjudicated all observed cardio-vascular and cerebro-vascular events, including MACE, in a blinded manner. In addition, an anaphylactic adjudication committee adjudicated any serious hypersensitivity reactions.

Table 44: Pivotal Phase 3 Psoriatic Arthritis Studies

	Study Population Study Number	
	Bio-IR and csDMARD-IR[a] M15-998	**csDMARD-IR[b] M16-011**
Background Therapy	Up to 2 csDMARDs	Up to 2 csDMARDs
Treatment Groups (N) in Period 1	Risankizumab 150 mg (224) Placebo (219)	Risankizumab 150 mg (483) Placebo (481)
Placebo Duration (Weeks)	24 weeks	24 weeks
Timepoint For Primary Endpoint	Week 24	Week 24
Timepoint For Final Analysis	Week 228	Week 228

a. The subject population was to consist of no more than 50% of subjects with a demonstrated inadequate response (lack of efficacy after a minimum 12 week duration of therapy) or intolerance to 1 or 2 biologic therapies (bio-IR). The rest of the subjects were to have a demonstrated inadequate response (lack of efficacy after a minimum 12 week duration of therapy) to previous or current treatment with at least 1 csDMARD at the maximally tolerated dose or an intolerance or contraindication to at least 1 csDMARD (csDMARD-IR).

b. Subjects must have demonstrated an inadequate response (lack of efficacy after minimum 12 week duration of therapy) to previous or current treatment with at least 1 csDMARD at maximally tolerated dose or have an intolerance to or contraindication for csDMARDs as determined by the investigator.

Table 45: Integrated Safety Analysis Sets

Analysis Set	Description and Objective	Data Cutoff Date	Pooled Studies	Summarized Treatment Group(s)	Treatment Comparison(s)
Phase 3 PsA PBO-Controlled Analysis Set	This analysis set includes subjects who received risankizumab 150 mg or placebo during the 24-week placebo-controlled period in Phase 3 Studies M15-998 and M16-011.	14 December 2020	M15-998 M16-011	Risankizumab 150 mg (N = 707) Placebo (N = 700)	Risankizumab 150 mg versus placebo
Phase 3 PsA Long-term Analysis Set	This analysis set assesses safety of risankizumab 150 mg through data cutoff at the time of submission. It includes subjects who received at least one dose of risankizumab 150 mg in Phase 3 Studies M15-998 and M16-011.	14 December 2020	M15-998 M16-011	Risankizumab 150 mg (No cross-over from placebo)[a] (N = 707) Any Risankizumab 150 mg[b] (N = 1,365)	None
All Risankizumab PsA Analysis Set	This analysis set assesses overall safety of risankizumab treatment through data cutoff at the time of submission. It includes subjects with active PsA in Phase 2 and Phase 3 PsA trials who received at least one dose of risankizumab.	14 December 2020	M15-998 M16-011 M16-002[c] M16-244[c]	All Risankizumab[d] (N = 1,542)	None

a. Includes any risankizumab 150 mg exposure of subjects starting on risankizumab 150 mg at randomization in Phase 3 studies.

b. Includes all Phase 3 study subjects who received risankizumab 150 mg. This comprises subjects who were either: (1) randomized to risankizumab 150 mg in Period 1 and continued on risankizumab 150 mg in Period 2 or (2) Randomized to placebo in Period 1 and subsequently received 150 mg risankizumab in Period 2.

c. Final data from completed Phase 2 studies.

d. Includes all Phase 2 and Phase 3 subjects who received risankizumab. This mainly comprises subjects who received risankizumab 150 mg and includes a small subset of subjects (N = 20) from Phase 2 Study M16-002 who received risankizumab 75 mg.

Patient exposure

One patient treatment year (PTY) is equivalent to an estimated usage of 8.6963 75-mg vials (652.2269 mg) for 150 mg dose and 4.3484 75-mg vials (326.1317 mg) for 75 mg dose (Japan only) (ADD × 365.25 days/year).

In Study M16-011 946 subjects were randomized and in Study M15-998 444 subjects were randomized.

In the Phase 3 PsA PBO-Controlled Analysis Set: 1,407 subjects received at least 1 dose of study drug (risankizumab or placebo) In the Phase 3 PsA Long-term Analysis Set: 1,365 subjects received at least 1 dose of risankizumab representing a total of 1,047.9 patient-years (PY) of long-term risankizumab exposure. Of these subjects in the Phase 3 PsA Long-term Analysis Set, 1,035 (75.8%) were treated with risankizumab for at least 6 months, and 372 (27.3%) were treated with risankizumab for at least 12 months. The All Risankizumab PsA Analysis Set included a total of 1,542 subjects who received at least one dose of risankizumab, with a total of 1259.7 PY of exposure.

Table 46: Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (Phase 3 PsA Long-term Analysis Set)

Duration	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) n (%)	Any Risankizumab 150 mg (N = 1365) n (%)
≥ 1 dose	707 (100)	1365 (100)
< 90 days (3 months)	5 (0.7)	57 (4.2)
≥ 90 days (3 months)	702 (99.3)	1308 (95.8)
≥ 180 days (6 months)	687 (97.2)	1035 (75.8)
≥ 360 days (12 months)	351 (49.6)	372 (27.3)
≥ 540 days (18 months)	20 (2.8)	20 (1.5)
≥ 720 days (24 months)	0	0
Mean duration (days)	353.7	274.9

Note: Duration of treatment = last dose date - first dose date + 84 days.

Table 47: Duration of Exposure

Duration Interval Days	All Risankizumab N = 5053
Cumulative for All Indications[a]	**Patients n (%)**
< 90 days (< 3 months)	194 (3.8)
≥ 90 days (3 months)	4859 (96.2)
≥ 180 days (6 months)	4462 (88.3)
≥ 360 days (12 months)	3119 (61.7)
≥ 540 days (18 months)	2252 (44.6)
≥ 720 days (24 months)	2125 (42.1)
≥ 900 days (30 months)	2038 (40.3)
≥ 1080 days (36 months)	1900 (37.6)
≥ 1260 days (42 months)	1461 (28.9)
≥ 1440 days (48 months)	1029 (20.4)

a. Includes data from the following indications: psoriasis (Studies 1311_0001, 1311_0002, 1311_0003, 1311_0004, 1311_0013, 1311_0028, 1311_0030, 1311_0038, M15-997, M15-999, M16-005, M16-007, M16-176, M16-177, M16-178, M16-766 and M19-164), Crohn's disease (Studies 1311_0006 and M15-989), ankylosing spondylitis (Study 1311_0008), asthma (Study 1311_0014), generalized pustular psoriasis or erythrodermic psoriasis (Study M15-988), and psoriatic arthritis (Studies 1311_0005, M16-244, M15-998, and M16-011).

Subject Disposition

At the time of data cut off (14 December 2020) 1217 (89.2%) of subjects were participating in ongoing Phase 3 psoriatic arthritis studies.

Table 48: Subject Disposition (Phase 3 PsA PBO-Controlled Analysis Set)

	Placebo (N = 700) n (%)	Risankizumab 150 mg (N = 707) n (%)	Total (N = 1407) n (%)
Overall			
Randomized	700 (100)	707 (100)	1407 (100)
Took at Least One Dose of Study Drug	700 (100)	707 (100)	1407 (100)
Completed 24 Weeks of Study Drug	658 (94.0)	680 (96.2)	1338 (95.1)
Premature Discontinuation of Study Drug Due to (Primary Reasons)	42 (6.0)	27 (3.8)	69 (4.9)
Adverse Event	10 (1.4)	5 (0.7)	15 (1.1)
Withdrew Consent	13 (1.9)	7 (1.0)	20 (1.4)
Lost to Follow-up	3 (0.4)	2 (0.3)	5 (0.4)
Lack of Efficacy	11 (1.6)	5 (0.7)	16 (1.1)
COVID-19 Logistical Restrictions	2 (0.3)	6 (0.8)	8 (0.6)
Other	3 (0.4)	2 (0.3)	5 (0.4)

Table 49: Subject Disposition (Phase 3 PsA Long-term Analysis Set)

	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) n (%)	Any Risankizumab 150 mg (N = 1365) n (%)
Overall		
Randomized	707 (100)	1365 (100)
Took at Least One Dose of Study Drug	707 (100)	1365 (100)
Ongoing	624 (88.3)	1217 (89.2)
Premature Discontinuation of Study Drug Due to (Primary Reasons)	83 (11.7)	148 (10.8)
Adverse Event	9 (1.3)	13 (1.0)
Withdrew Consent	18 (2.5)	27 (2.0)
Lost to Follow-up	4 (0.6)	8 (0.6)
Lack of Efficacy	17 (2.4)	30 (2.2)
< 20% Improvement in TJC/SJC Compared to Baseline	25 (3.5)	56 (4.1)
COVID-19 Logistical Restrictions	6 (0.8)	8 (0.6)
Other	4 (0.6)	6 (0.4)

Demographics

Table 50: Demographic Characteristics (Phase 3 PsA PBO-Controlled Analysis Set)

	Placebo (N = 700)	Risankizumab 150 mg (N = 707)	Total (N = 1407)
Sex - n (%)			
Female	368 (52.6)	355 (50.2)	723 (51.4)
Male	332 (47.4)	352 (49.8)	684 (48.6)
Age (years) - n (%)			
Mean ± SD	51.7 ± 12.28	51.9 ± 12.33	51.8 ± 12.30
< 65	584 (83.4)	592 (83.7)	1176 (83.6)
≥ 65	116 (16.6)	115 (16.3)	231 (16.4)
≥ 65 – < 75	100 (14.3)	99 (14.0)	199 (14.1)
≥ 75	16 (2.3)	16 (2.3)	32 (2.3)
Race - n (%)			
White	661 (94.4)	672 (95.0)	1333 (94.7)
Black or African American	5 (0.7)	6 (0.8)	11 (0.8)
Asian	25 (3.6)	15 (2.1)	40 (2.8)
Native Hawaiian or Other Pacific Islander	1 (0.1)	3 (0.4)	4 (0.3)
American Indian or Alaska Native	0	1 (0.1)	1 (< 0.1)
Multiple	8 (1.1)	10 (1.4)	18 (1.3)
Other	0	0	0
Geographic Region[a] – n (%)			
North America	142 (20.3)	146 (20.7)	288 (20.5)
South/Central America	109 (15.6)	102 (14.4)	211 (15.0)
Western Europe	53 (7.6)	74 (10.5)	127 (9.0)
Eastern Europe	299 (42.7)	289 (40.9)	588 (41.8)
Asia	26 (3.7)	17 (2.4)	43 (3.1)
Other	71 (10.1)	79 (11.2)	150 (10.7)
Ethnicity – n (%)			
Hispanic or Latino	135 (19.3)	135 (19.1)	270 (19.2)
Not Hispanic or Latino	565 (80.7)	572 (80.9)	1137 (80.8)

Table 51: Demographic Characteristics (Phase 3 PsA PBO-Controlled Analysis Set) (Continued)

	Placebo (N = 700)	Risankizumab 150 mg (N = 707)	Total (N = 1407)
Weight (kg) – n (%)			
< 100	525 (75.0)	527 (74.5)	1052 (74.8)
≥ 100	175 (25.0)	180 (25.5)	355 (25.2)
BMI (kg/m^2)			
Mean ± SD	30.6 ± 6.41	31.0 ± 6.96	30.8 ± 6.69
Median (min, max)	29.4 (15.5, 59.2)	29.9 (10.4, 87.2)	29.8 (10.4, 87.2)
BMI (kg/m^2) – n (%)			
< 25	127 (18.1)	120 (17.0)	247 (17.6)
25 – < 30	246 (35.1)	235 (33.2)	481 (34.2)
≥ 30	327 (46.7)	352 (49.8)	679 (48.3)

a. "Other" geographic region contains South Africa, Australia, New Zealand.

Note: Percentages calculated on non-Missing values.

Table 52: Baseline safety characteristics – Categorical Variables (Phase3 PsA PBO-Controlled Analysis Set)

	Placebo (N = 700)	Risankizumab 150 mg (N = 707)
Duration of PsA in Years		
n	700	707
Mean (SD)	7.44 (7.907)	7.47 (7.415)
Median	4.84	4.94
Min, Max	0.3, 59.8	0.4, 55.7
Duration of PsA in Years - n (%)		
<= 5	360 (51.4)	357 (50.5)
> 5 - <= 10	169 (24.1)	168 (23.8)
> 10	171 (24.4)	182 (25.7)
Number of Prior csDMARDs - n (%)		
0	13 (1.9)	13 (1.8)
1	436 (62.3)	467 (66.1)
2	192 (27.4)	162 (22.9)
>= 3	59 (8.4)	65 (9.2)
Number of Prior Biologics - n (%)		
0	597 (85.3)	599 (84.7)
>= 1	103 (14.7)	108 (15.3)

Note: Percentages calculated on non-missing values.

Table 53: Baseline Safety Characteristics – Categorical Variables (Phase 3 PsA Placebo-Controlled Analysis Set) - continued

	Placebo (N = 700)	Risankizumab 150 mg (N = 707)
Nonsteroidal Anti-Inflammatory Drug (NSAID) Use at Baseline - n (%)		
Yes	435 (62.1)	416 (58.8)
No	265 (37.9)	291 (41.2)
Oral Corticosteroid Use at Baseline - n (%)		
Yes	109 (15.6)	129 (18.2)
No	591 (84.4)	578 (81.8)
Concomitant csDMARD at Baseline - n (%)		
Any csDMARD	493 (70.4)	508 (71.9)
Any MTX	414 (59.1)	424 (60.0)
MTX alone	375 (53.6)	396 (56.0)
MTX and other csDMARD	39 (5.6)	28 (4.0)
csDMARD other than MTX	79 (11.3)	84 (11.9)
Any sulfasalazine, without MTX	31 (4.4)	29 (4.1)
Any leflunomide, without MTX	34 (4.9)	40 (5.7)
Any apremilast, without MTX	13 (1.9)	14 (2.0)
None	207 (29.6)	199 (28.1)
Psoriatic arthritis Biologic Treatment History - by Response to Prior Treatment - n (%)		
Inadequate Response/Loss of Response	23 (25.6)	37 (31.6)
Lack of Tolerability	21 (23.3)	17 (14.5)
Other	33 (36.7)	45 (38.5)
Unknown	13 (14.4)	18 (15.4)
Missing	610	590

Table 54: Concomitant csDMARDs by Generic Name (Phase 3 PsA Placebo-Controlled Analysis Set)

Generic Name (WHO 202003)	Placebo (N = 700) n (%)	Risankizumab 150 mg (N = 707) n (%)
Any Concomitant csDMARDs	504 (72.0)	511 (72.3)
APREMILAST	18 (2.6)	16 (2.3)
AZATHIOPRINE	1 (0.1)	0
CICLOSPORIN	4 (0.6)	2 (0.3)
HYDROXYCHLOROQUINE	0	5 (0.7)
HYDROXYCHLOROQUINE SULFATE	8 (1.1)	5 (0.7)
LEFLUNOMIDE	39 (5.6)	41 (5.8)
METHOTREXATE	387 (55.3)	405 (57.3)
METHOTREXATE SODIUM	32 (4.6)	21 (3.0)
SULFASALAZINE	63 (9.0)	55 (7.8)

Adverse events

Treatment-emergent adverse events (TEAEs) are defined as events with onset on or after the first dose of study drug and no more than 140 days after the last dose of study drug or up to the submission data cutoff date (14 December 2020), whichever occurs first. For the Phase 3 Placebo-Controlled Analysis Set, TEAEs are defined as AEs with an onset date that is on or after the first dose of study drug until the end of the placebo-controlled period (defined as the minimum of the last dose date prior to Week 24 + 140 days or the Week 24 dose date, or submission data cutoff date [14 December 2020]).

For the long term analysis sets, TEAEs are defined as AEs with onset date that is on or after the date of the first dose of risankizumab to the date of last dose of risankizumab prior to submission data cutoff

date + 140 days or the submission data cutoff date, whichever occurs first. To adjust for potentially different follow-up times between treatment groups, exposure adjusted event rates (EAER) will be provided in the reporting of TEAEs and ASIs.

For the purpose of event rate calculation, the numerator will be the total number of AEs reported for the event within a particular treatment group (i.e., a subject can contribute more than one event to the numerator), and the denominator will be the subject exposure summed across all treated subjects divided by 365.25 and rounded to 1 decimal place.

The number of AEs reported (numerator), the total number of years of study drug exposure (denominator), and the exposure-adjusted AE event rate per 100 PY, calculated as (numerator/denominator) x 100, will be presented for each treatment group. The EAER will be the main approach to evaluate AEs in the long-term analyses, and it will also be provided for key safety endpoints for the short-term analyses as well.

Table 55: Overview of Treatment-Emergent Adverse Events EAER Per 100 PY (Phase 3 PsA PBO-Controlled Analysis Set) and Comparison with Long-term Risankizumab Treatment (Phase 3 PsA Long-term Analysis Set)

	Phase 3 PsA PBO-Controlled Analysis Set					Phase 3 PsA Long-term Analysis Set
	Placebo (N = 700) (PY = 325.1)		Risankizumab 150 mg (N = 707) (PY = 328.5)		Treatment Comparison (95% CI)[a]-- Risankizumab 150 mg - Placebo	Any Risankizumab 150 mg (N = 1365) (PY = 1047.9)
	n (%) [SSA%]	Events (E/100 PY) [SSA E/100 PY]	n (%) [SSA%]	Events (E/100 PY) [SSA E/100 PY]	n (%) Rate Difference [95% CI]	Events (E/100 PY) [SSA E/100 PY]
Any TEAEs	307 (43.9) [43.9]	688 (211.6) [212.0]	322 (45.5) [45.5]	689 (209.7) [209.5]	1.6 (–3.5, 6.8)	1759 (167.9) [167.9]
Any COVID-19 related TEAEs	2 (0.3) [0.3]	2 (0.6) [0.6]	2 (0.3) [0.3]	2 (0.6) [0.6]	–0.0 (–0.6, 0.6)	39 (3.7) [3.7]
Any TEAE related to study drug according to the investigator	88 (12.6) [12.6]	178 (54.8) [54.9]	91 (12.9) [12.9]	166 (50.5) [50.5]	0.3 (–3.2, 3.7)	367 (35.0) [35.0]
Any serious TEAE	31 (4.4) [4.4]	38 (11.7) [11.7]	21 (3.0) [3.0]	29 (8.8) [8.8]	–1.5 (–3.4, 0.5)	79 (7.5) [7.5]
Any severe TEAE	17 (2.4) [2.4]	21 (6.5) [6.5]	16 (2.3) [2.3]	23 (7.0) [7.0]	–0.2 (–1.8, 1.4)	47 (4.5) [4.5]
Any TEAE leading to discontinuation of study drug	10 (1.4) [1.4]	11 (3.4) [3.4]	6 (0.8) [0.8]	9 (2.7) [2.7]	–0.6 (–1.7, 0.5)	18 (1.7) [1.7]
Any TEAE leading to death	0	0	1 (0.1) [0.1]	1 (0.3) [0.3]	0.1 (–0.1, 0.4)	1 (< 0.1) [< 0.1]
All Deaths[b]	0	0	1 (0.1) [0.1]	1 (0.3) [0.3]	0.1 (–0.1, 0.4)	1 (< 0.1) [< 0.1]

Table 56: Overview of Treatment-Emergent Adverse Events EAER Per 100 PY (Phase 3 PsA PBO-Controlled Analysis Set) and Comparison with Long-term Risankizumab Treatment (Phase 3 PsA Long-term Analysis Set) (continued)

	Phase 3 PsA PBO-Controlled Analysis Set					Phase 3 PsA Long-term Analysis Set
	Placebo (N = 700) (PY = 325.1)		Risankizumab 150 mg (N = 707) (PY = 328.5)		Treatment Comparison (95% CI)[a]-- Risankizumab 150 mg - Placebo	Any Risankizumab 150 mg (N = 1365) (PY = 1047.9)
	n (%) [SSA%]	Events (E/100 PY) [SSA E/100 PY]	n (%) [SSA%]	Events (E/100 PY) [SSA E/100 PY]	n (%) Rate Difference [95% CI]	Events (E/100 PY) [SSA E/100 PY]
COVID-19 related deaths	0	0	0	0	0.0	0
Deaths occurring ≤ 140 days after last dose of study drug	0	0	1 (0.1) [0.1]	1 (0.3) [0.3]	0.1 (–0.1, 0.4)	1 (< 0.1) [< 0.1]
Deaths occurring > 140 days after last dose of study drug	0	0	0	0	0.0	0

a. Study size adjusted risk difference between treatment groups.

b. Includes both treatment-emergent and non-treatment-emergent deaths.

Table 57: Overview of Treatment Emergent Adverse Events in Exposure Adjusted Event rate per 100 Patient Years (All Risankizumab PsA Analysis Set)

	All Risankizumab (N = 1542) (PYs = 1259.7) Events (E/100 PYs) [SSA E/100 PYs]
Any TEAEs	2259 (179.3) [179.3]
Any COVID-19 related TEAEs	39 (3.1) [3.1]
Any TEAE related to study drug according to the investigator	455 (36.1) [36.1]
Any serious TEAE	112 (8.9) [8.9]
Any severe TEAE	76 (6.0) [6.0]
Any TEAE leading to discontinuation of study drug	29 (2.3) [2.3]
Any TEAE leading to death	1 (<0.1) [<0.1]
All Deaths#	1 (<0.1) [<0.1]
COVID-19 related deaths	0
Deaths occurring <= 140 days after last dose of study drug	1 (<0.1) [<0.1]
Deaths occurring > 140 days after last dose of study drug	0

Serious adverse event/deaths/other significant events

Deaths:

In the Phase 3 PsA PBO-Controlled Analysis Set, one treatment-emergent death was reported in the risankizumab treatment group in a subject with dementia requiring hospitalization for pneumonia on post-treatment Day 62 (Study M16-011) The subject developed urosepsis and complications on post-treatment Day 96 resulting in death. The event of urosepsis was assessed by the investigator and sponsor as having no reasonable possibility of being related to study drug and was adjudicated by the Cardiovascular Adjudication Committee (CAC) as a non-CV death. There were no additional deaths in the Phase 3 PsA Long-term Analysis Set and no non-treatment-emergent deaths. The exposure adjusted death rate with long-term risankizumab exposure was < 0.1 E/100 PY.

Other Serious Adverse events:

Table 58: Number and percentage of subjects with Treatment-Emergent Serious Adverse Events by Primary MedDRA System Organ Class and Preferred Term (Phase 3 PsA Placebo-Controlled Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Placebo (N = 700) n (%) [SSA %]	Risankizumab 150 mg (N = 707) n (%) [SSA %]
Any adverse event	31 (4.4) [4.4]	21 (3.0) [3.0]
Blood and lymphatic system disorders	3 (0.4) [0.4]	1 (0.1) [0.1]
Anaemia	2 (0.3) [0.3]	0
Blood loss anaemia	0	1 (0.1) [0.1]
Iron deficiency anaemia	1 (0.1) [0.1]	0
Cardiac disorders	3 (0.4) [0.4]	0
Angina unstable	1 (0.1) [0.1]	0
Cardiac failure congestive	1 (0.1) [0.1]	0
Coronary artery disease	1 (0.1) [0.1]	0
Ear and labyrinth disorders	1 (0.1) [0.1]	0
Vertigo	1 (0.1) [0.1]	0
Gastrointestinal disorders	4 (0.6) [0.6]	1 (0.1) [0.1]
Colitis	0	1 (0.1) [0.1]
Duodenal ulcer	1 (0.1) [0.1]	0
Intestinal obstruction	1 (0.1) [0.1]	0
Small intestinal obstruction	1 (0.1) [0.1]	0
Gastrointestinal disorders (Cont.)		
Umbilical hernia	1 (0.1) [0.1]	0
Hepatobiliary disorders	1 (0.1) [0.1]	2 (0.3) [0.3]
Cholecystitis	0	1 (0.1) [0.1]
Cholelithiasis	1 (0.1) [0.1]	1 (0.1) [0.1]
Infections and infestations	11 (1.6) [1.6]	7 (1.0) [1.0]
Abscess	0	1 (0.1) [0.1]
Appendicitis perforated	1 (0.1) [0.1]	0
Cellulitis	1 (0.1) [0.1]	2 (0.3) [0.3]
Complicated appendicitis	1 (0.1) [0.1]	0
Dysentery	1 (0.1) [0.1]	0
Erysipelas	1 (0.1) [0.1]	0
Gastroenteritis	1 (0.1) [0.1]	1 (0.1) [0.1]
Gastroenteritis viral	0	1 (0.1) [0.1]
Oral bacterial infection	1 (0.1) [0.1]	0
Pneumonia	2 (0.3) [0.3]	1 (0.1) [0.1]
Pneumonia viral	0	1 (0.1) [0.1]

Note: Treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of study drug until the end of the placebo controlled period (defined as the minimum of the last dose date prior to Week 24 + 140 days and the Week 24 dose date (looking at AEs that occur prior to that dose).
SSA = Study size adjusted.

In the Phase 3 PsA PBO-Controlled Analysis Set, SAEs were reported in 3.0% of subjects in the risankizumab group and in 4.4% of the subjects in the placebo group. There were no meaningful differences in the types of SAEs across treatment groups and no notable patterns of SAEs within the risankizumab group.

Trends in the types of SAEs reported were anaemia (in the placebo group), cellulitis (in the risankizumab group), psoriatic arthropathy (in the placebo group), and pneumonia (in the placebo group), which were all reported in 2 subjects each in a treatment group, all other SAEs were reported in only one subject each in both the risankizumab and placebo groups.

In the Phase 3 PsA Long-term Analysis Set, the rates of SAEs were stable with long-term risankizumab exposure (7.5 E/100 PY) compared to the rates in Phase 3 PsA Placebo-Controlled Analysis Set (8.8 E/100 PY) The majority of SAEs reported in the any risankizumab 150 mg group were reported in single subjects.

The table below presents SAEs reported in more than one subject in the any risankizumab 150 mg group.

Table 59: Summary of SAEs Occurring in ≥2 Subjects in the Any Risankizumab 150 mg Group (Phase 3 PsA Long-term Analysis Set)

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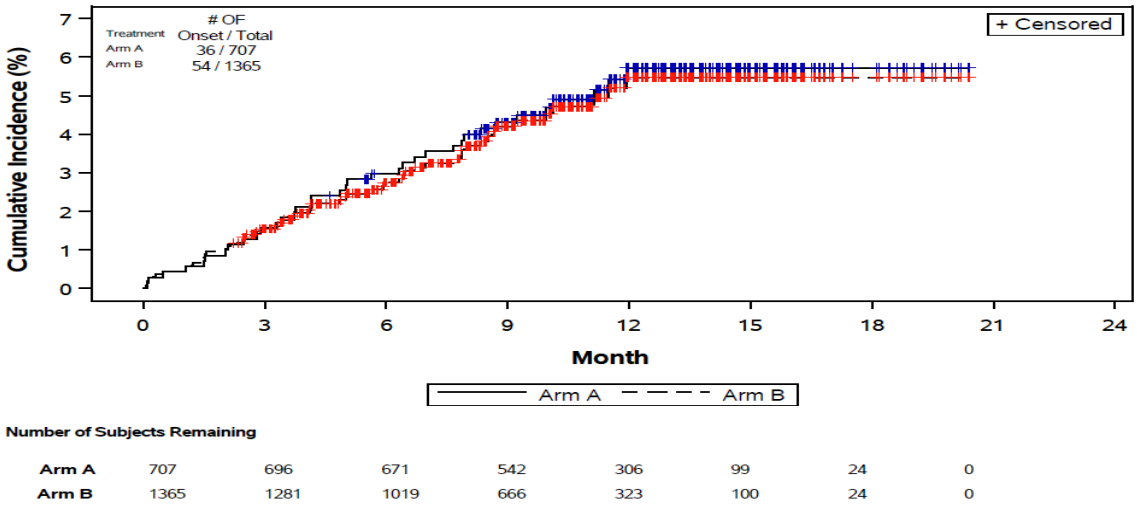
System Organ Class MedDRA 23.1 Preferred Term	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) n (%) [SSA %]	Any Risankizumab 150 mg (N = 1365) n (%) [SSA %]
Hepatobiliary disorders		
Cholelithiasis	3 (0.4) [0.4]	3 (0.2) [0.2]
Infections and infestations		
COVID-19	1 (0.1) [0.1]	4 (0.3) [0.3]
Cellulitis	2 (0.3) [0.3]	3 (0.2) [0.2]
Pneumonia	4 (0.6) [0.6]	4 (0.3) [0.3]
Musculoskeletal and connective tissue disorders		
Arthritis	2 (0.3) [0.3]	2 (0.1) [0.1]
Osteoarthritis	2 (0.3) [0.3]	2 (0.1) [0.1]

The SAEs with the highest rate with long-term risankizumab exposure were COVID-19 and pneumonia (Phase 3 PsA Long-term Analysis Set, both 0.4 E/100 PY). A total of 6 events of serious infections of pneumonia (4 events of pneumonia, 1 of COVID-19 pneumonia, and 1 event of pneumonia viral) were reported. Three cases of pneumonia were related to COVID-19 in subjects with risk factors such as obesity and diabetes. The other 3 cases of pneumonia had significant risk factors including medical history and/or concomitant medications, including one case with advanced age, pre-existing dementia, and delayed gastric emptying, another case with obesity and smoking history on concomitant steroid therapy, and the third case in an overweight subject on concomitant steroid and methotrexate (MTX) therapy.The cumulative incidence plot for treatment-emergent SAEs in the Phase 3 PsA Long-term Analysis Set.

Figure 19: Cumulative Incidence Plot of Treatment-Emergent Serious Adverse Events (Phase 3 PsA Long-Term Analysis Set)



Other Significant Adverse Events

Severe TEAEs

- Phase 3 PsA PBO-Controlled Analysis Set

The percentage of subjects with severe TEAEs in the risankizumab group (2.3%) was comparable to thepercentage in the placebo group (2.4%). No severe AE was reported in more than 2 subjects in either group with the exception of psoriatic arthropathy (3 subjects in the placebo group) and anaemia (2 subjects in the placebo group).

- Phase 3 PsA Long-term Analysis Set

The rate of severe TEAEs (4.5 E/100 PY) was less in subjects with long-term risankizumab exposure compared to rates in the risankizumab 150 mg group of the Phase 3 PsA PBO-Controlled Analysis Set (7.0 E/100 PY). There were no trends with regards to the nature of severe AEs reported.

Common Adverse Events

Across all psoriatic arthritis analysis sets, TEAEs were most commonly reported in the infections and infestations SOC which were reported at comparable frequency between the risankizumab and placebo group. The overall pattern of most common TEAEs reported in subjects receiving risankizumab was also similar across all analysis sets.

Most frequent TEAEs by SOC

Phase 3 PsA PBO-Controlled Analysis Set

Table 60: Number and Percentage of Subjects with Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term (Phase 3 PsA Placebo-Controlled Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Placebo (N = 700) n (%) [SSA %]	Risankizumab 150 mg (N = 707) n (%) [SSA %]
Infections and infestations	135 (19.3) [19.3]	134 (19.0) [18.9]
Abscess	0	1 (0.1) [0.1]
Abscess limb	1 (0.1) [0.1]	0
Acarodermatitis	0	1 (0.1) [0.1]
Acute sinusitis	0	1 (0.1) [0.1]
Anal abscess	0	1 (0.1) [0.1]
Appendicitis perforated	1 (0.1) [0.1]	0
Asymptomatic COVID-19	0	1 (0.1) [0.1]
Bronchiolitis	1 (0.1) [0.1]	0
Bronchitis	8 (1.1) [1.1]	6 (0.8) [0.8]
Bronchitis bacterial	0	1 (0.1) [0.1]
Burn infection	1 (0.1) [0.1]	0
COVID-19	2 (0.3) [0.3]	1 (0.1) [0.1]
Cellulitis	3 (0.4) [0.4]	3 (0.4) [0.4]
Complicated appendicitis	1 (0.1) [0.1]	0
Conjunctivitis	3 (0.4) [0.4]	1 (0.1) [0.1]

Note: Treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of study drug until the end of the placebo controlled period (defined as the minimum of the last dose date prior to Week 24 + 140 days and the Week 24 dose date (looking at AEs that occur prior to that dose).
SSA = Study size adjusted.

Table 61: TEAEs Reported in ≥ 1% of Subjects in the Risankizumab 150 mg Group by Decreasing Frequency in the Risankizumab 150 mg Group (Phase 3 PsA PBO-Controlled Analysis Set)

MedDRA 23.1 Preferred Term	Placebo (N = 700) n (%) [SSA%]	Risankizumab 150 mg (N = 707) n (%) [SSA%]
Upper respiratory tract infection	32 (4.6) [4.6]	29 (4.1) [4.1]
Nasopharyngitis	23 (3.3) [3.3]	25 (3.5) [3.5]
Hypertension	15 (2.1) [2.1]	19 (2.7) [2.7]
Alanine aminotransferase increased	12 (1.7) [1.7]	16 (2.3) [2.3]
Arthralgia	15 (2.1) [2.1]	15 (2.1) [2.1]
Headache	16 (2.3) [2.3]	15 (2.1) [2.1]
Psoriatic arthropathy	17 (2.4) [2.4]	15 (2.1) [2.1]
Aspartate aminotransferase increased	9 (1.3) [1.3]	13 (1.8) [1.8]
Nausea	9 (1.3) [1.3]	9 (1.3) [1.3]
Abdominal pain upper	1 (0.1) [0.1]	8 (1.1) [1.1]
Gamma-glutamyltransferase increased	5 (0.7) [0.7]	8 (1.1) [1.1]
Diabetes mellitus	7 (1.0) [1.0]	7 (1.0) [1.0]
Diarrhoea	11 (1.6) [1.6]	7 (1.0) [1.0]
Dizziness	4 (0.6) [0.6]	7 (1.0) [1.0]
Gastroenteritis	7 (1.0) [1.0]	7 (1.0) [1.0]

The most frequent TEAEs by SOC (≥ 10% of subjects) in the risankizumab group were infections and infestations (19.0%), which had a similar frequency (19.3%) in the placebo group.

Treatment-emergent adverse events that occurred in ≥ 1% of subjects by PT in the risankizumab group Phase 3 PsA PBO-Controlled Analysis Set are presented. The most frequently reported TEAEs (≥ 3% of subjects) were upper respiratory tract infection (4.1%) and nasopharyngitis (3.5%) in the risankizumab group. There were no TEAE PTs that occurred in ≥ 5% of subjects in any treatment group.

Phase 3 PsA Long-term Analysis Set

The overall pattern of most common TEAEs by PT and by SOC reported with long-term treatment with risankizumab 150 mg was consistent with that observed in the Phase 3 PsA PBO-Controlled Analysis Set.

Phase 3 PsA Long-term Analysis Set

The most common TEAEs (≥ 3%) reported with long-term risankizumab exposure in the any risankizumab 150 mg group were upper respiratory tract infection (4.3%) and nasopharyngitis (4.0%)

The overall pattern of most common TEAEs by PT and by SOC reported with long-term treatment with risankizumab 150 mg was consistent with that observed in the Phase 3 PsA PBO-Controlled Analysis Set.

Table 62: Number and Percentage of Subjects with Treatment-Emergent Adverse Events in Descending Order of Frequency of Preferred Term (Phase 3 PsA Long-Term Analysis Set)

MedDRA 23.1 Preferred Term	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) n (%) [SSA %]	Any Risankizumab 150 mg (N = 1365) n (%) [SSA %]
Upper respiratory tract infection	49 (6.9) [6.9]	59 (4.3) [4.3]
Nasopharyngitis	37 (5.2) [5.2]	55 (4.0) [4.0]
Hypertension	32 (4.5) [4.5]	39 (2.9) [2.9]
Psoriatic arthropathy	30 (4.2) [4.2]	37 (2.7) [2.7]
COVID-19	15 (2.1) [2.1]	32 (2.3) [2.3]
Alanine aminotransferase increased	20 (2.8) [2.8]	28 (2.1) [2.1]
Diarrhoea	19 (2.7) [2.7]	28 (2.1) [2.1]
Arthralgia	19 (2.7) [2.7]	24 (1.8) [1.8]
Headache	22 (3.1) [3.1]	24 (1.8) [1.8]
Aspartate aminotransferase increased	15 (2.1) [2.1]	21 (1.5) [1.5]
Nausea	14 (2.0) [2.0]	21 (1.5) [1.5]
Back pain	12 (1.7) [1.7]	20 (1.5) [1.5]
Urinary tract infection	11 (1.6) [1.6]	17 (1.2) [1.2]
Gamma-glutamyltransferase increased	9 (1.3) [1.3]	15 (1.1) [1.1]
Diabetes mellitus	11 (1.6) [1.6]	14 (1.0) [1.0]
Fall	11 (1.6) [1.6]	14 (1.0) [1.0]

Note: Treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of Risankizumab to the last dose date prior to cut-off date for database lock + 140 days or the cut-off date for database lock, whichever occurs first.
Events are presented by decreasing frequency of preferred terms in any risankizumab 150 mg treatment.
SSA = Study size adjusted.

Treatment-related adverse events are those considered related (possibly related) to the study drug.

The events most commonly considered by the investigators as having a reasonable possible relationship to study drug were generally comparable between the placebo and risankizumab groups The TEAEs that were most frequently assessed by the investigators as having a possible relationship to study drug in the risankizumab group (≥ 1% subjects) were upper respiratory tract infection (1.7%), alanine aminotransferase (ALT) increased (1.4%), and aspartate aminotransferase (AST) increased (1.0%). In the placebo group the TEAEs considered by the investigator to have a reasonable possibility of being related to study drug that were reported in ≥ 1% subjects were upper respiratory tract infection (1.7%), headache (1.0%), and ALT increased (1.0%).

Table 63: Number and Percentage of Subjects with Treatment-Emergent Adverse Events with Reasonable Possibility of Being Related to Study Drug by Primary MedDRA System Organ Class and Preferred Term (Phase 3 PsA Placebo-Controlled Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Placebo (N = 700) n (%) [SSA %]	Risankizumab 150 mg (N = 707) n (%) [SSA %]
Infections and infestations (Cont.)		
Postoperative abscess	1 (0.1) [0.1]	0
Respiratory tract infection	1 (0.1) [0.1]	1 (0.1) [0.1]
Rhinitis	1 (0.1) [0.1]	0
Sinusitis	1 (0.1) [0.1]	2 (0.3) [0.3]
Subcutaneous abscess	1 (0.1) [0.1]	0
Tonsillitis	0	2 (0.3) [0.3]
Tooth abscess	0	2 (0.3) [0.3]
Tracheobronchitis	1 (0.1) [0.1]	0
Upper respiratory tract infection	12 (1.7) [1.7]	12 (1.7) [1.7]
Upper respiratory tract infection bacterial	0	1 (0.1) [0.1]
Urinary tract infection	5 (0.7) [0.7]	2 (0.3) [0.3]
Viral infection	0	1 (0.1) [0.1]
Investigations	10 (1.4) [1.4]	18 (2.5) [2.6]
Alanine aminotransferase increased	7 (1.0) [1.0]	10 (1.4) [1.4]
Aspartate aminotransferase increased	4 (0.6) [0.6]	7 (1.0) [1.0]
Blood alkaline phosphatase increased	1 (0.1) [0.1]	0

Note: Treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of study drug until the end of the placebo controlled period (defined as the minimum of the last dose date prior to Week 24 + 140 days and the Week 24 dose date (looking at AEs that occur prior to that dose).
SSA = Study size adjusted.

Phase 3 PsA Long-term Analysis Set

The most common TEAEs considered by the investigator to have a reasonable possibility of being related to study drug (≥ 1% subjects) in subjects with long-term risankizumab exposure were overall consistent those in the Phase 3 PsA PBO-Controlled Analysis Set.

The TEAEs that were most frequently assessed by the investigators as having a possible relationship to study drug in the risankizumab group were upper respiratory tract infection (1.6%), alanine aminotransferase (ALT) increased (1.4%), and aspartate aminotransferase (AST) increased (1.0%)

Table 64: Number and Percentage of Subjects with Treatment-Emergent Adverse Events with Reasonable Possibility of Being Related to Study by Primary MedDRA System Organ Class and Preferred Term (Phase 3 PsA Long-Term Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) (PYs = 696.1) Events (E/100 PYs) [SSA E/100 PYs]	Any Risankizumab 150 mg (N = 1365) (PYs = 1047.9) Events (E/100 PYs) [SSA E/100 PYs]
Infections and infestations (Cont.)		
Otitis media	1 (0.1) [0.1]	1 (<0.1) [<0.1]
Paronychia	1 (0.1) [0.1]	1 (<0.1) [<0.1]
Periodontitis	1 (0.1) [0.1]	1 (<0.1) [<0.1]
Pharyngitis	2 (0.3) [0.3]	3 (0.3) [0.3]
Pneumonia	1 (0.1) [0.1]	1 (<0.1) [<0.1]
Pneumonia viral	1 (0.1) [0.1]	1 (<0.1) [<0.1]
Respiratory tract infection	1 (0.1) [0.1]	1 (<0.1) [<0.1]
Sinusitis	4 (0.6) [0.6]	5 (0.5) [0.5]
Suspected COVID-19	0	1 (<0.1) [<0.1]
Tinea pedis	1 (0.1) [0.1]	1 (<0.1) [<0.1]
Tonsillitis	4 (0.6) [0.6]	5 (0.5) [0.5]
Tooth abscess	3 (0.4) [0.4]	3 (0.3) [0.3]
Tooth infection	1 (0.1) [0.1]	1 (<0.1) [<0.1]
Upper respiratory tract infection	16 (2.3) [2.3]	17 (1.6) [1.6]
Upper respiratory tract infection bacterial	1 (0.1) [0.1]	1 (<0.1) [<0.1]
Urethritis	0	1 (<0.1) [<0.1]
Urinary tract infection	5 (0.7) [0.7]	5 (0.5) [0.5]
Vestibular neuronitis	2 (0.3) [0.3]	2 (0.2) [0.2]
Investigations	28 (4.0) [4.0]	44 (3.2) [3.2]
Alanine aminotransferase increased	13 (1.8) [1.8]	19 (1.4) [1.4]
Aspartate aminotransferase increased	9 (1.3) [1.3]	13 (1.0) [1.0]
Blood alkaline phosphatase increased	2 (0.3) [0.3]	3 (0.2) [0.2]

Table 65: Number and Percentage of Subjects with Treatment-Emergent Adverse Events with Reasonable Possibility of Being Related to Study Drug by Primary MedDRA System Organ Class and Preferred Term (Phase 3 PsA Placebo-Controlled Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Placebo (N = 700) n (%) [SSA %]	Risankizumab 150 mg (N = 707) n (%) [SSA %]
Infections and infestations (Cont.)		
Postoperative abscess	1 (0.1) [0.1]	0
Respiratory tract infection	1 (0.1) [0.1]	1 (0.1) [0.1]
Rhinitis	1 (0.1) [0.1]	0
Sinusitis	1 (0.1) [0.1]	2 (0.3) [0.3]
Subcutaneous abscess	1 (0.1) [0.1]	0
Tonsillitis	0	2 (0.3) [0.3]
Tooth abscess	0	2 (0.3) [0.3]
Tracheobronchitis	1 (0.1) [0.1]	0
Upper respiratory tract infection	12 (1.7) [1.7]	12 (1.7) [1.7]
Upper respiratory tract infection bacterial	0	1 (0.1) [0.1]
Urinary tract infection	5 (0.7) [0.7]	2 (0.3) [0.3]
Viral infection	0	1 (0.1) [0.1]
Investigations	10 (1.4) [1.4]	18 (2.5) [2.6]
Alanine aminotransferase increased	7 (1.0) [1.0]	10 (1.4) [1.4]
Aspartate aminotransferase increased	4 (0.6) [0.6]	7 (1.0) [1.0]
Blood alkaline phosphatase increased	1 (0.1) [0.1]	0

Adverse events of special interest (ASIs)

In addition to analysis of all treatment-emergent AEs (TEAEs), some categories of AEs were considered to be ASIs and were identified using standard MedDRA queries (SMQ) and company MedDRA queries (CMQ). The interest in these AEs is driven by their prevalence in the active psoriatic arthritis population, customary concerns with injected immunoglobulin products, the immunomodulatory activity of risankizumab, or regulatory interest.

Infections (including serious infections, active TB, opportunistic infections [excluding TB and herpes zoster], and herpes zoster); malignant tumours (excluding NMSC);

NMSC; hepatic disorder (including a comprehensive evaluation of hepatic events and hepatic laboratory data); major adverse cardiovascular event (MACE) and extended MACE; hypersensitivity reactions (including serious hypersensitivity reactions) and adjudicated anaphylactic reactions.

Table 66: Overview of Treatment-Emergent Adverse Events in Areas of Safety Interest EAER Per 100 PY (Phase 3 PsA PBO-Controlled Analysis Set) and Comparison with Long-term Risankizumab Treatment (Phase 3 PsA Long-term Analysis Set)

	Phase 3 PsA PBO-Controlled Analysis Set					Phase 3 PsA Long-term Analysis Set
	Placebo (N = 700) (PY = 325.1)		Risankizumab 150 mg (N = 707) (PY = 328.5)		Treatment Comparison (95% CI)[a]-- Risankizumab 150 mg - Placebo	Any Risankizumab 150 mg (N = 1365) (PY = 1047.9)
	n (%) [SSA%]	Events (E/100 PY) [SSA E/100 PY]	n (%) [SSA%]	Events (E/100 PY) [SSA E/100 PY]	n (%) Rate Difference [95% CI]	Events (E/100 PY) [SSA E/100 PY]
Any adjudicated MACE	0	0	1 (0.1) [0.1]	1 (0.3) [0.3]	0.1 (–0.1, 0.4)	3 (0.3) [0.3]
Any adjudicated extended MACE	1 (0.1) [0.1]	1 (0.3) [0.3]	1 (0.1) [0.1]	1 (0.3) [0.3]	–0.0 (–0.4, 0.4)	3 (0.3) [0.3]
Any serious infections	11 (1.6) [1.6]	13 (4.0) [4.0]	7 (1.0) [1.0]	9 (2.7) [2.7]	–0.6 (–1.8, 0.6)	27 (2.6) [2.6]
Any active tuberculosis	0	0	0	0	0.0	0
Any opportunistic infection excluding tuberculosis and herpes zoster	0	0	0	0	0.0	1 (< 0.1) [< 0.1]
Any herpes zoster	2 (0.3) [0.3]	2 (0.6) [0.6]	2 (0.3) [0.3]	2 (0.6) [0.6]	–0.0 (–0.6, 0.6)	4 (0.4) [0.4]
Any malignant tumours	3 (0.4) [0.4]	5 (1.5) [1.5]	1 (0.1) [0.1]	1 (0.3) [0.3]	–0.3 (–0.8, 0.3)	8 (0.8) [0.8]

Table 67: Overview of Treatment-Emergent Adverse Events in Areas of Safety Interest EAER Per 100 PY (Phase 3 PsA PBO-Controlled Analysis Set) and Comparison with Long-term Risankizumab Treatment (Phase 3 PsA Long-term Analysis Set) (Continued)

	Phase 3 PsA PBO-Controlled Analysis Set					Phase 3 PsA Long-term Analysis Set
	Placebo (N = 700) (PY = 325.1)		Risankizumab 150 mg (N = 707) (PY = 328.5)		Treatment Comparison (95% CI)[a]-- Risankizumab 150 mg - Placebo	Any Risankizumab 150 mg (N = 1365) (PY = 1047.9)
	n (%) [SSA%]	Events (E/100 PY) [SSA E/100 PY]	n (%) [SSA%]	Events (E/100 PY) [SSA E/100 PY]	n (%) Rate Difference [95% CI]	Events (E/100 PY) [SSA E/100 PY]
Any non-melanoma skin cancer (NMSC)	1 (0.1) [0.1]	3 (0.9) [0.9]	1 (0.1) [0.1]	1 (0.3) [0.3]	−0.0 (−0.4, 0.4)	6 (0.6) [0.6]
Any malignant tumours excluding NMSC	2 (0.3) [0.3]	2 (0.6) [0.6]	0	0	−0.3 (−0.7, 0.1)	2 (0.2) [0.2]
Any hypersensitivity	9 (1.3) [1.3]	10 (3.1) [3.1]	16 (2.3) [2.3]	18 (5.5) [5.5]	1.0 (−0.4, 2.3)	44 (4.2) [4.2]
Any serious hypersensitivity	0	0	0	0	0.0	0
Any adjudicated anaphylactic reactions	0	0	0	0	0.0	0
Any hepatic events	27 (3.9) [3.9]	41 (12.6) [12.6]	38 (5.4) [5.4]	55 (16.7) [16.8]	1.5 (−0.7, 3.7)	129 (12.3) [12.3]

a. Study size adjusted risk difference between treatment groups.

Note: MACE is defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.
Extended MACE is defined as CV death, non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for unstable angina, and coronary revascularization procedures.

Table 68: Overview of Number and Percentage of Subjects with Treatment Emergent Areas of Safety Interest (Phase 3 PsA Long-Term Analysis Set)

	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) n (%) [SSA %]	Any Risankizumab 150 mg (N = 1365) n (%) [SSA %]
Subjects with:		
Any adjudicated MACE	3 (0.4) [0.4]	3 (0.2) [0.2]
Any adjudicated extended MACE	3 (0.4) [0.4]	3 (0.2) [0.2]
Any serious infections	13 (1.8) [1.8]	22 (1.6) [1.6]
Any active tuberculosis	0	0
Any opportunistic infection excluding tuberculosis and herpes zoster	1 (0.1) [0.1]	1 (<0.1) [<0.1]
Any herpes zoster	3 (0.4) [0.4]	4 (0.3) [0.3]
Any malignant tumours	3 (0.4) [0.4]	7 (0.5) [0.5]
Any non-melanoma skin cancer (NMSC)	2 (0.3) [0.3]	5 (0.4) [0.4]
Any malignant tumours excluding NMSC	1 (0.1) [0.1]	2 (0.1) [0.1]

Table 69: Overview of Number and Percentage of Subjects with Treatment-Emergent Areas of Safety Interest (Phase 3 PsA Long-Term Analysis Set)

	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) n (%) [SSA %]	Any Risankizumab 150 mg (N = 1365) n (%) [SSA %]
Any hypersensitivity	27 (3.8) [3.8]	36 (2.6) [2.6]
Any serious hypersensitivity	0	0
Any adjudicated anaphylactic reactions	0	0
Any hepatic events	61 (8.6) [8.6]	86 (6.3) [6.3]

Note: Treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of Risankizumab to the last dose date prior to cut-off date for database lock + 140 days or the cut-off date for database lock, whichever occurs first.
MACE is defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.
Extended MACE is defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, and coronary revascularization procedures.
SSA = Study size adjusted.

Hepatic Events:

The MAH has performed a comprehensive review of hepatic events and laboratory data in the psoriatic arthritis analysis sets, Phase 3 PsA PBO-Controlled Analysis Set and Phase 3 PsA Long Term Analysis Set**,** All Risankizumab PsO Analysis Set**,** and Crohn's disease Phase 2 study (intravenous [IV] doses up to 600 mg)

For analysis of hepatic TEAEs, the MAH identified all hepatic events using the search criteria "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions" SMQ, "hepatitis, non-infectious"

SMQ, "cholestasis and jaundice of hepatic origin" SMQ, "liver related investigations, signs and symptoms" SMQ, and "liver-related coagulation and bleeding disturbances" SMQ.

Additionally, liver test data were analyzed to ensure a comprehensive assessment of liver disorder. This analysis of lab data included outlier analyses (biochemical Hy's law cases) and cases meeting the threshold of potentially clinically important [PCI] liver test elevations [≥ Grade 3 Common Terminology Criteria for Adverse Events (CTCAE) v4.03, hereafter referred to as Grade 3] of AST, ALT and bilirubin) as well as mean changes from baseline between treatment groups and within the risankizumab group over time. In this system, the following levels are used to assess severity, with the values expressed as multiples of the upper limit of the normal range (ULN).

The MAH outlines that although both ALT and AST were analyzed, as noted in the CIOMS drug induced liver injury (DILI) guidance, ALT is more specific for DILI than AST as AST can be derived from more sources than liver and is influenced by demographic factors including gender and ethnicity.

Liver test abnormalities (defined as transaminase levels ≥ 1.5 × upper limit of normal [ULN]) are relatively common (prevalence of 32%) in a longitudinal cohort study in Canada of patients with psoriatic arthritis with an incidence rate of 3.9 E/100 PY (Pakchotanon 2020). The most common risk factor associated with the liver test abnormalities was non-alcoholic fatty liver disease (NAFLD), which is known to be present at a higher rate in patients with psoriatic arthritis compared to the general population. Liver test abnormalities also can be associated with medications used to treat psoriatic arthritis such as MTX or leflunomide.

In the Phase 3 PsA Placebo-Controlled Analysis Set, 16.5% of total subjects reported a medical history of a hepatobiliary disorder at study entry. Methotrexate was the most commonly prescribed csDMARD in the risankizumab pivotal psoriatic arthritis studies (approximately 60% of subjects prescribed MTX at baseline. Hepatotoxicity is a well acknowledged AE with MTX therapy and periodic monitoring of liver enzymes is recommended in product labeling. In addition to increases in transaminases, a variety of other hepatic pathologies such as fatty changes, periportal fibrosis, cirrhosis, liver atrophy and necrosis have been reported with MTX therapy. Furthermore, some studies have suggested an increased incidence of hepatotoxicity with MTX therapy in patients with psoriatic arthritis compared to RA, provoking the question if patients with psoriatic arthritis are inherently at a higher risk of hepatotoxicity (Tilling 2006).

In the risankizumab Phase 3 studies, the inclusion criteria for transaminases were AST and ALT < 2 × ULN and total bilirubin ≤ 2.0 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome, at screening. Criteria for study drug discontinuation included ALT or AST > 8 × ULN; ALT or AST > 5 × ULN for more than 2 weeks; ALT or AST > 3 × ULN and (Total Bilirubin > 2 × ULN or international normalized ratio [INR] > 1.5); ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

An overview of hepatic events, hepatic laboratory data and Evaluation of drug-induced serious hepatotoxicity (eDISH) plots from the psoriatic arthritis clinical program are presented.

Hepatic events

Phase 3 PsA PBO-Controlled Analysis Set

In the Phase 3 PsA PBO-Controlled Analysis Set, the percentage of subjects with investigator reported hepatic TEAEs was slightly higher in the risankizumab 150 mg group (5.4%) compared to the placebo group (3.9%) The most common hepatic TEAEs were ALT, AST, and GGT increases in both groups. The rate in the Phase 3 PsA PBO-Controlled Analysis Set was (16.7 E/100 PY) as outlined in the below overview.

Table 70: Overview of Treatment-Emergent Areas of Safety Interest in Exposure-Adjusted Event Rate per 100 Patient Years (Phase 3 PsA Placebo-Controlled Analysis Set)

	Placebo (N = 700) (PYs = 325.1) Events (E/100 PYs) [SSA E/100 PYs]	Risankizumab 150 mg (N = 707) (PYs = 328.5) Events (E/100 PYs) [SSA E/100 PYs]	--Treatment Comparison (95% CI) [A]-- Risankizumab 150 mg - Placebo
Any adjudicated MACE	0	1 (0.3) [0.3]	0.3 (-0.3, 0.9)
Any adjudicated extended MACE	1 (0.3) [0.3]	1 (0.3) [0.3]	-0.0 (-0.8, 0.8)
Any serious infections	13 (4.0) [4.0]	9 (2.7) [2.7]	-1.3 (-4.1, 1.6)
Any active tuberculosis	0	0	0.0
Any opportunistic infection excluding tuberculosis and herpes zoster	0	0	0.0
Any herpes zoster	2 (0.6) [0.6]	2 (0.6) [0.6]	-0.0 (-1.2, 1.2)
Any malignant tumours	5 (1.5) [1.5]	1 (0.3) [0.3]	-1.2 (-2.7, 0.2)
Any non-melanoma skin cancer (NMSC)	3 (0.9) [0.9]	1 (0.3) [0.3]	-0.6 (-1.8, 0.6)
Any malignant tumours excluding NMSC	2 (0.6) [0.6]	0	-0.6 (-1.5, 0.2)
Any hypersensitivity	10 (3.1) [3.1]	18 (5.5) [5.5]	2.4 (-0.8, 5.6)
Any serious hypersensitivity	0	0	0.0
Any adjudicated anaphylactic reactions	0	0	0.0
Any hepatic events	41 (12.6) [12.6]	55 (16.7) [16.8]	4.2 (-1.7, 10.0)

Note: Treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of study drug until the end of the placebo controlled period (defined as the minimum of the last dose date prior to Week 24 + 140 days and the Week 24 dose date (looking at AEs that occur prior to that dose)).
MACE is defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.
Extended MACE is defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, and coronary revascularization procedures.
E/100 PYs = Events per 100 patient-years. SSA = Study size adjusted.
[A]: Study size adjusted risk difference between treatment groups.

Hepatic events with accompanying Grade $\geq$ 3 elevations in AST, ALT or bilirubin, regardless of seriousness or severity will be discussed in a later section.

Table 71: Number and Percentage of Subjects with Hepatic TEAEs (Phase 3 PsA PBO-Controlled Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Placebo (N = 700) n (%) [SSA%]	Risankizumab 150 mg (N = 707) n (%) [SSA%]
Any hepatic adverse event	27 (3.9) [3.9]	38 (5.4) [5.4]
Chronic hepatitis	1 (0.1) [0.1]	0
Hepatic function abnormal	1 (0.1) [0.1]	0
Hepatic steatosis	2 (0.3) [0.3]	3 (0.4) [0.4]
Hyperbilirubinaemia	0	1 (0.1) [0.1]
Liver injury	0	2 (0.3) [0.3]
Steatohepatitis	0	1 (0.1) [0.1]
Alanine aminotransferase increased	12 (1.7) [1.7]	16 (2.3) [2.3]
Aspartate aminotransferase increased	9 (1.3) [1.3]	13 (1.8) [1.8]
Blood alkaline phosphatase increased	1 (0.1) [0.1]	1 (0.1) [0.1]
Gamma-glutamyltransferase abnormal	1 (0.1) [0.1]	0
Gamma-glutamyltransferase increased	5 (0.7) [0.7]	8 (1.1) [1.1]
Hepatic enzyme increased	2 (0.3) [0.3]	4 (0.6) [0.6]
Liver function test increased	3 (0.4) [0.4]	1 (0.1) [0.1]
Transaminases increased	3 (0.4) [0.4]	4 (0.6) [0.6]

In the Phase 3 PsA PBO-Controlled Analysis Set, there were no serious hepatic events reported. Two severe hepatic events reported. The 2 reported cases of liver injury were reports of elevated hepatic transaminases of Grade 1 and Grade 2, respectively. Aminotransferase elevations for both subjects were transient, returning to baseline while on continued risankizumab therapy. There were 3 Hepatic disorder leading to discontinuation of study drug.

Phase 3 PsA Long-term Analysis Set

On the basis of the currently available data, the rate of hepatic events with long-term risankizumab exposure is (12.3 E/100 PY) in the any risankizumab 150 mg group compared to the rate in the Phase 3 PsA PBO-Controlled Analysis Set (16.7 E/100 PY).

The rate of hepatic events with long-term risankizumab exposure was (12.3 E/100 PY) in the any risankizumab group but 12.9/100PY in the no cross over from placebo group.

Table 72: Treatment-Emergent Hepatic Events in Exposure-Adjusted Event Rate Per 100 Patient Years Preferred Term (Phase 3 PsA Long-Term Analysis Set) in ≥ 1 E/100PY in Any Risankizumab 150 mg Group

System Organ Class MedDRA 23.1 Preferred Term	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) (PY = 696.1) Events (E/100 PY) [SSA E/100 PY]	Any Risankizumab 150 mg (N = 1365) (PY = 1047.9) Events (E/100 PY) [SSA E/100 PY]
Any hepatic adverse event	90 (12.9) [12.9]	129 (12.3) [12.3]
Hepatic steatosis	11 (1.6) [1.6]	15 (1.4) [1.4]
Alanine aminotransferase increased	24 (3.4) [3.4]	33 (3.1) [3.1]
Aspartate aminotransferase increased	17 (2.4) [2.4]	23 (2.2) [2.2]
Gamma-glutamyltransferase increased	10 (1.4) [1.4]	19 (1.8) [1.8]
Hepatic enzyme increased	8 (1.1) [1.1]	12 (1.1) [1.1]
Transaminases increased	6 (0.9) [0.9]	10 (1.0) [1.0]

There were no reports meeting biochemical Hy's law and no deaths or acute liver failure attributed to risankizumab. Small numbers of cases of hepatocellular injury were identified, the MAH outlines that most were attributed to alternative causes like concomitant medications.

The most common hepatic TEAEs were related to elevated liver aminotransferase levels. All hepatic TEAEs observed with risankizumab treatment were non serious, and the majority were mild to moderate in severity.

The most common hepatic TEAEs in the any risankizumab 150 mg group with rates of ≥ 1 E/100PY were ALT, AST and GGT increase, hepatic steatosis, hepatic enzyme increased, and transaminases increased

Hepatic events with accompanying ≥ Grade 3 elevations in AST, ALT or bilirubin, regardless of seriousness or severity are summarized

For cases with Grade 3 aminotransferase elevations without readily identifiable alternative etiologies, the MAH outlines that time to onset was typically > 6 months and most aminotransferase abnormalities resolved without discontinuation of risankizumab.

Hepatic steatosis was a frequently reported PT in risankizumab treated subjects. In the risankizumab Phase 3 psoriatic arthritis study population, the mean BMI was 30.8 kg/m^2 and a baseline medical history of hepatic steatosis 3.8% in the any risankizumab 150 mg group. Events of hepatic steatosis are not unexpected in the psoriatic arthritis population with high BMIs. Worldwide, NAFLD has a reported prevalence of 6% to 35% (median 20%) and is more common in the obese population (Sheth 2021). The MAH outlines that the closer follow-up in the setting of a clinical trial would result in enhanced detection of liver transaminase elevations and eventual diagnosis of NAFLD/hepatic steatosis.

Table 73 : Treatment-Emergent Severe Hepatic Events in Exposure-Adjusted Event Rate Per 100 Patient Years Preferred Term (Phase 3 PsA Long-Term Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) (PY = 696.1) Events (E/100 PY) [SSA E/100 PY]	Any Risankizumab 150 mg (N = 1365) (PY = 1047.9) Events (E/100 PY) [SSA E/100 PY]
Any hepatic adverse event	4 (0.6) [0.6]	5 (0.5) [0.5]
Hepatic steatosis	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Alanine aminotransferase increased	1 (0.1) [0.1]	2 (0.2) [0.2]
Aspartate aminotransferase increased	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Gamma-glutamyltransferase increased	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]

The rate of severe hepatic disorder events was low in the Phase 3 PsA Long-term Analysis Set with a rate of 0.5 E/100 PY in the any risankizumab 150 mg group and these hepatic events lead to discontinuation in the any risankizumab 150 mg group (0.5 E/100 PY).

The 5 severe hepatic events occurred in 3 subjects.

All Risankizumab PsA Analysis Set

All Risankizumab PsA Analysis Set, per 100 PY, treatment emergent hepatic events was 13.1/100 years.

ALT increase event rate was 3.7/100 years and AST event rate 2.9/100y, the MAH has highlighted in the submission ALT is more specific for DILI than AST.

One subject in the All Risankizumab PsA Analysis Set had ALT, AST, alkaline phosphatase (ALP), and Bilirubin elevations on Day 183 of study that met biochemical Hy's law. However, at the time of the elevation, the subject was confirmed to be Hepatitis E IgM positive and the liver biopsy revealed histological aspect in favor of alcohol induced steatohepatitis. Therefore, this case did not meet the criteria for biochemical Hy's law. There were 8 additional subjects within this data set who experienced a Grade 3 elevation in aminotransferases. These reports are discussed in the discussion section below.

Table 74: Treatment-Emergent Hepatic Events in Exposure-Adjusted Event Rate per 100 Patient Years by Primary MedDRA System Organ Class and Preferred Term (All Risankizumab PsA Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	All Risankizumab (N = 1542) (PYs = 1259.7) Events (E/100 PYs) [SSA E/100 PYs]
Any adverse event	165 (13.1) [13.1]
Hepatobiliary disorders	22 (1.7) [1.7]
Hepatic function abnormal	1 (<0.1) [<0.1]
Hepatic steatosis	15 (1.2) [1.2]
Hepatotoxicity	1 (<0.1) [<0.1]
Hyperbilirubinaemia	1 (<0.1) [<0.1]
Liver injury	2 (0.2) [0.2]
Steatohepatitis	2 (0.2) [0.2]
Investigations	143 (11.4) [11.4]
Alanine aminotransferase increased	47 (3.7) [3.7]
Aspartate aminotransferase increased	36 (2.9) [2.9]
Blood alkaline phosphatase increased	5 (0.4) [0.4]
Blood bilirubin increased	3 (0.2) [0.2]
Gamma-glutamyltransferase increased	23 (1.8) [1.8]
Hepatic enzyme increased	13 (1.0) [1.0]
Liver function test abnormal	1 (<0.1) [<0.1]
Liver function test increased	4 (0.3) [0.3]
Transaminases increased	11 (0.9) [0.9]

Serious and Severe Hepatic events:

In the All Risankizumab PsA Analysis Set there were 3 serious hepatic events reported. There were 9 severe hepatic events reported and 8 of these were related to ALT, AST, TBL and GGT increases.

Discontinuation

There were 6 treatment emergent hepatic events leading to discontinuation.

Table 75: Treatment-Emergent Hepatic Events Leading to Discontinuation of Study Drug in Exposure-Adjusted Event Rate per 100 Patient Years by Primary MedDRA System Organ Class and Preferred Term (All Risankizumab PsA Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	All Risankizumab (N = 1542) (PYs = 1259.7) Events (E/100 PYs) [SSA E/100 PYs]
Any adverse event	6 (0.5) [0.5]
Hepatobiliary disorders	1 (<0.1) [<0.1]
Hepatic steatosis	1 (<0.1) [<0.1]
Investigations	5 (0.4) [0.4]
Alanine aminotransferase increased	1 (<0.1) [<0.1]
Aspartate aminotransferase increased	1 (<0.1) [<0.1]
Gamma-glutamyltransferase increased	1 (<0.1) [<0.1]
Hepatic enzyme increased	2 (0.2) [0.2]

Table 76: Treatment-Emergent Hepatic Events Leading to Discontinuation of Study Drug in Exposure-Adjusted Event Rate per 100 Patients Years by Primary MedDRA System Organ Class and Preferred Term (All Risankizumab PsA Analysis Set)All Risankizumab PsO Analysis Set

System Organ Class MedDRA 23.1 Preferred Term	All Risankizumab (N = 1542) (PYs = 1259.7) Events (E/100 PYs) [SSA E/100 PYs]
Any adverse event	6 (0.5) [0.5]
Hepatobiliary disorders	1 (<0.1) [<0.1]
Hepatic steatosis	1 (<0.1) [<0.1]
Investigations	5 (0.4) [0.4]
Alanine aminotransferase increased	1 (<0.1) [<0.1]
Aspartate aminotransferase increased	1 (<0.1) [<0.1]
Gamma-glutamyltransferase increased	1 (<0.1) [<0.1]
Hepatic enzyme increased	2 (0.2) [0.2]

The All Risankizumab PsO Analysis Set is a supportive analysis set which includes all subjects who received risankizumab from the psoriasis studies included in original psoriasis Marketing Authorization Application submission (9 studies) and 8 additional completed psoriasis studies, including Studies M15-999 (150 mg new formulation/PFS) and M16-005 150 mg new formulation/auto injector) through a data cutoff of 20 October 2020.

Nine serious hepatic events have been reported overall of which 2 were discussed in the initial submission (PTs of liver injury and drug-induced liver injury), both of which were attributed to INH. 7 serious events have been reported since the original submission for the Psoriasis indication. A total of 5 subjects in the All Risankizumab PsO Analysis Set met the criteria for biochemical Hy's law case, all of these were identified since the initial submission.

Of the 7 serious events**,** 5 described hepatic cirrhosis (3 events, one of which was fatal), oesophageal varices haemorrhage, and hepatic enzyme increased.

Study M15-997, a subject experienced a fatal event of hepatic cirrhosis,the event was considered unrelated to risankizumab. Study M15-997, subject experienced an event of hepatic cirrhosis. The event was considered unrelated to risankizumab and was attributed to chronic alcohol consumption by the investigator. Studies M15-992/M15-997, a subject experienced an event of hepatic cirrhosis (reported term micronodular cirrhosis) after approximately 1 year and 3 months of risankizumab therapy. The event was considered unrelated to risankizumab and was attributed to pre-existing liver cirrhosis by the investigator.

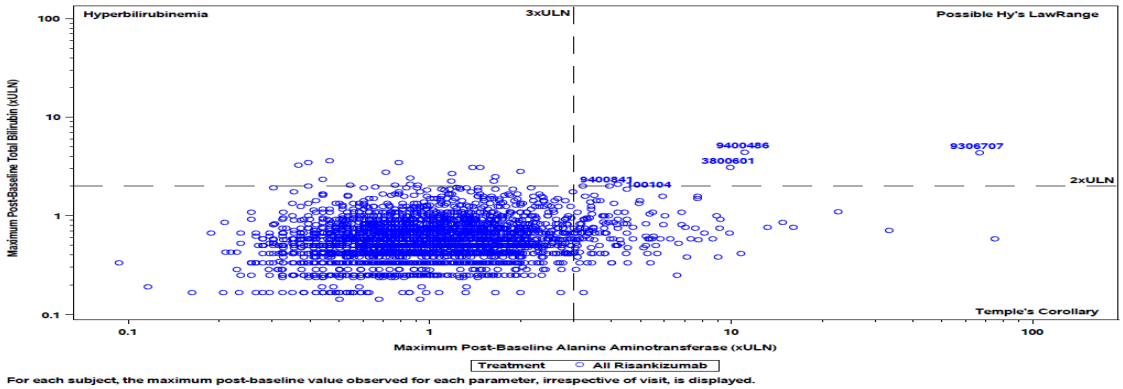
Study M19-164, - subject, experienced an event of oesophageal varices haemorrhage approximately1.5 months after risankizumab initiation. The event was considered unrelated to risankizumab and was attributed to pre-existing esophageal varices, portal hypertension, and fatty liver by the investigator and sponsor. Study M15-997, one subject experienced an event of hepatic enzyme increased approximately 2 years and 9 months after risankizumab initiation. The event was considered unrelated to risankizumab and attributed by the investigator to concomitant amiodarone use.

A total of 5 subjects in the All Risankizumab PsO Analysis Set met the criteria for biochemical Hy's law case all of these were identified since the initial submission (the cases with concurrent SAE reports are presented first.

Study M15-992, a subject had normal liver enzymes at screening and throughout the study while receiving risankizumab for ~1.5 years. SAE of liver injury. The investigator considered the liver injury as unrelated to risankizumab. The case is confounded by medications with known hepatotoxic potential (amiodarone and atorvastatin). Study M16-008/M15-997, a subject was treated for psoriasis with risankizumab for approximately 1 year and presented with Grade 4 lab elevations of ALT, AST, and Grade

3 total bilirubin, meeting criteria for potential Hy's law 1 month after last dose of risankizumab. A diagnosis of fulminant AIH and steatohepatitis was made on liver biopsy. The event was considered unrelated by both investigator and sponsor. Study 1311.2, During treatment, ALT elevations fluctuated between a CTCAE Grade 1and 2 elevation and AST remained at a Grade 1 elevation. On treatment Day 1372, the subject's total bilirubin was 2.08 × ULN though ALT was 1.49 × ULN and AST was normal. The aminotransferase and bilirubin elevations were not concurrent. Given the baseline elevation of liver enzymes and medical history of ALT and AST increase is a confounder. A causal role of risankizumab is unlikely**.** Study M16-004/M15-997, a subject experienced Grade 3 elevations in ALT, AST and bilirubin, meeting criteria for potential Hy's law on treatment Day 743. Subject was diagnosed with bile duct cancer (considered unrelated by the Investigator), which is most likely the cause of the elevated LFTs. On treatment Day 1372, the subject's total bilirubin was 2.08 × ULN though ALT was 1.49 × ULN and AST was normal. The aminotransferase and bilirubin elevations were not concurrent. Given the baseline elevation of liver enzymes and medical history of ALT and AST increase is a confounder. A causal role of risankizumab is unlikely**.**Study M15-992, a subject had normal aminotransferase levels through two treatment periods of risankizumab totaling 381 days on treatment (separated by a placebo period). On the last day of treatment**,** Day 575, the subject experienced elevations of ALT 3.93 × ULN, AST 2.78 × ULN and TBILI 2 × ULN. No causality has been provided.

Figure 20: Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) Plot (All Risankizumab PsO Analysis Set)



There is a notable difference in Treatment-Emergent Hepatic Events EAERs between the All Risankizumab PsA Analysis Set and All Risankizumab PsO Analysis Set outlined below:

All Risankizumab PsO Analysis Set vs All Risankizumab PsA Analysis Set

- Treatment-Emergent Hepatic Events EAERs ≥ 0.1 E/100 PY (All Risankizumab PsO Analysis Set)
- All Risankizumab PsO (N = 3131) (PY = 9081.2) Events (E/100PY)
- Hepatic events were 4.1/100 PY vs 13.1/100 PY in the all Risankizumab PsA Analysis Set,
- Alanine aminotransferase increased 0.8/100PY vs 3.7/100 PY in the all Risankizumab PsA Analysis Set,
- Gamma-glutamyltransferase increased 0.8/100 PY vs 1.8/100 PY in the all Risankizumab PsA Analysis Set,
- Aspartate aminotransferase increased 0.6/100 PY vs 2.9/100y in the all Risankizumab PsA Analysis Set,
- Hepatic steatosis 0.5/100PY vs 1.2 /100PY in the all Risankizumab PsA Analysis Set,
- Hepatic enzyme increased 0.3/100Py vs 1.0/100PY in the all Risankizumab PsA Analysis Set,
- Transaminases increased 0.3/100Py vs 0.9/100PY in the all Risankizumab PsA Analysis Set,
- Hepatic function abnormal 0.2 vs < 0.1/100PY in the all Risankizumab PsA Analysis Set,
- Liver function test increased 0.2 100Py vs 0.3/100PY in the all Risankizumab PsA Analysis Set,

Data from Phase 2 Crohn's Disease Study

A review of safety data with regard to hepatic disorders from a Phase 2 study (Study M15-993) for subjects with moderately to severely active Crohn's disease is also relevant as higher doses of IV risankizumab given q4w, translating into higher exposure, were administered in this study.

This study consisted of a 12-week blinded IV induction period (Period 1) in 39 subjects on placebo, 41 subjects on risankizumab 200 mg IV, and 41 subjects on risankizumab 600 mg IV (Study M15-993 Period 2 consisted of a 14-week open label (OL) 600 mg IV re induction (in subjects who were not in deep remission).

There were no subjects in the risankizumab DB IV 200 mg or 600 mg arms or OL IV risankizumab 600 mg arm with Grade 3 AST or ALT elevations (Study M15-993).The proportion of subjects with hepatic TEAEs during the DB IV Period 1 was small and comparable between the placebo group and total risankizumab group (2.6% vs 2.4%, respectively)

There were no serious hepatic TEAEs reported in Periods 1 or 2 with risankizumab treatment (Study M15-993) Review of the data indicates there was no dose-effect between risankizumab 200 mg and 600 mg dose arms. Overall, based on a comprehensive assessment of hepatic laboratory and AE data in the Phase 2 Crohn's disease program with higher risankizumab exposure, no concerns with regards to hepatic disorders were identified.

Analysis of Hepatic Laboratory Data

In the Phase 3 PsA PBO-Controlled Analysis Set, the proportions of subjects with PCI laboratory value changes in ALT, and AST, values were higher in the risankizumab groups but were <3%. (Table 77)

In **the Phase 3 PsA PBO-Controlled Analysis Set,** no subjects had laboratory values that met biochemical Hy's law

Table 77: Summary of Potentially clinically significant Liver test values.

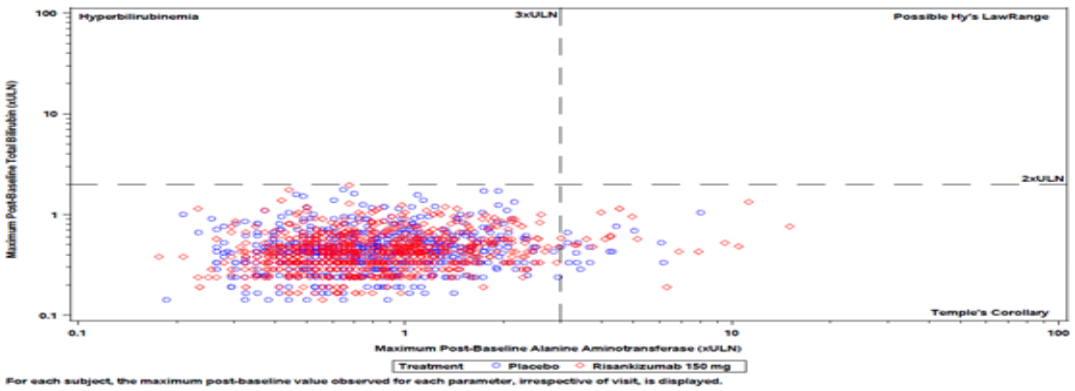
Summary of Potentially Clinically Significant Liver Test Values (Phase 3 PsA PBO-Controlled Analysis Set)

Criteria	Placebo (N = 700) n/N_OBS (%) [SSA%]	Risankizumab 150 mg (N = 707) n/N_OBS (%) [SSA%]	Treatment Comparison (95% CI)[a] Risankizumab 150 mg - Placebo
ALT ≥ 3 × ULN	17/693 (2.5) [2.4]	19/704 (2.7) [2.7]	0.3 [–1.4, 1.9]
ALT ≥ 5 × ULN	4/693 (0.6) [0.6]	8/704 (1.1) [1.1]	0.6 [–0.4, 1.5]
ALT ≥ 10 × ULN	0/693	3/704 (0.4) [0.4]	0.4 [–0.1, 0.9]
ALT ≥ 20 × ULN	0/693	0/704	0.0
AST ≥ 3 × ULN	7/693 (1.0) [1.0]	12/704 (1.7) [1.7]	0.7 [–0.5, 1.9]
AST ≥ 5 × ULN	2/693 (0.3) [0.3]	6/704 (0.9) [0.9]	0.6 [–0.2, 1.4]
AST ≥ 10 × ULN	0/693	3/704 (0.4) [0.4]	0.4 [–0.1, 0.9]
AST ≥ 20 × ULN	0/693	0/704	0.0
Alkaline phosphatase ≥ 1.5 × ULN	11/693 (1.6) [1.6]	16/704 (2.3) [2.3]	0.7 [–0.8, 2.1]
TBL ≥ 2 × ULN	0/693	0/704	0.0
ALT and/or AST ≥ 3 × ULN and TBL ≥ 1.5 × ULN	0/693	0/704	0.0
ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN	0/693	0/704	0.0

Note: N_OBS indicates the number of subjects with at least one post-Baseline value for the respective parameter.

a. Study size adjusted risk difference between treatment groups.

Figure 2. Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) Plot (Phase 3 PsA PBO-Controlled Analysis Set)



Cross reference: ISS (R&D/20/1090) Figure 2.5__1.1.4.3

MTX therapy

Further, to assess the impact of MTX therapy on aminotransferase elevations, a subgroup analysis was performed and presented by Grade of elevation. In the Phase 3 PsA PBO-Controlled Analysis Set, the subjects on baseline MTX treatment generally had more frequent Grade 1 and 2 elevations in ALT and AST but notably in those with no methotrexate at baseline the grade 3 elevations were higher 2.5% vs 0 for ALT and 1.4% vs 0 for AST.

Table 78: Frequency of Subjects with Transaminase Increases Post-Baseline by Methotrexate in the Phase 3 PsA Placebo-Controlled Period

	Through Week 24[a]			
	Placebo		Risankizumab 150 mg	
	MTX at Baseline N = 414 n/N OBS (%) [SSA%]	No MTX at Baseline N = 286 n/N OBS (%) [SSA %]	MTX at Baseline N = 424 n/N OBS (%) [SSA%]	No MTX at Baseline N = 283 n/N OBS (%) [SSA %]
CTCAE ALT elevations (U/L)				
Grade 1 (> 1 to ≤ 3 × ULN)	89/413 (21.5) [21.5]	40/280 (14.3) [14.3]	91/422 (21.6) [21.6]	39/282 (13.8) [13.8]
Grade 2 (> 3 to ≤ 5 × ULN)	9/413 (2.2) [2.2]	3/280 (1.1) [1.1]	6/422 (1.4) [1.4]	3/282 (1.1) [1.1]
≥ Grade 3 (> 5 × ULN)	4/413 (1.0) [1.0]	0/280	1/422 (0.2) [0.2]	7/282 (2.5) [2.5]
CTCAE AST elevations (U/L)				
Grade 1 (> 1 to ≤ 3 × ULN)	56/413 (13.6) [13.5]	28/280 (10.0) [10.0]	67/422 (15.9) [15.9]	34/282 (12.1) [12.0]
Grade 2 (> 3 to ≤ 5 × ULN)	4/413 (1.0) [1.0]	1/280 (0.4) [0.4]	0/422	6/282 (2.1) [2.1]
≥ Grade 3 (> 5 × ULN)	2/413 (0.5) [0.5]	0/280	2/422 (0.5) [0.5]	4/282 (1.4) [1.4]

a. Placebo-Controlled period.

Notes: Toxicity grading scale is based on NCI Common Terminology Criteria version 4.03. Grade also more extreme than the baseline grade.

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

Phase 3 PsA Long-term Analysis Set

The proportion of subjects with long-term risankizumab exposure with PCI liver transaminase elevations in the any risankizumab 150 mg group of the Phase 3 PsA Long-term Analysis Set was < 3%,

Table 79: Summary of Potentially Clinically Important Liver Function Test Values (Phase 3 PsA Long-term Analysis Set)

Criteria	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) n/N_OBS (%) [SSA%]	Any Risankizumab 150 mg (N = 1365) n/N_OBS (%) [SSA%]
ALT ≥ 3 × ULN	27/704 (3.8) [3.8]	37/1360 (2.7) [2.7]
ALT ≥ 5 × ULN	11/704 (1.6) [1.6]	11/1360 (0.8) [0.8]
ALT ≥ 10 × ULN	4/704 (0.6) [0.6]	4/1360 (0.3) [0.3]
ALT ≥ 20 × ULN	0/704	0/1360
AST ≥ 3 × ULN	15/704 (2.1) [2.1]	19/1360 (1.4) [1.4]
AST ≥ 5 × ULN	7/704 (1.0) [1.0]	8/1360 (0.6) [0.6]
AST ≥ 10 × ULN	3/704 (0.4) [0.4]	3/1360 (0.2) [0.2]
AST ≥ 20 × ULN	0/704	0/1360
Alkaline phosphatase ≥ 1.5 × ULN	17/704 (2.4) [2.4]	29/1360 (2.1) [2.1]
TBL ≥ 2 × ULN	0/704	0/1360
ALT and/or AST ≥ 3 × ULN and TBL ≥ 1.5 × ULN	0/704	0/1360
ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN	0/704	0/1360

Note: N_OBS indicates the number of subjects with at least one post-Baseline value for the respective parameter.

In this Phase 3 PsA Long-term Analysis Set there was 1 additional report of ALT > 10 × ULN and is described.

A subject from Study M16-011 had liver function test (LFT) elevations after treatment with amoxicillin/clavulanic acid and metronidazole, known to be associated with hepatotoxicity, with positive de-challenge to them.

In evaluating subjects with long-term risankizumab exposure (Phase 3 PsA Long-term Analysis Set) there were no laboratory values meeting the criteria for biochemical Hy's law with risankizumab treatment.

MTX therapy

Further, to assess the impact of MTX therapy on aminotransferase elevations, a subgroup analysis was performed and presented by Grade of elevation in table 22. In the Phase 3 PsA long term Analysis Set, the subjects on baseline MTX treatment generally had more frequent Grade 1 and 2 elevations in ALT and AST but notably in those with no methotrexate at baseline the grade 3 elevations were higher 1.3% vs 0.5 for ALT and 0.7vs 0.5 for AST

Table 80: Frequency of Subjects with Transaminase Increases Post-Baseline by Methotrexate in the Phase 3 PsA Long-Term Analysis Set

	Through 1 Year Any Risankizumab 150 mg	
	MTX at Baseline N = 824 n/N OBS (%) [SSA%]	No MTX at Baseline N = 541 n/N OBS (%) [SSA %]
CTCAE ALT elevation (U/L)		
Grade 1 (> 1 to ≤ 3 × ULN)	180/821 (21.9) [21.9]	89/539 (16.5) [16.5]
Grade 2 (> 3 to ≤ 5 × ULN)	16/821 (1.9) [1.9]	4/539 (0.7) [0.7]
≥ Grade 3 (> 5 × ULN)	4/821 (0.5) [0.5]	7/539 (1.3) [1.3]
CTCAE AST elevation (U/L)		
Grade 1 (> 1 to ≤ 3 × ULN)	148/821 (18.0) [18.0]	75/539 (13.9) [13.9]
Grade 2 (> 3 to ≤ 5 × ULN)	4/821 (0.5) [0.5]	7/539 (1.3) [1.3]
≥ Grade 3 (> 5 × ULN)	4/821 (0.5) [0.5]	4/539 (0.7) [0.7]

Notes: Toxicity grading scale is based on NCI Common Terminology Criteria version 4.03. Grade must also be more extreme than the baseline grade.

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

All Risankizumab PsA Analysis Set

The proportion of subjects in the All Risankizumab PsA Analysis Set with PCI liver test elevations are outlined above. Notably 3 % of patients had ALT values ≥ 3 x ULN

Table 81: Summary of Potentially Clinically Important Liver Function Test Values (All Risankizumab PsA Analysis Set)

Criteria	All Risankizumab (N = 1542) n/N_OBS (%) [SSA%]
ALT ≥ 3 × ULN	46/1537 (3.0) [3.0]
ALT ≥ 5 × ULN	14/1537 (0.9) [0.9]
ALT ≥ 10 × ULN	4/1537 (0.3) [0.3]
ALT ≥ 20 × ULN	0/1537
AST ≥ 3 × ULN	27/1537 (1.8) [1.8]
AST ≥ 5 × ULN	11/1537 (0.7) [0.7]
AST ≥ 10 × ULN	3/1537 (0.2) [0.2]
AST ≥ 20 × ULN	0/1537
Alkaline phosphatase ≥ 1.5 × ULN	30/1537 (2.0) [2.0]
TBL ≥ 2 × ULN	1/1537 (< 0.1) [< 0.1]
ALT and/or AST ≥ 3 × ULN and TBL ≥ 1.5 × ULN	1/1537 (< 0.1) [< 0.1]
ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN	1/1537 (< 0.1) [< 0.1]

Note: N_OBS indicates the number of subjects with at least one post-Baseline value for the respective parameter.

Case level summaries of all cases meeting PCI lab criteria, biochemical Hy's law cases serious hepatic TEAEs and hepatic events leading to discontinuation from the All Risankizumab PsA Analysis Set are presented in the clinical overview, key findings from this table are summarized in this section

Summary of Table 35, table titled: Summary of Subjects Who Experienced a Grade 3 ALT, AST (> 5 × ULN) or Bilirubin (> 3 × ULN) Elevation During Treatment with Risankizumab 150 mg (All Risankizumab PsA Analysis Set)

Of the subjects in the risankizumab group with an ALT and AST elevation of Grade 3, the MAH outlined that x 5 subjects had an ALT or AST ≥ 10 × ULN that four subjects had clear alternative etiologies for their liver test abnormalities and one pre-existing co-morbidities were considered the probable cause of the transaminase elevations. There appears to be a causal association with concomitant medications in 4 cases, pre-existing co-morbidities were considered the probable cause of the transaminase elevations in the other subject. In the subject with pre-existing co-morbidities (Study M16-011) the AST/ALT ratio was > 2, suggestive of possible alcohol abuse. We calculate x 6 subjects with an ALT or AST ≥ 10 × ULN. In addition to the x5 subjects discussed by the MAH another subjecthad an ALT levels 409 (U/L) (12.03 × ULN) this subject from Study M16-011 had liver function test (LFT) elevations after treatment with amoxicillin/clavulanic acid and metronidazole, known to be associated with hepatotoxicity, with positive de-challenge to them.

The MAH has outlined that 8 subjects had aminotransferase elevations that coincided with concomitant therapy with hepatotoxic medication with levels returning to normal upon withdrawal of the concomitant therapy but the MAH also states that in 5 of 8 of these subjects, aminotransferase levels returned to within normal limits while on continued use of risankizumab. This statement is contradictory the MAH is requested to clarify this statement.

Regarding the 10 other cases out of the total of 18 cases listed above the MAH outlines that 5 subjects had confounding underlying history, in 3 subjects the AST:ALT ratio, GGT levels and/or history was

suggestive of alcohol abuse, 1 subject had laboratory evaluations suggestive of an infectious etiology and 1 subject had relevant medical history of elevated liver enzymes and alcohol use.

Of the remaining 3 subjects without readily identifiable alternative etiologies, the time to onset of elevation were > 6 months, > 8 months and > 15 months from start of study drug.

One subject with time to onset > 8 months had their aminotransferase levels normalize in approximately 1 week. One subject with a time to onset of > 15 months, had their aminotransferase levels normalize in approximately 1 month. The remaining subject, time to onset was > 6 months and Grade 3 elevations showed gradual reductions over a 3-month period while still on study drug. The MAH argues that Idiosyncratic DILI is variable, but in most instances occurs within 6 months (DILI 2020). The long time to onset with short recovery times (limit to the first 2 cases) for these three subjects is not suggestive of DILI.

Major Adverse Cardiovascular Event (MACE):

MACE is an event of interest for biologics. In the risankizumab clinical program, potential MACE was reviewed and adjudicated by a team of independent external experts who were blinded to treatment assignment.Major adverse cardiac events confirmed by the external cardiac adjudication committee are included in the percentages and incidence rate calculations in this section.

Table 82: Summary of Treatment-emergent Adjudicated Cardiovascular Endpoints EAER Per 100 PY (Phase 3 PsA Long-term Analysis Set)

Event Category Adjudicated Term	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) (PY = 696.1) Events (E/100 PY) [SSA E/100 PY]	Any Risankizumab 150 mg (N = 1365) (PY = 1047.9) Events (E/100 PY) [SSA E/100 PY]
MACE	3 (0.4) [0.4]	3 (0.3) [0.3]
Cardiovascular Death	0	0
Non-fatal Myocardial Infarction	2 (0.3) [0.3]	2 (0.2) [0.2]
Non-fatal Stroke	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Extended MACE	3 (0.4) [0.4]	3 (0.3) [0.3]
Cardiovascular Death	0	0
Non-fatal Myocardial Infarction	2 (0.3) [0.3]	2 (0.2) [0.2]
Non-fatal Stroke	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Hospitalization for Unstable Angina	0	0
Coronary Revascularization Procedures	0	0

Note: Including subjects with adjudicated CV adverse events and subjects with adjudicated CV results based on review of other information.
Table should present all the categories (e.g., CV death, non-fatal stroke and non-fatal MI for MACE) by displaying 0 if no event and present respective sub-categories (for CV death) whenever there is occurrence of events associated with the subcategories.

Phase 3 PsA PBO-Controlled Analysis Set

2 extended MACE were reported

- Hospitalization for unstable angina in 1 subject in the placebo group.
- A 70-year-old subject in the risankizumab group with a history of hypertension experienced a MACE (1 nonfatal stroke) which was considered unrelated to study drug by both the investigator and sponsor.

Phase 3 PsA Long-term Analysis Set

In addition to the one MACE of nonfatal stroke noted above, 2 MACE of non-fatal MI were reported with long-term risankizumab exposure. One of the 2 cases of non-fatal MI was reported in a subject with a history of smoking and dyslipidemia, and the other case was reported in a subject with a history of smoking, coronary artery disease with previous MI and coronary stent, hyperlipidemia, and hypertension. Both cases were considered unrelated to study drug by both the investigator and sponsor.

Literature suggests that the risk of myocardial infarction (MI), stroke, and CV death is increased in patients with psoriatic arthritis compared to the general population. The rationale for a correlation between psoriasis, psoriatic arthritis, and atherosclerotic disease is not well understood. Although the increased prevalence of risk factors for CVD (obesity, hypertension [HTN], DM, hyperlipidemia, metabolic syndrome, and cigarette smoking) in patients with psoriasis and psoriatic arthritis likely contributes to the

elevated risk for atherosclerosis, the role of chronic inflammation in the pathogenesis of both disorders may also be a key factor (Reich 2012).

The MACE rate of 0.3 E/100 PY was within the range anticipated for the patient population (0.46 E/100 PY) No pattern with regard to time to event onset was identified (45 days, 308 days and 332 days, respectively, since first risankizumab exposure). There were no additional cases of extended MACE. The rates of MACE (0.3 E/100 PY) and extended MACE (0.3 E/100 PY) observed with long-term risankizumab treatment in the psoriatic arthritis population were lower than the rates observed in the All Risankizumab PsO Analysis Set (0.6 E/100 PY and 0.7 E/100 PY, respectively

Overall, the data did not suggest an increased risk of MACE with risankizumab treatment in patients with psoriatic arthritis. MACE is an important potential risk for risankizumab and will continue to be assessed in the long-term psoriasis safety studies and the ongoing Phase 3 psoriatic arthritis studies.

Infections (Including Serious Infection, Opportunistic Infection [Excluding TB and Herpes Zoster], TB, and Herpes Zoster)

Overall Infections

Phase 3 PsA PBO-Controlled Analysis Set

In the first 24 weeks of treatment, 19.0% of subjects in the risankizumab group reported infection AEs compared to 19.3% of subjects in the placebo group). The most common infection AEs in the risankizumab group (≥ 1% of subjects) were upper respiratory tract infection (4.1%), nasopharyngitis (3.5%), and gastroenteritis (1.0%).

Phase 3 PsA Long-term Analysis Set

The overall rates of infection were stable with long-term risankizumab therapy (43.0 E/100 PY, as compared to the rates in Phase 3 PsA Placebo-Controlled Analysis Set (51.1 E/100 PY)

The most common infection AEs in the any risankizumab 150 mg group (> 10 events) were nasopharyngitis (65 events), upper respiratory tract infection (61 events), COVID-19 (32 events), urinary tract infection (17 events), gastroenteritis (15 events), pharyngitis (13 events), bronchitis (12 events), and sinusitis (12 events). The majority of infections were nonserious and mild to moderate (Grade 1 or 2) in severity and did not lead to discontinuation of study drug.

Nasopharyngitis, upper respiratory tract infection, pharyngitis and sinusitis are ADRs identified in the psoriasis clinical development program. A comparison of grouped PTs representing urinary tract infections (including cystitis) and bronchitis did not reveal a disproportionality between risankizumab and placebo groups and therefore no new concerns with regard to overall infections were identified.

Serious infections

Due to the immunomodulatory effects of risankizumab, there is a risk for serious infections.Integrated risankizumab clinical trial data was used to assess the risk with risankizumab therapy, and epidemiologic data were used to contextualize the risankizumab data.

In the Phase 3 PsA PBO-Controlled Analysis Set the percentage of subjects with serious infections in the risankizumab group (1.0%) was comparable to the placebo group (1.6%). The only serious infections reported in ≥ 2 subjects in a group was cellulitis (2 subjects) in the risankizumab group and pneumonia (2 subjects) in the placebo group. None of the subjects in the risankizumab group had events of serious infection which led to discontinuation of study drug.

Table 53: Treatment-Emergent Serious Infections (Phase 3 PsA PBO-Controlled Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Placebo (N = 700) n (%) [SSA%]	Risankizumab 150 mg (N = 707) n (%) [SSA%]
Any serious infection adverse event	11 (1.6) [1.6]	7 (1.0) [1.0]
Abscess	0	1 (0.1) [0.1]
Appendicitis perforated	1 (0.1) [0.1]	0
Cellulitis	1 (0.1) [0.1]	2 (0.3) [0.3]
Complicated appendicitis	1 (0.1) [0.1]	0
Dysentery	1 (0.1) [0.1]	0
Erysipelas	1 (0.1) [0.1]	0
Gastroenteritis	1 (0.1) [0.1]	1 (0.1) [0.1]
Gastroenteritis viral	0	1 (0.1) [0.1]
Oral bacterial infection	1 (0.1) [0.1]	0
Pneumonia	2 (0.3) [0.3]	1 (0.1) [0.1]
Pneumonia viral	0	1 (0.1) [0.1]
Postoperative abscess	1 (0.1) [0.1]	0
Upper respiratory tract infection	1 (0.1) [0.1]	0
Urinary tract infection	1 (0.1) [0.1]	0
Urosepsis	0	1 (0.1) [0.1]
Viral upper respiratory tract infection	0	1 (0.1) [0.1]

Phase 3 PsA Long-term Analysis Set

The rate of **serious infections** was stable with long-term risankizumab exposure (2.6 E/100 PY) as compared to the rates in Phase 3 PsA Placebo-Controlled Analysis Set (2.7 E/100 PY)

The most common (≥ 0.1 E/100 PY) serious infections in the Phase 3 PsA Long-term Analysis Set analysis set were pneumonia and COVID-19 followed by cellulitis. The serious infection rate in the risankizumab treated subjects was within the range anticipated for the patient population.

A total of 6 events of serious infections related to pneumonia (4 events of pneumonia, 1 of COVID-19 pneumonia, and 1 event of pneumonia viral) were reported in the Phase 3 PsA Long-term Analysis Set.

Of the 6 pneumonia cases, 3 had a COVID-19 diagnosis reported. These subjects all had relevant risk factors such as obesity and diabetes. The other 3 cases of pneumonia had significant risk factors including one case with advanced age, pre-existing dementia, and delayed gastric emptying, another case with obesity and smoking history on concomitant steroid therapy, and the third case in an overweight subject on concomitant steroid and methotrexate (MTX) therapy.

There was a higher rate of **serious** infection in subjects ≥ 75 years old and who are obese which is expected given the decreased immunity and increased comorbidities predisposing to infection. Otherwise, there were no notable trends with regard to the gender or concomitant csDMARD therapies. One subject receiving risankizumab died due to an infectious cause (urosepsis)

Table 83: Treatment-Emergent Serious Infection EAER Per 100 PY (Phase 3 PsA Long-term Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) (PY = 696.1) Events (E/100 PY) [SSA E/100 PY]	Any Risankizumab 150 mg (N = 1365) (PY = 1047.9) Events (E/100 PY) [SSA E/100 PY]
Any serious infection adverse event	17 (2.4) [2.4]	27 (2.6) [2.6]
Abdominal wall abscess	0	1 (< 0.1) [< 0.1]
Abscess	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Anal abscess	0	1 (< 0.1) [< 0.1]
Appendicitis	0	1 (< 0.1) [< 0.1]
COVID-19	1 (0.1) [0.1]	4 (0.4) [0.4]
COVID-19 pneumonia	0	1 (< 0.1) [< 0.1]
Cellulitis	2 (0.3) [0.3]	3 (0.3) [0.3]
Diverticulitis	0	1 (< 0.1) [< 0.1]
Gastroenteritis	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Gastroenteritis viral	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Nasopharyngitis	0	1 (< 0.1) [< 0.1]
Otitis media	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Pneumonia	4 (0.6) [0.6]	4 (0.4) [0.4]
Pneumonia viral	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Staphylococcal sepsis	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Tonsillitis	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Urosepsis	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Vestibular neuronitis	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Viral upper respiratory tract infection	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]

The event rate with long-term risankizumab treatment in the psoriatic arthritis clinical trials was higher than the rate reported in the All Risankizumab PsO Analysis Set.

The rate of **serious infection** observed with long-term risankizumab treatment in the psoriatic arthritis population (2.6 E/100 PY), was higher than the rate observed in the All Risankizumab PsO Analysis Set (1.3 E/100 PY).

The rate of serious infections in the psoriatic arthritis program may reflect the fact that approximately 60% of subjects were on concomitant MTX and the majority of the psoriatic arthritis Phase 3 study periods were conducted during the COVID-19 pandemic. The rate of serious infections associated with long-term risankizumab exposure (2.6 events per 100 PY) is within the expected range for this patient population based on published estimates (3.98 events per 100 PY) (Shah 2017). The types of serious infections reported were consistent with those anticipated in a population of patients with psoriatic arthritis.

Opportunistic Infection (excluding TB and Herpes Zoster)

Phase 3 PsA PBO-Controlled Analysis Set

No subjects in either treatment group had an opportunistic infection in this analysis set.

Phase 3 PsA Long-term Analysis Set

One event (< 0.1 E/100 PY) of opportunistic infection (oral fungal infection) was reported with long-term risankizumab exposure in a subject with chronic use of inhaled steroids for seasonal allergies . Oral thrush is a known AE associated with use of inhaled steroids.

These results with long-term risankizumab treatment in the psoriatic arthritis population were the same as the rate of opportunistic infection in the All Risankizumab PsO Analysis Set (< 0.1 E/100 PY)

Active TB

There were no cases of active TB infection reported in the psoriatic arthritis development program across the analysis sets.

Assessment of Subjects with Latent TB With or Without Prophylaxis

Across the psoriatic arthritis clinical studies, 105 subjects with latent TB were concurrently treated with risankizumab and TB prophylaxis during the study and did not develop active TB during the mean follow-up of 1.0 year. Of the 132 subjects with latent TB who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 0.9 years.

Herpes zoster

Phase 3 PsA PBO-Controlled Analysis Set

Two subjects each (0.3%) in the risankizumab group and the placebo group reported an event of herpes zoster. None of the herpes zoster events were severe or led to discontinuation of study drug.

None of the cases were SAEs and both cases were limited to 1 – 2 dermatomal involvement; both events resolved with treatment. There were no recurrences despite continued risankizumab therapy.

Phase 3 PsA Long-term Analysis Set

The rate of herpes zoster was stable with long-term risankizumab exposure (0.4 E/100 PY) as compared to the rate in the Phase 3 PsA PBO-Controlled Analysis Set (0.6 E/100 PY)

Two additional cases of herpes zoster were reported with long-term exposure to risankizumab in the any risankizumab 150 mg group. Overall, none of the cases were severe or SAEs, all cases involved 1 –2 dermatomes, resolved with ongoing treatment, and did not lead to discontinuation of risankizumab Median age of these subjects was 54.5 years old (age > 50 years is a risk factor for herpes zoster) and there were no recurrences despite continued risankizumab therapy.

COVID-19 Infection

COVID-19 infection analysis was limited to the Phase 3 PsA PBO-Controlled Analysis Set and Phase 3 PsA Long-term Analysis Set as the Phase 2 trials included in the All Risankizumab PsA Analysis Set were completed prior to the onset of the pandemic.

Phase 3 PsA PBO-Controlled Analysis Set

A total of 2 subjects (0.3%) in the risankizumab group and 2 subjects (0.3%) in the placebo group had COVID-19 related TEAEs. None had COVID-19 related deaths. None of the subjects had COVID-19 related SAEs.

Phase 3 PsA Long-term Analysis Set

A total of 39 subjects (2.9%) in the any risankizumab 150 mg group had COVID-19 related TEAEs None had COVID-19 related deaths. Four subjects (0.3%) in the any risankizumab 150 mg group had SAEs of COVID-19 and 1 subject (< 0.1%) had an SAE of COVID-19 pneumonia. Only one subject with a COVID-

19 related SAE had study drug interrupted; the subject recovered and treatment was resumed. The remaining subjects continued with uninterrupted risankizumab treatment.

The risk of SARS-COV-2 infection and severe outcomes associated with COVID-19 are not yet well characterized for the psoriatic arthritis population. Current estimates are difficult to generalize because transmission and disease severity depend on key factors

Malignancy

While the pro-tumorigenic role of IL-23 has been shown in a number of studies, there are also reports supporting a tumor suppressive function of IL-23. One possible explanation is that the amount of IL-23 expressed in the tumor environment might determine the pro- or anti-tumorigenic role of the cytokine. In the latter case, blocking IL-23 could potentially increase the risk of carcinogenesis. Multiple factors may contribute to an increased rate of malignancy in patients using immunosuppressive or immunomodulatory therapies, which are used in psoriasis and psoriatic arthritis.

Psoriatic arthritis was not associated with increased risk of cancer overall in adult patients (risk ratio = 1.02; 95% CI, 0.97 - 1.08) (Vaengebjerg 2020). Integrated risankizumab clinical trial data was used to assess the risk with risankizumab therapy, and epidemiologic data were used to contextualize the risankizumab data.

Nonmelanoma Skin Cancer (NMSC)

Phase 3 PsA PBO-Controlled Analysis Set, 1 Nonmelanoma Skin Cancer (NMSC) of basal cell carcinoma was reported in the risankizumab group and 1 NMSC of Bowen's disease was reported in the placebo group.

Phase 3 PsA Long-term Analysis Set

4 basal cell carcinoma and 2 squamous cell carcinomas reported. The rate of NMSC with long-term risankizumab exposure was 0.6 events per 100 PYs and is within the epidemiological reference rate in the psoriatic arthritis population (0.61 events per 100PY) (Vaengebjerg 2020) and comparable to the rate observed in the All Risankizumab PsO Analysis Set (0.7 E/100 PY). There was a higher rate of malignancies in subjects ≥ 75 years old which is expected given the decreased immunity and comorbidities. Otherwise, there were no notable trends with regard to subgroups.

Table 54: Treatment-Emergent NMSC EAER Per 100 PY by SOC and PT (Phase 3 PsA Long-term Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) (PY = 696.1) Events (E/100 PY) [SSA E/100 PY]	Any Risankizumab 150 mg (N = 1365) (PY = 1047.9) Events (E/100 PY) [SSA E/100 PY]
Any NMSC adverse event	3 (0.4) [0.4]	6 (0.6) [0.6]
Basal cell carcinoma	2 (0.3) [0.3]	4 (0.4) [0.4]
Squamous cell carcinoma	1 (0.1) [0.1]	2 (0.2) [0.2]

Malignancies excluding NMSC

Phase 3 PsA PBO-Controlled Analysis Set

No malignancies excluding NMSC were reported in a subject in the risankizumab group and 2 were reported in the placebo group (breast cancer and non-small cell lung cancer).

Phase 3 PsA Long-term Analysis Set

The rate of malignancies excluding NMSC with long-term risankizumab exposure was 0.2 E/100 PY. A total of 2 malignancies excluding NMSC, acral lentiginous melanoma reported 78 days after first risankizumab exposure and papillary thyroid cancer reported 177 days after first risankizumab exposure, were observed with long-term risankizumab exposure.

Although it was diagnosed during the study, the subject with acral lentiginous melanoma had a hyperpigmented lesion in the foot nail that had appeared 3 years before it was excised (and the melanoma diagnosed). The time-to-onset of both events is biologically implausible for a causal role of risankizumab.

There is no evidence to suggest that the number of malignancies other than NMSC in subjects exposed to risankizumab is higher than what was expected. The long-term exposure-adjusted event rate of malignancies excluding NMSC was low with long-term risankizumab exposure (0.2 events per 100 PYs) and is within the epidemiologic reference rate in the psoriatic arthritis population (0.48 events per 100 PYs) (Vaengebjerg 2020). The rate of malignancies excluding NMSC with long-term risankizumab treatment in the psoriatic arthritis population was lower than that observed in the All Risankizumab PsO Analysis Set (0.6 E/100 PY) and there was no pattern with regard to the types of malignancies reported.

Table 84: Treatment-Emergent Malignancies Excluding NMSC EAER Per 100 PY by SOC and PT (Phase 3 PsA Long-term Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) (PY = 696.1) Events (E/100 PY) [SSA E/100 PY]	Any Risankizumab 150 mg (N = 1365) (PY = 1047.9) Events (E/100 PY) [SSA E/100 PY]
Any malignancies excluding NMSC adverse event	1 (0.1) [0.1]	2 (0.2) [0.2]
Acral lentiginous melanoma	0	1 (< 0.1) [< 0.1]
Papillary thyroid cancer	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]

Hypersensitivity reactions

As a biologic protein, systemic or subcutaneous administration of risankizumab may be associated with immunogenicity (i.e., development of anti-drug antibodies) as well as hypersensitivity reactions. In addition to assessment of the hypersensitivity reaction AEs, the incidence of hypersensitivity reactions was compared between ADA-positive and ADA-negative subjects to assess the impact of immunogenicity.

In the Phase 3 PsA PBO-Controlled Analysis Set, the percentages of subjects with hypersensitivity was higher in subjects in the risankizumab 150 mg group 16 subjects (2.3%) compared to the placebo group 9 subjects (1.3%) No subject had an event of hypersensitivity reaction that was serious or severe. One subject in the risankizumab group had a mild, nonserious event of swelling of face that led to discontinuation of study drug. The event lasted approximately 2 weeks and was not considered by the investigator as a manifestation of a hypersensitivity reaction. All hypersensitivity events were mild to moderate in severity and 1 event (mild, nonserious event of swelling of face) led to study drug discontinuation.

The rates of hypersensitivity reactions with long-term risankizumab exposure (Phase 3 PsA Long-term Analysis Set, 4.2 E/100 PY) was lower than rates in the Phase 3 PsA Placebo-Controlled Analysis Set (5.5

E/100 PY). The rate of hypersensitivity reactions in the Phase 3 PsA Long-term Analysis Set was lower than that reported for the psoriasis clinical studies. The most common hypersensitivity reaction reported in the Phase 3 PsA Long-term Analysis Set was rash followed by dermatitis and dermatitis contact.

The rates of hypersensitivity were numerically higher in ADA positive compared to ADA negative subjects, the rates were low, events were mild or moderate in severity and did not lead to discontinuation, indicating the impact of immunogenicity was not clinically meaningful. Based on this assessment, the MAH states that rash/hypersensitivity reaction does not warrant inclusion as an ADR.

The MAH outlines that Preferred Terms (PTs) in the Hypersensitivity Reaction SMQ include events that are known ADRs, for example, injection site reaction. Further, some PTs such as contact dermatitis and allergic rhinitis suggest alternate etiologies. Based on the exclusion of these events the overall rate of hypersensitivity reactions in risankizumab treatment group was 1.8% and 1.0% in the placebo treatment group. A review of the events reported in the risankizumab treatment group revealed alternate etiologies. The MAH states that the hypersensitivity reactions were mostly mild to moderate

in severity, and usually did not lead to discontinuation. Based on this assessment, the MAH states that rash and hypersensitivity reaction do not warrant inclusion as an ADR.

Table 85: Treatment-Emergent Hypersensivity Reactions EAER Per 100 PY (Phase 3 PsA Long-term Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) (PY = 696.1) Events (E/100 PY) [SSA E/100 PY]	Any Risankizumab 150 mg (N = 1365) (PY = 1047.9) Events (E/100 PY) [SSA E/100 PY]
Any adverse event	35 (5.0) [5.0]	44 (4.2) [4.2]
Eye disorders	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Swelling of eyelid	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Gastrointestinal disorders	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Gingival swelling	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
General disorders and administration site conditions	4 (0.6) [0.6]	4 (0.4) [0.4]
Face oedema	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Injection site rash	2 (0.3) [0.3]	2 (0.2) [0.2]
Swelling face	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Respiratory, thoracic and mediastinal disorders	3 (0.4) [0.4]	4 (0.4) [0.4]
Bronchospasm	0	1 (< 0.1) [< 0.1]
Rhinitis allergic	3 (0.4) [0.4]	3 (0.3) [0.3]
Skin and subcutaneous tissue disorders	26 (3.7) [3.7]	34 (3.2) [3.2]
Dermatitis	5 (0.7) [0.7]	6 (0.6) [0.6]
Dermatitis allergic	1 (0.1) [0.1]	2 (0.2) [0.2]
Dermatitis contact	5 (0.7) [0.7]	6 (0.6) [0.6]
Eczema	1 (0.1) [0.1]	2 (0.2) [0.2]
Rash	10 (1.4) [1.4]	13 (1.2) [1.2]
Rash macular	1 (0.1) [0.1]	2 (0.2) [0.2]
Rash pruritic	2 (0.3) [0.3]	2 (0.2) [0.2]
Urticaria	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]

Serious hypersensitivity reactions

In the Phase 3 long-term analysis set, no cases of **serious** hypersensitivity reaction were reported.

All Risankizumab PsA Analysis Set.

In a Phase 2 psoriatic arthritis trial, Study M16-002 1 subject had a **serious hypersensitivity reaction** of anaphylactic reaction**.** This biologic naïve subject without any past history of atopy experienced symptoms of dizziness and weakness followed by nausea, increased anxiety and macular rash on the thorax (décolleté) and neck on Day 1 of treatment. The subject did not experience respiratory symptoms, facial swelling, pruritus, or urticaria and did not require epinephrine or steroids. The subject's condition improved after treatment with IV fluids and H1/2 blockers (no epinephrine/steroids reported). The event was considered to have a reasonable possibility of relationship to study drug by the investigator and study drug was permanently discontinued. Based upon a comprehensive review of the clinical presentation and therapy, AbbVie does not consider the details of this case to be consistent with an IgE-mediated anaphylactic reaction. This event occurred in the Phase 2 study with a locked database which was out of scope of the adjudication charter.

As of 12 October 2020, the rate of serious hypersensitivity reactions was < 0.1 events per 100 PY and none of the events had a causal relation with risankizumab, as assessed by the sponsor in subjects treated across the Psoriasis development program. Assessment of post-marketing data has not changed characterization of the risk.

Serious hypersensitivity reactions and anaphylactic reactions are important potential risks for risankizumab and will continue to be assessed in the long-term psoriasis safety studies and the ongoing Phase 3 psoriatic arthritis studies.

Injection site reactions

In the Phase 3 PsA PBO-Controlled Analysis Set the percentage of subjects in the risankizumab group with injection site reactions (6 subjects, 0.8%) was higher than that in the placebo group (1 subject, 0.1%). In the risankizumab group, none of the events were severe in severity and no subjects discontinued study drug due to injection site reactions.

Table 86: Treatment-Emergent Injection Site Reaction EAERs Per 100 PY (Phase 3 PsA Long-term Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) (PY = 696.1) Events (E/100 PY) [SSA E/100 PY]	Any Risankizumab 150 mg (N = 1365) (PY = 1047.9) Events (E/100 PY) [SSA E/100 PY]
Any injection site reaction adverse event	10 (1.4) [1.4]	14 (1.3) [1.3]
Injection site bruising	0	1 (< 0.1) [< 0.1]
Injection site erythema	1 (0.1) [0.1]	3 (0.3) [0.3]
Injection site induration	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Injection site pain	0	1 (< 0.1) [< 0.1]
Injection site pruritus	4 (0.6) [0.6]	4 (0.4) [0.4]
Injection site rash	2 (0.3) [0.3]	2 (0.2) [0.2]
Injection site swelling	2 (0.3) [0.3]	2 (0.2) [0.2]

Injection site reaction

The rate of treatment-emergent injection site reactions with long-term risankizumab exposure was (1.3 E/100 PY, Table 29) compared to the rate in the Phase 3 PsA PBO-Controlled Analysis Set (2.4 E/100 PY) The rate of injection site reactions in the All Risankizumab PsO Analysis Set was 3.2 E/100 PY.
Two subjects in the any risankizumab 150 mg group who experienced injection site reactions (injection site pruritus and injection site swelling) were ADA positive. Injection site reactions are a known ADR that were observed in the psoriatic arthritis analysis sets within the frequency of the currently listed ADRs identified in the psoriasis development program.

ADA

Among the subjects who had ADA tests available in the Phase 3 PsA Long-term Analysis Set, the incidence of injection site reactions was higher in the risankizumab 150 mg (no cross-over from placebo) group ADA positive subjects (2.5%) compared to the ADA negative subjects (0.7%). However, the events in ADA positive subjects were mild, did not lead to discontinuation, and the overall incidence was low. These results suggest that immunogenicity to risankizumab did not have any clinically relevant impact on injection site reactions (Immunogenicity Report.

Among the subjects who had ADA tests available in the Phase 3 PsA Long-term Analysis Set, the incidence of hypersensitivity reactions was numerically higher in the risankizumab 150 mg (no cross-over from placebo) ADA positive subjects (6.3%) compared to ADA negative subjects (3.8%) However, given the overall low incidence, these results do not suggest that immunogenicity to risankizumab had any clinically relevant impact on the occurrence of hypersensitivity reactions

Laboratory findings

Table 87: Summary of Potentially Clinically Important Hematology Values (Grade ≥ 3) (Phase 3 PsA PBO-Controlled Analysis Set)

Variable (unit) Criteria	Placebo (N = 700) n/N_OBS (%) [SSA%]	Risankizumab 150 mg (N = 707) n/N_OBS (%) [SSA%]	Treatment Comparison (95% CI)[a] Risankizumab 150 mg - Placebo
Hemoglobin (g/L)			
Grade 3 (65.0 – < 80 g/L)	3/693 (0.4) [0.4]	0/704	–0.4 [–0.9, 0.1]
Grade 4 (< 65.0 g/L)	1/693 (0.1) [0.1]	0/704	–0.1 [–0.4, 0.1]
≥ Grade 3	4/693 (0.6) [0.6]	0/704	–0.6 [–1.1, –0.0]
Platelets (10^9/L)			
Grade 3 (25.0 – < 50.0 × 10^9/L)	1/692 (0.1) [0.1]	0/703	–0.1 [–0.4, 0.1]
Grade 4 (< 25.0 × 10^9/L)	0/692	0/703	0.0
≥ Grade 3	1/692 (0.1) [0.1]	0/703	–0.1 [–0.4, 0.1]
Leukocytes (10^9/L)			
Grade 3 (1.0 – < 2.0 × 10^9/L)	2/693 (0.3) [0.3]	0/704	–0.3 [–0.7, 0.1]
Grade 4 (< 1.0 × 10^9/L)	0/693	0/704	0.0
≥ Grade 3	2/693 (0.3) [0.3]	0/704	–0.3 [–0.7, 0.1]
Neutrophils (10^9/L)			
Grade 3 (0.5 – < 1.0 × 10^9/L)	2/692 (0.3) [0.3]	3/702 (0.4) [0.4]	0.1 [–0.5, 0.8]
Grade 4 (< 0.5 × 10^9/L)	0/692	0/702	0.0
≥ Grade 3	2/692 (0.3) [0.3]	3/702 (0.4) [0.4]	0.1 [–0.5, 0.8]

Lymphocytes (10^9/L)			
Grade 3 (0.2 – < 0.5 × 10^9/L)	4/692 (0.6) [0.6]	2/701 (0.3) [0.3]	–0.3 [–1.0, 0.4]
Grade 4 (< 0.2 × 10^9/L)	0/692	0/701	0.0
≥ Grade 3	4/692 (0.6) [0.6]	2/701 (0.3) [0.3]	–0.3 [–1.0, 0.4]

a. Study size adjusted risk difference between treatment groups.
Note: Toxicity grading scale is based on NCI Common Terminology Criteria version 4.03. Grade must also be more extreme than the baseline grade.The denominator N_OBS is defined as the number of subjects with at least one post-baseline value in Period 1 for the respective parameter.

Neutrophil count

There is a possible association between systemic blockade of IL-23 with subsequently lower IL-17 levels and reductions in peripheral neutrophil counts based on roles of IL-17A in innate immunity and neutrophil biology.

Phase 3 PsA PBO Controlled Analysis Set

There were 3 (0.4%) subjects in the risankizumab group in the Phase 3 PsA PBOControlled Analysis Set reporting a Grade 3 decrease in neutrophil count this was comparable to the placebo treatment group which showed 2 (0.3%) subjects reporting a Grade 3 decrease in neutrophil count. Among subjects treated with risankizumab who reported a decrease in neutrophil counts, treatment was not discontinued in any subject and the counts improved or resolved to normal despite continued therapy All 3 subjects treated with risankizumab had shifts in neutrophil count from Grade 0 or 1

at Baseline to Grade 3 for worst post-Baseline value.

One of the 2 subjects from Study M15-998, the first subjecthad an associated AE of neutropenia without any reports of infection. This AE was of mild severity and the subject fully recovered while on continued risankizumab treatment. The other subject (Study M15-998) had baseline low neutrophil count with Grade 3 decrease at Week 4. Neither subject discontinued study drug and the neutrophil counts in both subjects improved despite continuing risankizumab therapy. The remaining subject from Study M16-011, experienced a Grade 3 neutrophil count decrease on post treatment Day 168. This subject was lost to follow-up and had no confounding medications or medical history.

Phase 3 PsA Long-term Analysis Set

There were no additional Grade 3 hematology values among subjects with long-term risankizumab exposure in the Phase 3 PsA Long-term Analysis Set and Grade 4 hematology values were not observed in this analysis set.

Lymphocyte count :

Phase 3 PsA PBO-Controlled Analysis Set

2 (0.3%) subjects had a decrease in lymphocyte count, this was comparable to the placebo treatment group which showed 4 (0.6%) subjects with a decrease in lymphocyte count. Among subjects treated with risankizumab who reported a decrease in lymphocyte counts, treatment was not discontinued in any subject and the counts improved or resolved to normal despite continued therapy (Table 30).

There were 2 subjects with a Grade 3 lymphocyte count decrease (Study M15-998) Grade 3 lymphocyte count decrease was observed in 1 subject from Study M15-998 at Day 30 in a subject treated with MTX 25 mg/week. This subject has had lymphocyte count decrease Grade 1 – 2 since screening. No AEs were reported, and MTX was discontinued Lymphocyte count normalized, and MTX was reinitiated 2 months

later at a dose of 12.5 mg/week, and subsequently increased to 25 mg/week; study drug was not discontinued. One subject from Study M16-011 had Grade 3 lymphocyte count decrease during screening and chronically (8 times) during the study through the cutoff date. Relevant medical history for this subject includes low lymphocyte levels.

Grade 3 or 4 clinical chemistry values

Over the initial 24 weeks of exposure in the Phase 3 PsA PBO-Controlled Analysis Set, the proportions of subjects who had Grade 3 or 4 clinical chemistry values in the risankizumab treatment group were comparable to the placebo group There were no Grade 3 or 4 chemistry values observed in the risankizumab group for creatinine, calcium (hyper and hypo), sodium (hyper), potassium (hypo), glucose (hypo), and albumen.

Phase 3 PsA Long-term Analysis Set

The proportions of subjects with long-term risankizumab exposure (Phase 3 PsA Long-term Analysis Set, who had Grade 3 or 4 clinical chemistry values remained stable compared to the proportions observed in risankizumab subjects in the Phase 3 PsA PBO-Controlled Analysis Set. The majority of Grade 3 or 4 Chemistry laboratory changes were transient; and in some cases, the subjects had baseline level of Grade 3 values and the laboratory values remained consistent through the entire study.

There were no Grade 3 or 4 chemistry values observed for calcium (hypo and hyper), sodium (hyper), and albumin.

Table 88: Summary of Potentially Clinically Important Clinical Chemistry Values Except LFTs (Grade ≥3) (Phase 3 PsA PBO-Controlled Analysis Set)

Variable (unit) Criteria	Placebo (N = 700) n/N_OBS (%) [SSA%]	Risankizumab 150 mg (N = 707) n/N_OBS (%) [SSA%]	Treatment Comparison (95% CI)[a] Risankizumab 150 mg - Placebo
Glucose (mmol/L) - Hypo			
Grade 3 (1.7 ≤ 2.2 mmol/L)	0/693	0/704	0.0
Grade 4 (< 1.7 mmol/L)	0/693	0/704	0.0
≥ Grade 3	0/693	0/704	0.0
Glucose (mmol/L) - Hyper			
Grade 3 (13.9 ≤ 27.8 mmol/L)	10/693 (1.4) [1.4]	19/704 (2.7) [2.7]	1.2 [–0.2, 2.7]
Grade 4 (> 27.8 mmol/L)	0/693	1/704 (0.1) [0.1]	0.1 [–0.1, 0.4]
≥ Grade 3	10/693 (1.4) [1.4]	20/704 (2.8) [2.8]	1.4 [–0.1, 2.9]
Albumin (g/L)			
Grade 3 (< 20 g/L)	1/693 (0.1) [0.1]	0/704	–0.1 [–0.4, 0.1]
≥ Grade 3	1/693 (0.1) [0.1]	0/704	–0.1 [–0.4, 0.1]

Table 89: Summary of Potentially Clinically Important Clinical Chemistry Values Except Except LFTs (Grade ≥3) (Phase 3 PsA PBO-Controlled Analysis Set) (Continued)

Variable (unit) Criteria	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) n/N_OBS (%) [SSA%]	Any Risankizumab 150 mg (N = 1365) n/N_OBS (%) [SSA%]
Glucose (mmol/L) - Hypo		
Grade 3 (1.7 ≤ 2.2 mmol/L)	0/704	0/1360
Grade 4 (< 1.7 mmol/L)	0/704	1/1360 (< 0.1) [< 0.1]
≥ Grade 3	0/704	1/1360 (< 0.1) [< 0.1]
Glucose (mmol/L) - Hyper		
Grade 3 (13.9 ≤ 27.8 mmol/L)	32/704 (4.5) [4.5]	36/1360 (2.6) [2.6]
Grade 4 (> 27.8 mmol/L)	1/704 (0.1) [0.1]	1/1360 (< 0.1) [< 0.1]
≥ Grade 3	33/704 (4.7) [4.7]	37/1360 (2.7) [2.7]
Albumin (g/L)		
Grade 3 (< 20 g/L)	0/704	0/1359
≥ Grade 3	0/704	0/1359

Safety in special populations

Pregnancy:
There is a limited amount of data regarding the use of risankizumab in pregnant women.
Human IgG is known to cross the placental barrier especially in the third trimester; No maternal exposure pregnancies occurred in the psoriatic arthritis development program. One paternal exposure pregnancy occurred in the psoriatic arthritis development program Study M16-011 – on risankizumab: pregnancy is ongoing. Cumulative for all indications there have been 32 pregnancies with 24 in those plaque psoriasis studies.

Age
Phase 3 PsA PBO-Controlled Analysis Set

In the Phase 3 PsA PBO-Controlled Analysis Set, the percentages of subjects with TEAEs, SAEs, severe TEAEs, and AEs leading to discontinuation were numerically higher in subjects ≥ 75 years of age compared to younger subjects in both the risankizumab and placebo groups

TABLE 2.4 1.1.5.1.1

Overview of Number and Percentage of Subjects with Treatment-Emergent Adverse Events by Age
(Phase 3 PsA Placebo-Controlled Analysis Set)

	>= 65 and < 75 years		>= 75 years	
	Placebo (N = 100) n (%) [SSA %]	Risankizumab 150 mg (N = 99) n (%) [SSA %]	Placebo (N = 16) n (%) [SSA %]	Risankizumab 150 mg (N = 16) n (%) [SSA %]
Subjects with:				
Any TEAEs	49 (49.0) [49.4]	42 (42.4) [42.3]	8 (50.0) [49.2]	9 (56.3) [54.8]
Any COVID-19 related TEAEs	0	0	0	0
Any TEAE related to study drug according to the investigator	12 (12.0) [12.3]	13 (13.1) [13.1]	1 (6.3) [7.1]	1 (6.3) [7.1]
Any serious TEAE	6 (6.0) [6.0]	3 (3.0) [2.9]	1 (6.3) [7.1]	3 (18.8) [18.3]
Any severe TEAE	2 (2.0) [2.0]	2 (2.0) [1.9]	1 (6.3) [7.1]	1 (6.3) [5.6]
Any TEAE leading to discontinuation of study drug	1 (1.0) [1.0]	1 (1.0) [1.1]	1 (6.3) [7.1]	1 (6.3) [5.6]
Any TEAE leading to death	0	0	0	1 (6.3) [5.6]
All Deaths#	0	0	0	1 (6.3) [5.6]

Note: Treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of study drug until the end of the placebo controlled period (defined as the minimum of the last dose date prior to Week 24 + 140 days and the Week 24 dose date (looking at AEs that occur prior to that dose)).
# Includes both treatment-emergent and non-treatment-emergent deaths.
SSA = Study size adjusted.

Phase 3 PsA Long-term Analysis Set,

In the any risankizumab group of the Phase 3 PsA Long-term Analysis Set, 14.1% subjects were between the ages of 65 and 74 years and 2.1% of subjects were ≥ 75 years of age. In subjects with long-term risankizumab exposure in the Phase 3 PsA Long-term Analysis Set, the rates of these categories of events and the ASIs (MACE, serious infections, opportunistic infection [excluding TB and herpes zoster], NMSC, hepatic events) were generally numerically lower in the youngest age category (< 65 years) and higher in the oldest age group (≥ 75 years). Numbers are small in this population. The SmPC currently highlights that there is limited information in subjects aged ≥65 years, adverse events in this age group should continue to be monitored through routine pharmacovigilance.

Gender:

In the Phase 3 PsA PBO-Controlled Analysis Set and subjects with long-term risankizumab exposure in the Phase 3 PsA Long-term Analysis Set, the percentages of subjects with TEAEs, SAEs, severe TEAEs, and AEs leading to discontinuation were generally higher in females than males in both the risankizumab and placebo groups. Adverse events observed at a higher frequency in females included upper respiratory tract infection, psoriatic arthropathy, headache, and oropharyngeal pain. Female subjects generally had numerically higher rates of AEs, SAEs and adverse events leading to discontinuation of study drug in both the risankizumab and placebo groups. The types of events noted higher in females (psoriatic arthropathy and headache) are aligned with the generally higher rates of pain disorders in female population. Upper respiratory tract infection was also noted at a higher frequency in females. However, when upper respiratory tract infection is considered with nasopharyngitis (reported at a higher rate in males compared to females), the rates were not meaningfully different across the genders

BMI:

In the Phase 3 PsA PBO-Controlled Analysis Set and subjects with long-term risankizumab exposure in the Phase 3 PsA Long-term Analysis Set, no clear pattern was observed with respect to BMI for TEAE categories, including SAEs, severe TEAEs, and TEAEs leading to discontinuation.

Race:

The majority of subjects (94.8%) in the study population were white, limiting the subgroup analyses by race.In general, across the Phase 3 PsA PBO-Controlled Analysis Set across groups, the rates of TEAEs were higher for non whites than whites.

Table 90: Overview of Number and Percentage of Subjects with Treatment-Emergent Adverse Events by Race (Phase 3 PsA Placebo-Controlled Analysis Set)

	White		Non-white	
	Placebo (N = 661) n (%) [SSA %]	Risankizumab 150 mg (N = 672) n (%) [SSA %]	Placebo (N = 39) n (%) [SSA %]	Risankizumab 150 mg (N = 25) n (%) [SSA %]
Subjects with:				
Any TEAEs	281 (42.5) [42.6]	301 (44.8) [44.7]	26 (66.7) [66.7]	21 (60.0) [60.3]
Any COVID-19 related TEAEs	2 (0.3) [0.3]	2 (0.3) [0.3]	0	0
Any TEAE related to study drug according to the investigator	80 (12.1) [12.1]	87 (12.9) [12.9]	8 (20.5) [20.9]	4 (11.4) [11.6]
Any serious TEAE	28 (4.2) [4.2]	21 (3.1) [3.1]	3 (7.7) [8.0]	0
Any severe TEAE	14 (2.1) [2.1]	16 (2.4) [2.4]	3 (7.7) [7.6]	0
Any TEAE leading to discontinuation of study drug	9 (1.4) [1.4]	6 (0.9) [0.9]	1 (2.6) [2.7]	0
Any TEAE leading to death	0	1 (0.1) [0.1]	0	0
All Deaths‡	0	1 (0.1) [0.1]	0	0
COVID-19 related deaths	0	0	0	0
Deaths occurring <= 140 days after last dose of study drug	0	1 (0.1) [0.1]	0	0
Deaths occurring > 140 days after last dose of study drug	0	0	0	0

Note: Treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of study drug until the end of the placebo controlled period (defined as the minimum of the last dose date prior to Week 24 + 140 days and the Week 24 dose date (looking at AEs that occur prior to that dose)).
‡ Includes both treatment-emergent and non-treatment-emergent deaths.

In subjects with long-term risankizumab exposure in the Phase 3 PsA Long-term Analysis Set, rates of SAEs, severe TEAEs, and AEs leading to discontinuation were generally consistent between whites and nonwhites across the any risankizumab 150 mg group.

Geographic region

In the Phase 3 PsA PBO-Controlled Analysis Set and subjects with long-term risankizumab exposure in the Phase 3 PsA Long-term Analysis Set, no clear pattern was observed with respect to geographic region for TEAE categories, including SAEs, severe TEAEs, and TEAEs leading to discontinuation.

Duration of psoriatic arthritis

In the Phase 3 PsA PBO-Controlled Analysis Set and subjects with long-term risankizumab exposure in the Phase 3 PsA Long-termAnalysis Set, no clear pattern was observed with respect to duration of psoriatic arthritis diagnosis for any category of TEAE, including overall TEAEs, SAEs, severe TEAEs, and and TEAEs leading to discontinuation

Baseline Medication:

A total of 71.9% of the subjects in the any risankizumab 150 mg group of the Phase 3 PsA Long-term Analysis Set were on a concomitant csDMARD at Baseline and 60.4% were on MTX at Baseline.The MAH outlines that there was no clear pattern with respect to concomitant csDMARD use for any category of TEAEs and ASIs including serious infections and malignant tumors in the Phase 3 PsA PBO-Controlled Analysis Set or in subjects with long-term risankizumab exposure in Phase 3 PsA Long-term Analysis Set.

Table 91: Overview of Number and Percentage of Subjects with Treatment-Emergent Adverse Events by Concomitant csDMARD at Baseline (Phase 3 PsA Placebo-Controlled Analysis Set)

	MTX alone		MTX and other csDMARD	
	Placebo (N = 375) n (%) [SSA %]	Risankizumab 150 mg (N = 396) n (%) [SSA %]	Placebo (N = 39) n (%) [SSA %]	Risankizumab 150 mg (N = 28) n (%) [SSA %]
Subjects with:				
Any TEAEs	147 (39.2) [39.3]	163 (41.2) [41.0]	23 (59.0) [59.5]	16 (57.1) [57.0]
Any COVID-19 related TEAEs	1 (0.3) [0.3]	1 (0.3) [0.2]	0	0
Any TEAE related to study drug according to the investigator	52 (13.9) [14.0]	48 (12.1) [12.1]	6 (15.4) [15.6]	2 (7.1) [6.7]
Any serious TEAE	12 (3.2) [3.2]	10 (2.5) [2.5]	6 (15.4) [15.6]	2 (7.1) [7.0]
Any severe TEAE	8 (2.1) [2.1]	8 (2.0) [2.0]	3 (7.7) [7.9]	1 (3.6) [3.7]
Any TEAE leading to discontinuation of study drug	2 (0.5) [0.5]	3 (0.8) [0.8]	1 (2.6) [2.5]	0
Any TEAE leading to death	0	1 (0.3) [0.3]	0	0
All Deaths#	0	1 (0.3) [0.3]	0	0
COVID-19 related deaths	0	0	0	0
Deaths occurring <= 140 days after last dose of study drug	0	1 (0.3) [0.3]	0	0
Deaths occurring > 140 days after last dose of study drug	0	0	0	0

Note: Treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of study drug until the end of the placebo controlled period (defined as the minimum of the last dose date prior to Week 24 + 140 days and the Week 24 dose date (looking at AEs that occur prior to that dose)).
Includes both treatment-emergent and non-treatment-emergent deaths.

Table 92: Overview of Number and Percentage of Subjects with Treatment-Emergent Adverse Event by Concomitant csDMARD at Baseline(Phase 3 PsA Placebo-Controlled Analysis Set)

	csDMARD other than MTX		Any sulfasalazine, without MTX	
	Placebo (N = 79) n (%) [SSA %]	Risankizumab 150 mg (N = 84) n (%) [SSA %]	Placebo (N = 31) n (%) [SSA %]	Risankizumab 150 mg (N = 29) n (%) [SSA %]
Subjects with:				
Any TEAEs	35 (44.3) [44.2]	44 (52.4) [52.4]	14 (45.2) [45.5]	14 (48.3) [48.0]
Any COVID-19 related TEAEs	0	0	0	0
Any TEAE related to study drug according to the investigator	9 (11.4) [11.3]	12 (14.3) [14.2]	4 (12.9) [13.0]	1 (3.4) [3.5]
Any serious TEAE	4 (5.1) [5.0]	2 (2.4) [2.4]	2 (6.5) [6.5]	1 (3.4) [3.3]
Any severe TEAE	1 (1.3) [1.2]	3 (3.6) [3.6]	1 (3.2) [3.3]	0
Any TEAE leading to discontinuation of study drug	3 (3.8) [3.7]	0	2 (6.5) [6.7]	0
Any TEAE leading to death	0	0	0	0
All Deaths#	0	0	0	0
COVID-19 related deaths	0	0	0	0
Deaths occurring <= 140 days after last dose of study drug	0	0	0	0

Table 92: Overview of Number and Percentage of Subjects with Treatment-Emergent Adverse Event by Concomitant csDMARD at Baseline(Phase 3 PsA Placebo-Controlled Analysis Set)

	csDMARD other than MTX		Any sulfasalazine, without MTX	
	Placebo (N = 79) n (%) [SSA %]	Risankizumab 150 mg (N = 84) n (%) [SSA %]	Placebo (N = 31) n (%) [SSA %]	Risankizumab 150 mg (N = 29) n (%) [SSA %]
Deaths occurring > 140 days after last dose of study drug	0	0	0	0

Note: Treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of study drug until the end of the placebo controlled period (defined as the minimum of the last dose date prior to Week 24 + 140 days and the Week 24 dose date (looking at AEs that occur prior to that dose).
Includes both treatment-emergent and non-treatment-emergent deaths.

Table 94: Overview of Number and Percentage of Subjects with Treatment-Emergent Adverse Events by Concomitant csDMARD at Baseline(Phase 3 PsA Placebo-Controlled Analysis Set)

	csDMARD other than MTX		Any sulfasalazine, without MTX	
	Placebo (N = 79) n (%) [SSA %]	Risankizumab 150 mg (N = 84) n (%) [SSA %]	Placebo (N = 31) n (%) [SSA %]	Risankizumab 150 mg (N = 29) n (%) [SSA %]
Subjects with:				
Any TEAEs	35 (44.3) [44.2]	44 (52.4) [52.4]	14 (45.2) [45.5]	14 (48.3) [48.0]
Any COVID-19 related TEAEs	0	0	0	0
Any TEAE related to study drug according to the investigator	9 (11.4) [11.3]	12 (14.3) [14.2]	4 (12.9) [13.0]	1 (3.4) [3.5]
Any serious TEAE	4 (5.1) [5.0]	2 (2.4) [2.4]	2 (6.5) [6.5]	1 (3.4) [3.3]
Any severe TEAE	1 (1.3) [1.2]	3 (3.6) [3.6]	1 (3.2) [3.3]	0
Any TEAE leading to discontinuation of study drug	3 (3.8) [3.7]	0	2 (6.5) [6.7]	0
Any TEAE leading to death	0	0	0	0
All Deaths#	0	0	0	0
COVID-19 related deaths	0	0	0	0
Deaths occurring <= 140 days after last dose of study drug	0	0	0	0
Deaths occurring > 140 days after last dose of study drug	0	0	0	0

Table 94: Overview of Number and Percentage of Subjects with Treatment-Emergent Adverse Events by Concomitant csDMARD at Baseline(Phase 3 PsA Placebo-Controlled Analysis Set)

	--------csDMARD other than MTX----		--------Any sulfasalazine,---- - ---------without MTX----------	
	Placebo (N = 79) n (%) [SSA %]	Risankizumab 150 mg (N = 84) n (%) [SSA %]	Placebo (N = 31) n (%) [SSA %]	Risankizumab 150 mg (N = 29) n (%) [SSA %]

Note: Treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of study drug until the end of the placebo controlled period (defined as the minimum of the last dose date prior to Week 24 + 140 days and the Week 24 dose date (looking at AEs that occur prior to that dose)).
Includes both treatment-emergent and non-treatment-emergent deaths.

A total of 14.1% of the subjects in the any risankizumab 150 mg group of the Phase 3 PsA Long-term Analysis Set were on a prior biologic therapy.There was no clear pattern with respect to number of prior biologic therapies for any category of TEAEs and ASIs including serious infections and malignant tumors in the Phase 3 PsA PBO-Controlled Analysis Set or in subjects with long-term risankizumab exposure in Phase 3 PsA Long-term Analysis Set.

Table 96: Overview of Number and Percentage of Subjects with Treatment-Emergent Adverse Events by Number of Prior Biologic Therapies (Phase 3 PsA Placebo-Controlled Analysis Set)

	0				>= 1			
	Placebo (N = 597) n (%) [SSA %]		Risankizumab 150 mg (N = 599) n (%) [SSA %]		Placebo (N = 103) n (%) [SSA %]		Risankizumab 150 mg (N = 108) n (%) [SSA %]	
Subjects with:								
Any TEAEs	253 (42.4)	[42.4]	265 (44.2)	[44.2]	54 (52.4)	[52.4]	57 (52.8)	[52.9]
Any COVID-19 related TEAEs	2 (0.3)	[0.3]	2 (0.3)	[0.3]	0		0	
Any TEAE related to study drug according to the investigator	70 (11.7)	[11.7]	72 (12.0)	[12.0]	18 (17.5)	[17.4]	19 (17.6)	[17.7]
Any serious TEAE	25 (4.2)	[4.2]	18 (3.0)	[3.0]	6 (5.8)	[5.8]	3 (2.8)	[2.8]
Any severe TEAE	14 (2.3)	[2.3]	14 (2.3)	[2.3]	3 (2.9)	[2.9]	2 (1.9)	[1.9]
Any TEAE leading to discontinuation of study drug	7 (1.2)	[1.2]	4 (0.7)	[0.7]	3 (2.9)	[2.9]	2 (1.9)	[1.9]
Any TEAE leading to death	0		1 (0.2)	[0.2]	0		0	
All Deaths#	0		1 (0.2)	[0.2]	0		0	
COVID-19 related deaths	0		0		0		0	
Deaths occurring <= 140 days after last dose of study drug	0		1 (0.2)	[0.2]	0		0	
Deaths occurring > 140 days after last dose of study drug	0		0		0		0	

Note: Treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of study drug until the end of the placebo controlled period (defined as the minimum of the last dose date prior to Week 24 + 140 days and the Week 24 dose date (looking at AEs that occur prior to that dose)).
Includes both treatment-emergent and non-treatment-emergent deaths.

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 subjects with plaque psoriasis which was included in the risankizumab submission for psoriasis. 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. Additionally, population pharmacokinetics (PK) analyses based on data from Phase 2 and 3 studies indicated that the clearance of risankizumab was not impacted by concomitant MTX use, a csDMARD commonly used in the clinical studies by subjects with active psoriatic arthritis. Details of these assessments are presented in the Summary of Clinical PharmacologyNo case of risankizumab overdose has been reported and no dose-limiting toxicity was observed during clinical studies.

Discontinuation due to adverse events

Phase 3 PsA PBO-Controlled Analysis Set

The percentage of subjects with TEAEs leading to discontinuation of study drug in the risankizumab treatment group (0.8%) was lower than the placebo group (1.4%).

Phase 3 PsA Long-Term Analysis Set

The rate of TEAEs leading to discontinuation of study drug with long-term risankizumab exposure was (1.7 E/100 PY) compared to the rate in the Phase 3 PsA Placebo-Controlled Analysis Set (2.7 E/100 PY).Treatment-emergent adverse events leading to discontinuation of study drug were not reported in more than one subject (by PT) in the any risankizumab 150 mg group, except for psoriatic arthropathy (4 subjects). Of the TEAEs leading to discontinuation, 3 nonserious TEAEs (ADR [reported term was suspected IP reaction], psoriatic arthropathy and swelling face) were considered by the investigator to be possibly related to study drug and 1 SAE (myopathy) was considered by the investigator to be possibly related to study drug.

Table 97: Adverse Events in Risankizumab Subjects Leading to Discontinuation of Study Drug (Phase 3 PsA Long-Term Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Risankizumab 150 mg (No Cross-over from Placebo) (N = 707) n (%) [SSA %]	Any Risankizumab 150 mg (N = 1365) n (%) [SSA %]
Any adverse event	11 (1.6) [1.6]	15 (1.1) [1.1]
Cardiac disorders	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Acute myocardial infarction	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
General disorders and administration site conditions	1 (0.1) [0.1]	2 (0.1) [0.1]
Adverse drug reaction	0	1 (< 0.1) [< 0.1]
Swelling face	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Hepatobiliary disorders	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Hepatic steatosis	1 (0.1) [0.1]	1 (< 0.1) [<0 .1]
Infections and infestations	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Intervertebral discitis	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Investigations	2 (0.3) [0.3]	2 (0.1) [0.1]
Alanine aminotransferase increased	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Aspartate aminotransferase increased	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Gamma-glutamyltransferase increased	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Hepatic enzyme increased	1 (0.1) [0.1]	1 (< 0.1) [<0 .1]
Musculoskeletal and connective tissue disorders	4 (0.6) [0.6]	5 (0.4) [0.4]
Myopathy	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Psoriatic arthropathy	3 (0.4) [0.4]	4 (0.3) [0.3]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1) [0.1]	2 (0.1) [0.1]
Acral lentiginous melanoma	0	1 (< 0.1) [< 0.1]
Papillary thyroid cancer	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Reproductive system and breast disorders	0	1 (< 0.1) [< 0.1]
Adenomyosis	0	1 (< 0.1) [< 0.1]
Respiratory, thoracic and mediastinal disorders	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]
Pneumonia aspiration	1 (0.1) [0.1]	1 (< 0.1) [< 0.1]

Post marketing experience

Post-marketing exposure to risankizumab is estimated to be 47,997 patient treatment years (PTY) cumulatively as of 25 September 2020.Risankizumab 150 mg (75 mg/0.83 mL × 2 SC injections) administered by SC injection at Week 0, Week 4, and q12w thereafter was first approved for the treatment of moderate to severe plaque psoriasis in adults on 26 March 2019 (international birth date) in Japan. Through 25 September 2020, risankizumab has been approved in 67 countries with estimated cumulative postmarketing patient exposure since first approval of 47,997 patient treatment years across 58 countries.

The overall safety of risankizumab 150 mg was evaluated through review of postmarketing reports (spontaneous, solicited, literature) received from 26 March 2019 through 25 September 2020. Search of the MAH's global safety database retrieved 17,103 cases with 33,877 events that were predominantly reported in the psoriasis patients. Overall, 92.5% (15,820/17,103) of the reports were considered

nonserious and 95% (16,304/17,103) were from a solicited source, which were predominantly collected through patient support programs.

The most frequently reported MedDRA SOC (35% of all cases) was general disorders and administration site conditions, in which PTs of fatigue, drug ineffective, and therapeutic response shortened were most frequently reported.

The most commonly reported AEs included psoriasis (7.8%), fatigue (3.9%), drug ineffective (3.9%), pruritus (3.3%), and headache (3.2%). Fatigue, pruritis and headache are currently listed in the PI.

The most commonly reported SAE was death (0.17%). Of the 57 reports of death, 52 were from a solicited postmarketing source. Forty-nine reports contained limited information to establish a causal association with risankizumab and 8 death reports were attributable to the patient's significant comorbidities and natural causes. In 36 of the reports where age was reported, the majority of the deaths occurred in the elderly population with a median age of 69.5 years. Psoriasis is associated with multiple comorbidities that could increase the risk of mortality in this population evidenced in a cohort study reporting an increased overall mortality risk (HR, 1.5; 95% CI 1.3 – 1.7) in patients with severe psoriasis.

Though pneumonia and CV events such as cerebrovascular accident and MI were other most frequently reported SAEs, the events are uncommon. These events as part of serious infections and MACE, continue to be monitored as Important Potential Risks and no safety concerns have been identified. Studies have shown an increased prevalence of CV risk factors including diabetes, hypertension, and obesity in patients with psoriasis (Kimball 2010). Additionally, patients with moderate to severe psoriasis also have been shown to have an increased risk of MI (Gelfand 2006), stroke (Gelfand 2009), and CV mortality (Mehta 2010). Given SAEs were reported in less than 0.2% of the retrieved reports, and patients with psoriasis often have comorbidities that could increase the risk of mortality, these findings are not unexpected. Review of the postmarketing reports did not identify any new safety risks for the marketing of risankizumab.

2.5.1. Discussion on clinical safety

The safety assessment focuses on 3 integrated safety PsA populations. Two of the integrated data sets (Phase 3 PsA PBO-Controlled Analysis Set and Phase 3 PsA Long-term Analysis Set). The third, All Risankizumab PsA Analysis Set, included all subjects with psoriatic arthritis who received at least one dose of risankizumab, including the psoriatic arthritis Phase 2 study data.

An additional supportive analysis set (All Risankizumab PsO Analysis Set, data cutoff date, 12 October 2020) including cumulative safety data from 17 psoriasis studies (3,131 subjects and 9081.2 PY) was included as he full week 52 data set was requested by CHMP.

Phase 3 PsA PBO-Controlled Analysis Set:

1,407 subjects received at least 1 dose of study drug (risankizumab or placebo) and includes data from 707 subjects who received at least 1 dose of risankizumab for a median duration of 168.0 days.1,365 subjects received at least 1 dose of risankizumab for a median duration of 273.0 days representing a total of 1,047.9 patient-years (PY) of long-term risankizumab exposure. 1338 completed 24 weeks of treatment (95.1%), 15 subjects (1.1%) discontinued study drug due to an adverse event. The percentage of subjects with TEAEs leading to discontinuation of study drug in the risankizumab treatment group (0.8%) was lower than the placebo group (1.4%).Of these subjects , 1,035 (75.8%) were treated with risankizumab for at least 6 months, and 372 (27.3%) were treated with risankizumab for at least 12 months. long term exposure to risankizumab (>18months) is limited.

All Risankizumab PsO Analysis Set:

Atotal of 3131 subjects with 9,081.2 PY exposure; 2494 subjects (79.7%) were treated with risankizumab for at least 12 months and 1105 subjects (35.3%) were treated with risankizumab for at least 48 months.

Phase 3 PsA Long-term Analysis Set

Data for 1,365 subjects treated with risankizumab 150 mg from the ongoing global Phase 3 psoriatic arthritis studies are included in the data set and 1217 (89.2%) of subjects were ongoing at the time of data cutoff (14 December 2020). There were 148 subjects in the any risankizumab 150 mg group prematurely discontinued study drug. The most common reason for discontinuation was lack of efficacy. Adverse event was the reason in 1.0% (13 subjects) The rate of TEAEs leading to discontinuation of study drug with long-term risankizumab exposure was (1.7 E/100 PY) compared to the rate in the Phase 3 PsA Placebo-Controlled Analysis Set (2.7 E/100 PY). The overall rates of discontinuation of risankizumab 150mg due to adverse events was low (<2%).

Safety results

There were no clinically meaningful differences in demographics, disease history, medical history, prior medications, or concomitant medications between the Phase 3 PsA PBO-Controlled Analysis Set, Phase 3 PsA Long-term Analysis Set, and All Risankizumab PsA Analysis Set that would have influenced the overall safety conclusions. Overall, in the Psoriatic arthritis studies 212 subjects were aged 65 – 74 y and only 34 subjects over 75y. Most demographics were consistent between the psoriatic arthritis and psoriasis analysis sets (slightly higher percentage of male subjects, higher percentage of Black or African Americans and lower percentage of white subjects in the All Risankizumab PsO Analysis Set. Under representation of Black or African Americans in the Psoriatic arthritis development program was an initial concern however this was satisfactorily justified by the MAH.

Regarding background disease characteristics approximately 50% of subjects had psoriatic arthritis for more than 5 years. Other types of medical history were generally similar among the treatment groups. The majority had tried one DMARD approximately 60% and approximately 70 % were on a DMARD at baseline

15% of patients had been treated with a biologic and the numbers were evenly balanced between placebo and risankizumab. During Phase 3 PsA PBO-Controlled Analysis Set 72.3% in Risankizumab group and 72.0 % in placebo group were on concomitant DMARDS of these 57.3 % in Risankizumab group were on Methotrexate vs 55.3% in placebo group. 3.0% in the Risankizumab group were on methrotrexate sodium vs 4.6% in placebo group. Approximately 20% were on concomitant systemic corticosteroids and approximately 60% were on concomitant NSAIDs.

Exposure-adjusted TEAE rates for risankizumab 150mg calculated as events/100 PY were higher in the initial period than with longer exposure to risankizumab (209.7 vs 167.9). In the risankizumab 150 mg group SAEs were reported at a rate of 7.5 E/100PY compared to 11.7 E/100 PY for placebo. There was no increase in the event rate for AEs with longer exposure to risankizumab. Rates for any TEA were 167.9E/100PY for any Risankizumab group in the long-term analysis set vs 211.6E/100PY in the placebo group. Across the PsA clinical trials there was 1 death in the active treatment group reported. The rate of SAEs in the risankizumab treated psoriatic arthritis population is consistent with the rate observed in the All Risankizumab PsO Analysis Set (7.7 E/100 PY). The SAEs with the highest rate with long-term risankizumab exposure were COVID-19 and pneumonia (Phase 3 PsA Long-term Analysis Set, both 0.4 E/100 PY).

In the Phase 3 PsA PBO-Controlled Analysis Set: The most frequently reported TEAEs (≥ 3% of subjects) were upper respiratory tract infection (4.1%) and nasopharyngitis (3.5%) in the risankizumab group. There were no TEAE PTs that occurred in ≥ 5% of subjects in any treatment group. ALT increase occurred

in 16 (2.3 %) subjects in the Risankizumab group vs 12 subjects (1.7%) in the placebo group. AST increase 13 subjects (1.8%) in the in the Risankizumab group, 9 subjects (1.3%) in the placebo group.In the Phase 3 PsA Long-term Analysis Set the TEAEs that were most frequently assessed by the investigators as having a possible relationship to study drug in the risankizumab group were upper respiratory tract infection ALT increased and AST increased. These findings supported the need for the addition of increase in transaminase to section 4.8 of the SmPC. ALT occurred at a higher rate for Risankizumab versus placebo 1.8/100 PY vs 1.4/100 PY, AST 1.3/100PY vs 1.0/100 PY respectively.

Regarding ASIs in the Phase 3 PsA PBO-Controlled Analysis Set, any hepatic events occurred in 5.4% of risankizumab subjects vs 3.9 % subjects in placebo group. In the Phase 3 PsA Long-term Analysis Set there were 8.6% of subjects with any hepatic event in patients who continued Risankizumab thrpoughout the study vs 6.3% inpatients who crossed over form placebo, suggests that for patients treated for a longer duration with risankizumab experience an increases of hepatic events increases over time.

In the Phase 3 PsA PBO-Controlled Analysis Set, no subjects had laboratory values that met biochemical Hy's law. The rate of hepatic events with long-term risankizumab exposure was (12.3 E/100 PY) in the any risankizumab 150 mg group. All hepatic TEAEs observed with risankizumab treatment were non serious, and the majority were mild to moderate in severity. The rate of severe hepatic disorder events was low in the Phase 3 PsA Long-term Analysis Set with a rate of 0.5 E/100 PY in the any risankizumab 150 mg group) and these hepatic events lead to discontinuation in the any risankizumab 150 mg group (0.5 E/100 PY).The 5 severe hepatic events occurred in 3 subjects. Two of the 3 subjects did not have Grade 3 elevations in ALT or AST, and 1 subject with Grade 3 elevations in ALT and AST.

ALT increase event rate was 3.7/100 years and AST event rate 2.9/100y, as the MAH has highlighted in the submission ALT is more specific for DILI than AST. One SAE a single serious case associated with biochemical Hy's law was confounded by a confirmed positive.Hepatitis E IgM serology and excessive alcohol use and therefore was not deemed to be a Hy's law case.

The proportion of subjects with long-term risankizumab exposure with PCI liver transaminase elevations was < 3%, in the any risankizumab 150 mg group of the Phase 3 PsA Long-term Analysis Set but higher in those on Risankizumab without cross over from placebo.

In the All Risankizumab PsA Analysis Set notably 3 % of patients had ALT values ≥ 3 x ULN.46 subjects (3.0%) had ALT levels ≥ 3 ULN, 14 subjects (0.9%) had ALT levels ≥ 5 ULN, 4 subjects (0.3%) had ALT levels ≥10 ULN. 27 subjects (1.8%) had AST levels ≥ 3 ULN 11 subjects (0.7%) had AST levels ≥5 ULN 3 subjects (0.2%) had AST levels> ≥10 ULN.

In the All Risankizumab PsO Analysis Set nine serious hepatic events have been reported overall of which 2 were discussed in the initial submission (PTs of liver injury and drug-induced liver injury), both of which were attributed to INH. 7 serious events have been reported since submission**.** A total of 5 subjects in the All Risankizumab PsO Analysis Set met the criteria for biochemical Hy's law case,. it was clarified further that all 5 cases had clear alternative aetiologies and were not attributable to risankizumab-induced hepatocellular injury.

The hepatic safety profile in the psoriatic arthritis population (the rate of treatment-emergent hepatic events is 13.1/100PYs which is higher than the All Risankizumab PsO Analysis Set (5.6 E/100 PYs) this is a notable difference between the two sets, the MAH was requested to and did discuss howthe Known differences between the PsO and PsA populations would account for the difference in observed hepatic events between the populations.

In the initial PsA submission of 1365 subjects (1047.9 PY), the proportion of subjects reporting any hepatic event was 8.6%, with an event rate of 12.3 E/100 PY. In the 4-months safety update (1307.1 PY), 6.8% of subjects reported any hepatic event for an event rate of 10.9 E/100 PY. .

Patients with hepatic impairment were not excluded from the studies and an overview of safety in patients with hepatic impairment was subsequently provided, including all postmarketing cases with PTs relevant for liver injury.

In the Phase 3 PsA PBO-Controlled Analysis Set, the subjects on baseline MTX treatment generally had more frequent Grade 1 and 2 elevations in ALT and AST but notably in those on no methotrexate at baseline the grade 3 elevations were higher 2.5% vs 0 for ALT and 1.4% vs 0 for ASTIn the Phase 3 PsA long term Analysis Set, the subjects on baseline Methotrexate (MTX) treatment generally had more frequent Grade 1 and 2 elevations in ALT and AST but notably in those on no methotrexate at baseline the grade 3 elevations were higher 1.3% vs 0.5 for ALT and 0.7vs 0.5 for AST,

Overall the number hepatic events warranted further discussion, in particularthe potential for drug induced hepatotoxicity with risankizumab, a possible mechanistic basis for a drug related reaction, warning in osections4.4 of the SPC (warning for hepatotoxic potential, monitoring of hepatic enzymes) RMP update and possible pharmacovigilance or risk minimisation measures.

Hepatotoxicity is not considered to be a safety concern in risankizumab treatment at this time for the following reasons: Inhibition of IL-23 has not been linked to cases of idiosyncratic, clinically apparent liver injury;1 therefore, a mechanistic basis for drug-induced liver injury appears to be lacking. Animal GLP toxicology studies showed no evidence of hepatotoxicity with risankizumab administration

Hepatotoxicity is not a reported mechanistic effect of IL-23 inhibition, however this effect maybe due to concomitant use of other hepatotoxic drugs, which cannot be confirmed at this time.

Higher rates of liver elevations with risankizumab treatment in the PsA population compared with the PsO population were expected given the higher prevalence of liver test abnormalities among patients with PsA as well as differences in baseline characteristics between the placebo and risankizumab groups.There have been no Hy's law cases attributable to risankizumab across the clinical development program. There were no clinically meaningful differences between the risankizumab 150 mg group and the placebo group in regard to mean changes from Baseline or in instances of outliers of 3 × ULN. Assessment of postmarketing reports did not identify a trend nor provide clear evidence of an increased risk of hepatic disorders with the use of risankizumab.

In conclusion, based on the totality of data, the PRAC/CHMP was concluded that additional measures are not necessary at this time, hepatotoxicity is not considered a potential risk for the risankizumab RMP and further pharmacovigilance or risk minimisation measures are not warranted. In addition, a warning for hepatotoxic potential or a recommendation for monitoring for hepatic enzymes in Section 4.4 and identification of enzyme elevations as an ADR in Section 4.8 of the SmPC is not warranted.

A total of 3 cases of adjudicated **Major Adverse Cardiovascular Event (MACE)** were reported in the Phase 3 psoriatic arthritis studies. Overall, the data did not suggest an increased risk of MACE with risankizumab treatment in patients with psoriatic arthritis. MACE is an important potential risk for risankizumab in the RMP and will continue to be assessed in the long-term psoriasis safety studies and the ongoing Phase 3 psoriatic arthritis studies.

Infections (including serious infections, active tuberculosis (TB), opportunistic infections, and herpes zoster): In the Phase 3 PsA PBO-Controlled Analysis Set, the percentage of subjects with infections was comparable between the risankizumab (19.0%) and placebo (19.3%) groups. The overall rates of infection with long-term risankizumab therapy (Phase 3 PsA Long-term Analysis Set was E/100 PY) compared to the rates in Phase 3 PsA Placebo-Controlled Analysis Set (51.1 E/100 PY).

In the Phase 3 PsA PBO-Controlled Analysis Set, the percentage of subjects with serious infections in the risankizumab group (1.0%) was lower than the placebo group (1.6%), with an event rate of 2.7 per 100 PYs and 4.0 E/100 PY) in the placebo group. The only serious infections reported in ≥ 2 subjects in a

group was cellulitis (2 subjects) in the risankizumab group and pneumonia (2 subjects) in the placebo group. None of the subjects in the risankizumab group had events of serious infection which led to discontinuation of study drug. With long term risankizumab exposure (Phase 3 PsA Long-term Analysis Set, the rate was 2.6 E/100 PY) and higher than the rate observed in the All Risankizumab PsO Analysis Set (1.3 E/100 PY). The most common (≥ 0.1 events per 100 PY) serious infections with long-term risankizumab exposure were pneumonia and COVID-19 followed by cellulitis. There was 1 treatment-emergent death due to urosepsis considered unrelated to risankizumab in an elderly patient with dementia and multiple other comorbidities. The rate of serious infections associated with long-term risankizumab exposure (2.6 events per 100 PY) is within the expected range for this patient population based on published estimates (3.98 events per 100 PY).

The clinical presentation of COVID-19 in the risankizumab treated psoriatic arthritis population was consistent with that observed in the general population. A total of 4 nonserious cases of herpes zoster (0.4 E/100 PY) were reported with the long-term risankizumab exposure (Phase 3 PsA Long-Term Analysis Set) which was comparable to the rate in the All Risankizumab PsO Analysis Set (0.5 E/100 PY). All cases resolved with the subjects continuing risankizumab treatment. The rate of opportunistic infection (< 0.1 E/100 PY) was the same in the Phase 3 PsA Long-Term Analysis Set and All Risankizumab PsO Analysis Set. There were no cases of active TB infection reported in the psoriatic arthritis development program across the analysis sets which is consistent with the results observed in the All Risankizumab PsO Analysis Set. Across the psoriatic arthritis clinical studies, 105 subjects with latent TB were concurrently treated with risankizumab and TB prophylaxis during the study and did not develop active TB during the mean follow-up of 1.0 year. Of the 132 subjects with latent TB treated with risankizumab who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 0.9 years.

The rate of **Nonmelanoma Skin Cancer (NMSC)** with long-term risankizumab exposure was 0.6 events Per 100 PYs and is within the epidemiological reference rate in the psoriatic arthritis population (0.61 Events per 100PY) and comparable to the rate observed in the All Risankizumab PsO Analysis Set (0.7 E/100 PY). In the Phase 3 PsA Placebo-Controlled Analysis Set, 1 malignancy (NMSC) was reported in a subject in the risankizumab group (basal cell carcinoma) and 3 malignancies were reported in the placebo group(Bowen's disease, breast cancer, and non-small cell lung cancer).

The rate of **malignancies excluding NMSC** with long-term risankizumab exposure was 0.2 E/100 PY. It is consistent with the rates of malignancies excluding NMSC reported in population-based epidemiology studies of patients with psoriatic arthritis (0.48 E/100 PY).A total of 2 malignancies excluding NMSC, acral lentiginous melanoma reported 78 days after first risankizumab exposure and papillary thyroid cancer reported 177 days after first risankizumab exposure, were observed with long-term risankizumab exposure but causality was not attributable to risankizumab

In the Phase 3 PsA PBO-Controlled Analysis Set, the rate of **hypersensitivity reaction** with Risankizumab treatment (5.5 E/100 PY) was higher than that in placebo (3.1 E/100 PY). The MAH outlines that some of the preferred terms (PTs) in the hypersensitivity reaction category are related to injection site reactions (which are known ADRs for risankizumab) and some PTs suggest alternate aetiologies. The rate of hypersensitivity reaction was stable with long-term risankizumab exposure (Phase 3 PsA Long-term Analysis Set, 4.2 E/100 PY) The MAH outlined that rash was the most common hypersensitivity reaction reported however it was concluded that addition of this ADR is not warranted at this time.

In the Phase 3 PsA Long term Analysis Set there were 3.8% of subjects with any **hypersensitivity** reaction in the no cross over from placebo group vs 2.6% in the any risankizumab group, this raises the question about longer duration of treatment with risankizumab (i.e. no cross over from placebo) does the risk of any hypersensitivity reaction increases over time, the MAH was requested to and did discuss this

observation. The data show that new incidences of hypersensitivity reactions remain relatively stable for the first ~270 days of risankizumab exposure, then start to decline. The risk of hypersensitivity reaction in subjects treated with risankizumab does not increase over time.

No subjects experienced events of **serious hypersensitivity** reaction in the Phase 3 PsA Placebo-Controlled Analysis Set or in the Phase 3 PsA Long-term Analysis Set. Serious hypersensitivity reactions are listed as a potential risk in the RMP and will continue to be assessed in the long-term psoriasis safety studies and the ongoing Phase 3 psoriatic arthritis studies.

Immunogenicity to risankizumab had no clinically relevant impact on the safety as assessed for hypersensitivity and injection site reactions of risankizumab.

In the Phase 3 PsA PBO-Controlled Analysis Set, the rate of **injection site reactions** with risankizumab treatment (2.4 E/100 PY) was higher than that in placebo (0.3 E/100 PY) but within the frequency of the currently listed ADRs identified in the psoriasis development program (includes PT's of injection site bruising, erythema, hematoma, hemorrhage, irritation, pain, pruritus, reaction and swelling). Compared to the Phase 3 PsA PBO-Controlled Analysis Set rate, the rate of injection site reaction was stable with long-term risankizumab exposure (Phase 3 PsA Long-term Analysis Set, 1.3 E/100 PY) and was lower than the rate observed in the All Risankizumab PsO Analysis Set (3.2 E/100 PY).

The MAH clarified that **anti-drug antibodies/neutralizing antibodies** were actually lower in PsA at approximately 12% ADA and 0% NAb positive rates compared to 24% and 14% respectively in PsO, but noted that the immunogenicity assessment in PsA was based on Wk28 data which is different from the one in PsO which was based on Week 52 data.

Depression and Suicide was an ASI in the initial MA application for Psoriasis but has not been included as an ASI in this application nor has there been a discussion on these events, the MAH was requested to and did provide an overview of any cases of depression or suicide across the psoriatic arthritis development program. There was 1 subject (<0.1%) who experienced a serious event of suicide attempt due to worsening of pre-existing bipolar disorder. There were no completed suicides in the risankizumab PsA clinical studies. Overall exposure adjusted event rates for depression and SIB remained stable and low. In the Phase 3 PsA Placebo-Controlled Analysis set, event totals for risankizumab 150 mg were numerically lower when compared to placebo. No safety concern was identified upon review of depression and SIB events. Based on the available data, depression and SIB are not considered a potential risk for risankizumab.

There were 3 (0.4%) subjects in the risankizumab group in the Phase 3 PsA PBOControlled Analysis Set reporting a Grade 3 decrease in neutrophil count this was comparable to the placebo treatment group which showed 2 (0.3%) subjects reporting a Grade 3 decrease in neutrophil count. Among subjects treated with risankizumab who reported a decrease in neutrophil counts, treatment was not discontinued in any subject and the counts improved or resolved to normal despite continued therapy. .In view of the possible association between systemic blockade of IL-23 with subsequently lower IL-17 levels and reductions in peripheral neutrophil counts based on roles of IL-17A in innate immunity and neutrophil biology, the MAH further discussed the effect of long term exposure of risankizumab exposure on neutrophil cell counts and provided an overview of all grades of decrease in neutrophil across the analysis sets comparing the mean reductions in risankizumab group to placebo. Overall, most of the neutrophil reductions were an isolated occurrence with recovery of the neutrophil count to normal levels with continued risankizumab use. Since these were isolated incidences with recovery during continued use of risankizumab, there is no evidence to suggest that duration of therapy had any impact.

The majority of subjects (94.8%) in the study population were white, limiting the subgroup analyses by race. In general, across the Phase 3 PsA PBO-Controlled Analysis Set across groups, the rates of TEAEs were higher for non whites than whites. In subjects with long-term risankizumab exposure in the Phase 3

PsA Long-term Analysis Set, rates of SAEs, severe TEAEs, and AEs leading to discontinuation were generally consistent between whites and nonwhites across the any risankizumab 150 mg group.The majority of subjects (94.8%) in the study population were white, under representation of Black or African Americans in the Psoriatic arthritis development program is a concern. Following further discussion this information does not need to be added to the RMP as missing information as no differences in safety profile is expected with different racial background.

In the Phase 3 PsA PBO-Controlled Analysis Set and subjects with long-term risankizumab exposure in the Phase 3 PsA Long-term Analysis Set, no clear pattern was observed with respect to BMI with respect to geographic region or with respect to duration of psoriatic arthritis diagnosis for TEAE categories, including SAEs, severe TEAEs, and TEAEs leading to discontinuation.

There was no clear pattern with respect to concomitant csDMARD use for any category of TEAEs and ASIs including serious infections and malignant tumors in the Phase 3 PsA PBO-Controlled Analysis Set or in subjects with long-term risankizumab exposure in Phase 3 PsA.

2.5.2. Conclusions on clinical safety

The Full 52-week safety data for this new indication was provided by way of response during the procedure and no changes were observed in the profile of TEAEs, ASIs, and laboratory findings of clinical significance. Long term safety is considered missing information in the RMP for this new indication. This is endorsed.

The totality of data supports the position at this time that hepatotoxicity is not considered a potential risk for the risankizumab RMP and further pharmacovigilance or risk minimisation measures are not warranted. Neither a warning regarding hepatotoxic potential in Section 4.4 nor the identification of enzyme elevations as an ADR in Section 4.8 of the SmPC is warranted at this time.

From the available safety the safety profile in the PsA population was generally comparable with that established in the psoriasis population. The MAH has not proposed the addition of any new ADRs to the SmPC which is acceptable.

2.6. PSUR cycle

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

2.7. Risk management plan

The MAH submitted to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 3.2 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	• MACE • Serious infections • Malignancies • Serious hypersensitivity reactions
Missing information	• Use during pregnancy and lactation • Use in patients with chronic HBV or chronic HCV infection • Use in patients with any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix • Long-term safety

Pharmacovigilance plan

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 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	Potential risks of malignancies, MACE, serious infections, and serious hypersensitivity reactions 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 - 1st Interim report of study results (incl. data up to December 2024): December 2026 - 2nd Interim report of study results (incl. data up to December 2028): December 2030 - End of data collection (incl. data up to December 2032): December 2033 - Final report of study results: December 2034	Final study report: December 2034 (Protocol v1.3 accepted by EMA Pharmacovigilance Risk Assessment Committee (PRAC) as of 28 January 2021).

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	• MACE (defined as a composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death) • serious infections (incl. opportunistic infections) serious hypersensitivity reactions			

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: Q3 2024 - End of data collection: Q3 2029 - Final study report: Q3 2030	Final study report: Q3 2030 (Protocol v1.3 accepted by EMA PRAC as of 25 February 2021).
M15-997: A multicenter, open Label study to assess the safety and efficacy of risankizuMab for MaInTenance in moderate to severe pLaquE type pSoriaSis (LIMMITLESS)/ Ongoing	The primary objective of Study M15-997 is to investigate long-term safety and tolerability of risankizumab in subjects with psoriasis who have completed one of the preceding Phase 2/3 studies.	Potential risks of malignancies, MACE, serious infections and serious hypersensitivity reactions Missing information: long-term safety	Last subject last visit planned for November 2023.	Final Report Q2 2024

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
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.	Potential risks of malignancies, MACE, serious infections and serious hypersensitivity reactions Missing information: long-term safety	Final report Q3 2025	Last subject last visit planned for September 2024. Final report Q3 2025
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.	Potential risks of malignancies, MACE, serious infections and serious hypersensitivity reactions Missing information: long-term safety	Final report Q3 2025	Last subject last visit planned for May 2024. Final report Q3 2025

As part of this procedure two psoriatic arthritis studies were added to the RMP, namely KEEPsAKE 1 (study M16-011) and KEEPsAKE 2 (study M15-998).

Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
MACE	Routine risk minimization measures: No specific measures are required for patients receiving risankizumab; standard of care is adequate. Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: • Biweekly line listing review of all post-marketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials. • Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database. • Periodic reports to agencies (e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines. Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Real World Setting • Risankizumab Psoriasis Long-Term Extension Study LIMMITLESS • Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2

Serious infections	Routine risk minimization measures: Product labeling (SmPC Section 4.3, Contraindications and Section 4.4, Special warnings and precautions for use) Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: • Biweekly line listing review of all post-marketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials. • Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database. • Periodic reports to agencies (e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines. Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Real World Setting • Risankizumab Psoriasis Long-Term Extension Study LIMMITLESS • Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2

Malignancies	Routine risk minimization measures: No specific measures are required for patients receiving risankizumab; standard of care is adequate. Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: • Biweekly line listing review of all post-marketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials. • Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database. • Periodic reports to agencies (e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines. Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Real World Setting • Risankizumab Psoriasis Long-Term Extension Study LIMMITLESS • Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2

Serious hypersensitivity reactions	Routine risk minimization measures: 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 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 Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: • Biweekly line listing review of all post-marketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials. • Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database. • Periodic reports to agencies (e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines. Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Real World Setting • Risankizumab Psoriasis Long-Term Extension Study LIMMITLESS • Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2
Using during pregnancy and lactation	Routine risk minimization measures: SmPC Section 4.6 Fertility, pregnancy and lactation Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: • Biweekly line listing review of all post-marketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials. • Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database. • Periodic reports to agencies (e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines. Additional pharmacovigilance activities: Pregnancy Exposure and Outcomes for Women Treated with Risankizumab

Use in patients with chronic HBV or chronic HCV infection	Routine risk minimization measures: No specific measures are required for patients receiving risankizumab; standard of care is adequate. Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: • Biweekly line listing review of all post-marketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials. • Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database. • Periodic reports to agencies (e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines. Additional pharmacovigilance activities: None
Use in patients with any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix	Routine risk minimization measures: No specific measures are required for patients receiving risankizumab; standard of care is adequate. Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: • Biweekly line listing review of all post-marketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials. • Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database. • Periodic reports to agencies (e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines. Additional pharmacovigilance activities: Long-Term Prospective Cohort Study in Real World Setting

Long-term safety	Routine risk minimization measures: None. Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	• Long-Term Prospective Cohort Study in Real World Setting • Risankizumab Psoriasis Long-Term Extension Study LIMMITLESS • Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2

2.8. Update of the Product information

New therapeutic indication for the treatment of active psoriatic arthritis in adults. Consequently sections 4.1, 4.2, 4.8, 5.1 and 5.2 to the SmPC have been updated. The Package leaflet is updated accordingly. Minor update of Annex II is also introduced.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: limited changes introduced in the PI.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Psoriatic arthritis (PsA) is a chronic systemic inflammatory disease classified as a sub-type of spondyloarthritis (SpA) and characterized by the hallmark features of arthritis and psoriasis. The course of PsA is usually one of flares and remissions with varying combinations of disease manifestations affecting the synovium, tendons, entheses, skin, and bone. Under current clinical guidelines the primary goal of treatment is to maximize long-term health-related quality of life and treatment should be aimed at the target of remission, or low disease activity, by regular disease activity and appropriate adjustment of therapy (Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis. 2020;79(6):700-12).

3.1.2. Available therapies and unmet medical need

Initial treatment of musculoskeletal symptoms is with nonsteroidal anti-inflammatory drugs (NSAIDs) and local corticosteroid injections. Topical therapies are used for the initial treatment of psoriasis. In case of toxicity or lack of efficacy with these measures, clinical guidelines recommend systemic therapy with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (methotrexate [MTX], leflunomide [LEF], sulfasalazine [SSZ], or ciclosporin A), followed by biologic therapy (tumor necrosis factor [TNF], IL-17, or IL-12/23 inhibitors) in those who do not respond adequately to csDMARDs.

Primary or secondary non-response or intolerance to adverse effects of available therapies leaves patients with an unmet medical need. The development of other target-specific biologic therapies (e.g., IL-23

inhibitors) or targeted synthetic DMARDs (such as Janus kinase [JAK] inhibitors) provides additional therapy options.

3.1.3. Main clinical studies

In support of this application the risankizumab clinical development program for PsA includes one Phase 2 dose ranging study (Study M16-002), one Phase 2 open-label extension study (Study M16-244) and two pivotal Phase 3 studies (Studies M15-998 (n=443) and M16-011 (n=964)) designed to evaluate safety and efficacy of risankizumab as monotherapy and as combination therapy (with background csDMARDs) by enrolling adult subjects who had an inadequate response or intolerance to one or 2 biologic therapies (Bio-IR) and subjects who had an inadequate response or intolerance to at least one csDMARD (csDMARD IR). The Week 52 dataset for the Phase 3 trials was provided by the MAH by way of responses during the procedure; results were consistent with the Week 24 primary analysis and support maintenance of effect and inhibition of progression of structural joint damage through 24 and 52 weeks of treatment with RZB.

An integrated safety analyses of long-term data from studies of risankizumab in subjects with moderate to severe psoriasis (All Risankizumab PsO Analysis Set, which primarily examined the same dosing regimen as the psoriatic arthritis clinical studies) are provided to support the safety assessment of risankizumab for the treatment of subjects with PsA.

The primary endpoint, ACR 20 at week 24**,** is in line with the current PsA guidelines and with previous applications authorised in this condition.

The key secondary endpoints across the trials examined effects on a range of efficacy measurements such as HAQ DI, PASI, ACR 50, ACR 70, mNAPSI, symptom and physical function scores, effects on dactylitis and enthesitis and mTSS.

Additional endpoints included quality of life measurements, minimal and very low disease activity, PK exposure response relationship, antibody responses and subgroup analysis.

3.2. Favourable effects

The primary efficacy endpoint was reached in both phase 3 trials - risankizumab 150 mg at Week 0, Week 4 and 12 weekly thereafter was demonstrated as superior to placebo for ACR20 response at Week 24 ($p<0.001$). While ACR20 may be regarded as a relatively low bar, secondary endpoints and trends in available longer-term data are supportive of the primary efficacy endpoint for data submitted to date.

All ranked secondary endpoints were met in M15-998 and 8/11 ranked secondary endpoints were met in M16-011. Other secondary endpoints and subgroup analyses at Week 24 were supportive of efficacy of risankizumab in treating the signs and symptoms of PsA, with effects on physical function and health related quality of life evident within this time frame.

In both studies ACR20 response rates for risankizumab were noted at Week 4, and response rates were maintained over time to week 24. ACR50 response rate at Week 24 favoured risankizumab over placebo, however ACR70 response rate was not significant.

Subjects with psoriatic nail disease experienced statistically significant improvements from Baseline in mNAPSI and PGA-F at Week 24 with risankizumab compared to placebo arm.

Data for subjects with enthesitis and dactylitis in M15-998 was pooled and analysed under multiplicity control of M16-011. For subjects with enthesitis at Baseline, there was a statistically significant, higher percentage with resolution of enthesitis (LEI=0) at Week 24 with risankizumab compared to those on

placebo. For subjects with dactylitis at Baseline, there was a statistically significant, higher percentage with resolution of dactylytis (LDI=0) at Week 24 with risankizumab compared those on placebo.

There was a slightly higher response in ACR 20 in biologic naïve subjects in M16-011 (57.3% vs. 33.5% placebo; difference 24%) compared to M15-998, which included the Bio-IR cohort (51.3% vs. 26.5% placebo; difference 24.5%).

More than half of subjects recruited to M15-998 (n=251; 56.7%) had prior use of ≥2 csDMARDS, likely reflecting recruitment of BIO-IR subjects to that trial, with almost a third of subjects having prior use of ≥2 csDMARDS (n= 311; 32.3%) in M16-011.

Across both studies, 16.4% (231/1407) of subjects were >65 years, with 2.3% (32/1407)>75 years; response in the elderly is not expected to differ from that in younger age groups.

Rates of Period 1 completion were high in both trials, at over 97% in both arms in M16-011 with only 1 discontinuing due to lack of efficacy in the rizankinumab arm. In M15-988 Period 1 completion rates were lower, at over 90% for placebo and 96% for risankizumab, 93.5% overall. There were 2 discontinuations due to lack of efficacy in the risankizumab arm and 7 in placebo, noting the Bio-IR population enrolled in this trial.

3.3. Uncertainties and limitations about favourable effects

While risankizumab did not demonstrate a statistically significant effect versus placebo for the ranked secondary endpoint mTSS, reflecting radiographic joint progression at Week 24, the week 52 data analysis, consistent with the week-24 primary analysis, supports maintenance of effect and inhibition of progression of structural joint damage through 24 and 52 weeks of treatment with risankizumab.

In M15-988 46.5% (n=206) of subjects had been on a biologic therapy before. An active comparator was not used in M15-998 or M16-011. While this is not mandated under current guidelines, comparison with an available active comparator would have been useful to contextualise risankizumab efficacy further. It is noted that there was a strong placebo effect for biologic naïve subjects on csDMARDs at baseline in M15-998, compared to those who were on no csDMARD at baseline or to those BIO-IR subjects who had failed ≥1 prior biologic therapy (Table 9, M15-998 CSR). Placebo effects were observed in Study M16-011 for some clinical efficacy endpoints including ACR responses. The MAH justified with literature data that the baseline disease characteristics of patients in study M16-011 had somewhat more severe PsA than patients in Study M15-988.

While a dose-response relationship was not been clearly demonstrated clinically, and a lack of correlation between risaknkizumab trough concentrations and the IL17F levels, additional evidence showed that therapeutic risankizumab concentrations were however on the plateau of the concentration-response curve.

Regarding pooled data, overall, 197/206 (95.6%) of subjects in the Bio-IR cohort had prior exposure to TNF inhibitors, followed by abatacept (7/206; 3.4%), rituximab (1/205; 0.5%) and secukinumab (1/206; 0.5%). The baseline characteristics are balanced within and between csDMARD–IR and Bio-IR cohorts. The percentage difference for binary and continuous variables, within and between the csDMARD and BIO-IR cohorts are, in the main, in favour of the efficacy of RZB at week 24.

Over both trials, 19.6% of subjects recruited had spondylitis at baseline (276/1407; M15-998, n =87; M16-011, n=189), however the majority had a clinical rather than radiological diagnosis. While enthesitis and dactylitis at baseline are recorded for pooled analysis under M16-011, subgroup severity e.g. arthritis mutilans is not clear.

At Baseline, pre-existing ADAs and pre-existing NAbs were detected in 1.3% (5/376) and 0% (0/376) respectively. The incidence of treatment emergent ADAs to risankizumab in subjects who received at-least 150 mg dose of risankizumab at Weeks 0, 4, and 12 weekly thereafter (n=206) was 13% (27/206).

Of these 27 subjects, 24 did not have positive NAb results (3 were missing samples). The ADA titre values ranged from 10.0 to 2230 across study visits.

Up to week 28 in both studies, of 376 evaluable subjects in M15-09881 and of 863 evaluable subjects in M16-011, 1.3% (5/376) and 2.4% (21/863) respectively had pre-exisiting ADA positivity. In the risankizumab arms 13% (27/206) in M15-988 and 12% (52/442) developed ADA positivity and none developed NAb positivity. It is unknown what percentage of patients will develop ADA over time with chronic treatment and at what titre it would become clinically significant for patients. However, no impact of ADAs on risankizumab exposures was observed. Overall, the ADA formation rate by MTX co-treatment was found to be decreased by 24.4 %. The effect is moderate and corresponds to expectations.

3.4. Unfavourable effects

From the available safety the safety profile in the PsA population was generally comparable with that established in the psoriasis population. The MAH has not proposed the addition of any new ADRs to the SmPC but clarification on system organ class events have been introduced

Exposure-adjusted TEAE rates for risankizumab 150mg calculated as events/100 PY were higher in the initial period than with longer exposure to risankizumab (209.7 vs 167.9). urther longer exposure datawill ne collected to gather experience in the post marketing setting.

In the Phase 3 PsA PBO-Controlled Analysis Set the most frequent TEAEs by SOC (≥ 10% of subjects) in the risankizumab group were infections and infestations (19.0%), which had a similar frequency (19.3%) in the placebo group. The rate of SAEs in the risankizumab treated psoriatic arthritis population is consistent with the rate observed in the All Risankizumab PsO Analysis Set (7.7 E/100 PY).The SAEs with the highest rate with long-term risankizumab exposure were COVID-19 and pneumonia (Phase 3 PsA Long-term Analysis Set, both 0.4 E/100 PY).

A total of 6 events of serious infections of pneumonia (4 events of pneumonia, 1 of COVID-19 pneumonia**,** and 1 event of pneumonia viral) were reported with risankizumab.

The most frequently reported TEAEs (≥ 3% of subjects) were upper respiratory tract infection (4.1%) and nasopharyngitis (3.5%) in the risankizumab group. There were no TEAE PTs that occurred in ≥ 5% of subjects in any treatment group. In the Phase 3 PsA Long-term Analysis Set the TEAEs that were most frequently assessed by the investigators as having a possible relationship to study drug in the risankizumab group were upper respiratory tract infection ALT increased and AST increased.

The rate of MACE with long-term risankizumab treatment in the psoriatic arthritis program (Phase 3 PsA Long-term Analysis Set, 0.3 E/100 PY) is lower than the rate observed in the All Risankizumab PsO Analysis Set (0.6 E/100 PY).

The overall rates of infection were stable with long-term risankizumab therapy (43.0 E/100 PY, as compared to the rates in Phase 3 PsA Placebo-Controlled Analysis Set (51.1 E/100 PY)

The rate of Nonmelanoma Skin Cancer (NMSC) with long-term risankizumab exposure was 0.6 events Per 100 PYs and is within the epidemiological reference rate in the psoriatic arthritis population (0.61 Events per 100PY) and comparable to the rate observed in the All Risankizumab PsO Analysis Set (0.7 E/100 PY). In the Phase 3 PsA Placebo-Controlled Analysis Set, 1 malignancy (NMSC) was reported in a subject in the risankizumab group (basal cell carcinoma).

The rate of malignancies excluding NMSC with long-term risankizumab exposure was 0.2 E/100 PY. It is consistent with the rates of malignancies excluding NMSC reported in population-based epidemiology studies of patients with psoriatic arthritis (0.48 E/100 PY).A total of 2 malignancies excluding NMSC, acral lentiginous melanoma were reported.

In the Phase 3 PsA PBO-Controlled Analysis Set, the rate of hypersensitivity reaction with Risankizumab treatment (5.5 E/100 PY) was higher than that in placebo (3.1 E/100 PY). The rate of hypersensitivity reaction was stable with long-term risankizumab exposure (Phase 3 PsA Long-term Analysis Set, 4.2 E/100 PY) and was lower than the rate observed in the All Risankizumab PsO Analysis Set (5.2 E/100 PY).

Anti-drug antibodies/neutralizing antibodies were lower in PsA at approximately 12% ADA and 0% NAb positive rates compared to 24% and 14% respectively in PsO, but noted that the immunogenicity assessment in PsA was based on Wk28 data which is different from the one in PsO which was based on Week 52 data.

- Based on a comprehensive review of hepatic events and laboratory data in the psoriatic arthritis analysis sets**,** All Risankizumab PsO Analysis Set, and Crohn's disease Phase 2 study hepatic events were observed as follows: In the All Risankizumab PsO Analysis Set there were 7 additional serious hepatic events reported since the initial submission and a total of 5 subjects in the All Risankizumab PsO Analysis Set met the criteria for biochemical Hy's law but did not appear to be attributable to risankizumab induced hepatocellular injury .
- The hepatic safety profile in the psoriatic arthritis population ((13.1/100PYs) ws higher than the All Risankizumab PsO Analysis Set (5.6 E/100 PYs) this is a notable difference between the two sets.
- Notably the rate of hepatic events with long-term risankizumab exposure was (12.3 E/100 PY) (6.3%) in the any risankizumab group but 12.9/100PY (8.6% of subjects) in the no cross over from placebo group, ALT 1.8/100 PY vs 1.4/100 PY , AST 1.3/100PY vs 1.0/100 PY. Based on the totality of data, it was concluded that additional measures are not necessary at this time, hepatotoxicity is not considered a potential risk for the risankizumab RMP and further pharmacovigilance or risk minimisation measures are not warranted. In addition, a warning for hepatotoxic potential or a recommendation for monitoring for hepatic enzymes in Section 4.4 and identification of enzyme elevations as an ADR in Section 4.8 of the SmPC is not warranted.

3.5. Uncertainties and limitations about unfavourable effects

Uncertainties regarding the possibility of delayed or rare safety issues with long-term use of risankizumab in an active psoriatic arthritis population exist and will be monitored in the post marketing setting.

3.6. Effects Table

Table 98: Effects Table for rizankisumab (data cut-off: 02 November 2020)at primary endpoint, Week 24

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects Primary					**Multiplicity adjusted, Difference with PBO**	
ACR20	% achieving response at Week 24 (primary endpoint)					

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	M15-998	%	51.3	26.5	24.5% 95% CI [15.9%, 33.0%] P<0.001	CSR M15-998
	M16-011	%	57.3	33.5	24.0% 95% CI [18.0%, 30.0%] P<0.001	CSR M16-011
Common Ranked Key Secondary (*= change from baseline)						
HAQ-DI*	Assesses the degree of difficulty a person had in accomplishing tasks in 8 functional areas. Responses in each functional area were scored from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area					CSR M15-998 CSR M16-011
	M15-998	LS mean	-0.22	-0.05	-0.16 95% CI [−0.26, −0.07] P<0.001	
	M16-011	LS mean	-0.31	-0.11	-0.20 95% CI [−0.26, −0.14] P<0.001	
PASI 90 (BSA≥3%)	90% reduction on PASI score at week 24 in subjects with plaque psoriasis ≥body surface area					"
	M15-998	%	55.0	10.2	44.3% 95% CI [33.9%, 54.6%] P<0.001	
	M16-011	%	52.3	9.9	42.5% 95% CI [35.6%, 49.3%] P<0.001	
ACR20 @ Week 16	% achieving response at Week 16					"
	M15-998	%	48.3	25.3	22.6% 95% CI [13.9%, 31.2%] P<0.001	
	M16-011	%	56.3	33.4	23.1% 95%CI[16.8%, 29.4%] P<0.001	
MDA	A score for assessment of low disease activity based on meeting 5/7 of TJC ≤1, SJC ≤1, PASI ≤1 or BSA ≤3, patient Pain-VAS ≤15, PGA-Disease Activity VAS ≤20, HAQ-DI ≤0.5 & Tender entheseal points ≤1					"
	M15-998	%	25.6	11.4	14.0% 95% CI [7.0%, 21.0%] P<0.001	
	M16-011	%	25.0	10.2	14.8% 95% CI [10.2%, 19.4] P<0.001	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Unfavourable Effects						
	Phase 3 PsA long term analysis set any risankizumab 150mg	**Events [E/100PY]**	**Risankizumab 150mg**		**Treatment comparison 95% CI**	
Any adjudicated MACE]		3 [0.3]			0.1 (-0.1,0.4)	
any serious infection 27 (2.6%) [2.6]		27 [2.6]			-0.6 (-1.8,0.6)	
herpes zoster 4 (0.4%) [0.4]		4 [0.4]			-0.0(-0.6,0.6)	
Any malignant tumor 8 (0.8%) [0.8]		8 [0.8]			0.3(-0.8,0.3)	
Any non-melanoma skin cancer (NMSC)		6[0.6]			-0.0(-0.4,0.4)	
Any malignant tumours excluding NMSC2 (0.2%) [0.2]		2 [0.2]			-0.3(-0.7,0.1)	
Any hypersensitiv		44 [4.2]			1.0 (-0.4,2.3)	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
ity 4 (4.2%) [4.2] Any hepatic events 129 [12.3]		129 [12.3]			1.5 (-0.7,3.7)	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The week 52 data efficacy analysis is consistent with the week-24 primary analysis and supports maintenance of effect and inhibition of progression of structural joint damage through 24 and 52 weeks of treatment with RZB.

The recommendation that Skyrizi could be potentially combined with all cDMARDs was considered insufficiently justified given that the majority of patients treated with concomitant cDMARDs received MTX and the proposed indication was amended consequently

Skyrizi, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).

The full 52-week safety data are overall consistent with the known safety profile of risankizumab in the approved indication. However, clarification on SOC related events have been introduced in the PI.

At this time, additional updates to the summary of safety concerns are not warranted and hepatoxicity updates to the RMP (as an important potential risk) or PI are considered not necessary at this time. This risk will be monitored in the post marketing setting through PSURs

3.7.2. Balance of benefits and risks

The week 52 data analysis is consistent with the week-24 primary analysis and supports maintenance of effect and inhibition of progression of structural joint damage through 24 and 52 weeks of treatment with risankizumab.

Skyrizi has been shown to be effective as monotherapy or in combination with methotrexate (MTX), in adults with active psoriatic arthritis and who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).

3.8. Conclusions

The overall B/R of Skyrizi is positive.

4. Recommendations

Outcome

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

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

New therapeutic indication for the treatment of active psoriatic arthritis in adults. Consequently sections 4.1, 4.2, 4.8, 5.1 and 5.2 to the SmPC have been updated. The Package leaflet is updated accordingly. Minor update of Annex II is also introduced.

The RMP is also updated accordingly.

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

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.

In addition, 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.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Skyrizi-H-C-4759-II-14.

Attachments

SmPC Annex II, Package Leaflet (changes highlighted) as a relevant example with changes highlighted as adopted by the CHMP on 14 October 2021.