30 May 2024
EMA/282885/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Skyrizi

International non-proprietary name: Risankizumab

Procedure No. EMEA/H/C/004759/X/0043/G

Note

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

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List of abbreviations

ADCC	Antibody dependent cellular cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
Ala	Alanine
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
APG	Acidic Peak group
ASA	Aminosalicylic acid
AST	Aspartate aminotransferase
ATCC	American type culture collection
AUC	Area under the curve
BI	Boehringer Ingelheim
CCI	Container closure integrity
CCS	Container closure system
CD	Crohn's disease
CDC	Complement dependent cytotoxicity
CEX	Cation exchange chromatography
CFU	Colony forming unit
CGE	Capillary gel electrophoresis
COA	Certificate of analysis
CMV	Cytomegalovirus
COS	Certificate of Suitability
CP	Combination product
CQA	Critical quality attribute
CRC	Colorectal cancer
CRP	C reactive Protein
DILI	Drug induced liver injury
DMARD	Disease modifying antirheumatic drug
DP	Drug product
DS	Drug substance
ECL	Electrochemiluminescence
EMA	European Medicines Agency
ePPND	Enhanced Pre- and Post-natal Development
ER	Exposure response
FCP	Fecal calprotectin
FMEA	Failure mode and effects analysis

FSFV	First subject first visit
GMP	Good manufacturing practice
HC	Heavy chain
HEMI	Histologic endoscopic mucosal improvement
HRQoL	Health-related quality of life
IBD	Inflammatory bowel disease
ICH	International conference on harmonisation
IgG	Immunoglobulin class G
IL-23	Interleukin-23
IPC	In Process Control
ISO	International Organisation of Standardisation
ITT	Intention to treat
IV	Intravenous
JAK	Janus kinase
JP	Japanese Pharmacopoeia
LC	Light chain
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MI	Multiple Imputation
MTX	Methotrexate
mAb	Monoclonal antibody
MIA	Manufacturing import authorisation
Nab	Neutralising antibody
NHP	Non human primate
NOAEL	No observed adverse effect level
MCMC	Markov Chain Monte Carlo
MCP-Mod	Multiple comparison procedure and modelling
Mw	Molecular weight
NK	Natural killer
NMSC	Non-melanoma skin cancer
OBDS	On body delivery system
OBI	On body injector
OL	Open label
OC	Other concern
OOL	Out of limit
PAR	Proven acceptable range
PK	Pharmacokinetics
PVDF	Polyvinylidene fluoride
PFC	Pre-filled cartridge

Ph. Eur.	European pharmacopoeia
PPQ	Process performance qualification
PS20	Polysorbate 20
PT	Preferred term
PV	Process validation
QC	Quality control
RTB-MI	Multiple Imputation Incorporating Return-to-Baseline
SAE	Serious adverse event
SC	Subcutaneous
SF	Stool frequency
TNF	Tumor necrosis factor
TSA	Telescopic screw assembly
UC	Ulcerative Colitis
USP	United States Pharmacopoeia
WFI	Water for Injection

1. Background information on the procedure

1.1. Submission of the dossier

AbbVie Deutschland GmbH & Co. KG submitted on 24 August 2023 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

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

Extension application to add a new strength of 180 mg of risankizumab (solution for injection in cartridge) grouped with a type II variation extension of indication (C.I.6.a) to include treatment of adult patients with moderately to severely active ulcerative colitis based on final results from studies M16-067 substudy 2: a phase 2b/3 multicenter, randomized, double-blind, placebo-controlled induction study to evaluate the efficacy and safety of risankizumab in subjects with moderately to severely active ulcerative colitis, and M16-066 substudy 1: a multicenter, randomized, double-blind, placebo controlled 52-week maintenance and an open-label extension study of the efficacy and safety of risankizumab in subjects with ulcerative colitis, as well as DDI study M19-974. As a consequence of the extension of indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3, 6.5 and 6.6 of the SmPC are updated. The Annex II, Labelling and Package Leaflets are updated in accordance. Version 5.3 of the RMP has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMEA-001776-PIP04-17 (P/0231/2018) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001776-PIP04-17 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The MAH received Scientific advice from the CHMP on the development for the indication from the

CHMP on 18 May 2017 (EMEA/H/SA/3171/3/2017/III) and 28 May 2020 (EMEA/H/SA/3171/3/FU/1/2020/II). The Scientific advice pertained to quality, non-clinical, and clinical aspects.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur : Finbarr Leacy

The application was received by the EMA on	24 August 2023
The procedure started on	28 September 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 December 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 December 2023
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	04 January 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 February 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 January 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	23 February 2024
The CHMP Rapporteur circulated the CHMP Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 March 2024
The PRAC Rapporteur circulated the PRAC assessment Report on the responses to the List of Questions to all PRAC and CHMP members on	02 April 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP Rapporteur circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	18 April 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	25 April 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	01 May 2024
The CHMP Rapporteur circulated the preliminary Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 May 2024
The CHMP Rapporteur circulated the updated Report on the responses	23 May 2024

to the List of Outstanding Issues to all CHMP and PRAC members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Skyrizi on	30 May 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The active substance risankizumab has been authorised in adults in the European Union (EU) (Skyrizi; EU/1/19/1361/001-3) for the treatment of moderate to severe plaque psoriasis in subjects who are candidates for systemic treatment, active psoriatic arthritis (alone or in combination with MTX) in subjects who have had an inadequate response or who have been intolerant to one or more DMARDs, and in moderately to severely active Crohn's disease in subjects who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.

With this submission, the MAH was initially seeking to add an indication for *the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, lost response to, or were intolerant to conventional, or biologic, or JAK inhibitor therapy*.

The MAH applied also for a new strength of 180 mg risankizumab in Ulcerative Colitis (UC).

2.1.2. Epidemiology and risk factors, screening tools/prevention

A systematic review of studies evaluating the worldwide incidence and prevalence of inflammatory bowel disease reported that the prevalence rates for UC were:

- 140 to 286 per 100,000 persons in North America
- 2.4 to 505 per 100,000 persons in Europe
- 4.6 to 57.3 per 100,000 persons in Asia
- 4.7 to 44.3 per 100,000 persons in South America, and
- 10.6 per 100,000 persons in Africa (Ng et al. 2017)[1].

Diagnosis is based on symptoms using supportive evidence from an endoscopy, tissue biopsy and negative stool examination, while ruling out infectious disease.

There are no known preventative medical therapies available.

[1] NG, Siew C., SHI, Hai Yun, HAMIDI, Nima, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. The Lancet, 2017, vol. 390, no 10114, p. 2769-2778.

2.1.3. Biologic features / Aetiology and pathogenesis

The precise aetiology of UC is not well understood. A current hypothesis suggests that primary dysregulation of the mucosal immune system leads to an excessive immunologic response to normal microflora in a genetically susceptible host, finally leading to chronic intestinal inflammation.

The importance of the epithelial barrier in inflammatory bowel disease (IBD) predisposition is supported by reports of abnormal intestinal permeability in patients with IBD and some of their first-degree relatives. Alterations in the balance between proliferation and apoptosis are known to be involved in barrier dysfunction, which leads to IBD.

During the inflammatory phase, resident cells produce cytokines, which recruit immune cells to the site of injury. Infiltrating monocytes differentiate into macrophages, key players in driving an effective immune response through phagocytosis of pathogens and apoptotic neutrophils. Mediators released during the inflammatory phase also recruit fibroblasts to the wound region, thereby initiating the proliferative phase.

UC is a serious disease that, in some cases, may cause life-threatening complications that can be fatal. The most severe intestinal manifestations of UC are toxic megacolon and perforation.

Extra-intestinal complications include arthritis, dermatological conditions, uveitis, and primary sclerosing cholangitis.

The risk of colorectal cancer (CRC) has been suggested to markedly increase with cumulative probabilities of 2% by 10 years, 8% by 20 years, and 18% by 30 years.

The main risk factors for IBD-CRC include certain disease characteristics such as age at onset, extent and duration of disease, as well as non-IBD characteristics such as family history of CRC and concomitant diagnosis of primary sclerosing cholangitis.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Symptoms include diarrhoea, rectal bleeding, abdominal pain and bowel movement urgency. UC has a relapsing-remitting course, meaning that many patients have intermittent disease flares that are interspersed with periods of remission.

Diagnosis is made endoscopically. UC is a chronic disease characterised by diffuse mucosal inflammation of the colon. UC always involves the rectum (i.e., proctitis), and it may extend proximally in a contiguous pattern to involve the sigmoid colon (i.e., proctosigmoiditis), the descending colon (i.e., left-sided colitis), or the entire colon (i.e., pancolitis).

The onset of UCs is most common between 15 and 40 years of age, with a second peak in incidence between 50 and 80 years. The disease affects men and women at similar rates.

It is estimated that 3% to 8% of patients with UC have primary sclerosing cholangitis, a chronic disease of bile ducts that predisposes affected patients to increased risks of progressive liver disease and colorectal cancer (Tanaka and Mertens 2016[2]). Compared to those without UC, patients with UC are at an increased risk of developing and dying from colorectal cancer (Olén et al. 2020[3]). Fear of cancer and the frequency of endoscopic surveillance procedures to detect UC dysplasia may also impact HRQoL in patients with UC.

[2] TANAKA, Atsushi et MERTENS, Joachim C. Ulcerative colitis with and without primary sclerosing cholangitis: two different diseases?. Inflammatory intestinal diseases, 2016, vol. 1, no 1, p. 9-14.
[3] OLÉN, Ola, ERICHSEN, Rune, SACHS, Michael C., et al. Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study. The Lancet, 2020, vol. 395, no 10218, p. 123-131.

2.1.5. Management

Medical therapeutic decisions for UC are categorised into those for (a) induction and (b) maintenance, with a goal of obtaining and maintaining steroid-free remission.

Treatment goals in UC include induction of remission (typically within a 6 to 12 week time frame) and maintenance of remission in the longer term (assessed over 52 weeks of continuous treatment in clinical trials). In both clinical practice and in clinical trials, clinical response and clinical remission are assessed by a combination of endoscopy (improvement in the endoscopic appearance of the mucosa and healing of ulcers) and patient-reported outcomes, including a reduction in stool frequency (SF) and a resolution of RB (Levesque et al. 2015[4]). Control of intestinal inflammation in UC is also associated with a reduction in the risk of hospitalisation, colectomy, and in the longer term, UC associated dysplasia and colorectal cancer.

Medications used for the treatment of UC include 5-aminosalicylic acid (5-ASA)–containing medications (sulfasalazine, mesalazine, balsalazide, olsalazine), corticosteroids, immunomodulators such as AZA and 6-MP and biologic medications.

A significant proportion of patients with moderately to severely active UC may have an inadequate response to medicines such as 5-ASAs or corticosteroids, be unable to maintain a clinical response to 5-ASAs or AZA or be unable to discontinue corticosteroids without a relapse in disease activity (reviewed in Dignass et al. 2012[5]). Many of these patients require additional treatment with the next line of therapy, which could include medical treatment with a biologic medication or surgical treatment with a colectomy.

Biologics, including antitumor necrosis factor (TNF) antibodies (infliximab, adalimumab, golimumab) and vedolizumab, an anti-α4β7 integrin antibody, are indicated for the treatment of UC in patients who fail to respond to, have an inadequate response to, or are intolerant to other medications used in the treatment of UC medications and as a first-line treatment for UC in selected patients.

Approximately 40% to 50% of patients with moderately to severely active UC fail treatment with current biologic or small-molecule therapies in the first year of treatment. Therefore, there is a clear medical need for additional therapeutic options in UC for subjects with inadequate response to or intolerance to conventional therapies and biologic therapies.

2.2. About the product

Risankizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that is directed against IL-23 p19. The framework of the risankizumab antibody 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 (Th) 17 type cells, innate lymphoid cells, γδT cells, and natural killer (NK) cells responsible for tissue inflammation, destruction and aberrant tissue repair.

The pharmacological classification of risankizumab is: immunosuppressants, interleukin inhibitors, ATC code: L04AC18.

[4] LEVESQUE, Barrett G., SANDBORN, William J., RUEL, Joannie, et al. Converging goals of treatment of inflammatory bowel disease from clinical trials and practice. Gastroenterology, 2015, vol. 148, no 1, p. 37-51. e1.
[5] DIGNASS, Axel, ELIAKIM, Rami, MAGRO, Fernando, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. Journal of Crohn's and Colitis, 2012, vol. 6, no 10, p. 965-990.

2.3. Type of Application and aspects on development

The legal basis for this application refers to:

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

Scientific Advice

Scientific Advice was sought for this line extension in two procedures, first in 2018 and again in 2020. The CHMP was generally in agreement with the proposals of the MAH, although they had some concerns regarding the choice of the induction dose that resulted from Sub study 1 of the Phase 2b/3 induction study, M16-067.

Paediatric Development

The MAH has received a deferral from the Paediatric Committee (PDCO) for the completion of studies in children in UC. As such, no paediatric studies have been submitted as part of this application.

2.4. Quality aspects

2.4.1. Introduction

This line extension concerns a new strength of 180 mg of Skyrizi cartridge (solution for injection) co-packaged with a device on-body delivery system (OBDS).

The finished product is presented as a solution for injection containing 180 mg of risankizumab as active substance. Each cartridge contains 180 mg of risankizumab in 1.2 mL solution.

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

The product is available in a single use cartridge (pre-filled cartridge (PFC)) made with cyclic olefin resin with rubber septum and rubber piston as product-contact materials, and a resin cap. The cartridge is assembled with a telescopic screw assembly. The cartridge assembly is co-packed with an OBDS (administration device). The fluid path within the on-body injector contains polyvinyl chloride tubing and a stainless steel 29 gauge needle. The on-body delivery system contains silver oxide-zinc batteries and an adhesive skin patch made from polyester with an acrylic adhesive. The administration device is designed for use with the provided 180 mg cartridge.

Skyrizi 180 mg is available in packs containing 1 cartridge and 1 on-body injector.

2.4.2. Active Substance

Risankizumab is a humanised antibody of the IgG1 isotype with engineered Fc region, directed against p19 subunit of IL-23. The molecule is composed of two heterodimers. Each of the heterodimers is composed of a heavy chain (HC) and a light chain (LC). Disulphide bonds link the four chains of the antibody molecule together. Risankizumab is expressed in Chinese hamster ovary (CHO) cells.

No new information is provided for the active substance and there are no proposed changes for module 3.2.S versus the information approved for the risankizumab 360 mg/2.4 mL Pre-filled Cartridge (PFC) (solution for injection) with OBDS for Crohn's Disease (CD) indication (EC EMEA/H/C/004759/X/0020/G), approved on 22 Nov 2022.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Skyrizi 180 mg/1.2 mL PFC is supplied as a sterile solution at a concentration of 150 mg/mL for subcutaneous administration. Skyrizi 180 mg/1.2 mL PFC is to be administered using an OBDS device. The commercial container and closure system for the PFC finished product is described in Section 3.2.P.7 Container Closure System for the PFC. The PFC finished product is a buffered, isotonic, preservative-free, colourless to yellow, clear to slightly opalescent solution with an osmolality of 270 to 350 mOsmol/kg and a pH of 5.2 to 6.0.

The description and composition of the finished product are adequately detailed. The qualitative and quantitative composition of the finished product is described in Table 1 below.

Table 1 Composition of Skyrizi 180 mg/1.2 mL Pre-filled Cartridge (PFC)

Ingredient	Nominal Amount [mg/PFC]	Concentration [mg/mL]	Function	Reference to Standards
Risankizumab	180	150	Active pharmaceutical ingredient (API)	Refer to 3.2.S.4.1 Specification
Sodium acetate trihydrate	1.49	1.24	Buffer component	Ph. Eur., USP, JP
Glacial Acetic acid	0.065	0.054	Buffer component	Ph. Eur., USP, JP
Trehalose dihydrate	84.0	70.0	Tonicity agent	Ph. Eur., NF, JP
Polysorbate 20	0.24	0.20	Surfactant	Ph. Eur., NF, JPE
Water for Injection	ad 1.2 mL	ad 1.0 mL	Solvent	Ph. Eur., USP, JP

A minimum overfill is applied and the cartridges are filled at a target fill volume of 1.30 ± 0.03 mL to permit delivery of the labelled volume of at least 1.2 mL.

The product is supplied as a sterile finished product solution for subcutaneous administration in a PFC assembled with a telescopic screw assembly (TSA) co-packaged with an OBDS device that is CE marked. The composition of the OBDS devices is clearly described in P.1 of the dossier for the OBDS. The composition of the OBDS is identical to the authorised 360 mg/2.4 mL PFC/OBDS strength apart from a 1.2 mL TSA adaptor used for the proposed presentation due to the difference in fill volume. The pharmaceutical development of the proposed 180 mg/1.2 mL PFC and OBDS device was presented and assessed as part of the previous line extension (EC EMEA/H/C/004759/X/0020/G, approved on 22 Nov 2022). No changes are proposed, and no further information is required.

The container closure consists of a cyclic olefin polymer pre-filled cartridge (PFC). The septum and piston are laminated with a fluoropolymer film. The PFC cartridge and piston are sterilised by gamma irradiation and details of the sterilisation site are registered in the dossier (Sterigenics); a certificate of ISO conformance is provided in 3.2.R. The PFC is identical to that currently authorised for the 360 mg/2.4 mL PFC presentation for Skyrizi and is acceptable.

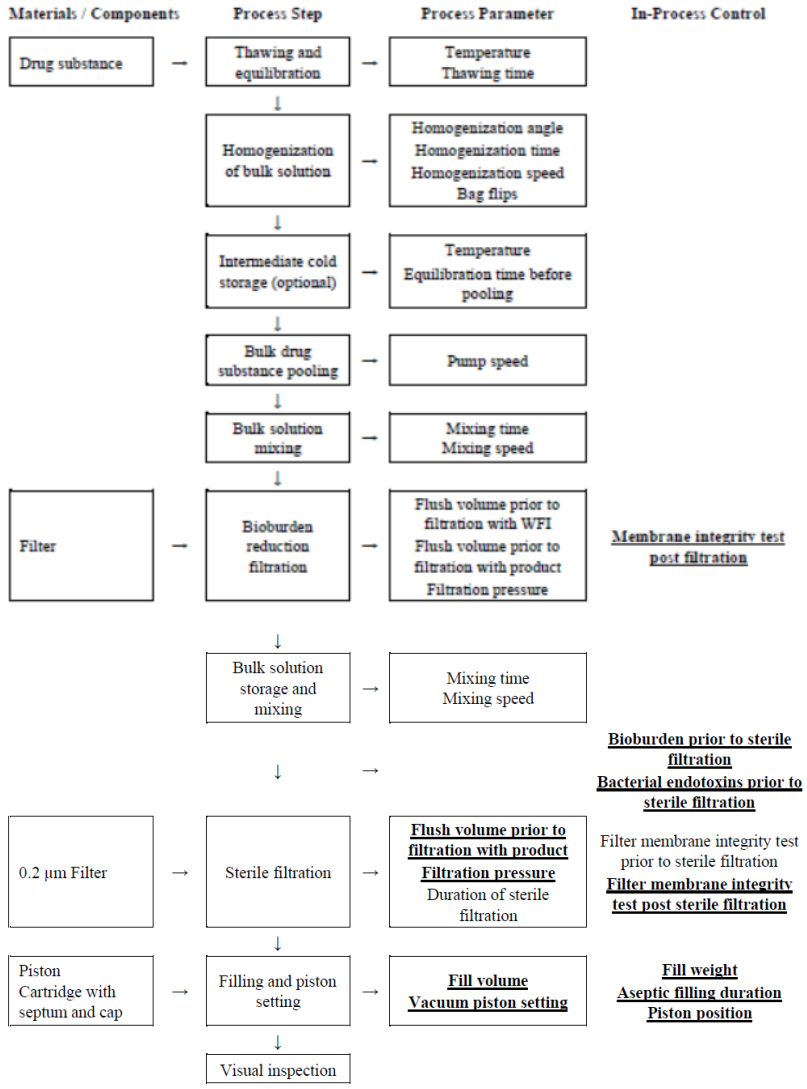
The proposed presentation uses a longer TSA adaptor to the currently approved 360 mg/2.4 mL presentation as the fill volume for the proposed presentation is 1.2 mL, details and technical drawings are provided. The rest of the components are identical to those approved for the 360 mg/2.4 mL

presentation and in general are acceptable. The testing performed on receipt of the TSA components to confirm identity has been clarified by the applicant and is acceptable.

2.4.3.2. Manufacture of the product and process controls

All sites responsible for manufacture and control of the finished product are in compliance with EU GMP. The manufacturing flow chart is provided in Error! Reference source not found. and identical to that authorised for the risankizumab 360 mg/2.4 mL PFC (solution for injection) with OBDS approved for Crohn's Disease (CD) indication (EC EMEA/H/C/004759/X/0020/G, approved on 22 Nov 2022).

Figure 1 Manufacturing flow chart of Skyrizi 180 mg/1.2 mL pre-filled cartridge (PFC)



The PFC finished product manufacturing process is standard for a monoclonal antibody and consists of active substance thawing and equilibration of formulated active substance, bulk solution homogenisation, pooling and mixing of the bulk solution, bioburden reduction filtration, bulk solution storage and mixing, sterile filtration, filling and piston setting of the cartridges, and visual inspection of the PFC. Cartridges are filled following sterile filtration and are 100% visually inspected. A manufacturing process flow diagram and sufficient details of the manufacturing process are registered, including in-process controls (IPCs), critical process parameters (CPPs) and non-CPPs and their

associated proven acceptable ranges (PARs). No reprocessing steps are proposed. The proposed manufacturing process is identical to the authorised process for the 360 mg/2.4 mL PFC with the exception of the filling and piston setting PARs. The justification for the PAR ranges are provided in P.2 and were assessed as part of previous line extension (EC EMEA/H/C/004759/X/0020/G, approved on 22 Nov 2022) and are acceptable. There are no proposed changes to authorised manufacturing process for the OBDS proposed as part of this line extension which is acceptable.

The proposed control strategy is identical to the authorised 360 mg/2.4 mL PFC with the exception of the filling volume, piston setting, piston position, and the fill weight which are specific to the 180 mg/1.2 mL PFC. The pharmaceutical development data provided in P.2 to support the control strategy is applicable to both PFC presentations and is considered acceptable. There are no changes to the authorised hold times which were supported by validation data for both the current 360 mg/2.4 mL PFC and proposed 180 mg/ 1.2 mL PFC presentations.

The proposed control strategy for the OBDS manufacturing process is unchanged from the authorised process and is acceptable.

Process validation / verification

Process validation is provided for 3 consecutive batches and an additional process performance qualification (PPQ) batch as supporting data. The data includes all CPPs, non-CPPs and IPCs, all of which were within the registered acceptance criteria with a minor deviation in the piston setting for one batch which is well described. A non-routine intervention was described during the filling process for one PPQ batch and additional information was provided to support the representativeness of this batch for the purposes of process validation which is acceptable. The duration of the filling for all PPQ batches was within the acceptance criteria of ≤ 24 hours which was in place at the time of validation, the proposed media fill time of ≤ 36 hours is adequately supported with media fill data and filter validation beyond the proposed criteria. The proposed hold times are adequality supported. Data on shipping qualification is provided, which covers the proposed shipping routes and conditions.

Two sites are responsible for manufacture of the OBDS. The validation was carried out using the 360 mg/ 2.4 mL OBDS presentation. The applicant proposes to leverage the validation data from the PPQ runs of the 360 mg/2.4 mL OBDS presentation to validate the proposed 180 mg/1.2 mL OBDS manufacturing process. This is based on the fact that there are minor differences in the components, the device assembly, and secondary packaging. The main difference is the length of the TSA which is slightly longer due to the reduced fill volume in the currently proposed PFC, although all components remain essentially the same. The IPC approved for the TSA-PFC assembly registered in P.3.4 are torque, force and gap between TSA gear and PFC flange, and are identical for both the 360 mg/ 2.4 mL presentation the proposed 180 mg/1.2 mL PFC.

The proposed approach to leverage the currently authorised 360 mg/ 2.4 mL OBDS manufacturing process data is acceptable. The applicant has taken this approach based on an failure modes and effects analysis (FMEA) for the OBDS and packaging sites which are provided in the dossier.

The finished product manufacturing process is considered validated.

2.4.3.3. Product specification

Specifications are proposed for the bulk PFC finished product and additional specifications are proposed for the final OBDS with the inserted cartridge product. The proposed release tests for the 180 mg/1.2 mL PFC product covers relevant aspects of appearance and description (appearance – clarity and degree of opalescence (Ph. Eur.), appearance – degree of coloration (Ph. Eur.), appearance – visible particles (Ph. Eur.), sub-visible particles (Ph. Eur.)), general tests (pH (Ph. Eur.), osmolality (Ph. Eur.),

extractable volume (Ph. Eur.)), identity (tryptic peptide mapping (RP-HPLC), heterogeneity (cation exchange chromatography), purity (size exclusion chromatography, capillary gel electrophoresis), potency (reporter gene bioassay), quantity (protein concentration), functional tests (container closure integrity, maximum force), microbiological tests (sterility and bacterial endotoxins) and excipients (polysorbate 20).

Skyrizi 180 mg/1.2 mL PFC specifications are presented in Table 2.

Table 2 Release and shelf-life specifications for Skyrizi 180 mg/1.2 mL PFC

Test	Analytical Procedure	Acceptance Criteria	Where applied	
			Release	Shelf-life
Appearance and Description				
Appearance - clarity and degree of opalescence	Ph. Eur. 2.2.1	Clear to slightly opalescent (≤ Reference suspension III)	X	X
Appearance - degree of coloration	Ph. Eur. 2.2.2	Colorless to yellow (≤ Reference solution BY3)	X	X
Appearance - visible particles	Ph. Eur. 2.9.20	Solution is free from foreign particles and practically free from product-related particles	X	X
Sub-visible particles Particle size ≥ 10 µm: Particle size ≥ 25 µm:	Ph. Eur. 2.9.19, USP <788> JP 6.07	 ≤ 6000 particles/container ≤ 600 particles/container	X	X
General Tests				
pH	Ph. Eur. 2.2.3 USP <791> JP 2.54	5.2 – 6.0	X	X
Osmolality	Ph. Eur. 2.2.35 USP <785> JP 2.47	270 – 350 mOsmol/kg	X	N/A
Extractable volume	Ph. Eur. 2.9.17 USP <697> JP 6.05	≥ 1.2 mL	X	N/A
Identity				
Tryptic peptide mapping (RP-HPLC)	In-house method	Profile qualitatively comparable to standard material	X	N/A
Heterogeneity				
Cation exchange chromatography (CEX-UV)	In-house method	APG: 16.0 – 32.3% Main peak: 61.3 – 77.4% BPG: ≤ 11.5%	X	N/A
		APG: 15.7 to 33.5% Main peak: 57.3 to 77.9%	N/A	X

Test	Analytical Procedure	Acceptance Criteria	Where applied	
			Release	Shelf-life
Purity				
Size exclusion chromatography (UP-SEC)	In-house method	HMW: ≤ 2.6% Monomer: ≥ 96.4%	X	N/A
		HMW: ≤ 3.4% Monomer: ≥ 95.5%	N/A	X
Capillary gel electrophoresis (CGE) non-reduced	In-house method	Main peak: ≥ 95.1% LMW: ≤ 3.6%	X	N/A
		Main peak: ≥ 93.7% LMW: ≤ 4.3%	N/A	X
Potency				
RGA bioassay biological activity relative to reference standard	In-house method	75 – 125%	X	X
Quantity				
Protein concentration	In-house method	135.0 – 161.0 mg/mL	X	N/A
Functional Tests				
Container closure integrity	In-house method	No blue dye incursion	N/A	X
Maximum force	In-house method	≤ 29.9 N	X	X
Microbiological Tests				
Sterility	Ph. Eur. 2.6.1 USP <71> JP 4.06	No growth	X	X
Bacterial endotoxins	Ph. Eur. 2.6.14 USP <85> JP 4.01	≤ 30 EU/mL	X	N/A
Excipients				
Polysorbate 20	In-house method	≥ 0.14 mg/mL	X	N/A

The bulk pre-filled cartridge (PFC) finished product is tested and released per defined acceptance criteria for the PFC. The specifications for the 180 mg/1.2 mL OBDS loaded with cartridge are listed below in Table 3.

Table 3: Specifications for the 180 mg/1.2 mL OBDS

Test	Acceptance Criteria	Where applied	
		Release	Shelf-life
Appearance and Description			
Appearance Cartridge label	TSA-pre-filled cartridge label is correctly positioned.	X	N/A
Functional Tests			
Delivery duration	< 300 s	X	X
	≥ 158 s	X	N/A
Delivered dose volume	≥ 1.2 mL	X	X
Device interface functionality	Verify visual and audible indicators.	X	X
Packaging Integrity			
Blistered device seal strength	> 2.54 N per 1" width	X	N/A

The proposed release tests are in line with the expectations of ICH Q6B and the Ph. Eur. monograph on monoclonal antibodies and are in general acceptable. It is noted that the specifications are identical to those approved for the 360 mg/2.4 mL PFC presentation with the exception of the extractable volume (≥ 1.2 mL) specification updated for the proposed 180 mg/1.2 mL PFC presentation.

Additional functional tests are included for the 180 mg/1.2 mL OBDS and include the delivery duration and delivered dose volume. The specifications are identical to those approved for the 360 mg/2.4 mL

OBDS presentation with the exception of delivered dose volume (≥ 1.2 mL) and delivery duration (< 300s). A lower limit for the delivery duration has been introduced (> 158s) and is suitably justified. Packaging integrity, device interface functionality (beeps, clicks and lights) and label controls are also included, and these specifications are considered appropriate.

The analytical procedures and reference standards are unchanged from the risankizumab 360 mg/2.4 mL PFC (solution for injection) with OBDS for Crohn's Disease indication (EC EMEA/H/C/004759/X/0020/G, approved on 22 Nov 2022), and are acceptable.

No additional batch data are provided and the batch analysis data for the risankizumab 180 mg/1.2 mL PFC were included in EC EMEA/H/C/004759/X/0020/G (approved on 22 Nov 2022) and are acceptable.

2.4.3.4. Stability of the product

The stability for the 180 mg/1.2mL and 360 mg/2.4 mL presentation were assessed together in the previous Crohn's Disease line extension (EC EMEA/H/C/004759/X/0020/G) and type II variation (EMEA/HC/004759/II/0042).

The application of the approved shelf life of 24 months with storage allowance for up to 24 hours at ≤ 25 °C for the 180 mg/ 1.2 mL OBDS is considered adequately supported and no queries are raised.

2.4.3.5. Adventitious agents

There are no changes proposed from risankizumab 360 mg/2.4 mL PFC (solution for injection) with OBDS for Crohn's Disease indication (EC EMEA/H/C/004759/X/0020/G, approved on 22 Nov 2022).

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

In this line extension for a new strength of Skyrizi there are no proposed changes to the active substance which is used to manufacture the currently authorised 360 mg/2.4 ml PFC, the 150 mg/mL prefilled syringe (PFS), and pen. Therefore, no new information is included for the same active substance in this submission, which was found acceptable.

The proposed finished product is supplied as a 180 mg/ 1.2 mL pre-filled cartridge (PFC) co-packaged with an on-body delivery system (OBDS) device. The presentation proposed is largely identical to the currently authorised 360 mg/2.4 mL PFC and OBDS approved as part of a recent line extension (EC EMEA/H/C/004759/X/0020/G, approved on 22 Nov 2022), which also included data from the currently proposed presentation which was developed in parallel. The main difference is in the fill volume, and therefore the finished product manufacturing and finished product are largely aligned. The cartridge container closure (PFC) and OBDS are identical to the currently authorised presentation with the exception of the telescopic screw assembly (TSA) adaptor which is longer for this presentation to account for the change in fill volume. As such additional information are only provided on the composition, batch formula, description of manufacturing process and controls, controls of critical steps and intermediates, process validation, specifications, justification of specifications, and the container closure.

The manufacturing process is standard for a monoclonal antibody. Appropriate process development data was provided which supports the control strategy. The manufacturing process for the proposed PFC has been appropriately validated. The validation of the manufacturing process is leveraged from the currently authorised process and the risk analysis to support this strategy has been provided. The process is considered validated. The specifications are largely aligned to the approved presentation and are in accordance with current guidance. Specifications are provided for the functionality of the PFC

when combined with the OBDS device and are acceptable. Specifications for the container closure TSA assembly are registered in the dossier.

Sufficient documentation has been provided to support the use of the PFC and OBDS device and a CE certificate from DEKRA for the OBDS is provided. The proposed 24 month shelf life for the PFC presentation is adequately supported with data provided in the recently approved line extension.

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

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

No new nonclinical studies have been performed in support of this application. The MAH has provided literature references and reference to the studies previously submitted for the CD extension of indication.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

No new pharmacodynamic studies have been conducted in support of this application. Primary pharmacodynamic data submitted in the initial MAA for Skyrizi are applicable to the extension for UC. The MAH provided a brief summary of studies performed in support of the CD indication (EMEA/H/C/004759/X/0020), which also serve as proof of concept for UC as both these chronic inflammatory bowel diseases have a shared pathophysiology.

2.5.2.2. Secondary pharmacodynamic studies

Studies previously submitted suggest that risankizumab has low potential for ADCC and no potential to elicit CDC activity.

2.5.2.3. Safety pharmacology programme

Stand-alone studies were not conducted.

2.5.2.4. Pharmacodynamic drug interactions

Due to the highly specific receptor targeting of the monoclonal antibodies, it was determined that there was a low risk for pharmacodynamic interactions and studies were not conducted.

2.5.3. Pharmacokinetics

No new pharmacokinetic studies have been performed.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Not applicable.

2.5.4.2. Repeat dose toxicity

No new repeat toxicity studies have been performed.

2.5.4.3. Genotoxicity

Based on the biophysical nature of monoclonal antibodies and mode of action for risankizumab, *in vitro* genetic toxicology studies were not conducted per ICH S6.

2.5.4.4. Carcinogenicity

Standard carcinogenicity bioassays are generally not required for biotechnology-derived pharmaceuticals (ICH S6). Furthermore, risankizumab is not pharmacologically active in rat or mouse.

2.5.4.5. Reproductive and developmental toxicity

No new toxicology studies were conducted with risankizumab for this application, reference is made to the studies submitted in the initial MAA.

2.5.4.6. Toxicokinetic data

Considering that the dose for the new indication, 1200 mg IV q4w, is higher than the authorised dose, 600 mg IV q4w for CD, the MAH calculated new margins of safety from the no-observed-adverse-effect level (NOAEL) in the chronic repeat dose toxicity study in NHPs and the ePPND study in the same species which indicate that exposures in excess of that seen clinically were achieved. These margins are low for the induction dose, however, considering the NOAEL was the highest dose tested and no significant findings were noted in the repeat dose toxicity studies they are acceptable.

Risankizumab showed significant pharmacological activity only in non-human primates, thus justifying the use of cynomolgus monkey as the single relevant toxicology test species.

The risankizumab toxicological assessment conducted in cynomolgus monkey did not identify any toxicologically significant findings in any of the repeat-dose studies. The NOAEL was 50 mg/kg/week, the highest dose tested.

Systemic exposures to risankizumab at the NOAEL dose level of 50 mg/kg/week in the pivotal toxicology studies are shown in Table 4.

Table 4 Comparison of exposures in non human primates to exposures in UC patients and associated safety margins

Toxicology Study	NOAEL Dose (mg/kg/week)	Mean Plasma AUC $AUC_{0\text{-}4wk}$/ $AUC_{0\text{-}8wk}$ (µg•day/mL)[a]	Human AUC $AUC_{Wks8\text{-}12}/AUC_{Wks40\text{-}48}$ at 180 mg or 360 mg (µg•day/mL)[b]	Safety Margins
26-Week SC NHP[c]	50	14,375/28,750	4595/633,1267	3/45,23
26-Week SC MaleNHP with FertilityEndpoints	50	20,333/40,667	4595/633,1267	4/64,32
ePPND SC NHP	50	20,500/41,000	4595/633,1267	5/65,32

AUC (area under the concentration-time curve); ePPND (enhanced pre- and postnatal development); NHP (nonhumanprimate (cynomolgus monkey)); SC (subcutaneous)

a. AUC values at steady state in the monkey studies ($AUC_{0\text{-}168hr}$ (one week)) were multiplied by four or eight weeksto provide an AUC value comparable to the human dosing interval. The units for the AUC values were modifiedfrom mg•hr/mL to µg•day/mL to align with the clinical reports.

b. R&D//23/0018 (induction dose of 1200 mg IV every four weeks at Weeks 0, 4, and 8 and maintenance doses of either 180 mg or 360 mg SC at Week 12 and thereafter every eight weeks; mean values for induction ($AUC_{Weeks8\text{-}12}$ = 4595 µg•day/mL) and maintenance at 180 mg ($AUC_{Weeks40\text{-}48}$ =633 µg•day/mL) and at 360 mg ($AUC_{Weeks40\text{-}48}$ = 1267 µg•day/mL)

2.5.4.7. Local tolerance

The local tolerance was evaluated following intramuscular and subcutaneous injection in rabbits in previous applications. This is applicable to the UC extension.

2.5.4.8. Other toxicity studies

Not applicable

2.5.5. Ecotoxicity/environmental risk assessment

Risankizumab is an antibody, specifically a monoclonal immunoglobulin, and as such is a natural substance. The excretion of risankizumab has not specifically been studied, but it is expected that a substantial percentage of the dosed compound will be degraded (to small peptides and amino acids) in the body. Any risankizumab that is excreted would degrade within a wastewater treatment plant or in the environment. The use of risankizumab will not alter the concentration or distribution of these substances (small peptides and amino acids) in the environment. Therefore, environmental fate and effects studies are not warranted as patient use of risankizumab is unlikely to result in any exposure or risk to the environment.

2.5.6. Discussion on non-clinical aspects

No new pharmacodynamic studies have been conducted in support of this application.

Risankizumab was not shown able to bind to the preformed complex of IL-23/IL-23Rα by SPR, indicating that risankizumab is a competitive inhibitor of the IL-23p19/IL-23Rα interaction. Studies

performed using a T cell transfer model of colitis were previously submitted in support of the CD indication. The CHMP agrees that these studies also serve as proof of concept for UC as both these chronic inflammatory bowel diseases have shared pathophysiology. Studies have also demonstrated the low potential for risankizumab to induce ADCC and CDC.

The CHMP concludes that the pharmacology package is acceptable to support the UC indication.

No new pharmacokinetic studies have been performed. The CHMP concludes that the pharmacokinetic studies supporting the initial MAA, which investigated both IV and SC routes of administration, are sufficient to support also the UC indication.

No new nonclinical toxicology studies have been performed. The CHMP concludes that the nonclinical toxicity studies previously submitted are adequate to support also the UC indication.

Considering that the dose for the new indication is higher than the authorised dose, the MAH calculated new margins of safety from the NOAEL in the chronic repeat dose toxicity study in NHPs and the ePPND study in the same species. The exposures were 5 times the clinical exposures during induction at a dose of 1 200 mg intravenously every 4 weeks and 65 or 32 times the clinical exposures for maintenance when given 180 or 360 mg subcutaneously every 8 weeks. These margins are low for the induction dose, however, considering the NOAEL was the highest dose tested and no significant findings were noted in the repeat dose toxicity studies they are acceptable to the CHMP.

Overall, the CHMP concludes that the nonclinical toxicity package is acceptable.

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

2.5.7. Conclusion on the non-clinical aspects

The cumulative data from safety pharmacology related endpoints, animal data regarding pharmacokinetic characteristics, and toxicology studies with risankizumab, along with exposure measurements in humans, indicate that the safety considerations have been adequately characterized for the treatment of UC patients.

Overall, the nonclinical data is acceptable in support of the UC indication.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- Tabular overview of clinical studies

Type of Study	Study ID	Location of Study Report	Objective of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 2b/3 Efficacy and Safety	M16-067	5.3.5.1	SS1 (Phase 2b induction): Characterize the efficacy, safety, and PK of RZB as induction treatment in subjects with moderately to severely active UC and identify the appropriate induction dose of RZB for further evaluation in SS2. SS2 (Phase 3 induction): Evaluate the efficacy and safety of RZB compared to PBO in inducing clinical remission in subjects with moderately to severely active UC.	Phase 2b/3, multicenter, randomized, DB, PBO-controlled	SS1 IP1 • RZB 1800 mg IV Wks 0, 4, 8 • RZB 1200 mg IV Wks, 0, 4, 8 • RZB 600 mg IV Wks 0, 4, 8 • PBO IV Wks 0, 4, 8 SS1 IP2 • RZB 1800 mg IV Wks 12, 16, 20 • RZB 360 mg SC Wks 12, 20 • RZB 180 mg SC Wks 12, 20 SS1 DS IP1 • OL RZB 1800 mg IV Wks 0, 4, 8	1558	Subjects with moderately to severely active UC	SS1 IP1, SS1 DS IP1, SS2 IP1: 12 weeks SS1 IP2, SS1 DS IP2, SS2 IP2: 12 weeks	Ongoing; Interim Full CSR
					SS1 DS IP2 • RZB 1800 mg IV Wks 12, 16, 20 • RZB 360 mg SC Wks 12, 20 • RZB 180 mg SC Wks 12, 20 SS2 IP1 • RZB 1200 mg IV Wks 0, 4, 8 • PBO IV Wks 0, 4, 8 SS2 IP2 • RZB 1200 mg IV Wks 12, 16, 20 • RZB 360 mg SC Wks 12, 20 • RZB 180 mg SC Wks 12, 20				

Type of Study	Study ID	Location of Study Report	Objective of the Study	Study Design and Type of Control	Test Products; 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	M16-066	5.3.5.1	SS1 Evaluate the efficacy and safety of RZB versus PBO as maintenance therapy in subjects with moderately to severely active UC who responded to IV RZB induction treatment in Study M16-067. SS2 Evaluate the efficacy and safety of 2 different dosing regimens for RZB (TDM vs CA for dose escalation) as maintenance therapy in subjects with moderately to severely active UC who responded to induction treatment in Study M16-067.	SS1 52-week randomized, DB, PBO-controlled maintenance study SS2 52-week randomized, exploratory maintenance study	SS1 • RZB 360 mg SC q8w • RZB 180 mg SC q8w • PBO SC q8w SS2 Week 0 • RZB 180 mg SC and placebo IV • PBO SC and RZB 1200 mg IV Week 8 • OL RZB 180 mg SC	1238	1. Completion of Study M16-067. 2. Achieved clinical response, at the last visit of Study M16-067.	SS1: 52 weeks SS2: 52 weeks	Ongoing; Interim Full CSR (SS1)
			SS3 Evaluate long-term safety of RZB in subjects who completed SS1 or SS2, or subjects who responded to induction treatment in Study M16-067 with no final endoscopy due to the COVID-19 pandemic. Further investigate long-term efficacy and tolerability of RZB.	SS3 OL LTE	SS3 • RZB 180 mg SC q8w • RZB 360 mg SC q8w • OL RZB 180 mg SC q8w • For Japan only: RZB 360 mg SC q8w *RZB rescue therapy on or after Week 16 (1 dose of OL RZB 1200 mg or 1800 mg IV followed by RZB 360 mg SC through the end of the study).			SS3: Approximately 240 weeks	
DDI	M19-974	5.3.3.4	Evaluate the effect of repeated IV infusions of risankizumab 1800 mg q4w on the PK of sensitive probe substrates of CYP enzymes in subjects with moderately to severely active UC or CD	Phase 1, multi-center, multiple-dose, open-label, two-period, single arm study	Period 1: Day 1: oral dose of midazolam 2 mg, caffeine 100 mg, warfarin 10 mg, Vitamin K 10 mg, omeprazole 20 mg, and metoprolol 50 mg	20 (11 with UC, 9 with CD)	Adults aged ≥ 18 to ≤ 80 with moderately to severely active UC or CD	Period 1: Single doses of multiple CYP probes on 1 day Period 2: RZB 1800 mg IV q4w for 12 weeks: single doses of multiple CYP probes on 1 day; optional RZB 180 SC q8w for 8 weeks	Complete; Full
					Period 2: Days 1, 29, and 57: RZB 1800 mg IV Day 64: oral dose of midazolam 2 mg, caffeine 100 mg, warfarin 10 mg, Vitamin K 10 mg, omeprazole 20 mg, and metoprolol 50 mg Days 85 and 141 (optional for continued RZB treatment): RZB 180 mg SC				

CA = clinical assessment; CD = Crohn's disease; CYP = cytochrome P450; DB = double-blind; DDI = drug-drug interaction; DS = Dose Selection; IP1 = Induction Period 1; IP2 = Induction Period 2; IV = intravenous(ly); LTE = long-term extension; OL = open-label; PBO = placebo; PK = pharmacokinetic(s); q4w = once every 4 weeks; q8w = once every 8 weeks; RZB = risankizumab; SC = subcutaneous(ly); SS1 = Substudy 1; SS2 = Substudy 2; SS3 = Substudy 3; UC = ulcerative colitis; TDM = therapeutic drug monitoring

2.6.2. Clinical pharmacology

Risankizumab is currently approved in the European Union, for the treatment of plaque psoriasis, psoriatic arthritis, and CD. To support the registration in UC, additional clinical pharmacology assessments were conducted in one pivotal Phase 2b/3 study (Study M16-067) and one pivotal Phase

3 study (Study M16-066) in subjects with UC. Combined data from the Phase 2b/3 and Phase 3 studies were utilized in the integrated analyses of population pharmacokinetics (PK) and exposure-response for efficacy and safety, as well as in analyses to evaluate the impact of immunogenicity on PK, safety, and efficacy. In addition, one Phase 1 drug-drug interaction study (Study M19-974) was conducted to evaluate the effect of repeated doses of risankizumab on the PK of sensitive probe substrates of CYP enzymes in subjects with CD or UC.

2.6.2.1. Pharmacokinetics

Bioanalytical methods

All bioanalytical methods for the determination of risankizumab concentrations, ADA, and NAb in human serum in studies pertinent to this submission are principally the same as those that have been previously authorised in the application for CD (EMEA/H/C/004759/X/0020).

Determination of Risankizumab Concentrations in Human Serum

For the Phase 1 Study M19-974, and Phase 2b/3 and Phase 3 UC Studies M16-067 and M16-066, a bridging electrochemiluminescence (ECL) assay was employed to determine risankizumab concentrations in human serum samples.

Selectivity for the matrix obtained from patients with UC was demonstrated in partial validation R&D/17/1135. For sample analysis of study samples collected in China, the serum ECL assay was transferred to WuXi AppTec (Shanghai, P.R. China). The method transfer included a validation as well as a cross-validation to the in-house validated serum assay (R&D/19/1058). Comparability of the two methods was demonstrated and cross-validation results are provided.

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

The assay for the detection of ADAs (anti-risankizumab antibodies) in human serum samples is a titre-based acid dissociation bridging ECL immunoassay. This is a quasi-quantitative assay.

A summary of bioanalytical methods for detection of anti-risankizumab antibodies is provided and the relevant validation reports.

Determination of Risankizumab neutralising antibodies (NAb) in human serum

For the Phase 1 Study M19-974, pivotal Phase 2b/3 and Phase 3 UC Studies, M16-067 and M16-066, a competitive ligand binding NAb assay employing a sample pre-treatment step to improve sensitivity and drug tolerance of the method was developed to determine NAb in human serum samples and a UC-specific cut point was established.

To enable sample analysis in China, the NAb assay was transferred to Chinese CRO. Cross-validation experiments using spiked QC samples demonstrated full comparability between in-house validated serum NAb assay.

Study M16-067

Study M16-067 was a Phase 2b/3, multicentre, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and pharmacokinetics of risankizumab as induction therapy in adult subjects with moderately to severely active UC. It was an operationally seamless design comprising of 2 sub studies: Phase 2b dose-ranging induction Sub study (sub study 1) and a Phase 3 induction Sub study (sub study 2).

Sub study 1 was a Phase 2b dose finding study and evaluated the efficacy, safety, and PK of risankizumab as induction treatment to identify the appropriate induction dose of risankizumab for

further evaluation in Sub study 2. There were two induction periods: Subjects who achieved a clinical response in Induction Period 1 were eligible to be enrolled in the maintenance study, Study M16-066. Subjects who did not achieve a clinical response in Induction Period 1 were eligible to enter Induction Period 2, to investigate reinduction with risankizumab versus staring a maintenance dose.

Sub study 2 was a Phase 3 induction study that was completed when the dose selection analysis in Sub study 1 was completed. Following Sub study 1, 1200 mg IV Q4W was selected as the induction dose. Subjects who achieved a clinical response in Induction Period 1 were eligible to be enrolled in the maintenance study, Study M16-066. Subjects who did not achieve clinical response in Induction Period 1 were randomized into induction Period 2, to investigate reinduction with risankizumab versus staring a maintenance dose.

Pharmacokinetic results

During Sub study 1 Induction Period 1, risankizumab serum trough levels were generally dose-proportional between 600 mg, 1200 mg, 1800 mg, and open-label (OL) 1800 mg dose levels across time, reaching geometric trough concentrations of 33.2 µg/mL, 53.3 µg/mL, 88.7 µg/mL, and 109 µg/mL at Week 12 for risankizumab 600 mg IV, risankizumab 1200 mg IV, risankizumab 1800 mg IV, and OL risankizumab 1800 mg IV, respectively.

Table 5 Substudy 1 Induction period 1 – summary of Risankizumab serum concentrations (µg/mL) at planned visits (12-week induction period)

	Geometric Mean (Arithmetic Mean, %CV) [N]							
		Week 8						
	Week 4 Pre-dose	Pre-dose	0 Hr Post-dose	2 Hr Post-dose	Week 9	Week 10	Week 11	Week 12 Pre-dose
RZB 600 mg IV	19.2 (21.3, 48) [53]	27.8 (29.9, 43) [52]	91.8 (119, 62) [8]	92.2 (126, 68) [7]	63.0 (69.9, 56) [3]	47.5 (49.5, 36) [3]	38.9 (41.3, 38) [3]	33.2 (37.7, 47) [52]
RZB 1200 mg IV	36.3 (39.5, 42) [56]	55.3 (80.5, 129) [56]	131 (206, 74) [15]	222 (328, 46) [16]	142 (151, 34) [12]	70.8 (87.1, 50) [12]	66.5 (76.3, 46) [12]	53.3 (61.9, 49) [56]
RZB 1800 mg IV	53.4 (59.7, 44) [51]	70.7 (93.2, 91) [56]	434 (469, 34) [13]	350 (522, 71) [12]	228 (234, 23) [7]	196 (201, 25) [7]	111 (123, 44) [7]	88.7 (101, 53) [54]
OL RZB 1800 mg IV	60.2 (67.5, 49) [305]	93.7 (107, 60) [312]	324 (458, 67) [28]	447 (538, 45) [24]	330 (336, 22) [3]	210 (212, 18) [2]	158 (158) [1]	109 (119, 42) [280]

During Sub study 2 Induction Period 1, risankizumab serum concentrations following 1200 mg IV q4w dosing reached a geometric mean trough concentration of 101 µg/mL at Week 12 (Table 6).

Table 6 Substudy 2 induction period 1 – summary of Risankizumab serum concentrations (µg/mL) at planned visits (12-week double-blind induction period)

	Geometric Mean (Arithmetic Mean, %CV) [N]							
		Wk 8						
	Wk 4 Pre-dose	Pre-dose	0 Hr Post-dose	2 Hr Post-dose	Wk 9	Wk 10	Wk 11	Wk 12 Pre-dose
RZB 1200 mg IV	57.0 (63.4, 42) [581]	85.4 (94.5, 41) [610]	375 (439, 59) [4]	369 (369) [1]	N/A	N/A	N/A	101 (112, 44) [596]

Study M16-066

Study M16-066 is a Phase 3, multicentre study that enrolled subjects who achieved clinical response at the last visit of induction Study M16-067. Study M16-066 consists of 3 sub studies, however only sub

study 1 was included as part of this submission. Sub study 1 is a 52-week randomized, double-blind, placebo-controlled maintenance study, which is the pivotal study evaluating the efficacy and safety of 2 maintenance doses of risankizumab.

Approximately 573 subjects who achieved clinical response to IV risankizumab at the end of Study M16-067 were re-randomized in a 1:1:1 ratio to one of the following 3 treatment groups: risankizumab 180 mg SC Q8W; risankizumab 360 mg SC Q8W; placebo SC Q8W.

Pharmacokinetic results

Overall, and regardless of prior induction treatment, risankizumab serum concentrations showed a generally dose-proportional, 2-fold difference between the 180 mg and 360 mg SC maintenance doses across the time course of Sub study 1, with overall consistent levels of pre-dose trough concentrations at Week 16, Week 32, and Week 48 within each dose arm, indicating achievement of steady state (Table 7). Placebo subjects had measurable serum exposures to risankizumab, up to Week 52, indicating a prolonged drug washout from the previous IV induction treatment due to the long elimination half-life of risankizumab.

Table 7 Summary of Risankizumab serum concentrations (µg/mL) at planned visits (Substudy 1) by maintenance regimen in randomized subjects who received 12 weeks of IV induction treatment

Maintenance Regimen	Geometric Mean (Arithmetic Mean, %CV) [N]			
	Week 16	Week 32	Week 48	Week 52
RZB 360 mg SC q8w	11.5 (15.6, 79) [196]	10.1 (13.5, 166) [166]	10.8 (12.3, 54) [151]	23.6 (25.8, 44) [142]
RZB 180 mg SC q8w	7.16 (9.62, 80) [213]	4.65 (5.62, 61) [186]	4.74 (5.73, 69) [174]	9.59 (10.8, 45) [170]
Placebo SC	4.02 (6.44, 105) [174]	0.316 (0.651, 175) [150]	0.051 (0.267, 760) [121]	0.032 (0.048, 160) [107]

Immunogenicity

Study M16-067

In both Sub studies 1 and 2, serum anti-drug antibodies and neutralizing anti-drug antibodies samples were taken prior to dosing at Weeks 4, 8, and 12 in Induction Period 1, at Week 24 in Induction Period 2, and unscheduled measurements could be taken when a subject came in for evaluation and assessment.

Immunogenicity results

Sub study 1

During Weeks 0-24 including Sub study 1 Induction Period 1 and Induction Period 2, treatment-emergent ADA and NAb incidences were approximately 1.9% and 0.5%, respectively, in evaluable subjects who were inadequate responders at Week 12 and received risankizumab during the Induction Period 2 (Table 8).

Table 8 Substudy 1 Induction period 2 – Incidence of ADA and NAb to Risankizumab during Weeks 0-24 in subjects who received Risankizumab during induction period 2

	Risankizumab Treatment During Induction Period 2													
	180 mg SC				360 mg SC				1800 mg IV					
	Treatment Received During Induction Period 1													
Description	IR Open-Label 1800 mg IV	IR 1800 mg IV	IR 1200 mg IV	IR 600 mg IV	IR Open-Label 1800 mg IV	IR 1800 mg IV	IR 1200 mg IV	IR 600 mg IV	IR Open-Label 1800 mg IV	IR 1800 mg IV	IR 1200 mg IV	IR 600 mg IV	IR Placebo	Total
Evaluable subjects; N	43	6	11	12	42	9	7	12	24	4	4	4	34	212
ADA incidence (treatment-emergent); n (%)	1 (2.3%)	0 (0%)	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8.3%)	1 (4.2%)	0(0%)	0 (0%)	0 (0%)	0 (0%)	4 (1.9%)
NAb incidence (treatment-emergent); n (%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)

Notes: Anti-drug antibody evaluable: subjects with at least 1 reportable assessment at any time in the study post Baseline. NAb was assessed only when the anti-drug antibody assessment was positive.

During Sub study 1 Induction Period 1, the majority of the geometric mean risankizumab trough serum concentrations were lower in ADA-positive subjects compared to ADA-negative subjects (Table 9). One subject developed NAb in the 1200 mg IV treatment arm whose risankizumab exposures were within the range of NAb negative subjects in the same treatment arm.

Table 9 Substudy 1 Induction period 1 – summary of Risankizumab trough serum concentrations (µg/mL) by ADA status (12-week induction)

	Geometric Mean (Arithmetic Mean, %CV) [N]											
	RZB 600 mg IV			RZB 1200 mg IV			RZB 1800 mg IV			OL RZB 1800 mg IV		
	Wk 4	Wk 8	Wk 12	Wk 4	Wk 8	Wk 12	Wk 4	Wk 8	Wk 12	Wk 4	Wk 8	Wk 12
ADA Positive	31.4 (40.4, 89) [2]	N/A	14.9 (14.9) [1]	20.6 (20.6) [1]	N/A	N/A	N/A	N/A	N/A	26.0 (32.2, 68) [5]	46.4 (46.4) [1]	N/A
ADA Negative	18.8 (20.6, 40) [51]	27.8 (29.9, 43) [52]	33.7 (38.1, 46) [51]	36.7 (39.8, 41) [55]	55.2 (80.9, 130) [55]	53.3 (61.9, 49) [56]	53.4 (59.7, 44) [51]	70.9 (93.7, 91) [55]	88.7 (101.3, 53) [54]	61.1 (68.1, 48) [297]	93.6 (106, 60) [310]	108 (119, 42) [276]

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

Sub study 2

During Weeks 0-24 including Sub study 2 Induction Period 1 and Induction Period 2, treatment-emergent ADA and NAb incidences were approximately 2.2% and 1.1%, respectively, in evaluable subjects who were inadequate responders at Week 12 and received risankizumab during the Induction Period 2 (Table 10).

Table 10 Substudy 2 Induction period 2 – incidence of ADA and NAb to Risankizumab during Weeks 0-24 in subjects who received Risankizumab during induction period 2

	Risankizumab Treatment During Induction Period 2				
	180 mg SC	360 mg SC	1200 mg IV		
	Treatment Received During Induction Period 1				
Description	IR 1200 mg IV	IR 1200 mg IV	IR 1200 mg IV	IR PBO	Total
Evaluable subjects; N	71	71	68	154	364
ADA incidence (treatment-emergent); N (%)	1 (1.4%)	5 (7.0%)	1 (1.5%)	1 (0.6%)	8 (2.2 %)
NAb incidence (treatment-emergent); N (%)	0 (0%)	2 (2.8%)	1 (1.5%)	1 (0.6%)	4 (1.1%)

Notes: Anti-drug antibody evaluable: subjects with at least 1 reportable assessment at any time in the study post-Baseline. NAb was assessed only when the anti-drug antibody assessment was positive.

During Sub study 2 Induction Period 1, the geometric mean risankizumab trough serum concentrations were either similar or slightly lower in ADA-positive subjects compared to ADA-negative subjects (Table 11). Five (5) subjects developed NAb in the 1200 mg IV treatment arm and their risankizumab exposures were within the range of NAb negative subjects in the same treatment arm.

Table 11 Substudy 2 Induction period 1 – summary of Risankizumab trough serum concentrations (µg/mL) by ADA status (12-week induction)

	RZB 1200 mg IV		
	Geometric Mean (Arithmetic Mean, %CV) [N]		
Description	Week 4	Week 8	Week 12
ADA-Positive	41.5 (48.5, 46) [7]	67.1 (71.7, 42) [5]	157 (157) [1]
ADA-Negative	57.2 (63.5, 42) [573]	85.6 (94.7, 41) [600]	101 (113, 44) [592]

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

Study M16-066

In Sub study 1, serum anti-drug antibodies and neutralizing anti-drug antibodies samples were taken prior to dosing at baseline Week 0, and at Weeks 16, 32, 48, and Week 52, during a rescue dose visit, and unscheduled measurements could be taken when a subject came in for evaluation and assessment.

Immunogenicity results

For randomized subjects who received 12 weeks of risankizumab IV induction followed by SC maintenance, the overall incidence (treatment-emergent) was low for both ADA (6.2%, 28/455) and NAb (3.1%, 14/455). The 180 mg dose arm showed slightly higher ADA (8.6%) and NAb (4.3%) incidence compared to the ADA (3.6%) and NAb (1.8%) incidence in the 360 mg dose arm. Slightly higher ADA (7.7 % to 16.7%) and NAb (0% to 7.3%) incidence was observed for the subjects who received 24-week IV induction or the non-randomized subjects, respectively (Table 12).

Risankizumab serum concentrations in the few subjects who developed ADA or NAb were within the range of concentrations in ADA or NAb-negative subjects within the same group at Week 16, Week 32, Week 48, and Week 52.

Table 12 Incidence of anti-drug antibodies and neutralizing antibodies to Risankizumab treatment during Week 0-52 (Substudy 1) in randomized subjects

Description	Risankizumab Maintenance Regimen in SS1			
	RZB 360 mg SC q8w	RZB 180 mg SC q8w	Placebo	RZB Total
a: Randomized Subjects Who Received 12 Weeks of IV Induction				
Evaluable subjects; N	222	233	186	455
Anti-drug antibody incidence (treatment-emergent); N (%)	8 (3.6%)	20 (8.6%)	9 (4.8%)	28 (6.2%)
NAb incidence (treatment-emergent); N (%)	4 (1.8%)	10 (4.3%)	2 (1.1%)	14 (3.1%)
b: Randomized Subjects Grouped by Induction Regimen				
	Risankizumab 1800 mg IV Induction for 12 weeks			
Evaluable subjects; N	76	76	75	--
Anti-drug antibody incidence (treatment-emergent); N (%)	1 (1.3%)	6 (7.9%)	2 (2.7%)	--
NAb incidence (treatment-emergent); N (%)	0 (0%)	3 (3.9%)	1 (1.3%)	--
	Risankizumab 1200 mg IV Induction for 12 weeks			
Evaluable subjects; N	88	84	89	--
Anti-drug antibody incidence (treatment-emergent); N (%)	3 (3.4%)	7 (8.3%)	6 (6.7%)	--
NAb incidence (treatment-emergent); N (%)	1 (1.1%)	6 (7.1%)	1 (1.1%)	--
	Risankizumab 600 mg IV Induction for 12 weeks			
Evaluable subjects; N	8	9	9	--
Anti-drug antibody incidence (treatment-emergent); N (%)	0 (0%)	0 (0%)	0 (0%)	--
NAb incidence (treatment-emergent); N (%)	0 (0%)	0 (0%)	0 (0%)	--
Description	**Risankizumab Maintenance Regimen in SS1**			
	RZB 360 mg SC q8w	**RZB 180 mg SC q8w**	**Placebo**	**RZB Total**
	Risankizumab IV Induction for 24 Weeks			
Evaluable subjects; N	9	12	13	--
Anti-drug antibody incidence (treatment-emergent); N (%)	0 (0%)	2 (16.7%)	1 (7.7%)	--
NAb incidence (treatment-emergent); N (%)	0 (0%)	0 (0%)	0 (0%)	--

Notes: Anti-drug antibody evaluable: subjects with at least 1 reportable assessment at any time in the study post Baseline. NAb was assessed only when the anti-drug antibody assessment was positive.

Population pharmacokinetic analyses

R&D/20/0608: Phase 2 population PK analyses of Risankizumab during induction treatment in ulcerative colitis

This was a Phase 2 population PK analyses of risankizumab, which included the data from the 12-week induction period of the ongoing Phase 2b/3 study (Study M16-067) in subjects with moderately to severely active UC. Data from Studies M16-513 (in healthy subjects) and M15-993 (in CD) were included in the analyses for robust model development, and to allow for comparisons between different IBD populations (UC and CD), and with the healthy subjects.

In total 2,282 risankizumab concentration measurements from 361 subjects who received at least one dose of risankizumab were available for the population PK model development. Of the 361 subjects, 179 subjects were subjects with moderate to severe UC.

A previously developed population PK model for CD was used as the starting model. The model was refined to fit data from subjects with UC. A two-compartment model with first-order absorption and elimination processes best described risankizumab PK. Body weight showed statistical significance for correlation with CL and Vc ($p < 0.001$ for both). Furthermore, baseline levels of albumin and faecal calprotectin (FCP) were identified to be statistically correlated with risankizumab CL ($p < 0.001$ for both). Key intrinsic factors such as age, sex, race, and liver function tests [total bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] were not statistically significant covariates for risankizumab PK parameters. Immunogenicity (both ADA and NAb) were evaluated and not found to be statistically correlated with risankizumab clearance.

The estimated PK parameter values and their associated variability for the selected final PK model are listed in Table 13. Figure 1 shows the VPC plots for the pre-dose samples for subjects with moderate to severe UC enrolled in Study M16-067.

Table 13 Fixed and random effects parameter estimates for Risankizumab final population pharmacokinetic model

Parameter	Population Estimate	%RSE[a]	95% Confidence Interval
Pharmacokinetic Parameters			
Clearance (CL; L/day)	0.319	2.3	0.305 to 0.333
Central Volume of Distribution (V_c; L)	4.60	5.6	4.092 to 5.108
Absorption Rate Constant (Ka; day^{-1})	0.175	10.0	0.141 to 0.209
Inter-Compartmental Clearance (Q; L/day)	0.543	7.9	0.459 to 0.627
Peripheral Volume of Distribution (V_p; L)	4.01	3.6	3.726 to 4.294
Absolute SC Bioavailability (F)[b]	0.748	11.9	0.697 to 0.793
Exponent for the Effect of Body Weight on Risankizumab Clearance (CL)	0.802	9.3	0.655 to 0.949
Exponent for the Effect of Body Weight on Risankizumab Central Volume of Distribution (V_c)	1.46	11.8	1.123 to 1.797
Exponent for the Effect of Fecal Calprotectin on Risankizumab Clearance (CL)	0.076	15.3	0.053 to 0.099
Exponent for the Effect of Serum Albumin on Risankizumab Clearance (CL)	–0.952	13.4	–1.203 to –0.701
Inter-Individual and Residual Variability			
Variance of Inter-Individual Variability in CL, %CV[c], exponential error model	0.0632, 26%	7.7	
Variance of Inter-Individual Variability in V_c, %CV[c], exponential error model	0.106, 33%	22.2	
Variance of Inter-Individual Variability in Ka, %CV[c], exponential error model	0.314, 61%	28.4	
Variance of Inter-Individual Variability in F[d]; additive error model in logit domain	0.462	31.4	
Variance of Proportional Residual Error	0.0717	2.1	

CL = clearance; Ka = first-order absorption rate constant; Q = inter-compartmental clearance; V_c = central volume of distribution; V_p = peripheral volume of distribution

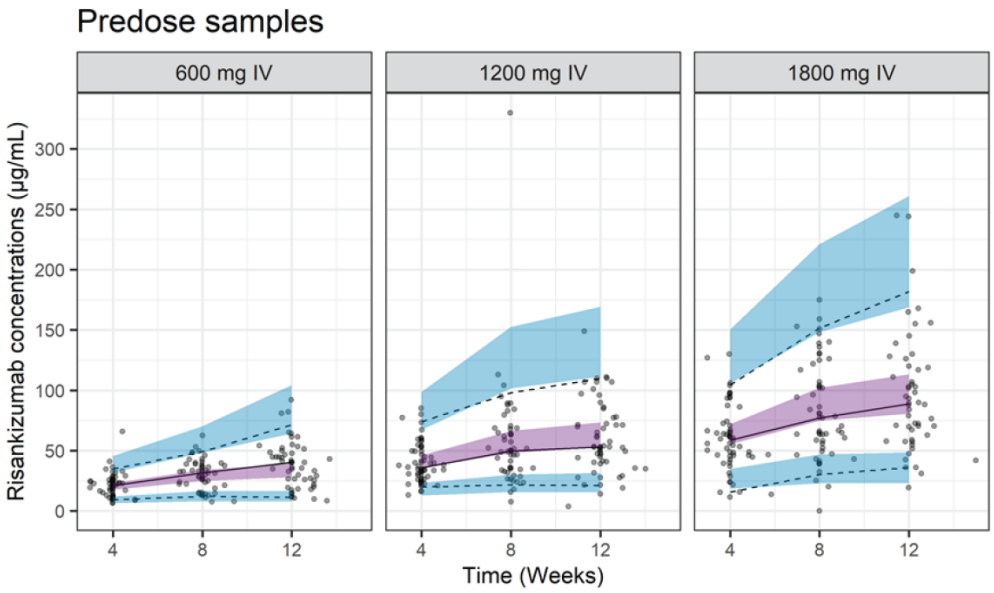
a. % Relative standard error (%RSE) was estimated as the standard error of the estimate divided by the population estimate multiplied by 100.

b. Estimate was back transformed from the logit scale (estimate on the logit scale was 1.09).

c. %CV = SQRT[exp(ω^2)-1]*100.

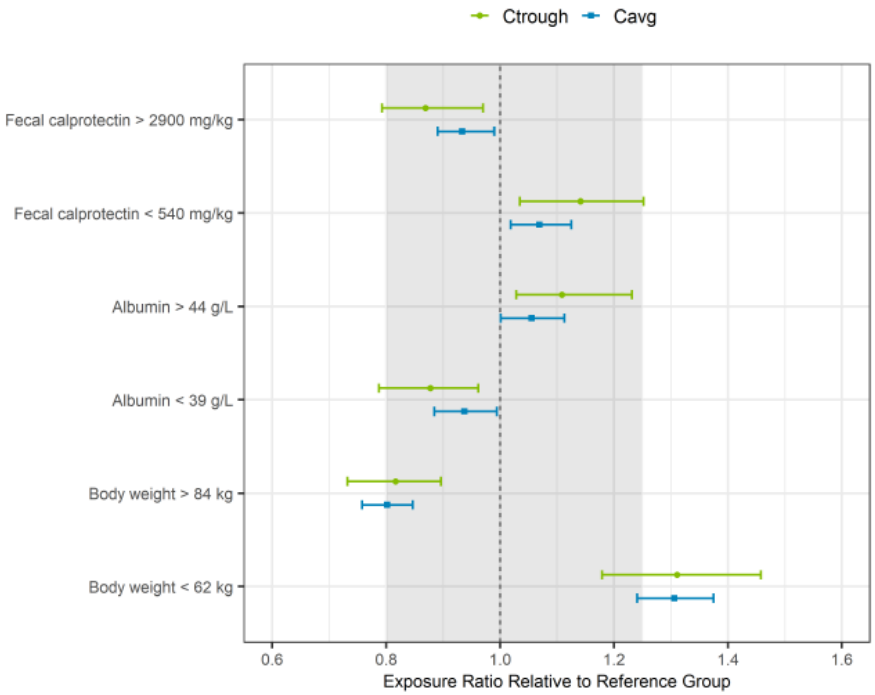
d. The estimates are provided in logit domain.

Figure 2 Visual predictive checks for pre-dose samples by induction dose using the final population pharmacokinetic model



The impact of covariates identified in the population PK analyses on risankizumab model predicted Week 12 exposure metrics Ctrough and Cavg is shown in Figure 2.

Figure 3 Forest plot to demonstrate the impact of covariates identified in the population pharmacokinetic analyses on Risankizumab exposures



Effect of covariates on risankizumab simulated exposures in subjects with ulcerative colitis. Points represent medians and error bars represent 95% confidence intervals of the normalized exposure ratios across 200 simulation replicates. C_{trough} is the model predicted trough concentration at Week 12, and C_{avg} is the model predicted average concentration over the 12 weeks induction period.

R&D/23/0018: Population pharmacokinetics of risankizumab in subjects with moderately to severely active ulcerative colitis

Data from subjects with moderate to severe CD in Phase 2 Study M15-993 (N=115) and data from subjects with moderately to severely active UC in Phase 2b/3 Studies M16-066 and M16-067 (N=1394) who received risankizumab and had at least one post-treatment measurable concentration were included in the analysis. The analysis dataset included 8185 concentration records.

A previously reported population PK model for subjects with CD was employed as the starting model for this analysis. This was a two-compartment model with first-order absorption and linear elimination.

The covariates body weight (on CL and Vc) and baseline serum albumin, baseline FCP, time-varying corticosteroid use, and sex (on CL) were retained and formed the base model for testing additional covariates. The subsequent covariate search identified advanced therapy inadequate response, hsCRP and baseline pancolitis status to be statistically correlated with CL. No other covariates were found to be statistically correlated with risankizumab PK.

Estimates of PK parameters and their associated variability based on the final model are shown in Table 14.

Figure 4 shows the VPC plots for the pre-dose samples for subjects in the 12-week Induction Period with time bins at Week 4, 8 and 12. Figure 5 shows the prediction corrected VPCs for the Maintenance Period at Week 16, 32 and 48.

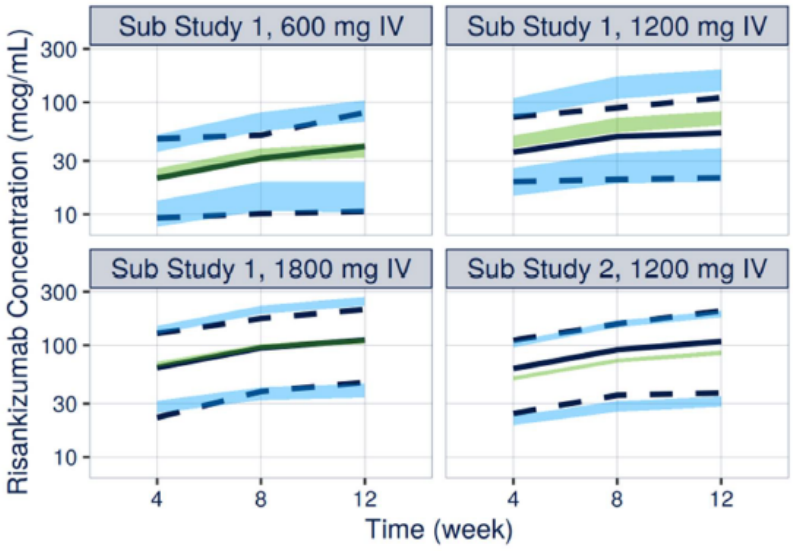
Table 14 Key parameter estimates and variability of Risankizumab pharmacokinetics

Parameter	Population Estimate	%RSE	95% Confidence Interval	CD Population Model Estimate
Clearance (CL; L/day)	0.269	1.61	(0.261, 0.278)	0.296
Central Volume of Distribution (Vc; L)	4.56	4.55	(4.15, 4.96)	4.98
Inter-Compartmental Clearance (Q; (L/day)	0.254	5.40	(0.227, 0.281)	0.255
Peripheral Volume of Distribution (Vp; L)	2.79	2.98	(2.63, 2.95)	2.70
Absorption Rate Constant (Ka; 1/day)	0.187	9.94	(0.151, 0.224)	0.121
Absolute SC Bioavailability (F)	0.830	1.40	(0.807, 0.853)	0.740
Exponent for the Effect of Body Weight on Risankizumab Clearance (CL)	0.679	6.62	(0.591, 0.767)	0.437
Exponent for the Effect of Body Weight on Risankizumab Central Volume of Distribution (Vc)	1.10	11.6	(0.852, 1.35)	0.911
Exponent for the Effect of Baseline Serum Albumin on Risankizumab Clearance (CL)	-1.21	5.75	(-1.35, -1.07)	-1.28
Exponent for the Effect of Baseline Fecal Calprotectin on Risankizumab Clearance (CL)	0.0164	33.1	(0.00577, 0.0271)	0.0482
Risankizumab Clearance (CL) Factor for Female Compared to Male	-0.0806	17.4	(-0.108, -0.0531)	-0.0723
Time varying Corticosteroid use on Risankizumab (CL)	0.0334	19.6	(0.0205, 0.0462)	0.0661
Risankizumab Clearance (CL) Factor for Advanced Therapy Inadequate Response (IR) No Compared to Yes	-0.116	12.4	(-0.144, -0.0878)	--
Exponent for the Effect of Baseline C-Reactive Protein High Sensitivity on Risankizumab Clearance (CL)	0.0396	14.1	(0.0286, 0.0506)	--
Risankizumab Clearance (CL) Factor for Baseline Pancolitis No Compared to Yes	-0.0557	23.2	(-0.0811, -0.0304)	--
Proportional Error	0.0676	0.917	(0.0664, 0.0688)	0.0553
Parameter	**Population Estimate**	**%CV**	**%Shrinkage**	
IIV on CL	0.0771	28.3	17.5	0.109
IIV on Vc	0.382	68.2	43.5	0.345
IIV on Ka	1.16	148	55.6	1.03

%RSE: % Relative standard error was calculated as the standard error of the estimator divided by the absolute value of the mean of the estimator multiplied by 100. %CV: % Coefficient of Variation was calculated as SQRT(exp(ω^2)-1)*100). Categorical covariates were implemented as "TV*(1+factor)."

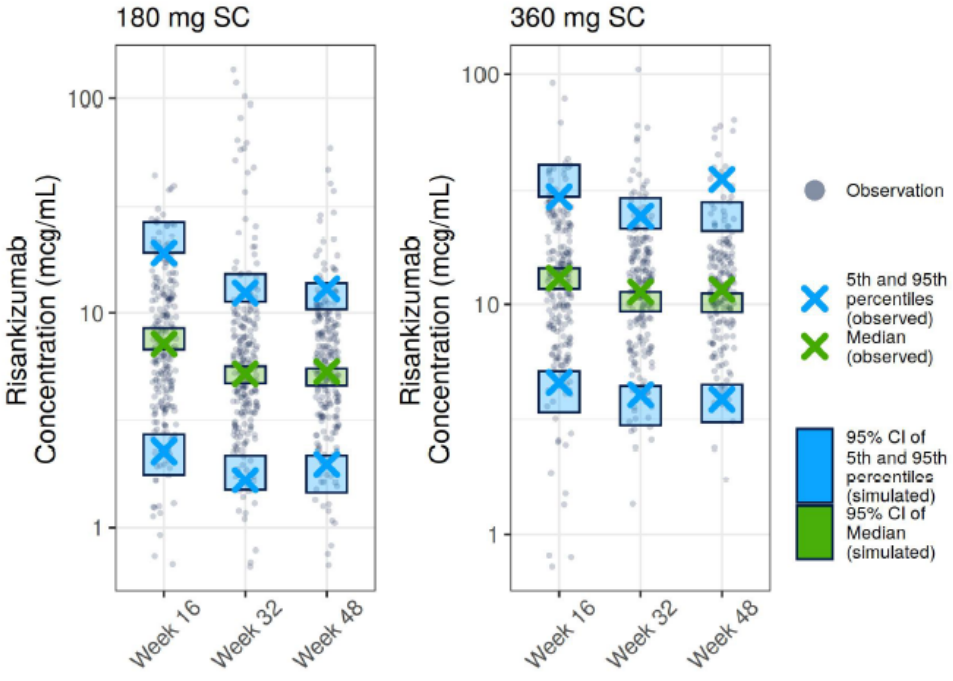
Cross reference: Population pharmacokinetic report (R&D/20/1547).[23]

Figure 4 Visual predictive checks for pre-dose samples by induction dose using the final population pharmacokinetic model – 12-week induction period



The shaded blue areas are the associated 95% CIs of the 5th and 95th percentiles of simulated concentrations. The green shaded area is the 95% CI of the predicted median. The solid black line and dashed black lines represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively.

Figure 5 Prediction corrected visual predictive checks by maintenance dose using the final population pharmacokinetic model

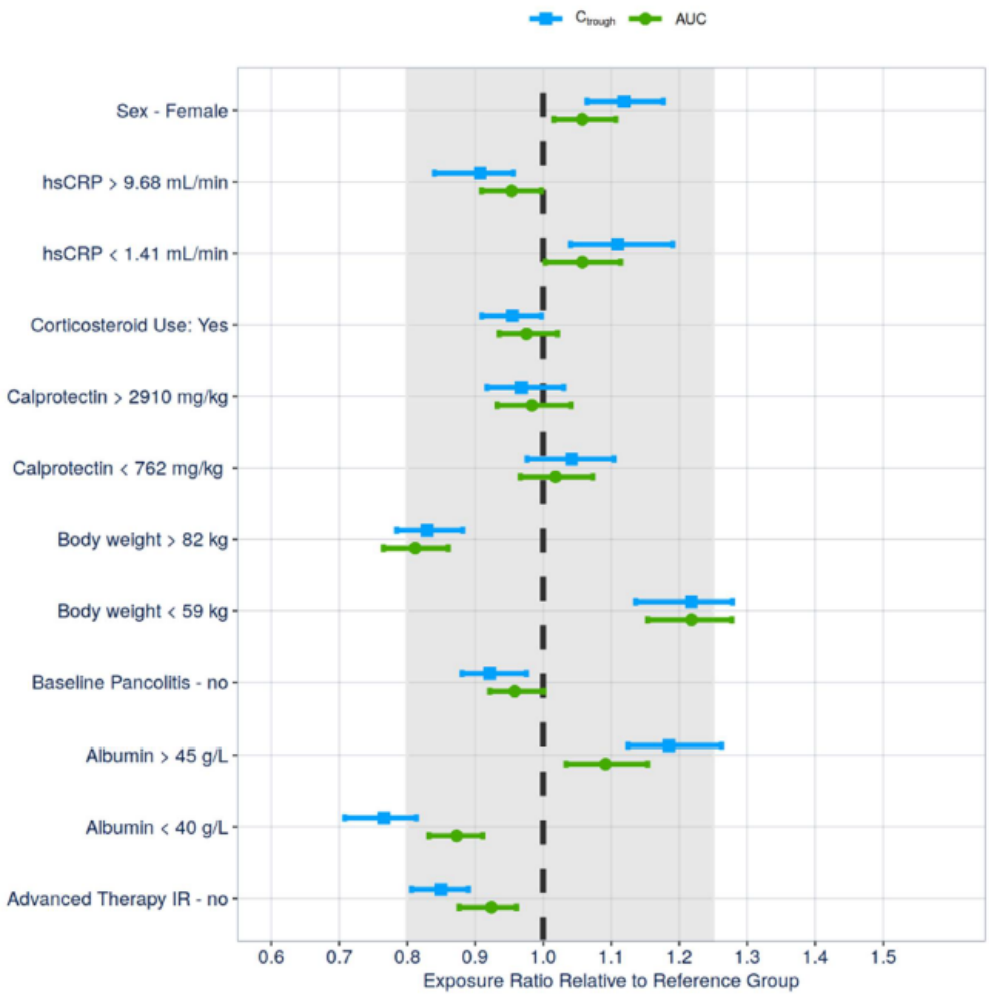


The shaded blue areas are the associated 95% CIs of the 5th and 95th percentiles of simulated concentrations. The green shaded area is the 95% CI of the predicted median. The green crosses and blue crosses represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively. Circles denote observed concentrations.

Note: Rescue subjects are included.

The impact of covariates identified in the population pharmacokinetic analyses on risankizumab model predicted Week 12 exposure metrics Ctrough and AUC are presented in Figure 6.

Figure 6 Forest plot to demonstrate the impact of covariates identified in the population pharmacokinetic analyses on Risankizumab exposures



Effect of covariates on risankizumab simulated exposures in subjects with UC. Points represent medians and error bars represent 95% CIs of the normalized exposure ratios across 200 simulation replicates. C_{trough} is the model predicted trough concentration at Week 12, and AUC is the model predicted average concentration over the 12-weeks Induction Period.

Simulations conducted using the population pharmacokinetic model showed that only low baseline serum albumin (< 40 g/L) had potentially meaningful impact on the Week 12 trough exposure of risankizumab in UC subjects. These subjects were predicted to have on average 23.6% lower Week 12 trough concentrations compared to subjects with serum albumin within the reference range (40 g/L to 45 g/L). The exposure metric that was used in the subsequent exposure-response analysis was the average concentration, which is derived from the AUC and is within the 0.8 to 1.25 reference range.

This analysis was also conducted for Week 48 trough concentration and AUC using the maintenance dosing regimens of 180 mg SC Q8W and 360 mg SC Q8W. Given the linearity of PK, the results for both maintenance regimens were similar and followed a similar trend to the results with the induction dosing regimen. The average concentration, derived from the AUC, was used in the exposure-response analysis for maintenance and is within the 0.8 and 1.25 reference range for all covariates.

Special populations

Impaired renal function

Risankizumab is not expected to undergo renal elimination. Therefore, no dedicated studies were conducted to evaluate risankizumab PK in patients with renal impairment. Based on the population PK analyses, serum creatinine level had no meaningful impact on risankizumab exposure.

Impaired hepatic function

Risankizumab is not expected to undergo metabolism by hepatic metabolic enzymes. Therefore, no dedicated studies were conducted to evaluate risankizumab PK in patients with hepatic impairment. Based on the population PK analyses, the liver function markers, including total bilirubin, AST, and ALT levels were not correlated with risankizumab clearance.

Gender

Based on the population PK analyses, gender had no clinically meaningful impact on risankizumab exposure.

Race

Based on the population PK analyses, race had no clinically meaningful impact on risankizumab exposure. Post-hoc model-predicted risankizumab exposures were similar in Asians vs non-Asians, among subjects in China or Japan compared to non-Asian countries.

Weight

Consistent with other IgG1 mAbs, risankizumab clearance and volume of distribution increase as body weight increases, but this was not considered to have a clinically relevant impact on risankizumab exposures.

Elderly

Of the 1512 subjects with UC exposed to risankizumab, 103 were 65 years or older and 8 subjects were 75 years or older. Based on the population PK analyses, age had no clinically meaningful impact on risankizumab exposure.

Pharmacokinetic interaction studies

One Phase I drug-drug interaction (DDI) study was conducted to evaluate the effect of repeated doses of Risankizumab on the pharmacokinetics of sensitive probe substrates of CYP enzymes in subjects with CD or UC. The MAH explained that the DDI study was performed since requested by the FDA for two reasons: 1) compared to PsO, IBD indications such as UC and CD may have a higher inflammatory burden which could impact the DDI potential for risankizumab, and 2) risankizumab doses in CD and UC indications are higher than that in PsO.

Study M19-974

Study M19-974 was a Phase 1, multi-centre, multiple-dose, open-label, two-period, single arm study (n=20). This study aimed to evaluate the effect of risankizumab 1800 mg IV Q4W × 3 doses (the highest dose tested in UC and CD clinical trials) on the activities of multiple cytochrome P450 (CYP) enzymes including CYP3A, 1A2, 2C9, 2C19, and 2D6 in CD and UC patients, by using probe substrates that are specific for the respective CYP enzymes and that do not interact among each other using a cocktail approach.

To assess the relative bioavailability of each of the CYP probe drugs and their possible metabolites, analyses were performed on log transformed AUCinf, AUCt and Cmax for each of the CYP probe drugs

and their metabolites and on log transformed metabolite-to-parent drug AUC ratios for all CYP drugs with metabolites, via 90% confidence intervals (CI) for the ratio of regimen central values.

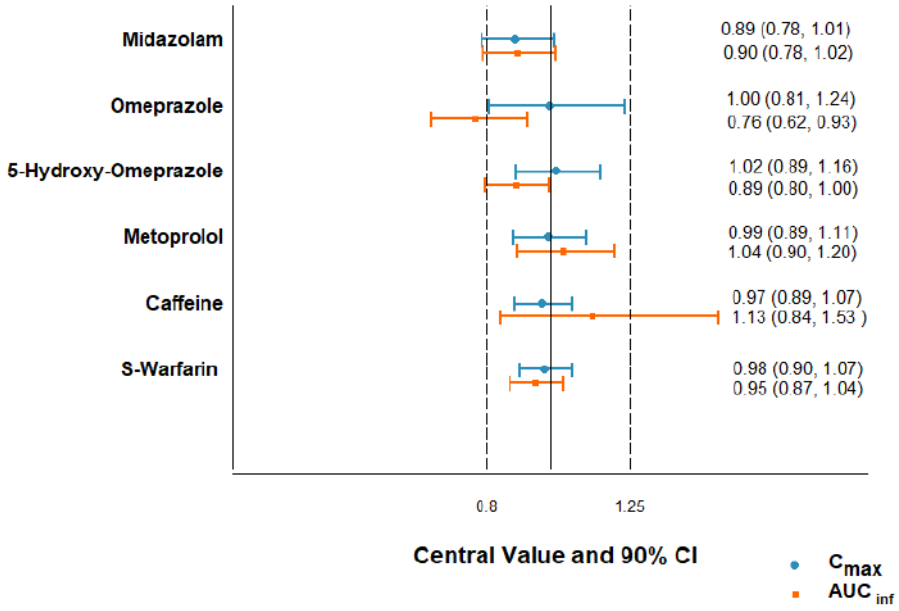
Pharmacokinetic Interactions Results

The point estimates and 90% CIs for the ratios of the probe substrates Cmax and AUC when administered after risankizumab 1800 mg IV Q4W versus when these substrates were administered prior to initiating risankizumab treatment were mostly aligned with the default no-effect boundaries of 0.8 to 1.25, except for omeprazole and caffeine.

The upper 90% CI for caffeine (0.84 - 1.53) AUCinf exceeded 1.25, however the point estimate (1.13) for AUCinf and the Cmax ratio (0.89 – 1.07) were within the boundary of 0.8-1.25.

For omeprazole, the lower bound of the 90% CI (0.62 – 0.93) and the point estimate (0.76) for the AUCinf were below the lower boundary for no-effect of 0.8, showing that there was a decrease in concentration following Risankizumab treatment. The exposures of its metabolite by CYP2C19 (5-OH-omeprazole) were comparable before and after risankizumab treatment (90% CI of Cmax and AUC ratios were within the range of 0.8-1.25), with a consistent metabolite-to-parent ratio with or without risankizumab, which in the MAH's view indicates limited impact of risankizumab treatment on the activities of CYP2C19.

Figure 7 Point estimates and 90% confidence intervals for the effect of Risankizumab 1800 mg IV Q4W on the pharmacokinetic parameters of CYP probe substrates



2.6.2.2. Pharmacodynamics

Primary and Secondary pharmacology

R&D/23/0656

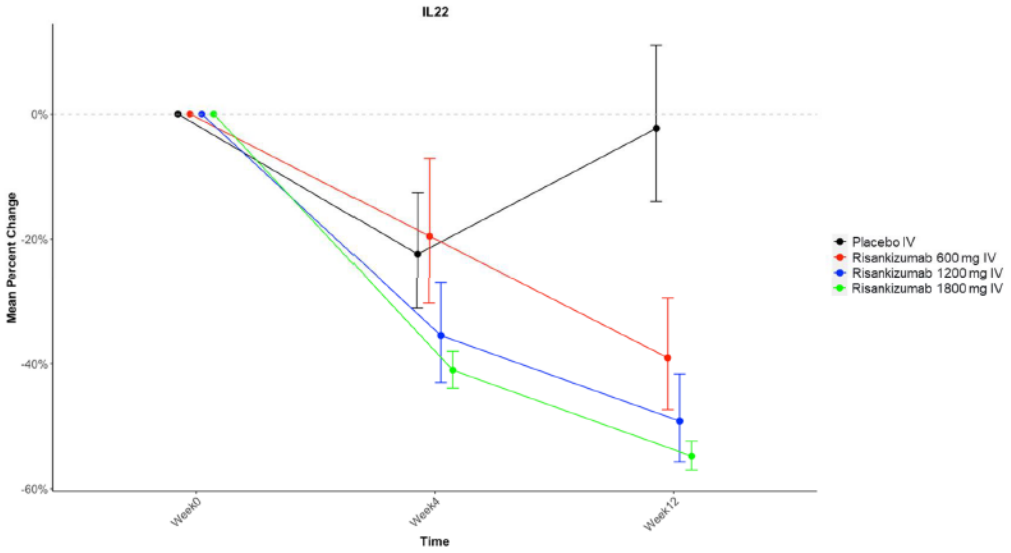
The purpose of this analyses was to assess the effect of treatment with risankizumab 600 mg IV, 1200 mg IV, or 1800 mg IV (administered at Week 0, Week 4 and Week 8) on a serum protein biomarker downstream of the IL-23 pathway (IL-22) at Week 12 in UC subjects enrolled in the M16-067 Phase 2b/3 induction study SS2 and open label dose-selection. It also assessed the effect of treatment with risankizumab 180 mg SC or 360 mg SC (administered Q8w) on a serum protein biomarker downstream of the IL-23 pathway (IL-22) at Week 52 in UC subjects enrolled in the M16-066 SS1

Phase 3 maintenance study. The analyses determined the change from baseline in IL-22 levels and a comparison in the change from baseline between the treatment groups in both studies.

Pharmacodynamic results

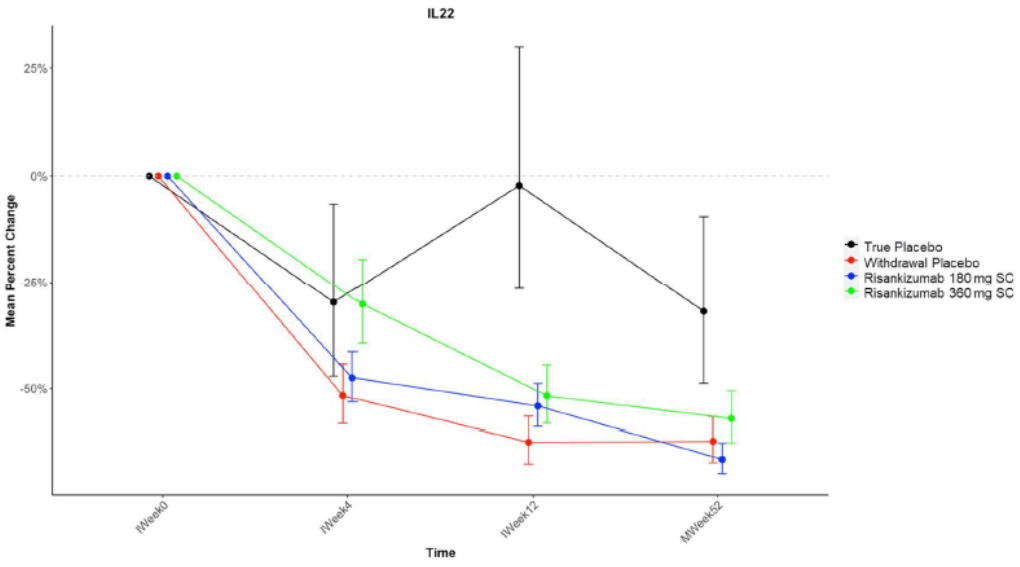
In M16-067, Serum IL-22 levels (Figure 8) decreased from baseline in risankizumab 600 mg risankizumab 1200 mg-, and risankizumab 1800 mg treated subjects at Week 12. Compared to placebo-treated subjects, IL-22 levels were significantly lower in risankizumab 600 mg, risankizumab 1200 mg and risankizumab 1800 mg treated subjects at Week 12.

Figure 8 Change from Baseline in IL-22 at Week 12 in M16-067



In M16-066, Serum IL-22 levels (Figure 9) decreased from baseline (baseline / Week 0 of induction) in the withdrawal placebo-, risankizumab 180 mg-, and risankizumab 360 mg-treated subjects at Week 52. Compared to true placebo subjects, IL-22 levels were significantly lower in risankizumab 180 mg-treated subjects at Week 52.

Figure 9 Change from Baseline in IL-22 over time in M16-066

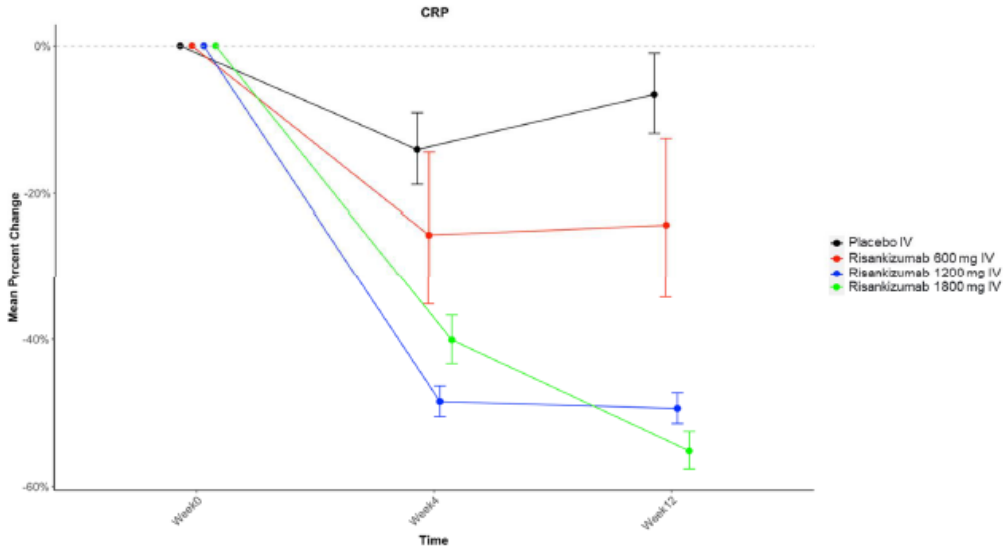


The purposes of these analyses were to assess the effect of treatment with risankizumab 600 mg IV, 1200 mg IV, or 1800 mg IV (administered at Week 0, Week 4 and Week 8) on disease biomarkers of inflammation (CRP and FCP) at Week 12 in UC subjects enrolled in the M16-067 Phase 2b/3 induction study SS2 and open label dose-selection. It also assessed the effect of treatment with risankizumab 180 mg SC or 360 mg SC (administered Q8w) on disease biomarkers of inflammation (CRP and FCP) at Week 52 in UC subjects enrolled in the M16-066 SS1 Phase 3 maintenance study. The analyses determined the change from baseline in IL-22 levels and a comparison in the change from baseline between the treatment groups in both studies.

Pharmacodynamic results

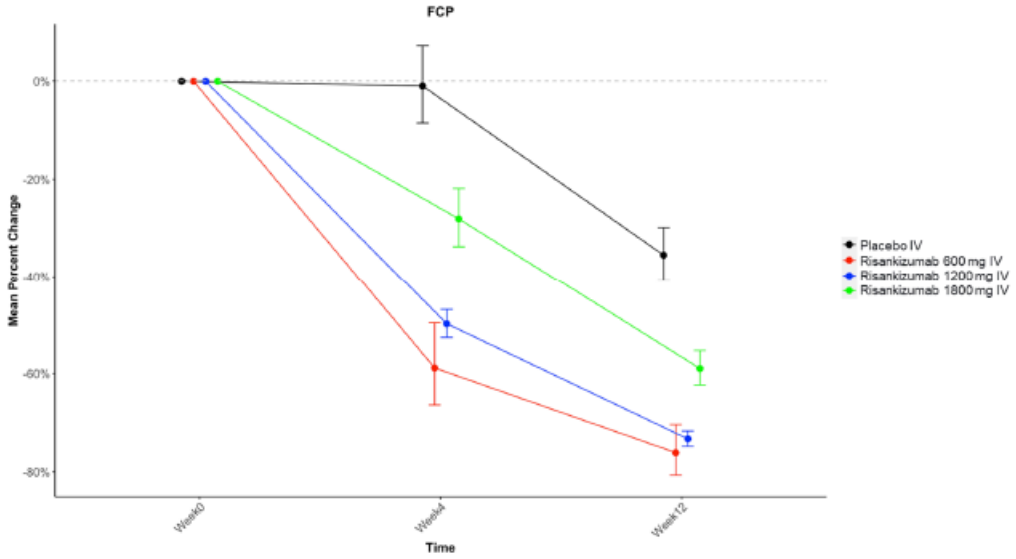
In M16-067, CRP levels (Figure 10) decreased from baseline in risankizumab 1200 mg- and risankizumab 1800 mg treated subjects at Week 12. Compared to placebo treated subjects, CRP levels were significantly lower in risankizumab 1200 mg- and risankizumab 1800 mg treated subjects at Week 12. Additionally, compared to Risankizumab 600 mg treated subjects, CRP levels were significantly lower in risankizumab 1200 mg- and risankizumab 1800 mg treated subjects at Week 12.

Figure 10 Change from baseline in CRP at Week 12 in M16-067



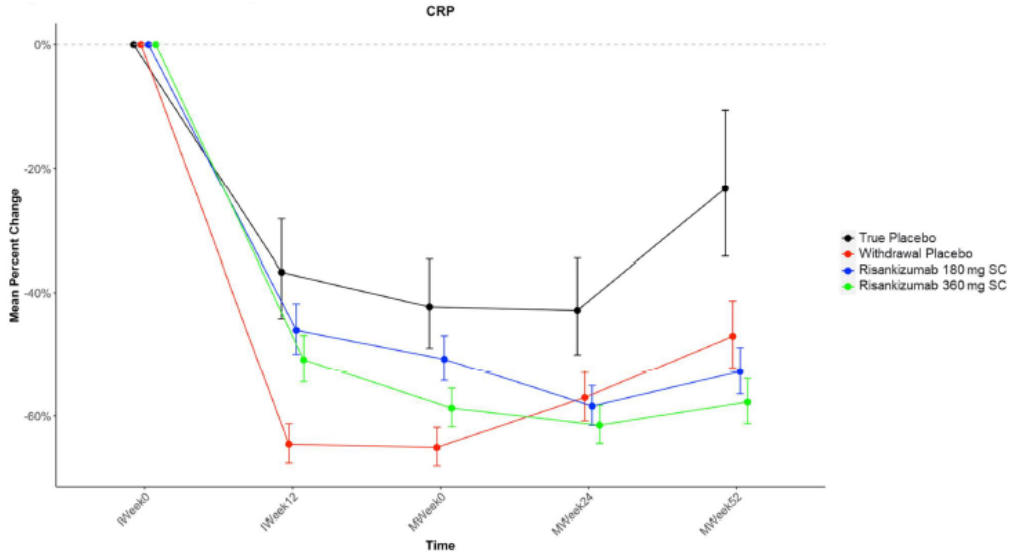
In M16-067, FCP levels (Figure 11) decreased from baseline in the placebo-, risankizumab 600 mg-, risankizumab 1200 mg-, and risankizumab 1800 mg-treated subjects at Week 12. Compared to placebo-treated subjects, FCP levels were significantly lower in risankizumab 600 mg-, risankizumab 1200 mg-, and risankizumab 1800 mg treated subjects at Week 12. Additionally, compared to Risankizumab 1800 mg treated subjects, FCP levels were significantly lower in risankizumab 600 mg and risankizumab 1200 mg treated subjects at Week 12.

Figure 11 Change from baseline in FCP at Week 12 in M16-067



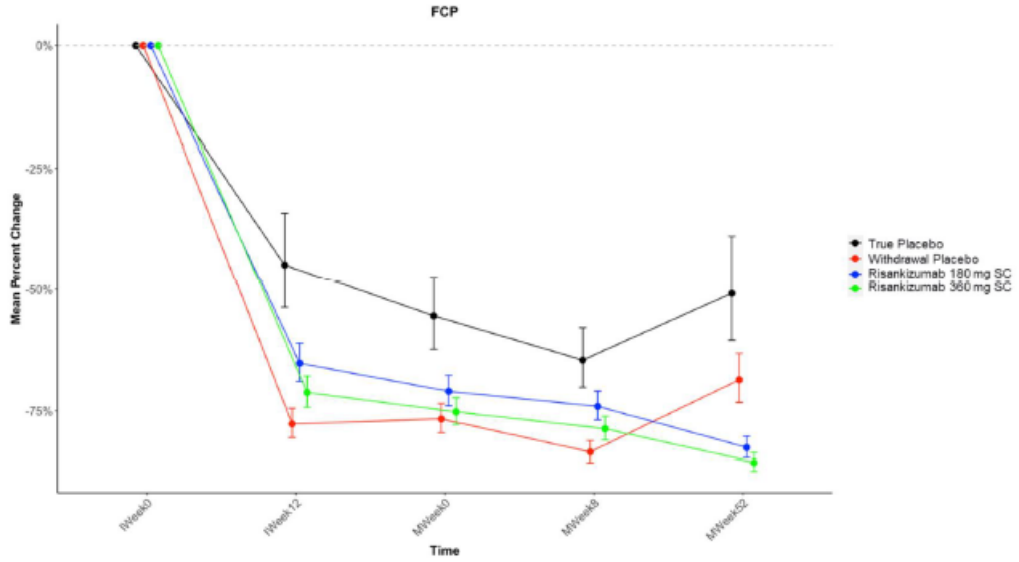
In M16-066, CRP levels (Figure 12) decreased from baseline in the true placebo, withdrawal placebo, risankizumab 1800 mg-, and risankizumab 360 mg-treated subjects at Week 52. Compared to true placebo-treated subjects, CRP levels were significantly lower in withdrawal placebo- and both risankizumab-treated groups at Week 52.

Figure 12 Change from baseline in CRP ovedr time in M16-066



In M16-066, FCP levels (Figure 13) decreased from baseline in the true placebo, withdrawal placebo, risankizumab 1800 mg-, and risankizumab 360 mg-treated subjects at Week 52. Compared to true placebo-treated subjects, FCP levels were significantly lower in both risankizumab 180 mg- and risankizumab 360 mg-treated groups at Week 52. Compared to withdrawal placebo-treated subjects, FCP levels were significantly lower in both risankizumab 180 mg- and risankizumab 360 mg-treated groups at Week 52.

Figure 13 Change from baseline in FCP over time in M16-066



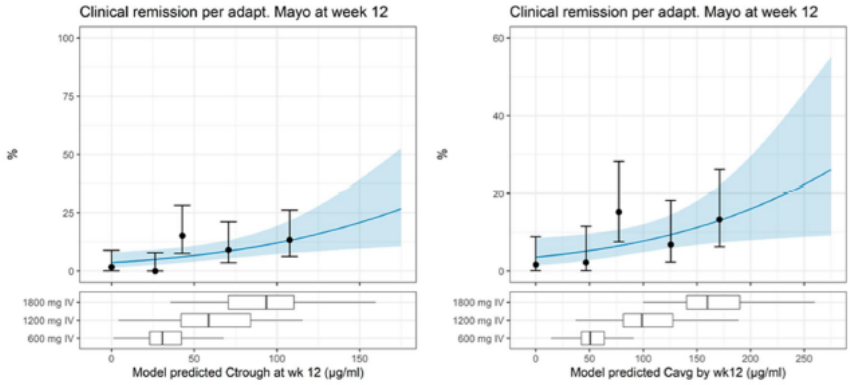
Exposure-response analyses

R&D/20/0609: Phase 2 exposure-response analyses of risankizumab for efficacy and safety during induction treatment in ulcerative colitis.

Exposure-response analyses were conducted using data from Phase 2b induction study in subjects with UC (Study M16-067 Sub study 1) to support dose selection for the Phase 3 induction study, Study M16-067 Sub study 2 (R&D/23/1137). The analyses characterised the relationships between risankizumab exposures and efficacy as well as safety in subjects with UC using data from subjects in the Phase 2b study.

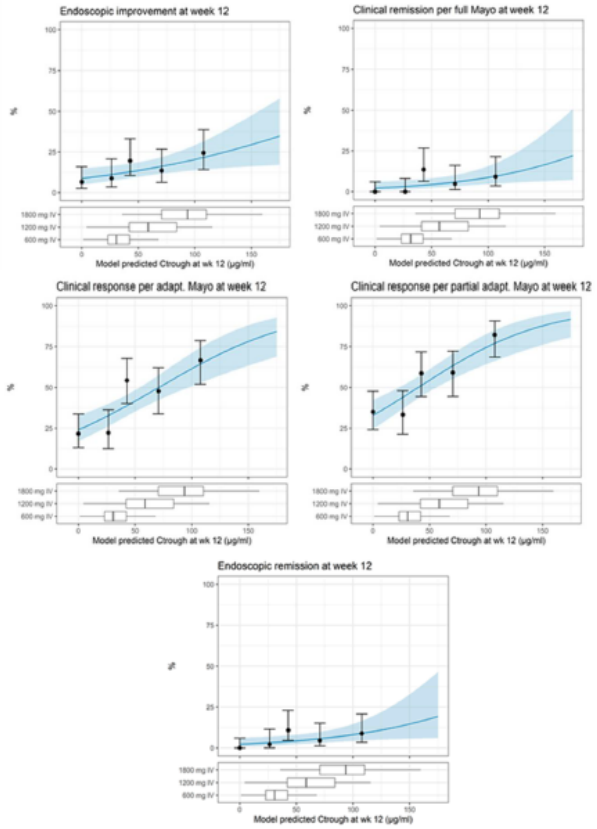
As shown in Figure 14 and Figure 15, steep exposure-response relationships were observed for endpoints that did not include endoscopy, or with less stringent criteria for defining endoscopic response (including clinical response per partial Mayo score and clinical response per Adapted Mayo score at Week 12). For other endpoints such as clinical remission per Adapted Mayo score, endoscopic improvement, clinical remission per full Mayo score, and endoscopic remission at Week 12, shallower, yet statistically significant (not for Cavg by Week 12 related to endoscopic improvement), exposure-response relationships were observed. Overall, the models predict incremental efficacy with increasing doses from 600 to 1800 mg. Exposure-response models for efficacy also showed that none of the covariates included in the dataset, including body weight, had any significant effect on the efficacy.

Figure 14 Predicted ER relationship based on logistic regression versus observed proportion of subjects achieving efficacy endpoints for primary clinical endpoint of clinical remission per adapted Mayo at Week 12 with C_{trough} at Week 12 and C_{avg} by Week 12 as exposure metrics



Black dots show the observed proportions of responders and error bars show their 95% exact binomial confidence intervals at the midpoint of each quartile of the risankizumab exposure. Thick blue line shows logistic regression model predicted exposure-response. Shaded areas show the 95% confidence interval around model predictions. Box plots represent the predicted exposures for each regimen.

Figure 15 Predicted ER relationship based on logistic regression for secondary efficacy endpoints at Week 12 with C_{trough} at Week 12 as exposure metrics



Black dots show the observed proportions of responders and error bars show their 95% exact binomial confidence intervals at the midpoint of each quartile of the risankizumab exposure. Thick blue line shows logistic regression model predicted exposure-response. Shaded areas show the 95% confidence interval around model predictions. Box plots represent the predicted exposures for each regimen.

Overall, greater efficacy was expected at higher risankizumab exposures and both doses of risankizumab 1200 mg and 1800 mg IV were expected to provide better efficacy than risankizumab 600 mg IV for subjects with UC during the induction period. While there was incremental efficacy

predicted with doses increasing from risankizumab 1200 mg to 1800 mg IV, due to the proximity of the two doses resulting in overlapping distributions of exposure, the magnitude of the difference in efficacy was modest especially for endoscopy-driven endpoints for which shallow exposure-response relationships were observed.

Exploratory analyses of the safety variables indicated no apparent relationship between risankizumab exposures (Ctrough at Week 12 or Cavg by Week 12) and any AE, SAE, infection and infestation, or serious infection.

R&D/23/0018: Exposure-response analyses for risankizumab efficacy and safety in subjects with moderately to severely active ulcerative colitis

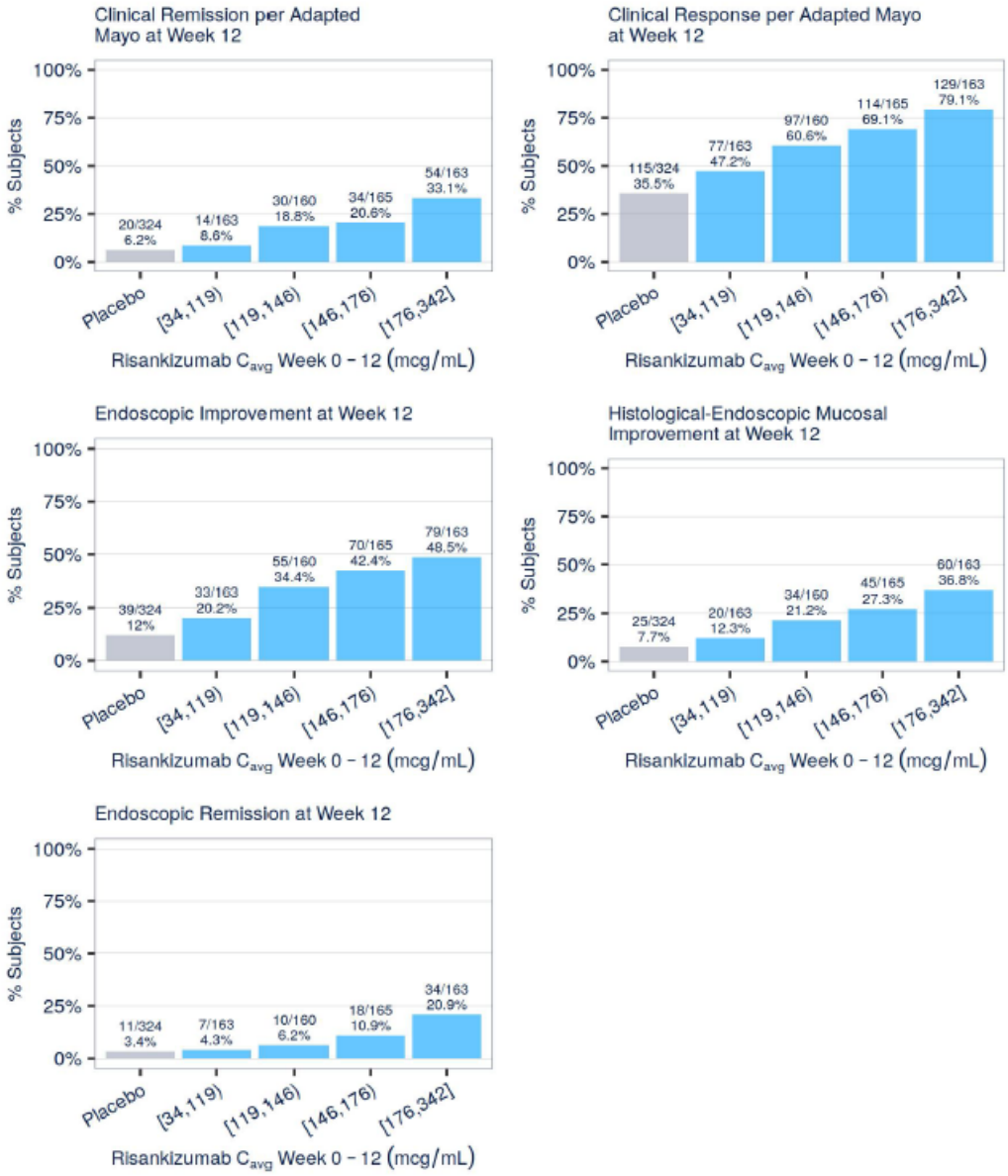
Data from subjects with moderately to severely active UC in the Phase 3 portion of induction Study M16-067 (N=975) and Sub study 1 of Study M16-066 (N=548 for efficacy, N=584 for safety) who were randomised to receive placebo or risankizumab were included in the exposure-response analyses. For the exposure-response analyses for efficacy, all endpoints were evaluated at Week 12 (end of first 12-weeks Induction Period) and Week 52 (end of maintenance).

Risankizumab exposure-response relationships for efficacy and safety parameters were evaluated using quartile plots. Quartile plots for safety were evaluated using Cavg and Cmax. Non-linear and linear logistic regression analyses for the efficacy endpoints were evaluated to characterise the relationship between risankizumab exposures, like Cavg as a predictor variable and the different endpoints (as binary variables). A treatment effect model (risankizumab versus placebo) with no exposure-response relationship as well as different drug effect exposure-response models (linear, logarithmic, and maximum response [Emax]) were evaluated to determine the best model describing the risankizumab effect on the probability of each efficacy outcome.

Exposure-response analyses for efficacy in the 12-Week induction period

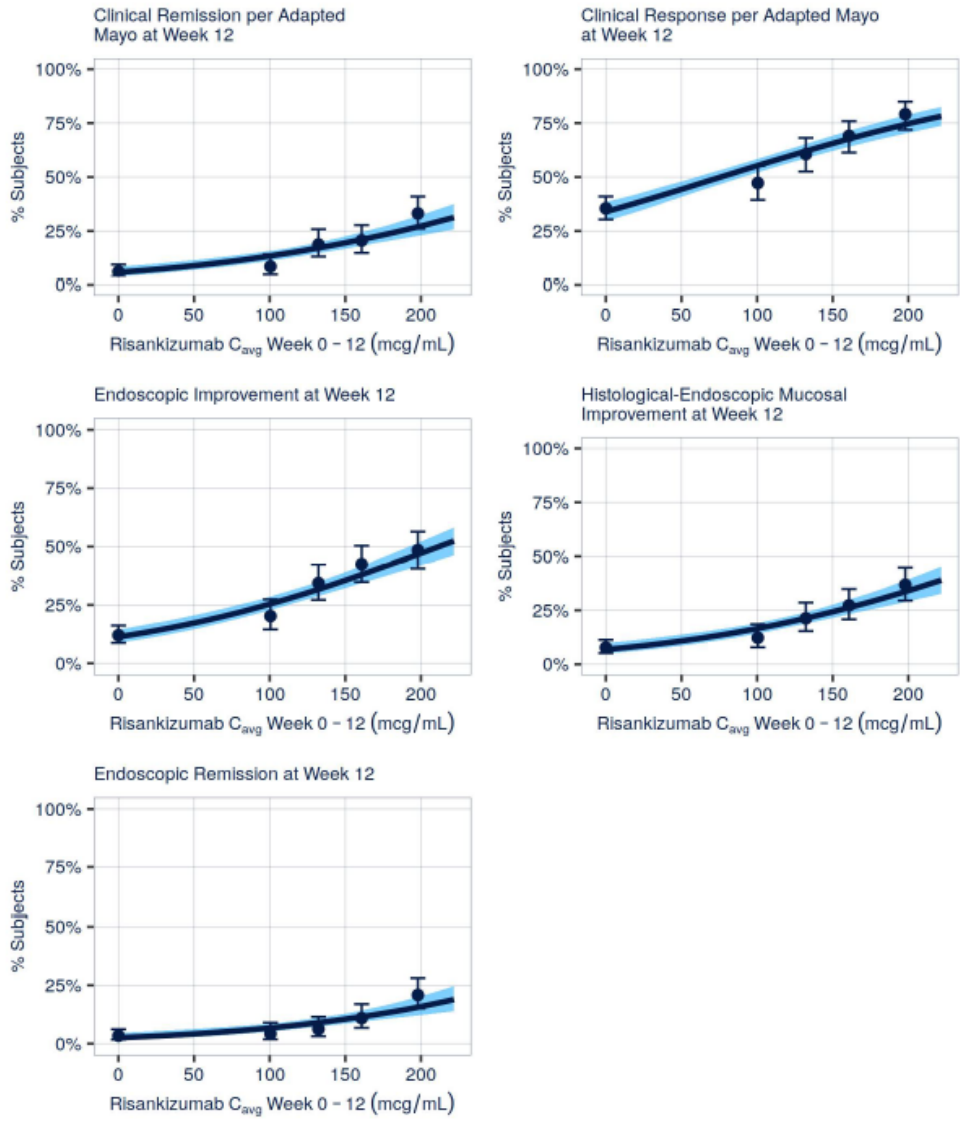
The exposure-response relationship between risankizumab Cavg, Week0-12 and the efficacy endpoints at Week 12 were analysed using data from the 12-Week Induction Period of the Phase 3 Study M16-067 evaluating 1200 mg IV at Weeks 0, 4, and 8 as an induction regimen in comparison to placebo. Results showed that subjects treated with risankizumab achieved higher efficacy response rates than the placebo subjects for all the endpoints. In addition to this, a clear exposure-dependent increase in efficacy was observed across all endpoints at Week 12 (Figure 16).

Figure 16 Relationship between Risankizumab $C_{avg,Week0-12}$ and Efficacy responses at Week 12 of the induction period



Logistic regression models were developed relating risankizumab Cavg, Week0-12 to the achievement of different efficacy endpoints. Comparisons between the observed data and the model predictions are shown in Figure 17. The models were capable of adequately capturing the observed data for all endpoints.

Figure 17 Observed versus Model-Predicted Exposure-Response relationships between Risankizumab $C_{avg.Week0-12}$ and efficacy endpoints evaluated at Week 12



The solid line represents median predicted response and the shaded areas represent 95% CI of the response. The dots and error bars represent median and 95% binomial CIs of binned observed responses.

Of the stratification factors, advanced therapy inadequate response had a statistically significant impact ($p < 0.01$) on all efficacy endpoints evaluated at Week 12, with subjects that had inadequate response to prior advanced therapies showing lower probability of achieving a response than the subjects who were advanced therapy naïve. The other two stratification factors of baseline steroid use and baseline adapted Mayo score did not have a significant relationship with the various responses.

Based on the exposure-response models, an induction regimen of 1200 mg IV at Weeks 0, 4, and 8, is predicted to have about 11.2 – 20.0% higher response rates in advanced therapy naïve subjects as compared to the advanced therapy inadequate response subjects across the endpoints (based on numerical differences in median % response rates).

Statistically significant covariates on the exposure-response relationships were Asian race on endoscopic improvement, histological mucosal endoscopic improvement and endoscopic remission at Week 12, and baseline serum albumin on clinical response per adapted Mayo score and endoscopic improvement at Week 12. Asian subjects are generally predicted to have only 2.00 – 4.67% lower

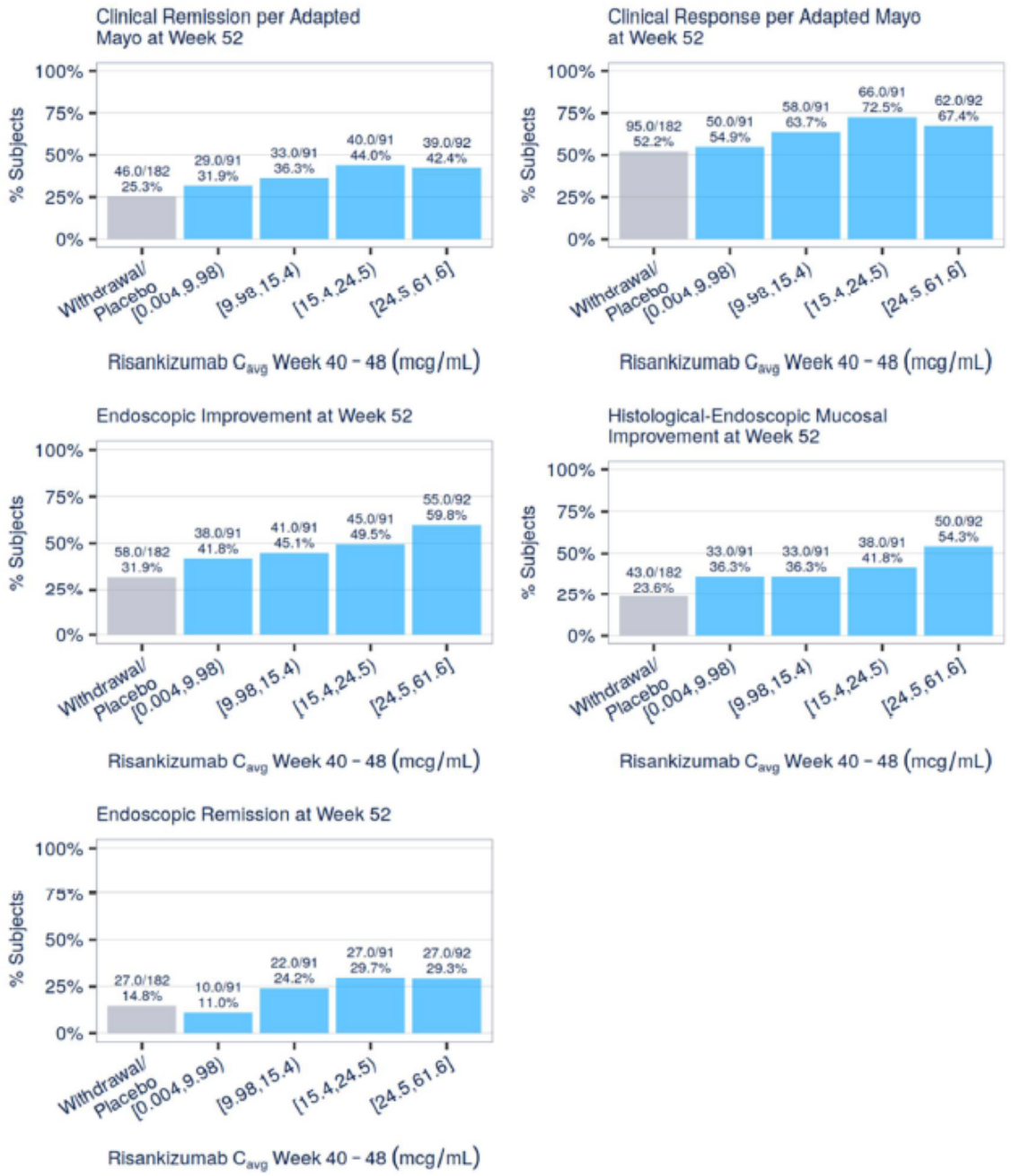
efficacy rates as compared to the non-Asian subjects for endoscopic endpoints in placebo as well as treated group. Subjects with higher baseline albumin levels are predicted to have 14.2 – 16.5% higher probability to attain clinical response and endoscopic improvement at Week 12 than the subjects with low baseline albumin levels.

Exposure-response analyses for efficacy in the maintenance period

The exposure-response relationship between risankizumab Cavg,Week40-48 and the efficacy endpoints at Week 52 were analysed using data from the 52-Week Maintenance Period of the Phase 3 Study M16-066 (sub study 1) evaluating 180 mg SC and 360 mg SC at Q8W as a maintenance regimen in comparison to placebo, in subjects who were treated with risankizumab IV doses in the 12-Week Induction Period or Induction Period 2 of the Study M16-067.

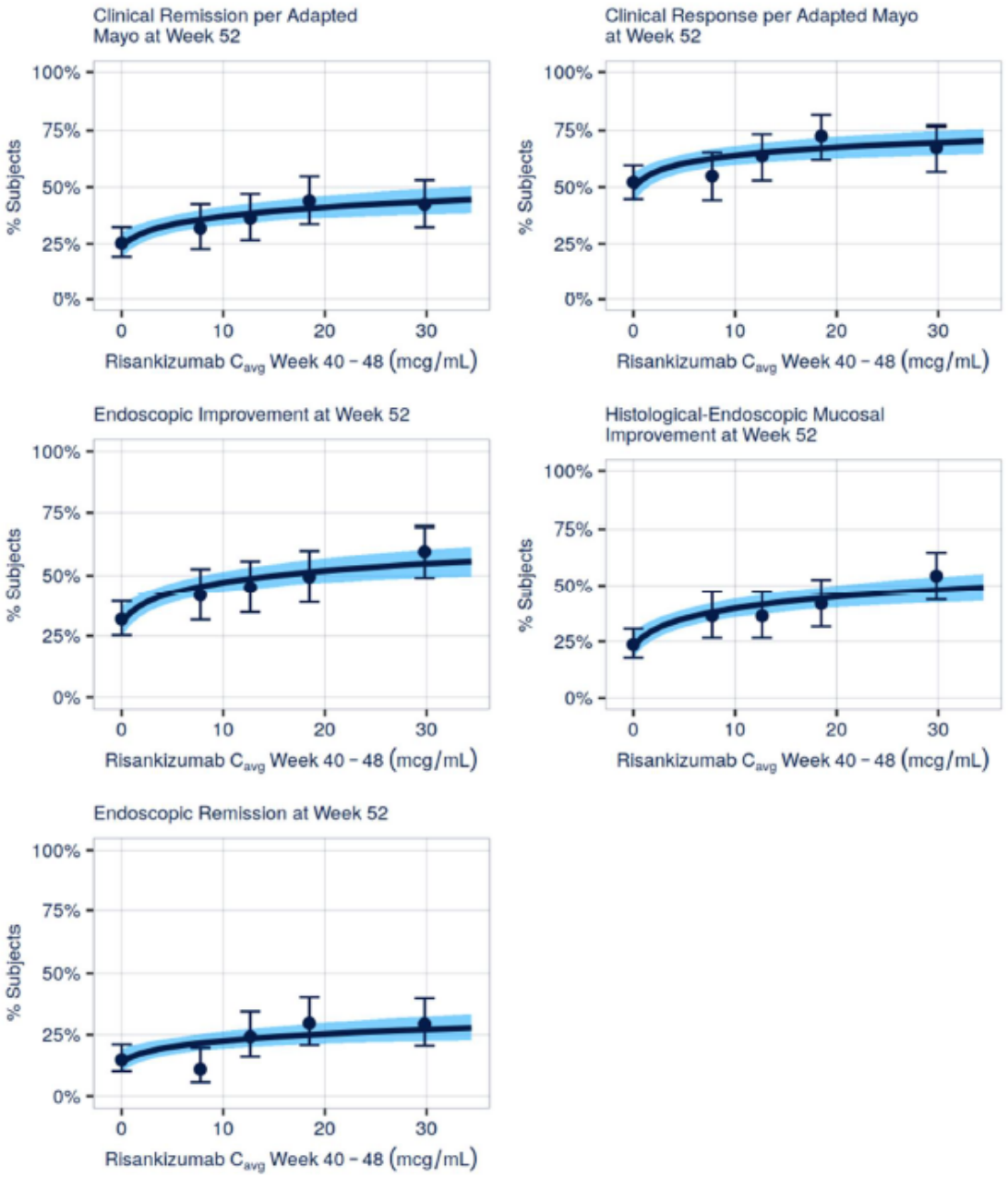
Results showed that subjects treated with risankizumab achieved higher efficacy response rates than placebo subjects for all the endpoints. In addition to this, an exposure-dependent increase for the lower risankizumab exposure quartiles and an efficacy saturation at the upper exposure-quartiles were observed for the primary endpoint of clinical remission per adapted Mayo score and secondary endpoints of clinical response per adapted Mayo score and endoscopic remission at Week 52. For the remaining endoscopy-related secondary endpoints (endoscopic improvement and histological-endoscopic mucosal improvement), a clear exposure-dependent increase in efficacy without an apparent plateau was observed at Week 52 (Figure 18).

Figure 18 Relationship between Risankizumab $C_{avg.Week40-48}$ and responses at Week 52 in maintenance period



Logistic regression models were developed relating risankizumab Cavg,Week40-48 to the achievement of different efficacy endpoints (Figure 19). Comparisons between the observed data and the model predictions are shown in Figure 19. The models were capable of adequately capturing the observed data for all endpoints.

Figure 19 observed versus model-predicted exposure-response relationships between Risankizumab $C_{avg.Week40-48}$ and efficacy endpoints evaluated at Week 52



The solid line represents median predicted response and the shaded areas represent 95% CI of the response. The dots and error bars represent median and 95% binomial CIs of binned observed responses.

Of the stratification factors, advanced therapy inadequate response had a statistically significant impact ($p < 0.01$) on clinical remission per adapted Mayo score, clinical response per adapted Mayo score and endoscopic remission at Week 52, with subjects that had inadequate response to prior advanced therapies showing lower probability of achieving a response than the subjects who were advanced therapy naïve. Clinical remission per adapted Mayo score at the end of Induction Period had a significant effect on the exposure-response relationship for clinical remission per adapted Mayo score, endoscopic improvement, histological mucosal endoscopic improvement, and endoscopic remission at Week 52, with responders to clinical remission during the Induction Period showing higher probability of achieving response in the Maintenance Period. The stratification factor of induction IV

dose (600 mg vs 1200 mg vs 1800 mg) was not identified as a significant stratification factor for efficacy.

Model predictions for the response rates at Week 52 indicated 2.50 – 4.50% higher efficacy rates (based on differences in median % response rates) for the maintenance regimen of 360 mg SC Q8W compared to the 180 mg SC Q8W.

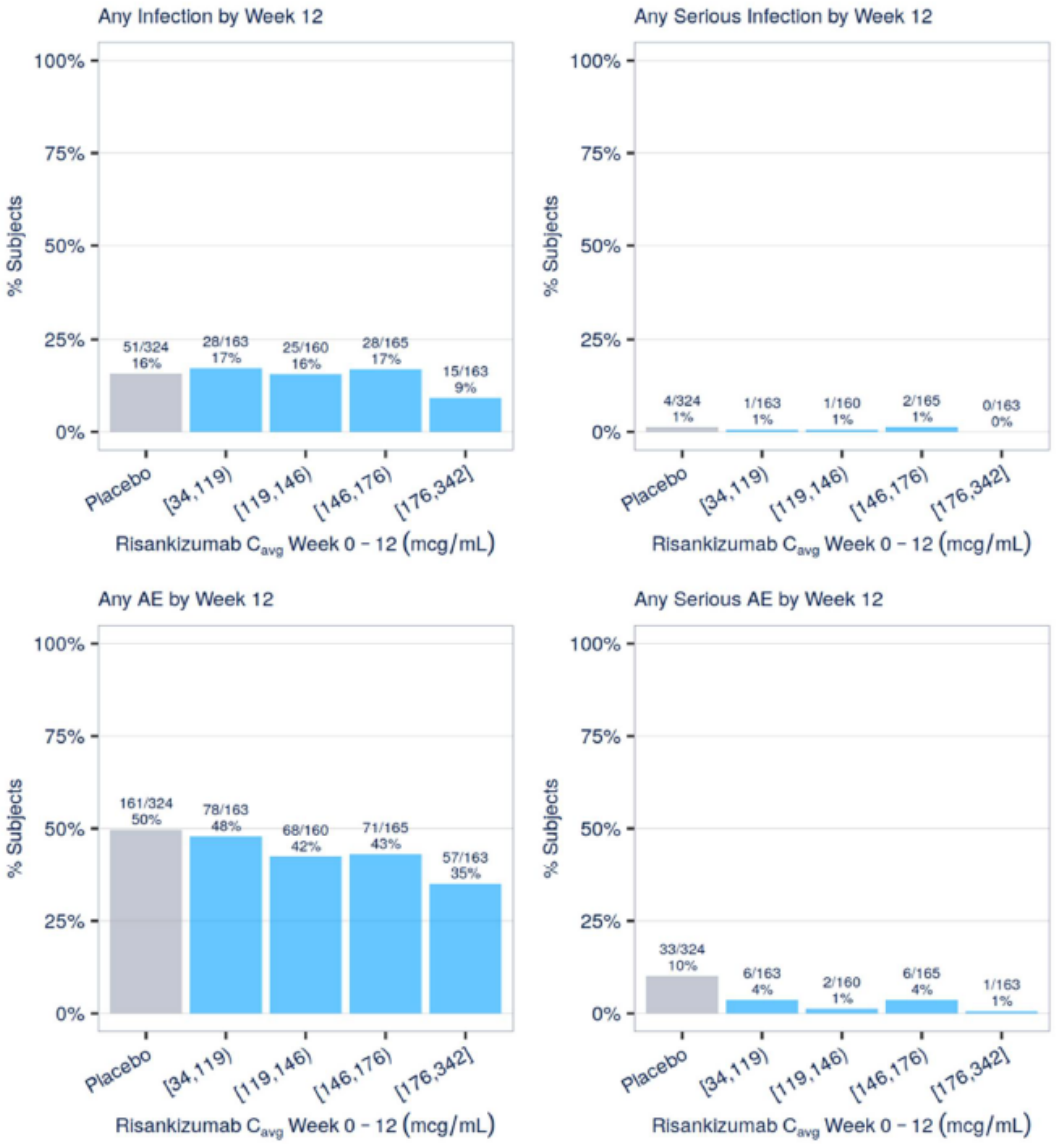
Model predictions stratified by advanced therapy inadequate response and clinical remission at the end of induction for efficacy endpoints where they were statistically significant indicated that the response rates for the subgroups are consistent with the overall predictions, 360 mg SC Q8W is associated with a modest numerical increase in efficacy response compared to 180 mg SC Q8W, with the 95% CI around the predictions largely overlapping between the two doses.

None of the tested covariates, including exposures (Cavg,Week0-12) during the 12-week Induction Period, had a significant effect on the relationship between Cavg,Week40-48 and any efficacy endpoint at Week 52.

Exposure-response analyses for safety in the 12-Week induction period

The relationship between model-predicted risankizumab Cavg,Week0-12 and percentage of subjects who experienced any AE, SAE, infection, and serious infection over the first 12 weeks (Week 0 – 12) duration, are presented in Figure 20. As shown in Figure 20, there was no apparent relationship between risankizumab exposures (Cavg,Week0-12) and any AE, SAE, infection, and serious infection over the first 12 weeks. Overall, during the 12-week Induction Period, the incidences of safety variables of interest were equal or lower on the risankizumab treated subjects compared to the placebo-treated subjects. Similar results were observed in the graphical analyses for the relationship between maximum concentration during the 12-week Induction Period (Cmax,Week0-12) and any AE, SAE, infection, and serious infection.

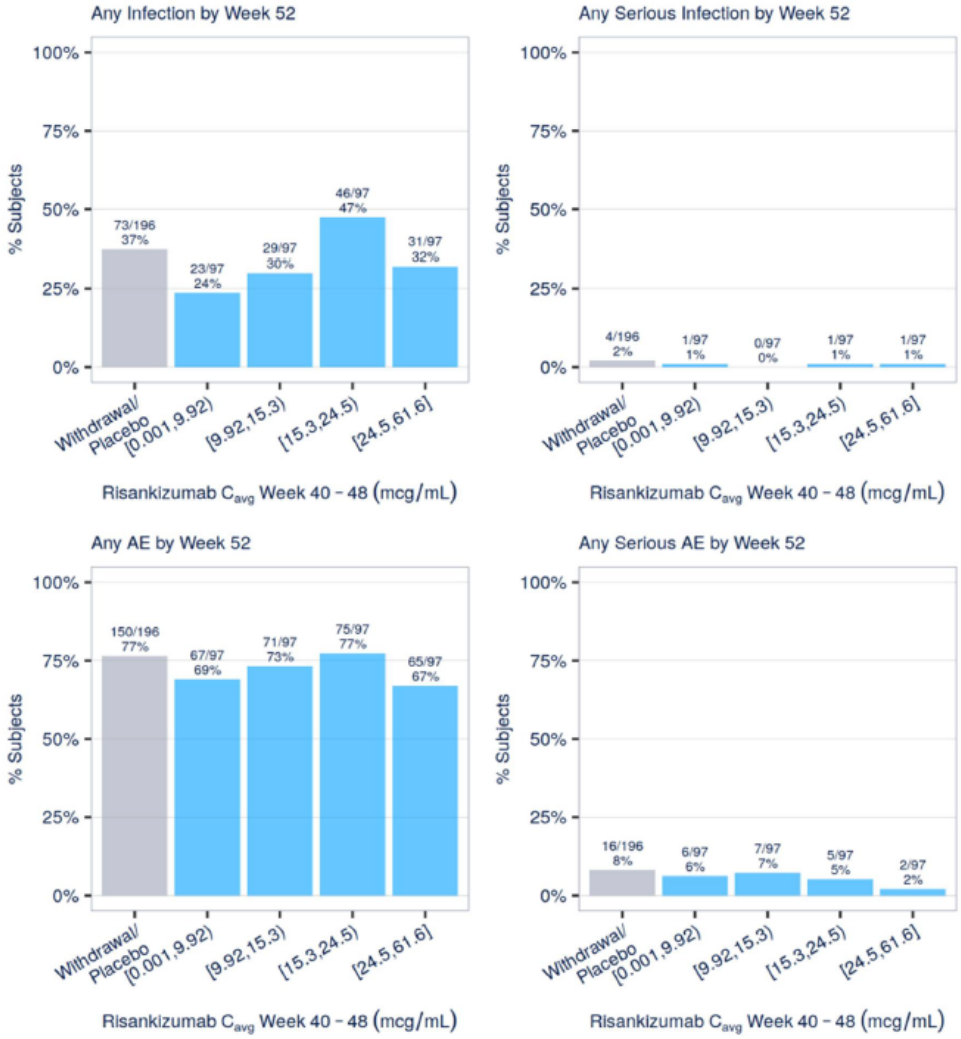
Figure 20 Exposure-response relationships between Risankizumab $C_{avg.Week0-12}$ and safety events of interest over the first 12 weeks



Exposure-response analyses for safety in the maintenance period

The relationship between model-predicted risankizumab Cavg,Week40-48 and percentage of subjects who experienced any AE, SAE, infection and serious infection over 52 weeks of maintenance treatment are presented in Figure 21. As shown in Figure 21, no exposure-dependent worsening in safety was seen over 52 weeks of the Maintenance Period. The response rates of AE, SAE, and serious infection in all risankizumab exposure quartiles were numerically lower compared to the withdrawal/placebo arm. For any infection, only the third exposure quartile showed 10% higher events than the placebo. Similar results were observed in the graphical analyses for the relationship between maximum concentration during the Maintenance Period (Cmax,Week0-52) and any AE, SAE, infection, and serious infection.

Figure 21 Exposure-response relationships between Risankizumab $C_{avg.Week40-48}$ and safety events of interest in maintenance period



2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalytical methods

Determination of Risankizumab Concentrations in Human Serum

A bridging Electrochemiluminescence (ECL) assay was developed and validated at AbbVie site in Germany to quantitatively determine risankizumab concentration in human serum samples from clinical studies. The method validation was previously assessed during the line extension for Skyrizi 150 mg formulation in healthy and Psoriasis patient's serum and deemed to have been suitably validated (EMEA/H/C/004759/X/012). This method was also partially validated for selectivity/matrix interference for CD patient's serums (EMEA/H/C/004759/X/020).

The selectivity for the matrix from UC patients is demonstrated in partial validation using serum samples each from 10 drug naïve healthy control and 10 drug naïve UC patient samples. The CHMP concluded that the method is selective for risankizumab analysis in serum of patients with UC.

Sample analysis for risankizumab concentrations in human serum for the pivotal Phase 2b/3 (M16-067) and phase 3 (M16-066) UC Studies was conducted at 2 sites. The method used at both sites is the same as that used in the authorised Crohn's indication procedure (EMEA/H/C/004759/X/020). Cross validation is demonstrated between the sites and is acceptable to the CHMP.

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

The assay used to determine ADA in the pivotal studies is a titre-based acid dissociation bridging ECL immunoassay. The ADA analytical method was first established at AbbVie site in Germany– this method is validated for UC and PsA patients. The method validation approach is based on the validation of the same method for the CD indication previously authorised in (EMEA/H/C/004759/X/020) and is acceptable to the CHMP. To enable sample analysis in a contract research organization (CRO), the ADA assay was transferred. Cross-validation experiments using spiked QC samples demonstrated full comparability between in-house validated serum ECL assay and assay validated at the CRO. Validation of the current method at the CRO with UC specific patient samples was provided and is acceptable to the CHMP.

Amendments to the method used for determination of anti-abbv-066 antibodies included partial assay validation to support the addition of indications (UC) and a change of critical reagents introducing new lots of anti-Id ABBV-066 control material, biotinylated ABBV-066 and Sulfo-labelled ABBV-066. The CHMP concluded that adequate drug tolerance, sensitivity and selectivity is demonstrated.

Determination of Risankizumab neutralising antibodies (NAb) in human serum

The assay to determine risankizumab neutralising antibodies (NAb) in human serum is the same as that used for the authorised Crohn's indication procedure (EMEA/H/C/004759/X/020). It is acceptable to the CHMP. The method was successfully transferred to a CRO . The cut point for UC patient samples was determined using standard methodology and is acceptable to the CHMP. Ten individual UC serum samples were tested in the validation and selectivity was demonstrated using unspiked samples and spiked samples at 130 ng/mL (LQC) 1250 ng/mL (HQC). All system suitability criteria were met. There was a deviation in the inter-run precision which was above the pre-determined criteria of < 25% (18.6 to 36.6). This result was reported as a deviation due to variation between analysts and was previously reviewed and accepted by the CHMP (EMEA/H/C/004759/X/020). The CHMP concluded that the assay is validated for the UC indication at both sites.

Study M16-067

There were no specific endpoints or analyses for the pharmacokinetic objective in this study, except to evaluate serum concentrations. The sampling time-points were selected to show the trough concentrations at Weeks 4, 8, and 12 in Induction Period 1, and trough concentration at Week 24 in Induction Period 2, in both sub study 1 and sub study 2. The overall study design for study M16-067 is acceptable to the CHMP for the pharmacokinetic objective.

In sub study 1, Induction Period 1, following the administration of risankizumab at Weeks 0, 4, and 8, generally dose-proportional trough concentrations were observed at Weeks 4, 8, and 12 between the three induction doses in the double-blinded groups: 600 mg IV, 1200 mg IV, and 1800 mg IV risankizumab. The open-label 1800 mg IV group showed higher geometric means for serum concentrations at all time-points than the double-blind 1800 mg IV risankizumab. Double-blind 1800 mg IV risankizumab compared with open-label 1800 mg risankizumab geometric mean serum concentrations at Week 4 (53.4 µg/mL vs 60.2 µg/mL), at Week 8 (70.7 µg/mL vs 93.7 µg/mL) and at Week 12 (88.7 µg/mL vs 109 µg/mL) were all lower. However, the CHMP considered that the ranges are acceptable.

In sub study 1, Induction Period 2, the geometric mean risankizumab concentrations were similarly all generally dose proportional at Week 24. The geometric mean serum concentration for the subjects originally in the double blinded risankizumab IV 1800 mg group that were re-inducted on 1800 mg risankizumab are substantially lower than subjects re-inducted to 1800 mg IV risankizumab from the other groups. However, the CHMP noted that the number of subjects in this group is small (n=4) and that the results should be interpreted cautiously.

In sub study 2 Induction Period 1, following the administration of 1200 mg IV risankizumab at Weeks 0, 4, and 8, the geometric mean trough plasma concentrations were higher than the trough concentrations seen for the same induction dose of 1200 mg IV risankizumab in sub study 1, Induction Period 1 (101 µg/mL vs 53.3 µg/mL respectively at Week 12), and in fact similar to the trough concentrations seen for the open-label risankizumab from sub study 1, Induction Period 1 (101 µg/mL vs 109 µg/mL respectively at Week 12). The 1200 mg IV risankizumab dose from sub study 2 Induction Phase 1 achieved similar trough concentrations to the 1800 mg IV risankizumab dose from sub study 1 Induction Phase 1. Upon the CHMP's request, the MAH investigated a number of factors to explain the observed data. The MAH concluded that the differences seen are the result of random variability across the substudies. From the summary of the investigation presented, there does not seem to be any notable difference between the two substudy populations or conduct of the studies that could explain the differences seen. The MAH's conclusion that this difference was caused by random variability is accepted by the CHMP.

In sub study 2, Induction Period 2 the geometric mean risankizumab concentrations were all generally dose proportional at Week 24.

Study M16-066

There were no specific endpoints or analyses for the pharmacokinetic objective in this study, except to evaluate serum concentrations. The sampling time-points were selected to show the baseline concentrations at Week 0 and trough concentrations at Weeks 16, 32, 48, and final concentration at Week 52, and are acceptable to the CHMP. The overall study design for study M16-066 is acceptable to the CHMP for the pharmacokinetic objective.

The trough concentrations measured at Weeks 16, 32, and 48 and the final concentration measured at Week 52 were generally dose proportional with the 360 mg SC risankizumab maintenance therapy showing approximately 2-fold the concentrations seen in the 180 mg SC risankizumab maintenance therapy group. Steady state appears to have been reached by Week 16 in the 360 mg SC risankizumab maintenance therapy group, with steady state being reached in the 180 mg SC risankizumab maintenance therapy group by Week 32. This would be expected given the long elimination half-life of risankizumab. The placebo group had measurable risankizumab concentrations up to Week 52, showing the prolonged drug washout due to the long elimination half-life of risankizumab.

The data provided also shows that after 16 weeks, risankizumab concentrations were similar in the groups receiving maintenance risankizumab regardless of the prior induction therapy. In the group receiving placebo there was dose-proportional concentration of risankizumab still detectable at Week 16 based on the prior induction dose.

Overall, prior induction dose did not have a large impact on the long-term pharmacokinetics after Week 16 in any of the maintenance therapy groups as steady state was reached by Week 32 in all maintenance therapy groups.

Immunogenicity

Study M16-067

The overall baseline prevalence and incidence of treatment emergent ADAs and NAbs was low across both sub study 1 and 2 in Study M16-067.

In Induction Period 1 of sub study 1 and sub study 2 of study M16-067 respectively, decreased risankizumab trough concentrations in ADA positive subjects were observed when compared to ADA negative subjects in the same treatment arms. Overall, there was no apparent impact of ADA or NAb incidence on risankizumab levels. However, the CHMP noted that the small number of subjects who presented with ADAs and NAbs during the study limits the interpretation of this data.

Study M16-066

The overall baseline prevalence and incidence of treatment emergent ADAs and Nabs was low in sub study 1 in Study M16-066. There was higher incidence of ADA and NAb in the subjects who received 24-week IV induction or the non-randomized subjects. However, the CHMP considered that this should be interpreted cautiously as the number of subjects in this group was low and the incidence of ADAs and NAbs was also low.

Similar to the Study M16-067, the risankizumab concentrations in Study M16-066 were overall lower in ADA positive subjects. However, the concentrations were still within range of the ADA negative subjects. Overall, there was no apparent impact of ADA or NAb incidence on risankizumab levels. However, the CHMP noted that the small number of subjects who presented with ADAs and NAbs during the study limits the interpretation of this data.

Population PK analyses

R&D/20/0608: Phase 2 population PK analyses of Risankizumab during induction treatment in ulcerative colitis

Risankizumab PK data from one Phase 1, and two Phase 2 studies in healthy subjects and subjects with moderate to severe inflammatory bowel diseases, both UC and CD, were included in this analysis. The objectives of this analysis were to describe population PK of risankizumab and to identify patient-specific factors that may explain PK variability of risankizumab in subjects with moderately to severely active UC. The methods used for model development and evaluation are acceptable to the CHMP. Data exclusions were detailed and acceptable to the CHMP.

The final model, a two-compartment model with first-order absorption for SC administration and first-order elimination, adequately described the risankizumab PK. The parameters of the final population PK model were estimated with adequate precision (all %RSE between approximately 2% to 31%). The IIV shrinkages for clearance and volume of central compartment were 9% and 48%, respectively. As such, the CHMP concluded that the exposure metric, Caverage, used in the subsequent ER analysis is reliable. Model evaluation using goodness-of-fit plots and visual predictive checks indicated that the model adequately described risankizumab PK. Overall, the model was acceptable to the CHMP.

These analyses indicated that risankizumab exhibits linear PK across the range of doses evaluated and up to 1800 mg IV Q4W, which was the highest dose evaluated in the induction period in Study M16-067 in UC subjects. Risankizumab PK parameter estimates were shown to be consistent with previously reported estimates for typical IgG1 monoclonal antibodies and parameter estimates in subjects with moderate to severe chronic plaque psoriasis and CD.

Baseline albumin and FCP were statistically correlated to risankizumab clearance. However, neither had a meaningful impact (risankizumab exposures were well within the default 80 to 125% equivalence boundaries over the range of covariate values observed in subjects with moderate to severe UC).

Body weight was correlated with risankizumab clearance and volume of distribution. Subjects with body weight >84 kg (upper weight quartile) were predicted to have on average 20% lower exposures

compared to the reference group. Subjects with body weight <62 kg (lower weight quartile) were predicted to have on average 30% higher exposures compared to the reference group. Based on these predictions and the fact that body weight was not found to be a significant covariate in the exposure-efficacy analyses, the MAH considered that the impact of body weight on risankizumab PK is not clinically relevant. This was not fully agreed by the CHMP but not pursued further for this analysis, since the purpose of the subsequent ER analysis was to select an induction dose for the Phase 3 study.

ADAs (anti-risankizumab antibodies) did not impact risankizumab clearance. The MAH acknowledged that the emergence of relatively high titers of ADAs observed in only 1.5% of the plaque psoriasis patients was previously identified as a significant covariate for risankizumab clearance. A probable explanation for this discrepancy between indications is that previous analyses included data collected over 52 weeks after starting treatment and for up to 104 weeks for one of the studies. In contrast, this analysis was based on data collected during the induction period only (i.e., 12 weeks), with only two subjects showing treatment emergent ADAs, and with relatively low titers. Further, a relatively large database is needed to have adequate statistical power to capture the effect observed in such a low proportion of subjects. The MAH's explanation was agreed by the CHMP. Further immunogenicity data will be collected (throughout the rest of the study for these subjects, and for other subjects to be recruited in Sub-Study 2 and other studies in UC). The analyses will be updated. Therefore, the issue was not further pursued.

R&D/23/0018: Population pharmacokinetics of risankizumab in subjects with moderately to severely active ulcerative colitis

PK data following induction and maintenance treatment with risankizumab in patients with UC from the Phase 2b/3 Study M16-067 and Phase 3 Study M16-066 were included in this analysis. The methods used for model development and evaluation are acceptable to the CHMP. Data exclusions were detailed and acceptable to the CHMP.

The final model was a two-compartment model with first-order absorption for SC administration and first-order elimination. The parameters of the final population PK model were estimated with adequate precision (all %RSE ≤33.1%). IIV shrinkage was relatively low for CL (17.5%) but relatively high for Vc (43.5%) and Ka (55.6%). As such, model predicted Cavg was selected as a primary exposure metric for the exposure-response analyses and Ctrough was visualized only for exploratory purposes. This is acceptable to the CHMP. Model evaluation using goodness-of-fit plots and visual predictive checks indicated that the model adequately described risankizumab PK. Risankizumab PK parameter estimates were consistent with previously reported estimates for typical IgG1 monoclonal antibodies, and parameter estimates in subjects with moderate to severe CD.

Among the various covariates evaluated, body weight was correlated with risankizumab clearance and volume of distribution. For the induction regimen (1200 mg Q4W) and the maintenance regimens (180/360 mg Q8W), subjects with body weight >82 kg (upper weight quartile) were predicted to have on average 19% and 18% lower AUC compared to the reference group. However, subjects with body weight at the upper limit of the 95% CI for the upper weight quartile were predicted to have 23.5% and 24% lower AUC compared to the reference group for the induction and maintenance regimens, respectively. However, these differences in exposure are within the expected PK variability of risankizumab in patients with UC. Additional analyses to assess the impact of lower exposures on efficacy in heavier subjects were also conducted. The results of these analyses support the use of the recommended induction and maintenance doses across the entire body weight range. Therefore, is the CHMP agreed that a dose adjustment for heavier subjects (>100 kg) is not warranted.

Lower baseline albumin levels (< 40 g/L) were predicted to be associated with lower Week 12 risankizumab trough levels that fell below the 80 – 125% boundary suggesting a potentially meaningful impact on exposure. However, this was not the case for AUC which is directly correlated to Cavg. While

the impact of baseline albumin was not considered significant for AUC/Cavg, the exposure-response relationships between Cavg and Week 12 efficacy endpoints (clinical response and endoscopic improvement) showed that subjects with lower baseline albumin (< 43 g/L) tended to respond less to risankizumab treatment (about 14.2-16.5% lower without placebo adjustment or 4.17 – 10.5% lower with placebo adjustment). The MAH considered that this may potentially be due to higher disease severity in subjects with low baseline albumin since low serum albumin has been reported to be a marker for severe disease and poor outcomes in patients with inflammatory bowel disease. This explanation seemed reasonable to the CHMP. It was agreed that a dose adjustment in patients with low albumin is not warranted.

Special Populations

Renal impairment, hepatic impairment, gender, and race have no clinically relevant effect on risankizumab exposure. Thus, the CHMP concluded that dose adjustments for these subpopulations are not warranted.

As expected, body weight was correlated with risankizumab clearance and volume of distribution. The MAH considers that the impact of body weight on risankizumab PK is not clinically relevant. This is agreed by the CHMP. Further details are included in the discussion of the population PK analyses above.

Interactions

Study M19-974

The overall design and methodology of the drug interaction study (M19-974) are acceptable to the CHMP. Standard non-compartmental models were used to derive the pharmacokinetic parameters for the probe drugs in this study, which is acceptable. The statistical methods described are acceptable to the CHMP.

A DDI study has previously been performed in the PSO disease state (Study M16-007). Study M19-974 was performed based on advice from the FDA as the dose in the CD and UC indication was higher and that compared to the PSO, CD and UC may have a higher inflammatory burden than PSO which could affect the DDI interactions. The patient population of patients with CD or UC for the study is acceptable to the CHMP.

Levels of the chosen probe substrates were investigated before dosing with Risankizumab and after dosing with Risankizumab. The dosing regimen of 1800mg Risankizumab Q4W for 12 weeks (3 doses) as an induction dose is in line the highest induction dose tested in Study M16-067 with and exceeds the induction dose for the expected dosing regimen for CD and UC patients. Hence, the probe substrates are expected to be investigated with therapeutic or supra-therapeutic levels of Risankizumab for CD and UC, which is acceptable to the CHMP for investigating drug interactions.

The cytochrome P450 enzymes and probe substrates selected for investigation are generally in line with the EMA Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr.).

The pharmacokinetic data shows that the point estimates and 90% CIs for the ratios of the probe substrates Cmax and AUCinf when administered after risankizumab 1800 mg IV Q4W versus when these substrates were administered prior to initiating risankizumab treatment were mostly within the no-effect boundaries of 0.8 – 1.25 for the midazolam (CYP3A), S-warfarin (CYP2C9), and metoprolol (CYP2D6). Caffeine (CYP1A2) showed a high upper bound for the 90% CI (0.84 – 1.53) for the AUCinf, however the point estimate (1.13) and the Cmax were contained within the bounds of 0.8 – 1.25. Hence, the CHMP concluded that Risankizumab 1800 mg IV Q4W had no clinically relevant impact on the activities of CYP3A, CYP1A2, CYP2C9, and CYP2D6.

The lower bound for the 90% CI (0.62 – 0.93) and the point estimate (0.76) for the ratios of omeprazole (CYP2C19) for AUCinf were below the no-effect boundary of 0.8 – 1.25. The MAH provided data and discussion to show that the exposures of its metabolite (5-OH-omeprazole) were still comparable and that there was a consistent metabolite to parent ratio. As the ratio of drug (omeprazole) to metabolite (5-OH-omeprazole) were comparable between treatment periods, this would indicate that the activity of CYP2C19 was not impacted by treatment with risankizumab.

The PK interaction study has shown that risankizumab is unlikely to have drug-drug interactions with substrates of CYP3A, 1A2, 2C9, 2C19, and 2D6 in the UC and CD patient population.

Pharmacodynamics

Primary pharmacology

R&D/23/0656

IL-23 promotes Th17 cells leading to the expression and release of their effector cytokines, including IL-22. The selection of IL-22 as a biomarker for inhibition of the IL-23 pathway, and thus risankizumab selective inhibition of IL-23 is acceptable to the CHMP, as collection of samples for biomarker assessments were voluntary in nature and dependent upon the subject's consent for collection.

In study M16-067, induction treatment with risankizumab showed a significant reduction in IL-22 compared to baseline, and in all risankizumab induction groups compared to placebo at Week 12. There was no statistically significant difference seen in the pharmacodynamic effect on the IL-23 pathway when comparing the different induction doses at Week 12. The pharmacodynamic effect of induction treatment with risankizumab 600 mg, 1200 mg, or 1800 mg IV does impact the IL-23 pathway and leads to reduction in IL-22 levels up to Week 12.

In study M16-066, there was a statistically significant reduction in IL-22 levels compared with baseline in the withdrawal placebo group, and the risankizumab 180 mg and 360 mg groups, with no significance seen in the true placebo group at Week 52. For the withdrawal placebo group, this indicates that the 12-week induction with risankizumab maintained a significant reduction in IL-22 levels compared to baseline up to Week 52. As there was no statistically significant difference between the withdrawal placebo group and the risankizumab 180 mg and 360 mg maintenance doses in the reduction of IL-22 at Week 52, the benefit of a maintenance dose compared to withdrawal placebo can be questioned regarding the pharmacodynamic impact. A longer study on a withdrawal placebo group after induction would be required to show when the pharmacodynamic benefit of maintenance risankizumab in the reduction of IL-22 is seen. However, in view of the efficacy data available supporting the maintenance dose, the issue was not pursued.

R&D/23/0657

IL-23 is an inflammatory cytokine with activity in UC and CD. CRP is a biomarker for inflammation and FCP is an inflammatory marker in organic bowel disease i.e., UC or CD. They are common inflammatory biomarkers used in the assessment of patients with UC and CD, and so are acceptable biomarkers to measure pharmacodynamic response to risankizumab in UC patients. All patients from both studies M16-067 and M16-066 were included in this analysis which is acceptable to the CHMP.

In study M16-067, 1200 mg and 1800 mg induction doses of risankizumab showed a significant reduction in CRP compared to baseline at Week 12. 600 mg, 1200 mg, and 1800 mg induction risankizumab showed a decrease in FCP levels compared to baseline at Week 12. Each dose also showed a statistically significant reduction in both CRP and FCP compared to placebo. These results show that risankizumab has anti-inflammatory action in UC patients.

In study M16-066, the true placebo, withdrawal placebo, 180 mg and 360 mg risankizumab showed a significant reduction in both CRP and FCP from baseline at Week 52. There was a statistically significant difference between true placebo and the 3 other treatment group: withdrawal placebo, 180 mg and 360 mg risankizumab maintenance treatment for CRP levels. For FCP levels there was a significant difference in true placebo compared with both 180 mg and 360 mg maintenance doses, but not between the true placebo and the withdrawal placebo. There was no significant difference between the withdrawal placebo group and the 180 mg and 360 mg maintenance dose groups in CRP levels.

The withdrawal placebo shows a statistically significant reduction in both inflammatory biomarker levels compared to baseline up to Week 52. This is in line with the results of the IL-22 biomarker analysis which showed a similar reduction in IL-22 at Week 52. Due to the long half-life of risankizumab measurable concentrations were shown at Week 52, and this low plasma concentration still shows pharmacodynamic action up to Week 52. Pharmacodynamic analysis of a longer study would be beneficial to demonstrate the need for a maintenance dose for a pharmacodynamic effect. However, the efficacy results in M16-066 do show a decrease in efficacy in the withdrawal placebo group in comparison to the 180 mg and 360 mg risankizumab treatment groups. The issue was therefore not further pursued.

Exposure-response analyses

R&D/20/0609: Phase 2 exposure-response analyses of risankizumab for efficacy and safety during induction treatment in ulcerative colitis.

Exposure-response analyses (R&D/20/0609) were conducted using data from the Phase 2b induction study in subjects with UC (Study M16-067 sub study 1) to identify the optimal induction dose for further study in the Phase 3 induction study M16-067 (Sub Study 2). Doses of 600 mg, 1200 mg, and 1800 mg IV risankizumab at Weeks 0, 4, and 8 were evaluated. Overall, the models predicted incremental efficacy with increasing doses from 600 to 1800 mg. The 1200 mg dose was selected for the Phase 3 study because of the overlapping exposure distributions between these two higher doses and only a modest difference in efficacy, especially for the endoscopy-driven endpoints. None of the evaluated covariates, including body weight, had any significant effect on the efficacy.

R&D/23/0018: Exposure-response analyses for risankizumab efficacy and safety in subjects with moderately to severely active ulcerative colitis

The methods used for these analyses are acceptable to the CHMP. The exposure-response relationships for efficacy and safety following induction and maintenance treatment with risankizumab in subjects with UC were adequately characterised using data from the Phase 2b/3 Study M16-067 and Phase 3 Study M16-066.

Exposure-response analyses for efficacy in the 12-Week induction period

Exposure-response analyses of risankizumab efficacy following a 12-week induction regimen of 1200 mg IV at Weeks 0, 4 and 8 showed statistically significant trends of exposure-dependent increase in efficacy, with higher response rates observed in the higher exposure quartiles across all evaluated endpoints at Week 12. These observed trends align with expectations based on the Phase 2 exposure-response results since the wide range of exposures in the Phase 3 study had a significant overlap with the range of exposures tested in the Phase 2 study analyses (which analysed data from subjects who received a 600 mg, 1200 mg or 1800 mg IV Q4W induction regimen for 12 weeks).

Evaluations on covariates for exposure-response analyses for efficacy during the Induction Period showed that the Asian race had a statistically significant impact on endoscopic improvement, histological mucosal endoscopic improvement, and endoscopic remission at Week 12 for both placebo and risankizumab treated subjects. However, for the recommended 1200 mg IV Q4W induction

regimen, Asian subjects are predicted to have only marginally lower efficacy rates as compared to the non-Asian subjects for endoscopic endpoints (2.00 – 4.67% lower or 0.83 – 1.50% lower with placebo correction), indicating lack of need for dose adjustment due to Asian race. Like baseline serum albumin, Asian race was not found to be a significant covariate for the exposure-response relationship during Maintenance Period. Additionally, advanced therapy inadequate response had a significant effect on all efficacy endpoints at Week 12 and the predicted response rates were higher in the advanced therapy naïve subjects as compared to advanced therapy inadequate response subjects irrespective of treatment (placebo or 1200 mg IV), but regardless of the advanced therapy status, all subjects showed better efficacy response following risankizumab treatment compared to placebo.

Exposure-response analyses for efficacy in the maintenance period

Exposure-response analyses following risankizumab maintenance treatment showed an exposure-dependent increase in efficacy across all evaluated endpoints at Week 52, with greater efficacy noted in the higher exposure quartiles associated with the 360 mg SC Q8W group. Efficacy appeared to reach a plateau for clinical remission, clinical response, and endoscopic remission, but for endoscopic improvement and histological-endoscopic mucosal improvement, efficacy rates were the highest in the uppermost quartiles without reaching an apparent plateau. The model-predicted percentage point improvement in efficacy ranged from 2.50 – 4.50 when increasing the dose from 180 mg to 360 mg across the evaluated efficacy endpoints, with largely overlapping 95% CIs between the two doses.

Of the tested stratification factors, advanced therapy inadequate response had a statistically significant impact on clinical remission per adapted Mayo score, clinical response per adapted Mayo score and endoscopic remission at Week 52, with subjects that had inadequate response to prior advanced therapies generally showing a lower probability of achieving a response than the subjects who were advanced therapy naïve, similar to the findings from the Induction Period. Similarly, clinical remission per adapted Mayo score at the end of Induction Period had a significant effect on the exposure-response relationship for certain efficacy endpoints, with responders to clinical remission during the Induction Period generally showing higher probability of achieving response in the Maintenance Period compared to non-responders. However, the differences in the model-predicted efficacy response rates between the 180 and 360 mg SC Q8W dose levels were modest and were generally consistent regardless of the stratifications.

Overall, the results of these analyses provide support for efficacy of the proposed risankizumab induction and maintenance regimens relative to placebo in patients with UC.

Exposure-response analyses for safety in the 12-Week induction and maintenance periods

Exposure-response analyses for safety revealed that the incidences of safety events in the Induction as well as the Maintenance Period were numerically lower in risankizumab treated subjects compared to placebo-treated subjects, with no apparent trends of exposure-dependent worsening observed.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology of risankizumab in patients with UC has been adequately characterised.

2.6.5. Clinical efficacy

To support this application, the MAH has included the clinical study reports for two studies, a 12-week induction study (M16-067) and a 52-week maintenance study (M16-066). Details of the probe study M19-974 can be found elsewhere in this report.

2.6.5.1. Dose response study(ies)

Study M16-067 was a Phase 2b/3, multicentre, randomized, double-blind, placebo- controlled study designed to evaluate the efficacy and safety of risankizumab as induction therapy in adult subjects with moderately to severely active UC.

Study M16-067 was an operationally seamless design comprising of 2 substudies: a Phase 2b dose-ranging induction Substudy 1 and a Phase 3 induction Substudy 2. The purpose of this design was to transition from the Phase 2b induction study to the Phase 3 induction study without an enrolment pause.

The objective of Sub-study 1 was to characterize the efficacy, safety, and pharmacokinetics of risankizumab as induction treatment in subjects with moderately to severely active UC and to identify the appropriate induction dose of risankizumab for further evaluation in Sub-study 2 (Phase 3 induction). Three doses of risankizumab (600mg, 1200mg, and 1800mg) were assessed versus placebo.

Study design

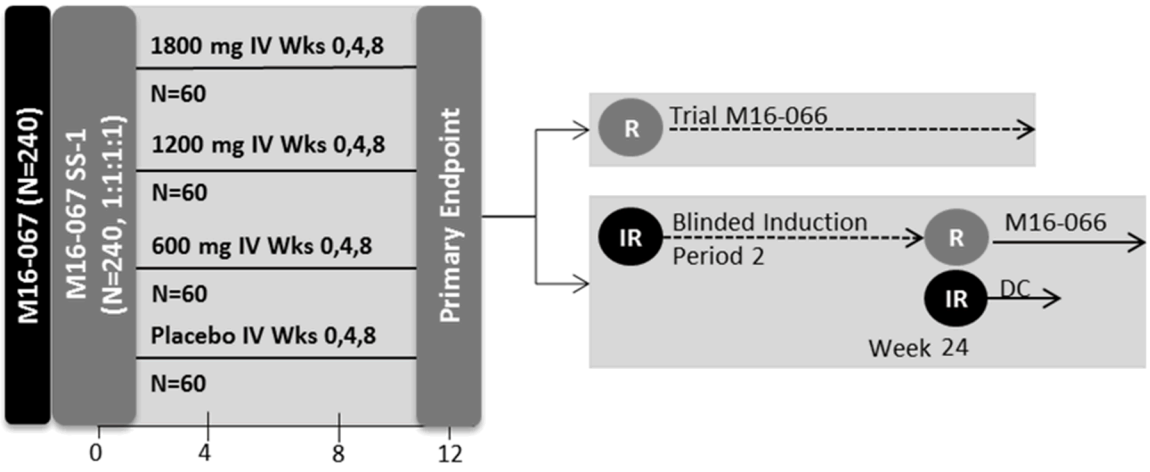
Subjects (n = 240) who met eligibility criteria were planned to be randomised in a 1:1:1:1 ratio to one of the following double-blinded induction treatment groups:

- Group 1: Risankizumab 1800 mg IV Weeks 0, 4, 8 (n = 60)
- Group 2: Risankizumab 1200 mg IV Weeks, 0, 4, 8 (n = 60)
- Group 3: Risankizumab 600 mg IV Weeks 0, 4, 8 (n = 60)
- Group 4: Placebo IV Weeks 0, 4, 8 (n = 60)

After all subjects completed the 12-week Induction Period 1, dose response and exposure response analyses for the key efficacy and safety variables were performed. During this analysis, subjects could continue to enrol in the highest dosing arm (risankizumab 1800 mg IV Weeks 0, 4, 8) on an open-label basis.

Subjects in Sub study 1 who achieved clinical response after completion of the 12-week Induction Period 1 were eligible to be enrolled into maintenance Study M16-066. Clinical response was defined as a decrease from Baseline in the Adapted Mayo score ≥ 2 points and ≥ 30% from Baseline, PLUS a decrease in rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1.

Figure 22 Study M16-067 Sub study 1 Induction Period 1 Study Design (Phase 2b)



Sub study 1 Induction Period 2

At Week 12, subjects who did not achieve clinical response were randomised to Induction Period 2, a double-blind, double-dummy 12-week treatment period to evaluate the efficacy and safety of reinduction with risankizumab versus starting maintenance dosing.

Subjects who received IV risankizumab induction during Induction Period 1were randomized 1:1:1 to:

- Group 1: Risankizumab 1800 mg IV Weeks 12, 16, 20
- Group 2: Risankizumab 360 mg SC Weeks 12, 20
- Group 3: Risankizumab 180 mg SC Weeks 12, 20

Sample Size and randomization

Sub-Study 1 Induction Period 1

For Sub-Study 1 (Phase 2b portion of the study), a total of 240 subjects were equally randomized with 1:1:1:1 ratio to three risankizumab treatment groups (600 mg, 1200 mg and 1800 mg IV Q4W) and the placebo group. Assuming clinical remission rate of 7% in the placebo arm and maximum of 25% in at least one of the risankizumab treatment groups at Week 12, a sample size of 60 subjects per treatment group was considered sufficient to test for the presence of a dose response signal with an average power of approximately 87% at 5% level of significance (one-sided), via modelling using Multiple comparison procedure and modelling (MCP-Mod) approach.

Treatments

For Sub study 1 Induction Period 1, each dose of blinded study drug (risankizumab 600 mg, risankizumab 1200 mg, risankizumab 1800 mg, or placebo) was administered intravenously to subjects over 3 hours during the Baseline, Week 4, and Week 8 visits.

For Sub study 1 Induction Period 2, each dose of blinded study drug (risankizumab 1800 mg IV, or risankizumab 180 mg SC, or risankizumab 360 mg SC) was administered either intravenously at Weeks 12, 16 and 20 or subcutaneously at Weeks 12 and 20.

Blinding

Blinding was achieved using matched placebos.

Efficacy and Immunogenicity endpoints

The following efficacy evaluations were collected or calculated during the study: Mayo score (Adapted, Partial), SFS, RBS, PGA, Geboes score, endoscopy subscore, bowel urgency, abdominal pain, hsCRP, IBDQ, UCEIS, UC-SQ, FACIT-Fatigue, SF-36, EQ-5D-5L, WPAI, PGIC, PGIS, UC-related hospitalizations, faecal incontinence, tenesmus, nocturnal bowel movement, and sleep disturbance.

Blood samples for serum risankizumab concentrations, ADA and NAb assessments were also collected.

Study Subjects

During Sub study 1, a total of 581 subjects (240 subjects in the randomized dose-ranging cohort and 341 subjects in the open-label cohort) were enrolled at 195 sites across 34 countries.

Demographic and Baseline medical characteristics were generally balanced between the randomised arms.

Efficacy results

Primary outcome analysis

In pairwise comparisons, subjects who received risankizumab (600 mg IV, 1200 mg IV, 1800 mg IV) achieved higher rates of clinical remission per Adapted Mayo Score at Week 12 compared to subjects who received placebo, with all risankizumab arms achieving nominal P values < 0.05.

Efficacy results for the primary endpoint of clinical remission per Adapted Mayo Score at Week 12 across most subgroups were generally consistent with those of the overall population.

In subjects who received open-label risankizumab 1800 mg IV, efficacy results for the primary endpoint of clinical remission per Adapted Mayo Score at Week 12 across most subgroups were also consistent with the overall results.

Table 15 Proportion of subjects with clinical remission per Adapted Mayo Score at Week 12 (NRI) (Substudy 1 – ITT1A population)

		Risankizumab		
	Placebo IV n (%)	600 mg IV n (%)	1200 mg IV n (%)	1800 mg IV n (%)
Clinical Remission per Adapted Mayo Score at Week 12	(N=60)	(N=61)	(N=61)	(N=58)
Yes	1 (1.7)	7 (11.5)	6 (9.8)	6 (10.3)
No	59 (98.3)	54 (88.5)	55 (90.2)	52 (89.7)
Risk Difference[A]		9.8	8.2	8.7
Adjusted Risk Difference[A,B]		9.6	8.4	8.7
P-Value[B]		0.0324*	0.0460*	0.0397*
90% Confidence Interval[B]		(2.2,17.0)	(1.5,15.3)	(1.7,15.6)

Note: ITT1A includes all randomized subjects who received at least one dose of study drug during Induction Period 1 from Sub-Study 1. Clinical remission per adapted Mayo score was defined as stool frequency subscore (SFS) <= 1, and not greater than baseline, rectal bleeding subscore (RBS) of 0, and endoscopic subscore <= 1.
[A]: Risk difference = (Risankizumab - Placebo).
[B]: Based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline corticosteroid use (yes, no) and baseline adapted Mayo score (<= 7, > 7).
[C]: P-Value was calculated based on Chi-square test or Fisher's exact test if >= 20% of the cells have expected cell count < 5.
[D]: 90% confidence intervals for risk difference were calculated based on normal approximation using PROC FREQ.
+ P-value <= 0.1; * P-value <= 0.05; ** P-value <= 0.01; *** P-value <= 0.001.

2.6.5.2. Main studies

2.6.5.2.1. Study M16-067 Sub Study 2 – Induction Study

Study M16-067 sub study 2 was a phase 3 multicentre, randomized, double-blind, placebo-controlled Induction study to evaluate the efficacy and safety of risankizumab in subjects with moderately to severely active UC.

- Objectives

The objective of the study was to evaluate the efficacy and safety of risankizumab compared to placebo in inducing clinical remission in subjects with moderately to severely active UC, defined as Adapted Mayo score of 5 – 9 points (using the Mayo scoring system, excluding Physician's Global Assessment) with an endoscopic subscore of 2 or 3 on screening endoscopy, confirmed by central review.

- Study Participants

Sub study 2 enrolled subjects who had intolerance or inadequate response to advanced therapy (Advanced Therapy-IR) and subjects who had an inadequate response or intolerance to conventional therapy (non-Advanced Therapy-IR).

Approximately 966 subjects were anticipated to randomize in the double-blind portion of Sub study 2.

Methods

Sub study 2 Induction Period 1:

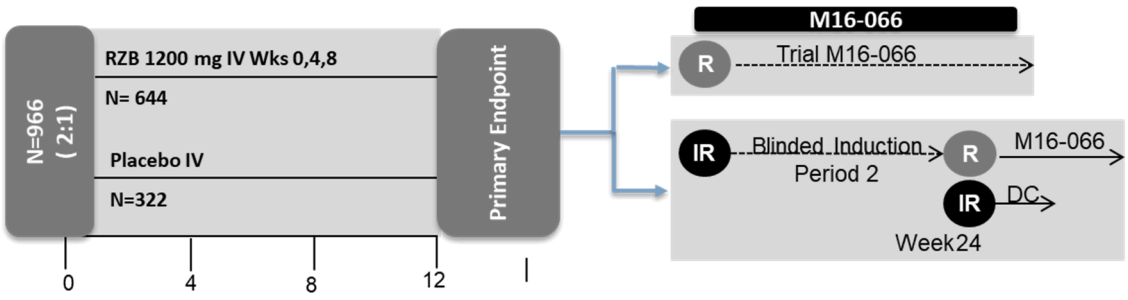
Eligible subjects were enrolled into the double-blind 12-week study and randomized in a 2:1 ratio to one of the following treatment groups:

- Group 1: Risankizumab 1200 mg Weeks 0, 4, 8.
- Group 2: Placebo IV Weeks 0, 4, 8.

The randomization at Baseline was stratified by number of prior failed biologics (0, 1 vs > 1), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7). Endoscopy evaluation occurred at Week 12. A post-hoc re-analysis stratified by prior failed biologics (0, 1 or 2, 3 or more) was also performed following comments by the CHMP.

Subjects in sub study 2 who achieved clinical response per Adapted Mayo score (locally read Mayo endoscopic subscore) after completion of the 12-week Induction Period 1 were eligible to be enrolled into maintenance Study M16-066.

Figure 23 Study M16-067 Sub study 2 Induction Period 1 Study Design (Phase 3)



Sub study 2 Induction Period 2

At Week 12, subjects who did not achieve clinical response were randomized by IRT to Induction Period 2, a double-blind, double-dummy 12-week treatment period to evaluate reinduction with risankizumab versus starting maintenance dosing.

Subjects who received IV risankizumab were randomized 1:1:1 to:

- Group 1: Risankizumab 1200 mg IV Weeks 12, 16, and 20.
- Group 2: Risankizumab 360 mg SC Weeks 12, and 20.
- Group 3: Risankizumab 180 mg SC Weeks 12, and 20.

Subjects who received placebo induction treatment were to receive:

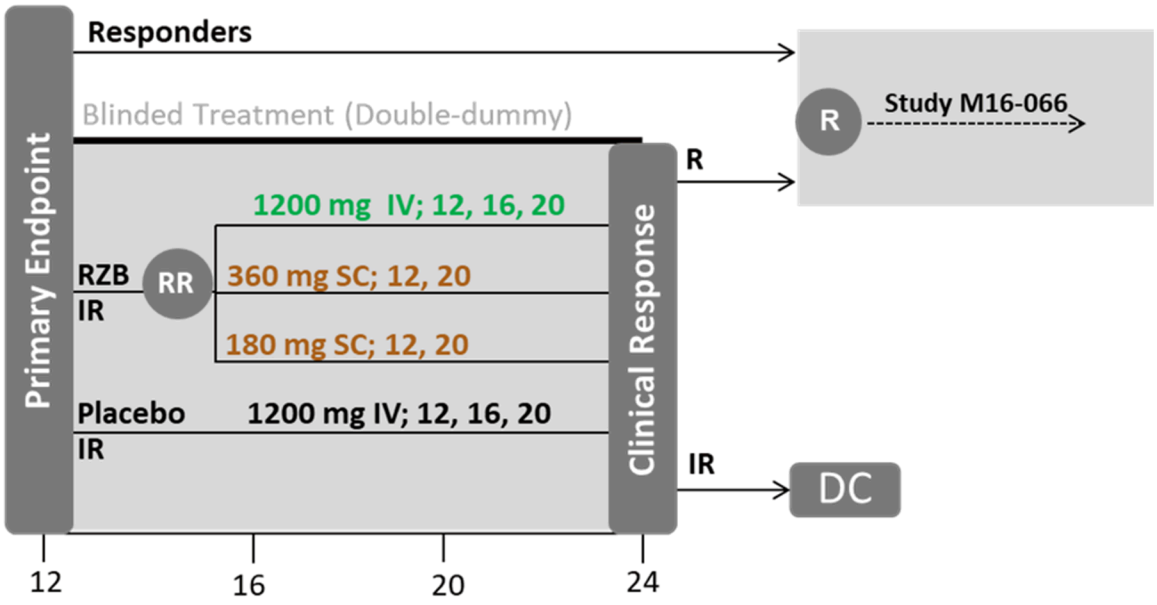
- Group 4: Risankizumab 1200 mg IV Weeks 12, 16, and 20.

- Treatments

Subjects randomized to Groups 1 and 4 received placebo SC and subjects randomized to Groups 2 and 3 received placebo IV to maintain the blind. The risankizumab IV dose or matching placebo IV was given at Weeks 12, 16, and 20. The SC risankizumab dose or matching SC placebo was given at Weeks 12, and 20. At Week 24, subjects who received blinded risankizumab (IV or SC) during the Induction Period 2 were reassessed and underwent a third endoscopy for evaluation of mucosal inflammation. Subjects who achieved clinical response per Adapted Mayo score (using locally read Mayo endoscopic subscore) at Week 24 were eligible to enter maintenance Study M16-066.

Subjects without clinical response at Week 24, as well as all subjects who terminated the study early (including subjects who were eligible for but did not receive blinded risankizumab therapy during Induction Period 2), were discontinued and had a follow-up call 140 days from the last dose of study drug to obtain information on any new or ongoing AEs.

Figure 24 Study M16-067 Sub study 2 Induction Period 2 Study Design (Phase 3)



- Outcomes/endpoints

Efficacy, Pharmacokinetic, and Immunogenicity Variables

The following efficacy evaluations were collected or calculated during the Sub study 1 and Sub study 2: Mayo score (Adapted, Partial), SFS, RBS, PGA, Geboes score, endoscopy subscore, bowel urgency, abdominal pain, hsCRP, IBDQ, UCEIS, UC-SQ, FACIT-Fatigue, SF-36, EQ-5D-5L, WPAI, PGIC, PGIS, UC-related hospitalizations, faecal incontinence, tenesmus, nocturnal bowel movement, and sleep disturbance.

Blood samples for serum risankizumab concentrations, ADA and NAb assessments were taken during Sub study 2.

Immunogenicity

Immunogenicity of risankizumab was assessed using a 3-tiered approach. In this tiered approach, all ADA samples were first analysed 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) in which titers were determined for the confirmed positive samples. The confirmed positive samples were also evaluated in the NAb assay to detect the presence of NAb.

For immunogenicity assessment, the evaluable subjects (subjects with at least 1 reportable immunogenicity assessment for at least 1 sampling time during the study after Week 0) were used to calculate the ADA (treatment-emergent) or NAb incidence.

Incidence of ADAs (treatment-emergent) to risankizumab was defined when a subject was (1) ADA–negative or missing assessment at Baseline and became ADA-positive at 1 or more time points post Week 0 visit in this study, or (2) ADA-positive at Baseline and showed a 4-fold or greater increase in titer values relative to Baseline.

Data Sets Analysed

The following population sets were used for the statistical analyses for Sub study 2.

Intent-to-Treat Population

Induction Period 1:

ITT2 included all randomized subjects who received at least one dose of study drug during Induction Period 1 in Sub study 2. ITT2 was used for all efficacy and demographic/baseline analyses for Induction Period 1. Subjects were included in the analysis according to the treatment groups to which they were randomized.

Induction Period 2:

ITT2_P2 included all subjects who received at least one dose of risankizumab during Induction Period 2 in Sub study 2. Subjects were included in the analysis according to the treatment groups that they were re-randomized to the Induction Period 2 and the subjects who received placebo induction treatment during the 12-Week Induction Period 1 and entered the Induction Period 2 were also included (denoted as placebo/risankizumab). This analysis population was used for efficacy analysis in Induction Period 2.

Safety Analysis Set

The safety analysis was based on the corresponding safety analysis sets. Subjects were analysed in a treatment group based on the treatment actually received.

sub study 2 – Induction Period 1:

SA2 consists of all subjects who received at least one dose of study drug during Induction Period 1 in Sub study 2.

Sub study 2 Induction Period 2:

SA2_P2 consists of all subjects who received at least one dose of risankizumab during the Induction Period 2 after Week 12 in Sub study 2.

All Risankizumab:

SA2_ALL includes all subjects who received at least one dose of risankizumab at any time during Sub study 2.

- Sample size

For Sub-Study 2, a total of 966 subjects were allocated to risankizumab 1200 mg IV dose or placebo in a randomization ratio of 2:1. The sample size was re-assessed after analysing the combined PK, safety and efficacy results from Sub-Study 1. It was determined to provide adequate powers for the primary endpoint and selected ranked secondary endpoints and adequate responders to meet the sample size requirement for Study M16-066. Assuming clinical remission rate of 6% in the placebo arm and 16% of the risankizumab treatment arm at Week 12, a sample size of 644:322 subjects per arm was anticipated to provide at least 90% power to detect the 10% treatment difference in the primary endpoint using two sided Miettinen and Nurminen test at a 0.05 significant level.

- Randomisation and Blinding (masking)

The study was carried out in a double-blind manner using matched placebo.

- Statistical methods

Sub-Study 2 Induction Period 1:

ITT2 included all randomized subjects who received at least one dose of study drug during Induction Period 1. The ITT2 was used for all efficacy analysis, and demographic and baseline characteristics summary for Induction Period 1. Subjects were included in the analysis according to the treatment groups to which they were randomized.

Sub-Study 2 Induction Period 2:
ITT2_P2 included all subjects who received at least one dose of risankizumab during Induction Period 2 from Sub-Study 2. Subjects were included in the analysis according to the treatment groups to which they were re-randomized in Induction Period 2, and the subjects who received placebo induction treatment during 12-Week Induction Period 1 and entered the Induction Period 2 were also included (denoted as placebo/risankizumab). This analysis population was used for efficacy analysis in Induction Period 2.

Estimand:

The applicant did not identify an estimand strategy as per ICH E9 (R1).

For the primary outcome, achievement of clinical remission per adapted Mayo score at week 12, the population of analyses was the ITT2, considered to approximate a treatment policy approach, with 3 types of intercurrent events (IE's) defined: premature discontinuation (IE1), initiation or dose escalation of UC-related steroids (IE2), occurrence of UC related surgery (IE3). All data after IE1 were to be used; all subjects were to be considered as non-responder on or after the date of IE2 or IE3. The primary endpoint was summarized as Proportion of subjects achieving clinical remission per Adapted Mayo score.

For secondary outcomes, the estimand approaches for secondary outcomes were stated again in the context of an ITT2 analysis population intended to be commensurate with a treatment policy approach.

Continuous secondary efficacy variables were to be analysed using a Mixed-Effect Model Repeated Measures (MMRM) method. Analysis of Covariance (ANCOVA) models using LOCF imputation method were also stated as sensitivity analyses. Specifically, CMH adjusting for stratification factors were to be used to construct the treatment difference, the associated 95% CI and p-value between risankizumab 1200 mg IV group and placebo group using an NRI-MI as the primary approach for missing data handling in the analyses of binary secondary efficacy endpoints except for occurrence of UC-related hospitalization, of which as observed (AO) data was be used.

Statistical Analysis Methods (sub study 2, induction period 1)

For the primary outcome of Achievement of clinical remission per Adapted Mayo score at Week 12, the ITT2 population was used and subject to an NRI-MI for missing data handling using the CMH test stratified by Advanced Therapies-IR status (yes vs no), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7). Point estimate, 95% CI and nominal p-value for the treatment effects were planned. Missing data were subject to various analyses with NRI using MI.

The primary approach for handling missing data in the analysis of binary endpoints except for occurrence of hospitalization and the occurrence of UC-related surgeries was to use Non-Responder Imputation while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19 or due to geo-political conflict in Ukraine or surrounding area (NRI-MI). The NRI-MI would categorize any subject who does not have an evaluation during a pre-specified visit window (either due to missing assessment or due to early withdrawal from the study) as a non-responder for the visit. The only exception was that missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic or due to geo-political conflict in Ukraine or surrounding area was to be handled by Multiple Imputation (MI).

At each visit, subjects were characterized as responders or non-responders based on MI imputed values if missing due to COVID-19 or due to geo-political conflict in Ukraine or surrounding area; otherwise, subjects were to be considered as non-responders for missing due to other reasons in the NRI-MI approach. In addition, on or after the date of the UC-related corticosteroids intercurrent event or the occurrence of the UC-related surgery, subjects would be counted as non-responders.

Multiple Imputation (MI) for NRI-MI was planned to be undertaken using Markov Chain Monte Carlo (MCMC) first to augment data into monotonic missing pattern, where applicable, and PROC MI (in the SAS program) was be used to generate 30 datasets using the regression method. The variables to be included in the imputation model were treatment group, Advanced Therapies-IR status (yes vs no), baseline corticosteroid use (yes vs. no), baseline Adapted Mayo score (≤ 7 vs. > 7)), baseline measurement, and if applicable, postbaseline measurements at each visit up to the end of the analysis period.

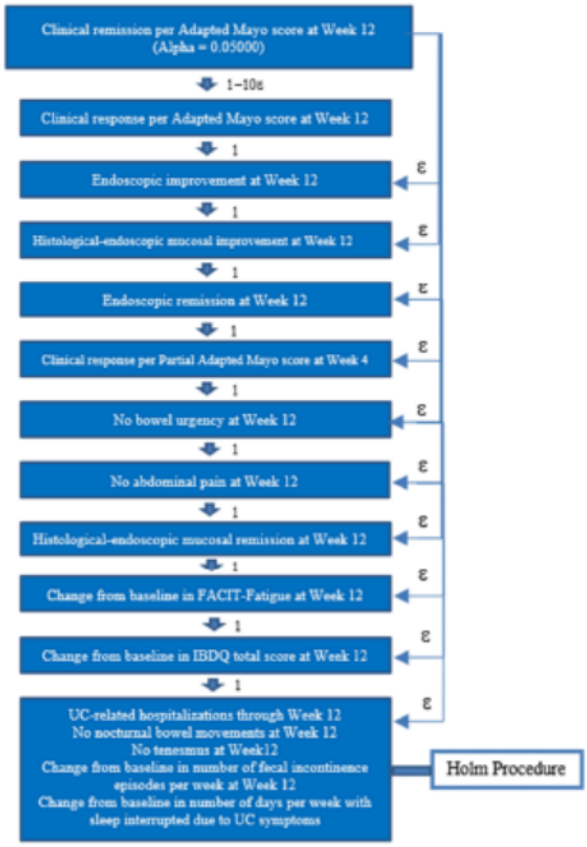
The MI procedure was to assume that the data are missing at random (MAR). That is, for an outcome variable Y, the probability that an observation is missing depends only on the observed values of other variables, not on the unobserved values of the outcome variable Y. Statistical inference from the MI procedure is considered to be valid under the MAR assumption.

Type I error Control

The overall type I error rate of the primary and secondary endpoints was to be strongly controlled using a graphical multiple-testing procedure as described below. The primary endpoint was to be tested at the pre-specified significance level of 0.05 (2-sided). The secondary efficacy endpoints were to be divided into two groups. The first group included the first ten secondary endpoints. The second group included all the remaining five secondary endpoints which were to be tested using the Holm procedure.

If the primary endpoint achieved statistical significance, continued testing would follow a pre-specified weight of αallocation specified in Figure 25 in the SAP (shown below). In the graph, the arrows specify the weight of α allocation between nodes. Once a hypothesis is rejected (i.e., deemed the endpoint is significant) at its assigned significance level, its significance level was to be allocated to the subsequent node. If more than one arrow originates from a node, the significance level was to be split between multiple subsequent nodes following the pre-specified weight. The numbers on the arrows denote the weights. For example, the weight 1 denotes 100% transfer of significance level to the next node, and the weight ε denotes 0.02% of the overall significance level (corresponding to α of 0.02%*0.05=of 0.00001) to be transferred. Overall Type I control would not be applied to additional efficacy endpoints.

Figure 25 Graphical multiple testing procedure for primary and secondary efficacy endpoints



Results

- Participant flow

During Sub study 2, a total of 977 subjects were randomized across 261 sites in 41 countries.

Subject disposition is provided in the table below.

Table 16 Subject disposition (Substudy 2)

	SS2 Induction Period 1			SS2 Induction Period 2				
Status	PBO IV	RZB 1200 mg IV	Total	RZB 180 mg SC	RZB 360 mg SC	RZB 1200 mg IV	PBO IV/ RZB 1200 mg IV	Total
All enrolled subjects - N	325	652	977	71	71	68	174	384
Treated - N	325	650	975	71	70	68	173	382
Completed study drug - N	298	637	935	67	65	61	164	357
Discontinued study drug - N	27	13	40	4	5	7	9	25
Safety Analysis Set - N	324	651	975	71	69	68	173	381
Intent-to-Treat Population - N	325	650	975	71	70	68	173	382
Primary reason for study drug discontinuation - n (%)	27 (8.3)	13 (2.0)	40 (4.1)	4 (5.6)	5 (7.1)	7 (10.3)	9 (5.2)	25 (6.5)
Adverse event - n (%)	12 (3.7)	2 (0.3)	14 (1.4)	0	0	1 (1.5)	3 (1.7)	4 (1.0)
Withdrew consent - n (%)	6 (1.8)	4 (0.6)	10 (1.0)	3 (4.2)	0	2 (2.9)	0	5 (1.3)
Lack of efficacy - n (%)	5 (1.5)	1 (0.2)	6 (0.6)	0	5 (7.1)	3 (4.4)	5 (2.9)	13 (3.4)
COVID-19 infection - n (%)	0	1 (0.2)	1 (0.1)	0	0	0	0	0
COVID-19 logistical restrictions - n (%)	0	1 (0.2)	1 (0.1)	0	0	0	0	0
Other - n (%)	4 (1.2)	4 (0.6)	8 (0.8)	1 (1.4)	0	1 (1.5)	1 (0.6)	3 (0.8)

Table 17 Baseline Characteristics (Substudy 2, ITT2 Population)

Status	PBO IV (N = 325)	RZB 1200 mg IV (N = 650)	Total N = 975
Ulcerative colitis (UC) disease duration – n (%)			
≤ 3 years	84 (25.8)	172 (26.5)	256 (26.3)
> 3 years	241 (74.2)	478 (73.5)	719 (73.7)
Disease extent- n (%)			
Left sided UC	150 (46.2)	313 (48.2)	463 (47.5)
Extensive UC/pancolitis	174 (53.5)	334 (51.4)	508 (52.1)
Limited to rectum	1 (0.3)	3 (0.5)	4 (0.4)
Number of prior failed advanced therapies – n (%)			
0	155 (47.7)	317 (48.8)	472 (48.4)
1	80 (24.6)	153 (23.5)	233 (23.9)
2	55 (16.9)	112 (17.2)	167 (17.1)
> 2	35 (10.8)	68 (10.5)	103 (10.6)
Advanced Therapy – IR Status – n (%)			
Yes	170 (52.3)	333 (51.2)	503 (51.6)
No	155 (47.7)	317 (48.8)	472 (48.4)
Baseline corticosteroid use - Yes, n (%)	112 (34.5)	236 (36.3)	348 (35.7)
Baseline immunosuppressant use - Yes, n (%)	53 (16.3)	108 (16.6)	161 (16.5)
Baseline aminosalicylates use - Yes, n (%)	238 (73.2)	475 (73.1)	713 (73.1)

Status	PBO IV (N = 325)	RZB 1200 mg IV (N = 650)	Total N = 975
Adapted Mayo Score - n	325	649	974
Mean (SD)	7.052 (1.2800)	7.068 (1.2173)	7.063 (1.2380)
Median	7.000	7.000	7.000
Partial Adapted Mayo Score - n	325	649	974
Mean (SD)	4.342 (1.1818)	4.389 (1.1510)	4.373 (1.1610)
Median	4.000	4.330	4.000
hsCRP (mg/L) - n	318	638	956
Mean (SD)	9.823 (16.8311)	8.601 (16.3303)	9.007 (16.4998)
Median	3.990	3.445	3.560
Fecal calprotectin (mg/kg) - n	302	602	904
Mean (SD)	3166.4 (4732.52)	3043.4 (4739.78)	3084.5 (4735.09)
Median	1624.0	1530.0	1543.0
Endoscopy subscore - n	325	650	975
Mean (SD)	2.7 (0.45)	2.7 (0.47)	2.7 (0.46)
Median	3.0	3.0	3.0
IBDQ score – total - n	320	640	960
Mean (SD)	125.5 (35.37)	123.0 (36.25)	123.8 (35.96)
Median	127.0	122.0	124.0
FACIT-Fatigue Total Score - n	320	637	957
Mean (SD)	29.0 (12.53)	28.1 (12.55)	28.4 (12.54)
Median	30.0	29.0	29.0

Notes: ITT2 includes all randomized subjects who received at least one dose of study drug during Induction Period 1 from Substudy 2.

The categorical variables regarding medication use are assumed to be UC-related.

Percentages were calculated on non-missing values.

Patient disease activity was moderate (mMS ≤7) in 58% of subjects and severe (mMS >7) in 42% of subjects.

Conduct of the study

Protocol deviations were defined in accordance with the ICH guidelines and included, but were not limited to, the following during Sub study 2, Period 1: subject entered into the study even though they did not satisfy entry criteria (4.0% of total subjects), subject received the wrong treatment or incorrect dose of study drug (0.7% of total subjects), and subject received excluded concomitant treatment (4.4% of total subjects). Deviations were assessed for their impact on analyses and data integrity or subject safety. None of the deviations were considered to have affected the study outcome, interpretation of the study results, or conclusions.

- Outcomes and estimation

Primary Efficacy analysis

At Week 12, a statistically significantly greater (P value < 0.00001) proportion of subjects in the risankizumab 1200 mg IV arm achieved the primary endpoint of clinical remission per Adapted Mayo Score compared to the placebo arm.

Table 18 Proportion of subjects achieving clinical remission per Adapted Mayo Score at Week 12 (Substudy 2, IIT2 Population, NRI-MI)

Treatment	N	Missing due to COVID/GP	Responder		Response Rate Difference Compared to Placebo		
			n (%)	[95% CI][a]	Adjusted Difference[b]	[95% CI] [b]	*P* value[c]
Placebo	325	1	20 (6.2)	[3.6, 8.9]	14.0	[10.0, 18.0]	<0.00001[S]
Risankizumab 1200 mg IV	650	1	132 (20.3)	[17.2, 23.4]			

a. 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure.

b. Adjusted risk difference and 95% CI for adjusted difference are calculated based on Mantel-Haenszel common rate difference.

c. Analysis based on Cochran-Mantel-Haenszel (CMH) test stratified by Advanced Therapy-IR status (yes vs no), Baseline steroid use (yes vs. no) and Baseline Adapted Mayo Score ($\leq 7, > 7$).

S: Achieved statistical significance at the 2-sided α level of 0.05 under overall Type I error rate control.

Notes: NRI-MI: Non-Responder Imputation while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19 or due to geo-political conflict in Ukraine or surrounding area

In general, similar trends were observed in the key subgroup populations of Advanced Therapy-IR and non-Advanced Therapy-IR as compared to the full ITT2 Population for the primary endpoint.

Subgroup analyses showed that, with the exception of subgroups relating to geographical area (US) and prior immunosuppressant use (yes), all other subgroup analyses showed superiority of treatment with Risankizumab over placebo.

Secondary efficacy analyses

The risankizumab 1200 mg IV arm demonstrated statistically significant improvements in all secondary endpoints compared to the placebo arm, according to the prespecified Type I error control plan.

Selected endpoints are reported as follows:

- Patients achieving both MH and symptomatic remission

A statistically significant difference was seen in the rates of mucosal improvement between treatment and placebo groups at week 12 (24.5% vs 7.7% respectively).

A statistically significant rate of mucosal remission was also seen between the treatment and placebo groups at week 12 (6.3% vs 0.6% respectively)

- Patients achieving response

A statistically significant rate of clinical response per adapted Mayo score was seen between the treatment and placebo groups at week 12 (64.3% vs 35.7% respectively).

A statistically significant rate of endoscopic improvement was seen between the treatment and placebo groups at week 12 (36.5% vs 12.1% respectively).

- Patients achieving endoscopic remission

A statistically significant rate of endoscopic remission was seen between the treatment and placebo groups at week 12 (10.6% vs 3.4% respectively).

- Changes in stool frequency

A statistically significant difference was seen between the treatment and placebo groups in the proportion of patients reporting no nocturnal bowel movements at week 12 (67.3% vs 43.1% respectively).

Time to response

A statistically significantly greater proportion of subjects treated with risankizumab achieved clinical response at Week 4 compared to placebo (52% vs 31%, respectively).

hsCRP and FCP assessments

During Sub study 2 Induction Period 1, subjects in the risankizumab 1200 mg IV arm had larger mean reductions from Baseline at Week 12 in both hsCRP and FCP compared to the placebo arm (nominal P values < 0.001 for both endpoints). Greater numeric decreases in hsCRP and FCP were observed for subjects in the risankizumab 1200 mg IV arm.

Sub study 2 Induction Period 2: Clinical Response and Clinical Remission at Week 24

Subjects who failed to achieve a clinical response at week 12 were able to participate in Induction period 2, where they were randomised to receive risankizumab 1200mg Q4W, risankizumab 180mg SC Q8W, or risankizumab 360mg Q8W in a blinded double dummy manner. Efficacy assessments were then again conducted at week 24 to determine the rate of clinical response as before.

The results from this second induction period suggested that while clinical response rates were similar across the three arms with risankizumab 1200mg Q4W, risankizumab 180mg SC W8W, or risankizumab 360mg Q8W showing clinical response rates of 50%, 56.3%, and 57.1% respectively. There were different rates between the treatment arms with respect to the achievement of clinical remission, with risankizumab 1200mg Q4W, risankizumab 180mg SC W8W, or risankizumab 360mg Q8W, achieving rates of 8.8%, 12.7% and 15.7% respectively.

The results suggest that there is no benefit in delaying the initiation of maintenance treatment in favour of reinduction with IV therapy in patients who had failed to achieve a sufficient clinical response at week 12, while also supporting the current recommendation to re-evaluate clinical response at week 24 and reconsider treatment should a clinical response not be evident at that stage.

Table 19 Clinical remission and clinical response per adapted Mayo score at Week 24 (Substudy 2, IIT2_P2 Population, NRI_MI)

Endpoint Treatment	N	Missing due to COVID/ GP	n (%)	[95% CI]
Clinical remission per Adapted Mayo Score at Week 24				
Risankizumab 180 mg SC	71	0	9 (12.7)	[4.9, 20.4]
Risankizumab 360 mg SC	70	0	11 (15.7)	[7.2, 24.2]
Risankizumab 1200 mg IV	68	0	6 (8.8)	[2.1, 15.6]
Clinical response per Adapted Mayo Score at Week 24				
Risankizumab 180 mg SC	71	0	40 (56.3)	[44.8, 67.9]
Risankizumab 360 mg SC	70	0	40 (57.1)	[45.5, 68.7]
Risankizumab 1200 mg IV	68	0	34 (50.0)	[38.1, 61.9]

Immunogenicity Results

At Baseline (prior to the first risankizumab dose), pre-existing ADAs and pre-existing NAbs were detected in 2.9% (18/630) and 1.0% (6/630) respectively of the subjects who received at least 1 dose of 1200 mg IV risankizumab during Induction Period 1 (Week 0-12).

Across the study durations of Week 0 to 12 and Week 0 to 24, the incidence of treatment- emergent ADAs in subjects who received risankizumab is summarized below:

- During Sub study 2 Induction Period 1, treatment-emergent ADA and NAb incidences were approximately 1.7% and 0.8%, respectively, in evaluable subjects who received the 1200 mg IV risankizumab induction regimen.

- During Weeks 0-24 including Sub study 2 Induction Period 1 and Induction Period 2, treatment-emergent ADA and NAb incidences were approximately 2.2% and 1.1%, respectively, in evaluable subjects who were inadequate responders at Week 12 and received risankizumab during the Induction Period 2.
- The time to the first appearance of treatment-emergent ADA ranged from 4.0 to 42.0 weeks following the first risankizumab treatment.
- The ADA titer values ranged from 10 to 228 across study visits among subjects who received risankizumab.

Further information on in the immunogenicity of the product can be found in the Clinical Pharmacology and Clinical Safety sections of this report.

2.6.5.2.2. Study M16-066 – A Multicentre, Randomized, Double-Blind, Placebo-Controlled 52-Week Maintenance and an Open-Label Extension Study of the Efficacy and Safety of Risankizumab in Subjects with Ulcerative Colitis

- Methods

Study M16-066 was a Phase 3, multicentre study that enrolled subjects who achieved clinical response at the last visit of induction Study M16-067. Clinical response was defined as a decrease in the Adapted Mayo Score ≥ 2 points and ≥ 30% from baseline, as well as a decrease in rectal bleeding sub score [RBS] ≥ 1 or an absolute RBS ≤ 1.

Study M16-066 consists of 3 sub studies: Sub study 1 was a 52-week randomized, double-blind, placebo-controlled maintenance study, which was the pivotal study evaluating the efficacy and safety of 2 maintenance doses of risankizumab. Sub study 2 is a 52-week randomized, exploratory maintenance study. Sub study 3 is an OL long-term extension for subjects who completed sub study 1 or 2, and subjects who responded to induction treatment in Study M16-067 with no final endoscopy due to the COVID-19 pandemic.

This assessment report focuses on the results from Sub study 1, as the other two sub studies are ongoing.

The MAH has committed to presenting the results of these additional sub studies once available.

Subjects from study M16-067 who achieved clinical response to IV risankizumab at the end of that study were to be re-randomized in a 1:1:1 ratio to one of the following 3 treatment groups:

- Group 1: Risankizumab 180 mg SC q8w (n = 191)
- Group 2: Risankizumab 360 mg SC q8w (n = 191)
- Group 3: Placebo (n = 191)

Subjects continued to enrol until a minimum of 573 subjects with clinical response to IV risankizumab were enrolled.

Subjects who demonstrated inadequate response based upon increased symptom activity and/or endoscopic confirmation of inflammation during Sub study 1 were eligible to receive risankizumab rescue therapy starting at the Week 16 Visit.

Only subjects who received IV therapy in the induction study (either period 1 or period 2) were randomised to the various treatment arms in Study M16-066. Subjects who received SC re-induction in Induction Period 2 in the preceding study were maintained on this dose and were not included in the analysis.

- Study Participants

Subjects who participated in Study M16-067 and achieved a clinical response following induction Periods 1 or 2 were eligible to be enrolled into this trial. The trial continued to enrol patients until a minimum of 573 subjects had been enrolled.

The study anticipated to enrol approximately 458 biologic/tofacitinib-IR subjects (~80%) who achieved clinical response to IV risankizumab. In order to maintain a balance between biologic/tofacitinib-IR subjects and non-biologic/tofacitinib-IR subjects in Sub study 1, once approximately 458 biologic/tofacitinib-IR subjects who achieved clinical response to IV risankizumab were enrolled, the remaining biologic/tofacitinib-IR subjects with clinical response at the end of induction entered sub study 2. The biologic/tofacitinib-IR population (hereafter referred to as the Advanced Therapy-IR population) was defined as subjects with documented intolerance or inadequate response to advanced therapy including one or more of the approved biologics for UC, approved JAK inhibitors for UC, and/or S1P receptor modulators.

The trial population was appropriate and in line with the relevant guidance and received scientific advice.

- Treatments

Blinded risankizumab (180 mg or 360 mg) or placebo was dispensed and administered SC onsite at Sub study 1 study visits. Subjects could have up to 2 rescue visits during Sub study 1 if qualified for rescue therapy per protocol.

Subjects who received risankizumab rescue therapy were administered risankizumab for one 1200 mg or 1800 mg IV dose, followed by risankizumab 360 mg SC dosing q8w through the end of the study.

- Objectives

The primary objective of this trial was to evaluate the efficacy and safety of risankizumab versus placebo as maintenance therapy in subjects with moderately to severely active UC who responded to IV risankizumab induction treatment in Study M16-067.

Secondary objectives included the assessment of safety and immunogenicity outcomes.

- Outcomes/endpoints

Efficacy evaluations/endpoints included clinical remission and response, endoscopic endpoints, histological-endoscopic endpoints, symptomatic endpoints, health- related QoL endpoints and UC-related hospitalizations, corticosteroid use, hs-CRP and FCP endpoints, and SFS and RBS.

Summary of serum risankizumab concentrations and ADA were also evaluated.

- Randomisation and blinding (masking)

Subjects entering Study M6-066 were randomised in a 1:1:1 double-blind manner to receive either risankizumab 180mg SC, risankizumab 360mg SC, or matched placebo.

- Statistical Methods

Sample size

For Sub-study 1, the sample size is based on the expected proportion of subjects who achieve clinical remission per Adapted Mayo score at Week 52. Assuming clinical remission rate of 22% in the placebo arm and 42% in one of the risankizumab treatment arms at Week 52, a sample size of 191 subjects in placebo and 191 subjects in each of the risankizumab groups will have more than 90% power to detect the 20% treatment difference in the primary endpoint between a risankizumab dose and placebo using

two sided Miettinen and Nurminen test at a 0.025 significance level, reflecting a multiplicity adjustment for both comparisons based on the overall 0.05 significance level.

Analysis populations

Intent-to-Treat Analysis Set – Sub study 1:

The Intent-to-Treat population for Sub study 1 (ITT1) includes subjects who received at least 1 dose of study drug in Sub study 1. Subjects are included in the analysis according to the treatment arms that they are randomized to, regardless of the treatment actually received.

- ITT1RN_A includes all randomized subjects who received at least 1 dose of study drug in Sub study 1 after receiving IV risankizumab (either 600 mg, 1200 mg, or 1800 mg) for only 1 period of 12 weeks in the induction Study M16-067. This is the primary analysis set for the Baseline summary and efficacy analysis in Sub study 1.
- ITT1RN_B includes the subset of subjects in ITT1RN_A who received risankizumab 1200 mg IV in the induction Study M16-067. This population is used for supplementary efficacy analysis.
- ITT1RN_C includes all randomized subjects who received at least 1 dose of study drug in Sub study 1 after receiving IV risankizumab for 2 periods (24 weeks) in the induction Study M16-067. This population is used for exploratory purposes.
- ITT1NRN includes all the non-randomized subjects who received at least 1 dose of study drug in M16-066 Sub study 1 after receiving SC risankizumab of 180 mg or 360 mg during Induction Period 2 in Study M16-067 or placebo during Induction Period 1 in Study M16-067. This population is used for exploratory purposes.

Estimands

The MAH adopted an estimand strategy commensurate with a treatment policy where IEs were for the main part handled through a NRI approach. For the primary outcome, achievement of clinical remission per adapted Mayo score at week 52, the population of analyses was the ITT2, considered to approximate a treatment policy approach, with 3 types of intercurrent events (IE's) defined: premature discontinuation (IE1), initiation or dose escalation of UC-related steroids (IE2), occurrence of UC related surgery (IE3). All data after IE1 were to be used; all subjects were to be considered as non-responder on or after the date of IE2 or IE3. The primary endpoint was summarized as Proportion of subjects achieving clinical remission per Adapted Mayo score.

Analysis Methods of Primary Endpoint

The primary analysis of the primary endpoint was conducted on the ITT1RN, a population using NRI-MI for missing data handling. Point estimate and 95% CI using normal approximation were to be provided for the response rate for each randomized treatment group. The difference between each of the risankizumab dose group vs placebo in the primary efficacy endpoint were assessed using CMH test stratified by induction Baseline Advanced Therapy-IR status, clinical remission status per Adapted Mayo score at Week 0 (per central read after adjudication, when applicable) and last IV risankizumab induction dose. Point estimates, two-sided 95% CI and nominal p-value for the treatment comparison were to be presented. In addition, several sensitivity analyses were conducted, including tipping point, taking into account the conflict in Ukraine and COVID-19.

Secondary endpoints

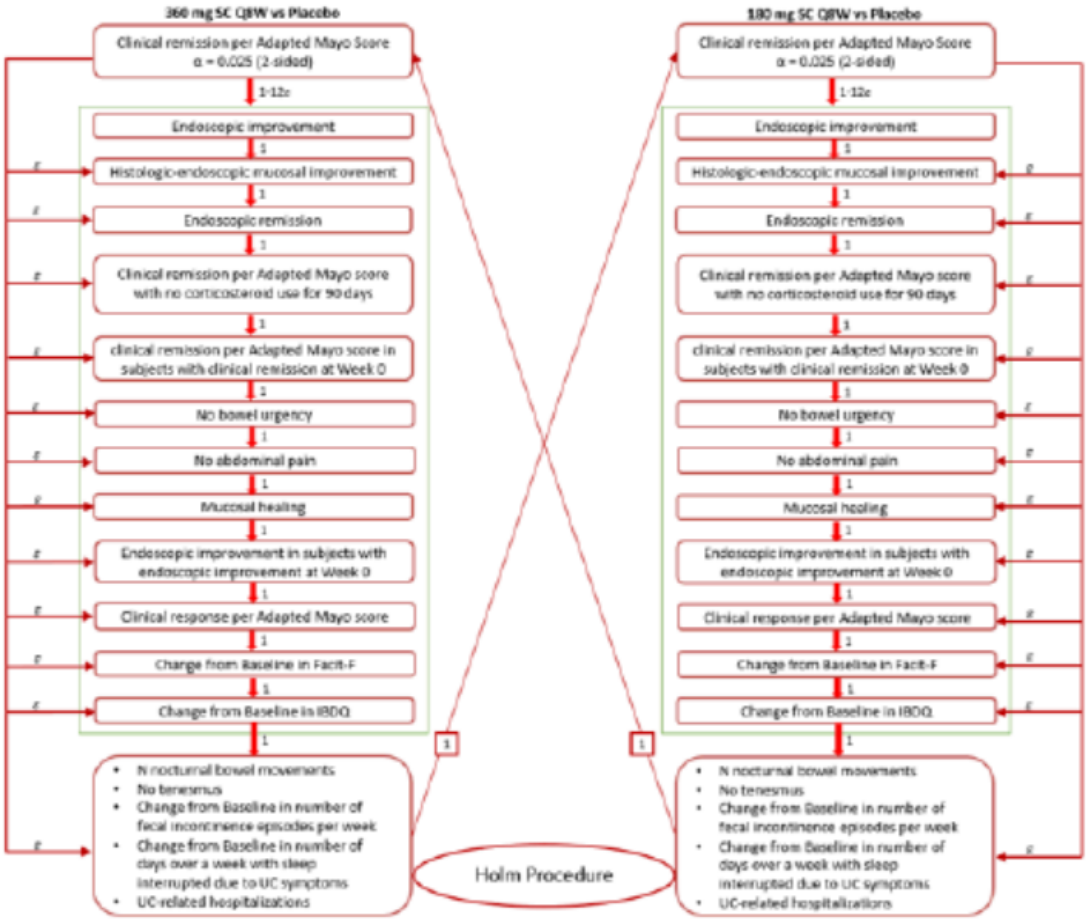
Statistical analyses of the secondary endpoints followed similar approaches to the secondary endpoints for main Phase 3 trial (sub study 1 induction period 2), where categorical secondary endpoints were to be analysed based on ITT1RN, specifically, CMH tests adjusting for stratification factors. Continuous

secondary endpoints were to be analysed based on ITT1RN using various methods, depending on the outcome such as MMRM, ANCOVA, normal approximations (in case of Poisson distributed data) as well as imputation methods such as Multiple Imputation Incorporating Return-to-Baseline (RTB-MI).

Multiplicity

The MAH has proposed to analyse a very large number of secondary endpoints, with the first 17 secondary endpoints being controlled for multiplicity. A further 28 'Additional' endpoints were stated in the SAP. There was an amendment to the SAP that changed the nature of multiplicity adjustment from a Hochberg approach to a Holm approach for the first 17 of these endpoints. The approach to multiplicity is shown below. In the graph, the arrows specify weight of α allocation between nodes. Once a hypothesis is rejected (i.e., deemed the endpoint is significant) at its assigned significance level, its significance level was to be allocated to the subsequent node. If more than one arrow originates from a node, the significance level was to be split between multiple subsequent nodes following the pre-specified weight. The numbers on the arrows denote the weights. For example, the weight 1 denotes 100% transfer of significance level to the next node, and the weight ε denotes 0.04% of the overall significance level each dose starts with (corresponding to α of 0.04%*0.025=0.00001) to be transferred. No Type I error control was applied to the additional efficacy endpoints. The analysis for additional efficacy endpoints were to be performed at the nominal α level of 0.05 (two-sided) for each dose.

Figure 26 Graphical multiple testing procedure for primary and secondary efficacy endpoints



Results

Participant flow

The disposition and flow of patients in Study M16-066 can be seen in the table below.

Table 20 Subject disposition and primary reasons for study drug discontinuation (Substudy 1 – ITT1RN_A Population)

		RZB			
	PBO SC (N=183) n (%)	180 mg SC (N=179) n (%)	360 mg SC (N=186) n (%)	Total (N=365) n (%)	Total (N=548) n (%)
Completed study drug	165 (90.2)	167 (93.3)	165 (88.7)	332 (91.0)	497 (90.7)
Discontinuation due to					
Any reason	18 (9.8)	12 (6.7)	21 (11.3)	33 (9.0)	51 (9.3)
Adverse event	1 (0.5)	3 (1.7)	2 (1.1)	5 (1.4)	6 (1.1)
Lack of efficacy	5 (2.7)	5 (2.8)	8 (4.3)	13 (3.6)	18 (3.3)
Lost to follow-up	1 (0.5)	0	1 (0.5)	1 (0.3)	2 (0.4)
Withdrawal by subject	5 (2.7)	3 (1.7)	7 (3.8)	10 (2.7)	15 (2.7)
Covid-19 infection	0	0	0	0	0
Covid-19 logistical restrictions	0	0	0	0	0
Logistical problem (geo-political restrictions)	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Other	6 (3.3)	1 (0.6)	2 (1.1)	3 (0.8)	9 (1.6)
Subjects receiving rescue medication	78 (42.6)	34 (19.0)	49 (26.3)	83 (22.7)	161 (29.4)

Note: ITT1RN_A Population includes all randomized subjects who received at least 1 dose of study drug in Substudy 1 after receiving IV risankizumab (either 600 mg, 1200 mg or 1800 mg) for only 1 period of 12 weeks in the induction Study M16-067. Percentages calculated on N in the header.

- Recruitment

754 subjects were enrolled across 238 sites in 36 countries, 16 of which were within the EU. The FSFV date was August 28th, 2018, and the data cut-off date for subject analysis in sub study 1 was March 30th, 2023.

The recruitment to the study was appropriate and the representation of EU subjects acceptable.

- Conduct of the study

Five protocol amendments were submitted and approved during the course of the study, although only three occurred after patients had been recruited to the trial.

The protocol amendments were not deemed by the sponsor to have adversely affected the integrity of the trial or the interpretability of the trial results.

- Baseline data

While most disease characteristics were generally well balanced across the arms, imbalances in some key factors were noted. In the risankizumab 360 mg SC arm, the mean disease duration was longer (9.271 years), the proportion of subjects failing > 2 advanced prior treatments was higher (25.3%), and the proportion of subjects with clinical remission at Week 0 (entrance of the maintenance study) was lower (21.6%), when compared to the risankizumab 180 mg SC arm and the placebo arm.

The MAH has clarified that the differences seen in this regard contributed to the apparent differences seen in the efficacy results, but also stated that any apparent differences is in line with what would be anticipated in patients with more severe or prolonged illness. This can be accepted.

- Outcomes and estimation

Primary efficacy outcome

For the primary endpoint, both the risankizumab 180 mg and 360 mg SC arms demonstrated a statistically significantly higher rate of clinical remission per Adapted Mayo score at Week 52 compared to the placebo arm (ITT1RN_A) (P-values < 0.01 for each dose.

Table 21 Clinical remission per Adapted Mayo Score at Week 52 (Substudy 1, ITT1RN_A Population, NRI-MI)

Treatment	N	Responder (NRI-MI) n (%)	[95% CI][a]	Missing due to Logistic Restrictions n	Response Rate Diff Compared to Placebo			
					Diff (%)[b]	Adjusted Diff (%)[c]	[95% CI][c]	P-value[c]
All								
Placebo SC	183	46 (25.1)	[18.9, 31.4]	0				
Risankizumab 180 mg SC	179	72 (40.2)	[33.0, 47.4]	1	15.0	16.3	[7.4, 25.3]	0.0004[S]
Risankizumab 360 mg SC	186	70 (37.6)	[30.7, 44.6]	1	12.5	14.2	[5.3, 23.2]	0.0019[S]

S = Achieved statistical significance at the 2-sided α level of 0.05 under overall Type I error rate control

a. 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure.

b. Risk difference = (risankizumab – placebo).

c. Adjusted risk difference and 95% CI for adjusted difference are calculated based on Mantel-Haenszel common rate difference. P-value is calculated according to the Cochran-Mantel-Haenszel (CMH) test adjusted for strata (induction Baseline Advanced Therapy-IR status [yes vs no], clinical remission status per Adapted Mayo score at Week 0 [per central read] [yes vs no] and last IV risankizumab induction dose [600 mg vs 1200 mg vs 1800 mg]).

Note: NRI-MI: non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19 or due to geo-political conflict in Ukraine or surrounding area.

The results of the primary analysis showed that patients receiving either the 180mg or the 360mg dose had a higher rate of maintenance of clinical remission (40.2% and 37.6% respectively) than that seen in patients receiving placebo (25.1%), and that these differences over placebo were statistically significant after adjusting for multiplicity at the 2.5% level.

Subgroup analyses

Response rates for the primary endpoint generally favoured both risankizumab treatment arms compared to placebo in the subgroup populations of Advanced Therapy-IR and Non-Advanced Therapy-IR. Response rates were generally lower in the Advanced Therapy-IR group for all 3 treatment arms than in the Non-Advanced Therapy-IR group as expected for those populations (ITT1RN_A).

Table 22 Clinical Remission per Adapted Mayo Score at Week 52 by Advance Therapy-IT Status (Substudy 1, ITT1RN_A Population, NRI-MI)

Subgroup Category Treatment	N	Responder (NRI-MI)		Missing Due to Logistic Restrictions	Response Rate Diff Compared to Placebo	
		n (%)	[95% CI][a]	n	Diff (%)[b]	[95% CI][c]
Advanced Therapy-IR						
Placebo SC	138	32 (23.2)	[16.1, 30.2]	0		
Risankizumab 180 mg SC	134	49 (36.6)	[28.4, 44.7]	0	13.4	[2.6, 24.2]
Risankizumab 360 mg SC	139	41 (29.5)	[21.9, 37.1]	0	6.3	[-4.0, 16.7]
Non-Advanced Therapy-IR						
Placebo SC	45	14 (31.1)	[17.6, 44.6]	0		
Risankizumab 180 mg SC	45	23 (50.9)	[36.2, 65.6]	1	19.8	[-0.2, 39.7]
Risankizumab 360 mg SC	47	29 (61.7)	[47.8, 75.6]	1	30.6	[11.2, 50.0]

a. 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure.

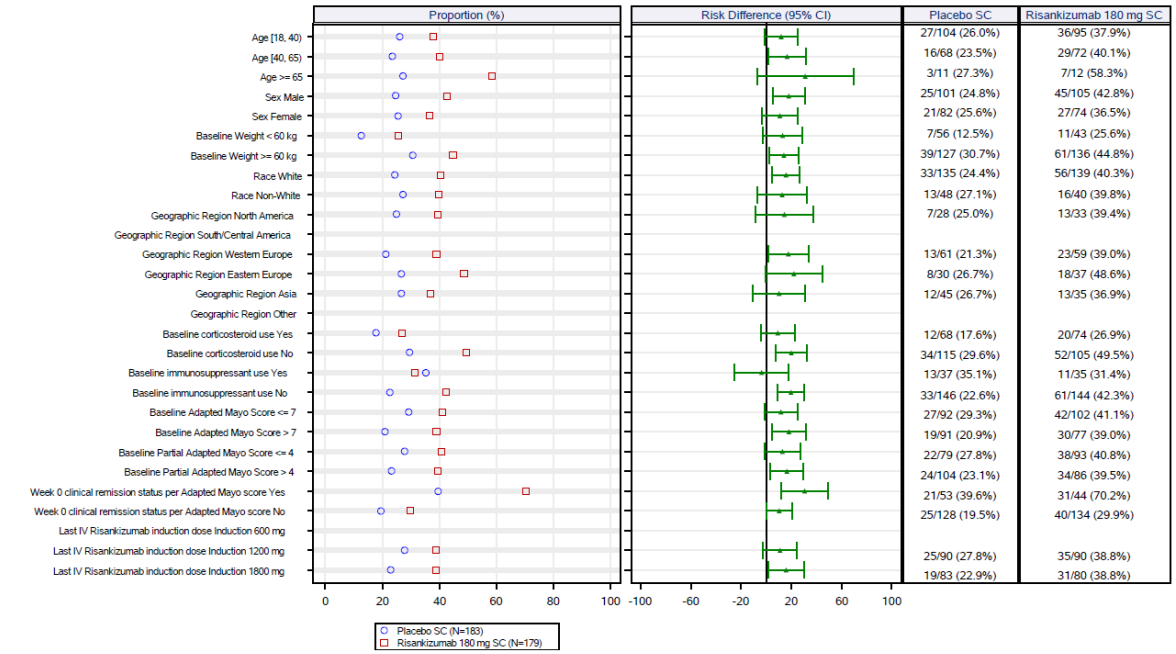
b. Risk difference = (risankizumab – placebo).

c. 95% CI for difference are calculated using normal approximation to the binomial distribution. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or non-responder imputation only if there are no missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions).

Other subgroup analyses

Efficacy results for the primary endpoint of clinical remission per Adapted Mayo Score at Week 52 across most subgroups are shown below.

Table 23 Summary of achievement of clinical remission per adapted Mayo Score at Week 52 by Subgroups (NRI-MI) (Substudy 1 – ITT1RN_A Population)



Note: ITT1RN_A Population includes all randomized subjects who received at least one dose of study drug in Sub-study 1 after received IV risankizumab (either 600 mg, 1200 mg or 1800 mg) for only one period of 12 weeks in the induction Study M16-067.
Clinical remission per Adapted Mayo score is defined as stool frequency subscore (SFS) <= 1, and not greater than baseline, rectal bleeding subscore (RBS) = 0, and endoscopic subscore <= 1 without the evidence of friability.
If any of the resulting subgroups except for age, sex and race has fewer than 10% of the planned study size, the subgroup analyses for that category are not presented.
Risk difference = (Risankizumab - Placebo).
95% CI for difference are calculated using normal approximation to the binomial distribution. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or non-responder imputation only if there are no missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions).

The small number of patients in each of these subgroups makes interpretation of the findings less reliable.. As such the results of the subgroup analyses can only be seen as supportive.

Secondary efficacy outcome analyses

Results for the risankizumab 180 mg and 360 mg SC arms were numerically better and showed greater clinical improvement compared to placebo for all secondary endpoints, with endoscopic improvement, HEMI, endoscopic remission, and corticosteroid-free clinical remission at Week 52, meeting statistical significance for both doses. Additionally, the risankizumab 180 mg SC arm demonstrated statistically significant differences compared to placebo for the secondary endpoints of clinical remission per Adapted Mayo Score at Week 52 in subjects with clinical remission at Week 0, no bowel urgency at Week 52, and no abdominal pain at Week 52.

Selected key secondary endpoints

- Mucosal healing

There was a statistically significant improvement in the rates of mucosal improvement seen in patients receiving either Risankizumab 180 mg SC or Risankizumab 360 mg SC than that seen in patients receiving placebo (42.8%, 42.2%, and 23.5% respectively).

- Steroid free clinical remission

There was a statistically significant improvement in the rates of clinical remission seen in patients with no corticosteroid use in 90 days receiving either Risankizumab 180 mg SC or Risankizumab 360 mg SC than that seen in patients receiving placebo (39.6%, 37.1%, and 25.1% respectively).

- Changes in stool frequency

There was a statistically significant reduction in reports of bowel urgency in patients receiving Risankizumab 180 mg SC versus those receiving placebo (53.6% vs 31.1%). No statistically significant difference was seen in patients receiving Risankizumab 360 mg SC.

Sensitivity C-reactive Protein and Faecal Calprotectin

Subjects receiving risankizumab 180 mg and 360 mg SC had larger mean reductions at Week 52 from Week 0 in both hs-CRP and FCP compared to the placebo arm. Over the course of the maintenance Period, mean reduction in risankizumab arms compared to the placebo arm generally increased, and subjects who were in the placebo arm had a higher level of these inflammatory markers at Week 52 compared to Week 0.

Efficacy results in patients receiving rescue medication

Overall, 11.7% (20/179) patients who received risankizumab 180mg required rescue treatment and had Week 52 data collected, of whom 17 (85%) later achieved clinical response as defined. In contrast, 18.9% (35/186) patients who received risankizumab 360mg required rescue therapy and had Week 52 data collected, of whom 26 (74.3%) achieved a clinical response.

- Summary of main efficacy results

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

Table 24 Summary of efficacy for trial M16-067

<table>
<tr><td colspan="4">Title: A Multicentre, Randomized, Double-Blind, Placebo Controlled Induction Study to Evaluate the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Ulcerative Colitis</td></tr>
<tr><td>Study identifier</td><td colspan="3">M16-067 Sub study 2</td></tr>
<tr><td rowspan="4">Design</td><td colspan="3">Study M16-067 Sub study 2 consists of a Screening Period (approximately 35 days), 12-Week Induction Period, Induction Period 2, and 20-week follow-up period.
The 12-Week Induction Period is a 12-week randomized, double-blind, placebo-controlled IV therapy induction period. Eligible subjects were randomized to risankizumab (RISA) 1200 mg intravenously (IV) or placebo (PBO) in a 1:1 ratio through Week 12. Dosing in the 12-Week Induction Period was at Week 0, Week 4, and Week 8.
Induction Period 2 is a 12-week randomized, double-blind, double-dummy re-induction period for subjects who do not achieve clinical response at Week 12. At Week 12, eligible subjects were re-randomized to receive RISA 1200 mg IV, RISA 180 mg subcutaneously (SC) or RISA 360 mg SC in a 1:1:1 ratio through Week 24, and subjects who received placebo induction treatment during the 12-Week Induction Period were assigned to receive RISA 1200 mg IV in Induction Period 2.</td></tr>
<tr><td colspan="2">Duration of main phase:</td><td>12 weeks (12-Week Induction Period: double-blind period)</td></tr>
<tr><td colspan="2">Duration of run-in phase:</td><td>Not applicable</td></tr>
<tr><td colspan="2">Duration of extension phase:</td><td>Not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority of RISA vs. PBO at Week 12</td></tr>
<tr><td rowspan="2">Treatment groups</td><td rowspan="2">12-Week Induction Period</td><td>RISA 1200 mg IV</td><td>RISA 1200 mg IV at Week 0, 4 and 8</td></tr>
<tr><td>PBO</td><td>PBO at Week 0, 4 and 8</td></tr>
</table>

Endpoints and definitions	Primary	Clinical remission per adapted Mayo score at Week 12	The achievement of clinical remission per adapted Mayo score at Week 12
	Secondary	Clinical response per adapted Mayo score at Week 12	The achievement of clinical response per adapted Mayo score at Week 12
		Endoscopic improvement at Week 12	The achievement of endoscopic improvement at Week 12
		HEMI at Week 12	The achievement of histologic endoscopic mucosal improvement (HEMI) at Week 12
		Endoscopic remission at Week 12	The achievement of endoscopic remission at Week 12
		Clinical response per partial adapted Mayo score at Week 4	The achievement of clinical response per partial adapted Mayo score at Week 4
		No bowel urgency at Week 12	The achievement of no bowel urgency at Week 12
		No abdominal pain at Week 12	The achievement of no abdominal pain at Week 12
		HEMR at Week 12	The achievement of histologic endoscopic mucosal remission (HEMR) at Week 12
		FACIT-Fatigue at Week 12	Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) at Week 12
		IBDQ total score at Week 12	Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) total score at Week 12
		UC-related hospitalization through Week 12	Occurrence of UC-related hospitalization through Week 12
		No nocturnal bowel movements at Week 12	The achievement of no nocturnal bowel movements Week 12
		No tenesmus at Week 12	The achievement of no tenesmus at Week 12
		Number of fecal incontinence episodes at Week 12	Change from Baseline to Week 12 in number of fecal incontinence episodes per week
		Number of days per week with sleep interrupted due to UC symptoms at Week 12	Change from Baseline to Week 12 in number of days per week with sleep interrupted due to UC symptoms

Database lock	06 March 2023		
Analysis population and time point description	The Intent-to-Treat population (ITT2) includes all randomized subjects who received at least one dose of study drug in the 12-Week Induction Period of Study M16-067 Sub study 2. The ITT2 Population was used for all efficacy and demographic/baseline analyses for the 12-Week Induction Period. Subjects were included in the analysis according to the treatment groups to which they were randomized. A graphical multiple testing procedure was used to provide strong control of the overall type I error rate at alpha level of 0.05 (2-sided) in Sub study 2 across analyses comparing the risankizumab IV dose arm to placebo with respect to the primary and secondary endpoints.		
Results and Analysis			
Analysis description	**Primary and Secondary Analysis**		
Descriptive statistics and estimate variability	Treatment group	PBO	RISA 1200 mg IV
	Number of Subjects	325	650
	Clinical remission per adapted Mayo score at Week 12 (NRI-MI), n/N (%)	20/325 (6.2%)	132/650 (20.3%)
	Clinical response per adapted Mayo score at Week 12 (NRI-MI), n/N (%)	116/325 (35.7%)	418/650 (64.3%)
	Endoscopic improvement at Week 12 (NRI-MI), n/N (%)	39/325 (12.1%)	237/650 (36.5%)
	HEMI at Week 12 (NRI-MI), n/N (%)	25/325 (7.7%)	159/650 (24.5%)
	Endoscopic remission at Week 12 (NRI-MI), n/N (%)	11/325 (3.4%)	69/650 (10.6%)
	Clinical response per partial adapted Mayo score at Week 4 (NRI-MI), n/N (%)	99/325 (30.5%)	339/650 (52.2%)
	No bowel urgency at Week 12 (NRI-MI), n/N (%)	90/325 (27.7%)	287/650 (44.1%)
	No abdominal pain at Week 12 (NRI-MI), n/N (%)	86/325 (26.5%)	232/650 (35.8%)
	HEMR at Week 12 (NRI-MI), n/N (%)	2/325 (0.6%)	41/650 (6.3%)
	FACIT-Fatigue at Week 12 (RTB-MI), N; LS-Mean Change from Baseline [95% CI]	N = 308 3.3 [2.12, 4.50]	N = 614 7.9 [7.03, 8.69]
	IBDQ total score at Week 12 (RTB-MI), N; LS-Mean Change from Baseline [95% CI]	N = 310 24.3 [20.19, 28.46]	N = 619 42.6 [39.72, 45.57]
	UC-related hospitalization through Week 12 (AO), n/N (%)	18/325 (5.5%)	5/650 (0.8%)
	No nocturnal bowel movements at Week 12 (NRI-MI), n/N (%)	140/325 (43.1%)	437/650 (67.3%)
	No tenesmus at Week 12 (NRI-MI), n/N (%)	98/325 (30.2%)	317/650 (48.7%)

	Number of fecal incontinence episodes at Week 12 (RTB-MI), N; LS-Mean Change from Baseline [95% CI]	N = 288 -2.213 [-2.8526, -1.5726]	N = 602 -3.839 [-4.2687, -3.4099]
	Number of days per week with sleep interrupted due to UC symptoms at Week 12, N; LS-Mean Change from Baseline [95% CI]	N = 288 -1.505 [-1.7969, -1.2122]	N = 602 -2.485 [-2.6872, -2.2831]

Effect estimate per comparison	Clinical remission per adapted Mayo score at Week 12 (NRI-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	14.0%
		95% CI	[10.0%, 18.0%]
		P-value	< 0.00001[S]
	Clinical response per adapted Mayo score at Week 12 (NRI-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	28.6
		95% CI	[22.3%, 34.8%]
		P-value	< 0.00001[S]
	Endoscopic improvement at Week 12 (NRI-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	24.3%
		95% CI	[19.3%, 29.4%]
		P-value	< 0.00001[S]
	HEMI at Week 12 (NRI-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	16.6%
		95% CI	[12.3%, 21.0%]
		P-value	< 0.00001[S]
	Endoscopic remission at Week 12 (NRI-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	7.2%
		95% CI	[4.2%, 10.2%]
		P-value	< 0.00001[S]
	Clinical response per partial adapted Mayo score at Week 4 (NRI-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	21.8%
		95% CI	[15.6%, 28.1%]
		P-value	< 0.00001[S]
	No bowel urgency at Week 12 (NRI-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	16.3%
		95% CI	[10.3%, 22.4%]
		P-value	< 0.00001[S]
	No abdominal pain at Week 12 (NRI-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	9.3%
		95% CI	[3.4%, 15.3%]
		P-value	0.00213[S]
	HEMR at Week 12 (NRI-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	5.6%
		95% CI	[3.5%, 7.7%]

		P-value	< 0.00001[S]
	FACIT-Fatigue at Week 12 (RTB-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	4.5
		95% CI	[3.13, 5.97]
		P-value	< 0.00001[S]
	IBDQ total score at Week 12 (RTB-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	18.3
		95% CI	[13.38, 23.25]
		P-value	< 0.00001[S]
	UC-related hospitalization through Week 12 (AO)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	-4.8
		95% CI	[-7.3, -2.2]
		P-value	< 0.00001[S]
	No nocturnal bowel movements at Week 12 (NRI-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	24.2%
		95% CI	[17.9%, 30.5%]
		P-value	< 0.00001[S]
	No tenesmus at Week 12 (NRI-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	18.6%
		95% CI	[12.4%, 24.8%]
		P-value	< 0.00001[S]
	Number of fecal incontinence episodes at Week 12 (RTB-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	-1.627
		95% CI	[-2.3846, -0.8689]
		P-value	0.00003[S]
	Number of days per week with sleep interrupted due to UC symptoms at Week 12 (RTB-MI)	Comparison groups	RISA 1200 mg IV vs PBO
		Difference	-0.981
		95% CI	[-1.3285, -0.6326]
		P-value	< 0.00001[S]

Notes	AO = as observed; CI = confidence interval; LS = least square; NRI-MI = non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19 or due to geo-political conflict in Ukraine or surrounding area; RTB-MI = multiple imputation incorporating return-to-Baseline; UC = ulcerative colitis Treatment differences presented above were adjusted for the stratification factors of prior biologic and/or JAK inhibitor failure (yes or no), baseline corticosteroid use (yes or no), and baseline Adapted Mayo score (≤ 7 vs > 7). S = Statistically significant difference compared to placebo.

Table 25 Summary of efficacy for trial M16-066

Title: A Multicenter, Randomized, Double-Blind, Placebo Controlled 52-Week Maintenance and an Open-Label Extension Study of the Efficacy and Safety of Risankizumab in Subjects with Ulcerative Colitis			
Study identifier	M16-066 Sub-Study 1		
Design	The M16-066 Sub-Study 1 consists of a 52-Week maintenance period and 140-day Follow-up Period. **52-Week Maintenance Period** is a 52-week randomized, double-blind, placebo-controlled SC injection maintenance period. Eligible subjects with clinical response to induction treatment with intravenous risankizumab were randomized to risankizumab (RISA) 360 mg SC, RISA 180 mg SC or placebo (PBO) in 1:1:1 ratio through Week 52 and dosing in 52-Week maintenance period were at Week 0, Week 8, Week 16, Week 24, Week 32, Week 40 and Week 48.		
	Duration of main phase:		52 weeks (double-blind period)
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority of RISA vs. PBO at Week 52		
Treatment groups	52-Week maintenance period	RISA 360 mg SC	RISA 360 mg SC Q8W
		RISA 180 mg SC	RISA 180 mg SC Q8W
		PBO	PBO Q8W
Endpoints and definitions	Primary	Clinical remission (per adapted Mayo score) at Week 52	The achievement of clinical remission (per adapted Mayo score) at Week 52
	Secondary	Endoscopic improvement at Week 52	The achievement of endoscopic improvement at Week 52.
		HEMI improvement at Week 52	The achievement of histologic endoscopic improvement of the mucosa (HEMI) at Week 52.
		Endoscopic remission at Week 52	The achievement of endoscopic remission at Week 52.

		Clinical remission per at Week 52 with no corticosteroid use for 90 days	The achievement of clinical remission per Adapted Mayo score at Week 52 with no corticosteroid use for 90 days.
		Maintenance of clinical remission at Week 52	The achievement of clinical remission per Adapted Mayo score at Week 52 in subjects with clinical remission at Week 0.
		No bowel urgency at Week 52	The achievement of no bowel urgency at Week 52.
		No abdominal pain at Week 52	The achievement of no abdominal pain at Week 52.
		HEMR at Week 52	The achievement of histologic endoscopic mucosal remission (HEMR) at Week 52.
		Endoscopic improvement at Week 52 in subjects with endoscopic improvement at Week 0	The achievement of endoscopic improvement at Week 52 in subjects with endoscopic improvement at Week 0.
		Clinical response at Week 52	The achievement of clinical response per Adapted Mayo score at Week 52.
		FACIT-Fatigue at Week 52	Change from Baseline (of induction) to Week 52 in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue.
		IBDQ at Week 52	Change from Baseline (of induction) to Week 52 in Inflammatory Bowel Disease Questionnaire (IBDQ) total score.
		No nocturnal bowel movements at Week 52	The achievement of no nocturnal bowel movements at Week 52.
		No tenesmus at Week 52	The achievement of no tenesmus at Week 52.
		Fecal incontinence episodes per week at Week 52	Change from Baseline (of induction) to Week 52 in number of fecal incontinence episodes per week.
		Sleep interrupted due to UC symptoms at Week 52	Change from Baseline (of induction) to Week 52 in number of days over a week with sleep interrupted due to UC symptoms.
		UC-related hospitalizations through Week 52	Exposure adjusted occurrence of UC-related hospitalizations from Week 0 through Week 52.

Database lock	05 May 2023			
Analysis population and time point description	The Intent-to-Treat population for Sub study 1 (ITT1) included subjects who received at least one dose of study drug in Sub study 1. Subjects were included in the analysis according to the treatment arms that they were randomized to, regardless of the treatment actually received. The primary efficacy analyses were conducted based on ITT1RN_A population, which included all randomized subjects who received at least one dose of study drug in Sub study 1 after receiving IV risankizumab (either 600 mg, 1200 mg or 1800 mg) for only one period of 12-week induction treatment. A graphical multiple testing procedure was used to provide strong control of the overall type I error rate at alpha level of 0.05 (2-sided) in Sub study 1 across analyses comparing each risankizumab SC dose group to placebo with respect to the primary and secondary endpoints.			
	Results and Analysis			
Analysis description	**Primary and Secondary Analysis**			
Descriptive statistics and estimate variability	Treatment group	PBO SC	RISA 180 mg SC	RISA 360 mg SC
	Number of Subjects	183	179	186
	Clinical remission (Per Adapted Mayo Score) at Week 52 (NRI-MI), n/N (%)	46/183 (25.1%)	72/179 (40.2%)	70/186 (37.6%)
	Endoscopic Improvement at Week 52 (NRI-MI), n/N (%)	58/183 (31.7%)	91/179 (50.8%)	90/186 (48.3%)
	Histological-Endoscopic Mucosal Improvement at Week 52 (NRI-MI), n/N (%)	43/183 (23.5%)	77/179 (42.8%)	79/186 (42.2%)
	Endoscopic Remission at Week 52 (NRI-MI), n/N (%)	27/183 (14.8%)	41/179 (23.2%)	45/186 (24.3%)
	Clinical Remission per Adapted Mayo Score at Week 52 with No Corticosteroid Use for 90 days (NRI-MI), n/N (%)	46/183 (25.1%)	71/179 (39.6%)	69/186 (37.1%)
	Maintenance of Clinical Remission per Adapted Mayo Score at Week 52 (NRI-MI), n/N (%)	21/53 (39.6%)	31/44 (70.2%)	20/40 (50.0%)
	No Bowel Urgency at Week 52 (NRI-MI), n/N (%)	57/183 (31.1%)	96/179 (53.6%)	92/186 (49.4%)
	No Abdominal Pain at Week 52 (NRI-MI), n/N (%)	54/183 (29.5%)	84/179 (46.9%)	70/186 (37.8%)
	Histologic Endoscopic Mucosal Remission at Week 52 (NRI-MI), n/N (%)	18/183 (9.8%)	23/179 (12.9%)	29/186 (15.6%)
	Endoscopic Improvement at Week 52 in Subjects with Endoscopic Improvement at Week 0 (NRI-MI), n/N (%)	37/78 (47.4%)	45/61 (73.6%)	37/68 (54.1%)

	Clinical Response per Adapted Mayo Score at Week 52 (NRI MI), n/N (%)	95/183 (51.9%)	122/179 (68.2%)	116/186 (62.3%)
	Change from Baseline of the Induction Study in FACIT-Fatigue at Week 52 (RTB-MI), LS-Mean Change from Baseline [95% CI]	N = 171 7.0 [4.89, 9.19]	N = 166 10.9 [8.77, 13.08]	N = 163 10.3 [8.12, 12.47]
	Change from Baseline of the Induction Study in IBDQ at Week 52 (RTB-MI), LS-Mean Change from Baseline [95% CI]	N = 172 35.0 [27.15, 42.92]	N = 168 52.6 [44.93, 60.20]	N = 168 50.3 [42.20, 58.36]
	No Nocturnal Bowel Movements at Week 52 (NRI-MI), n/N (%)	55/183 (30.1%)	75/179 (41.9%)	81/186 (43.5%)
	No Tenesmus at Week 52 (NRI-MI), n/N (%)	43/183 (23.5%)	66/179 (36.9%)	68/186 (36.8%)
	Change from Baseline of the Induction Study in Number of Fecal Incontinence Episodes per Week at Week 52 (RTB-MI), LS-Mean Change from Baseline [95% CI]	N = 69 -2.765 [-4.1891, -1.3399]	N = 66 -3.440 [-4.7227, -2.1580]	N = 70 -2.867 [-4.2762, -1.4587]
	Change from Baseline of the Induction Study in Number of Days per Week with Sleep Interrupted due to UC symptoms at Week 52 (RTB-MI), LS-Mean Change from Baseline [95% CI]	N = 69 -1.772 [-2.2987, -1.2455]	N = 66 -2.571 [-3.1181, -2.0236]	N = 70 -2.482 [-3.0135, -1.9511]
	Exposure Adjusted Occurrence of UC-Related Hospitalizations from Week 0 through Week 52, n/PYS (%)	5/163.3 (3.1)	1/172.8 (0.6)	2/164.7 (1.2)

Effect estimate per comparison	Clinical remission (Per Adapted Mayo Score) at Week 52 (NRI-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	16.3%	14.2%
		95% CI	[7.4, 25.3]	[5.3, 23.2]
		P-value	0.0004[S]	0.0019[S]
	Endoscopic Improvement at Week 52 (NRI-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	20.1%	17.4%
		95% CI	[10.6, 29.6]	[7.9, 26.9]
		P-value	0.00003[S]	0.00032 [S]
	Histological-Endoscopic Mucosal Improvement at Week 52 (NRI-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	20.2%	19.8%
		95% CI	[11.2, 29.2]	[10.8, 28.8]
		P-value	0.00001[S]	0.00001[S]
	Endoscopic Remission at Week 52 (NRI-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	9.5%	9.6%
		95% CI	[1.9, 17.1]	[2.0, 17.1]
		P-value	0.01399[S]	0.01303[S]
	Clinical Remission per Adapted Mayo Score at Week 52 with No Corticosteroid Use for 90 days (NRI-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	15.8%	13.7%
		95% CI	[6.9, 24.8]	[4.8, 22.7]
		P-value	0.00052[S]	0.00268[S]
	Clinical Remission per Adapted Mayo Score at Week 52 in Subjects with Clinical Remission at Week 0 (NRI-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	29.2%	12.5%
		95% CI	[10.1, 48.2]	[-7.6, 32.7]
		P-value	0.00269[S]	0.22343
	No Bowel Urgency at Week 52 (NRI-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	22.6%	18.4%
		95% CI	[13.1, 32.2]	[8.8, 28.0]
		P-value	< 0.00001[S]	0.00018
	No Abdominal Pain at Week 52 (NRI-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	17.0%	8.2%

		95% CI	[7.4, 26.7]	[-1.3, 17.7]
		P-value	0.00053[S]	0.08954
	Histologic Endoscopic Mucosal Remission at Week 52 (NRI-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	4.0%	6.1%
		95% CI	[-2.2, 10.3]	[-0.3, 12.5]
		P-value	0.20616	0.06176
	Endoscopic Improvement at Week 52 in Subjects with Endoscopic Improvement at Week 0 (NRI-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	23.9%	4.8%
		95% CI	[8.6, 39.2]	[-11.4, 20.9]
		P-value	0.00217	0.56286
	Clinical Response per Adapted Mayo Score at Week 52 (NRI-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	17.1%	11.5%
		95% CI	[7.5, 26.6]	[1.7, 21.2]
		P-value	0.00045	0.02119
	Change from Baseline of the Induction Study in FACIT-Fatigue at Week 52 (RTB-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	3.9	3.3
		95% CI	[1.21, 6.57]	[0.57, 5.94]
		P-value	0.00454	0.01765
	Change from Baseline of the Induction Study in IBDQ at Week 52 (RTB-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	17.5	15.2
		95% CI	[8.01, 27.06]	[5.18, 25.31]
		P-value	0.00032	0.00308
	No Nocturnal Bowel Movements at Week 52 (NRI-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	12.0%	14.8%
		95% CI	[3.3, 20.6]	[6.1, 23.5]
		P-value	0.00691	0.00090
	No Tenesmus at Week 52 (NRI-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	13.1%	14.4%
		95% CI	[4.6, 21.7]	[5.7, 23.0]
		P-value	0.00258	0.00110

	Change from Baseline of the Induction Study in Number of Faecal Incontinence Episodes per Week at Week 52 (RTB-MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	-0.676	-0.103
		95% CI	[-2.5628, 1.2111]	[-2.1254, 1.9195]
		P-value	0.48140	0.92009
	Change from Baseline of the Induction Study in Number of Days per Week with Sleep Interrupted due to UC symptoms at Week 52 (RTB MI)	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	-0.799	-0.710
		95% CI	[-1.5570, -0.0405]	[-1.4442, 0.0238]
		P-value	0.03896	0.05788
	Exposure Adjusted Occurrence of UC-Related Hospitalizations from Week 0 through Week 52	Comparison groups	RISA 180 mg SC vs PBO	RISA 360 mg SC vs PBO
		Difference	-2.5	-1.8
		95% CI	[-5.4, 0.4]	[-5.0, 1.3]
		P-value	0.09485	0.25307
Notes	NRI-MI = non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19 or due to geo-political conflict in Ukraine or surrounding area. RTB-MI = Multiple Imputation Incorporating Return-to-Baseline. Exposure adjusted occurrence of UC-related hospitalization were analyzed based on observed data before receiving any risankizumab rescue therapy. Treatment differences presented above were adjusted for the stratification factors of prior biologic and/or JAK inhibitor failure at Baseline (yes vs no), clinical remission status per Adapted Mayo score at Week 0 (per central read) (yes vs no) and last IV risankizumab induction dose (600 mg vs 1200 mg vs 1800 mg). S = Statistically significant difference compared to placebo.			

2.6.5.3. Supportive study(ies)

Not applicable

2.6.6. Discussion on clinical efficacy

To support the demonstration of efficacy of risankizumab in the treatment of patients with moderate to severe UC, the MAH submitted the results of a phase 2b/3 randomized double-blind 12-week placebo-controlled induction study (M16-067) and a randomized double-blind 52-week placebo-controlled maintenance study (M16-066).

Design and conduct of clinical studies

Study M16-067 comprised of 2 pivotal sub studies. Sub study 1 was a 4-arm randomized double-blind placebo-controlled dose finding study designed to investigate the efficacy of three doses of the product over placebo. The doses investigated were 600 mg IV Q4W, 1200 mg IV Q4W, and 1800 mg IV Q4W.

The primary endpoint of the study was the rate of clinical remission at week 12, as assessed by the adapted Mayo score. Secondary endpoints included endoscopic improvement, endoscopic remission, and clinical response as defined by way of relevant symptom scores.

Subjects who had moderate to severe UC who had failed to achieve clinical response to either advanced or conventional therapies were eligible to be recruited to the trial. Advanced therapies included biological medicinal products and JAK inhibitors.

Immunogenicity was assessed using a tiered approach, which is acceptable to the CHMP.

Sub study 2 was a follow on 12-week double-blind placebo-controlled induction study using the dose that was determined to be most effective following the analysis of results of sub study 1. The design of sub study 2 was similar to that for sub study 1. The primary endpoint was also clinical remission at week 12 as assessed by the adapted Mayo score. Secondary endpoints were similar to those in sub study 1.

Patients entering sub study 2 were randomized to receive either placebo or risankizumab 1200 mg IV Q4W. During Sub study 2 Induction Period 1, demographic and baseline medical characteristics were generally balanced between arms. In addition, no significant impact on the interpretability of the trial results was anticipated from the prior or concomitant medicine use profile reported by the applicant.

Patients who achieved a clinical response in the induction study were entitled to enter the maintenance study M16-066. Patients who failed to achieve a clinical response at week 12 were entitled to enter a reinduction phase consisting of randomized allocation to either risankizumab 1800 mg IV Q4W, risankizumab 180mg SC Q8W, or risankizumab 360mg SC Q8W in a blinded double dummy design, with assessment of response occurring at week 24. Patients who achieved a clinical response to re induction at week 24 were entitled to enter the maintenance study although only patients who received IV treatment were randomized. Patients who received SC therapy during the reinduction phase remained on their allocated dose in a blinded manner.

Study M16-066 was a randomized double-blind placebo-controlled 52-week maintenance study. Three treatment arms were assessed in this study and patients were randomized to receive either risankizumab 180mg SC Q8W, risankizumab 360mg SC Q8W, or placebo.

The primary endpoint of the study was the rate of clinical remission at week 52, as assessed by the adapted Mayo score. Secondary endpoints included endoscopic remission, endoscopic response, and clinical response as defined by relevant symptom scores as before. Subgroup analysis conducted on the primary endpoint included prior advanced or conventional therapy, age, sex, geographical region, and prior immunosuppressant use.

In the maintenance study, patients who experienced a loss of clinical effect were entitled to receive up to 2 doses of rescue treatment, comprising of risankizumab 1200mg IV followed by risankizumab 360mg SC Q8W.

The MAH's decision to assess the efficacy of risankizumab using induction and maintenance studies was endorsed during scientific advice and is acceptable to the CHMP. The proposals are broadly in line with the advice received at that time, and with the relevant guidance on the investigation of products for the treatment of UC that have been published by the EMA. The MAH clarified that any differences from the advice received reflect advances in regulatory and clinical perspectives since the time when the advice was given, and this is accepted by the CHMP.

Efficacy data and additional analyses

In summary, results of sub study 1 of induction study M16-067 indicated that all 3 doses studied were superior to placebo at inducing clinical remission. The MAH considered that the totality of the clinical and exposure/response evidence suggested that the 1200mg dose was the best dose to be carried forward into the pivotal induction study, Sub study 2.

The results of the analysis of the primary efficacy endpoint in sub study 2 indicated that risankizumab 1200mg IV Q4W was superior to placebo, inducing clinical remission in patients with moderate to severe UC at a statistically significantly greater rate than that seen in patients who received placebo. The results of the secondary efficacy analysis support this conclusion, as do the results of the subgroup analysis.

Patients who failed to achieve a clinical response at week 12 who then received re-induction therapy also showed benefit from receiving reinduction. Although broadly similar results were seen across the three re-induction arms, a slightly greater response was seen with SC therapy. This supports the recommendation that patients proceed to SC maintenance therapy at week 12 regardless of whether they have achieved a clinical response at that time. The MAH also presented data showing that patients who failed to achieve a satisfactory clinical response at Week 12 who then received the higher 360mg maintenance dose had better clinical and endoscopic outcomes at Week 52 than those who received the lower 180 mg maintenance dose. This supports the recommendation that patients who fail to achieve a satisfactory clinical response at Week 12 receive the 360mg maintenance dose, and this is reflected in the SmPC Section 4.2.

Re-evaluation of the clinical response at Week 24 is recommended to determine whether patients should continue treatment, based on the observed clinical response by that timepoint.

The results of the analysis of the primary efficacy endpoint in the 52 week maintenance study, M16-066 showed a statistically significantly improved rate of clinical remission in patients who received either risankizumab 180mg SC Q8W or risankizumab 360mg SC Q8W when compared to the rate of clinical remission seen in patients who received placebo. Upon the CHMP's request, the MAH clarified that the apparent lack of difference between the 180mg SC and 360mg SC arms relates to imbalances in baseline disease status between treatment arms, as patients who had previously failed to achieve a clinical response to either multiple therapies or to advanced therapies are likely to have had more severe or prolonged baseline disease, and so are also more likely to have structural bowel changes such that they are likely to have less pronounced responses to anti-inflammatory therapies. This was supported by additional stratified analyses. Hence, the MAH's explanation is agreed by the CHMP.

Patients who received rescue treatment during the maintenance study seemed to derive benefit from this rescue treatment, although the numbers of patients receiving rescue treatment is quite small and so cannot be relied upon as the basis for specific posology recommendations in this regard.

The MAH presented additional subgroup analyses to support the request to specifically include a reference to JAK inhibitors in the indication statement initially claimed. While it appeared that patients who had previously failed to achieve a response with a JAK inhibitor and who subsequently received risankizumab had a higher incidence of clinical remission and endoscopic improvement at week 12 following induction, inconsistent results were observed for maintenance treatment. Efficacy results were therefore not considered convincing in this patient subgroup.

In addition, most patients who had previously failed to achieve a response with a JAK inhibitor had also failed to achieve a response with biological therapy and few patients who had previously failed any type of UC-related advanced therapy had failed a JAK inhibitor only. It could be inferred that at most 15 (6 Placebo, 9 risankizumab 1200 mg IV) of the 90 patients who had failed a JAK inhibitor prior to

induction study baseline, and at most 4 (1 Placebo, 2 risankizumab 180 mg SC, 1 risankizumab 360 mg SC) of the 78 patients who had failed a JAK inhibitor prior to maintenance study baseline, had not also failed another type of UC-related advanced therapy. Hence, the proposal to include reference to JAK inhibitors in the indication was not agreed by the CHMP. The MAH agreed to remove the reference to JAK inhibitors in the indication statement.

2.6.7. Conclusions on the clinical efficacy

The efficacy of risankizumab has been demonstrated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.

The available data support the use of risankizumab in patients with UC with the following posology:

The recommended induction dose is 1200 mg administered by intravenous infusion at week 0, week 4, and week 8. Starting at week 12 and every 8 weeks thereafter, the recommended maintenance dose is based on individual patient presentation:

- A dose of 180 mg administered by subcutaneous injection is recommended for patients with adequate improvement in disease activity after induction
- A dose of 360 mg administered by subcutaneous injection is recommended for patients with inadequate improvement in disease activity after induction

Consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit by week 24.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The pivotal studies represent 64 weeks of overall study drug treatment (12-week induction and 52-week maintenance). As of the data cut-off dates (23 January 2023 and 30 March 2023), 1,103 subjects had received risankizumab at the proposed induction dose of risankizumab 1200 mg IV for a median exposure of 84.0 days. A total of 344 subjects had received at least 12 months of the 180 mg SC regimen and 309 subjects had received at least 12 months of the 360 mg SC regimen.

To assess the safety of risankizumab across the risankizumab UC development program, subject data were integrated into multiple safety analysis sets. The first 2 analysis sets provide placebo-controlled assessments of data through 12 weeks of induction and through 52 weeks of maintenance treatment in subjects with clinical response to IV risankizumab induction treatment, respectively.

The Placebo-Controlled 12-Week Induction Period Safety Analysis Set (ISS1) includes 1,095 subjects who received at least 1 dose of risankizumab 1200 mg IV (N = 712) or placebo (N = 383). The median duration of exposure for each treatment group was 84.0 days.

The Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set (SA1RN) includes data from 388 subjects who received at least 1 dose of risankizumab (N = 193 and N = 195 for the risankizumab 180 mg and 360 mg SC arms, respectively) for a median duration of 389.0 days of maintenance treatment, and 196 subjects who received at least 1 dose of placebo for a median duration of 373.5 days in Study M16-066 Sub study 1.

The All Treated Safety Analysis Set (ISS2) includes data from all 1,512 subjects in the Phase 2b and Phase 3 UC studies who received at least 1 dose of risankizumab for a median duration of 353.5 days across risankizumab UC clinical studies.

Table 26 Safety Analysis Set

Analysis Set	N	Integration Status / Studies / Treatment Periods or Sub-Studies	Study Population	Treatment Groups	Key Analyses or Purpose
Placebo-Controlled 12-Week Induction Period Safety Analysis Set (ISS1)[a]	1095	Integrated M16-067 DB SS1 Induction Period 1 (12-week induction period); M16-067 DB SS2 Induction Period 1; (12-week induction period)	All subjects who received at least 1 dose of study drug (RZB 1200 mg IV or placebo IV) during Study M16-067 in the treatment periods indicated	RZB 1200 mg IV PBO IV	Safety of risankizumab as induction treatment[a]
Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set[b]	584	Not integrated M16-066 DB SS1	All randomized subjects who received at least 1 dose of study drug in M16-066 SS1 after achieving clinical response to IV risankizumab induction	RZB 180 mg SC RZB 360 mg SC Placebo SC	Safety of risankizumab as maintenance treatment in subjects with clinical response to IV risankizumab induction
All Treated Safety Analysis Set (ISS2)[b]	1555	Integrated M16-067 DB SS1, Period 1, Period 2 M16-067 OL SS1 Period 1, Period 2 M16-067 DB SS2 Period 1, Period 2 M16-066 SS1, SS2, SS3	All subjects who received at least 1 dose of study drug from all Phase 2b and 3 UC studies	RZB 1200 mg IV RZB 1800 mg IV RZB 180 mg SC RZB 360 mg SC Any RZB IV (including 600 mg IV) Any RZB SC Any RZB (including 600 mg IV) PBO IV/SC (RZB naïve)	Comprehensive overview of safety and exposure to RZB and PBO in all Phase 2b and 3 studies PBO subjects were included to capture all events and exposure time attributed to PBO IV and SC therapy up until their first dose of RZB (RZB naïve)

a. Risankizumab 1800 mg IV and 600 mg IV treatment groups are not included in ISS1.

b. Equivalent to the SA1RN Population (Safety Population in Substudy 1 for randomized subjects) from Study M16-066.

The number of subjects who received at least 1 dose of risankizumab (N = 1,512 with a total 2,220.9 PY of exposure) and who had at least 12 months of exposure to risankizumab (N = 741) included in the safety analyses is consistent with ICH E1 recommendations.

Demographic and baseline characteristics were not well presented in the Summary of Clinical Safety report but in general were balanced between arms and consistent with a subject population with moderately to severely active UC.

Imbalances were observed between the risankizumab 180 mg and 360 mg SC arms in relation to disease characteristics. Imbalances in disease characteristics suggested that subjects in the risankizumab 360 mg SC arm may have had disease that was more difficult to treat. These imbalances included a greater proportion of subjects with failure of > 2 advanced therapies, and a lower proportion of subjects with clinical remission at Week 0. The Applicant also noted a longer duration of disease in the risankizumab 360 mg SC arm; however, a minimal difference between groups was noted.

Overall, the demographic and baseline characteristics were generally balanced between arms and appropriate or evaluating the safety of risankizumab in the target population of moderate to severe UC.

2.6.8.2. Adverse events

In the 12-Week induction period, the proportions and event rates of subjects with AEs, SAEs, severe AEs, and AEs leading to study drug discontinuation were lower in the risankizumab group compared with the placebo group; differences between the 2 groups were largely attributable to more events related to underlying disease in the placebo group.

The most frequent AEs by SOC (> 9.0% of subjects) in both treatment groups were Infections and infestations and Gastrointestinal disorders. The most common AEs (> 3.5% of subjects) in the risankizumab group were COVID-19 and anaemia.

In the 52-Week maintenance period, the percentages and event rates of subjects with AEs and AEs leading to discontinuation of study drug in each risankizumab arm were generally comparable to the placebo arm, with no evidence of a dose-dependent pattern between the risankizumab arms. The percentages and event rates of subjects with SAEs and severe AEs were lower in the risankizumab arms compared to the placebo arm with no dose-dependent pattern; this was attributable to events related to underlying disease in the placebo arm.

The SOCs with the most frequently reported AEs (≥ 28.0% of subjects in each treatment arm) were Infections and infestations and Gastrointestinal disorders. The percentages and patterns of SOCs reported were similar in the Total Risankizumab group and the placebo arm and seen in the 12-Week induction period.

The overall pattern of the most frequently reported AEs and study related AEs were consistent with the known safety profile and the underlying disease. *In the 12-Week induction period,* the most commonly reported AEs were generally comparable between the risankizumab and placebo groups, except a greater proportion of subjects with AEs of arthralgia and headache in the risankizumab group.

Study-related AEs were most frequently reported (≥ 2.0%) in the SOCs of Skin and subcutaneous tissue disorders and Infections and infestations. The AEs most frequently assessed by the investigator as having a possible relationship to study drug (≥ 0.8%) were headache and arthralgia in the risankizumab group.

In the 52-Week maintenance period, the most common AEs (> 5.0% of subjects) in the Total Risankizumab group were colitis ulcerative, COVID-19, nasopharyngitis, and arthralgia.

Study-related AEs were most frequently reported in the SOC of Infections and infestations in the Total Risankizumab group (5.7%). The most frequently reported (> 3 subjects in any treatment arm) AEs considered related to study drug were colitis ulcerative and injection site erythema in the risankizumab 180 mg SC arm, arthralgia in the risankizumab 360 mg SC arm, and nasopharyngitis, colitis ulcerative, and headache in the placebo arm and were generally comparable among the 3 treatment arms.

In the 12-Week induction period, a lower proportion of subjects in the risankizumab group had severe AEs compared to subjects in the placebo group. Severe AEs were most frequently reported in the SOC of Blood and lymphatic disorders in the risankizumab group (0.9% of subjects). The most common severe AE was anaemia in the risankizumab group (0.9% of subjects).

In the 52-Week maintenance period, severe AEs were most frequently reported in the SOCs of Infections and infestations in the Total Risankizumab group (1.0% of subjects). The proportions of subjects with severe AEs were lower in the risankizumab arms (3 subjects [1.6%] in the risankizumab 180 mg SC arm and 6 subjects [3.1%] in the risankizumab 360 mg SC arm) compared with the placebo arm (10 subjects [5.1%]). No clear dose-dependent pattern was observed for severe AEs. The most common severe AEs (≥ 1.0% of subjects) were appendicitis (1.0%) in the risankizumab 180 mg SC arm and colitis ulcerative (2.0%) in the placebo arm. No severe AEs occurred in ≥ 1.0% of subjects in the risankizumab 360 mg SC arm.

Adverse Drug Reactions

Overall, no new ADRs were identified by the MAH in subjects with UC treated with risankizumab 1200 mg IV and risankizumab 180 mg and 360mg SC.

In the *Placebo-Controlled 12-Week Induction Period Safety Analysis Set*, headache and folliculitis were determined to be ADRs for patients with moderate to severe UC during induction treatment (headache: 3.1% in the risankizumab group and 2.5% in the placebo group; folliculitis: 0.4% in the risankizumab group and 0.3% in the placebo group). Notably, the percentage rates of grouped terms upper respiratory tract infections, fatigue, tinea infections, and ISRs (including infusion-related reactions and

infusion site reactions) were lower than or the same as those in the placebo group. No events of infusion-related reaction were reported in subjects treated with risankizumab 1200 mg IV. While a numerically higher proportion of subjects in the risankizumab group had AEs of arthralgia compared to subjects in the placebo group 3.3% vs. 1.4%, respectively), arthralgia is recognized as an extra-intestinal manifestation (EIM) of UC and therefore not considered as an ADR.

Eczema (0.4% in the risankizumab group and 0.0% in the placebo group), and rash (1.7% in the risankizumab group and 0.4% in the placebo group) were determined to be ADRs for patients with moderate to severe UC during the 12-Week induction treatment. These events were previously identified as ADRs based on post-marketing experience. Rash is reflected in the current product label. The PTs for the grouped term "Rash" are "*Under Hypersensitivity SMQ Narrow, any PTs that contain rash*". Reported in the 52-Week maintenance period, eczema (1.8% in the Total Risankizumab group and 1.5% in the placebo arm), rash (2.3% in the Total Risankizumab group and 1.5% in the placebo arm).

In the *Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set*, fatigue, injection site reactions, and tinea infections were determined to be ADRs and occurred at higher rates for subjects who received risankizumab compared to subjects who received placebo during the 52-week maintenance treatment.

The other grouped events, upper respiratory tract infections and headache, were not considered as ADRs for maintenance as the percentage rates in the risankizumab arms were lower than those in placebo (as observed in the CD clinical development program). The non-grouped event of folliculitis was not considered an ADR based on the assessment that only 1 event occurred in the risankizumab 180 mg SC arm and no event occurred in the risankizumab 360 mg SC arm.

In addition, assessment of maintenance data identified eczema (1.8% in the Total Risankizumab group and 1.5% in the placebo arm), rash (2.3% in the Total Risankizumab group and 1.5% in the placebo arm) and urticaria (1.8% in the Total Risankizumab Group and 0.5% in the placebo arm) as ADRs for patients with moderate to severe UC during maintenance treatment. Arthralgia was recognized as an EIM in IBD and not considered as an ADR during maintenance treatment.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Three deaths were reported in the Phase 3 UC studies, all in subjects treated with risankizumab. AEs leading to deaths in subjects being treated with risankizumab were: COVID-19 pneumonia, adenocarcinoma of the colon (this condition existed prior to the subject entering the induction study), and haemorrhage intracranial.

The event of COVID-19 pneumonia was considered by the investigator to have a reasonable possibility of being related to study drug, while the other 2 events were considered by the investigator to have no reasonable possibility of being related to study drug. None of the fatal AEs were considered by the MAH to have a reasonable possibility of being related to study drug. The MAH's assessment is accepted.

SAEs

Overall, the proportion of subjects with SAEs in the risankizumab groups were lower than that of subjects in the placebo group, predominantly due to fewer SAEs related to underlying disease in the risankizumab group.

SAEs were most frequently reported in the Risankizumab safety sets in the SOCs of Infections and infestations and Blood and lymphatic system disorders. For subjects in the placebo group, SAEs were

most frequently reported in the SOC of Gastrointestinal disorders. The most frequently reported SAE was anaemia in the risankizumab IV group, colitis ulcerative, appendicitis, and renal colic in the Risankizumab SC groups and colitis ulcerative in the placebo group. The higher event rate of SAEs of colitis ulcerative in the placebo group compared with the risankizumab group likely reflects the underlying disease.

No discernible pattern was found on analysis of SAEs in terms of relatedness and discontinuations in the Risankizumab arms within the 12-Week induction set and the 52-Week maintenance set. The overall event rates of SAEs and the types of SAEs in the Any Risankizumab SC group of the All Treated Safety Analysis Set (8.2 E/100 PY) were similar to those observed in the Total Risankizumab group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set (6.1 E/100 PY).

An imbalance was noted in the SAE pulmonary embolism, a total of 6 subjects in the Any Risankizumab group of the All Treated Safety Analysis Set had SAEs of pulmonary embolism compared to 1 subject in the placebo IV/SC (risankizumab-naïve) group.

Covid-19

Across the risankizumab UC program, 316 (20.9%) subjects in the Any Risankizumab group experienced COVID-19 related AEs. The single fatal event of COVID-19 pneumonia in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set was the only COVID-19 related AE that resulted in study drug discontinuation in any subject in the All Treated Safety Analysis Set. Most COVID-19 events were non-serious, mild or moderate in severity, and assessed by the investigator to have no reasonable possibility of being related to study drug.

AESI

During the induction period and maintenance period, the percentages and event rates of AEs in the Areas of Safety Interest (ASI) categories were generally comparable between the risankizumab and placebo groups.

Notable differences reported in the 12-Week Induction period include lower percentages and event rates of hepatic events and ISRs in the risankizumab group compared to placebo group and a higher event rate of hypersensitivity reactions in the risankizumab group compared to the placebo group.

Notable differences reported in the 52-Week Maintenance period included rates of hypersensitivity AEs, which were higher in the risankizumab 180 mg SC arm, and rates of hepatic events, which were higher in the risankizumab 360 mg SC arm. The event rates of ISRs were similar in the risankizumab treatment arms and higher than the placebo arm.

MACE

No events of adjudicated MACE or adjudicated extended MACE were reported in the Risankizumab arms in the induction or maintenance period. A total of 3 subjects (incidence rate: 0.1/100 PY) in the Any Risankizumab group had an adjudicated MACE. One case resulted in death (haemorrhage intracranial) and two of the subjects with an adjudicated MACE had cardiovascular risk factors. The incidence rate of MACE in the Any Risankizumab group was not higher than the rate in the general UC population based on the literature.

Infections

The percentages of subjects with infection AEs and serious infections were comparable between the risankizumab 1200 mg IV group and the placebo group during the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), and the percentages and event rates of infections and serious infections were comparable between each risankizumab arm and the placebo arm during the

maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), with no apparent dose dependent pattern between the risankizumab 180 mg and 360 mg SC arms.

In the induction and maintenance periods, the most common infections were COVID-19 and nasopharyngitis in risankizumab-treated subjects. In the induction period, 5 serious infections (abscess limb, COVID-19, COVID-19 pneumonia, large intestine infection, and pneumonia) were reported in 1 subject each. In the maintenance period, 3 serious infections (appendicitis in 2 subjects and gastroenteritis viral in 1 subject) were reported in the Total Risankizumab group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set.

The majority of infection events in the Any Risankizumab group of the All Treated Safety Analysis Set were non-serious, mild or moderate in severity, and few events led to discontinuation of study drug. The most frequently reported serious infections were COVID-19, appendicitis, and anal abscess in the Any Risankizumab group.

The incidence rate of serious infections (2.2/100 PY) in the Any Risankizumab group of the All Treated Safety Analysis Set was not higher than the rate based on published estimates for IBD patients treated with anti-TNF agents (8/100 PY) or ustekinumab (3.19/100 PY).

Patients with UC are at increased risk for opportunistic infections, due in part to immunomodulatory treatment. The most common infections include viral infections (including CMV and herpes zoster) and aspergillosis and TB in both treated and untreated IBD patients.

Across the UC clinical development programme, a total of 8 events of opportunistic infection (excluding TB and herpes zoster) were reported in 8 subjects. Opportunistic infections included CMV infection in 4 subjects, and oral fungal infection, oral herpes zoster, Aeromonas infection, and eczema herpeticum in 1 subject each. Most of the opportunistic infections in the Any Risankizumab group of the All Treated Safety Analysis Set were non-serious and none led to study drug discontinuation. CMV infection was the only serious opportunistic infection and serious CMV infection occurred in 2 subjects.

All events of CMV infection resolved, were assessed by the investigator as having no reasonable possibility of being related to study drug and did not result in study drug discontinuation. Of note, the prevalence of CMV infection in patients with moderate to severe UC ranges from 16% – 34% and CMV reactivation is not uncommon in UC patients (Park 2017[6]).

No events of active TB were reported in the risankizumab UC clinical programme. Among subjects with latent TB who were treated with risankizumab, there was no evidence of an increased risk of developing active disease.

Malignancies

The incidence rate of malignancy for the Any Risankizumab group (0.7/100 PY) of the All Treated Safety Analysis Set was lower than the Placebo IV/SC (RZB naive) group (1.4/100 PY) and the background rate (1.34/100 PY) for this patient population based on published estimates.

Across the risankizumab UC clinical development program, a total of 19 malignancies were reported for 16 subjects in the Any Risankizumab group (All Treated Safety Analysis Set), of which 12 were serious. No malignancies of colorectal cancer were reported as related in subjects with risankizumab exposure. Most malignancies in risankizumab-treated subjects led to study drug discontinuation and were assessed by the investigator and MAH to have no reasonable possibility of being related to study drug. Most risankizumab-treated subjects with malignancies had relevant risk factors, relevant medical history, or the time to onset suggested an incompatible temporal relationship with risankizumab. The

[6] Park SC, Jeen YM, Jeen YT. Approach to cytomegalovirus infections in patients with ulcerative colitis. Korean J Intern Med. 2017;32(3):383-92.

types of malignancies most frequently reported in the UC program (e.g., basal cell carcinoma [NMSC] and thyroid cancer).

Hepatic Disorders

In the induction period, a lower proportion of subjects in risankizumab group (1.5 E/100 PY) experienced hepatic events compared to the placebo group (4.2 E/100 PY). All hepatic events in the risankizumab group were representative of laboratory abnormalities with the exception of 1 event of DILI reported as "hepatotoxicity due to statins treatment".

In the 12-week induction period, less than 1.0% of subjects in the risankizumab group had ALT (≥ 3 × ULN), AST (≥ 3 × ULN), TBL (≥ 2 × ULN), or ALP (≥ 2 × ULN) elevations and there was no meaningful difference between the risankizumab and placebo groups in the percentage of subjects with an ALT or AST ≥ 3 × ULN. One risankizumab-treated subject had ALT and AST values ≥ 10 × ULN. No subject in the risankizumab group had ALT or AST ≥ 3 × ULN and TBL ≥ 2 × ULN (potential Hy's law).

During maintenance treatment, the hepatic event rates were similar in the risankizumab 180 mg SC (1.6 E/100 PY) and placebo arms (1.7 E/100 PY) and higher in the risankizumab 360 mg SC arm (10.9 E/100 PY) compared to the risankizumab 180 mg SC and placebo arms.

There was also a significant difference for treatment comparison between the placebo arm and risankizumab 360 mg SC arm in the maintenance period, 6.2% (95% CI: 2.5, 9.8).

There were no serious hepatic events across treatment arms, and all hepatic events were mild or moderate in severity. Between Week 0 and Week 52 of the maintenance period, the proportions of subjects who had ALT or AST values ≥ 3 × ULN or elevations of TBL or ALP ≥ 2 × ULN were in general low. A slightly higher proportion of subjects in the risankizumab 360 mg SC arm had ALT or AST ≥ 3 × ULN or TBL ≥ 2 × ULN (2.5%, 3.1% and 1.9% respectively) compared to the risankizumab 180 mg SC arm (0.6%, 1.1% and 0.6% respectively) and ≥ 5 × ULN in ALT or AST in the risankizumab 360 mg SC arm (0.6% and 1.3% respectively compared to zero in the risankizumab 180 mg SC arm).

In the Any Risankizumab group of the All Treated Safety Analysis Set, no serious hepatic events were reported, and only a single subject discontinued study drug due to a hepatic event. The majority of hepatic events represented liver test elevations and the incidence rate of hepatic events decreased over time.

The EAER per 100 PY of hepatic events were:

- In the All Treated Safety Analysis Set: for the Risankizumab 180mg and 360mg SC groups (2.5 E/100 PY and 3.5 E/100 PY, respectively), the Any Risankizumab group (3.5 E/100 PY) and the Any Risankizumab SC group (2.9 E/100 PY).
- In the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set: for the risankizumab 360 mg SC arm (10.9 E/100 PY).

Weak trends continued to show increased hepatic enzymes in the risankizumab 360 mg SC arm versus the risankizumab 180 mg SC arm and placebo when analysed by level of ULN, below.

The proportion of subjects with ≥3 × ULN elevations in aminotransferases was 2.0% and with ≥5 × ULN elevations was 0.9% in the risankizumab 360mg SC arm in the All Treated Safety Analysis Set. The majority of enzyme elevations were asymptomatic. For subjects with ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN (potential Hy's law), and for subjects with ALT and AST ≥ 10 and ≥ 20 × ULN, case narratives confirmed alternative aetiologies to risankizumab. No confirmed Hy's law cases were identified.

One borderline case was further explored given the relatively healthy subject (with UC as the main confounding disease) and the normalisation of hepatic enzyme values while on all concomitant medication. The MAH submitted further characterisation of the events of hepatic enzyme increased for the case. Further justification including that the peak serum ALT measurements never exceeded the international consensus criteria for DILI (5 × ULN) and the peak serum AST only just exceeded this threshold was accepted. Other factors such as the timing and character of the liver enzyme elevations also do not strongly indicate a case of Hy's law for this subject.

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

Review of the cumulative data from the risankizumab UC program did not suggest an increase in hypersensitivity events with increased duration of risankizumab treatment. Immunogenicity to risankizumab did not have any clinically relevant impact on hypersensitivity reactions.

No adjudicated anaphylactic reactions were reported in the induction or maintenance period. There was only one serious hypersensitivity event reported in 1 subject in the Any Risankizumab group of the All Treated Safety Analysis Set. This subject experienced a serious hypersensitivity event during Induction Period 2 of Study M16-067 Sub study 1.

For subjects with UC treated with risankizumab at the recommended intravenous induction and subcutaneous maintenance doses (180 mg or 360 mg) for up to 64 weeks in UC clinical trials, treatment-emergent anti-drug antibodies and neutralizing antibodies were detected in 8.9% (8/90) and 6.7% (6/90) for the 180 mg SC dose, or 4.4% (4/91) and 2.2% (2/91) for the 360 mg SC dose, of evaluated subjects, respectively.

Injection site reactions

The percentage and rate of ISRs (including infusion site and infusion-related reactions) were lower in the risankizumab group compared to the placebo group with no infusion-related reactions reported in the risankizumab group during the induction period and higher in the risankizumab arms compared to the placebo arm with no dose-dependent pattern observed between risankizumab arms during the maintenance period. The most frequently reported ISRs in the Any Risankizumab group of the All Treated Safety Analysis Set were injection site erythema, injection site reaction, and injection site pain. None of the ISR events in the Any Risankizumab group were serious, and none led to study drug discontinuation. The majority of ISR events were mild in severity.

Among the subjects in the Any Risankizumab group of the All Treated Safety Analysis Set who had ADA tests available, the percentage of ADA-positive subjects with ISRs was comparable to that of ADA-negative subjects, indicating immunogenicity to risankizumab did not have clinically relevant impact on ISRs.

2.6.8.4. Laboratory findings

Evaluation of mean changes over time and individual subject changes in haematology and clinical chemistry values, as well as PCS abnormalities in haematology and clinical chemistry during induction and maintenance treatment, did not reveal any dose-dependent patterns or any significant safety concerns with risankizumab treatment and were generally similar when compared to placebo.

The decrease in mean platelet counts (31.2×10^9) and increases in mean total cholesterol (8.773 mg/dL) and LDL-C (6.736 mg/dL) from Baseline with risankizumab 1200 mg IV induction treatment were small and not considered to be clinically meaningful. The majority of risankizumab-treated subjects with Grade 3 values in haemoglobin had an associated AE of anaemia. A total of 4 subjects

with Grade 3 haemoglobin values had SAEs of anaemia. All AEs and SAEs of anaemia in subjects with Grade 3 haemoglobin values were assessed as having no reasonable possibility of being related to study drug by the investigator, and none led to study drug discontinuation, anaemia being a common condition related to UC.

There were no clinically meaningful findings in vital sign parameters among risankizumab-treated subjects.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

No clear trends were observed with regard to differences between subgroups in AEs, SAEs, severe AEs, AEs leading to discontinuation, or AEs in ASI categories when evaluated by intrinsic factors, suggesting there was no clinically meaningful interaction between risankizumab treatment and intrinsic factors. In particular, there were no new safety risks attributable to risankizumab identified in subjects ≥ 65 years of age with risankizumab treatment. The data supported an acceptable safety profile of risankizumab in elderly subjects. The safety profile was generally similar between Advanced Therapy-IR and non-Advanced Therapy-IR subjects and consistent with trends observed in the full data sets.

There is a prospective pregnancy exposure registry (Study P23-653) that monitors outcomes in women who become pregnant while treated with risankizumab. The registry will be extended to include patients with UC. Another population-based, non-interventional pregnancy study using electronic health records is planned for patients with CD. Patients with UC will be included in this study (see Section 2.7.2 Pharmacovigilance Plan of the RMP).

2.6.8.7. Immunological events

In subjects who received the proposed IV induction treatment followed by the proposed maintenance regimen of 180 or 360 mg SC q8w, treatment-emergent ADAs and NAbs were detected in 8.9% (8/90) and 6.7% (6/90), and 4.4% (4/91) and 2.2% (2/91) of evaluated subjects, respectively, over 64 weeks of exposure. Treatment-emergent ADAs were reported in low numbers and not associated with meaningful changes in safety. All hypersensitivity reactions events in treatment-emergent ADA positive subjects were mild in severity and none of these events led to treatment discontinuation. All injection and infusion site reactions in treatment-emergent ADA positive subjects were mild in severity.

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

As an anti-IL-23 p19 monoclonal antibody, a theoretical potential exists for risankizumab to indirectly increase the activity/expression of CYP enzymes via the reduction of pro-inflammatory cytokines in patients treated with risankizumab. In a previous drug interaction study conducted in subjects with plaque psoriasis, repeated administration of risankizumab 150 mg SC had no effect on the exposures of probe substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A (Study M16-007). However, given that CD and UC are different diseases with potentially higher inflammatory burden than plaque psoriasis, and that the risankizumab therapeutic doses evaluated in CD and UC are higher than the therapeutic dose in psoriasis, it was considered necessary to conduct a similar drug interaction study at higher risankizumab exposures in subjects with CD or UC.

Results based on Study M19-974 PK data of CYP probe substrates and the relevant metabolites before and after risankizumab administration indicated that risankizumab 1800 mg IV q4w had no clinically relevant impact on the activities of CYPA2, CYP2C9, CYP2D6 or CYP3A. The MAH was requested to discuss whether Risankizumab should be classified as a mild CYP2C19 inducer. There were no deaths, no serious events, and no AEs leading to discontinuation from the study or reported in ASI. No clinically significant vital signs or laboratory measurements were observed during the study. This is discussed in full in Section 2.6.3.

2.6.8.9. Discontinuation due to adverse events

The proportions of subjects with AEs leading to discontinuation of study drug were lower in the risankizumab group compared to the placebo group during the induction period, due to more UC-related events occurring in the placebo group. The event rates were comparable between risankizumab- and placebo-treated subjects during the maintenance period. The overall event rate and pattern of AEs leading to study drug discontinuation was similar in the Any Risankizumab SC group of the All Treated Safety Analysis Set to that observed in the Total Risankizumab group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set.

2.6.8.10. Post marketing experience

The review of the post-marketing reports did not identify new safety risks for risankizumab.

2.6.9. Discussion on clinical safety

The risankizumab UC clinical development programme was designed to evaluate the efficacy and safety of risankizumab in subjects with moderately to severely active UC who were either advanced therapy-IR or non-advanced therapy-IR. A 12-week Phase 3 induction study (Study M16-067 Sub study 2) and a 52-week Phase 3 maintenance study (Study M16-066 Sub study 1) were presented for the pivotal supporting data. Together the pivotal portions of the induction and maintenance studies represent up to 64 weeks of blinded, placebo-controlled assessment of risankizumab. The pivotal studies design and duration are deemed adequate to support the safety analysis of the sought indication.

To assess the safety of risankizumab across the UC development programme, subject data were integrated into multiple safety analysis sets. The first 2 analysis sets provide placebo-controlled assessments of data through 12 weeks of induction and through 52 weeks of maintenance treatment in subjects with clinical response to IV risankizumab induction treatment, respectively.

As of the data cut-off dates (23 January 2023 and 30 March 2023), 1,103 subjects received risankizumab at the proposed induction dose of risankizumab 1200 mg IV for a median exposure of 84.0 days. A total of 344 subjects received at least 12 months of the 180 mg SC regimen and 309 subjects received at least 12 months of the 360 mg SC regimen.

The number of subjects who received at least 1 dose of risankizumab (N = 1,512 with a total 2,220.9 PY of exposure) and who had at least 12 months of exposure to risankizumab (N = 741) included in the safety analyses is consistent with ICH E1 recommendations.

Demographic and baseline characteristics were balanced between arms and consistent with a subject population with moderately to severely active UC.

While no statistical comparisons were presented, observed imbalances were seen between the risankizumab 180 mg and 360 mg SC arms in relation to disease characteristics. Imbalances in disease

characteristics suggested that subjects in the risankizumab 360 mg SC arm may have had disease that was more difficult to treat. These imbalances included a greater proportion of subjects with failure of > 2 advanced therapies, and a lower proportion of subjects with clinical remission at Week 0. The MAH also noted a longer duration of disease in the risankizumab 360 mg SC arm, however, a minimal difference between groups was noted.

Overall, the demographic and baseline characteristics were generally balanced between arms and appropriate for evaluating the safety of risankizumab in the target population of moderate to severe UC.

Adverse events

For TEAEs in both the induction and maintenance periods, the percentages and event rates of subjects with SAEs and severe AEs were lower in the risankizumab arms compared to the placebo arm with no dose-dependent pattern in the maintenance SC arms; this was attributable to events related to underlying disease in the placebo arm.

The SOCs with the most frequently reported AEs were Infections and infestations and Gastrointestinal disorders. The overall pattern of the most frequently reported AEs and study related-AEs were consistent with the known safety profile of risankizumab and the underlying disease. In the 12-Week induction period, the most commonly reported AEs were generally comparable between the risankizumab and placebo groups, except a greater proportion of subjects with AEs of arthralgia and headache in the risankizumab group in the induction study and UC, COVID-19, nasopharyngitis, and arthralgia in the maintenance study. Study related AEs were consistent with the known safety profile of risankizumab and known conditions associated with UC.

In the 12-Week induction period, a lower proportion of subjects in the risankizumab group had severe AEs compared to subjects in the placebo group. Severe AEs were most frequently reported in the SOC of Blood and lymphatic disorders in the risankizumab group (0.9% of subjects). The most common severe AE was anaemia in the risankizumab group (0.9% of subjects).

In the 52-Week maintenance period, severe AEs were most frequently reported in the SOCs of Infections and infestations in the Total Risankizumab group (1.0% of subjects). The proportions of subjects with severe AEs were lower in the risankizumab arms (3 subjects [1.6%] in the risankizumab 180 mg SC arm and 6 subjects [3.1%] in the risankizumab 360 mg SC arm) compared with the placebo arm (10 subjects [5.1%]). No clear dose-dependent pattern was observed for severe AEs.

Trends in the *All Treated Safety analysis Set* were comparable to those reported in the 12-Week Induction period and the 52-Week maintenance period with no apparent dose-dependent pattern with the exception of, the event rate of severe AEs in the Any Risankizumab SC group of the All Treated Safety Analysis Set (6.0 E/100 PY) was higher than that observed in the Total Risankizumab group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set (2.8 E/100 PY). No discernible differences were noted by SOC or PT. The MAH was requested to present and provide a brief summary to characterise the severe AEs in the Any Risankizumab SC group of the All Treated Safety Analysis Set (6.0 E/100 PY) versus the Total Risankizumab group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set (2.8 E/100 PY). The MAH described event rates mainly related to UC disease as rationale for differences seen in event rate of severe AEs reported in the Any Risankizumab SC group of the All Treated Safety Analysis Set versus the Total Risankizumab group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set. This rationale was acceptable to the CHMP.

Adverse drug reactions

The method of analysis for ADRs was adequately described. Overall, no new ADRs were identified by the MAH in subjects with UC treated with risankizumab 1200 mg IV and risankizumab 180 mg and 360mg SC.

In the Placebo-Controlled 12-Week Induction Period Safety Analysis Set, headache and folliculitis were determined to be ADRs for patients with moderate to severe UC during induction treatment (headache: 3.1% in the risankizumab group and 2.5% in the placebo group; folliculitis: 0.4% in the risankizumab group and 0.3% in the placebo group).

Eczema (0.4% in the risankizumab group and 0.0% in the placebo group), and rash (1.7% in the risankizumab group and 0.4% in the placebo group) were determined to be ADRs for patients with moderate to severe UC during the 12-Week induction treatment. These events were previously identified as ADRs based on post-marketing experience. Rash is reflected as ADR with a frequency common in the SmPC Section 4.8. The PTs for the grouped term “Rash” are “Under Hypersensitivity SMQ Narrow, any PTs that contain rash”. In the 52-Week maintenance period, eczema was reported for 1.8% in the Total Risankizumab group and 1.5% in the placebo arm, and rash was reported for 2.3% in the Total Risankizumab group and 1.5% in the placebo arm. The MAH clarified how eczema is categorised/grouped and proposed to include a new ADR of “eczema” frequency “common” as an addition to SmPC Section 4.8. Based on the data presented, the addition of eczema as an ADR is accepted by the CHMP for the UC population. The MAH confirmed that the frequency of “common” can be applied to all indications based on the assessment of the frequency of eczema observed across indications.

In the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set, fatigue, injection site reactions, and tinea infections were determined to be ADRs and occurred at higher rates for subjects who received risankizumab compared to subjects who received placebo during the 52-week maintenance treatment.

Deaths

Three deaths were reported in the Phase 3 UC studies, all in subjects treated with risankizumab. AEs leading to deaths in subjects being treated with risankizumab were: COVID-19 pneumonia, adenocarcinoma of the colon (this condition existed prior to the subject entering the induction study), and haemorrhage intracranial.

The event of COVID-19 pneumonia was considered by the investigator to have a reasonable possibility of being related to study drug, while the other 2 events were considered by the investigator to have no reasonable possibility of being related to study drug. None of the fatal AEs were considered by MAH to have a reasonable possibility of being related to study drug. The MAHs assessment is accepted.

SAEs

Overall, the proportion of subjects with SAEs in the risankizumab groups were lower than that of subjects in the placebo group, predominantly due to fewer SAEs related to underlying disease in the risankizumab group.

SAEs were most frequently reported in the Risankizumab safety sets in the SOCs of Infections and infestations and Blood and lymphatic system disorders. For subjects in the placebo group, SAEs were most frequently reported in the SOC of Gastrointestinal disorders. The most frequently reported SAE was anaemia in the risankizumab IV group, colitis ulcerative, appendicitis, and renal colic in the Risankizumab SC groups and colitis ulcerative in the placebo group. The higher event rate of SAEs of colitis ulcerative in the placebo group compared with the risankizumab group likely reflects the underlying disease.

No discernible pattern was found on analysis of SAEs in terms of relatedness and discontinuations in the Risankizumab arms within the 12-Week induction set and the 52-Week maintenance set. The overall event rates of SAEs and the types of SAEs in the Any Risankizumab SC group of the All Treated Safety Analysis Set (8.2 E/100 PY) were similar to those observed in the Total Risankizumab group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set (6.1 E/100 PY).

An imbalance was noted in the SAE pulmonary embolism, a total of 6 subjects in the Any Risankizumab group of the All Treated Safety Analysis Set had SAEs of pulmonary embolism compared to 1 subject in the placebo IV/SC (risankizumab-naïve) group. For 4 risankizumab treated subjects, the events of pulmonary embolism did not lead to study drug discontinuation; the other 2 subjects discontinued study drug due to pulmonary embolism. For 4 risankizumab treated subjects, the events were considered unrelated to study drug by the investigator. The MAH assessed all pulmonary embolism events to be unrelated to study drug due to medical histories of VTE or known baseline risk factors for pulmonary embolism (e.g., obesity, former smoker, older age, or UC itself [which has an associated increased risk of VTE]). Overall, the incidence rate of pulmonary embolism in the Any Risankizumab group was 0.3/100 PY compared to 0.7/100 PY in the placebo IV/SC (Risankizumab naïve) group. The MAH's presentation of the cases of pulmonary embolism in the context of UC and underlying risk factors was acknowledged by the CHMP. The CHMP considered that the relatedness assessment of the MAH was reasonable, and the issue was not further pursued by the CHMP.

AESI

During the induction period and maintenance period, the percentages and event rates of AEs in the AESI categories were generally comparable between the risankizumab and placebo groups.

Notable differences reported in the 12-Week Induction period include lower percentages and event rates of hepatic events and ISRs in the risankizumab group compared to placebo group and a higher event rate of hypersensitivity reactions in the risankizumab group compared to the placebo group.

Notable differences reported in the 52-Week Maintenance period included rates of hypersensitivity AEs, which were higher in the risankizumab 180 mg SC arm, and rates of hepatic events, which were higher in the risankizumab 360 mg SC arm. The event rates of ISRs were similar in the risankizumab treatment arms and higher than the placebo arm.

MACE

No events of adjudicated MACE or adjudicated extended MACE were reported in the Risankizumab arms in the induction or maintenance period. A total of 3 subjects (incidence rate: 0.1/100 PY) in the Any Risankizumab group had an adjudicated MACE. One case resulted in death (haemorrhage intracranial) and 2 of the subjects with an adjudicated MACE had cardiovascular risk factors. The incidence rate of MACE in the Any Risankizumab group was not higher than the rate in the general UC population based on the literature.

Infections

The rate of infections in the pooled data from the 12-week induction study was 78.3 events per 100 subject years in subjects treated with risankizumab 1 200 mg intravenously compared to 74.2 events per 100 subject years in placebo. The rate of serious infections was 3.0 events per 100 subject-years in subjects treated with risankizumab 1 200 mg intravenously compared to 5.4 events per 100 subject years in placebo.

The rate of infections in the 52-week maintenance study was 67.4 events per 100 subject years in subjects treated with risankizumab 180 mg subcutaneously and 56.5 events per 100 subject years in subjects treated with risankizumab 360 mg subcutaneously after risankizumab induction compared to 64.6 events per 100 subject years in subjects who received placebo after risankizumab induction. The

rate of serious infections was 1.1 events per 100 subject-years in subjects treated with risankizumab 180 mg subcutaneously and 0.6 events per 100 subject-years in subjects treated with risankizumab 360 mg subcutaneously after risankizumab induction compared to 2.3 events per 100 subject years in subjects who received placebo after risankizumab induction.

The percentages of subjects with infection AEs and serious infections were comparable between the risankizumab 1200 mg IV group and the placebo group during the induction period, and the percentages and event rates of infections and serious infections were comparable between each risankizumab arm and the placebo arm during the maintenance period, with no apparent dose dependent pattern between the risankizumab 180 mg and 360 mg SC arms.

In the induction and maintenance periods, the most common infections were COVID-19 and nasopharyngitis in risankizumab-treated subjects. In the induction period, 5 serious infections (abscess limb, COVID-19, COVID-19 pneumonia, large intestine infection, and pneumonia) were reported in 1 subject each. In the maintenance period, 3 serious infections (appendicitis in 2 subjects and gastroenteritis viral in 1 subject) were reported in the Total Risankizumab group.

The majority of infection events in the Any Risankizumab group of the All Treated Safety Analysis Set were non-serious, mild or moderate in severity, and few events led to discontinuation of study drug. The most frequently reported serious infections were COVID-19, appendicitis, and anal abscess in the Any Risankizumab group.

The incidence rate of serious infections (2.2/100 PY) in the Any Risankizumab group of the All Treated Safety Analysis Set was not higher than the rate based on published estimates for IBD patients treated with anti-TNF agents (8/100 PY)23 or ustekinumab (3.19/100 PY).

Based on this review of the risankizumab IV doses in induction as well as both risankizumab SC doses in long-term maintenance therapy, the character and types of infection were consistent with the identified ADRs for the Crohn's population. Serious infections are identified as an important potential risk in the RMP.

Across the UC clinical development programme, a total of 8 events of opportunistic infection (excluding TB and herpes zoster) were reported in 8 subjects. Opportunistic infections included CMV infection in 4 subjects, and oral fungal infection, oral herpes zoster, Aeromonas infection, and eczema herpeticum in 1 subject each. CMV infection was the only serious opportunistic infection and serious CMV infection occurred in 2 subjects.

No events of active TB were reported in the risankizumab UC clinical programme. Among subjects with latent TB who were treated with risankizumab, there was no evidence of an increased risk of developing active disease. The incidence rate of herpes zoster in the Any Risankizumab group of the All Treated Safety Analysis Set (0.9/100 PY) was within the expected range for this patient population (1.36/100 PY) (Singer 2023[7]). Overall, the data did not suggest an increased risk of herpes zoster with risankizumab treatment in subjects with UC.

Overall, the reported opportunistic infections, including TB and herpes zoster, were consistent with the expected range for the UC population and the known safety profile of risankizumab.

Malignancies

Across the risankizumab UC clinical development programme, a total of 19 malignancies were reported for 16 subjects in the Any Risankizumab group (All Treated Safety Analysis Set), of which 12 were serious. No malignancies of colorectal cancer were reported as related in subjects with risankizumab

[7] SINGER, David, THOMPSON-LEDUC, Philippe, GUPTA, Deepshekhar, et al. Incidence and risk of herpes zoster in patients with ulcerative colitis and Crohn's disease in the USA. Gastroenterology Report, 2023, vol. 11, p. goad016.

exposure. Most malignancies in risankizumab-treated subjects led to study drug discontinuation and were assessed by the investigator and MAH to have no reasonable possibility of being related to study drug. Most risankizumab-treated subjects with malignancies had relevant risk factors, relevant medical history, or the time to onset suggested an incompatible temporal relationship with risankizumab. The types of malignancies most frequently reported in the UC programme (e.g., basal cell carcinoma [NMSC] and thyroid cancer) were consistent with the most common malignancies reported in either the general population or in the UC population. No safety concern was identified with regards to malignancies in subjects with UC exposed to risankizumab. Malignancies are identified as an important potential risk in the RMP.

Hepatic Disorders

The inclusion/exclusion criteria and discontinuation criteria of the risankizumab Phase 3 studies were adequate to screen for hepatic events. No evidence of hepatotoxicity was observed with risankizumab administration in animal studies.

In the placebo-controlled 52-week maintenance period safety analysis set, there were no serious hepatic events across treatment arms, and all hepatic events were mild or moderate in severity. No hepatic events led to study drug discontinuation except for an AE of liver function test increased in 1 subject in the risankizumab 360 mg arm who met potential Hy's law criteria discussed above. A review of this case concluded it did not meet the criteria for Hy's Law and the event is unlikely related to risankizumab treatment.

In the 360 mg arm, the majority of hepatic events (17 of 19 events) were isolated liver test increases; the remaining 2 hepatic events which were not reported as liver test increases were mild hepatitis acute (erroneously reported and later corrected and removed) and mild hepatic steatosis.

Of the 17 events related to increases in liver chemistries in the risankizumab 360 mg SC group, 13 events were alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) increases reported in 7 subjects. Further review of these events revealed the majority of events were mild (10 mild and 3 moderate), asymptomatic (12 events), resolved spontaneously on continued risankizumab treatment (12 events) with no clinically significant increase in ALT or AST (≥ 3 × ULN) (11 events), and were assessed by the investigator as having no reasonable possibility of being related study drug (10 events). One event of liver function test increased that led to study drug discontinuation was related to the borderline Hy’s law case discussed above. Of these 13 events of ALT and/or AST elevations, 3 events of ALT increased, and 3 events of AST increased were reported from a single subject who experienced infection that had compatible temporal relationship with liver enzyme increases. All 6 events were considered as unrelated to study drug per the investigator.

The other 4 of 17 events related to increases in liver chemistries were blood bilirubin increased reported in 4 subjects (2 subjects with Gilbert's syndrome) without accompanying elevations in ALT or AST. All 4 AEs were non-serious, mild or moderate in severity, and assessed by the investigator as having no reasonable possibility of being related to study drug. All 4 subjects continued to receive study drug.

While the numbers overall were low, a dose-dependent trend was further discussed based on the differences seen in the proposed posology of risankizumab 360mg SC compared to the placebo arms. A review of hepatic AEs and laboratory data did not identify any severe or serious safety concerns with regard to hepatic disorders with risankizumab treatment in subjects with UC. The MAH was requested to consider the addition of hepatic enzymes increased to the known ADRs mainly based on the disproportionally higher frequency compared to the placebo-treated subjects to the risankizumab 360mg SC arm. As rationalised by the MAH, the totality of the evidence does not strongly support an addition of hepatic enzymes increased as an ADR to the Risankizumab safety profile and further review

of all cases with ≥ 3 × ULN ALT/AST elevations in subjects treated with risankizumab revealed alternate aetiologies, or the temporality of hepatic enzyme elevations was incompatible with risankizumab treatment, or the increases reversed despite continuous risankizumab treatment. This is agreed by the CHMP.

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

Review of the cumulative data from the risankizumab UC programme did not suggest an increase in hypersensitivity events with increased duration of risankizumab treatment. Immunogenicity to risankizumab did not have any clinically relevant impact on hypersensitivity reactions.

No adjudicated anaphylactic reactions were reported in the induction or maintenance period. There was only one serious hypersensitivity event reported in 1 subject in the Any Risankizumab group of the All Treated Safety Analysis Set. This subject experienced a serious hypersensitivity event. While the temporal relationship is not convincing for relatedness to risankizumab, no alternative aetiology was proposed. Upon the CHMP's request, the MAH agreed to update the existing warning in the SmPC Section 4.4 on Hypersensitivity (addition in bold): "If a serious hypersensitivity reaction, **including anaphylaxis**, occurs, administration of risankizumab should be discontinued immediately and appropriate therapy initiated". Serious hypersensitivity reactions is an important potential risk and pharmacovigilance activities are planned to further characterise this risk (see Section 2.7.2 Pharmacovigilance Plan of the RMP)).

Injection site reactions

The percentage and rate of ISRs (including infusion site and infusion-related reactions) were lower in the risankizumab group compared to the placebo group with no infusion-related reactions reported in the risankizumab group during the induction period and higher in the risankizumab arms compared to the placebo arm with no dose-dependent pattern observed between risankizumab arms during the maintenance period. The most frequently reported ISRs in the Any Risankizumab group of the All Treated Safety Analysis Set were injection site erythema, injection site reaction, and injection site pain. None of the ISR events in the Any Risankizumab group were serious, and none led to study drug discontinuation. The majority of ISR events were mild in severity.

Among the subjects in the Any Risankizumab group of the All Treated Safety Analysis Set who had ADA tests available, the percentage of ADA-positive subjects with ISRs was comparable to that of ADA-negative subjects, indicating immunogenicity to risankizumab did not have clinically relevant impact on ISRs.

Laboratory findings and vital signs

Evaluation of mean changes over time and individual subject changes in haematology and clinical chemistry values, as well as potentially clinically significant abnormalities in haematology and clinical chemistry during induction and maintenance treatment, did not reveal any dose-dependent patterns or any significant safety concerns with risankizumab treatment and were generally similar when compared to placebo. There were no clinically meaningful findings in vital sign parameters among risankizumab-treated subjects.

Special populations

The following subgroups were examined: age, sex, weight, race, geographic region, number of prior biologics failed, Advanced Therapy-IR status, baseline corticosteroid use, and baseline immunosuppressant use.

There were no new safety risks attributable to risankizumab identified in subjects ≥ 65 years of age with risankizumab treatment. The safety profile was generally similar between Advanced Therapy-IR and non-Advanced Therapy-IR subjects.

There is a prospective pregnancy exposure registry that monitors outcomes in women who become pregnant while treated with risankizumab. The registry will be extended to include patients with UC (see Section 2.7.2 Pharmacovigilance Plan of the RMP). Another population-based, non-interventional pregnancy study using electronic health records is planned for patients with CD. Patients with UC will be included in this study (see Section 2.7.2 Pharmacovigilance Plan of the RMP).

Immunogenicity

Treatment-emergent ADAs (positive/negative or titre) were in line with the known safety profile for hypersensitivity reactions and injection and infusion site reactions of risankizumab.

The proportions of subjects with AEs leading to discontinuation of study drug were lower in the risankizumab group compared to the placebo group during the induction period, due to more UC-related events occurring in the placebo group. The event rates were comparable between risankizumab and placebo-treated subjects during the maintenance period. The overall event rate and pattern of AEs leading to study drug discontinuation was similar in the Any Risankizumab SC group of the All Treated Safety Analysis Set to that observed in the Total Risankizumab group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set.

For subjects with UC treated with risankizumab at the recommended intravenous induction and subcutaneous maintenance doses (180 mg or 360 mg) for up to 64 weeks in UC clinical trials, treatment-emergent anti-drug antibodies and neutralizing antibodies were detected in 8.9% (8/90) and 6.7% (6/90) for the 180 mg SC dose, or 4.4% (4/91) and 2.2% (2/91) for the 360 mg SC dose, of evaluated subjects, respectively. This is adequately reflected in the SmPC Section 4.8.

Injection site reaction is listed as an ADR in SmPC Section 4.8 under the frequency common. The footnote in the table ADR is updated to mention that injection site reactions include infusion site erythema, extravasation, reaction, swelling.

The review of the post-marketing reports did not identify any new safety risks for risankizumab.

2.6.10. Conclusions on the clinical safety

The safety profile of risankizumab in the UC population was consistent with the known safety profile of the product in the CD population. Eczema was added to the SmPC Section 4.8 as ADR under the frequency common.

2.7. Risk Management Plan

2.7.1. 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 • Long-term safety

2.7.2. 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 Patients with Psoriasis in Real World Setting/Ongoing	Estimate the risks of the following events in individuals with psoriasis exposed to risankizumab relative to individuals with psoriasis (including patients with arthropathic psoriasis [PsA]) exposed to other systemic psoriasis treatments: i) TNF-α inhibitors; ii) other IL inhibitors; and iii) non-biological systemic treatments: • overall malignancy excluding NMSC • NMSC	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	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		- End of data collection (incl. data up to December 2032): December 2033 - Final report of study results: December 2034	

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
P16-751: Pregnancy Exposures and Outcomes in Women with Psoriasis Treated with Risankizumab: A Cohort Study Utilizing Large Electronic Healthcare Databases with Mother-Baby Linkage in the United States/Ongoing	The specific objectives of this study are to: - Evaluate the rate of major congenital malformations in infants born to women exposed to risankizumab during pregnancy compared to those exposed to other systemic treatments (primary outcome for sample size estimation). - Evaluate and compare pregnancy outcomes (i.e., live birth, spontaneous abortion, elective abortion, stillbirth) among women exposed to risankizumab versus comparators during pregnancy - Assess and compare infant outcomes (neonatal deaths, serious infections up to 1 year of age) among infants born to women exposed to risankizumab during pregnancy compared to those exposed to other biologic treatments.	Missing information on the use during pregnancy.	- Estimated start of data collection (when Q2 2019 data become available): Q1 2021 - Study progress: 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).

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
P23-653: Pregnancy Exposure and Outcomes for Women with Crohn's Disease Treated with Risankizumab/Planned AbbVie proposes to add the UC study population to planned Study P23-653 once the study protocol has been approved for CD and procedure MEA009 has concluded.	The clinical trial programs did not assess the safety of risankizumab use during pregnancy. In addition to the study of risankizumab exposure in psoriasis patients, a study of pregnancy outcomes in patients with Crohn's disease who are exposed to risankizumab, compared to alternative biologic treatments, will be conducted. A comparative cohort study will be conducted to describe risankizumab exposure in pregnant patients with Crohn's disease, and compare pregnancy and infant outcomes to pregnant patients with Crohn's disease who were treated with alternative therapies (e.g., biologics). In addition, descriptive analyses of pregnancy outcomes in patients with Crohn's disease without exposure to any treatments under investigation will also be conducted.	Missing information: use during pregnancy.	- Final protocol submitted to EMA: Q1 2023 - Start data collection period: Q2 2024 - Progress report: Q3 2027 - End data collection period: Q3 2031 - Final report: Q1 2032	Final report: Q1 2032
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	Final Report Q4 2024	Final Report Q4 2024

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
P23-654: Long-Term Comparative Cohort Study in Patients with Crohn's Disease in a Real World Setting/Planned **AbbVie proposes to add the UC study population to planned Study P23-654 once the study protocol has been approved for CD and procedure EMEA/H/C/004759/MEA/010 has concluded.**	The clinical trial program was not able to fully characterize the safety profile of risankizumab in the Crohn's disease populations. Additional long-term data are needed from the real-world experience of patients with Crohn's disease treated with risankizumab to assess product potential risks. A comparative cohort study will be conducted to estimate rates of malignancy (malignancy excluding NMSC, NMSC), serious infections, serious hypersensitivity reactions, and MACE in risankizumab treated patients with Crohn's disease, relative to alternative systemic therapies (e.g., biologics).	Potential risks of malignancies, serious infections, serious hypersensitivity reactions, and MACE. Missing information: long-term safety	- Start data collection period: Q4 2024 - Interim report: Q4 2029 - End data collection period: Q4 2032 - Final report: Q2 2034	Final report: Q2 2034
M16-011: A Phase 3, Randomized, Double-Blind, Study Comparing Risankizumab to Placebo in Subjects with Active Psoriatic Arthritis (PsA) Who Have a History of Inadequate Response to or Intolerance to at Least One Disease Modifying Anti-Rheumatic Drug (DMARD) Therapy (KEEPsAKE 1)/ Ongoing	The primary objective of the open-label Period 2 of Study M16-011 is to evaluate the long-term safety, tolerability and efficacy of risankizumab 150 mg in subjects with psoriatic arthritis who have completed the double-blind period.	Potential risks of malignancies, MACE, serious infections and serious hypersensitivity reactions Missing information: long-term safety	Final report Q3 2025	Final report Q3 2025

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
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	Final report Q3 2025

2.7.3. Risk minimisation measures

No additional risk minimisation measures.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 5.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the 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.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Skyrizi 30 mg solution for injection in cartridge. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

UC is a serious disease. The onset of UC is most common between 15 and 40 years of age, with a second peak in incidence between 50 and 80 years. The disease affects men and women at similar rates.

Symptoms include diarrhoea, rectal bleeding, abdominal pain and bowel movement urgency. UC is a relapsing-remitting course, meaning that many patients have intermittent disease flares that are interspersed with periods of remission.

Extra-intestinal complications include arthritis, dermatological conditions, uveitis, and primary sclerosing cholangitis.

The most severe intestinal manifestations of UC are toxic megacolon and perforation.

The precise aetiology of UC is not well understood. A current hypothesis suggests that primary dysregulation of the mucosal immune system leads to an excessive immunologic response to normal microflora in a genetically susceptible host, finally leading to chronic intestinal inflammation.

A systematic review of studies evaluating the worldwide incidence and prevalence of inflammatory bowel disease reported that the prevalence rates for UC were:

- 140 to 286 per 100,000 persons in North America
- 2.4 to 505 per 100,000 persons in Europe
- 4.6 to 57.3 per 100,000 persons in Asia
- 4.7 to 44.3 per 100,000 persons in South America, and
- 10.6 per 100,000 persons in Africa (Ng et al. 2017[8]).

Diagnosis is based on symptoms using supportive evidence from an endoscopy, tissue biopsy and negative stool examination, while ruling out infectious disease.

3.1.2. Available therapies and unmet medical need

Medical therapeutic decisions for UC are categorised into those for (a) induction and (b) maintenance, with a goal of obtaining and maintaining steroid-free remission.

Treatment goals in UC include induction of remission (typically within a 6-to-12-week time frame) and maintenance of remission in the longer term (assessed over 52 weeks of continuous treatment in clinical trials). In both clinical practice and in clinical trials, clinical response and clinical remission are assessed by a combination of endoscopy (improvement in the endoscopic appearance of the mucosa and healing of ulcers) and patient-reported outcomes, including a reduction in stool frequency (SF) and a resolution of RB (Levesque et al. 2015[9]). Control of intestinal inflammation in UC is also associated

[8] NG, Siew C., SHI, Hai Yun, HAMIDI, Nima, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. The Lancet, 2017, vol. 390, no 10114, p. 2769-2778.
[9] LEVESQUE, Barrett G., SANDBORN, William J., RUEL, Joannie, et al. Converging goals of treatment of inflammatory bowel disease from clinical trials and practice. Gastroenterology, 2015, vol. 148, no 1, p. 37-51. e1.

with a reduction in the risk of hospitalisation, colectomy, and in the longer term, UC associated dysplasia and colorectal cancer.

There are no known preventative medical therapies available.

Medications used for the treatment of UC include 5-aminosalicylic acid (5-ASA)–containing medications (sulfasalazine, mesalazine, balsalazide, olsalazine), corticosteroids, immunomodulators such as AZA and 6-MP and biologic medications.

A significant proportion of patients with moderately to severely active UC may have an inadequate response to medicines such as 5-ASAs or corticosteroids, be unable to maintain a clinical response to 5-ASAs or AZA or be unable to discontinue corticosteroids without a relapse in disease activity (reviewed in Dignass et al. 2012). Many of these patients require additional treatment with the next line of therapy, which could include medical treatment with a biologic medication or surgical treatment with a colectomy.

Biologics, including antitumor necrosis factor (TNF) antibodies (infliximab, adalimumab, golimumab) and vedolizumab, an anti-α4β7 integrin antibody, are indicated for the treatment of UC in patients who fail to respond to, have an inadequate response to, or are intolerant to other medications used in the treatment of UC medications and as a first-line treatment for UC in selected patients.

Approximately 40% to 50% of patients with moderately to severely active UC fail treatment with current biologic or small-molecule therapies in the first year of treatment. Therefore, there is a clear medical need for additional therapeutic options in UC for subjects with inadequate response to or intolerance to conventional therapies and biologic therapies.

3.1.3. Main clinical studies

To support the demonstration of efficacy of risankizumab in the treatment of patients with moderate to severe UC, the MAH has submitted the results of a phase 2b/3 randomized double-blind 12-week placebo-controlled induction study (M16-067) and a randomized double-blind 52-week placebo-controlled maintenance study (M16-066).

Study M16-067 comprised 2 pivotal sub studies. Sub study 1 was a 4-arm randomized double-blind placebo-controlled dose finding study designed to investigate the efficacy of three doses of the product over placebo. The doses investigated were 600 mg IV Q4W, 1200 mg IV Q4W, and 1800 mg IV Q4W.

The primary endpoint of the study was the rate of clinical remission at week 12, as assessed by the adapted Mayo score. Secondary endpoints included endoscopic improvement, endoscopic remission, and clinical response as defined by way of relevant symptom scores.

Subjects who had moderate to severe UC who had failed to achieve clinical response to either advanced or conventional therapies were eligible to be recruited to the trial. Advanced therapies included biological medicinal products and JAK inhibitors.

Immunogenicity was assessed using a tiered approach.

Sub study 2 was a follow on 12-week double-blind placebo-controlled induction study using the dose that was determined to be most effective following the analysis of results of sub study 1. The design of sub study 2 was similar to that for sub study 1. The primary endpoint was also clinical remission at week 12 as assessed by the adapted Mayo score. Secondary endpoints were similar to those in sub study 1.

Patients entering sub study 2 were randomized to receive either placebo or risankizumab 1200 mg IV Q4W.

Patients who achieved a clinical response in the induction study were entitled to enter the maintenance study M16-066. Patients who failed to achieve a clinical response at week 12 were entitled to enter a reinduction phase consisting of randomized allocation to either risankizumab 1800 mg IV Q4W, risankizumab 180mg SC Q8W, or risankizumab 360mg SC Q8W in a blinded double dummy design, with assessment of response occurring at week 24. Patients who achieved a clinical response to re induction at week 24 were entitled to enter the maintenance study although only patients who received IV treatment were randomized. Patients who received SC therapy during the reinduction phase remained on their allocated dose in a blinded manner.

Study M16-066 was a randomized double-blind placebo-controlled 52-week maintenance study. Three treatment arms were assessed in this study and patients were randomized to receive either risankizumab 180mg SC Q8W, risankizumab 360mg SC Q8W, or placebo.

The primary endpoint of the study was the rate of clinical remission at week 52, as assessed by the adapted Mayo score. Secondary endpoints included endoscopic remission, endoscopic response, and clinical response as defined by relevant symptom scores as before. Subgroup analysis conducted on the primary endpoint included prior advanced or conventional therapy, age, sex, geographical region, and prior immunosuppressant use.

In the maintenance study, patients who experienced a loss of clinical effect were entitled to receive up to 2 doses of rescue treatment, comprising of risankizumab 1200mg IV followed by risankizumab 360mg SC Q8W.

3.2. Favourable effects

Results of sub study 1 of induction study M16-067 indicated that all 3 doses studied were superior to placebo at inducing clinical remission in patients with moderate to severe UC (11.5%, 9.8%, and 12.4% for the 600mg, 1200mg, and 1800mg arms respectively, versus 1.7% for placebo).

The results of the analysis of the primary efficacy endpoint in sub study 2 of the 12 week induction study M16-0667 indicated that risankizumab 1200mg IV Q4W was superior to placebo, inducing clinical remission in patients with moderate to severe UC at a statistically significantly greater rate than in patients who received placebo (responder rates for treatment and placebo being 20.3% versus 6.2% respectively). The results of the secondary efficacy analyses supported this conclusion, the majority of which showed a statistically significant difference over placebo for all the key secondary efficacy endpoints. The results of the subgroup analyses were also supportive.

The study protocol allowed for patients who had failed to achieve a satisfactory clinical response at week 12 to receive re-induction therapy with either risankizumab 1200mg Q4W, risankizumab 180mg SC Q8W, or risankizumab 360mg Q8W in a double blinded and randomized manner. The results from the second induction period for patients who had failed to achieve a satisfactory response by Week 12 suggested that the clinical response rates were similar across the three arms with risankizumab 1200mg Q4W, risankizumab 180mg SC Q8W, or risankizumab 360mg Q8W showing clinical response rates of 50%, 56.3%, and 57.1% respectively. In addition, subjects with inadequate improvement in disease activity after induction were more likely to achieve the desired therapeutic effect when treated with the higher 360mg maintenance dose at Week 52, while for subjects with greater improvement after induction, the 180 mg dose may be adequate. As such, patients who failed to achieve a clinical response at Week 12 should proceed to maintenance therapy with the aim of achieving a satisfactory clinical response by Week 24. This is adequately reflected in SmPC Section 4.2.

A statistically significant difference in the rates of mucosal improvement was seen between treatment and placebo groups at week 12 (24.5% vs 7.7% respectively).

A statistically significant rate of mucosal remission was also seen between the treatment and placebo groups at week 12 (6.3% vs 0.6% respectively)

A statistically significant rate of clinical response per adapted Mayo score was seen between the treatment and placebo groups at week 12 (64.3% vs 35.7% respectively).

A statistically significant rate of endoscopic improvement was seen between the treatment and placebo groups at week 12 (36.5% vs 12.1% respectively).

In the 52-week maintenance study M16-066, the results of the analysis of the primary efficacy endpoint showed a statistically significantly improved rate of clinical remission in patients who received either risankizumab 180mg SC Q8W or risankizumab 360mg SC Q8W when compared to the rate of clinical remission seen in patients who received placebo. The results of the primary analysis showed that patients receiving either the 180mg or the 360mg dose had a higher rate of maintenance of clinical remission (40.2% and 37.6% respectively) than in patients receiving placebo (25.1%), and that these differences over placebo were statistically significant after adjusting for multiplicity at the 2.5% level.

Results for the risankizumab 180 mg and 360 mg SC arms were numerically better and showed greater clinical improvement compared to placebo for all secondary endpoints, with endoscopic improvement, HEMI, endoscopic remission, and corticosteroid-free clinical remission at Week 52, meeting statistical significance for both doses. Additionally, the risankizumab 180 mg SC arm demonstrated statistically significant differences compared to placebo for the secondary endpoints of clinical remission per Adapted Mayo Score at Week 52 in subjects with clinical remission at Week 0, no bowel urgency at Week 52, and no abdominal pain at Week 52.

In the maintenance study, patients who experienced a loss of clinical effect were entitled to receive up to 2 doses of rescue treatment, comprising of risankizumab 1200mg IV followed by risankizumab 360mg SC Q8W. Overall, 11.7% (20/179) patients who received risankizumab 180mg required rescue treatment, and had Week 52 data collected of whom 17 (85%) later achieved clinical response as defined. In contrast, 18.9% (35/186) patients who received risankizumab 360mg required rescue therapy and had Week 52 data collected of whom 26 (74.3%) achieved a clinical response. This compares to 68.2% and 62.3% of patients in the 180mg and 360mg arms respectively who achieved a clinical response in the overall analysis of that secondary endpoint.

There was a statistically significant improvement in the rates of mucosal improvement seen in patients receiving either Risankizumab 180 mg SC or Risankizumab 360 mg SC than in patients receiving placebo (42.8%, 42.2%, and 23.5% respectively).

There was a statistically significant improvement in the rates of clinical remission seen in patients with no corticosteroid use in 90 days receiving either Risankizumab 180 mg SC or Risankizumab 360 mg SC than in patients receiving placebo (39.6%, 37.1%, and 25.1% respectively).

There was a statistically significant reduction in reports of bowel urgency in patients receiving Risankizumab 180 mg SC versus those receiving placebo (53.6% vs 31.1%).

3.3. Uncertainties and limitations about favourable effects

Induction study M16-067

In Sub study 1 of Study M16-067, the results of the primary efficacy analysis did not show that there were any marked differences between the doses over placebo (11.5% 9.8%, and 0.3% for risankizumab 600mg IV Q4W, risankizumab 1200mg IV Q4W. and risankizumab 1800mg IV Q4W respectively) that would clearly indicate the superiority of one dose over another. As such, it was

initially unclear from an efficacy perspective why the 1200mg dose was chosen as the dose carried forward into Sub study 2 of the induction study. The MAH clarified that the decision to proceed with the 1200mg IV infusion dose was based on both the clinical efficacy evidence, as well as the exposure/response modelling, the totality of which supported the 1200mg dose over the alternative options. This was accepted by the CHMP.

In the second re-induction period, there were different response rates seen between the treatment arms with respect to the achievement of clinical remission, with risankizumab 1200mg IV Q4W, risankizumab 180mg SC W8W, or risankizumab 360mg Q8W achieving rates of 8.8%, 12.7% and 15.7% respectively. The MAH was requested to consider a re-induction instead of recommending to proceed directly to maintenance therapy for patients who did not achieve a clinical response. The MAH clarified that, as the response to the maintenance arms was equivalent to that of the IV reinduction arm, there was no benefit in choosing IV reinduction over proceeding directly to maintenance. This was agreed by the CHMP.

Maintenance study M16-066

The results of the primary efficacy analysis in the 52-week maintenance study M16-066 showed that clinical remission was lower in patients who received risankizumab 360mg SC Q8W than in patients who received the 180mg SC dose.

Patients who had experienced treatment failure following advanced therapies (defined as one or more of the approved biologics, JAK inhibitors for UC, and/or S1P receptor modulators) who received the higher maintenance dose of 360mg SC had a lower rate of maintenance of clinical remission than patients receiving the 180mg dose (29.5% versus 36.6%). Moreover, the 95% CI of the point estimate for the differences in the rates of maintenance of clinical remission in patients receiving 360 mg versus that seen in patients receiving placebo crossed zero (-4.1 – 16.7), suggesting that no significant differences were seen in the rates of maintenance of clinical emission seen between those two groups. The MAH clarified that the proportion of patients who had either failed to achieve a clinical response with advanced therapies, or had previously failed a greater number of therapies was greater in the 360mg arm than in the 180mg arm. Given that patients with prolonged or more severe disease are likely to be represented in these two cohorts, and that such patients are also more likely to have structural bowel changes related to their disease, the MAH considered reasonable to anticipate that such patients would have a lower response to anti-inflammatory therapies. To support this, the MAH conducted additional post-hoc analyses stratified according to the number of prior failed therapies. These analyses showed a similar outcome between the 360mg and 180 mg arms. In addition, in the cohort of patients who had failed to achieve a clinical response with non-advanced therapies, there was a numerically higher rate or response in the 360 mg arm than in the 180mg arm. This further supports that the efficacy in the 360mg arm is at least equivalent to the 180mg arm. The CHMP accepted the MAH's explanation.

The MAH presented additional subgroup analyses to support the request to specifically include a reference to JAK inhibitors in the indication statement. While it appeared that patients who had previously failed to achieve a response with a JAK inhibitor and who subsequently received risankizumab had a higher incidence of clinical remission and endoscopic improvement at week 12 following induction, inconsistent results were observed for maintenance treatment. Efficacy results were therefore not considered convincing in this patient subgroup.

In addition, most patients who had previously failed to achieve a response with a JAK inhibitor had also failed to achieve a response with biological therapy and few patients who had previously failed any type of UC-related advanced therapy had failed a JAK inhibitor only. It could be inferred that at most 15 (6 Placebo, 9 risankizumab 1200 mg IV) of the 90 patients who had failed a JAK inhibitor prior to induction study baseline, and at most 4 (1 Placebo, 2 risankizumab 180 mg SC, 1 risankizumab 360

mg SC) of the 78 patients who had failed a JAK inhibitor prior to maintenance study baseline, had not also failed another type of UC-related advanced therapy. As such, the proposal to include reference to JAK inhibitors in the indication was not agreed by the CHMP. The MAH agreed to remove the reference to JAK inhibitors in the indication.

3.4. Unfavourable effects

The safety profile presented for the UC population was in line with the known safety profile of the product in the CD population. Key unfavourable effects of infections, hepatic disorders and immunogenicity/hypersensitivity reactions are discussed further.

Infections

Patients with UC were reported to have an increased risk of common infections, serious infections, viral infections, and GI infections. The European Crohn's and Colitis Foundation states that IBD patients treated with immunomodulators, especially in combination, and those with malnutrition are at risk for opportunistic infections. The most common infections include viral infections (including CMV and herpes zoster) and aspergillosis and TB in both treated and untreated IBD patients.

The percentages of subjects with infection AEs and serious infections were comparable between the risankizumab 1200 mg IV group and the placebo group during the induction period, and the percentages and event rates of infections and serious infections were comparable between each risankizumab arm and the placebo arm during the maintenance period, with no apparent dose dependent pattern between the risankizumab 180 mg and 360 mg SC arms.

A review of infections reported for the risankizumab IV doses in induction as well as both risankizumab SC doses in long-term maintenance therapy, indicated that the character and types of infection were consistent with the identified ADRs for the Crohn’s population.

Across the UC clinical development programme, a total of 8 events of opportunistic infection (excluding TB and herpes zoster) were reported in 8 subjects. Opportunistic infections included CMV infection in 4 subjects, and oral fungal infection, oral herpes zoster, Aeromonas infection, and eczema herpeticum in 1 subject each. CMV infection was the only serious opportunistic infection and serious CMV infection occurred in 2 subjects.

No events of active TB were reported in the risankizumab UC clinical programme. The data did not suggest an increased risk of herpes zoster with risankizumab treatment in subjects with UC.

Overall, the reported opportunistic infections were consistent with the expected range for the UC population and the known safety profile of risankizumab.

Hepatic events

Hepatobiliary disorders (including non-alcoholic fatty liver disease [the most common cause], primary sclerosing cholangitis, autoimmune hepatitis, primary biliary cholangitis, choledocholithiasis, amyloidosis, and portal vein thrombosis) occur in patients with UC and may happen at any time during the natural course of disease (Klein 2020[10]). Although the incidence of SAEs related to liver toxicity remains low in inflammatory bowel disease, methotrexate and thiopurines have been associated with an increased risk for hepatotoxicity, and in many cases, dose adjustment may normalize the liver biochemical tests.

[10] KLEIN, Macarena, NÚÑEZ, Paulina, BAY, Constanza, et al. Liver disorders in inflammatory bowel disease. HEPATOLOGY, 2020.

There were no serious hepatic events across treatment arms, and all hepatic events were mild or moderate in severity. No hepatic events led to study drug discontinuation except for an AE of liver function test increased in 1 subject in the risankizumab 360 mg arm who met potential Hy's law criteria discussed above. A review of this case concluded it did not meet the criteria for Hy's Law and the event is unlikely related to risankizumab treatment.

Immunogenicity/hypersensitivity reactions

As an immunoglobulin protein, systemic (IV) or SC administration of risankizumab may be associated with immunogenicity (i.e., development of ADAs), as well as hypersensitivity reactions – both immediate and delayed. 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.

A review of the cumulative data from the risankizumab UC programme did not suggest an increase in hypersensitivity events with increased duration of risankizumab treatment. Immunogenicity to risankizumab did not have any clinically relevant impact on hypersensitivity reactions.

The most frequently reported ISRs in the Any Risankizumab group were injection site erythema, injection site reaction, and injection site pain. None were serious.

A review of ADA tests indicated that immunogenicity to risankizumab did not have clinically relevant impact on ISRs.

Assessment of maintenance data identified eczema (1.8% in the Total Risankizumab group and 1.5% in the placebo arm) as new ADRs for patients with moderate to severe UC. Hence, eczema was added to the SmPC Section 4.8 as ADR under the frequency common.

3.5. Uncertainties and limitations about unfavourable effects

Immunogenicity/hypersensitivity reactions

No adjudicated anaphylactic reactions were reported in the induction or maintenance period. There was one serious hypersensitivity event reported in 1 subject in a patient treated with risankizumab. Upon the CHMP's request, the MAH agreed to update the existing warning in the SmPC Section 4.4 on Hypersensitivity (addition in bold): "If a serious hypersensitivity reaction, **including anaphylaxis**, occurs, administration of risankizumab should be discontinued immediately and appropriate therapy initiated". Serious hypersensitivity reactions is an important potential risk in the RMP and pharmacovigilance activities are already planned to further characterise this risk (see Section 2.7.2 Pharmacovigilance Plan of the RMP)).

Use during pregnancy is identified as missing information in the RMP. The registry will be extended to include patients with UC. Pharmacovigilance activities are planned to further characterise this safety concern (see Section 2.7.2 Pharmacovigilance Plan of the RMP).

3.6. Effects Table

Table 27 Effects Table for risankizumab induction and maintenance.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Clinical Remission - induction	per adapted Mayo score at Week 12	%	1200 mg IV Q4W – 20.3	Placebo – 6.2	p- value - 0. 00001	M16-067 Sub study 2
Clinical remission - maintenance	per adapted Mayo score at week 52	%	180 mg SC – 40.2 360 mg SC – 37.6	Placebo – 25.1		M16-066 Sub study 1
Mucosal improvement - induction	HEMI at Week 12	%	1200mg IV 24.5	Placebo – 7.7	p-value <0.01	M16-067 Sub study 2
Mucosal remission - induction	HEMR at Week 12	%	1200mg IV – 6.3	Placebo – 0.6		M16-067 Sub study 2
Clinical response - induction	At week 12	%	1200mg IV – 64.3	Placebo – 35.7		M16-067 Sub study 2
Endoscopic improvement - induction	At Week 12	%	1200mg IV – 36.5	Placebo – 12.1		M16-067 Sub study 2
Mucosal improvement - maintenance	At week 52	%	180mg SC – 42.8 360mg SC – 42.2	Placebo – 23.5		M16-066 Sub study 1
Clinical remission without steroid use - maintenance	per Adapted Mayo Score at week 52	%	180mg SC - 39.6 360mg SC – 37.2	Placebo – 25.1		M16-066 Sub study 1
No bowel urgency - maintenance	At week 52	%	180mg SC – 53.6 360mg SC – 49.4	Placebo –31.1		M16-066 Sub study 1
Unfavourable Effects						
Infections	Known ADR-URTI.	%	1200mg IV 9.6	10.4	Consistent with the known safety profile	M16-067.
		%	180mg/360mg SC 23.8/26.2	28.6		Study M16-000
	Potential Risk-Serious infections.	(E/100 PY)	1200mg IV 2.9	5.1		M16-067
		(E/100 PY)	180mg/360mg SC 2.0/1.0	2.3		Study M16-000
	Opportunistic infections	(E/100 PY)	1200mg IV 1.2	1.0		M16-067
		(E/100 PY)	180mg/ 360mg SC 0/0.6	0		Study M16-000

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Immunogenicity	Known ADR-injection site reactions.	%	1200mg IV 0.7	1.6	Consistent with the known safety profile	M16-067.
		%	180mg/ 360mg SC 3.6/2.6	1.0		Study M16-000.
	Potential Risk-Serious hypersensitivity reactions	%	1200mg IV 3.5	2.6		M16-067.
		E/100 PY	180mg/ 360mg SC 12.4/8.6	5.7		Study M16-000.
Hepatic events	ALT increased	SSA %	1200mg IV 0.4	1.0	Mild to moderate. Trends not noted in the higher IV dose of 1200mg.	M16-067.
		E/100 PY	180mg/ 360mg SC 0.5/3.5	0	Treatment difference between placebo and 360mg SC arm for hepatic events 6.2% (2.5, 9.8 95% CI). Also ≥2% reported in each ALT/AST increase.	Study M16-000.
	AST increased	SSA %	1200mg IV 0.7	1.0		M16-067. SCS
		E/100 PY	180mg/ 360mg SC 0/2.3	0		Study M16-000.

Notes: Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The differences seen in the efficacy results shown for both induction and maintenance with risankizumab versus placebo for the treatment of patients with moderate or severe UC are statistically significant and clinically relevant. The efficacy of the higher 360mg maintenance dose is slightly higher at Week 52 for patients who have failed to achieve a satisfactory clinical response to induction at Week 12. This is adequately reflected in the SmPC Section 4.2.

The safety profile of risankizumab is similar to the known safety profile of the product. Eczema was added to the SmPC Section 4.8 as ADR under the frequency common. One serious hypersensitivity event was reported in the clinical programme in UC, this is adequately reflected in the SmPC Section

4.4. Furthermore, pharmacovigilance activities are planned to further characterise the risk of serious hypersensitivity reactions (see Section 2.7.2 Pharmacovigilance Plan of the RMP)).

Use during pregnancy is identified as missing information in the RMP. Pharmacovigilance activities are planned to further characterise this safety concern.

3.6.2. Balance of benefits and risks

A clinically relevant effect of risankizumab has been demonstrated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy. A positive benefit-risk balance could not be demonstrated in patients with prior JAK inhibitor therapy. The MAH agreed to remove this statement from the indication.

The available data supported a positive benefit risk to recommend the use of risankizumab with the following posology:

The recommended induction dose is 1200 mg administered by intravenous infusion at week 0, week 4, and week 8. Starting at week 12 and every 8 weeks thereafter, the recommended maintenance dose is based on individual patient presentation:

- A dose of 180 mg administered by subcutaneous injection is recommended for patients with adequate improvement in disease activity after induction
- A dose of 360 mg administered by subcutaneous injection is recommended for patients with inadequate improvement in disease activity after induction

Consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit by week 24.

3.6.3. Additional considerations on the benefit-risk balance

Not applicable.

3.7. Conclusions

The overall benefit/risk balance of Skyrizi is positive for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Skyrizi new 180 mg strength (solution for injection in cartridge) is favourable in the following indication:

Ulcerative colitis

Skyrizi is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Skyrizi subject to

the following conditions:

Conditions or restrictions regarding supply and use

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

Periodic Safety Update Reports

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

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

- Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

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

Not applicable.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		Type	Annexes affected
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, II, IIIA and IIIB
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 and IIIB

Extension application to introduce a new strength of 180 mg of risankizumab (solution for injection in cartridge), grouped with a type II variation extension of indication (C.I.6.a) to add a new indication (treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy). As a consequence of the extension of indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3, 6.5 and 6.6 of the SmPC are updated. The Annex II, Labelling and Package Leaflets are updated in accordance. In addition, the marketing authorisation holder has taken the opportunity to update the list of local representatives in the PL. The RMP version 5.3 is adopted.