15 September 2022
EMA/887275/2022
Committee for Medicinal Products for Human Use (CHMP)

# CHMP assessment report on group of extensions of marketing authorisation

Skyrizi

International non-proprietary name: risankizumab

Procedure No. EMEA/H/C/004759/X/0020/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

| | |
|---|---|
| 5-ASA | 5-aminosalicylic acid |
| Ab | antibody |
| ACG | American College of Gastroenterology |
| ADA | antidrug antibody |
| ADR | adverse drug reaction |
| AE | adverse event |
| AI | autoinjector |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AO | As Observed |
| APS | abdominal pain score |
| ASI | areas of special interest |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| AUCinf | area under the concentration-time curve from time 0 to infinite time |
| AUCt | area under the concentration-time curve from time 0 to time of last measurable concentration |
| BI | Boehringer Ingelheim International GmbH |
| Bio-IR | biologic therapy-intolerant or inadequate responder |
| BLA | Biologic License Application |
| CD | Crohn's disease |
| CDAI | Crohn's disease activity index |
| CE mark | European conformity mark |
| CFR | Code of Federal Regulations |
| CHMP | Committee for Human Medicinal Products |
| CI | confidence interval |
| Cmax | maximum observed serum concentration |
| CMQ | company MedDRA query |
| CMV | cytomegalovirus |
| CRP | C-reactive protein |
| CSE | Summary of Clinical Efficacy |
| CSR | Clinical Study Report |

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|---|---|
| CSS | Summary of Clinical Safety |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | coefficient of variation |
| DILI | drug induced liver injury |
| E1 | estrone |
| ECCO | European Crohn's and Colitis Organisation |
| eCTD | electronic common technical document |
| EIMs | extra-intestinal manifestations |
| EMA | European Medicines Agency |
| EOP2 | End-of-Phase 2 |
| EU | European Union |
| FACIT | Functional Assessment of Chronic Illness Therapy |
| FCP | fecal calprotectin |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GI | gastrointestinal |
| hs-CRP | high-sensitivity C-reactive protein |
| IBD | inflammatory bowel disease |
| IBDQ | Inflammatory Bowel Disease Questionnaire |
| IC50 | concentration producing 50% inhibition |
| ICH | International Council for Harmonisation |
| IL | interleukin |
| ILI | influenza- like illness |
| IND | Investigational New Drug |
| IR | inadequate response |
| ISE | Integrated Summary of Efficacy |
| ISRs | injection-site reactions |
| ISS | Integrated Summary of Safety |
| ITT | intent-to-treat |
| IV | intravenous |
| Kd | dissociation constant |
| MACE | major adverse cardiovascular event |

| | |
|---|---|
| MedDRA | Medical Dictionary for Regulatory Activities |
| MWPC | meaningful within-patient change |
| Nab | neutralizing antibody |
| NAFLD | non-alcoholic fatty liver disease |
| NCI | National Cancer Institute |
| NMSC | non-melanoma skin cancer |
| NRI | non-responder imputation |
| NSP | needle stick protection device |
| OBDS | on-body delivery system |
| OBI | on-body injector |
| OL | open-label |
| OLE | open-label extension |
| OUS | outside the US |
| PBC | primary biliary cholangitis |
| PBO | placebo |
| PCS | potentially clinically significant |
| PD | pharmacodynamic |
| PFC | prefilled cartridge |
| PFS | pre-filled syringe |
| PGIC | patient global impression of change |
| PGIS | patient global impression of disease severity |
| PIND | pre-investigational new drug |
| PK | pharmacokinetics |
| pM | picomolar |
| PMDA | Pharmaceutical and Medical Devices Agency |
| PML | progressive multifocal leukoencephalopathy |
| PRO | patient reported outcomes |
| PsA | psoriatic arthritis |
| PsO | plaque psoriasis |
| PT | preferred term |
| PY | patient-year |
| q12w | every 12 weeks |
| q4w | every 4 weeks |

| | |
|---|---|
| q8w | every 8 weeks |
| QoL | quality of life |
| R&D | research and development |
| RZB | risankizumab |
| SAEs | serious AEs |
| SAP | statistical analysis plan |
| SC | subcutaneous |
| SES-CD | Simple Endoscopic Score - CD |
| SF | stool frequency |
| SF/APS | stool frequency and abdominal pain score |
| SMQ | standard MedDRA queries |
| TB | tuberculosis |
| TEAEs | treatment-emergent AEs |
| TNF | tumor necrosis factor |
| UC | ulcerative colitis |
| ULN | upper limit of normal |
| URTI | upper respiratory tract infection |
| US | United States |
| UTI | urinary tract infection |
| vs. | versus |
| WRO | written response only |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

AbbVie Deutschland GmbH & Co. KG submitted on 25 November 2021 extensions of the marketing authorisation.

The Marketing Authorisation Holder (MAH) applied for:
- an addition of a new strength (600 mg), addition of a new pharmaceutical form (concentrate for solution for infusion), and addition of a new route of administration (intravenous use).
- an addition of a new strength (360mg), for solution for injection (in cartridge) for subcutaneous use.

The above new presentations are proposed for a new indication:

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

The RMP (version 4.5) is updated in accordance.

## *1.2. Legal basis, dossier content*

**The legal basis for this application refers to:**

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

## *1.3. Information on Paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0230/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP 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:

- July 2016 (EMEA/SAH/631/1/2016), pertained to preclinical and clinical development
- June 2019 (EMEA/H/SA/3171/4/FU/1/2019/II) and Clarification Letter October 2019

(EMEA/H/SA/3171/4/FU/1/2019/II), pertained to clinical development

- November 2019 (EMEA/H/SA/3171/4/FU/2/2019/III), pertained to quality and clinical development
- October 2020 (EMEA/H/SA/3171/4/FU/3/2020/I), pertained to quality development
- June 2021 - A pre-submission meeting (PSM) was held with the HPRA and EMA

The advice received was taken into consideration in the design of the Phase 3 programme and the presentation of the dossier. The CHMP scientific advice letters and minutes of the PSM and a summary of Scientific Advice (appended to the Notes to Reviewer) are provided in module 1.2.

## *1.6. Steps taken for the assessment of the product*

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

Rapporteur: Jayne Crowe Co-Rapporteur: N/A

CHMP Peer reviewer(s): N/A

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| The application was received by the EMA on | 25 November 2021 |
| The procedure started on | 24 December 2021 |
| The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 16 March 2022 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 23 March 2022 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 07 April 2022 |
| The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on | 22 April 2022 |
| The MAH submitted the responses to the CHMP consolidated List of Questions on | 20 May 2022 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on | 24 June 2022 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 07 July 2022 |
| The CHMP agreed on a list of outstanding issues to be sent to the MAH on | 21 July 2022 |
| The MAH submitted the responses to the CHMP List of Outstanding Issues on | 15 August 2022 |
| The CHMP Rapporteurs circulated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 31 August 2022 |

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| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 01 September 2022 |
| 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 | 15 September 2022 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

Crohn's Disease (CD) is a chronic relapsing, remitting inflammatory disease of the gastrointestinal (GI) tract, the cause of which remains unknown. Extra-intestinal manifestations include ocular inflammation, arthropathies, skin lesions and a spectrum of hepatic diseases.

CD encompasses a spectrum of clinical and pathological processes manifested by focal asymmetric, transmural, and occasionally granulomatous inflammation which can affect any segment of the GI tract.

The exact cause of CD is still unknown but is hypothesized to be the result of a dysregulated immune system in the context of a genetically susceptible individual. It is thought that a combination of a patient's genetics, microbiome, immune response, and the environment result in an excessive and abnormal immune response in the gut that results in pathology seen in CD.

The Marketing Authorization Holder (MAH) applies for the following indication for Skyrizi (risankizumab) in CD:

'Skyrizi is indicated for the treatment of patients 16 years and older with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy, or if such therapies are not advisable.'

The proposed posology is RZB 600 mg administered by intravenous infusion at Week 0, Week 4, and Week 8, followed by RZB 360 mg administered by subcutaneous injection at Week 12, and every 8 weeks thereafter.

### 2.1.2. Epidemiology

The incidence of CD worldwide has increased over the last three decades, particularly in newly industrialized countries. CD incidence is highest in North America and Europe, with estimates of 23.8 and 15 per 100,000 person-years in North America and Europe, respectively. The burden of CD also remains substantial, with the highest prevalence estimates in Europe (322 per 100,000 persons) and North America (319 per 100,000 persons).

The incidence of CD worldwide has increased over the last 3 decades, particularly in newly industrialized countries.

## 2.1.3. Clinical presentation, diagnosis and stage/prognosis

The disease affects the GI tract discontinuously from mouth to anus, but most commonly the disease is located both in ileum and colon (approximately 40%), followed by a disease in the small bowel only (approximately 30%), in the colon only (approximately 25%), and other locations (approximately 5%). Some patients may have a continuously clinically active disease. A diagnosis is usually based on composite clinical and pathological features and the exclusion of alternative disease states.

CD has been classified by disease phenotype into primarily inflammatory disease, stricturing disease or penetrating disease modified by the presence of upper gastrointestinal or perianal disease (in up to 20%) (Montreal classification 2005). Over the course of the disease, phenotype commonly changes from predominantly inflammatory disease to stricturing and/or penetrating disease.

CD may present with symptoms of fatigue, prolonged diarrhoea with or without gross bleeding, abdominal pain, weight loss, and fever. The major signs and symptoms are diarrhoea, abdominal pain and weight loss, partly determined by the anatomical location and the severity of the disease. There may be no direct correlation between an individual's symptoms and endoscopic and radiological findings.

## 2.1.4. Management

The goal of treating CD is achieving and maintain symptomatic and endoscopic remission. Treatment of CD is a sequential continuum of induction to treat acute disease and maintenance to maintain response or remission.

Remission can be achieved either by medical treatment or surgery. Medical therapy recommended by clinical guidelines includes corticosteroids, immunosuppressant drugs and biologics (anti-tumour necrosis factor (TNF) α agents and adhesion molecule inhibitors). Nutritional support has a role as primary therapy (in children) or as adjunct to other treatment. When medical treatment is unsuccessful or with certain complications, surgery is indicated. More than 70% of patients with ileal disease will require surgery at least once during the course of their disease (Guideline on the development of new medicinal products for the treatment of Crohn's Disease, CPMP/EWP/2284/99 R2, 28 June 2018).

Treatment of moderately to severely active CD consists of conventional pharmaceutical therapies such as aminosalicylates, corticosteroids, and immunomodulators [e.g., thiopurines and methotrexate], as well as biologic therapies. While frequently used, aminosalicylates and oral locally acting corticosteroids are of limited benefit and not recommended for long-term treatment.

Systemic corticosteroids, while recommended for short-term use, are ineffective as maintenance therapy, do not consistently achieve mucosal healing, and even short-term use may be accompanied by important AEs (such as bone loss, mood disorder, insomnia, hypertension, elevated blood glucose, narrow angle glaucoma, acne, weight gain, and hypoadrenalism).

Immunomodulators have a slow onset of action, have limited efficacy and are associated with AEs, such as allergic reactions, pancreatitis, myelosuppression, nausea, infections, hepatotoxicity, and malignancy.

The advent of biologics has revolutionized treatment of patients with moderately to severely active Crohn's disease. However, despite the benefits of available biologic therapies, such as infliximab, adalimumab, certolizumab, natalizumab, vedolizumab, and ustekinumab, many patients do not respond to initial treatment (primary non-response) or lose treatment over time (secondary loss of response).

An important area of unmet need is treatment of paediatric patients with CD, where the potential impact of uncontrolled CD on growth, pubertal and emotional development, underlines the need for safe and efficacious treatment.

## 2.2. About the product

Risankizumab (RZB) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that selectively binds with high affinity to the p19 subunit of the human cytokine interleukin (IL)-23. By blocking IL-23 from binding to its receptor, RZB inhibits IL-23 dependent cell signaling and release of pro inflammatory cytokines, and thus has the potential to treat immune-mediated inflammatory diseases including CD.

The pharmacological classification of RZB is:

Immunosuppressants, interleukin inhibitors, ATC code: L04AC18

RZB is approved for marketing in the European Union (EU) (Skyrizi; EU/1/19/1361/001-3), United States (US), Japan, and other countries for the treatment of moderate to severe plaque psoriasis in adults. RZB is approved for the treatment of active psoriatic arthritis in the EU, USA, Japan and Russia. RZB is being developed for the treatment of other indications, including CD and ulcerative colitis.

## 2.3. Type of Application and aspects on development

This is an Extension Application for two new dose strengths and presentations to support the new indication in Crohn's Disease.

The MAH applied for the following **indication** for Skyrizi (risankizumab) in CD:

'Skyrizi is indicated for the treatment of patients 16 years and older with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy, or if such therapies are not advisable.'

The proposed **posology** is RZB 600 mg administered by intravenous infusion at Week 0, Week 4, and Week 8, followed by RZB 360 mg administered by subcutaneous injection at Week 12, and every 8 weeks thereafter. The MAH has developed two new dose strengths and presentations to support the new indication Crohn's Disease:

- **Vial** containing 600 mg of Risankizumab (concentrate for solution for infusion) for i.v. administration: Crohn's Disease induction treatment
- **Cartridge** containing 360 mg of Risankizumab (solution for injection) co-packaged with a device (on-body injector, OBI) for s.c. administration: Crohn's Disease maintenance treatment

The CE mark was not available for submission with this initial dossier. At the pre-submission meeting, EMA confirmed that for medical devices that are co-packaged, it is not required to submit the CE-certificate as part of the MAA dossier and MAHs have the responsibility to ensure the co packaged device is CE marked in accordance with the relevant legislation on medical devices prior to placing the product on the market.

The MAH informed EMA (9 November 2021) that the device manufacturer is in progress to obtain the CE mark from the Notified Body and the CE mark may be available only later in the process.

In support of this application the RZB clinical development program to demonstrate the safety and efficacy of risankizumab (RZB) for the treatment of patients with moderately to severely active Crohn's Disease (CD) who are 16 years of age and older for CD includes:

- four Phase 1 studies (M16-324, M19-128, M16-533 & M17-318),
- one Phase 2 dose ranging study (M15-993) & one Phase 2 open-label extension study (M15-989),
- two pivotal Phase 3 induction studies (M15-991 & M16-006) & one pivotal Phase 3 maintenance study (M16-000).

## *2.4. Quality aspects*

### 2.4.1. Introduction

The active substance (AS) risankizumab is a humanised monoclonal antibody of the IgG1 isotype with engineered Fc region, directed against IL-23p19.

Skyrizi is currently authorised as solution for subcutaneous injection:

- 75 mg strength (75 mg in 0.83 mL) in pre-filled syringe (glass) + alcohol pads (packs of 2 each);

- 150 mg strength (150 mg in 1 mL) in pre-filled syringe (glass) and pre-filled pen (glass) (pack of 1 each).

The scope of this line extension is the registration of new pharmaceutical form, new route of administration and new strengths as follows:

- 360 mg solution for subcutaneous injection in a cartridge containing 360 mg of risankizumab in 2.4 mL solution (concentration 150 mg/mL) co-packaged with an on-body injector (pack of 1 each, for single use);

- 600 mg concentrate for solution for infusion in a single use vial containing 600 mg of risankizumab in 10 mL of solution (concentration 60 mg/mL) (pack of 1 vial).

The qualitative composition in excipients for the new presentations is the same as Skyrizi 150 mg solution for injection in pre-filled pen and pre-filled syringe.

Elements of Quality by Design have been used in the pharmaceutical development of the finished product (e.g. formulation development), however no regulatory flexibility is applied for.

### 2.4.2. Active Substance

#### *2.4.2.1. General information*

Risankizumab is composed of two heterodimers. Each of the heterodimers is composed of a heavy and a light polypeptide chain. Each heavy chain (γ HC) is composed of 449 amino acids and each light chain (κ LC) contains 214 amino acids. The active substance, risankizumab is a humanised IgG1 monoclonal antibody that selectively binds to IL-23p19 and therefore inhibits binding of IL-23 to its receptor. The framework of the antibody has been engineered with two mutations in the Fc region, Leu234Ala and Leu235Ala to reduce the potential effector function. The C-terminal lysine of the heavy chain has been deleted to reduce potential charge heterogeneity. Each HC contains a single N-linked glycosylation site at asparagine 297. The predicted molecular weight (MW) of aglycosylated, native risankizumab is 146 kDa.

### *2.4.2.2. Manufacture, characterisation and process controls*

***Description of manufacturing process and process controls***

**A) Skyrizi 360 mg solution for injection in a cartridge**

The AS used to manufacture the finished product (FP) for the cartridge presentation is produced using the approved CMC2 process. As part of this application, sections S.2.1, S.2.5 and S.2.6 for this manufacturing process have been updated. The active substance is manufactured at Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Str. 65, 88397 Biberach a.d.R., Germany. The MAH provided a summary of the shipping process qualification report to justify shipment of the CMC2 AS from Boehringer Ingelheim Pharma (BI) in Germany to the pre-filled cartridge FP site, using the currently approved shipping process. This is acceptable.

All sites involved in the manufacture, control and testing of the AS operate in accordance with EU GMP.

**B) Skyrizi 600 mg concentrate for solution for infusion**

The AS is manufactured at AbbVie Bioresearch Center Inc., 100 Research Drive, Worcester, MA 01605, USA with a new version of the process is largely aligned with the authorised CMC2 process approved under EU procedure EMEA/H/C/004759/X/0012.

All sites involved in the manufacture, control and testing of the AS operate in accordance with EU GMP.

The new procedure has been well described. The MAH has provided information on the buffer composition to be used throughout the procedure. Process parameters for this step have been provided and is considered appropriate.

***Control of materials***

The cell banks and the raw materials are similar to those used in manufacture of the currently approved active substance.

Details of compendial and non-compendial raw materials are provided. Acceptable specifications are registered for all non-compendial raw materials.

Changes are being introduced for the CMC2 process and the material of construction have been registered in the dossier and a certificates of analyses (COA) for both has been provided and found satisfactory.

***Control of critical steps and intermediates***

Critical process parameters (CPPs), acceptable ranges, and associated critical quality attributes (CQAs) are aligned to the approved process or tighter, and three control tests for bioburden, endotoxin, and step yield are included which is considered appropriate as they are in line with the currently approved in-process controls (IPCs).

Hold times and holding conditions for process intermediates are site specific and were re-established for the ABC site. The hold times are supported based on hold time validation studies. Overall the control strategy in terms of CPPs and IPCs is considered acceptable to ensure adequate control of the active substance manufacturing process.

Details of the qualification of the IPC analytical methods are also presented. All methods are the same as the approved CMC2 process at the ABL site.

***Process validation***

Process performance qualification (PPQ) runs were performed on consecutive batches. IPC and process parameter results, including CPPs and non-CPPs, have been provided for each manufacturing step for each of the process performance qualification (PPQ) batches. All IPCs met their acceptance criteria for the cell culture stage, primary recovery and capture and fine purification.

As the new process is aligned with the CMC2 process, full viral clearance studies were not performed, this is agreed. However, viral clearance studies were performed using the new process conditions.

Impurity validation has been performed which adequately demonstrates the process is sufficient to remove process related impurities.

The majority of the hold times for the process intermediates can be considered validated based on the data provided, however, a request was made to provide sufficient data to support the process intermediate hold time point. The data provided to support this hold time has been provided and found acceptable.

The reprocessing validation study is supported by process characterisation studies.

Shipping validation for the risankizumab CMC2 active substance manufactured at Boehringer Ingelheim (BI) in Biberach, Germany, and transported to the finished product manufacturing site at AbbVie Biotechnology, Ltd. (ABL) in Puerto Rico has been previously provided during EU procedure EMEA/H/C/004759/X/0012. An equivalency study demonstrated that shipment of AS from BI to ABL is comparable to shipping of risankizumab AS manufactured at ABC to the FP manufacturing site.

There are no changes to the container closure system from the registered container closure system.

***Manufacturing process development***

A detailed description has been provided on the manufacturing process development, including the control strategy, manufacturing process history, process characterization studies, impurity clearance studies, and extractables and leachables assessment.

A new process characterisation study (PCS) was performed in the scaled-down model (SDM) representative of the commercial scale. The data from the SDM demonstrates it is equivalent to the large scale process. The proposed new CPP and process parameters are agreed.

***Characterisation***

The active substance has previously been characterised in the approved marketing authorisation (MA) for the 90 mg/mL AS. An extended study was additionally performed on AS batches and included testing to evaluate primary, secondary and higher order structures, heterogeneity, biological activity. The characterisation studies have been carried out in a very comprehensive manner and cover all relevant aspects for a monoclonal antibody. The results of the extended characterisation study demonstrate the formulation or process changes made did not impact the structure, physicochemical characteristics or biological activity of risankizumab.

### *2.4.2.3. Specification*

The tests, analytical procedures and acceptance criteria listed are largely the same as the CMC2 AS, these specifications are considered acceptable.

The proposed panel of release tests cover identity, quantity, purity, potency, charge and microbial assurance. In general, the panel of tests are in line with ICH Q6B and are considered appropriate for routine control of a monoclonal antibody both at release and shelf life. The specification acceptance criteria are clinically qualified.

***Analytical methods***

The analytical methods have been sufficiently described and are aligned with the authorised CMC2 150 mg/mL analytical tests apart from the HCP test. The new HCP version 2 procedure was approved as part of a Type II variation (EMEA/H/C/004759/II/0019/G).

The analytical procedures have been appropriately validated in accordance with ICH Q2(R1). Compendial methods have been verified as appropriate for their intended use while the non-compendial methods have been appropriately validated. No new methods are being used, therefore, the majority of the validation has been previously assessed and found acceptable.

***Batch analysis***

Batch analysis data is provided. The results are within the specifications and confirm consistency of the manufacturing process.

***Reference materials***

The approach to reference standards has not changed from the approved dossier. The current reference standards were assessed during the initial marketing authorisation and continue to be acceptable, and the protocol for establishing new primary reference standards is appropriate.

#### *2.4.2.4. Stability*

Stability studies have been performed in accordance with ICH guidelines for testing frequency and storage conditions. Overall the data provided support of the claimed shelf-life for active substance.

## 2.4.3. Finished Medicinal Product

#### *2.4.3.1. Description of the product and pharmaceutical development*

Two presentations are proposed for the finished product (FP), a single use 600 mg/10 mL vial, and a 360 mg/ 2.4 mL pre-filled cartridge (PFC) co-packaged with an on-body delivery system (OBDS) device. Each presentation will be addressed separately where necessary in this report.

600 mg/10 mL vial

Skyrizi 600 mg/10.0 mL vial is supplied as a sterile solution for intravenous administration (IV) after dilution with 5% dextrose in water. The solution is colourless to slightly yellow and clear to slightly opalescent. The FP is a buffered and preservative-free solution that is diluted to an isotonic solution for IV administration.

360 mg/2.4 mL Pre-filled Cartridge (PFC) and OBDS combination

Skyrizi 360 mg/2.4 mL PFC is supplied as a sterile solution at a concentration of 150 mg/mL for subcutaneous administration. The PFC finished product is a buffered, isotonic, preservative-free, colorless to yellow, clear to slightly opalescent solution. Skyrizi 360 mg/2.4 mL PFC is to be administered using an on-body delivery system (OBDS) device and 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.

Development of the 60 mg/mL vial formulation and the 150 mg/mL PFC formulation is based on the manufacturer's experience with the authorised 90 and 150 mg/mL PFS formulations. The excipients are standard for parenteral presentations and extensive formulation development data including design of

experiments (DoE) multivariate studies are provided to establish a formulation design space for the vial and PFC formulations. The formulation robustness data show that the chosen formulations are appropriate to control the stability of the vial and PFC presentations over the intended shelf life.

The process flow for the FP manufacturing of the vial and the PFC presentations is clearly outlined and there is a good understanding of the risks and critical quality attributes (CQA) identified at each stage of the process. Based on the Quality Target Product Profiles (QTPP) and CQAs, an initial risk assessment was conducted for the manufacturing process development to identify variables and process parameters that may have a potential impact on the CQAs. The manufacturing steps were then assessed by process characterisation studies evaluating the significance of changing process parameters on the quality of the product. Justification for the proposed critical process parameters (CPP) is considered acceptable. Mixing times and speeds are supported by computational fluid dynamics studies (CFD) and are validated. Filtration pressure is listed as a CPP for the sterile filtration process step and small-scale studies were conducted at worst-case filtration pressures demonstrating it does not impact finished product quality. Process parameters are controlled. Extractables and leachables testing was carried out for the contact materials DS bags, bioburden reduction filter, tubing and single use bags. Extractables with a maximum daily exposure (MDE) above the threshold of toxicological concern (TTC) were assessed for toxicological risk and considered to pose negligible risk to the patient. The leachables studies for both presentations are ongoing and any leachables identified above the calculated PDE will be reported.

600 mg/10.0 mL Vial

The proposed commercial manufacturing process of Skyrizi 600 mg/10.0 mL vial was established based on the clinical manufacturing process at the finished product manufacturing site. Comparability was demonstrated between the commercial 60 mg/mL formulation and the 90 mg/mL formulation used in the three clinical phase 3 studies. Comparability was based on FP release data, extended characterisation and stability study data. Differences in the versions of the process are described and include the new AS manufacturing process and AS formulation, a change in the FP formulation (including protein concentration), a new FP manufacturing site, batch size and vial size. Seven 600 mg/10 mL vial FP batches have been manufactured to the commercial process and includes three PPQ batches.

360 mg/2.4 mL PFC

The proposed commercial manufacturing process for the Skyrizi 150 mg/mL PFC was established based on prior knowledge gained during the development of the Skyrizi 90 mg/mL PFS and the Skyrizi 150 mg/mL PFS process development. The intended manufacturing process for the Skyrizi 150 mg/mL PFC is similar to the versions of the process used for Skyrizi 90 mg/mL PFS and Skyrizi 150 mg/mL PFS. The commercial manufacturing process for Skyrizi 150 mg/mL PFC was implemented at the FP manufacturing site. Comparability was demonstrated between the commercial 150 mg/mL formulation and the 90 mg/mL formulation used in the phase 3 clinical studies. Comparability was based on FP release data, extended characterisation and stability study data. During development, two different fill volumes were explored for Skyrizi 150 mg/mL PFC to provide the required doses for clinical studies, resulting in Skyrizi 180 mg/1.2 mL PFC and Skyrizi 360 mg/2.4 mL PFC. Development experiments may have been performed using one or both of the finished product presentations, as applicable, for increased process experience and batch data.

360 mg/2.4 mL OBDS Combination Product

The OBDS device development is described and design choice of the device and rationale is provided. The functional aspects of the device in combination with the PFC are addressed including minimising needle stick injuries, delivery initiation force, and needle insertion depth and delivery profile. The dose

delivery and duration is adequately addressed in the design. The microbiological attributes and compatibility of the device with the finished product have been adequately addressed. There were minor changes made to the device during development to accommodate a new battery and these changes are considered acceptable and to have no impact on the device function.

Adequate descriptions are provided for the components of the container closure for the 600 mg/10 mL vial. Schematics and specifications and example CoA for the vial, stopper and flip cap are provided. The components are manufactured in accordance with the appropriate Ph. Eur. monographs and are acceptable. The extractables and leachables study design is supported and the leachables study is ongoing. A commitment has been provided to report any leachable identified above the calculated PDE over the duration of the studies.

The container closure for the 360 mg/2.4 mL PFC consists of a pre-filled cartridge (PFC). The septum and piston are laminated. The PFC cartridge and piston are sterilised by and details of the sterilisation site are registered in the dossier, a certificate of ISO conformance is provided. Details of the methods, cycles and validation for sterilisation of the pistons and cartridge are provided in accordance with the EMA guideline on sterilisation (EMA/CHMP/CVMP/QWP/850374/2015).

The information provided for the OBDS combination device is considered to be in accordance with the 'guideline on quality documentation for medicinal products when used with a medical device' (EMA/CHMP/QWP/BWP/259165/2019) with cross reference made to 3.2.R for further general comments on the data provided to support the device. The OBDS device does not currently have a CE mark, however in accordance with EU legislation, a CE mark is required prior to marketing the product with the OBDS. Therefore, some aspects of OBDS will be assessed by the relevant Notified Body.

#### *2.4.3.2. Manufacture of the product and process controls*

The name, address, and responsibility of each manufacturer, and each proposed production site or facility involved in the manufacturing and testing of the Vial and PFC presentation is provided and the sites are appropriately GMP certified.

The manufacturing process is standard for both the vial and PFC presentations. The vial manufacturing process includes AS thawing, bulk solution homogenisation and pooling, compounding of bulk FP solution, bioburden reduction filtration, storage and mixing of the bulk solution, sterile filtration, filling and stopper setting, crimping of vials and visual inspection. Vials are filled following sterile filtration and are 100% visually inspected. The PFC manufacturing includes AS thawing and equilibration of formulated AS, 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. The hold times for the versions of the manufacturing process for both the vial and PFC are the accumulated time over the FP manufacturing process.

Ranges have been registered for CPPs and IPCs and have been justified in the dossier for each process and the control strategies are for the most part aligned with the approved 90 and 150 mg/ml formulations and considered acceptable.

The manufacturing process was validated based on production of consecutive batches at routine production scale. The validation is acceptable and the process is demonstrated to be capable of producing batches of consistent quality. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are considered to be adequate.

### *2.4.3.3. Product specification*

The proposed release tests are in line with the expectations of ICHQ6B and the Ph. Eur. monograph on monoclonal antibodies and are therefore acceptable. Furthermore, the tests for the Skyrizi 600 mg/10.0 mL vial are the same as for the approved 150 mg/ml PFS presentation with the exception of functional tests for the PFS. The FP release limits are based on the AS shelf life limits and found acceptable. To assess shelf-life limits for Skyrizi 60 mg/mL FP, statistical evaluations were conducted and proposed limits are supported.

The proposed release tests for the 360 mg/2.4 mL PFC product are in line with the expectations of ICHQ6B and the Ph. Eur. monograph on monoclonal antibodies and are therefore acceptable. Furthermore, the tests for the bulk 360 mg/2.4 mL PFC FP are the same as those approved for the 150 mg/ml PFS presentation with functional tests for the maximum force for the assembled PFC-TSA. To assess shelf-life limits for Skyrizi 360 mg/2.4 mL FP, statistical evaluations were conducted, and proposed limits are supported.

Additional functional tests are included for the OBDS combination. Packaging integrity, device interface functionality and label controls are also included, and these specifications are considered appropriate. The shelf life acceptance criteria are identical to the release specifications.

#### *Analytical methods*

The analytical procedures used for release and shelf life testing of the vial and PFC FP are same for the AS, and described in the respective AS section. Additional methods are used for vial and PFC FP release testing. Details of the in-house methods and validation are provided in the dossier and are acceptable. For the OBDS combination product, descriptions are provided.

#### *Batch analysis*

Batch data has been provided for vial and PFC FP batches The batches include stability batches, clinical batches and PPQ batches. All the batches were within specification and show consistent results indicating a controlled manufacturing process. Data are also provided for OBDS combination product batches. The data shows that the finished product manufacturing process results in batches of consistent quality. PPQ batches were tested for and met all specifications for the OBDS combination product.

#### *Reference materials*

For discussion on reference standards, please refer to the active substance part of this report.

### *2.4.3.4. Stability of the product*

For the 600 mg/10 mL vial, stability testing was performed in line with ICH Q5C. Up to 24 months stability data is available from the primary stability batches at long term conditions (2- 8 °C). In addition, up to 18 months stability data is available from the PPQ batches at long term conditions. Up to 6 months data is provided at accelerated and stressed conditions. Primary stability and PPQ batches were manufactured at the proposed commercial manufacturing site are representative of the commercial process and are stored in the proposed container closure.

A photostability study was performed according to the conditions outlined in ICH Q1B. Results indicate that the FP is light sensitive but that the intended secondary packaging is sufficient to protect from light.

Product quality was not affected during dilution, storage or by contact with the infusion materials. Direct sunlight should be avoided, and this is included in the SmPC.

For the 360 mg/2.4 mL PFC, stability testing was also performed in line with ICH Q5C. In addition to the stability data presented for the PFC, data is presented to support the functionality of the final assembled/blistered OBDS combination product.

Up to 24 months stability data is available from the primary PFC stability batches at long term conditions (2- 8 °C). In addition, up to 12 months stability data is available from the 360 mg/2.4 ml PFC PPQ batches at long term conditions. Up to 6 months data is provided at accelerated and stressed conditions. Primary stability and PPQ batches were manufactured at the proposed commercial manufacturing site, are representative of the commercial process and are stored in the proposed container closure.

The annual stability protocols are presented are acceptable. A temperature cycling study was performed for vial and PFC presentations and the results support the permitted temperature excursions.

On the basis of the combined stability data from the PFC and the OBDS combination pack, a shelf-life of 24 months with storage conditions of 2 – 8 °C and a direction to protect from light. This is acceptable.

In use stability of the OBDS combination product is addressed as part of the design verification and in the human factors engineering / usability engineering summative validation report. This will be assessed as part of the CE certification and cross reference is made to 3.2.R for general comments.

#### *2.4.3.5. Adventitious agents*

CMC2 process

The information provided for the adventitious agent safety evaluation for the AS used to manufacture the PFC presentation is identical to the authorised AS used to manufacture the pre-filler syringe presentation. The only difference is new BSE/TSE certifications for the FP container closure have been added which show compliance of no material of animal origin. This is acceptable.

New version of CMC2 process

The information provided for the adventitious agent safety evaluation for the AS used to manufacture the vial presentation is largely identical to the authorised AS used to manufacture the pre-filler syringe presentation.

Modifications in this line extension and certificates of compliance from the supplier have been submitted to demonstrate compliance with the TSE Note for Guidance, these are deemed appropriate. No new raw materials of biological origin have been introduced during this procedure, therefore, the same approved raw materials used for the 150 mg/ml risankizumab AS manufacturing process are provided in this dossier.

Viral clearance studies in accordance with ICHQ5A were performed. Viral clearance studies were performed within the manufacturing NORs established in S.2.2. The new viral studies presented are considered sufficient and have demonstrated no negative impact on viral clearance.

## 2.4.4. Discussion on chemical, pharmaceutical and biological aspects

In this line extension for these two new finished product presentations of risankizumab (vial and cartridge), there are two new active substance dossier sections provided. The AS used to manufacture the FP for the cartridge presentation will be the authorised CMC2 process. The information provided for the CMC2 process included clarification over the manufacturer’s operations, a qualification assessment

that demonstrated the shipping process for the 90 mg/mL and 150 mg/mL are comparable, and updated batches for the 10 mg/mL and 90 mg/mL AS batches produced from the CMC1 process and batches for the CMC2 process have been provided and all batches met the acceptance criteria.

The active substance manufacturing process used for the production of 600 mg/10.0 mL Vial FP is the modified CMC2 process. The process is a standard manufacturing process for a monoclonal antibody. The manufacturing process is essentially the same as the validated and approved historical CMC2 AS versions of the process. The process has been well described and there has been some minor changes to the normal operating ranges and proven acceptable ranges. The comparability performed was very detailed and showed that the new process was comparable to the old versions of the process. Extended characterisation showed there has been no change to the mAb and it is identical to the previous versions of the process. No new impurities were identified. All specifications are the same as the authorised versions of the process and all the analytical methods are appropriately validated. The methods and acceptance criteria used for testing of specifications are appropriately justified. Long-term storage was proposed for 24 months and has been supported by 24 months of data for batches.

The FP is supplied as a 600 mg/10 mL vial (concentrate for solution for infusion) and as a 360 mg/2.4 mL pre-filled cartridge (PFC) (solution for injection) co-packaged with an on body delivery system (OBDS) device. Sufficient formulation development data was provided to justify the final formulation. Comparability of the commercial manufacturing process for both the vial and PFC presentation was shown compared to the 90 mg/mL batches used in the phase 3 trials. The manufacturing process is standard for a monoclonal antibody. Appropriate process development data was provided which supports the control strategy. The manufacturing process of the vial and the PFC has been appropriately validated. The specifications are largely aligned to the approved 90 and 150 mg/ml PFS 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. The analytical procedures have been appropriately validated and sufficient batch data has been provided.

Sufficient documentation has been provided to support the use of the PFC and OBDS device. This included compatibility data, extractables and leachables studies and human factors studies. It is noted that the on-body delivery system will require CE marking prior to being placed on the market and will undergo conformity assessment by a notified body. Appropriate stability data has been provided to support the proposed 24 month shelf life for the vial presentation and 24 month shelf life for the PFC presentation.

The safety of the product with respect to adventitious agents has been appropriately justified. The results of the viral clearance study demonstrated that the production process has sufficient capacity to inactivate or remove viruses.

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

## 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. Recommendation(s) for future quality development

Not applicable.

# *2.5. Non-clinical aspects*

## 2.5.1. Introduction

Risankizumab is a humanized immunoglobulin G1 monoclonal antibody directed against interleukin (IL)-23 p19 and is currently authorised for the treatment of moderate to severe plaque psoriasis and active psoriatic arthritis in adults (Skyrizi; EU/1/19/1361/001-3).

This is an Extension Application for two new dose strengths and presentations to support the new indication Crohn's Disease. Limited *in vitro* and *in vivo* primary pharmacology studies were conducted to support this application; no additional pharmacokinetic or toxicology studies were conducted.

## 2.5.2. Pharmacology

### *2.5.2.1. Primary pharmacodynamic studies*

A limited package of nonclinical pharmacology studies was performed to support the new indication for the treatment of Crohn's disease.

An *in vitro* surface plasmon resonance study investigated the potential of risankizumab to bind to IL-23 which is already bound to its receptor, IL-23R$\alpha$. The analysis revealed no binding of risankizumab to the IL-23/IL-23R$\alpha$ complexes suggesting that it binds to a site involved in receptor binding and thereby prevents this interaction from occurring.

Two additional *in vivo* studies were performed in mouse models of colitis. In both the anti-CD40-induced model, and T cell transfer induced model, decreased disease severity was seen when the mice were treated with the surrogate mouse anti-IL-23p19 antibody as assessed by endoscopic examination and macrophage infiltration. These studies can be seen to serve as proof of concept of the potential efficacy of risankizumab in Crohn's disease.

### *2.5.2.2. Secondary pharmacodynamic studies*

The ability of risankizumab to induce ADCC or CDC was investigated. No activation of the FcγRIIIa mediated luciferase signal was seen in the ADCC reporter assay suggesting low potential for ADCC. In addition, no complement activation in human serum was observed with risankizumab, indicating no potential to elicit CDC activity.

### *2.5.2.3. Safety pharmacology programme*

n/a

### *2.5.2.4. Pharmacodynamic drug interactions*

n/a

## 2.5.3. Pharmacokinetics

No additional pharmacokinetic studies were conducted to support this application which is considered acceptable. The previously assessed pharmacokinetic studies for the original MAA, which investigated both IV and SC routes of administration, are considered sufficient to support this extension application.

## 2.5.4. Toxicology

No new nonclinical toxicology studies have been performed. The previously assessed nonclinical toxicity studies are considered sufficient to support the current application for the treatment of Crohn's disease. Considering that the dose for the new indication is higher than that authorised dose, the MAH has 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. These indicate that exposures in excess of that seen clinically were achieved.

## 2.5.5. Ecotoxicity/environmental risk assessment

The European Medicines Agency's (EMA) "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" states that an environmental risk assessment (ERA) must be provided for "products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s)." However, the "ERA may consist of a justification for not submitting ERA studies, e.g., due to their nature they are unlikely to result in a significant risk to the environment." With this, the following justification is provided in support of not completing the full suite of Phase I and II environmental studies for the ERA to be submitted with the Marketing Authorisation Application for risankizumab.

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

Only limited *in vitro* and *in vivo* primary pharmacology studies were conducted to support this application, and which provide proof of concept for the potential efficacy of risankizumab in the treatment of Crohn's disease.

No additional pharmacokinetic or toxicology studies were conducted which is acceptable and the previously assessed nonclinical toxicity studies are considered sufficient to support the current application.

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 provided nonclinical package is considered sufficient to support this extension application for the new clinical indication for the treatment of Crohn's disease.

# *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 | Objectives of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Phase 1 PK and safety | M16-533 | 5.3.3.3 | Assess the PK, safety, tolerability and immunogenicity following a single IV infusion of RZB in healthy Japanese and Caucasian subjects | Phase 1 randomized, DB, PBO-controlled study | RZB 1800 mg IV | 17 | Healthy adult[a] male Japanese and Caucasian subjects | Single dose | Complete; Full |
| Phase 1 PK and safety | M17-381 | 5.3.3.3 | Assess the PK, safety, tolerability and immunogenicity following a single SC or IV dose of RZB in healthy Chinese subjects | Phase 1 OL study | RZB 1800 mg IV<br>RZB 360 mg SC<br>RZB 150 mg SC | 30 | Healthy adult[a] male and female Chinese subjects | Single dose | Complete; Full |

| Type of Study | Study ID | Location of Study Report | Objectives of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Phase 1, BA | M16-324 | 5.3.1.1 | Evaluate the effect of rate and volume of administration on the BA of RZB after SC administration. Evaluate the safety and tolerability of RZB after SC administration. | Phase 1 randomized, OL parallel-group study | RZB 216 mg administered as 3 SC injections of 0.8 mL each,<br>RZB 216 mg SC administered over 3 minutes with syringe pump,<br>RZB 216 mg SC administered over 6 minutes with syringe pump,<br>RZB 180 mg administered as single 2 mL injection | 48 | Healthy adult[b] male subjects | Single dose | Complete, Full |

| Type of Study | Study ID | Location of Study Report | Objectives of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Phase 1, BE | M19-128 | 5.3.1.2 | Substudy 1: Assess the relative BA of RZB in the to-be-marketed 360 mg OBDS vs the 90 mg PFS used in the Phase 3 studies following a single SC administration at the dose of 360 mg.<br>Assess the PK of RZB in a to-be-marketed 180 mg OBDS following a single SC administration at the dose of 180 mg.<br>Substudy 2: Assess the relative bioavailability of risankizumab in the to-be-marketed 600 mg liquid vial versus the 300 mg liquid vial used in the Phase 3 studies following a single IV administration of 1800 mg. | Phase 1, randomized, OL, parallel-group study | Substudy 1:<br>RZB (90 mg/mL) 90 mg PFS × 4 SC,<br>RZB (150 mg/mL) 360 mg OBDS × 1 SC,<br>RZB (150 mg/mL) 180 mg OBDS × 1 SC<br><br>Substudy 2:<br>RZB (90 mg/mL) 1800 mg IV,<br>RZB (60 mg/mL) 1800 mg IV | 394 | Healthy adult[c] subjects | Single dose | Complete; Full |

| Type of Study | Study ID | Location of Study Report | Objectives of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Phase 2 Efficacy and Safety | M15-993 (1311.6) | 5.3.5.1 | Evaluate the efficacy of RZB in inducing clinical remission, defined as CDAI < 150, after 12 weeks of treatment.<br>Evaluate the efficacy of RZB in inducing endoscopic response, clinical response, mucosal healing, and deep remission.<br>Evaluate the safety of RZB<br>Explore the PK and PD of RZB therapy in CD | Randomized, DB, PBO-controlled, parallel-group, dose-ranging | RZB 200 mg IV q4w,<br>RZB 600 mg IV q4w,<br>RZB 180 mg SC q8w | 121 | Adult[d] of risankizumab in subjects with moderately to severely active CD | 67 weeks | Complete; Full |

| Type of Study | Study ID | Location of Study Report | Objectives of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Phase 2 Efficacy and Safety | M15-989 (1311.20) | 5.3.5.2 | Investigate long-term safety of RZB in patients with moderately to severely active Crohn's disease, who showed a clinical response or remission on previous treatment with RZB and were receiving long-term treatment.<br>Investigate long-term efficacy, tolerability, PK, PD, and immunogenicity of RZB | OL, single group, roll-over LTE | RZB 180 mg SC q8w<br>RZB 600 mg IV q4w | 65 | Adults[d] with moderate to severely active CD with clinical response or remission after previous treatment with RZB | Approx. 4 years | Complete; Abbreviated |
| Phase 3 Efficacy and Safety | M15-991 (1311.7) | 5.3.5.1 | Evaluate the efficacy and safety of RZB vs PBO as induction therapy in subjects with moderately to severely active CD who have failed a prior biologic | Randomized, DB, PBO-controlled | RZB:<br>1200 mg IV q4w<br>600 mg IV q4w<br>360 mg SC q8w<br>180 mg SC q8w | 618 | Adults[e] and adolescents (16 to < 18 years) with moderate to severely active CD | 20 weeks | Complete; Full |

| Type of Study | Study ID | Location of Study Report | Objectives of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Phase 3 Efficacy and Safety | M16-006 | 5.3.5.1 | Evaluate the efficacy and safety of RZB vs PBO during induction therapy in subjects with moderately to severely active CD | Randomized, DB, PBO-controlled | RZB:<br>1200 mg IV q4w<br>600 mg IV q4w<br>360 mg SC q8w<br>180 mg SC q8w | 931 | Adults[e] and adolescents (16 to < 18 years) with moderate to severely active CD | 20 weeks | Complete; Full |
| Phase 3 Efficacy and Safety | M16-000 Substudy 1 | 5.3.5.1 | Evaluate the efficacy and safety of risankizumab vs PBO as maintenance therapy in subjects with moderately to severely active CD who responded to IV risankizumab induction treatment in Study M16-006 or Study M15-991 | Randomized, DB, PBO-controlled | RZB:<br>360 mg SC q8w<br>180 mg SC q8w<br>1200 mg IV | 1250 | Adults[e] and adolescents (16 to < 18 years) with moderate to severely active CD subjects who have completed Study M16-006 or Study M15-991 and have achieved clinical response, defined as ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score and both not worse than BL of the induction study | 52 weeks | Ongoing; Interim; Full (Substudy 1) |

AP = abdominal pain; BA = bioavailability; BE = bioequivalence; BL = Baseline; CD = Crohn's Disease; CDAI = CDAI = Crohn's Disease Activity Index; CSR = clinical study report; DB = double-blind; DDI = drug-drug interaction; IV = intravenous; LTE = long-term extension; OBDS = on-body delivery system; OL = open-label; PBO = placebo;

Only part of Phase 3 study M16-000, Sub-Study 1, is included in this assessment as pivotal.

Sub-Study 2, also a 52-week maintenance study, is an ongoing randomized study with the objective of evaluating 2 methods of dose-escalation for subjects with loss of response during maintenance treatment; results are not included in this submission.

Sub-Study 3 is an ongoing open-label (OL) extension with the objective of collecting long-term safety data; results are not included in this submission.

## 2.6.2. Clinical pharmacology

### *2.6.2.1. Pharmacokinetics*

The pharmacokinetics, pharmacodynamics, immunogenicity, and exposure-response relationships for efficacy and safety of risankizumab have been well characterized in healthy subjects and subjects with moderate to severe plaque psoriasis. The MAH submitted 4 phase I studies: M16-324 which compared the bioavailability of Rizankizumab following IV and different methods of SC administration and aimed to inform drug product development; M19-128, which aimed to demonstrate bioequivalence between the to be marketed product (administered SC via an 'on-body delivery system') and the formulation and method of administration used in the pivotal phase III studies; M16-533 and M17-381 investigating PK following administration of Rizankizumab to Japanese and Chinese subjects respectively. To support the registration in CD, additional clinical pharmacology assessments were conducted in two Phase II studies (Studies M15-993 and M15-989) and three pivotal Phase III studies (Studies M15-991, M16-006, and M16-000) in subjects with CD.

Bioanalytical methods

*Risankizumab serum concentration*

During the previously approved line extension for the 150 mg/mL formulation of Skyrizi (EMEA/H/C/004759/X/012) in both pre-filled syringe and pre-filled pen, a bridging Electrochemiluminescence (ECL) assay was developed and validated to quantitatively determine risankizumab (ABBV-066) 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 as per the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009/Rev. 1). This method was also partially validated for selectivity/matrix interference for CD patient's serums. The method was transferred and validation performed using healthy and CD patient's serum. The defined assay performance specifications and the method validation carried are in general, in line with the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 rev.1 corr.2). Sample analysis for Risankizumab concentrations in human serum for the pivotal Phase 3 CD Studies was conducted at two sites. A cross-validation for the validated serum assay and results show the methods to be comparable.

*Anti-drug antibody assay*

The overall approach to measuring immunogenicity is in line with the recommendations of the EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1) and the EMA Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use (EMA/CHMP/BMWP/86289/2010).

The ADA method was validated as per the recommendations of the relevant EMA guidelines. The approach taken is acceptable and follows the principles of the previous method validations to establish cut-points for CD patients' serum.

A cross-validation for the validated serum assay was also performed. The data presented demonstrate full comparability of serum assay results.

*Neutralising antibody assay*

The MAH has provided an adequate method description and validation of the method used to evaluate neutralizing anti- Risankizumab (NAb) levels in human serum of healthy donors and CD patients. The overall approach to measuring immunogenicity is in line with the recommendations of the EMA

Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1) and the EMA Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use (EMA/CHMP/BMWP/86289/2010).

Population PK Analyses

The popPK analyses included data from subjects with moderately to severely active CD in Phase 2 Studies M15-993 and M15-989, Phase 3 Induction Studies M15-991and M16-006, and Phase 3 Maintenance Study M16-000 and healthy volunteers in Phase 1 Study M16-533. A total of 6851 concentrations from 1404 subjects (1392 CD subjects and 12 healthy subjects) were included in the analyses.

A previously developed popPK model that described risankizumab pharmacokinetics in patients with moderate to severe plaque psoriasis and CD served as the starting model for the analyses. The final

model was a two-compartment model with a first-order absorption for SC administration and first-order elimination. Parameter estimates for the final model are presented in Table 1.

*Table 1 Fixed and Random Effects Parameter Estimates for Risankizumab Final Population Pharmacokinetic Model*

| Parameter | Population Estimate (SEE) | %RSE[a] | 95% Confidence Interval |
|---|---|---|---|
| **Pharmacokinetic Parameters** | | | |
| Clearance (CL; L/day) | 0.296 (0.00460) | 1.55 | (0.287, 0.305) |
| Central Volume of Distribution ($V_c$; L) | 4.98 (0.187) | 3.76 | (4.61, 5.35) |
| Inter-Compartmental Clearance (Q; L/day) | 0.255 (0.0107) | 4.20 | (0.234, 0.276) |
| Peripheral Volume of Distribution ($V_p$; L) | 2.70 (0.0572) | 2.12 | (2.59, 2.81) |
| Absorption Rate Constant (Ka; $day^{-1}$) | 0.121 (0.00997) | 8.24 | (0.101, 0.141) |
| Absolute SC Bioavailability (F) | 0.740 (0.00663) | 0.896 | (0.727, 0.753) |
| Exponent for the Effect of Body Weight on Risankizumab Clearance (CL) | 0.437 (0.0577) | 13.2 | (0.324, 0.550) |
| Exponent for the Effect of Body Weight on Risankizumab Central Volume of Distribution ($V_c$) | 0.911 (0.144) | 15.8 | (0.629, 1.19) |
| Exponent for the Effect of Baseline Serum Albumin on Risankizumab Clearance (CL) | -1.28 (0.0650) | 5.08 | (-1.41, -1.15) |
| Exponent for the Effect of Baseline Fecal Calprotectin on Risankizumab Clearance (CL) | 0.0482 (0.00656) | 13.6 | (0.0353, 0.0611) |
| Time varying Corticosteroid use on Risankizumab (CL) | 0.0661 (0.00943) | 14.3 | (0.0476, 0.0846) |
| Exponent for the Effect of Baseline Creatinine Clearance on Risankizumab Clearance (CL) | 0.180 (0.0315) | 17.5 | (0.118, 0.242) |
| Exponent for the Effect of Sex on Risankizumab Clearance (CL) | -0.0723 (0.0150) | 20.7 | (-0.102, -0.0429) |
| **Inter-Individual and Residual Variability** | | | |
| Variance of Inter-Individual Variability in CL, %CV[b], exponential error model | 0.109, 33.9 | 3.17 | (0.102, 0.116) |
| Variance of Inter-Individual Variability in $V_c$, %CV[b], exponential error model | 0.345, 64.2 | 7.10 | (0.297, 0.393) |
| Variance of Inter-Individual Variability in Ka, %CV[b], exponential error model | 1.03, 134 | 7.51 | (0.878, 1.18) |
| Variance of Covariance between Inter-Individual Variability in CL and $V_c$, %CV[b], %Correlation | 0.122, 62.9 | 6.91 | (0.105, 0.139) |
| Variance of Proportional Residual Error | 0.0553 (0.000487) | 0.881 | (0.0543, 0.0563) |

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. %CV = SQRT[exp($\omega^2$)-1]*100.

Risankizumab systemic clearance (CL), central volume of distribution (Vc), peripheral volume of distribution (Vp), volume of distribution at steady state (Vss), bioavailability (F), and terminal half-life

(t1/2) were estimated to be approximately 0.296 L/day, 4.98 L, 2.70 L, 7.68 L, 74.0%, and 21 days respectively, for a 70 kg subject. These estimates were similar to those in subjects with moderate to severe chronic plaque psoriasis and psoriatic arthritis.

The VPCs for the final model are shown in Figures 1, 2 and 3.

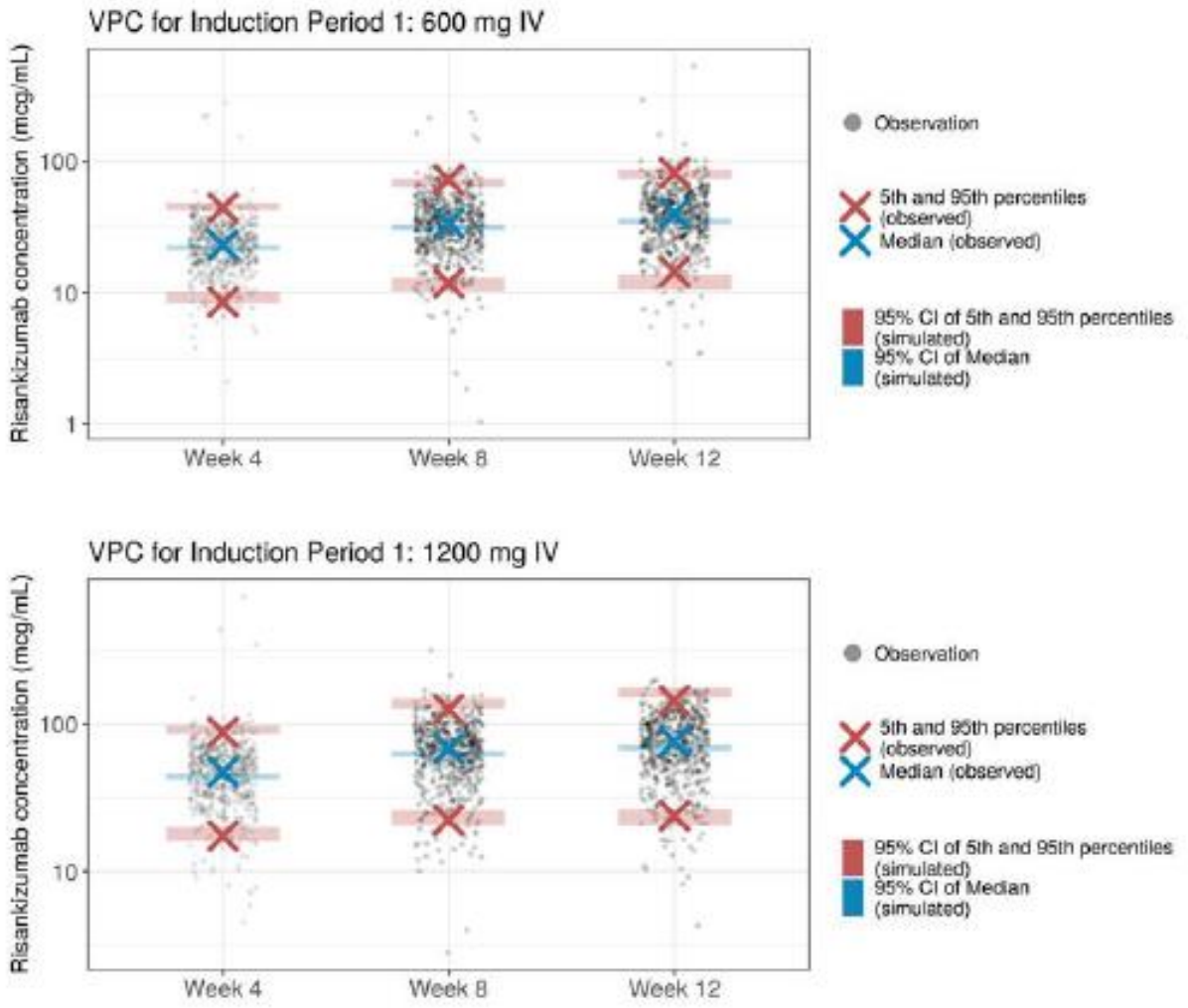



*Figure 1 Visual Predictive Checks for Pre-Dose Samples by Induction Dose Using the Final Population Pharmacokinetic Model - 12-week Induction Period*

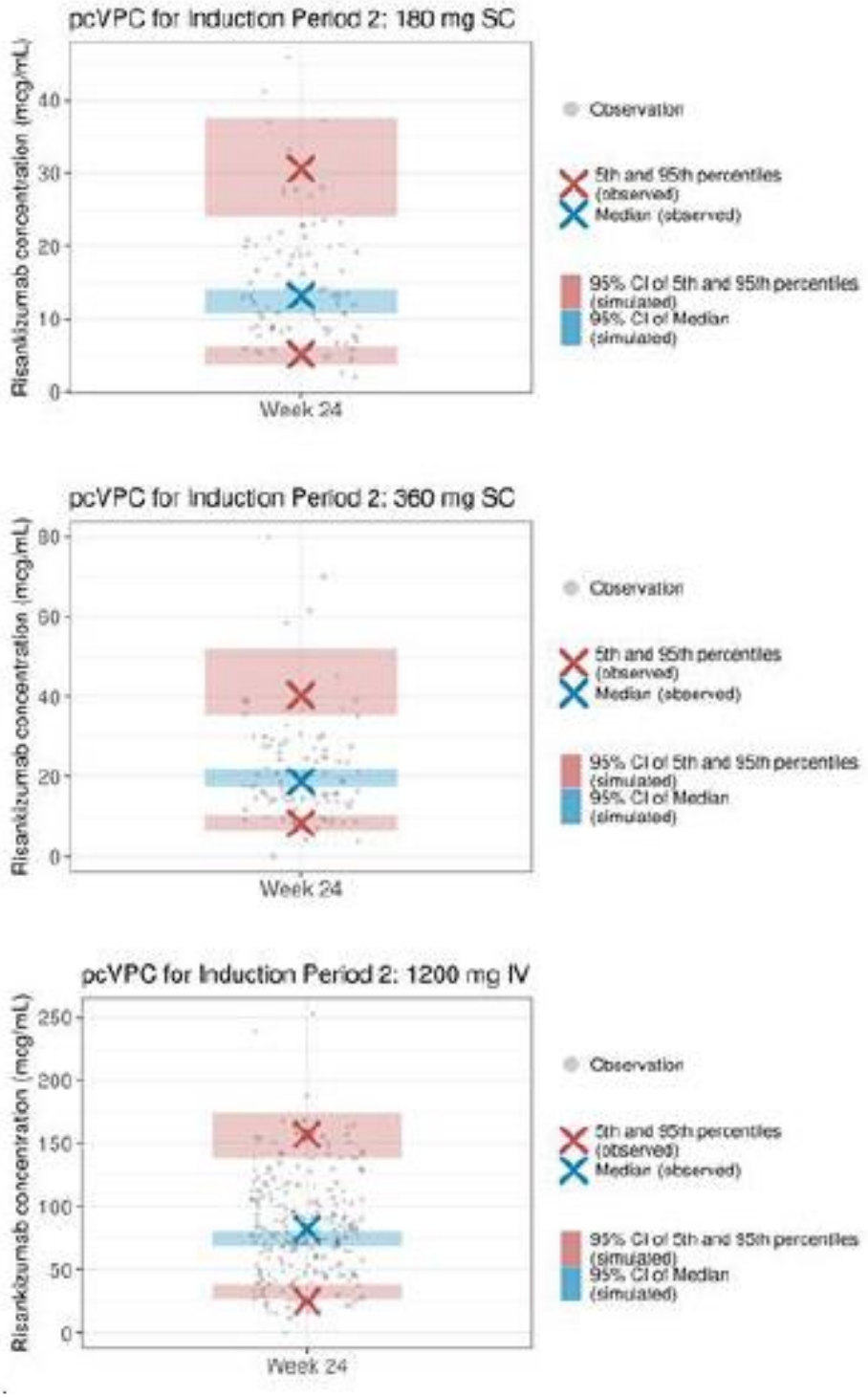



*Figure 2 Prediction Corrected Visual Predictive Checks for Pre-Dose Samples by Induction Dose Using the Final Population Pharmacokinetic Model - Induction Period 2*

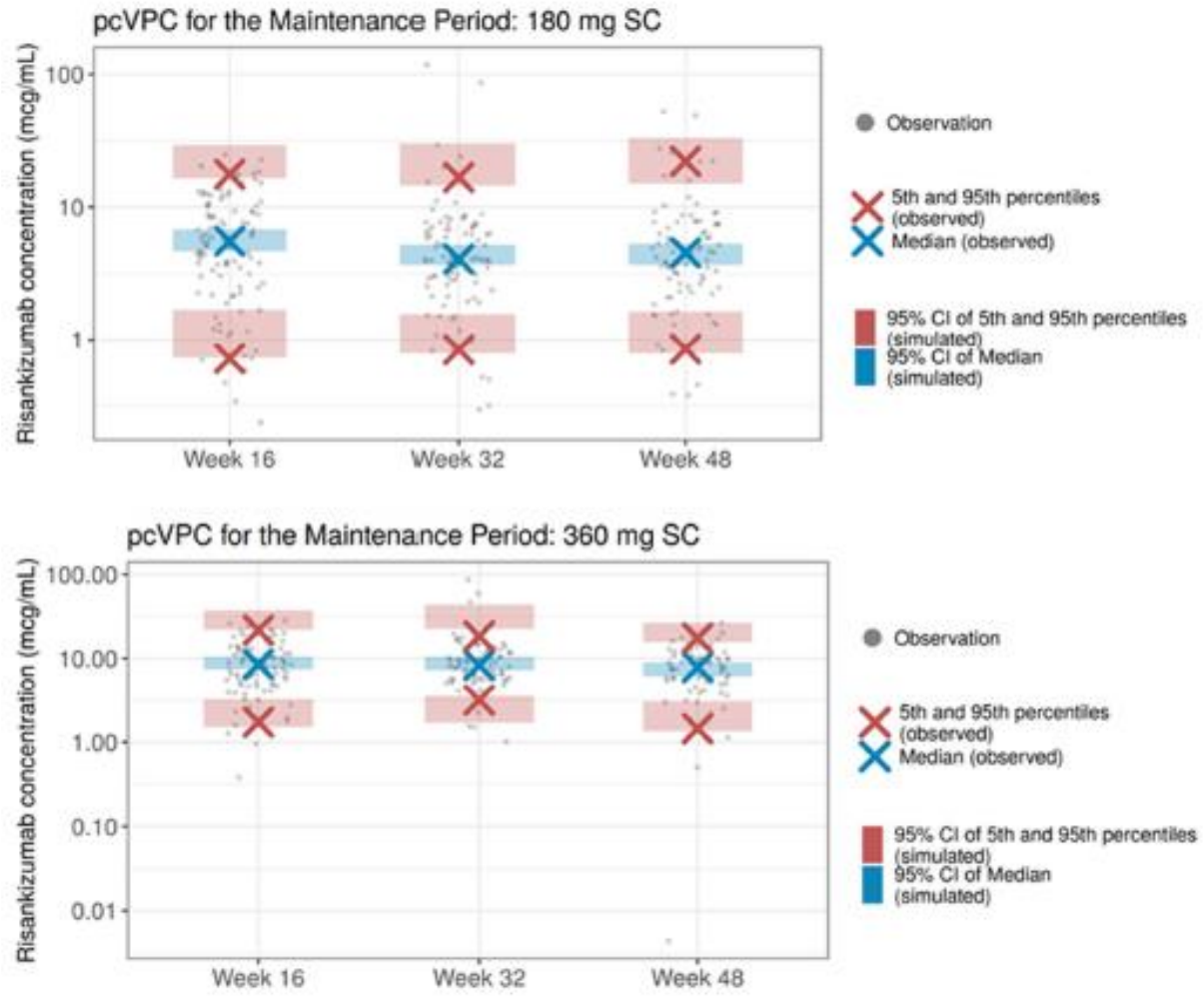
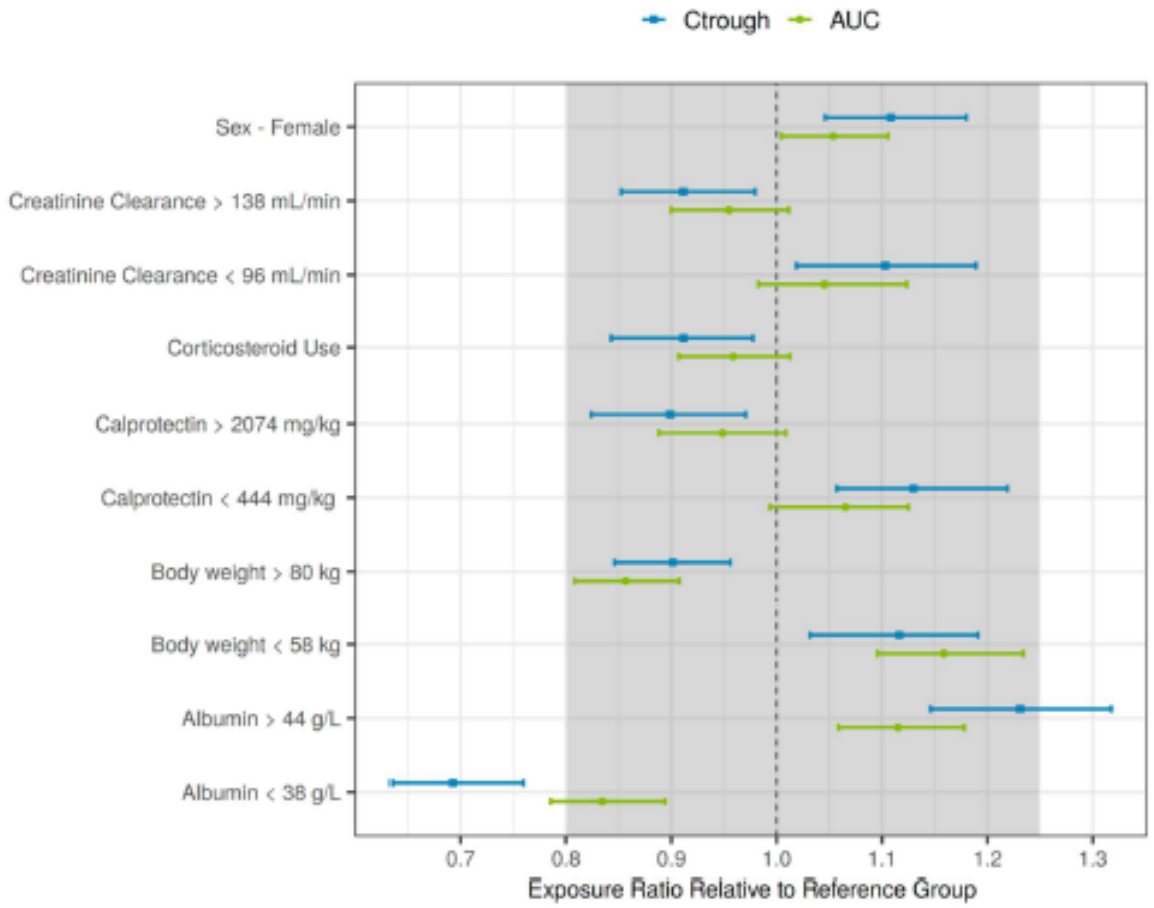



*Figure 3 Prediction Corrected Visual Predictive Checks by Maintenance Dose Using the Final Population Pharmacokinetic Model*

*Impact of covariates on risankizumab exposures*

Simulations showed that only low baseline serum albumin (< 38 g/L) had potentially meaningful impact on the Week 12 trough exposure of risankizumab in CD subjects. These subjects were predicted to have on average 31% lower Week 12 trough exposures compared to subjects with serum albumin within the reference range (38 g/L to 44 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 (Figure 4).

Besides baseline serum albumin, none of the other statistically significant covariates identified showed a meaningful impact on risankizumab exposures. Over the evaluated covariate ranges for body weight, faecal calprotectin, corticosteroid use, and creatinine clearance, risankizumab exposures were estimated to be within the default equivalence boundaries of 0.8 to 1.25 relative to the reference groups (Figure 4).




Effect of covariates on risankizumab simulated exposures in subjects with CD. 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 AUC is the model predicted average concentration over the 12 weeks induction period.

*Figure 4 Forest Plot to Demonstrate the Impact of Covariates Identified in the Population Pharmacokinetic Analyses on Risankizumab Exposures*

Race, age, anti-drug antibodies and neutralizing antibodies were not identified as statistically significant covariates during the covariate search.

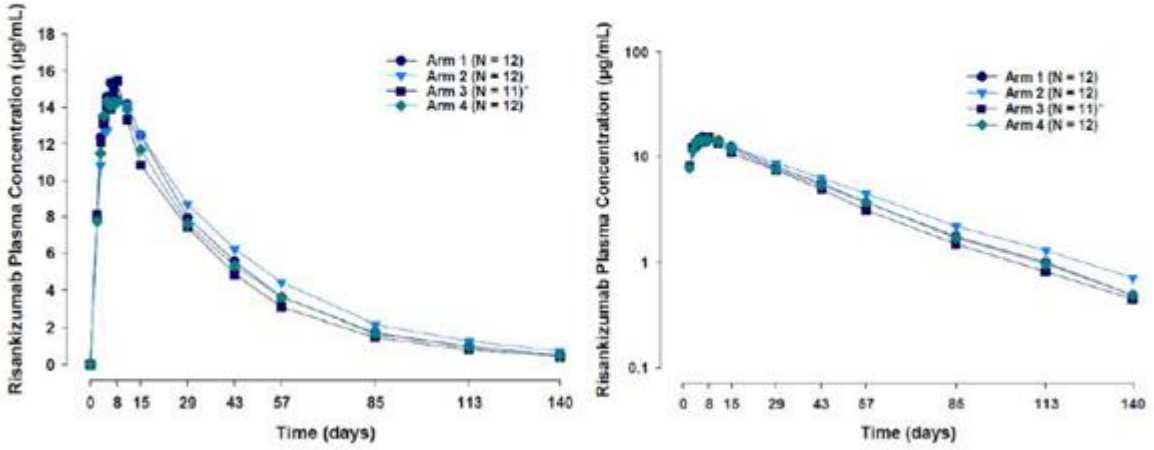
***Absorption***

Bioavailability

Study M16-324 was a Phase 1, single-dose, 4-arm, open-label, randomized, parallel-group study to determine the relative bioavailability of risankizumab and the extent of injection-site related pain following SC administration at varying rates and volumes of risankizumab in healthy subjects. The results of the study were used to inform the development of the "to-be-marketed" drug presentation for SC administration. The study enrolled 48 adult male subjects and randomised them to receive either: Three SC injections of 0.8 mL each (216 mg; Reference); 2.4 mL administered SC using a syringe pump over 3 minutes (216 mg; Test); 2.4 mL administered SC using a syringe pump over 6 minutes (216 mg; Test); or one SC injection of 2 mL (180 mg; Test). Blood samples for analysis of risankizumab concentrations were collected on Days 1 (pre-dose), 2, 3, 4, 5, 6, 7, 8, 11, 15, 29, 43, 57, 85, 113, and 140. ADA samples were collected on Days 1 (pre-dose), 15, 29, 57, 85, and 140.

*Results*

**Mean Risankizumab Plasma Concentration-Time Profiles Following a Single SC Dose Administration in Healthy Subjects, Linear and Log-Linear Scales (Study M16-324)**




**Geometric Mean (Arithmetic Mean, % CV) Pharmacokinetic Parameters of Risankizumab Following a Single SC Dose Administration in Healthy Subjects**

| Pharmacokinetic Parameters (units) | Risankizumab | | | |
|---|---|---|---|---|
| | Arm 1<br>Three 0.8 mL SC injections<br>(216 mg, Reference)<br>N = 12 | Arm 2<br>2.4 mL syringe pump over<br>3 mins<br>(216 mg, Test)<br>N = 12 | Arm 3<br>2.4 mL syringe pump over<br>6 mins<br>(216 mg, Test)<br>N = 11[a] | Arm 4<br>One 2 mL SC injection<br>(180 mg, Test)<br>N = 12 |
| $C_{max}$ (µg/mL) | 15.6 (16.0, 22) | 15.0 (15.6, 29) | 15.8 (16.1, 21) | 15.0 (15.7, 29) |
| $T_{max}$[b] (day) | 6 (4 – 10) | 7 (4 – 14) | 6 (2 – 7) | 6 (3 – 10) |
| $AUC_t$ (µg•day/mL) | 609 (616, 16) | 656 (671, 20) | 537 (555, 28) | 583 (594, 20) |
| $AUC_{inf}$ (µg•day/mL) | 628 (636, 17) | 689 (707, 22) | 554 (577, 32) | 605 (616, 19) |
| $C_{max}$/Dose (µg/mL)/mg | 0.072 (0.074, 22) | 0.070 (0.072, 29) | 0.073 (0.075, 21) | 0.084 (0.087, 29) |
| $AUC_{inf}$/Dose (µg•day/mL)/mg | 2.91 (2.94, 17) | 3.19 (3.27, 22) | 2.56 (2.67, 32) | 3.36 (3.42, 19) |
| $t_{1/2}$[c] (day) | 25.9 (5.59) | 30.9 (7.03) | 21.7 (8.59) | 28.6 (7.72) |
| CL/F (L/day) | 0.344 (0.349, 17) | 0.313 (0.323, 28) | 0.390 (0.405, 28) | 0.298 (0.303, 22) |

a. One subject prematurely discontinued from the study and was included in the descriptive statistics for pharmacokinetic parameters except for: $C_{max}$, $T_{max}$ and dose-normalized $C_{max}$.

b. Median (minimum through maximum).

c. Harmonic mean (pseudo-standard deviation); evaluations of $t_{1/2}$ were based on statistical tests for β.

**90% CIs for the Two One-Sided Tests Procedures for Risankizumab $C_{max}$ and AUC across Arms 2 through 4 Relative to Arm 1**

| Regimens Test vs. Reference | Pharmacokinetic Parameter (units) | Central Values[a] | | Relative Bioavailability | |
|---|---|---|---|---|---|
| | | Test | Reference | Point Estimate[b] | 90% CI[c] |
| Arm 2: 216 mg administered (2.4 mL) over 3 minutes with syringe pump vs. Arm 1: 216 mg administered as three 0.8 mL SC injections | $C_{max}$ (µg/mL) | 15.11 | 15.60 | 0.968 | 0.810 – 1.157 |
| | $AUC_t$ (µg•day/mL) | 658 | 609 | 1.079 | 0.926 – 1.258 |
| | $AUC_{inf}$ (µg•day/mL) | 691 | 628 | 1.100 | 0.932 – 1.299 |
| Arm 3: 216 mg administered (2.4 mL) over 6 minutes with syringe pump vs. Arm 1: 216 mg administered as three 0.8 mL SC injections | $C_{max}$ (µg/mL) | 15.61 | 15.60 | 1.001 | 0.837 – 1.196 |
| | $AUC_t$ (µg•day/mL)[d] | 535 | 609 | 0.878 | 0.750 – 1.026 |
| | $AUC_{inf}$ (µg•day/mL)[d] | 552 | 628 | 0.878 | 0.741 – 1.041 |
| Arm 4: 180 mg administered as single 2 mL injection vs. Arm 1: 216 mg administered as three 0.8 mL SC injections | $C_{max}$/Dose (µg/mL)/mg | 0.08 | 0.07 | 1.149 | 0.935 – 1.412 |
| | $AUC_t$/Dose (µg•day/mL)/mg | 3.22 | 2.83 | 1.137 | 1.002 – 1.290 |
| | $AUC_{inf}$/Dose (µg•day/mL)/mg | 3.34 | 2.92 | 1.145 | 1.007 – 1.301 |

a. Antilogarithm of the least squares means for logarithms.
b. Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.
c. Antilogarithm of the endpoints of confidence intervals for the difference of logarithms means.
d. Subject 229 prematurely discontinued from the study and was not included in this analysis.

Baseline and treatment-emergent ADA incidence ranged from 8.3% to 25% and 0% to 50%, respectively, across all treatment arms, with no apparent impact on pharmacokinetics or safety.

Bioequivalence

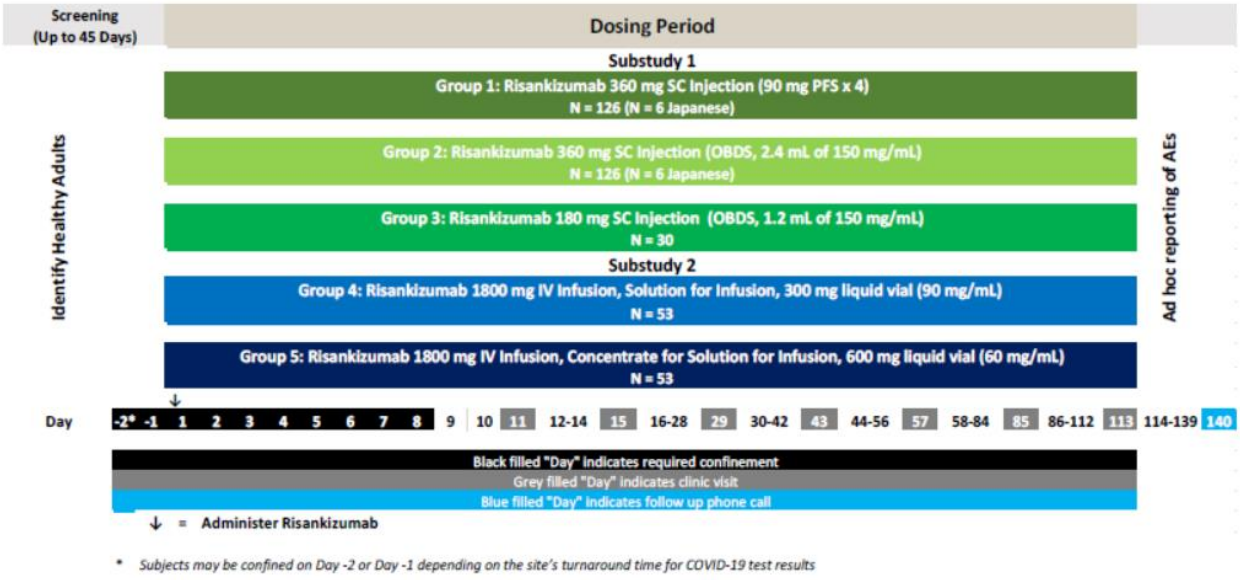
Study M19-128 was a Phase 1, single-dose, randomized, open-label, multi-center study, comprised of two substudies, in healthy volunteers.

Substudy 1 was designed to assess the relative bioavailability of risankizumab in the to-be-marketed 360 mg OBDS (single SC administration of 2.4 mL) versus the 90 mg PFS (4 × SC administrations of 1 mL) used in the Phase 3 CD studies. Additionally, Substudy 1 assessed the pharmacokinetics of risankizumab in a 180 mg OBDS following a single SC administration of 1.2 mL at the dose of 180 mg. Substudy 2 was designed to assess the relative bioavailability of risankizumab in the to-be-marketed 600 mg liquid vial versus the 300 mg liquid vial used in the Phase 3 CD studies following a single IV administration of 1800 mg.

The study recruited healthy male and female participants aged between 21 and 58 years old with a BMI of between 19-32 kg/m2. Enrolment was stratified by body weight as per the table below:

| Weight Category | Body Weight (kg) |
|---|---|
| 1 | < 60 |
| 2 | ≥ 60 to < 70 |
| 3 | ≥ 70 to < 80 |
| 4 | ≥ 80 to < 90 |
| 5 | ≥ 90 to < 100 |

A total of 394 subjects were randomized 4:4:1 in Sub-Study 1 and 1:1 in Sub-Study 2, and a total of 393 subjects received a single dose of risankizumab as follows:




Baseline demographics and datasets analysed

The mean age in groups 1 through 5 were 38.4, 37.9, 37.4, 39.3 and 40.6 years respectively. Mean BMI was 25.6, 25.5, 26.5, 25.6, and 25.5 kg/m$^2$ for groups 1 through 5 respectively.

Available data from all subjects (N = 393, Substudy 1 (N = 286) and Substudy 2 (N = 107)) were included in the safety analyses, and data from 356 subjects (Substudy 1 (N = 258) and Substudy 2 (N = 98)) who received risankizumab were included in the statistical analyses of the pharmacokinetic parameters, with the exceptions noted below.

Substudy 1:

- Ten subjects had OBDS-related dosing failures. One of those subjects did not receive a risankizumab dose and was excluded from all pharmacokinetic parameter calculations.
- One subject experienced drug leakage following OBDS drug administration.
- One subject violated the study protocol by enrolling in two treatment groups of Substudy 1 and thus had two unique subject IDs.
- Eight subjects violated study protocol by enrolling in both Substudy 1 and Substudy 2, and thus had two unique subject IDs.
- Eight subjects discontinued from the study and therefore had incomplete pharmacokinetic profiles that were not sufficient to allow for reliable non-compartmental estimates of pharmacokinetic parameters.

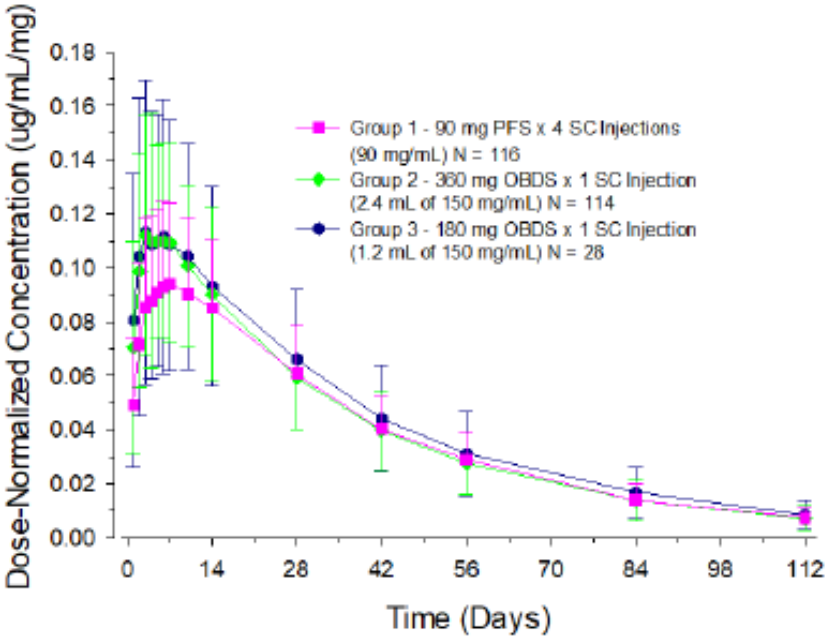
Substudy 2:

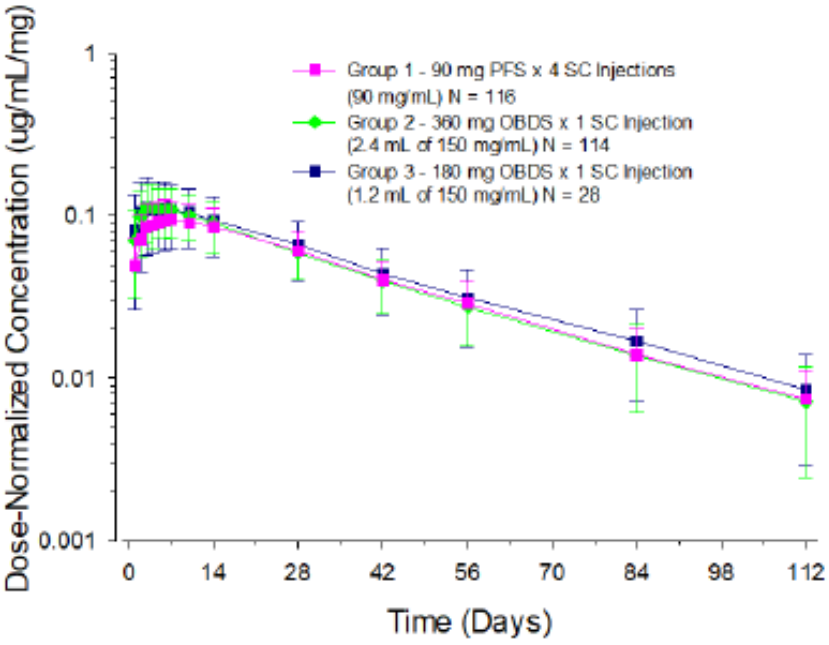
- One subject (risankizumab 1800 mg IV, Group 4) withdrew consent on Day 2 and had only 24 hours of concentration-time profile, which was not sufficient to allow for reliable non-compartmental estimates of pharmacokinetic parameters.
- Eight subjects violated study protocol by enrolling in both Substudy 1 and Substudy 2, and thus had two unique subject IDs.

Pharmacokinetic results

*Sub-study 1*

Geometric mean serum Rizankizumab concentration versus time curves on linear and log-linear scales are presented by treatment group below:




A summary of the pharmacokinetic parameters of risankizumab by group following a single SC dose administration in healthy subjects is shown in Table 2.

*Table 2 Geometric Mean (Arithmetic Mean, % CV) Pharmacokinetic Parameters of Risankizumab Following a Single SC Dose Administration in Healthy Subjects*

| | Risankizumab | | | | |
|---|---|---|---|---|---|
| Pharmacokinetic Parameters (units) | Group 1 360 mg SC injection (90 mg PFS × 4) N = 116 | Group 2 360 mg OBDS SC injection (2.4 mL of 150 mg/mL) N = 114 | Group 3 180 mg OBDS SC Injection (1.2 mL of 150 mg/mL) N = 28 | Group 1 (Japanese) 360 mg SC injection (90 mg PFS × 4) N = 7 | Group 2 (Japanese) 360 mg OBDS SC injection (2.4 mL of 150 mg/mL) N = 8 |
| $C_{max}$ (µg/mL) | 34.3 (36.1, 32) | 42.1 (44.6, 39) | 20.2 (22.1, 45) | 42.3 (44.4, 30) | 40.8 (42.1, 25) |
| $T_{max}$[a] (day) | 7.0 (2.0 – 30.0) | 5.0 (2.0 – 14.0) | 5.0 (2.0 – 28.0) | 10.0 (3.0 – 14.0) | 5.5 (3.0 – 14.0) |
| $t_{1/2}$[b] (day) | 27.0 (5.54)[c] | 26.2 (5.86) | 27.8 (6.26) | 26.6 (6.44) | 29.5 (6.93) |
| $AUC_t$ (µg•day/mL) | 1440 (1510, 30) | 1500 (1590, 36) | 755 (830, 47) | 1700 (1800, 36) | 1710 (1760, 23) |
| $AUC_{inf}$ (µg•day/mL) | 1570 (1650, 30)[c] | 1640 (1730, 37) | 902 (983, 50) | 1820 (1930, 37) | 1870 (1920, 25) |
| $C_{max}$/Dose (µg/mL)/mg | 0.0951 (0.100, 32) | 0.117 (0.124, 39) | 0.112 (0.123, 45) | 0.118 (0.123, 30) | 0.113 (0.117, 25) |
| $AUC_t$/Dose (µg•day/mL)/mg | 4.01 (4.19, 30) | 4.17 (4.41, 36) | 4.20 (4.61, 47) | 4.72 (5.00, 36) | 4.76 (4.88, 23) |
| $AUC_{inf}$/Dose (µg•day/mL)/mg | 4.36 (4.57, 30)[c] | 4.57 (4.81, 37) | 5.01 (5.46, 50) | 5.05 (5.36, 37) | 5.19 (5.34, 25) |

a. Median (minimum through maximum).

b. Harmonic mean (pseudo-standard deviation); evaluations of $t_{1/2}$ were based on statistical tests for β.

c. N = 114

Note: 28 subjects from Substudy 1 are excluded from analysis (11 subjects for dosing failures or related issues; 8 subjects for incomplete pharmacokinetic profiles without terminal phase; 8 subjects for violating eligibility criterion #23 from protocol by enrolling in both substudies; 1 subject for violating eligibility criterion #23 from protocol by enrolling in two treatment groups of Substudy 1).

Following the administration of a single 360 mg SC dose, mean risankizumab concentrations in Group 2 (360 mg OBDS × 1 SC injection) were higher during the absorption phase when compared to Group 1 (90 mg PFS × 4 SC injections), but overlapping pharmacokinetic profiles were observed during the elimination phase. Thus, the pharmacokinetic parameters between the 90 mg PFS (4 × 90 mg/mL) and 360 mg OBDS groups were largely comparable with the exception of a higher Cmax for the 360 mg OBDS group. The dose-normalized risankizumab concentration-time profiles were overlapping between Group 2 (360 mg OBDS × 1 SC injection) and Group 3 (180 mg OBDS × 1 SC injection), with comparable pharmacokinetic parameters, indicating linearity between the 360 and 180 mg SC doses when administered via the OBDS device.

Following SC administration of a single 360 mg or 180 mg dose across Groups 1 to 3, median time to maximum serum concentrations was approximately five days after dosing with the OBDS device and approximately seven days after dosing with PFS, however, the Tmax ranges overlapped across the three groups. Risankizumab t1/2 was generally comparable across drug presentations and doses, with harmonic means ranging from 26 to 28 days.

Bioequivalence assessment

The relative bioavailability of the risankizumab 360 mg OBDS compared to the risankizumab 90 mg PFS (4 × 90 mg/mL) based on log-transformed Cmax, AUCt and AUCinf is presented below. The relative bioavailability of the risankizumab 180 mg OBDS compared to the risankizumab 360 mg OBDS based on dose-normalized log-transformed Cmax, AUCt and AUCinf is also presented in Table 3.

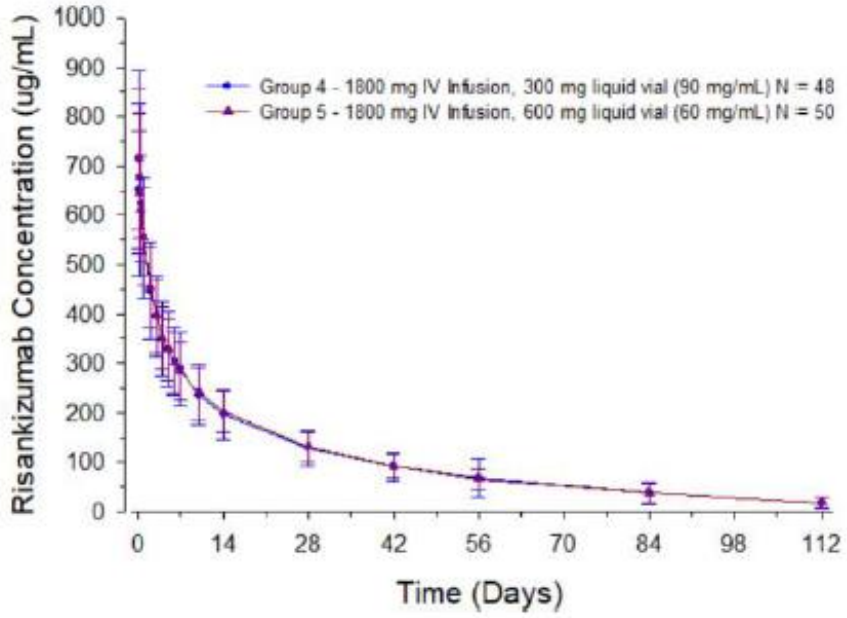
*Table 3 Point Estimate and 90% Confidence Interval for the Bioavailability of the Risankizumab 360 mg OBDS Relative to the 90 mg PFS and Risankizumab 180 mg OBDS Relative to the 360 mg OBDS*

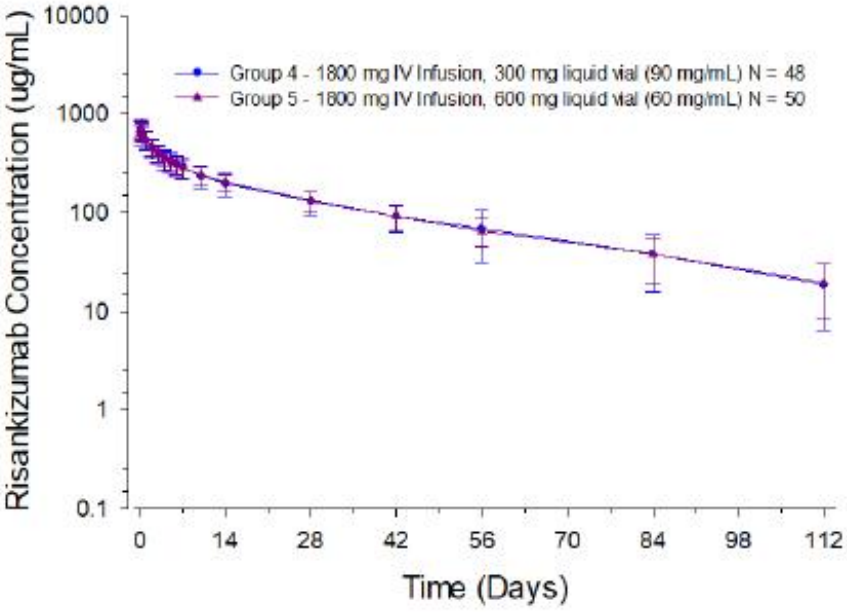
| Groups<br>Test vs. Reference | Pharmacokinetic Parameter (units) | Central Values | | Relative Bioavailability | |
|---|---|---|---|---|---|
| | | Test | Reference | Point Estimate | 90% Confidence Interval |
| **Group 2: Risankizumab 360 mg OBDS × 1 SC Injection (2.4 mL of 150 mg/mL) vs. Group 1: Risankizumab 90 mg PFS × 4 SC Injections (4 mL of 90 mg/mL)** | $C_{max}$ (µg/mL) | 43.1 | 34.1 | 1.263 | 1.184 – 1.347 |
| | $AUC_t$ (µg•day/mL) | 1555 | 1461 | 1.065 | 1.000 – 1.134 |
| | $AUC_{inf}$ (µg•day/mL) | 1700 | 1588 | 1.070 | 1.010 – 1.134 |
| **Group 3: Risankizumab 180 mg OBDS × 1 SC Injection (1.2 mL of 150 mg/mL) vs. Group 2: Risankizumab 360 mg OBDS × 1 SC Injection (2.4 mL of 150 mg/mL)** | $C_{max}$/Dose (µg/mL/mg) | 0.110 | 0.114 | 0.967 | 0.861 – 1.087 |
| | $AUC_t$ /Dose (µg•day/mL/mg) | 4.257 | 4.225 | 1.008 | 0.894 – 1.137 |
| | $AUC_{inf}$ /Dose (µg•day/mL/mg) | 5.057 | 4.596 | 1.100 | 0.994 – 1.218 |

Note: 28 subjects from Substudy 1 are excluded from analysis (11 subjects for OBDS-dosing failures or related issues; 8 subjects for incomplete pharmacokinetic profiles without terminal phase; 8 subjects for violating eligibility criterion #23 from the protocol by enrolling in both substudies; 1 subject for violating eligibility criterion #23 from the protocol by enrolling in two treatment groups of Substudy 1).

*Sub-study 2*

Geometric mean serum Rizankizumab concentration versus time curves on linear and log-linear scales are presented by treatment group below:




A summary of the pharmacokinetic parameters of risankizumab by group following a single IV dose administration in healthy subjects is shown in Table 4.

*Table 4 Geometric Mean (Arithmetic Mean, % CV) Pharmacokinetic Parameters of Risankizumab Following a Single IV Dose Administration in Healthy Subjects*

| Pharmacokinetic Parameters (units) | Group 4 Risankizumab 1800 mg IV (300 mg liquid vial) N = 48 | Group 5 Risankizumab 1800 mg IV (600 mg liquid vial) N = 50 |
|---|---|---|
| $C_{max}$ (µg/mL) | 723 (742, 25) | 716 (730, 20) |
| $T_{max}$[a] (day) | 0.167 (0.125 – 0.500) | 0.167 (0.125 – 1.00) |
| $t_{1/2}$[b] (day) | 27.1 (6.15) | 28.3 (6.71) |
| $AUC_t$ (µg•day/mL) | 10700 (11100, 30) | 11400 (11700, 23) |
| $AUC_{inf}$ (µg•day/mL) | 12000 (12500, 29) | 12300 (12700, 25) |
| $C_{max}$/Dose (µg/mL)/mg | 0.402 (0.412, 25) | 0.398 (0.405, 20) |
| $AUC_{inf}$/Dose (µg•day/mL)/mg | 6.67 (6.93, 29) | 6.86 (7.06, 25) |

a. Median (minimum through maximum).

b. Harmonic mean (pseudo-standard deviation); evaluations of $t_{1/2}$ were based on statistical tests for β.

Note: Nine subjects from Substudy 2 are excluded from analysis (1 subject prematurely discontinued from the study at Day 2; 8 subjects for violating eligibility criterion #23 from the protocol by enrolling in both substudies).

Following the administration of a single 1800 mg IV dose, the risankizumab concentration-time profiles were overlapping with comparable parameters across Groups 4 and 5, indicating similar pharmacokinetic characteristics regardless of the difference in drug product formulations.

Bioequivalence assessment

The relative bioavailability of the risankizumab 600 mg vial (Group 5, test) compared to the risankizumab 300 mg vial (Group 4, reference) based on log-transformed Cmax, AUCt and AUCinf is presented in Table 5.

*Table 5 Relative Bioavailability and 90% Confidence Intervals for the Two One-sided Tests Procedures for Risankizumab Pharmacokinetic Parameters*

| Regimens Test vs. Reference | Pharmacokinetic Parameter | Central Value | | Relative Bioavailability | |
|---|---|---|---|---|---|
| | | Test | Reference | Point Estimate | 90% Confidence Interval |
| 600 mg liquid vial (Group 5) vs. 300 mg liquid vial (Group 4) | $C_{max}$ (µg/mL) | 735 | 736 | 0.998 | 0.952 – 1.046 |
| | $AUC_t$ (µg•day/mL) | 11500 | 10700 | 1.079 | 1.001 – 1.164 |
| | $AUC_\infty$ (µg•day/mL) | 12400 | 11900 | 1.044 | 0.976 – 1.117 |

Note: Nine subjects from Substudy 2 are excluded from analysis (1 subject prematurely discontinued from the study at Day 2; 8 subjects for violating eligibility criterion #23 from the protocol by enrolling in both substudies).

Pharmacokinetics in target population

*Study M15-993*

Study M15-993 was a Phase 2, proof-of-concept, multi-center, randomized, double-blind,

multiple-dose, placebo-controlled, parallel-group study to evaluate the efficacy of risankizumab in patients with moderately to severely active CD who were naïve to or previously treated with anti-tumor necrosis factor (TNF) therapy. A total of 121 subjects with active CD were randomized in a three-period study.

Approximate dose-proportional increases in risankizumab plasma trough concentrations were observed in subjects with CD who received risankizumab induction treatment of 200 mg IV and 600 mg IV at Weeks 0, 4, and 8 during Period 1. Comparable risankizumab trough concentrations relative to Period 1 were observed during Period 2 in subjects who received 600 mg IV dose. Following the Period 3 regimen of 180 mg SC q8w starting at Week 26, near steady-state levels were achieved by Week 42.

Treatment-emergent ADA-positive responses were observed in 8% (9/108) of the subjects who received at least one dose of risankizumab. The time to appearance of the first ADA-positive sample for the risankizumab-treated subjects ranged from 12 to 18 weeks following start of treatment. None of the ADA-positive subjects were found to have positive NAb assessment during the study. Although the number of ADA-positive subjects was limited, there did not appear to be any impact of ADA on risankizumab plasma concentrations.

*Study M15-989*

Study M15-989 was a Phase 2, open-label extension (OLE) study that investigated the long-term safety and efficacy of risankizumab in subjects with moderately to severely active CD who enrolled from Study M15-993. A total of 65 subjects were enrolled and received the following treatment:

- CDAI clinical response, but not CDAI clinical remission at Week 26 of Study M15-993; subjects started on risankizumab 180 mg SC q8w;
- CDAI clinical response and/or CDAI clinical remission at Week 52 of Study M15 993; subjects started on risankizumab 180 mg SC q8w; or
- Subjects with loss of response at Week 26 or Week 52 of Study M15-993 received risankizumab 600 mg IV at Weeks 0, 4, and 8; if subjects achieved CDAI clinical response and/or clinical remission at Week 12 they were continued on risankizumab 180 mg SC q8w.
- Subjects who completed Study M15-989 could elect to continue in Study M16-000 Sub-Study 3 (Phase 3 OLE study).

Trough plasma concentration data at the time relative to first SC dosing are summarized for all enrolled subjects regardless of their SC treatment initiation time during the study to provide an overview of risankizumab exposure following maintenance therapy. Following administration of risankizumab 180 mg SC q8w dose in all enrolled subjects with moderate to severe CD, steady-state plasma exposures were reached by Week 24 after the first SC dose, and median trough concentrations ranged from 3.66 µg/mL to 4.23 µg/mL. Overall, out of 65 subjects who received at least one dose of risankizumab during the study, eight subjects (12%) developed largely low titer ADAs (titer ranged from 1 to 64) that were not neutralizing. Development of ADAs did not appear to have a clear impact on risankizumab plasma exposures.

Risankizumab exposure appeared to be impacted by the development of ADA in one subject, but no such observations were made in the other ADA positive subjects. Overall, considering the variability across individuals in trough concentrations and the small number of ADA positive subjects (8/65 [12%]), risankizumab trough plasma concentrations appear to be largely comparable between ADA positive and ADA negative subjects. These results indicated that the development of ADAs did not have a consistent apparent impact on risankizumab plasma exposures.

Intra-subject assessment of the effect of ADA positive response on risankizumab plasma concentrations was also conducted. Based on the small number of subjects who were ADA positive after approaching steady-state (only observed in subjects from Subpopulation 2, plasma concentrations stabilized in these subjects by Week 14, therefore allowing some informative assessment), there was no clear intra–subject effect of ADAs on risankizumab exposure.

Immunogenicity

The summary of the incidence of ADA and NAb to risankizumab across the first 12 weeks (Week 0-12) in the Phase 2 Study M15-993 and Phase 3 induction studies, Studies M15-991 and M16-006, and across 24 weeks in the Phase 3 induction studies (Studies M15-991 and M16-006) are presented in Table 6 and Table 7, respectively.

*Table 6 Summary of Incidence of Treatment-Emergent ADA and NAb to Risankizumab Over 12 Weeks of Induction in the Phase 2 and Phase 3 Studies*

| Week 0 to Week 12 | Risankizumab Study | | | |
|---|---|---|---|---|
| ADA Evaluable Subjects, N | M15-993 [Phase 2] [N = 77] | M15-991 [Phase 3] [N = 397] | M16-006 [Phase 3] [N = 736] | Total [N = 1210] |
| **Risankizumab 200 mg IV at Weeks 0, 4 and 8** | | | | |
| Evaluable subjects; n | 38 | - | - | 38 |
| ADA incidence; n (%) | 2 (5.0%) | - | - | 2 (5%) |
| NAb incidence; n (%) | 0 (0%) | - | - | 0 (0%) |
| **Risankizumab 600 mg IV at Weeks 0, 4 and 8** | | | | |
| Evaluable subjects; n | 39 | 200 | 368 | 607 |
| ADA incidence; n (%) | 1 (3.0%) | 5 (2.5%) | 7 (1.9%) | 13 (2.1%) |
| NAb incidence; n (%) | 0 (0%) | 1 (0.5%) | 1 (0.3%) | 2 (0.3%) |
| **Risankizumab 1200 mg IV at Weeks 0, 4 and 8** | | | | |
| Evaluable subjects; n | -- | 197 | 368 | 565 |
| ADA incidence; n (%) | -- | 1 (0.5%) | 3 (0.8%) | 4 (0.7%) |
| NAb incidence; n (%) | -- | N/A | 0 (0%) | 0 (0%) |

ADA = anti-drug antibody; IV = intravenous NAb; = neutralizing antibody

Notes: ADA evaluable: subjects with at least 1 reportable assessment at any time in the study post Baseline.
NAb was assessed only when the ADA assessment was positive.
Clinical Responders defined as subjects who achieve a ≥ 30% decrease in average daily stool frequency and/or ≥ 30% decrease in average daily abdominal pain score (both not worse than Baseline) at Week 12.
Inadequate Responders defined as subjects who fail to meet the criteria for Clinical Response at Week 12.

*Table 7 Summary of Incidence of Treatment-Emergent ADA and NAb to Risankizumab Over 24 Weeks of Treatment in Subjects Who Underwent Treatment During Induction Period 2 in the Phase 2 Studies*

| Week 0 to Week 24 | Risankizumab Study | | |
|---|---|---|---|
| ADA Evaluable Subjects, N | M15-991 [N = 193] | M16-006 [N = 269] | Total [N = 462] |
| **Treatment with Risankizumab 1200 mg IV at Weeks 12, 16 and 20** | | | |
| Evaluable subjects; n | 110 | 135 | 245 |
| ADA incidence; n (%) | 0 (0%) | 0 (0%) | 0 (0%) |
| NAb incidence; n (%) | N/A | N/A | N/A |
| **Treatment with Risankizumab 180 mg SC at Weeks 12 and 20** | | | |
| Evaluable subjects; n | 41 | 66 | 107 |
| ADA incidence; n (%) | 2 (4.9%) | 1 (1.5%) | 3 (2.8%) |
| NAb incidence; n (%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Treatment with Risankizumab 360 mg SC at Weeks 12 and 20** | | | |
| Evaluable subjects; n | 42 | 68 | 110 |
| ADA incidence; n (%) | 1 (2.4%) | 2 (2.9%) | 3 (2.7%) |
| NAb incidence; n (%) | 0 (0%) | 1 (1.5%) | 1 (0.9%) |

ADA = anti-drug antibody; IV = intravenous; NAb = Neutralizing Antibody; SC = subcutaneous

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

The summary of the incidence of ADA and NAb to risankizumab for up to 52 weeks of maintenance treatment from the Phase 3 maintenance study (Study M16-000) is presented in Table 8.

*Table 8 Summary of Incidence of Treatment-Emergent ADA and NAb to Risankizumab in Randomized Subjects Over 52 Weeks of Exposure in the Phase 3 Maintenance Study*

| | Study M16-000 (Sub-Study 1) | |
|---|---|---|
| | **Risankizumab 180 mg SC Q8W** | **Risankizumab 360 mg SC Q8W** |
| Evaluable subjects; n | 117 | 107 |
| ADA incidence; n (%) | 3 (2.6%) | 1 (0.9%) |
| NAb incidence; n (%) | 1 (0.9%) | 0 (0%) |

ADA = anti-drug antibody; NAb = neutralizing antibody; SC = subcutaneous; Q8W = every 8 weeks

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

Additionally, in subjects who received the proposed induction dose of 600 mg IV at Weeks 0, 4 and 8, followed by the proposed SC maintenance dose of 360 mg SC at Week 12 and Q8W thereafter up to Week 52, incidence of ADA and NAb to risankizumab was 3.4% (2/58) and 0% (0/58), respectively, over 64 weeks of exposure. In all subjects who received any risankizumab dose during the induction period followed by risankizumab treatment during the maintenance period, incidence of ADA and Nab was 2.2% (7/325) and 0.3% (1/325), respectively, over up to 76 weeks of exposure.

ADA incidence was also assessed in the pivotal phase 1 BE study (Table 9).

*Table 9 Incidence of ADA at Baseline and Treatment-Emergent ADA Following Single SC and IV infusion Doses of Risankizumab*

| Treatment Group | Baseline ADA Incidence n/N (%) | Treatment-Emergent ADA Incidence n/N (%) | Time to Appearance of ADA[a] (range in days) | Range of ADA Titers in Treatment-Emergent ADA+ Samples |
|---|---|---|---|---|
| Substudy 1 | | | | |
| Group 1<br>360 mg SC injection<br>(90 mg PFS × 4) | 5/120 (4.2%) | 7/117 (6.0%) | 29 – 113 | 10 – 5880 |
| Group 2<br>360 mg OBDS SC injection<br>(2.4 mL of 150 mg/mL) | 8/118 (6.8%) | 16/123 (13%) | 13 – 114 | 10 – 1330 |
| Group 3<br>180 mg OBDS SC Injection<br>(1.2 mL of 150 mg/mL) | 2/29 (6.9%) | 1/27 (3.7%) | 15 | 10 – 22.9 |
| Substudy 2 | | | | |
| Group 4<br>1800 mg IV<br>(300 mg liquid vial) | 1/49 (2.0%) | 2/48 (4.2%) | 15 – 56 | 10 – 423 |
| Group 5<br>1800 mg IV<br>(600 mg liquid vial) | 1/50 (2.0 %) | 1/50 (2.0 %) | 29 | 10 – 87.3 |

a. Incidence of anti-drug antibody (treatment emergent) to risankizumab was defined when a subject was (1) anti-drug antibody negative or missing assessment at baseline (prior to the first risankizumab dose) and became anti-drug antibody positive at one or more time points post baseline; or (2) anti-drug antibody positive at baseline and showed a 4-fold or greater increase in titer values relative to baseline.

Notes:

1. Nine subjects from Substudy 1 are excluded from analysis (8 subjects for violating eligibility criterion #23 of the protocol by enrolling in both substudies; 1 subject for violating eligibility criterion #23 of the protocol by enrolling in two treatment groups of Substudy 1).
2. Eight subjects from Substudy 2 are excluded from analysis for violating eligibility criterion #23 of the protocol by enrolling in both substudies.

Effects of ADA

Comparison of risankizumab serum trough concentrations by ADA status (positive or negative) using pooled data across the first 12 weeks of induction from the Phase 3 induction studies are presented in Table 10.

*Table 10 Summary of Risankizumab Serum Trough Concentrations (µg/mL) by ADA Status Across the First 12 Weeks from the Phase 3 Induction Studies*

| | 12-Week Induction Period[a] | | | | | |
|---|---|---|---|---|---|---|
| | Week 4 | | Week 8 | | Week 12 | |
| Treatment Regimen | ADA+ | ADA– | ADA+ | ADA– | ADA+ | ADA– |
| Risankizumab 600 mg IV at Weeks 0, 4 and 8 | 19.6 (31.0, 169) [16] | 22.4 (25.4, 73) [508] | 30.7 (49.9, 144) [7] | 32.9 (37.4, 58) [515] | 26.7 (28.3, 38) [5] | 37.7 (43.6, 74) [504] |
| Risankizumab 1200 mg IV at Weeks 0, 4 and 8 | 40.1 (42.7, 40) [4] | 44.0 (50.1, 78) [513] | -[b] | 62.8 (70.7, 47) [540] | 69.2 (69.2, -) [1] | 70.2 (79.8, 46) [519] |

ADA = anti-drug antibody (anti-risankizumab antibody); IV = intravenous; %CV = coefficient of variation

Results summarized as Geometric Mean, Arithmetic Mean, %CV) [n].

a. Integrated results from the two Phase 3 CD induction studies, Studies M15-991[3] and M16-006.[4]

b. None of the subjects randomized to the 1200 mg IV Q4W regimen were ADA+ at Week 8 of the 12-Week Induction Period.

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

Total duration of risankizumab treatment ranges from 64 to 76 weeks and includes both induction and maintenance periods across the Phase 3 studies.

Comparison of risankizumab serum trough concentrations by ADA status (positive or negative) using data across 52 weeks of maintenance treatment from the Phase 3 maintenance Study M16-000 are presented in Table 11.

*Table 11 Summary of Risankizumab Serum Trough Concentrations (µg/mL) by ADA Status Across 52 Weeks of Maintenance Treatment from the Phase 3 Maintenance Study*

| Treatment Regimen | Maintenance Period[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Week 16 | | Week 32 | | Week 48 | | Week 52 | |
| | ADA+ | ADA– | ADA+ | ADA– | ADA+ | ADA– | ADA+ | ADA– |
| Risankizumab 180 mg SC Q8W | 2.28 (2.88, 72) [5] | 4.71 (6.80, 78) [88] | 3.97 (4.12, 38) [2] | 3.79 (4.54, 52) [72] | --[b] | 3.44 (4.31, 64) [62] | 10.3 (10.3, -) [1] | 8.88 (9.86, 43) [53] |
| Risankizumab 360 mg SC Q8W | --[c] | 7.84 (10.1, 65) [85] | --[c] | 7.94 (9.12, 48) [57] | 3.87 (3.87, -) [1] | 7.12 (9.11, 50) [51] | --[c] | 18.0 (19.6, 35) [49] |

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

a. Results from the Phase 3 Maintenance study, Study M16-000.[5]

b. None of the subjects randomized to the 180 mg SC treatment group were ADA+ at Week 48 of the 52-week maintenance period.

c. None of the subjects randomized to the 360 mg SC treatment group were ADA+ at Weeks 16, 32 or 52 of the 52-week maintenance period.

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

Results summarized as Geometric Mean (Arithmetic Mean, %CV) [n].

Total duration of risankizumab treatment ranges from 64 to 76 weeks and includes both induction and maintenance periods across the Phase 3 studies.

In pivotal phase 1 BE study (M19-128), the potential impact of ADA on risankizumab exposure and safety was evaluated by comparing treatment-emergent ADA-positive versus ADA-negative subjects within each group (Table 12).

*Table 12 Summary of Risankizumab Exposures by Treatment-emergent ADA Status Across Treatment Groups in Substudy 1 and Substudy 2*

| Treatment Group | Risankizumab $AUC_{inf}$ (µg/day/mL) | |
|---|---|---|
| | ADA + | ADA - |
| **Substudy 1** | | |
| Group 1: 360 mg SC injection (90 mg PFS × 4) | 1750 (834 – 2120) [7] | 1580 (639 – 3070) [107] |
| Group 2: 360 mg OBDS SC injection (2.4 mL of 150 mg/mL) | 1330 (920, 2770) [16] | 1700 (788 – 6170) [97] |
| Group 3: 180 mg OBDS SC Injection (1.2 mL of 150 mg/mL) | 644 (--) [1] | 871 (392 – 2630) [26] |
| **Substudy 2** | | |
| Group 4: 1800 mg IV (6 × 300 mg liquid vials) | 9260 (8940 – 9580) [2] | 12100 (7880 – 22100) [46] |
| Group 5: 1800 mg IV (3 × 600 mg liquid vials) | 9810 (--) [1] | 12400 (7350 – 20900) [49] |

Results summarized as Median (Range) [n].

Summary of Effect of Immunogenicity on Risankizumab Exposure

Based on the inter-subject assessment across the Phase 3 studies, risankizumab serum trough concentrations (central tendency and distribution) were comparable between subjects who were ADA positive and those who were ADA negative. Limited data available for the intra-subject assessment indicated that there was no clear intra-subject effect of ADAs on risankizumab exposures.

Based on the population pharmacokinetic analyses, treatment-emergent ADAs did not show statistically significant effects on risankizumab clearance or exposure.

Effect of ADA status on Risankizumab safety

*Hypersensitivity reactions*

Among subjects who received the proposed induction regimen of 600 mg IV at Weeks 0, 4 and 8, in the All Treated Safety Analysis Set, the incidence of hypersensitivity reactions was numerically higher among treatment-emergent ADA positive (2/26, 7.7%) than the ADA negative (34/651, 5.2%) subjects, but this observation should be interpreted with caution given the small number of treatment-emergent ADA positive subjects (26/677, 3.8%). Among subjects who received the proposed maintenance regimen of 360 mg SC Q8W, in the All Treated Safety Analysis Set, the incidence of hypersensitivity reactions was numerically higher among treatment-emergent ADA positive (1/11, 9.1%) than the ADA negative (28/465, 6.0%) subjects, again based on the small number of treatment-emergent ADA positive subjects (11/476, 2.3%). All hypersensitivity reactions events in treatment emergent ADA positive subjects were mild or moderate in severity and none of these events led to treatment discontinuation with exception of one event. One treatment emergent ADA positive subject who received a single dose of the 200 mg IV induction regimen in Phase 2 Study M15-993 experienced a non-serious AE of moderate infusion related reaction on Day 1 that led to study drug withdrawn. Given the low overall hypersensitivity reaction rates, these differences are not clinically relevant.

*Injection and infusion site reactions*

Among subjects who received the proposed induction regimen of 600 mg IV at Weeks 0, 4 and 8, in the All Treated Safety Analysis Set, the incidence of injection site reactions (including infusion site reactions) was numerically higher in treatment-emergent ADA positive subjects (3.8%, 1/26) than the ADA negative (1.7%, 11/651) subjects, based on the small number of treatment-emergent ADA positive subjects (26/677, 3.8%). Among subjects who received the proposed maintenance regimen of 360 mg SC Q8W, the incidence of injection site reactions was numerically higher among treatment-emergent ADA positive (9.1%, 1/11) subjects than the ADA negative (5.2%, 24/465) subjects, based on the small number of treatment-emergent ADA positive subjects (11/476, 2.3%). All injection and infusion site reactions in treatment-emergent ADA positive subjects were mild or moderate in severity. One ADA positive subject experienced a moderate infusion related reaction that led to study drug discontinuation, as described above. Given the low overall injection site reactions rates, these differences between treatment-emergent ADA positive and ADA negative subjects are not considered clinically relevant.

Overall, these results indicate that immunogenicity to risankizumab had no clinically relevant impact on the safety of risankizumab as assessed by hypersensitivity reactions, injection and infusion site reactions.

Effect of ADA status on Risankizumab efficacy

The comparison of CDAI clinical remission, SF/APS clinical remission and endoscopic response endpoints at Week 12 by ADA and NAb status (positive or negative) using pooled data from the Phase 3 induction studies and comparison of CDAI clinical remission, SF/APS clinical remission and endoscopic response endpoints at Week 52 by ADA and NAb status (positive or negative) using data from the Phase 3 maintenance study was presented. Response rates at the end of the 12-Week Induction Period and at Week 52 were largely comparable between subjects who were ADA positive and those who were ADA negative. The number of NAb positive subjects was too small to make a meaningful comparison with NAb negative subjects.

*Table 13 Risankizumab Efficacy by Treatment-Emergent ADA and NAb Status at Week 12 from the Phase 3 Induction Studies*

| | Response to Clinical Endpoints at Week 12, n (%) (ISE1A Population) | | | |
|---|---|---|---|---|
| **Risankizumab 600 mg IV Q4W (N = 523)** | **ADA Positive (N = 12)** | **ADA Negative (N = 511)** | **NAb Positive (N = 2)** | **NAb Negative (N = 521)** |
| CDAI Remission | 4 (33.3%) | 228 (44.6%) | 1 (50.0%) | 231 (44.3%) |
| SF/APS Clinical Remission | 6 (50.0%) | 206 (40.3%) | 1 (50.0%) | 211 (40.5%) |
| Endoscopic Response | 4 (33.3%) | 186 (36.4%) | 0 (N/A) | 190 (36.5%) |
| **Risankizumab 1200 mg IV Q4W (N = 525)** | **ADA Positive (N = 4)** | **ADA Negative (N = 521)** | **NAb Positive (N = 0)** | **NAb Negative (N = 525)** |
| CDAI Remission | 1 (25.0%) | 217 (41.7%) | N/A | 218 (41.5%) |
| SF/APS Clinical Remission | 2 (50.0%) | 213 (40.9%) | N/A | 215 (41.0%) |
| Endoscopic Response | 1 (25.0%) | 172 (33.0%) | N/A | 173 (33.0%) |

ADA = anti-drug antibodies; CDAI = Crohn's disease activity index; IV = intravenous; SF/APS = stool frequency and abdominal pain score

Notes: ISE1A population includes randomized subjects who had baseline eligibility SES-CD of >= 6 (>= 4 for isolated ileal disease) and have received at least one dose of study drug in 12-Week Induction Period from two global Phase 3 induction studies: Studies M15-991 and M16-006.

CDAI clinical remission is defined as CDAI < 150.

*Table 14 Risankizumab Efficacy by Treatment-Emergent ADA at Week 52 from the Phase 3 Maintenance Study*

| | Response to Clinical Endpoints at Week 52 in Study M16-000 (Sub-Study 1), n (%) | | | |
|---|---|---|---|---|
| **180 mg SC Q8W (N=118)** | **ADA Positive (N = 3)** | **ADA Negative (N = 115)** | **NAb Positive (N = 1)** | **NAb Negative (N = 117)** |
| CDAI Remission | 2 (66.7%) | 83 (72.2%) | 1 (100%) | 84 (71.8%) |
| SF/APS Clinical Remission | 2 (66.7%) | 69 (60.0%) | 1 (100%) | 70 (59.8%) |
| Endoscopic Response | 2 (66.7%) | 71 (61.7%) | 1 (100%) | 72 (61.5%) |
| **360 mg SC Q8W (N=107)** | **ADA Positive (N = 1)** | **ADA Negative (N = 106)** | **NAb Positive (N = 0)** | **NAb Negative (N = 107)** |
| CDAI Remission | 1 (100%) | 71 (66.6%) | N/A | 72 (66.9%) |
| SF/APS Clinical Remission | 1 (100%) | 70 (66.1%) | N/A | 71 (66.4%) |
| Endoscopic Response | 1 (100%) | 63 (59.1%) | N/A | 64 (59.4%) |

ADA = anti-drug antibodies; CDAI = Crohn's disease activity index; SF/APS = stool frequency and abdominal pain score

***Special populations***

*Impaired renal function*

In the population PK analysis, creatinine clearance was statistically correlated with risankizumab clearance. However, the impact on risankizumab exposures over the evaluated range for creatinine clearance (25-291 mL/min) was not clinically relevant.

*Impaired hepatic function*

In the population PK analysis, liver function markers aspartate aminotransferase, alanine aminotransferase and total bilirubin were not identified as statistically significant covariates.

*Gender*

In the population PK analysis, sex was identified as a statistically significant covariate on risankizumab clearance. However, the difference in risankizumab exposures between males and females was not clinically meaningful.

*Race*

Study M16-533

Study M16-533 was a Phase 1, double-blind, randomized, placebo-controlled, single-center study designed to assess the pharmacokinetics, safety, tolerability, and immunogenicity following a single IV administration of risankizumab or placebo in healthy Japanese and Caucasian subjects. A total of 16 subjects were randomized to risankizumab or placebo in a ratio of 6:2 in each group as follows:

- Group 1: Japanese 1800 mg IV
- Group 2: Caucasian 1800 mg IV

The ratios and 90% confidence intervals of Cmax and AUC values of risankizumab in healthy Japanese subjects relative to healthy Caucasian subjects without adjusting for body weight differences (body weight was not found to be statistically significant when tested as a covariate) are presented in the CSR.

These results indicate that following a single infusion of risankizumab 1800 mg IV, risankizumab exposures in Japanese subjects were similar to Caucasian subjects. Low titer treatment-emergent ADAs were detected in three subjects (1/6 [17%] in Japanese and 2/6 [33%] in Caucasian) in the study with no apparent impact on risankizumab exposure.

Study M17-381

Study M17-381 was a Phase 1, open-label, three-arm, single-centre study conducted in mainland China in healthy Chinese subjects. Subjects were enrolled and received the following doses of risankizumab:

- Arm 1: 1800 mg IV (N = 10)
- Arm 2: 360 mg SC (N = 10)
- Arm 3: 150 mg SC (N = 10)

Following administration of a single SC dose of risankizumab 150 or 360 mg in healthy Chinese subjects, risankizumab serum concentrations peaked in approximately three days on average, with dose-dependent increase in exposure and a mean terminal t1/2 of approximately 29 days. Risankizumab exposures (AUC) were dose-proportional between the 150 and 360 mg SC doses. Following administration of the single 1800 mg IV dose, risankizumab serum concentrations declined in a biphasic manner with the terminal phase decline in parallel with the SC dosing arms and a mean t1/2 of approximately 35 days. Following administration of single SC or IV doses of risankizumab, there was no incidence of treatment-emergent ADA across the three arms.

Overall, race did not have an impact on risankizumab clearance. A cross-study comparison of non-compartmental pharmacokinetic parameters in Chinese (Study M17-381), Japanese (Study M16-533), and Western (Studies M16-533 and M19-128) subjects also demonstrated similarity across the groups, indicating the lack of ethnic sensitivity.

Population PK Analyses

Race was not identified to be statistically correlated to risankizumab PK during the covariate search step of the model development process. To highlight the lack of impact of race on risankizumab PK, model predicted risankizumab exposures at the proposed clinical induction and maintenance dosing regimen in Asian subjects and non-Asian subjects are shown in Figure 5.

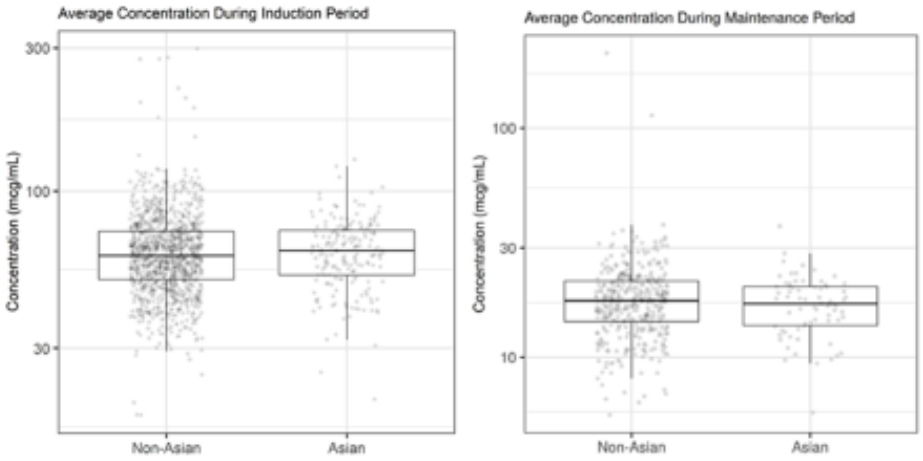



*Figure 5 Model Predicted Risankizumab Exposures at the Proposed Clinical Induction and Maintenance Dosing Regimen in Asian Subjects and non-Asian Subjects*

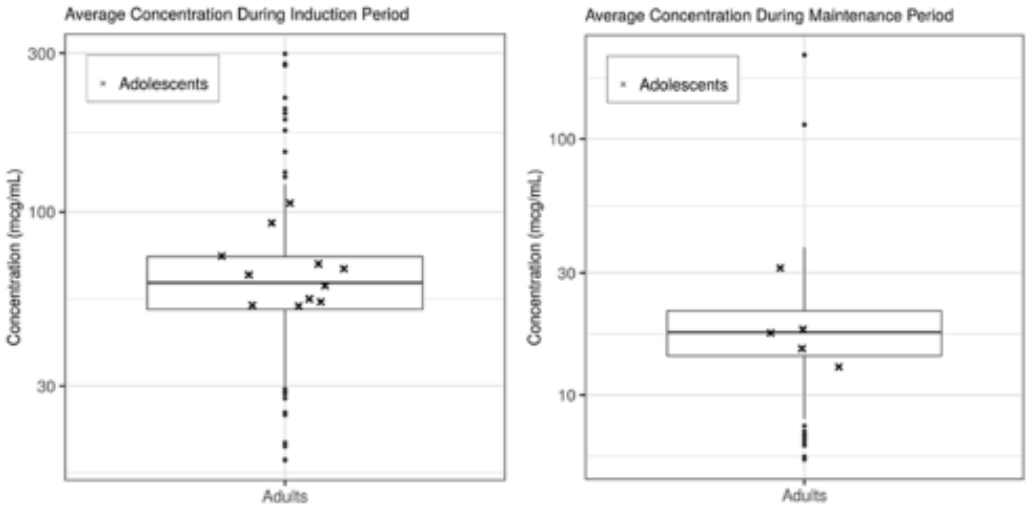
*Weight*

Body weight was significantly correlated with risankizumab clearance and volume of distribution. However, over the evaluated range of body weights (32-159 kg), risankizumab exposures were estimated to be within the default equivalence boundaries of 0.8 to 1.25 relative to the reference group.

*Age*

The age of subjects included in the population PK analysis ranged between 16 and 79 years. There was limited information in subjects aged >65 years. Age was not identified as a significant covariate during the covariate search.

Figure 6 shows the exposures in adolescents and adults. Figure 7 shows a comparison of the simulated exposures in adolescents and adults during the induction period and maintenance period.




The boxplot and dots (outliers) are model-predicted exposures for adults, and crosses are the individual model-predicted exposures for adolescents enrolled in the study and dosed with risankizumab.

*Figure 6 Model Predicted Risankizumab Exposures at the Proposed Clinical Induction and Maintenance Dosing Regimen in Adolescents and Adults*

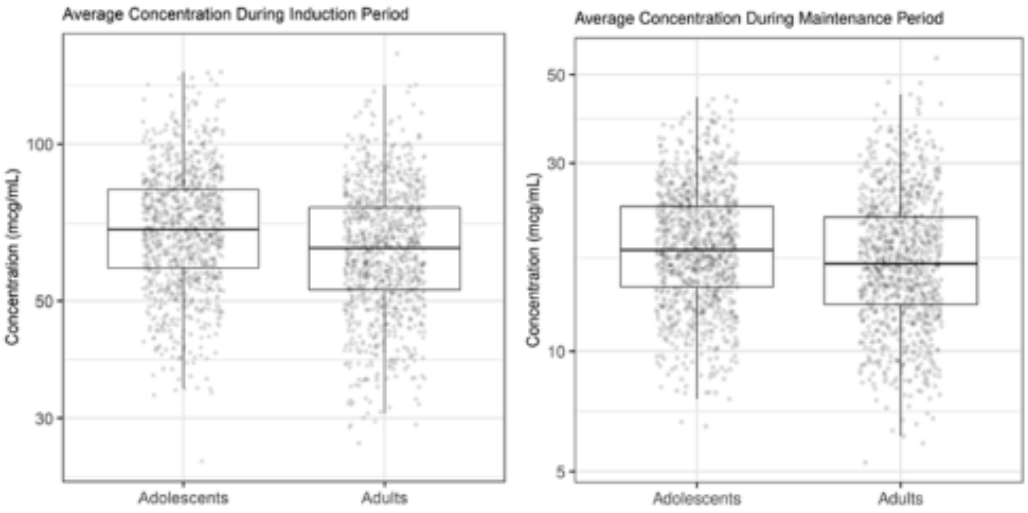



*Figure 7 Simulated Risankizumab Exposures at the Proposed Clinical Induction and Maintenance Dosing Regimen in Adolescents and Adults*

*Exposure relevant for safety evaluation*

Model predicted risankizumab exposures during the 12-week induction period and at steady-state for maintenance in subjects with moderate to severe CD following administration of risankizumab at the proposed induction dosing regimen of 600 mg IV every 4 weeks (Q4W) and proposed maintenance dosing regimen of 360 mg SC Q8W are summarized in Table 15.

*Table 15 Model-Predicted Risankizumab Exposures in Subjects with Moderate to Severe CD During the 12-week Induction Period at the Proposed Induction Dosing Regimen of 600 mg IV Q4W and During Maintenance Period at the Proposed Maintenance Dosing Regimen of 360 m*

| Exposure | Statistic | First Dosing Interval (Weeks 0-4) | Second Dosing Interval (Weeks 4-8) | Third Dosing Interval (Weeks 8-12) | Steady State Maintenance Dosing interval (Weeks 40-48) |
|---|---|---|---|---|---|
| $C_{max}$ (mcg/mL) | Mean (SD) | 136 (93.2) | 160 (99.4) | 171 (104) | 29.9 (16.9) |
| | Median | 125 | 146 | 156 | 28.0 |
| | 5th Percentile | 68.6 | 89.2 | 96.2 | 16.1 |
| | 95th Percentile | 222 | 258 | 275 | 47.1 |
| $C_{trough}$ (mcg/mL) | Mean (SD) | 24.9 (10.3) | 35.9 (17.5) | 41.0 (22.6) | 9.19 (11.1) |
| | Median | 23.9 | 34.2 | 38.8 | 8.13 |
| | 5th Percentile | 11.5 | 14.6 | 15.4 | 2.23 |
| | 95th Percentile | 40.3 | 60.4 | 71.5 | 16.7 |
| $C_{average}$ (mcg/mL) | Mean (SD) | 50.9 (15.4) | 67.7 (23.5) | 75.4 (29.3) | 18.6 (12.9) |
| | Median | 49.1 | 64.7 | 71.8 | 17.6 |
| | 5th Percentile | 31.7 | 40.5 | 42.7 | 9.45 |
| | 95th Percentile | 75.0 | 104 | 120 | 28.8 |
| $AUC_{tau}$ (mcg*day/mL) | Mean (SD) | 1424 (432) | 1896 (659) | 2111 (820) | 1043 (721) |
| | Median | 1375 | 1812 | 2010 | 985 |
| | 5th Percentile | 887 | 1133 | 1196 | 529 |
| | 95th Percentile | 2099 | 2917 | 3346 | 1617 |

### *2.6.2.2. Pharmacodynamics*

***Mechanism of action***

Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of human interleukin 23 (IL-23) cytokine without binding to IL12 and inhibits its interaction with the IL-23 receptor complex. IL-23 is a cytokine that is involved in inflammatory and immune responses. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.

***Primary and Secondary pharmacology***

Consistent with the mechanism of action of inhibiting IL-23 p19 binding to its receptor and subsequent downstream signaling, treatment with risankizumab down-modulated genes associated with the inflammatory response and the IL-23/T helper 17 axis in gut tissue of patients with CD in the Phase 2 Study M15-993 (Visvanathan 2018).

The IL-23 associated pharmacodynamic biomarker, IL-22, and the inflammatory biomarkers, hs-CRP and FCP, were evaluated in a subset of subjects with CD selected to reflect the response rate, demographics, and clinical characteristics of the Phase 3 induction studies, Studies M15-991 (n = 122 subjects) and M16-006 (n = 123 subjects), and the maintenance study, Study M16-000 Sub-Study 1 (n = 92 subjects).

In Study M15-991 and Study M16-006, treatment with risankizumab 600 mg IV and 1200 mg IV significantly decreased the levels of IL-22 at Week 12, confirming the pharmacodynamic effect of risankizumab on the IL-23 pathway in patients with CD.

Treatment with risankizumab 600 mg IV and 1200 mg IV also significantly decreased hs-CRP levels at Week 12, confirming the anti-inflammatory effect of risankizumab in patients with CD. Additionally, treatment with risankizumab 600 mg and 1200 mg significantly decreased FCP levels at Week 12 in Study M16-006 and elicited a similar trend of response at Week 12 in Study M15-991, confirming the anti-inflammatory effect of risankizumab in patients with CD.

In Study M16-000 Sub-Study 1, treatment with risankizumab 180 mg SC and 360 mg SC in subjects with clinical response to IV risankizumab induction, continued to inhibit IL-22 levels and maintained the pharmacodynamic effect on the IL-23 pathway to a similar degree at Week 52. The robust pharmacodynamic effect elicited after 12 weeks of induction treatment was also observed in the withdrawal (placebo SC) group at Week 52, where IL-22 levels remained below what was observed at baseline of induction.

Finally, treatment with risankizumab 180 mg SC and 360 mg SC continued to inhibit hs-CRP and FCP levels and maintained the anti-inflammatory effect to a similar degree between doses at Week 52, which contrasts with increasing levels in the withdrawal (placebo SC) subjects at Week 52 as compared to Week 0.

*Relationship between plasma concentration and effect*

Exposure-response analyses for efficacy of risankizumab in subjects with active Crohn's Disease

Data from subjects with active CD in the Phase 2 Study M15-993 Period 1 (N = 121), Phase 3 induction Studies M15-991 (N = 569) and M16-006 (N = 850), and Phase 3 maintenance Study M16-000 Sub-study 1 (N = 462) who received placebo or at least one dose of risankizumab were included in the efficacy exposure-response analyses.

The relationships between the efficacy endpoints (Crohn's disease activity index [CDAI] clinical remission, CDAI clinical response, stool frequency [SF]/abdominal pain score [APS] clinical remission, SF/APS clinical response, endoscopic response, endoscopic remission, stool frequency remission, abdominal pain remission, and ulcer free endoscopy) and risankizumab exposures were evaluated at Week 12 (end of first 12-week Induction Period) and Week 52 (end of maintenance). Additionally, an exploratory exposure-response analysis was carried out for these endpoints at Week 24 (end of Induction Period 2). The relationships were investigated using graphical analyses (at the end of Weeks 12, 24 and 52) and logistic regression analyses (at Weeks 12 and 52).

The exposure metrics used for the analyses were derived using the empirical Bayesian estimates of the individual PK parameters based on the population PK analyses and the actual dosing history of each subject. Caverage was used as the primary exposure metric.

*Results*

12-week induction period

*Graphical analyses*

Exposure-response graphical analyses demonstrated that exposures associated with 600 mg risankizumab intravenous (IV) at Weeks 0, 4 and 8 as an induction regimen rendered favourable efficacy results compared to the 200 mg IV every 4 weeks (Q4W) regimen for the clinical endpoints evaluated in the Phase 2 Study M15-993.

For CDAI and SF/APS endpoints, results overall showed an increasing trend in response with increasing risankizumab concentrations, without an apparent plateau of efficacy for CDAI response, SF/APS clinical response and SF/APS clinical remission as shown in Figure 8. For endoscopic endpoints, no conclusive exposure-response trends were observed, yet subjects treated with risankizumab showed favourable efficacy compared to placebo. Similar trends were seen when efficacy response rates were plotted against Ctrough, Week 12.

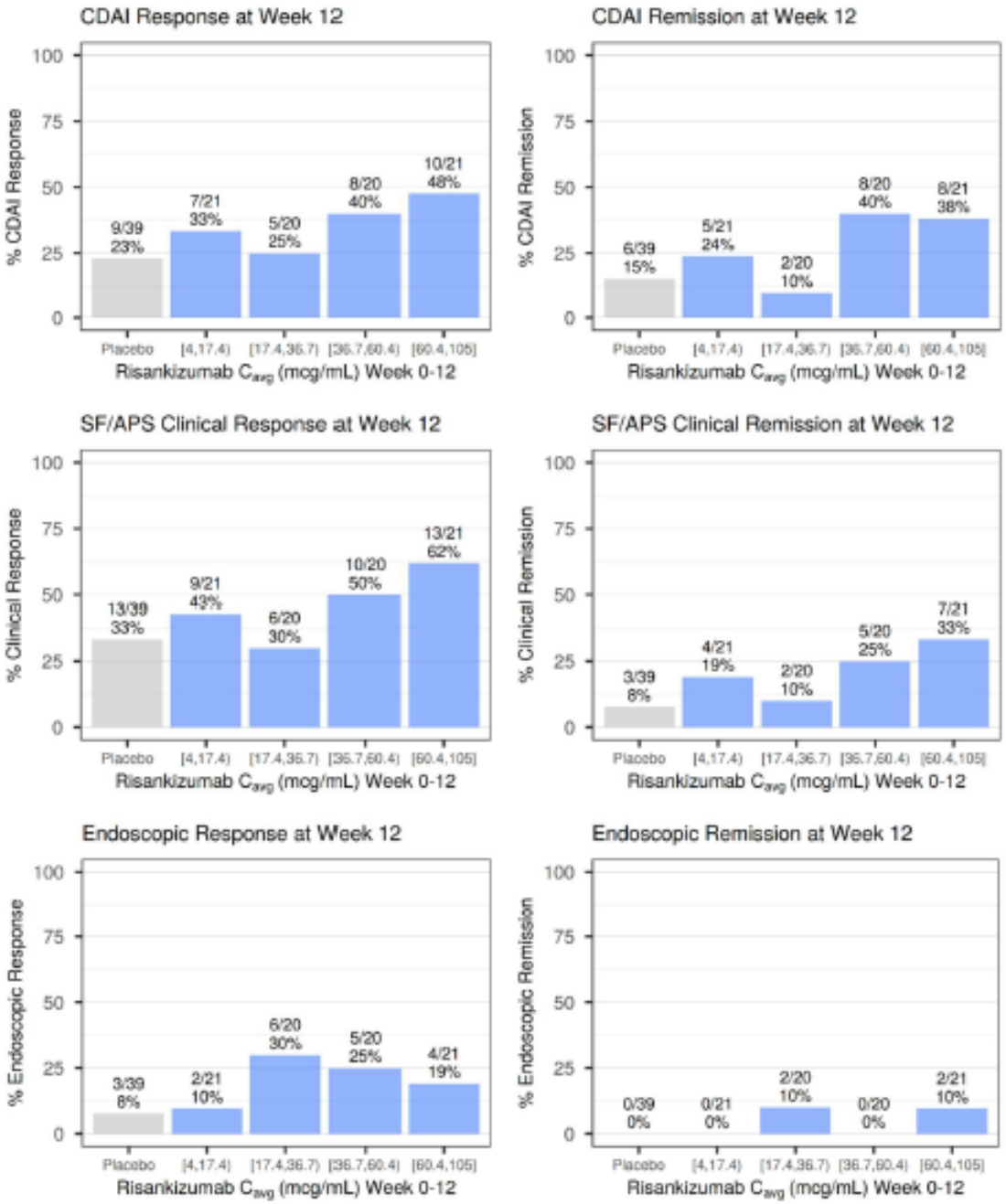
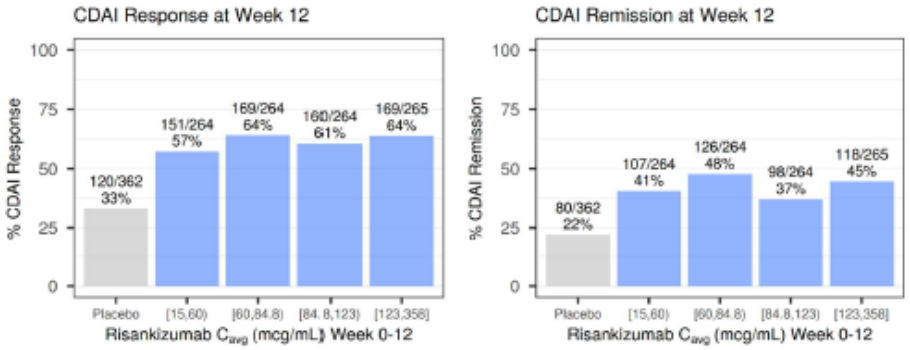
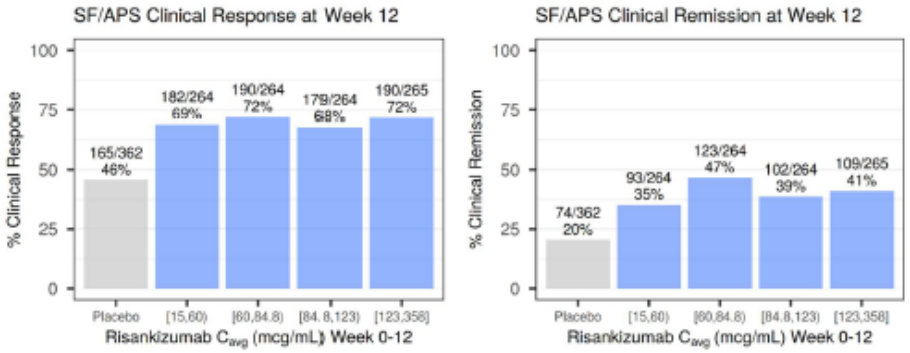



*Figure 8 Relationship Between Risankizumab model-Predicted $C_{avg,\ Week0\text{-}12}$ and Responses at Week 12 in Phase 2 Study (Study-M15-993)*

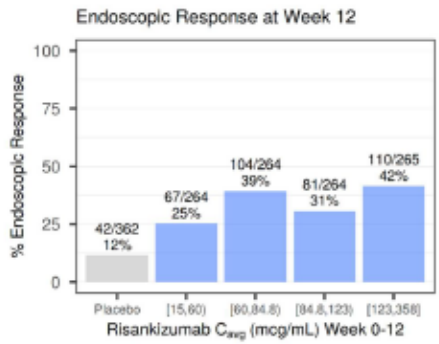
Results from the Phase 3 induction studies showed that subjects treated with risankizumab achieved higher response rates compared to placebo, but with no clear exposure-response trends in any of the evaluated efficacy endpoints (Figure 9). The suggested that 600 mg risankizumab IV at Weeks 0, 4 and 8 as an induction regimen achieved near maximal efficacy, with no clear added benefit from the 1200 mg IV at Weeks 0, 4, and 8 regimen.

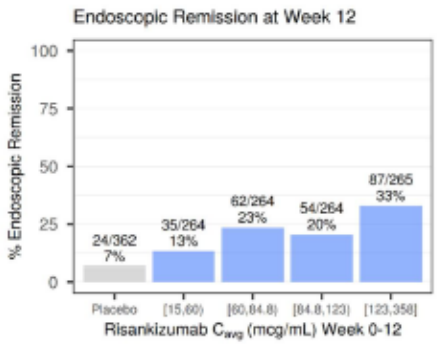

CDAI Response at Week 12
% CDAI Response
120/362 33%
151/264 57%
169/264 64%
160/264 61%
169/265 64%
Placebo
[15,60)
[60,84.8)
[84.8,123)
[123,358]
Risankizumab Cavg (mcg/mL) Week 0-12

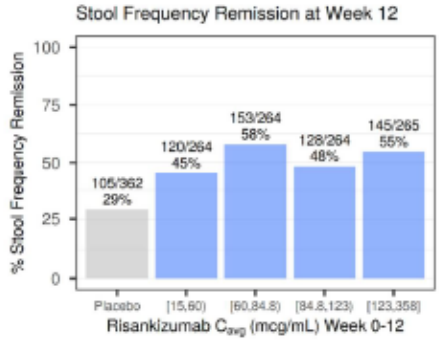

CDAI Remission at Week 12
% CDAI Remission
80/362 22%
107/264 41%
126/264 48%
98/264 37%
118/265 45%
Placebo
[15,60)
[60,84.8)
[84.8,123)
[123,358]
Risankizumab Cavg (mcg/mL) Week 0-12

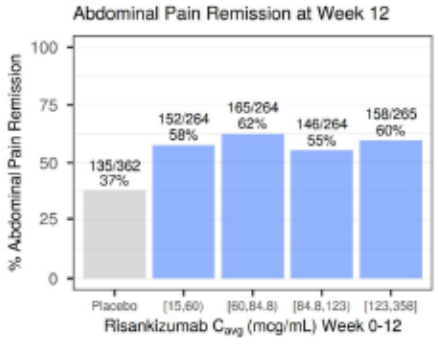

SF/APS Clinical Response at Week 12
% Clinical Response
165/362 46%
182/264 69%
190/264 72%
179/264 68%
190/265 72%
Placebo
[15,60)
[60,84.8)
[84.8,123)
[123,358]
Risankizumab Cavg (mcg/mL) Week 0-12


SF/APS Clinical Remission at Week 12
% Clinical Remission
74/362 20%
93/264 35%
123/264 47%
102/264 39%
109/265 41%
Placebo
[15,60)
[60,84.8)
[84.8,123)
[123,358]
Risankizumab Cavg (mcg/mL) Week 0-12


Endoscopic Response at Week 12
% Endoscopic Response
42/362 12%
67/264 25%
104/264 39%
81/264 31%
110/265 42%
Placebo
[15,60)
[60,84.8)
[84.8,123)
[123,358]
Risankizumab Cavg (mcg/mL) Week 0-12


Endoscopic Remission at Week 12
% Endoscopic Remission
24/362 7%
35/264 13%
62/264 23%
54/264 20%
87/265 33%
Placebo
[15,60)
[60,84.8)
[84.8,123)
[123,358]
Risankizumab Cavg (mcg/mL) Week 0-12


Stool Frequency Remission at Week 12
% Stool Frequency Remission
105/362 29%
120/264 45%
153/264 58%
128/264 48%
145/265 55%
Placebo
[15,60)
[60,84.8)
[84.8,123)
[123,358]
Risankizumab Cavg (mcg/mL) Week 0-12


Abdominal Pain Remission at Week 12
% Abdominal Pain Remission
135/362 37%
152/264 58%
165/264 62%
146/264 55%
158/265 60%
Placebo
[15,60)
[60,84.8)
[84.8,123)
[123,358]
Risankizumab Cavg (mcg/mL) Week 0-12

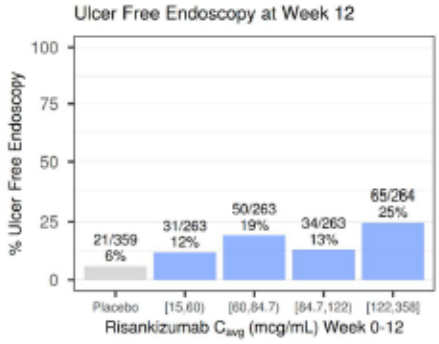

Ulcer Free Endoscopy at Week 12
% Ulcer Free Endoscopy
21/359 6%
31/263 12%
50/263 19%
34/263 13%
65/264 25%
Placebo
[15,60)
[60,84.7)
[84.7,122)
[122,358]
Risankizumab Cavg (mcg/mL) Week 0-12

*Figure 9 Relationship Between Risankizumab Model-Predicted $C_{avg, Week0-12}$ and Responses at Week 12 of the Induction Period in Phase 3 Studies (Studies M15-991 and M16-006)*

*Logistic Regression Analyses*

Model predictions for the response rates at Week 12 for the two regimens tested in Phase 3, 600 and 1200 mg IV at Weeks 0, 4, and 8 are provided for the clinical and endoscopic endpoints in Table 16 and Table 17, with the latter showing endpoints where Bio-IR as a stratification factor was statistically significant.

*Table 16 Model Predictions of Response Rates at Week 12 for Clinical Endpoints*

| | Response Rate (%) (95% Confidence Interval) | |
|---|---|---|
| Response Variable | 600 mg IV at Weeks 0, 4, and 8 | 1200 mg IV at Weeks 0, 4, and 8 |
| CDAI Response | 58.2 (54.6 - 62.7) | 62.5 (58.3 - 67.1) |
| CDAI Remission | 40.2 (36.0 - 44.0) | 43.9 (39.1 - 48.2) |
| SF/APS Clinical Response | 67.3 (63.8 - 71.3) | 70.6 (66.8 - 74.7) |
| Stool Frequency Remission | 50.0 (46.3 - 53.9) | 53.3 (49.2 - 57.3) |
| Abdominal Pain Remission | 57.2 (53.2 - 61.0) | 60.3 (55.8 - 64.1) |

*Table 17 Model Predictions of Response Rates at Week 12 for SF/APS Clinical Remission and Endoscopic Endpoints*

| Response Variable | Response Rate (%) (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|
| | non-Bio-IR | | Bio-IR = 1 | | Bio-IR > 1 | |
| | 600 mg | 1200 mg | 600 mg | 1200 mg | 600 mg | 1200 mg |
| SF/APS Clinical Remission | 44.0 (37.5 – 50.9) | 47.8 (41.4 – 54.8) | 40.6 (34.5 – 46.8) | 44.4 (38.3 – 51.0) | 31.4 (25.7 – 37.2) | 34.8 (28.8 – 41.2) |
| Endoscopic Response | 43.4 (36.8 – 50.0) | 48.4 (42.0 - 55.4) | 34.2 (28.3 – 40.0) | 39.0 (33.0 - 45.5) | 22.2 (17.2 – 27.5) | 26.0 (20.4 – 32.2) |
| Endoscopic Remission | 32.2 (25.6 - 39.0) | 37.6 (31.3 - 44.4) | 22.4 (17.0 – 27.7) | 27.0 (21.7 – 33.1) | 10.4 (7.10 – 14.6) | 12.8 (9.00 – 17.3) |
| Ulcer free Endoscopy | 26.2 (20.3 – 31.9) | 29.6 (23.7 – 36.3) | 17.2 (13.5 - 22.6) | 20.2 (15.8 – 25.5) | 7.80 (5.20 - 11.9) | 9.20 (6.10 - 13.5) |

Bio-IR = 1: inadequate response to one prior biologic therapy.

Bio-IR > 1: inadequate response to more than one prior biologic therapy.

600 mg: 600 mg IV at Weeks 0, 4, and 8.

1200 mg: 1200 mg IV at Weeks 0, 4, and 8.

Of the covariates explored for their potential effects, the following covariates were found to be statistically significant ($p < 0.001$): Asian race for SF/APS clinical remission and stool frequency remission; duration of disease at baseline for stool frequency remission; baseline albumin levels for endoscopic endpoints (endoscopic response, endoscopic remission, and ulcer free endoscopy); baseline isolated ileitis for endoscopic response and abdominal pain remission.

Based on the exposure-response models, an induction regimen of 1200 mg IV at Weeks 0, 4, and 8, was predicted to render about 1 – 5% higher response rates compared to the 600 mg IV dose level across the endpoints. A similar result was predicted for the covariate subgroups.

Induction Period 2 (exploratory)

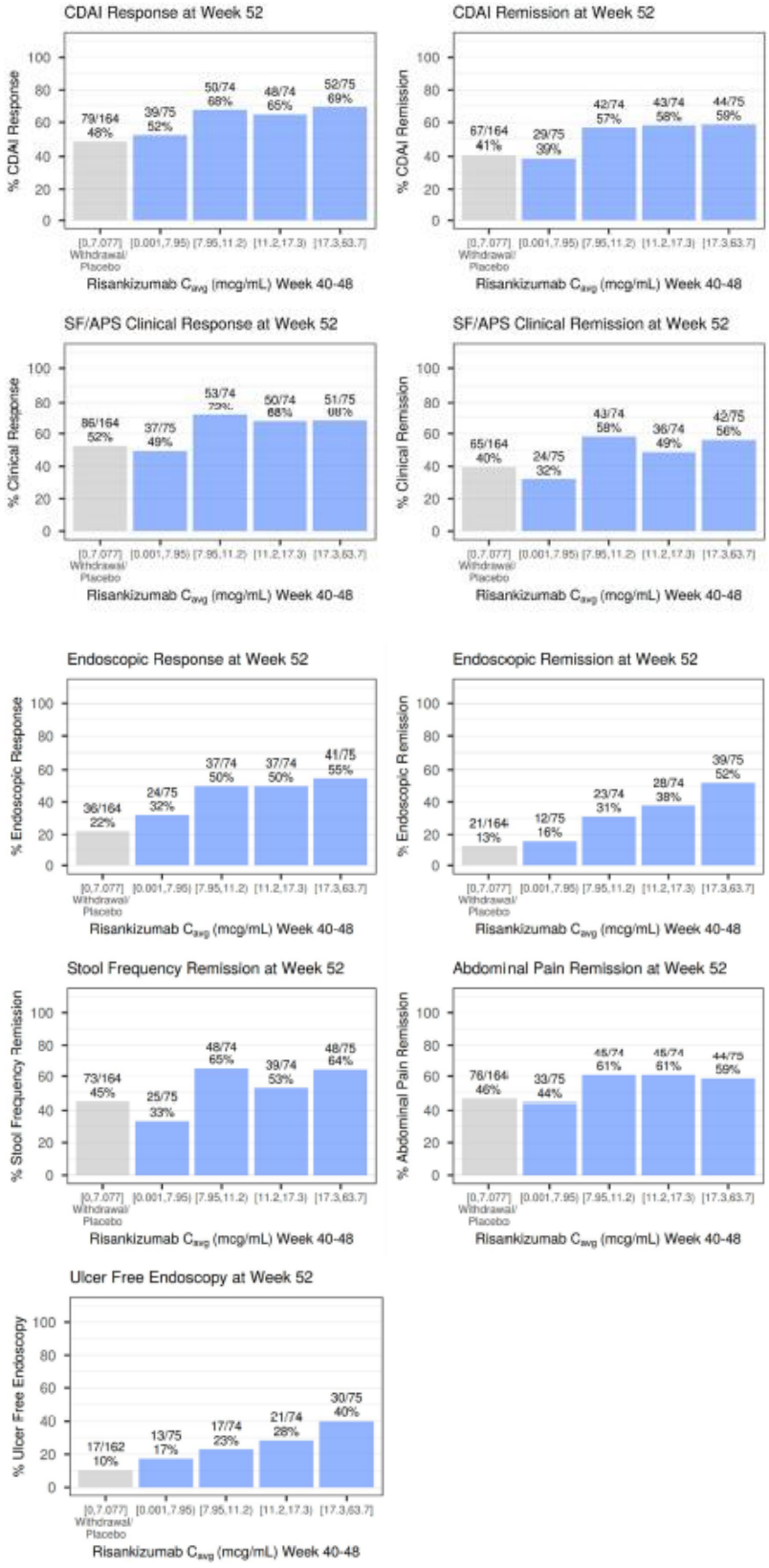
*Graphical analyses*

Overall results indicate that for the clinical endpoints, subjects who did not achieve clinical response at Week 12 and initiated maintenance therapy with 180 or 360 mg SC Q8W demonstrated similar efficacy as subjects who underwent re-induction with the 1200 mg IV Q4W regimen. For the endoscopic endpoints, patients in the higher quartiles (associated with the 360 mg SC Q8W and 1200 mg IV Q4W regimens) had higher response rates.

Maintenance period

*Graphical analysis*

Sub-study 1 of the 52-week maintenance period of the Phase 3 study evaluated two maintenance regimens of 180 mg and 360 mg SC Q8W in comparison with placebo. The graphical exposure-response analyses showed trends of higher response rates in the higher range of exposures associated with the 360 mg SC Q8W regimen for most evaluated efficacy endpoints, particularly for difficult to treat endpoints, endoscopic remission and ulcer free endoscopy (Figure 10).




Graphical exposure-response analyses for efficacy endpoints using the NRI imputation method. For subjects not receiving the OL rescue therapy, exposures reflect model predicted average risankizumab concentration across dosing interval between Week 40 to Week 48 ($C_{avg,Week40-48}$) based on actual dosing history. For subjects receiving OL rescue therapy, exposures reflect a nominal $C_{avg,SS}$ assuming the assigned dose at randomization for Study M16-000 was continued.

Note: One of the subjects in the withdrawal arm who did not receive OL rescue therapy had seemingly erroneous measurements for the PK sample, which is reflected in the upper range of the withdrawal arm.

*Figure 10 Relationship Between Risankizumab Model-Predicted $C_{avg,\ Week40\text{-}48}$ and Responses at Week 52 in maintenance Period (Study M16-000)*

*Logistic regression analyses*

Model predictions for the response rates at Week 52 for the two maintenance regimens tested in Phase 3, 180 and 360 mg SC Q8W, are provided for clinical endpoints and endoscopic endpoints in Table 18 and Table 19, respectively, grouped by the statistically significant stratification factors.

*Table 18 Model Predictions of Response Rates at Week 52 Stratified by SF/APS Clinical Remission*

| | Response Rate (%) (95% Confidence Interval) | | | |
|---|---|---|---|---|
| | Non-Clinical Remission at End of Induction | | Clinical Remission at End of Induction | |
| Response Variable | 180 mg SC Q8W | 360 mg SC Q8W | 180 mg SC Q8W | 360 mg SC Q8W |
| CDAI Response | 49.2 (41.6 - 57.5) | 55.4 (46.2 - 64.2) | 73.4 (67.4 - 80.5) | 75.0 (68.2 - 82.0) |
| CDAI Remission | 34.0 (27.2 - 41.9) | 40.0 (31.4 - 48.6) | 67.2 (60.4 - 74.8) | 68.8 61.3 - 76.6) |
| SF/APS Clinical Remission | 28.2 (21.9 - 35.8) | 33.4 (25.4 - 41.9) | 64.2 (56.7 - 72.4) | 65.6 (58.0 - 74.2) |
| Stool Frequency Remission | 34.7 (27.7 - 42.8) | 40.4 (31.6 - 48.6) | 69.0 (62.2 - 76.5) | 70.2 (62.7 - 77.8) |
| Abdominal Pain Remission | 41.5 (33.9 - 50.4) | 46.0 (37.2 - 55.2) | 67.2 (60.1 - 75.2) | 68.6 (60.8 - 76.2) |

Q8W = every 8 weeks

*Table 19 Model Predictions of Response Rates at Week 52 Stratified by Endoscopic Response*

| | Response Rate (%) (95% Confidence Interval) | | | |
|---|---|---|---|---|
| | Non-Endoscopic Response at Week 12 | | Endoscopic Response at Week 12 | |
| Response Variable | 180 mg SC Q8W | 360 mg SC Q8W | 180 mg SC Q8W | 360 mg SC Q8W |
| CDAI Remission | 44.0 (35.9 - 51.4) | 48.0 (39.3 - 55.2) | 67.2 (59.6 - 74.7) | 65.2 (56.7 - 73.1) |
| SF/APS Clinical Response | 56.4 (47.8 - 63.7) | 60.4 (51.5 - 68.7) | 76.0 (68.4 - 82.5) | 76.2 (68.0 - 82.6) |
| Endoscopic Response | 28.2 (21.2 - 35.0) | 34.4 (26.1 - 42.0) | 67.0 (59.2 - 74.6) | 71.4 (62.6 - 78.7) |
| Endoscopic Remission | 17.3 (11.7 - 23.3) | 23.0 (15.9 - 30.2) | 53.6 (45.1 - 61.8) | 60.8 (51.0 - 69.8) |
| Stool Frequency Remission | 45.6 (37.2 - 53.0) | 49.3 (40.9 - 56.3) | 68.0 (60.7 - 75.5) | 65.7 (57.1 - 73.6) |
| Ulcer free Endoscopy | 11.4 (7.20 - 16.5) | 15.0 (9.60 - 21.4) | 46.0 (36.1 - 54.8) | 50.6 (41.4 - 60.5) |

Q8W = every 8 weeks

For the clinical endpoints (CDAI Response, CDAI Remission, SF/APS Clinical Response, SF/APS Clinical Remission, Abdominal Pain Remission, Stool Frequency Remission), the exposure-response models predicted that there was minimal difference in response rates with the 180 and 360 mg SC Q8W maintenance regimens. For the endoscopic endpoints (Endoscopic Response, Endoscopic Remission, and Ulcer free Endoscopy), the 360 mg SC Q8W regimen was predicted to result in 3-7% higher response rates compared to the 180 mg SC Q8W maintenance regimen (based on numerical differences in tabulated mean % response rates).

Exposure-response analyses for safety of risankizumab in subjects with active Crohn's Disease

Data from subjects with active CD in the Phase 3 Induction Studies M15-991 (N = 605) and M16-006 (N = 926), and Phase 3 maintenance Study M16-000 (N = 462) who received placebo or at least one dose of risankizumab were included in the safety exposure-response analyses.

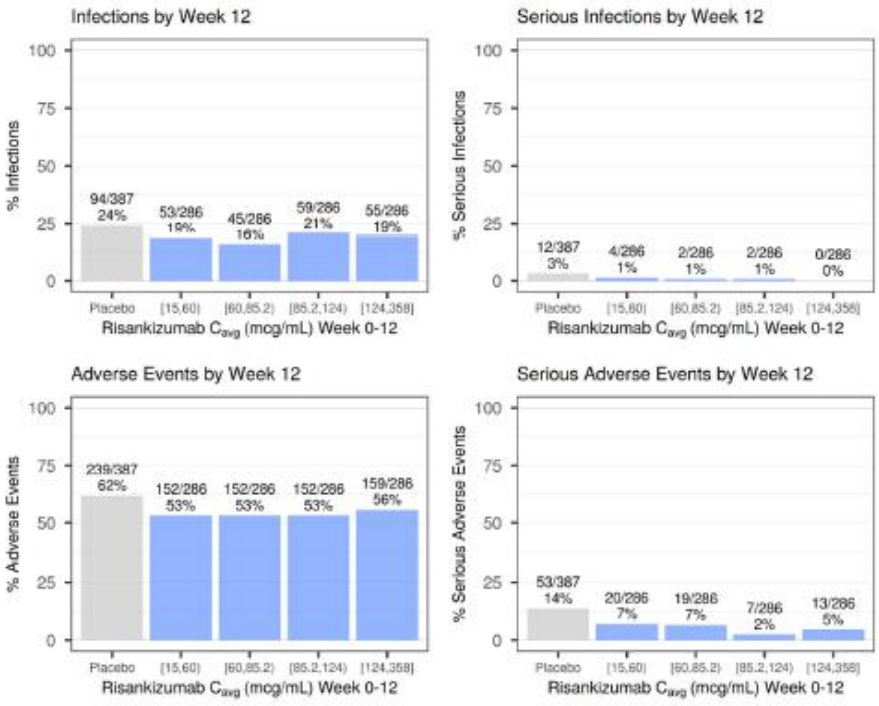
The proportions of subjects who experienced any of the key safety variables of interest (any adverse event [AE], any serious AE [SAE], any infection, and any serious infection) through Weeks 12 (end of the 12-Week Induction Period), Week 24 (end of Induction Period 2), and Week 52 (end of Maintenance Period) of the Phase 3 CD studies (Studies M15-991, M16-006, and M16-000 Sub-study

1), were determined among subjects who received placebo (Week 12 and Week 52) and in each observed risankizumab exposure quartile. Caverage and Cmax (maintenance period) were the exposure metrics used for these analyses.

*Results*

*12-week induction period*

As shown in Figure 11, there was no apparent relationship between risankizumab exposures and any AE, SAE, infection or serious infection over the first 12 weeks. Overall, during the 12-week Induction Period (Weeks 0 – 12), the incidences of safety variables of interest were lower in the risankizumab treated subjects compared to the placebo-treated subjects.

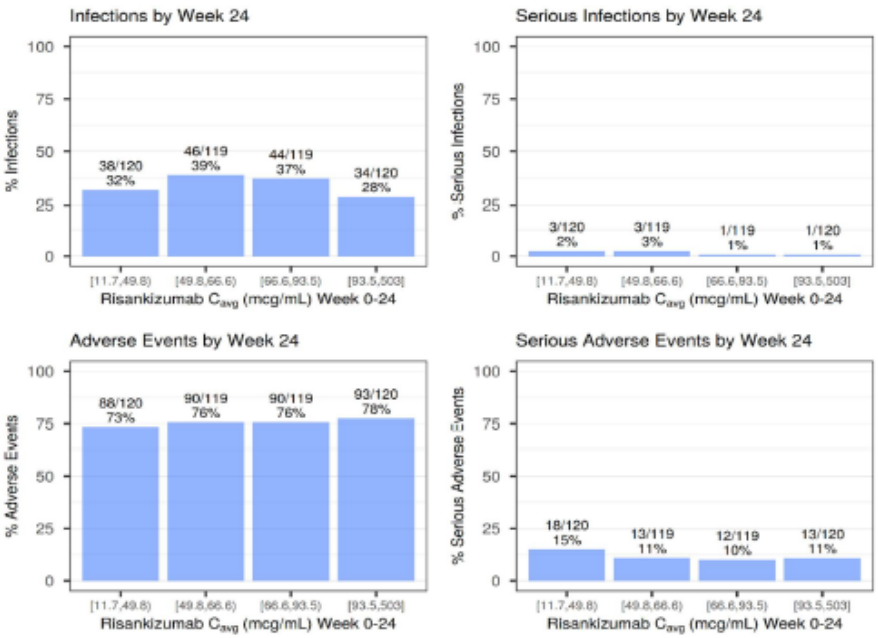



Note: Subjects who had baseline eligible SES-CD of < 6 (< 4 for isolated ileal disease) were included in the safety analyses.

*Figure 11 Exposure-Response Relationship Between Risankizumab $C_{avg, Week0-12}$ and Safety Events of Interest Over the First 12 Weeks for Subjects Enrolled in the Phase 3 Studies (Studies M15-991 and M16-006)*

*Induction Period 2*

The exposure-response relationship between risankizumab Cavg, Week 0-24 and the safety variables of interest by Week 24 are shown in Figure 12. No exposure-response trends for any of the safety variables evaluated were observed.

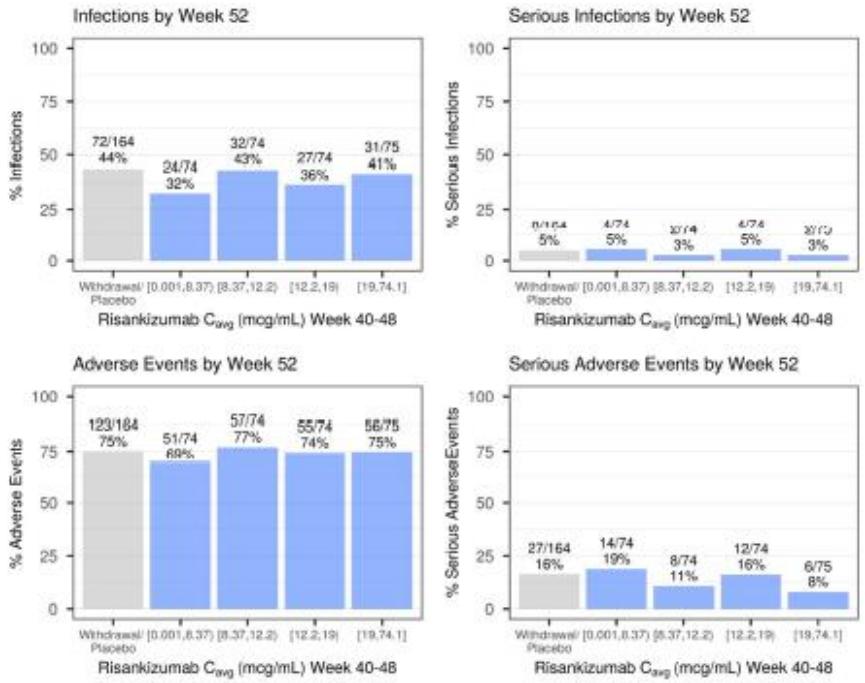



Note: Subjects who achieved clinical response at Week 12 and incorrectly entered Induction Period 2 were included in the safety analyses. N = 6 subjects were excluded from these plots since their Week 24 visit which had a PK sample collected deviated by more than 6 weeks from the planned time.

*Figure 12 Exposure-Response Relationship Between Risankizumab $C_{avg, Week0-24}$ and Safety Events of Interest Over the First 24 Weeks for Subjects in Induction Period 2 of the Phase 3 Studies (Studies M15-991 and M16-006)*

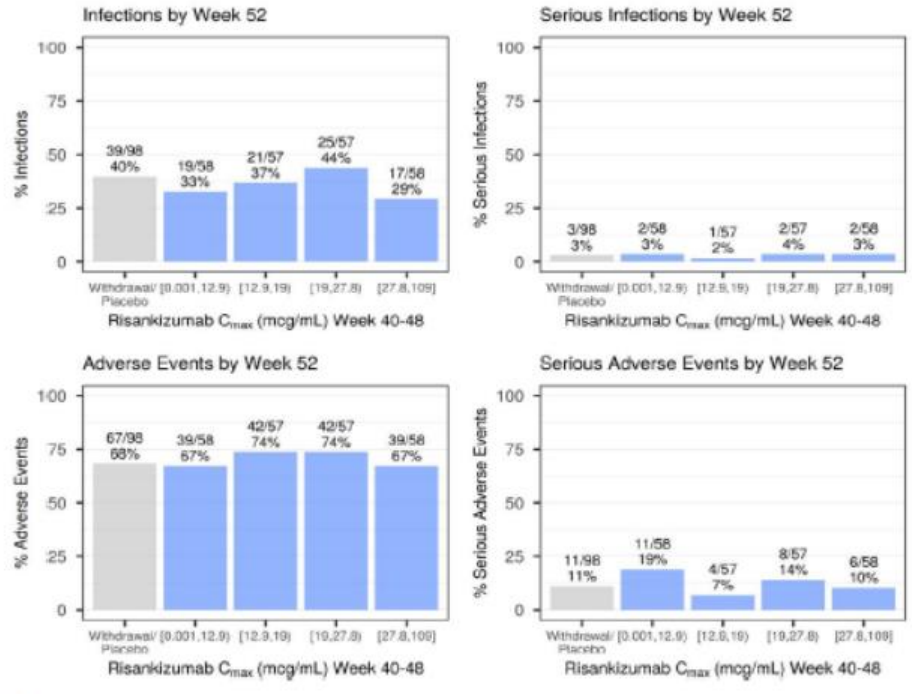
*Maintenance period*

As shown in Figure 13 (Cavg Week 40-48) and Figures 14 and 15 (Cmax at steady state), there was no apparent relationship between risankizumab exposure and any AE, SAE, infection or serious infection over 52 weeks of the Maintenance Period.




Note: One subject was excluded from these plots since its Week 52 visit which had a PK sample collected deviated by more than 6 weeks from the planned time.

*Figure 13 Exposure-Response Relationship Between Risankizumab $C_{avg}$, and Safety Events of Interest in Maintenance Period (Study M16-000)*




$C_{max}$ = maximum serum concentration

*Figure 14 Exposure-Response Relationship Between Risankizumab $C_{max}$, and Safety Events of Interest Over 52 Weeks of Maintenance Period (Study M16-000)*

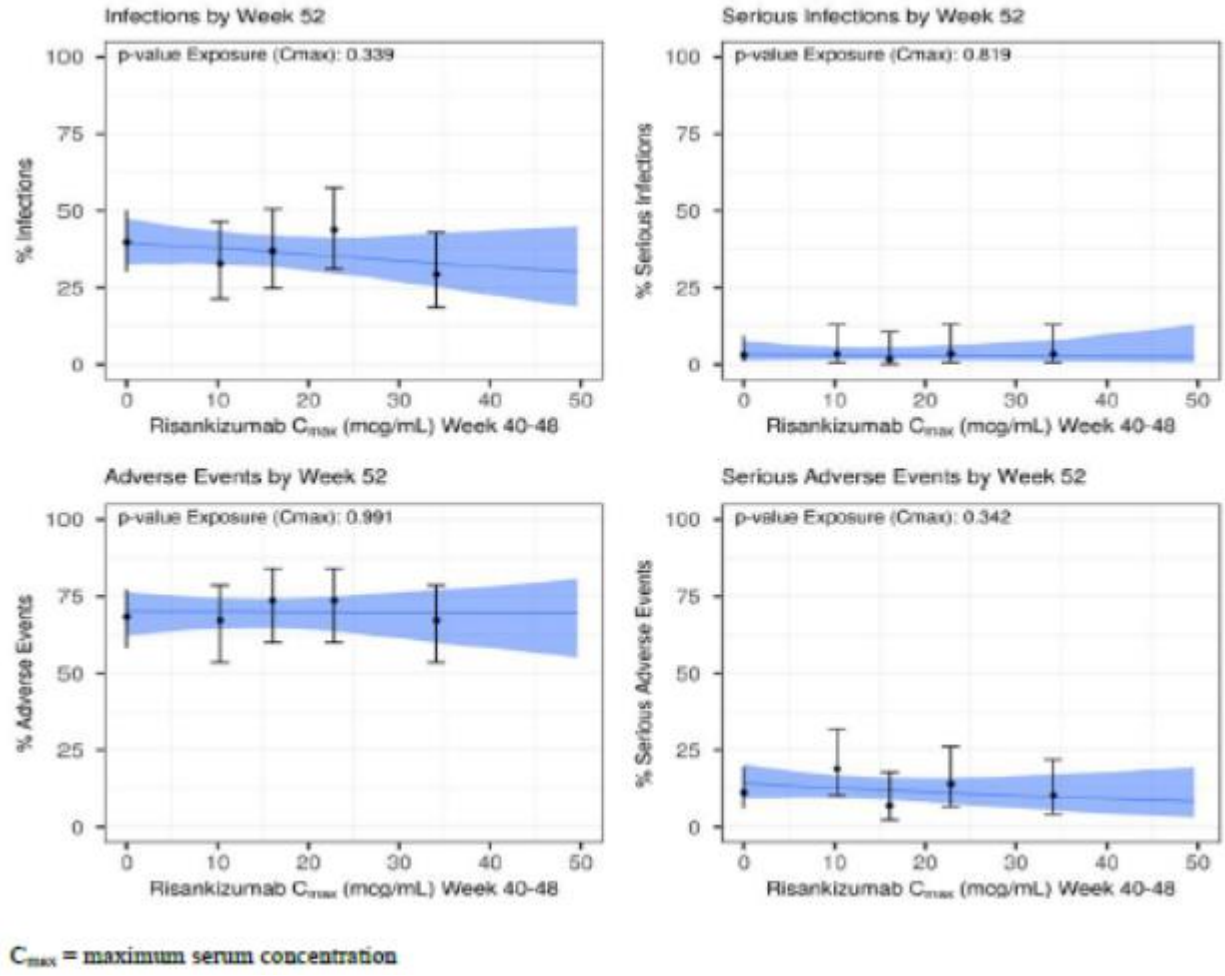



*Figure 15 Observed vs. Predicted Exposure-Response Relationship Via Linear Logistic Regression for Safety Events of Interest Over 52 Weeks of Maintenance Period (Study M16-000)*

## 2.6.3. Discussion on clinical pharmacology

**Pharmacokinetics**

*Bioanalytical methods*

The Method for determination of Risankizumab serum concentration is an Electrochemiluminescence (ECL) assay. The method was validated at both analytical sites as sample analysis for Risankizumab concentrations in human serum for the pivotal Phase 3 CD Studies was conducted at both sites. The method has been suitably validated as per the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009/Rev. 1).

For the anti-drug antibody (ADA assay the overall approach to measuring immunogenicity is in line with the recommendations of the EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1) and the EMA Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010). A titre-based acid dissociation bridging Electrochemiluminescence (ECL) immunoassay was developed and indication specific cut points were established. The ADA assay was also validated at both analytical sites as testing

occurred at both sites. Cross validation is presented demonstrating comparability of the method at both sites.

The MAH has provided an adequate method description and validation of the method used to evaluate neutralizing anti- Risankizumab (NAb) levels in human serum of healthy donors and CD patients. The method was validated as per the relevant EMA guidelines hence acceptable. The NAb assay was also validated at both analytical sites as testing occurred at both sites. Cross validation is presented demonstrating comparability of the method at both sites.

*Population PK Analyses*

The methods used for model development and evaluation are deemed acceptable. Data exclusions were well documented and acceptable. The linear two-compartment model, with first-order absorption for SC administration, provided an adequate fit to the PK of risankizumab in subjects with CD. Final model parameters (fixed and random effects) were estimated with good precision (all %RSE <21%). The computed η-shrinkage for CL was reasonably low (12.6%), whilst η-shrinkages for Vc and Ka were relatively high (44% and 59%, respectively). As such, individual EBEs for AUC and hence Caverage, which was used as the primary exposure metric in the exposure-response analyses, can be considered reliable. On the other hand, individual EBEs for Cmax, an appropriate exposure metric for exposure-safety analyses, would be considered less reliable (see Exposure-Safety analyses for further discussion). The goodness-of-fit plots showed that the final model described the data well. The VPCs showed that the prediction performance of the final model was acceptable.

Age, race and body weight did not show a clinically relevant effect on risankizumab PK. When evaluated in terms of AUC, the impact of low serum albumin on risankizumab exposure is unlikely to be of clinical relevance. No other covariates tested showed a clinically meaningful impact on risankizumab PK. Thus, from a PK perspective, a dose adjustment of risankizumab does not appear to be warranted in terms of the identified covariates in adolescent (aged ≥16 years) and adult patients with CD.

*Bioavailability*

Study M16-324 was a phase I development study which examined the PK and immunogenicity of Rizankizumab following administration of either: Three SC injections of 0.8 mL each (216 mg; Reference); 2.4 mL administered SC using a syringe pump over 3 minutes (216 mg; Test); 2.4 mL administered SC using a syringe pump over 6 minutes (216 mg; Test); or one SC injection of 2 mL (180 mg; Test). In general, PK parameters were reasonably comparable between these differing methods of administration. A slightly higher exposure relative to reference (in terms of AUCt/AUCinf) was evident in group 2 (administered 216 mg SC over 3 minutes). Treatment emergent ADA incidence ranged from 0-50% and was highest (50 %) in group 3 (administered 216 mg SC over 6 minutes). Although this is a high incidence relative to the rest of the clinical development programme, the numbers in each group of this study were low (50% represents 6/12 in that group). Furthermore, the method of administration and dose used in this study is not representative of the proposed to be marketed device. Therefore, querying this high ADA incidence is not considered unlikely to add significantly to the clinical benefit risk assessment of Risankizumab at this time. ADA incidence did not appear to have a significant effect of Risankizumab exposures.

*Bioequivalence*

Study M19-128 was a phase I single-dose, open label bioequivalence study in healthy volunteers. The study was split into two sub-studies. The first aimed to bridge the on-body delivery system (OBDS - a medical device which controls an SC administration of 360 mg of Risankizumab in 2.4 ml of a 150 mg/ml formulation over approximately 5 minutes to be used in the maintenance phase) proposed for marketing to the pre-filled syringe (PFS) presentation (90 mg/ml administered as four 1 ml SC injections) as used

in the pivotal phase 3 maintenance study (M16-000). The second sub-study aimed to assess the relative bioavailability of risankizumab following IV administration of the to be marketed 600 mg liquid vial versus the 300 mg liquid vial used in the pivotal phase III studies (M15-991 and M16-006).

The MAH received scientific advice of the design of this study from CHMP (EMA/CHMP/SAWP/591772/2019) including separate questions on the design of the 2 sub-studies. It should be noted that only limited data was presented at the time of the SA submission, but the proposed design was endorsed by CHMP. Furthermore, the proposed product design approach (i.e. the PK bridging exercise, with no direct clinical evaluation of the OBDS device) was also endorsed.

In general, the study appears to have been appropriately designed in line with the relevant EMA guidance. Of note, there were a number of OBDS related dosage failures in sub-study 1 (this occurred in 11 subjects who were excluded from the PK analysis set). However, the MAH adequately justified that the findings do not raise a concern for the efficacy or safety of the OBDS. Interim results of a currently ongoing RLHS, using the updated IFU, suggest a relatively low rate of dosing failures (2.7%) for OBDS self-administration. In all three dosing failure cases, the OBDS performed as intended and notified the subject of the error so that each subject received their dose with a replacement device. It is agreed that the interim results do not suggest any unanticipated clinical concerns or harms associated with the use of the OBDS. Finally, the risk mitigation measures implemented by the MAH are considered acceptable.

In sub-study 1, the point estimate for the LS mean ratios of serum rizankizumb (360 mg OBDS/4 × 90 mg/mL PFS) and associated 90% CI of Cmax, AUC 0-t and AUC 0-∞ were 1.263 [1.184, 1.347]; 1.065 [1.001, 1.164] and 1.070 [1.01, 1.134]. Bioequivalence in terms of AUC 0-t and AUC 0-∞ between the two presentations was demonstrated. Bioequivalence in terms of Cmax was not demonstrated. The MAH contends that the observed difference in terms of Cmax is not clinically relevant based of tolerability at higher exposures observed during the IV induction phase at doses of up to 1800 mg and 1200 mg in healthy and CD patients, respectively. In addition, there was no trend of increased adverse events with increasing exposure and there were no clinical consequences of treatment-emergent ADAs. This is considered sufficient to rule out potential safety implications of the slightly higher Cmax with the OBDS during the maintenance phase. Therefore, the lack of formal bioequivalence of Cmax between OBDS and PFS can be accepted based on the totality of PK and PK/PD information.

For the 180 mg OBDS formulation, the MAH examined for bioequivalence between the 360 mg and the 180 mg OBDS presentations, rather than as a 3 way bioequivalence with the 90 mg/ml PFS which would have been a more direct comparison. However, as the 180 mg OBDS presentation is not proposed for marketing this is not being raised at this time. Bioequivalence between the 180 mg and 360 mg OBDS presentations in terms of Cmax, AUC0-t and AUC0-∞ was demonstrated.

The dose chosen in substudy 2 (1800 mg) IV is higher than that used in the phase II induction studies (mx dose of 1200 mg IV used in both M15-991 and M16-006) and the 600 mg IV induction dose proposed for marketing. Dose proportional increases in rizankizumab exposures following IV administration have previously demonstrated and therefore this is considered acceptable. The point estimate for the LS mean ratios of serum rizankizumb (600 mg vial/300 mg vial) and associated 90% CI of Cmax, AUC0-t and AUC0-∞ were 0.998 [0.952, 1.046]; 1.079 [1.001, 1.164] and 1.044 [0.976, 1.117]. Bioequivalence in terms of Cmax, AUCt and AUC∞ between the two formulations was demonstrated.

*PK in target population*

Study M15-993 is a dose ranging phase 2 study evaluating risankizumab in patients with moderate to severe active CD, compared with placebo. While the main objectives were efficacy and safety, (see further sections of the AR below), PK Ctrough levels were collected. Ctrough levels of Rizankizumab for the proposed induction dose of IV 600mg ranged between 31.5 and 35.5 µg/mL across period 1

(weeks 8 -12) and 2 (weeks 22-26) and are comparable to the figure quoted in the SmPC (38.8 µg/mL). For the maintenance dose tested in this study, SC 180mg Rizankizumab Ctrough levels ranged between 3.6 and 4.4 µg/mL in period 3 (weeks 42 – 50). This is roughly dose proportional to the 360mg Ctrough figure quoted in the SmPC of 8.13 ug/mL. Treatment-emergent ADA-positive responses were observed in 8% of the subjects who received at least one dose of risankizumab.

Ctrough concentrations were also comparable for the OLE extension study M15-989, and ranged from 3.22 µg/mL to 4.22 µg/mL following SC 180 mg once steady state had been reached (week 24). ADAs were observed in 12% of subjects who received at least one dose of risankizumab during the study. Ctrough plasma concentrations of risankizumab in ADA-positive patients appeared lower than in ADA-negative patients, however overall PK plasma concentrations were largely influenced by a single patient in which Risankizumab exposure appeared to be impacted by the development of ADA.

Overall, the number of patients involved is too small to draw any conclusion from the impact of ADAs on plasma concentrations of risankizumab.

*Immunogenicity*

In general, treatment emergent ADA incidence was low across the CD clinical development programme and ranged from 0-5% across all studies. A notable exception to this was ADA incidence in the pivotal phase I bioequivalence study which assessed the BE of the to be marketed on body delivery system (OBDS) in which treatment emergent ADA incidence of up to 13 % were observed. However, the MAH showed that, while a higher anti-drug antibody (ADA) incidence was observed in the 360 mg OBDS group (13%) compared to the 90 mg/mL PFS group (6%), the treatment-emergent ADA incidences across all groups were within the range observed in previous Phase 1 single dose studies. There were minimal differences in risankizumab exposure between ADA-positive and ADA-negative groups and ADAs had no impact on immune-related safety events. Therefore, it is agreed that the higher ADA incidence for OBDS vs PFS observed in Study M19-128 is unlikely to result in clinically meaningful consequences for safety.

ADA positivity was consistently associated with a small numerical decrease in mean serum trough levels in the IV administration induction studies, however, such sub-group difference were small and variable. It is accepted these are unlikely to be of any clinical relevance. In phase 3 maintenance study (M16-000), only one subject in the 360 mg SC Q8W arm tested positive for ADA (at week 48), this subject displayed approximately 50 % of the mean serum trough levels in the ADA negative subjects at this time point group. It is noted that in this subject, the ratio of steady state trough serum concentrations after versus before ADA detection was equal to 0.98, suggesting no significant effect of ADA of PK in this individual. Furthermore, it is noted that ADA or NAb status did not have a significant effect on risankizumab exposure based on the population pharmacokinetic analyses. PopPK analyses did not reveal a significant effect of ADA status on clearance. A comparison of AEs with the PTs of injection site reactions and hypersensitivity reaction did not reveal any significant relationship to ADA status. Although incidence of hypersensitivity reactions was higher in the treatment emergent ADA positive sub groups, given the low incidence, no causal association can be inferred. Similarly, although minor differences in terms of efficacy assessments were observed between subgroups, such differences were minor and given the low incidence a causal association cannot be drawn. In general, it is accepted that ADA incidence did not appear to exhibit a significant effect on risankizumab exposure, safety or efficacy in the pivotal studies in the CD clinical development programme.

*Special populations*

Overall, a dose-adjustment of risankizumab is not deemed necessary in terms of special populations in subjects with CD aged 16 years and over.

*Race*

The MAH presents study M16-533 comparing a single IV dose of 1800 mg Rizankizumab in Japanese and Caucasian healthy volunteers. In general, PK data indicated similar Cmax, AUCt and AUCinf parameters in both races. ADA incidence did not appear to have a significant effect of Rizankizumab exposures.

The MAH also presents study M17-381 comparing a single dose of IV 1800 mg, SC 360 mg and SC 150 mg Rizankizumab in Chinese healthy volunteers. Risankizumab exposures (AUC) appeared dose-proportional between the 150 and 360 mg SC doses. There were no treatment emergent ADAs in these trial subjects.

**Pharmacodynamics**

***Primary Pharmacology***

In phase III induction studies M15-991 and M16-006 risankizumab treatment at 600 mg and 1200 mg was associated with a reduction in serum CRP, FCP and IL-22 levels. These changes were maintained following maintenance therapy at 180 mg and 360 mg in study M16-000. It should be noted that not all such changes were statistically significant or dose proportional. In general, the submitted PD data support the proposed mechanism of action and efficacy in the proposed patient population.

***Exposure-response analyses for efficacy***

Induction period

Graphical quartile analyses based on the Phase 3 studies suggested that exposures associated with the 600 mg induction regimen achieved near maximal efficacy for all endpoints evaluated, with no additional benefit observed for the 1200 mg regimen.

The logistic regression models described the exposure-response relationships for efficacy adequately. In line with the graphical analyses, model predictions suggested that the 600 mg induction regimen achieves near maximal efficacy across all efficacy endpoints. However, a small added benefit of 1-5% was predicted for the 1200 mg induction regimen.

Induction period 2

For subjects who did not achieve a clinical response at Week 12 and entered an exploratory, 12-week double-blinded re-induction period, graphical quartile analyses suggested that initiation of maintenance therapy with 180 or 360 mg SC Q8W at Week 12 resulted in similar response rates as re-induction with a 1200 mg IV Q4W regimen across all efficacy endpoints evaluated at Week 24.

Maintenance

Graphical quartile analyses at Week 52 showed trends of higher response in the higher range of exposures associated with the 360 mg SC Q8W regimen for most of the evaluated efficacy endpoints, particularly for the more stringent endoscopic endpoints such as endoscopic remission and ulcer free endoscopy.

The logistic regression models described the exposure-response relationships adequately. Model predictions at Week 52 suggested that response rates for endoscopic endpoints are about 3-7% higher with the 360 mg SC Q8W maintenance regimen vs the 180 mg Q8W regimen.

Overall, the results of the exposure response analyses for efficacy, provide support for the proposed clinical dosing regimen of risankizumab for subjects with moderately to severely active CD; an induction regimen of 600 mg IV at Weeks 0, 4 and 8, followed by a maintenance regimen of 360 mg SC Q8W.

***Exposure-response analyses for safety***

The exposure-response analyses for safety did not identify any apparent relationship between risankizumab Cavg and safety events during either induction or maintenance treatment periods. There was also no apparent relationship between risankizumab Cmax at steady-state and any safety event over 52 weeks of the Maintenance Period.

## 2.6.4. Conclusions on clinical pharmacology

The Clinical pharmacology has been well characterised and is acceptable.

## 2.6.5. Clinical efficacy

The MAH submitted 2 Phase II studies (M15-993, M15-989) and 3 Phase III studies (M15-991, M16-006, M16-000) in this application. Only M16-000 Sub-Study 1 was included in this assessment; Sub-Study 2 and Sub-Study 3 are ongoing and results were not included in the submission.

The MAH stated that, to meet regional regulatory requirements, each pivotal study was associated with two protocols - a United States (US) protocol and a protocol for outside the US (OUS). These protocols were identical in study design and analysed in the same population; specified co-primary and key secondary endpoints were different.

The MAH stated that study-specific SAPs were finalized prior to unblinding the studies.

### *2.6.5.1. Dose response studies*

**Study M15-993 (1311.6)**

Title: A Phase 2, Multicentre, Randomized, Double-Blind, Multiple Dose, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Pharmacokinetics, and Safety of BI 655066 (Risankizumab), an IL-23 p19 Antagonist Monoclonal Antibody, in Patients With Moderately to Severely Active Crohn's Disease Who Are Naïve to or Were Previously Treated With Anti-TNF Therapy

| **No. of study centres / locations** | **Design** | **Study Posology** | **Subjs by arm entered/ compl.** | **Duration** | **Diagnosis Incl. criteria** |
|---|---|---|---|---|---|
| 36 sites in 9 countries (BE, DE, NL, PL, ES; UK, USA, Canada, Rep. Korea) | Randomized, DB, PBO controlled, parallel group, dose ranging | RZB 200 mg IV q4w, RZB 600 mg IV q4w, RZB 180 mg SC q8w | N=121<br><br>108/121 completed Period 1<br><br>Male=47 Female=74 Mean age 38.1 yrs | 67 weeks | Adults with CD for at least 3 months, confirmed by endoscopic or imaging examination + moderate to severe CD (CDAI ≥ 220 and ≤ 450 + mucosal ulcers in at least 1 segment of the ileum or colon + CDEIS ≥ 7 (for subjects with isolated ileitis ≥ 4) + naïve or experienced to 1 or more tumor necrosis factor (TNF) antagonists (infliximab, adalimumab, or certolizumab pegol) at a dose approved for CD. |
| **Study Objectives** | | | | | |
| Evaluate the efficacy of RZB in inducing clinical remission, defined as CDAI < 150, after 12 weeks of treatment. Evaluate the efficacy of RZB in inducing endoscopic response, clinical response, mucosal healing, and deep remission. Evaluate the safety of RZB. Explore the PK and PD of RZB therapy in CD. | | | | | |
| **Primary Endpoint** | | | | | |
| Clinical remission, defined as a CDAI < 150, at Week 12. | | | | | |

First subject first visit: 25 February 2014 Last subject last visit: 18 November 2016

This was a proof-of-concept, double-blind, dose-ranging study of RZB in subjects with moderately to severely active CD. A screening period of up to 4 weeks was followed by Period 1 (12-week blinded IV period), Period 2 (14-week open-label (OL) IV/wash-out period), Period 3 (26-week SC period) and follow up (15 weeks).

Inclusion and exclusion criteria allowed for subjects with a diagnosis of moderately to severely active CD. Allowable concomitant medications were pre-specified; corticosteroids (CS) must have been discontinued at least 3 weeks prior to the study.

Up to 120 eligible patients were to be randomised 1:1:1 in to parallel treatment arms in Period 1, stratified according to previous experience with anti-TNF therapy (naïve vs. experienced). PBO and RZB infusions were matched to maintain blinding.

*Treatments*

Period 1: PBO vs. RZB 600 mg IV vs. RZB 200mg IV (3 infusions; weeks 0, 4, 8) (blinded)

Period 2: RZB 600 mg IV (3 infusions; 4 weeks apart) or washout (open label)

Period 3: RZB 180 mg SC (4 doses; 8 weeks apart) or RZB stopped (open label)

*Analysis set*

The primary efficacy endpoint was clinical remission, defined as a CDAI < 150, at Week 12.

The Period 1 Full Analysis Set (FAS-P1) population included all randomized subjects who had taken at least one dose of study drug in the double-blind IV period; subjects were assessed according to assigned treatment at randomization. Statistical tests were 2-sided, at a significance level of α = 0.10, with no adjustment for multiple comparisons. A stratified Cochran-Mantel-Haenszel test with randomisation factor of naïve or experienced to TNF antagonists as the stratification variable was used for the binary primary endpoint

*Results*

In total, 121 subjects were enrolled, 74 females and 47 males. Mean age was 38.1 years. Demographic characteristics were balanced with regard to sex, age, race, ethnicity, weight, and country of origin. Average duration of CD was 13.4 years. Most subjects (67.8%) had at least 1 CD-specific therapy within 90 days prior to participation in the study (40.5% IMM therapy; 33.1% CSs; 17.4% ASAs. Almost all subjects (114/121; 94.2%) had received previous anti-TNF therapy.

Of 121 subjects enrolled, 89% (108/121) completed Period 1. Among 13 subjects who discontinued in Period 1, the most common reason was due to 'AE' (PBO: 6; RZB 200 mg: 5; RZB 600 mg: 1). Protocol violations (n=3) were not considered to have affected study outcome or interpretation of study results.

Primary Efficacy Endpoint – Period 1

*Table 20 Summary of CDAI Clinical Remission at Week 12 (NRI; FAS-P1)*

| Treatment | Remission n/N | Remission Rate (%) (95% CI)[a] | Comparison | Remission Rate Diff (%) (95% CI)[b] | *P* value |
|---|---|---|---|---|---|
| Placebo (A) | 6/39 | 15.4 (5.9, 30.5) | | | |
| Risankizumab 200 mg IV (B) | 8/41 | 19.5 (8.8, 34.9) | [B vs A] | 4.1 (–12.4, 20.6) | 0.6278 |
| Risankizumab 600 mg IV (C) | 15/41 | 36.6 (22.1, 53.1) | [C vs A] | 20.9 (2.6, 39.2) | 0.0252 |
| Risankizumab 200 + 600 mg IV (D) | 23/82 | 28.0 (18.7, 39.1) | [D vs A] | 12.6 (–2.2, 27.5) | 0.0955 |
| | | | [C vs B] | 16.8 (–2.0, 35.6) | 0.0799 |

a. Exact 95% CI by Clopper and Pearson.
b. Statistics for the difference are calculated using the Cochran-Mantel-Haenszel (CMH) risk difference stratified by TNF-exposure.

At week 12, the RZB 600 mg IV group demonstrated a statistically significantly greater difference in the proportion of subjects achieving CDAI clinical remission versus PBO (remission rate RZB 600 mg IV 36.6% vs. PBO 15.4%; difference 20.9% (95% CI 2.6 – 39.2), p=0.0252).

The RZB 200 mg IV group demonstrated a non-statistically significant, higher proportion achieving CDAI clinical remission compared to PBO (remission rate difference 4.1% (95% CI -12.4, 20.6), p=0.6278).

With regard to secondary endpoints, deep remission, defined as CDAI <150 and CDEIS ≤ 4 (≤ 2 for patients with isolated ileal disease), confirmed by central independent reviewer, was achieved at Week 12 by 0/39 (0 %), 1/41 (2.4%) and 5/41 (12.2%) patients in the PBO, 200 and 600 mg RZB IV groups, respectively (FAS-NRI).

In Period 1, approximate dose-proportional increases in RZB plasma trough concentrations were observed in subjects who received RZB IV. With RZB 180 mg SC dose Q8w starting at Week 26, near steady state levels were achieved by Week 42.

After 26 weeks of 180 mg SC q8w maintenance therapy, of subjects who achieved clinical remission to RZB induction treatment, approximately 30% lost clinical remission and a majority did not achieve the stringent endpoints of endoscopic remission or deep remission.

Treatment-emergent ADA-positive responses were low (8%) and the majority transient, appearing from 12 to 18 weeks post first treatment. No ADA-positive subjects became positive for nAb during the study and RZB plasm concentrations appeared unaffected.

No new safety concerns or dose-dependent increase in AEs were observed.

The results indicate a dose dependent response, supporting the higher RZB dose (600 mg) for induction and at least a dose of RZB 180 mg SC for maintenance of effect. However, an upper dose-response limit, for induction or maintenance, is not deduced.

**Study ID – M15-989, (1311.20)**

Title: An Open Label, Single Group, Long Term Safety Extension Trial of BI 655066/ABBV-066 (Risankizumab), in Patients with Moderately to Severely Active Crohn's Disease

| **No. of study centres (locations)** | **Design** | **Study Posology** | **Subjs by arm entered/ compl.** | **Diagnosis Incl. criteria** |
|---|---|---|---|---|
| 28 sites in 9 countries (BE, DE, NL, PL, ES; UK, USA, Canada, Rep. Korea) | OL, single group, rollover LTE<br><br>**Duration**<br><br>Approx. 4 years | RZB 180 mg SC q8w<br><br>RZB 600 mg IV q4w | N=65<br><br>44/65 completed<br><br>Male=29<br>Female=36<br><br>Median age 34 yrs | Adults with moderate to severely active CD with clinical response or remission after previous treatment with RZB<br>Subjects with CD who had successfully:<br>- completed M15-993 Period 2 with a clinical response (drop in CDAI from baseline by ≥ 100) but no remission (CDAI < 150)<br>- completed M15-993 Period 3 with a clinical response (drop in CDAI from baseline by ≥ 100) and/or remission (CDAI < 150)<br>- completed Period 2 or 3 in Study M15-993 (1311.6) per protocol with a clinical response or remission before initiation of Study M15-989 (1131.20) - could have rolled-over either directly if response/remission was maintained or through an open-label (OL) intravenous (IV) re-induction phase if previous response/remission lost |

In total, 65 subjects were enrolled from Study M15-933 and all 65 received at least 1 dose of RZB in Study M15-989, forming the Intention-to-Treat analysis set (n=65).

M15-989 was terminated early by the sponsor so that subjects could roll over into Phase 3 Study M16-000 Sub-study 3 OLE, which is ongoing. Efficacy endpoints (observed data "by visit" time points) showed that trends in response rate for clinical remission (CDAI < 150) and endoscopic remission (CDEIS ≤ 4 or CDEIS ≤ 2 for patients with initial isolated ileitis) were sustained throughout the study.

No new safety signals were identified. On administration of RZB 180 mg SC q8w, steady-state plasma exposures were reached by Week 24 after the first SC dose. Median trough concentrations ranged from 3.66-4.23 µg/mL. Emergence of ADA was low and of no apparent impact on RZB concentrations.

The descriptive results presented are supportive of the efficacy and safety of at least RZB 180 mg SC as a long-term treatment in patients with moderately to severely active CD, who showed a clinical response, or remission on previous treatment with RZB.

#### *2.6.5.2. Main studies*

*Table 21. Overview of Risankizumab Pivotal Phase 3 Studies*

| | M15-991 12-Week Induction Period | M16-006 12-Week Induction Period | M16-000 Sub-Study 1 |
|---|---|---|---|
| **Population** | Subjects with moderately to severely active CD who were Bio-IR[a] | Subjects with moderately to severely active CD who were Bio-IR[a] or Non-Bio-IR[b] | Subjects who achieved SF/APS clinical response[c] at Week 12 or Week 24 of the induction studies |
| **Risankizumab Dose** | RZB 1200 mg IV or RZB 600 mg IV q4w for 3 doses | RZB 1200 mg IV or RZB 600 mg IV q4w for 3 doses | RZB 180 mg SC or RZB 360 mg SC q8w |
| **Duration** | 12 weeks | 12 weeks | 52 weeks |
| **Comparator** | PBO IV q4w for 3 doses | PBO IV q4w for 3 doses | PBO SC q8w |
| **Primary Objective** | Evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in subjects with moderately to severely active CD. | Evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in subjects with moderately to severely active CD. | Evaluate the efficacy and safety of risankizumab versus placebo as maintenance therapy in subjects with moderately to severely active CD who responded to 12 weeks of risankizumab IV induction treatment. |
| **Number of subjects exposed to at least 1 dose of study drug (SA1)[d]** | Total = 618<br>RZB 600 mg IV = 206<br>RZB 1200 mg IV = 205<br>PBO IV = 207 | Total = 931<br>RZB 600 mg IV = 373<br>RZB 1200 mg IV = 372<br>PBO IV = 186 | Total = 712<br>Randomized Subjects[e]<br>RZB 180 mg SC = 179<br>RZB 360 mg SC = 179<br>Withdrawal (PBO SC) = 184<br>Non-Randomized Subjects[f]<br>RZB 180 mg SC = 31<br>RZB 360 mg SC = 33<br>PBO SC = 106 |
| **Number of subjects included in the primary population for efficacy (ITT1A)[g]** | Total = 569<br>RZB 600 mg IV = 191<br>RZB 1200 mg IV = 191<br>PBO IV = 187 | Total = 850<br>RZB 600 mg IV = 336<br>RZB 1200 mg IV = 339<br>PBO IV = 175 | Total = 462<br>RZB 180 mg SC = 157<br>RZB 360 mg SC = 141<br>Withdrawal (PBO SC) = 164 |
| **Status** | Complete | Complete | Primary data base lock completed, final data base lock pending 140-day follow up |

a. Bio-IR population: subjects with documented intolerance or inadequate response to one or more approved biologics for CD (infliximab, adalimumab, certolizumab, natalizumab, vedolizumab, and/or ustekinumab).

b. Non-Bio-IR population: subjects who had an inadequate response or intolerance to one or more conventional therapies (aminosalicylates, oral locally acting steroids, systemic corticosteroids, or immunomodulators); also included subjects who received prior biologic therapy but stopped therapy based on reasons other than inadequate response or intolerance (e.g., change in reimbursement coverage, well-controlled disease).

c. SF/APS clinical response: ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily APS and both not worse than Baseline.

d. SA1 population: enrolled subjects in the safety population who received at least one dose of study drug.
e. All randomized subjects achieved clinical response to risankizumab IV at Week 12 or Week 24 of the induction studies.
f. All non-randomized subjects achieved clinical response to IV placebo at Week 12 or risankizumab SC at Week 24 of the induction studies.
g. ITT1A Primary efficacy population: all randomized subjects who received at least one dose of study drug with a baseline SES-CD, excluding the narrowing component, of ≥ 6, or ≥ 4 for isolated ileal disease, confirmed by a blinded central reviewer; excludes subjects from a non-compliant site. In addition, for Study M16-000 Sub-Study 1, all randomized subjects received at least one dose of study drug in the Sub-Study 1 and received 12-weeks of risankizumab IV induction treatment.

**Induction Studies M15-991 and M16-006**

M15-991 - A multicenter, randomized, double-blind, placebo controlled induction study to assess the efficacy and safety of risankizumab in subjects with moderately to severely active Crohn's disease who failed prior biologic treatment

M16-006 –A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease

*Methods*

The Phase 3 induction studies (Study M15-991 and Study M16-006) were multicenter, randomized, double-blind, placebo-controlled evaluations of risankizumab (risankizumab 600 mg IV or 1200 mg IV at Weeks 0, 4, and 8) in subjects 16 years and older with moderately to severely active CD defined as:

- a CDAI of 220 to 450,
- a daily average stool frequency (SF) of ≥ 4 and/or average daily abdominal pain score (APS) ≥2,
- and a Simple Endoscopic Score (SES) – CD (excluding the narrowing component) of ≥ 6, or ≥ 4 for isolated ileal disease, confirmed by central review (known as original SES-CD).

Of note, with global protocol Amendment 5 for Study M15-991 and global protocol Amendment 4 for Study M16-006, subjects with a lower SES-CD were also enrolled and capped at 10% of the total population of each study. Lower SES-CD was defined as a SES-CD of 3 to 5 for colonic or ileocolonic disease or a 3 for isolated ileal disease. Enrollment of subjects with lower SES-CD was undertaken to explore efficacy and safety of risankizumab in subjects with confirmed active moderate to severe clinical symptoms and a lesser degree of active endoscopic disease.

***Study Participants***

Study M15-991 was designed to enroll approximately 579 subjects who had a documented inadequate response or intolerance to use of an approved biologic agent (Bio-IR), such as infliximab, adalimumab, certolizumab, natalizumab, ustekinumab and/or vedolizumab.

Study M16-006 was designed to enroll approximately 855 subjects who were Bio-IR or subjects who were Non-Bio-IR. The non-bio-IR population included subjects who had an IR or intolerance to conventional therapy, but not biologic therapy. Conventional therapy was defined as one or more of the following: aminosalicylates, oral locally acting steroids (e.g., budesonide, beclomethasone), systemic corticosteroids (prednisone or equivalent), or immunomodulators. This population also included subjects who received biologic therapy in the past but stopped therapy based on reasons other than IR or intolerance (e.g., change in reimbursement coverage, well-controlled disease). In

each study the number of subjects with prior exposure to ustekinumab was capped at 20% of the total population.

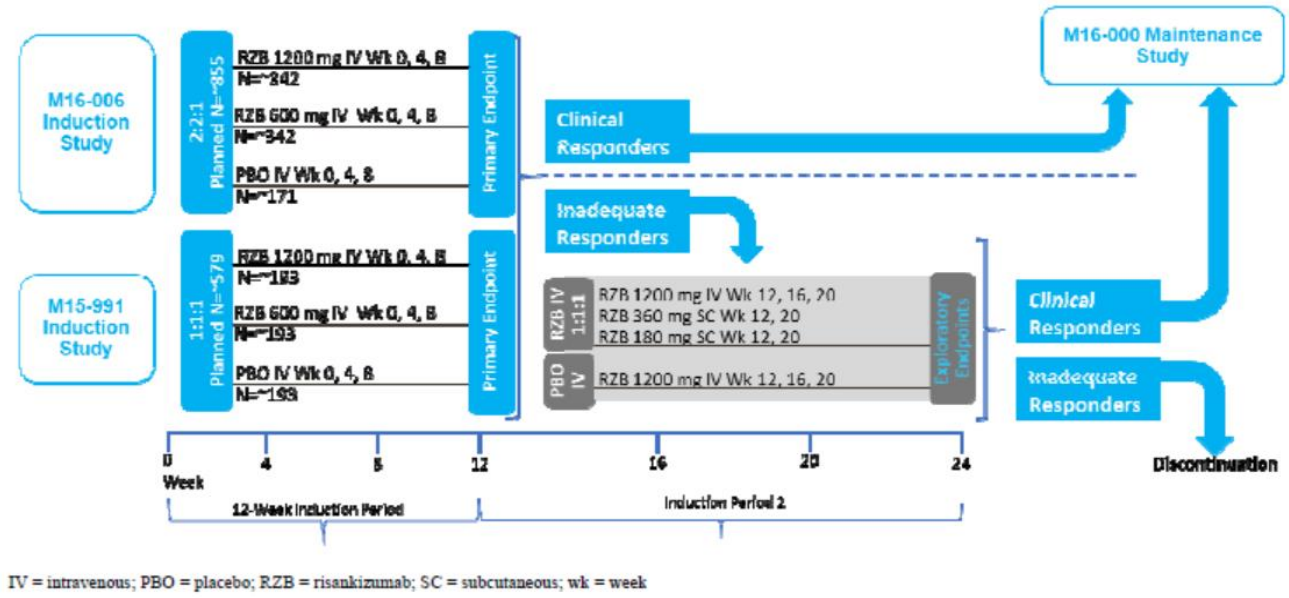
Each induction study duration was estimated to be up to 49 weeks, including a Screening period of 35 days, a 12-week induction period, a 12-week Induction Period 2 for subjects who did not achieve clinical response at Week 12, and a 140-day follow-up period from the last dose of study drug.

At the Baseline visit, subjects who met all the inclusion criteria and none of the exclusion criteria were enrolled into the double-blind 12-Week Induction Period and randomized to receive either risankizumab 600 mg IV, risankizumab 1200 mg IV, or placebo IV q4w for 3 doses. The randomization at Baseline was stratified by the number of prior biologics failed, steroid use at Baseline, and Baseline SES-CD (original versus lower). The 12-Week Induction Period was the pivotal portion of the study design.

At Week 12, subjects who did not achieve SF/APS clinical response, defined as a ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily APS and both not worse than Baseline of the induction study, were eligible to enter Induction Period 2, a double-blind, double-dummy 12-week treatment period. Subjects who received IV risankizumab during the 12-week induction period were randomized 1:1:1 to either risankizumab 1200 mg IV, risankizumab 180 mg SC, or risankizumab 360 mg SC. Subjects who received IV placebo induction treatment received risankizumab 1200 mg IV. The risankizumab IV dose or matching placebo IV was given at Weeks 12, 16, and 20. The risankizumab SC dose or matching placebo SC was given at Weeks 12 and 20.

Subjects who achieved clinical response at Week 12 or Week 24 were eligible to enter Study M16-000. 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 participate in the blinded 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 and/or ongoing adverse events (AE).

Initiation of, increase in dose, or decrease in dose of concomitant CD-medications (i.e., aminosalicylates, oral locally acting steroids, systemic corticosteroids, or immunomodulators) was prohibited during the 12-Week Induction Period. Subjects who initiated new or exceeded their baseline dose of corticosteroids were imputed as non-responders for the co-primary endpoints.




IV = intravenous; PBO = placebo; RZB = risankizumab; SC = subcutaneous; wk = week

*Figure 16 Induction Studies Schematic (Studies M15-991 and M16-006)*

***Treatments***

Blinded study drug (risankizumab 1200 mg, risankizumab 600 mg, or placebo) was administered intravenously (IV) during 12-Week Induction Period at Weeks 0, 4, and 8.

Blinded study drug (risankizumab 1200 mg) was administered IV during Induction Period 2 at Weeks 12, 16, and 20. Blinded study drug (360 mg risankizumab, or 180 mg risankizumab) was administered subcutaneously (SC) in Induction Period 2 at Weeks 12 and 20.

Risankizumab was provided as 90 mg/mL solution for infusion in vial and 90 mg/mL solution for injection in pre-filled syringe (PFS).

***Objectives***

The objective of the induction studies is to evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in subjects with moderately to severely active Crohn's disease.

***Outcomes/endpoints***

The co-primary endpoints for the outside the United States (OUS) protocol were:

- Proportion of subjects with SF/APS clinical remission at Week 12
- Proportion of subjects with endoscopic response at Week 12

The co-primary endpoints for the US protocol were:

- Proportion of subjects with CDAI clinical remission at Week 12
- Proportion of subjects with endoscopic response at Week 12

The ranked secondary endpoints for the OUS protocol were:

1. Proportion of subjects with CDAI clinical remission at Week 12
2. Proportion of subjects with CDAI clinical response at Week 4
3. Proportion of subjects with SF/APS clinical remission at Week 4

4. Proportion of subjects with CDAI clinical response at Week 12
5. Mean change from baseline of induction in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT) fatigue at Week 12
6. Mean change from baseline of induction in Inflammatory Bowel Disease Questionnaire (IBDQ) total score at Week 12
7. Proportion of subjects with enhanced SF/APS clinical response and endoscopic response at Week 12
8. Proportion of subjects with endoscopic remission at Week 12
9. Proportion of subjects with enhanced SF/APS clinical response at Week 4
10. Proportion of subjects with ulcer-free endoscopy at Week 12
11. Enhanced SF/APS clinical response at Week 12
12. Proportion of subjects with resolution of extra-intestinal manifestations (EIMs) at Week 12, in subjects with any EIMs at Baseline
13. Proportion of subjects with CD-related hospitalization through Week 12
14. Proportion of subjects without draining fistulas at Week 12 in subjects with draining fistulas at Baseline
15. Change from baseline in Work Productivity and Impairment Questionnaire – Crohn's disease (WPAI-CD) overall work impairment at Week 12
16. Change from baseline in 36-Item Short Form Health Survey (SF-36) physical component summary score at Week 12

Pharmacokinetics and Immunogenicity:

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

Definition of Efficacy Endpoints for Induction Studies

| Term | Definition |
|---|---|
| CDAI clinical remission | Proportion of subjects with CDAI < 150 |
| SF/APS Clinical remission | Proportion of subjects with average daily SF ≤ 2.8 and not worse than Baseline AND average daily APS ≤ 1 and not worse than Baseline |
| CDAI clinical response | Proportion of subjects with reduction of CDAI ≥ 100 points from baseline |
| SF/APS clinical response | Proportion of subjects with ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score and both not worse than Baseline |
| Enhanced SF/APS clinical response | Proportion of subjects with ≥ 60% decrease in average daily SF and/or ≥ 35% decrease in |

| | |
|---|---|
| | average daily AP score and both not worse than Baseline, and/or clinical remission |
| Endoscopic response | Proportion of subjects with a decrease in SES-CD > 50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2-point reduction from Baseline), as scored by central reviewer |
| Endoscopic remission | Proportion of subjects with SES-CD ≤ 4 and at least a 2-point reduction versus Baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer |
| Ulcer-free endoscopy | Proportion of subjects with SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore ≥ 1 at baseline, as scored by a central reviewer |
| Change from Baseline in FACIT-fatigue | Mean change from Baseline in FACIT-fatigue |
| Change from Baseline in SF-36 | Mean change from Baseline in SF-36 Physical Component Summary score |
| Change from Baseline in WPAI | Mean change from Baseline in WPAI-CD Overall Work Impairment |
| Resolution of EIMs | Proportion of subjects with resolution of EIMs in subjects with any EIMs at baseline of induction |
| No draining fistulas | Proportion of subjects with resolution of draining fistulas in subjects with draining fistulas at baseline of induction |
| CD-Hospitalisations | Proportion of subjects with CD-related hospitalization |

***Induction Study M15-991***

***Sample size***

Sample size calculation was based on the larger sample size needed to detect treatment differences between the risankizumab treatment arms and the placebo arm for each of the co-primary endpoints. Assuming the clinical remission (SF/APS) rate at Week 12 would be 23.5% for one of the risankizumab treatment arms and 10% for the placebo arm, a sample size of 193 subjects for each risankizumab arm and 193 for the placebo arm would have approximately 89% power to detect the treatment difference between risankizumab and placebo using a Fisher's exact test at alpha level of 0.025 (two-sided). Assuming the CDAI clinical remission rate at Week 12 would be 34% for one of the risankizumab treatment arms and 15% for the placebo arm, this sample size would have 97% power to detect the treatment difference between risankizumab and placebo using a Fisher's exact test at a 0.025 significant level (two-sided). Assuming the endoscopic response rate at Week 12 will be 17% for one of the risankizumab treatment arms and 5% for the placebo arm, this sample size would have

93% power to detect treatment difference between risankizumab and placebo using a Fisher's exact test at a 0.025 significant level (two-sided). Further details on sample size calculation is presented in the Protocol and SAP.

***Randomisation***

At baseline, eligible patients were randomized to three parallel groups with 1200 mg IV and 600 mg IV dose of risankizumab treatments or placebo in a 1:1:1 ratio. The 12-Week Induction Period randomization were stratified by number of prior biologics failed (1, > 1), baseline steroid use (Yes, No), and baseline eligible SES-CD (original, alternative), where the stratum of "original" includes the patients with baseline eligible SES-CD of ≥ 6 (or ≥ 4 for subjects with isolated ileal disease), and the stratum of "alternative" includes the patients with baseline eligible SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease.

Subjects with clinical non-response to risankizumab at Week 12 were to be re-randomized in a 1:1:1 ratio to risankizumab 1200 mg IV dose group, risankizumab 360 mg SC dose group, or risankizumab 180 mg SC dose group in the Induction Period 2. Subjects with clinical non-response to placebo at Week 12 blindly received risankizumab 1200 mg IV dose. No stratification was made for the Induction Period 2 randomization.

***Blinding (masking)***

It is unclear whether or not participants, those administering interventions and those assessing outcomes were aware of group assignment and if not, how the success of masking was assessed.

***Statistical methods***

A statistical analysis plan (SAP) was written and signed off prior to data base lock which included a number of amendments. These amendments are unlikely to have influenced the analyses outcomes for the primary outcome as far as can be ascertained.

The primary hypotheses for the co-primary endpoint were stated as:

(i) The proportion of subjects achieving clinical remission treated with risakizumab is greater than that treated with placebo at Week 12

(ii) The proportion of subjects achieving endoscopic response treated with risakizumab is greater than that treated with placebo at Week 12

The estimands corresponding to the primary efficacy objective for global protocol outside US were stated to have been defined mainly as a definition of the outcome. Intercurrent events were specified as: 1) premature discontinuation of study drug and 2) initiation or dose escalation of CD-related corticosteroids.

Several analyses populations were defined, with the key one for the purposes of this assessment being the Intent-to-Treat Population (ITT) that included subjects who received at least one dose of study drug; for the 12-Week Induction Period, ITT1 was defined as randomized subjects who received at least one dose of study drug during the 12-Week Induction Period.

For the primary outcome, the Cochran Mantel-Haenszel (CMH) test adjusting for stratification factors was used. If there was a stratum for a treatment group that had no subjects in it, a value of 0.1 was used.

Point estimates and 95% confidence interval (CI)s for the difference in proportions between each of risankizumab treatment groups and placebo were be provided. Construction of CI for the common risk difference was based on the Mantel-Haenszel estimate adjusting for stratification factors.

For analysis of continuous Variables a Mixed-Effect Model Repeated Measurement (MMRM) model was used. A hierarchical Multiplicity approach was adopted that split the initial 5% alpha to each of the two doses (testing each dose at 2.5% level) and then sequentially testing secondary endpoints, after both co-primary endpoints were rejected. A sequential testing approach thereafter was adopted until the last 10 secondary endpoints were reached after which a Bonferroni-Holm procedure was adopted.

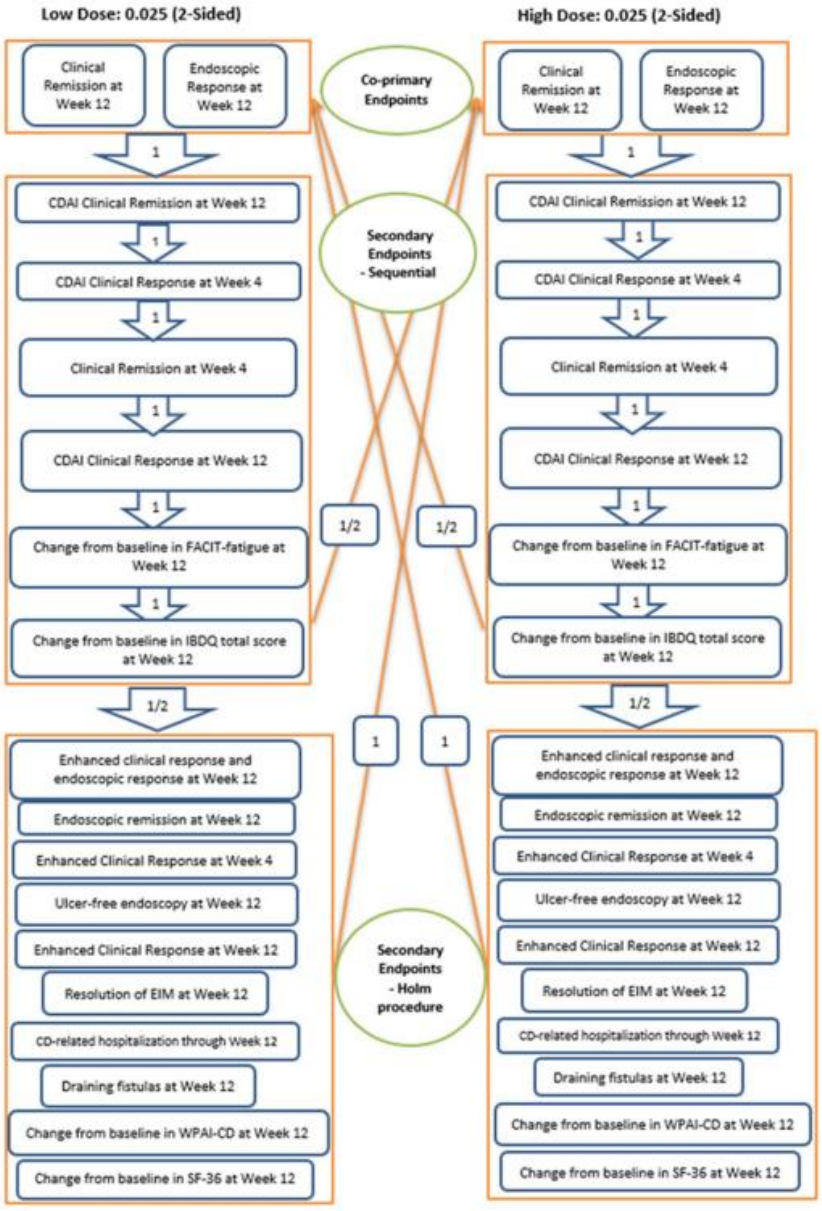
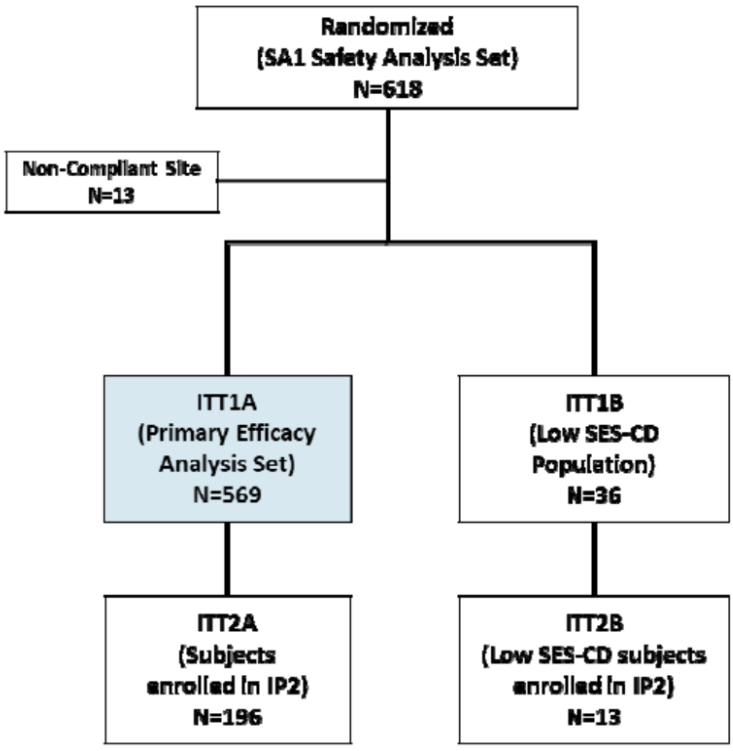



*Figure 17 Graphical Multiple Testing Procedure for Global Protocol Outside US*

## Results

### *Participant flow*




*Study Populations*

The ITT population for the 12-Week Induction Period (denoted as ITT1) included randomized subjects who received at least 1 dose of study drug during this period.

- ITT1A: includes the subjects with a baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease); the primary population for efficacy analysis. N = 569 (191 subjects in the risankizumab 600 mg arm, 191 subjects in the risankizumab 1200 mg arm, and 187 subjects in the placebo arm).
- ITT1B: includes the subjects who are not included in ITT1A because they did not have baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). These subjects had a lower baseline eligible SES-CD and were used for exploratory efficacy analyses. N = 36 (11 subjects in the risankizumab 600 mg arm, 10 subjects in the risankizumab 1200 mg arm, and 15 subjects in the placebo arm).

Thirteen subjects from a non-compliant site were excluded from the efficacy analyses for the 12-Week Induction Period (12 subjects excluded from ITT1A: 4 subjects in the risankizumab 600 mg IV arm, 3 subjects in the risankizumab 1200 mg IV arm, and 5 subjects in the placebo arm; 1 subject in the risankizumab 1200 mg IV arm excluded from ITT1B).

Induction Period 2

The ITT population for the Induction Period 2 (denoted as ITT2) includes subjects who were randomized and received at least 1 dose of risankizumab during the Induction Period 2, and the subjects who received placebo induction treatment during 12-Week Induction Period and entered the Induction Period 2 (denoted as placebo/risankizumab).

The placebo/risankizumab subjects were analyzed as a separate treatment group in the Induction Period 2.

- ITT2A: includes subjects who had baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). N =196 (39 in the risankizumab 180 mg SC arm, 41 subjects in the risankizumab 360 mg SC arm, 37 subjects in the risankizumab 1200 mg IV arm, and 79 subjects in the placebo IV/risankizumab arm).
- ITT2B: includes the subjects who did not have baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). These subjects had a lower baseline eligible SES-CD and were used for exploratory efficacy analysis. N = 13 (1 subject in the risankizumab 180 mg SC arm, 1 subject in the risankizumab 360 mg SC arm, 5 subjects in the risankizumab 1200 mg IV arm, and 6 subjects in the placebo IV/risankizumab arm).

Two subjects from a non-compliant site were excluded from the efficacy analyses for Induction Period 2 (excluded from ITT2A: 1 subject in the risankizumab 180 mg SC arm and 1 subject in the placebo IV/risankizumab arm).

For the corresponding ITT populations, subjects were assigned to a treatment group based on the randomization or re-randomization schedule, regardless of the treatment actually received. The demographics/baseline and efficacy analyses were based on the corresponding ITT population.

Disposition of Subjects

A total of 618 subjects were randomized in the study and received at least 1 dose of study drug. During the first 12-week induction period, a higher percentage of subjects in the risankizumab 600 mg and risankizumab 1200 mg treatment arms compared to placebo completed study drug. The most frequent primary reason for discontinuation of study drug in all treatment arms was AE, and the number of subjects who discontinued study drug due to AE was numerically higher in the placebo arm compared to either risankizumab arm. The most frequently reported AE that led to discontinuation of study drug was Crohn's disease (1 subject in the risankizumab 600 mg arm, 1 subject in the risankizumab 1200 mg arm, and 13 subjects in the placebo arm), suggesting a lack of efficacy of study drug in these subjects. Subject final status and reasons for discontinuation during the first 12-Week induction period are shown in Table 22.

*Table 22 Subject Disposition and All Reasons for Study Drug Discontinuation for the 12-Week Induction Period (SA1 Population)*

| | Placebo IV (N = 207) n (%) | Risankizumab 600 mg IV (N = 206) n (%) | Risankizumab 1200 mg IV (N = 205) n (%) | Total (N = 618) n (%) |
|---|---|---|---|---|
| Completed induction period study drug | 186 (89.9) | 202 (98.1) | 199 (97.1) | 587 (95.0) |
| Discontinuation due to (primary reason) | | | | |
| Any reason | 21 (10.1) | 4 (1.9) | 6 (2.9) | 31 (5.0) |
| AE | 9 (4.3) | 0 | 4 (2.0) | 13 (2.1) |
| Lack of efficacy | 6 (2.9) | 1 (0.5) | 2 (1.0) | 9 (1.5) |
| Lost to follow-up | 2 (1.0) | 0 | 0 | 2 (0.3) |
| Withdrawal by subject | 2 (1.0) | 1 (0.5) | 0 | 3 (0.5) |
| COVID-19 | 0 | 0 | 0 | 0 |
| COVID-19 logistical restrictions | 0 | 0 | 0 | 0 |
| Other | 2 (1.0) | 2 (1.0) | 0 | 4 (0.6) |
| Discontinuation due to (all reasons)[a] | | | | |
| Any reason | 21 (10.1) | 4 (1.9) | 6 (2.9) | 31 (5.0) |
| AE | 11 (5.3) | 0 | 4 (2.0) | 15 (2.4) |
| Lack of efficacy | 7 (3.4) | 1 (0.5) | 2 (1.0) | 10 (1.6) |
| Lost to follow-up | 2 (1.0) | 0 | 0 | 2 (0.3) |
| Withdrawal by subject | 4 (1.9) | 1 (0.5) | 1 (0.5) | 6 (1.0) |
| COVID-19 | 0 | 0 | 0 | 0 |
| COVID-19 logistical restrictions | 0 | 0 | 0 | 0 |
| Other | 3 (1.4) | 2 (1.0) | 0 | 5 (0.8) |

AE = adverse event; COVID-19 = coronavirus disease - 2019; IV = intravenous; SA = safety population

a. Subjects may have reported more than 1 reason for discontinuation.

Protocol Deviations

Protocol deviations were collected for all subjects in the 12-Week Induction Period and Induction Period 2 and are presented for the subjects in ITT1A. Protocol deviations were defined in accordance with the ICH guidelines and included, but were not limited to, the following: inclusion/exclusion criteria violation (49 [8.6%] total subjects), receipt of wrong treatment or incorrect dose of study drug (2 [0.4%] total subjects), development of withdrawal criteria without being withdrawn (no subjects) and use of prohibited concomitant medications (21 [3.7%] total subjects).

Deviations were assessed for their impact on analyses and data integrity or subject safety.

Efficacy data for subjects enrolled at an investigational site with significant noncompliance were excluded from the statistical analyses. Otherwise, reported protocol deviations did not have an impact on analyses and data integrity.

TABLE 14.1__1.4

Summary of Major Protocol Deviations
(ITT1A Population)

| Protocol Deviation@ | Placebo IV (N=187) n (%) | Risankizumab 600 mg IV (N=191) n (%) | Risankizumab 1200 mg IV (N=191) n (%) | Total (N=569) n (%) |
|---|---|---|---|---|
| Subjects who had at least one protocol deviation | 26 (13.9) | 26 (13.6) | 18 (9.4) | 70 (12.3) |
| Subject entered into the study even though did not satisfy entry criteria | 15 (8.0) | 21 (11.0) | 13 (6.8) | 49 (8.6) |
| Inclusion criteria | | | | |
| 3 | 8 (4.3) | 8 (4.2) | 3 (1.6) | 19 (3.3) |
| 4 | 0 | 1 (0.5) | 1 (0.5) | 2 (0.4) |
| 5 | 8 (4.3) | 9 (4.7) | 6 (3.1) | 23 (4.0) |
| 6 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| 7 | 0 | 0 | 2 (1.0) | 2 (0.4) |
| 8 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Any inclusion criteria not met | 15 (8.0) | 17 (8.9) | 10 (5.2) | 42 (7.4) |
| Exclusion criteria | | | | |
| 4 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| 7 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| 11 | 0 | 2 (1.0) | 2 (1.0) | 4 (0.7) |
| 21 | 0 | 1 (0.5) | 1 (0.5) | 2 (0.4) |
| 23 | 1 (0.5) | 1 (0.5) | 0 | 2 (0.4) |
| 30 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Any exclusion criteria met | 2 (1.1) | 5 (2.6) | 4 (2.1) | 11 (1.9) |
| Subject received wrong treatment or incorrect dose | 2 (1.1) | 0 | 0 | 2 (0.4) |

Note: ITT1A Population includes randomized subjects who received at least one dose of study drug during the 12-Week Induction Period, and had baseline eligible SES-CD of >= 6 (>= 4 for isolated ileal disease).
Percentages calculated based on N in the header.
@ Only 4 ICH major protocol deviations were included this analysis. A subject may have more than one deviation.

**Recruitment**

First subject first visit: 18th December 2017 Last subject last visit: 19th May 2021

Database lock 20th May 2021

**Conduct of the study**

The original protocol (17 February 2017, 0 subjects) had 7 global amendments, 8 country specific amendments, and 4 administrative changes.

The global amendments and number of subjects enrolled under each amendment were described as follows:

- Amendment 1 (29 March 2017, 0 subjects). Change in title to remove doubledummy and prior anti-TNF to biologic; text change to support removal of vedolizumab comparator from the protocol and better explanation of biopsies during endoscopy and to remove patient reported diary parameter.
- Amendment 2 (substantial) (05 July 2017, 1 subject). Addition of CDAI criteria to the inclusion criteria; update to instruction on which haematocrit (Hct) value to use in calculating the CDAI for inclusion; added "psychological or psychiatric cause" to exclusion criterion 29; updated overall study design and plan: description, of study schematic figure, to remove reference to Weeks 2 and 6; updated discontinuation of individual subjects, for subjects who do not have clinical response at Week 12; updated contraception recommendations, and exclusion criterion 28; updated pregnancy, for pregnancy reporting timing; clarification of the blind-breaking process; updated tuberculosis (TB) requirements in exclusion criteria, benefits and risks, and

efficacy and safety measurements assessed and flow chart; added assent information for subjects less than 18 years old; clarification of stratification criteria.

- Amendment 3 (substantial) (29 September 2017, 113 subjects). Addition of an anaphylaxis adjudication committee; revisions to allow for local regulations for the difference in minimum age for adults; update of exclusion criterion 18 for CD related complications; update of prohibited medications; addition of international normalized ratio (INR) and anaphylaxis testing; addition of endoscopic remission to ranked secondary endpoints and Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) to non-ranked secondary endpoints; addition of clinical and endoscopic remission over time as endpoints; updated criteria for discontinuation of individual subjects; revisions to reduce redundancy; revisions to algin with common toxicity criteria for adverse events (CTCAE) grading criteria for adverse events (AE)s; revisions to allow for additional types of anaphylactic reactions and to provide investigators with guidance on reporting of events; updates for alignment with template requirements and for consistency across the risankizumab programs; clarifications of sample size calculations; update to reflect the most recent subject diary entries and addition of patient-reported outcome (PRO) for collection; updates in the schedule of activities to reflect changes made in the body of the protocol; addition of information on the sample collection schedule; revision to align with regulatory agency feedback.
- Amendment 4 (substantial) (09 July 2018, 94 subjects). Extension of the AE collection period duration, final follow-up call, and period for prohibition of vaccines; modified benefits and risks to align with the IB; addition of blood collection for tryptase following a suspected drug administration hypersensitivity reaction; addition of "worsening" CD to common AEs associated with underlying disease; addition of "intramuscular" as possible route of administration for prohibited anti-infectives; exclusion of subjects who receive exclusive enteral nutrition to treat CD; addition of height measurement for pediatric subjects; prohibition of local, routine testing for fecal calprotectin (FCP) and high-sensitivity C-reactive protein; modification of contraception language; modification of statistical methods for secondary endpoints to align with regulatory feedback; removal of stool sample collection for FCP at screening; clarified repeat screening tests and the qualifications for a screening period extension; documentation of the DMC opinion to continue the trial and pediatric enrollment; clarification of language to allow repeat testing if screening and baseline testing were more than 14 days apart and the circumstances that would qualify for a screening period extension; clarification that indeterminate tuberculosis (TB) test results must be repeated.
- Amendment 5 (22 February 2019, 281 subjects). Documentation of the data monitoring committee (DMC) opinion to continue the trial and enrol 16-17-year olds; addition of language to allow single repeat testing of transient exclusionary laboratory values during the screening period; clarification of the types of prohibited corticosteroids; modification to permit enrollment of not more than 20% subjects with prior exposure, including intolerance or inadequate response, to ustekinumab; specification that enrolment of subjects with Baseline SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or Baseline SES-CD of 3 for isolated ileal disease, excluding the narrowing component, would be no more than 10% of the total population; addition of stratification factor of Baseline SES-CD; update definitions of endoscopic remission and endoscopic response; revision to allow a commercially available assay to determine approved biologic washout; clarification that TB prophylaxis is permissible; revision of the order and addition of ranked secondary endpoints, update of ranked secondary endpoints to non-ranked secondary endpoints, and addition of non-ranked secondary endpoint; addition of CTCAE version; clarification of timing of database lock (DBL); update of statistical assumptions

for sample size determination; addition of details of multiplicity adjustment; update of the missing imputation methodology to remove last observation carried forward (LOCF).

- Amendment 6 (substantial) (19 December 2019, 65 subjects). Specifying the total N of 579 for the primary ITT population used for efficacy analysis, that number of subjects with lower SES-CD subjects will be no more than 58, and that data collected from subjects with the lower SES-CD will be analyzed as an exploratory efficacy analysis; specifying that Hct from the preceding visit may be used to calculate the CDAI if there are technical issues; revision of definition of endoscopic remission; revision of the term "endoscopic healing" to "ulcer-free endoscopy;" update of secondary endpoint ranking and combining and adding new ranked secondary endpoints; clarification of timing of DBL; removing the missing imputation method OC from the sensitivity analysis of the continuous efficacy variables; addition of missing data handling methods; clarification of the way continuous laboratory and vital signs would be summarized; removed Fisher's exact test for risankizumab treatment group differences versus placebo for AEs; addition of "Optional Blood Sample for Biologic Drug Level."
- Amendment 7 (substantial) (28 July 2020, 0 subjects). Additions/revisions due to the COVID-19 pandemic, including benefit and risk, criteria to exclude subjects with active COVID-19, addition of COVID-19 AE data collection process, modification of study visits/protocol-specified procedures impacted by changes in local regulations, protocol deviations, missing data, data monitoring, and COVID-19 testing; addition of language regarding site responsibility; and clarification of HIV results language.

***Baseline data***

12 – Week Induction Period

Key baseline demographics were generally balanced between the three treatment groups (Table 23). Overall, the majority of subjects were white, not Hispanic or Latino, were between the ages of 18 and < 40, were of normal weight according to body mass index (BMI).

*Table 23 Baseline Demographic Characteristics of Subjects for 12-Week Induction Period (ITT1A Populations)*

| Variable | Placebo IV (N = 187) | Risankizumab 600 mg IV (N = 191) | Risankizumab 1200 mg IV (N = 191) | Total (N = 569) |
|---|---|---|---|---|
| Sex – n (%) | | | | |
| Female | 88 (47.1) | 99 (51.8) | 89 (46.6) | 276 (48.5) |
| Male | 99 (52.9) | 92 (48.2) | 102 (53.4) | 293 (51.5) |
| Age (years) | | | | |
| n | 187 | 191 | 191 | 569 |
| Mean (SD) | 39.3 (13.47) | 40.2 (13.58) | 39.3 (12.94) | 39.6 (13.31) |
| Median | 37.0 | 38.0 | 39.0 | 38.0 |
| Min, Max | 17, 80 | 17, 74 | 16, 74 | 16, 80 |
| Age category – n (%) | | | | |
| < 18 | 2 (1.1) | 1 (0.5) | 1 (0.5) | 4 (0.7) |
| [18, 40] | 104 (55.6) | 100 (52.4) | 97 (50.8) | 301 (52.9) |
| [40, 65] | 71 (38.0) | 78 (40.8) | 87 (45.5) | 236 (41.5) |
| ≥ 65 | 10 (5.3) | 12 (6.3) | 6 (3.1) | 28 (4.9) |
| Race – n (%) | | | | |
| White | 162 (86.6) | 176 (92.1) | 168 (88.0) | 506 (88.9) |
| Black or African American | 7 (3.7) | 7 (3.7) | 8 (4.2) | 22 (3.9) |
| Asian | 15 (8.0) | 8 (4.2) | 14 (7.3) | 37 (6.5) |
| American Indian/Alaska Native | 0 | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 2 (1.1) | 0 | 0 | 2 (0.4) |
| Multiple | 1 (0.5) | 0 | 1 (0.5) | 2 (0.4) |
| Ethnicity – n (%) | | | | |
| Hispanic/Latino | 19 (10.2) | 16 (8.4) | 15 (7.9) | 50 (8.8) |
| Non-Hispanic/Latino | 168 (89.8) | 175 (91.6) | 176 (92.1) | 519 (91.2) |

| Variable | Placebo IV (N = 187) | Risankizumab 600 mg IV (N = 191) | Risankizumab 1200 mg IV (N = 191) | Total (N = 569) |
|---|---|---|---|---|
| Body weight (kg) | | | | |
| N | 187 | 191 | 191 | 569 |
| Mean (SD) | 72.815 (19.0761) | 72.742 (20.2498) | 73.467 (17.6459) | 73.009 (18.9893) |
| Median | 70.000 | 70.100 | 71.000 | 70.300 |
| Min, Max | 35.00, 140.00 | 35.00, 145.15 | 38.10, 120.00 | 35.00, 145.15 |
| BMI ($kg/m^2$) | | | | |
| N | 187 | 191 | 191 | 569 |
| Mean (SD) | 25.10 (5.835) | 25.32 (6.447) | 25.29 (5.682) | 25.24 (5.988) |
| Median | 24.30 | 24.49 | 24.37 | 24.38 |
| Min, Max | 14.7, 46.2 | 14.7, 52.4 | 14.5, 46.6 | 14.5, 52.4 |
| BMI category – n (%) | | | | |
| Underweight [< 18.5 $kg/m^2$] | 18 (9.6) | 20 (10.5) | 18 (9.4) | 56 (9.8) |
| Normal [≥ 18.5 and < 25 $kg/m^2$] | 88 (47.1) | 83 (43.5) | 87 (45.5) | 258 (45.3) |
| Overweight [≥ 25 and < 30 $kg/m^2$] | 46 (24.6) | 49 (25.7) | 49 (25.7) | 144 (25.3) |
| Obese [≥ 30 $kg/m^2$] | 35 (18.7) | 39 (20.4) | 37 (19.4) | 111 (19.5) |

BMI = body mass index; ITT = intent-to-treat; IV = intravenous; max = maximum; min = minimum; SD = standard deviation

Use of any prior Crohn's disease related medication was reported by 100% of subjects. The most frequently reported prior CD-related medications used by the treatment groups were adalimumab (71.4% of subjects) and infliximab (65.2% of subjects). Use of prior CD-related biologics/small molecules, immunomodulators (IMMs), steroids, and aminosalicylates is detailed in Table 24.

*Table 24 Prior Crohn's Disease-Related Biologics, Immunomodulators, and Steroids (ITT1A Population)*

| Generic Name (WHO 2018Q1) | Placebo IV (N = 187) n (%) | Risankizumab 600 mg IV (N = 191) n (%) | Risankizumab 1200 mg IV (N = 191) n (%) | Total (N = 569) n (%) |
|---|---|---|---|---|
| CD-related medication | 187 (100) | 191 (100) | 191 (100) | 569 (100) |
| **Biologic/Small Molecule Medications** | | | | |
| **Anti-TNFs** | | | | |
| Adalimumab | 132 (70.6) | 138 (72.3) | 136 (71.2) | 406 (71.4) |
| Infliximab | 123 (65.8) | 122 (63.9) | 126 (66.0) | 371 (65.2) |
| Certolizumab | 8 (4.3) | 9 (4.7) | 8 (4.2) | 25 (4.4) |
| Certolizumab pegol | 11 (5.9) | 9 (4.7) | 8 (4.2) | 28 (4.9) |
| Golimumab | 2 (1.1) | 6 (3.1) | 4 (2.1) | 12 (2.1) |
| **Anti-integrins** | | | | |
| Etrolizumab | 1 (0.5) | 2 (1.0) | 3 (1.6) | 6 (1.1) |
| Natalizumab | 1 (0.5) | 1 (0.5) | 0 | 2 (0.4) |
| Vedolizumab | 65 (34.8) | 60 (31.4) | 67 (35.1) | 192 (33.7) |
| **Anti-p40s** | | | | |
| Ustekinumab | 42 (22.5) | 38 (19.9) | 36 (18.8) | 116 (20.4) |

| Generic Name (WHO 2018Q1) | Placebo IV (N = 187) n (%) | Risankizumab 600 mg IV (N = 191) n (%) | Risankizumab 1200 mg IV (N = 191) n (%) | Total (N = 569) n (%) |
|---|---|---|---|---|
| **Other Biologics** | | | | |
| Interleukin inhibitors | 0 | 1 (0.5) | 1 (0.5) | 2 (0.4) |
| **Small Molecule** | | | | |
| Filgotinib | 3 (1.6) | 6 (3.1) | 4 (2.1) | 13 (2.3) |
| Tofacitinib | 1 (0.5) | 3 (1.6) | 2 (1.0) | 6 (1.1) |
| Upadacitinib | 0 | 0 | 2 (1.0) | 2 (0.4) |
| Laquinimod | 1 (0.5) | 0 | 0 | 1 (0.2) |
| **Immunomodulators** | | | | |
| Azathioprine | 105 (56.1) | 103 (53.9) | 119 (62.3) | 327 (57.5) |
| Mercaptopurine | 20 (10.7) | 16 (8.4) | 11 (5.8) | 47 (8.3) |
| Methotrexate | 42 (22.5) | 30 (15.7) | 41 (21.5) | 113 (19.9) |
| Tacrolimus | 0 | 1 (0.5) | 4 (2.1) | 5 (0.9) |
| Thalidomide | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Tioguanine | 0 | 1 (0.5) | 0 | 1 (0.2) |
| **Corticosteroids (any route of Administration)** | | | | |
| Beclometasone | 1 (0.5) | 1 (0.5) | 0 | 2 (0.4) |
| Betamethasone | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Budesonide | 37 (19.8) | 34 (17.8) | 27 (14.1) | 98 (17.2) |
| Corticosteroids | 3 (1.6) | 0 | 0 | 3 (0.5) |
| Deflazacort | 0 | 2 (1.0) | 0 | 2 (0.4) |
| Dexamethasone | 2 (1.1) | 1 (0.5) | 0 | 3 (0.5) |
| Hydrocortisone | 4 (2.1) | 3 (1.6) | 2 (1.0) | 9 (1.6) |
| Meprednisone | 2 (1.1) | 1 (0.5) | 1 (0.5) | 4 (0.7) |
| Methylprednisolone | 13 (7.0) | 7 (3.7) | 12 (6.3) | 32 (5.6) |
| Prednisolone | 30 (16.0) | 25 (13.1) | 34 (17.8) | 89 (15.6) |
| Prednisone | 59 (31.6) | 54 (28.3) | 55 (28.8) | 168 (29.5) |
| Proctosedyl | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Steroids | 0 | 0 | 1 (0.5) | 1 (0.2) |

| Generic Name (WHO 2018Q1) | Placebo IV (N = 187) n (%) | Risankizumab 600 mg IV (N = 191) n (%) | Risankizumab 1200 mg IV (N = 191) n (%) | Total (N = 569) n (%) |
|---|---|---|---|---|
| **Aminosalicylates** | | | | |
| Balsalazide | 0 | 1 (0.5) | 2 (1.0) | 3 (0.5) |
| Mesalazine | 78 (41.7) | 72 (37.7) | 78 (40.8) | 228 (40.1) |
| Olsalazine | 0 | 1 (0.5) | 1 (0.5) | 2 (0.4) |
| Sulfasalazine | 7 (3.7) | 6 (3.1) | 4 (2.1) | 17 (3.0) |

CD = Crohn's disease; IMM = immunomodulator; ITT = intent-to-treat; IV = intravenous; Q1 = first quarter; TNF = tumor necrosis factor; WHO = World Health Organization

Note: This table includes Crohn's disease-related biologics, IMMs, and steroids with a start date before the first study drug dose date.

Baseline disease characteristics were generally well balanced among treatment arms (Table 25). In the ITT1A population 47.1% of subjects failed 1 biologic and 52.9% of subjects failed more than 1 biologic.

The most common CD location per SES-CD was in the ileal-colonic region at 46.9%. Overall, approximately 34% and approximately 23% of subjects were on concomitant corticosteroids and/or immunomodulators at baseline, respectively.

*Table 25 Baseline Disease Characteristics, Selective Variables (ITT1A Population)*

| Variable | Placebo IV (N = 187) | Risankizumab 600 mg IV (N = 191) | Risankizumab 1200 mg IV (N = 191) | Total (N = 569) |
|---|---|---|---|---|
| Crohn's disease duration (years) | | | | |
| N | 187 | 191 | 191 | 569 |
| Mean (SD) | 12.520 (9.7351) | 10.875 (7.7073) | 11.787 (9.0940) | 11.722 (8.8894) |
| Median | 10.467 | 8.690 | 9.383 | 9.394 |
| Min, Max | 0.375, 61.517 | 0.422, 39.499 | 0.320, 47.622 | 0.320, 61.517 |

| Variable | Placebo IV (N = 187) | Risankizumab 600 mg IV (N = 191) | Risankizumab 1200 mg IV (N = 191) | Total (N = 569) |
|---|---|---|---|---|
| Biologics failure history (≤ 1, > 1) – n (%) | | | | |
| ≤ 1 | 88 (47.1) | 92 (48.2) | 88 (46.1) | 268 (47.1) |
| > 1 | 99 (52.9) | 99 (51.8) | 103 (53.9) | 301 (52.9) |
| Baseline CDAI | | | | |
| N | 186 | 191 | 190 | 567 |
| Mean (SD) | 319.62 (69.785) | 310.70 (63.556) | 312.46 (61.206) | 314.21 (64.911) |
| Median | 314.50 | 300.00 | 306.45 | 307.00 |
| Min, Max | 72.4, 650.8 | 131.9, 526.0 | 176.0, 469.0 | 72.4, 650.8 |
| Baseline SES-CD | | | | |
| N | 187 | 191 | 191 | 569 |
| Mean (SD) | 15.0 (8.08) | 14.4 (7.61) | 15.1 (7.63) | 14.8 (7.77) |
| Median | 13.0 | 13.0 | 13.0 | 13.0 |
| Min, Max | 4, 40 | 4, 35 | 4, 37 | 4, 40 |
| CD location per SES-CD – n (%) | | | | |
| Ileal only | 26 (13.9) | 33 (17.3) | 21 (11.0) | 80 (14.1) |
| Colonic only | 73 (39.0) | 75 (39.3) | 74 (38.7) | 222 (39.0) |
| Ileal-colonic | 88 (47.1) | 83 (43.5) | 96 (50.3) | 267 (46.9) |
| Average daily stool frequency | | | | |
| n | 186 | 191 | 190 | 567 |
| Mean (SD) | 6.431 (2.8784) | 6.206 (3.0855) | 5.874 (2.7943) | 6.168 (2.9263) |
| Median | 6.000 | 5.571 | 5.286 | 5.571 |
| Min, Max | 0.000, 16.286 | 0.429, 19.143 | 0.000, 19.857 | 0.000, 19.857 |
| Average daily abdominal pain score | | | | |
| n | 186 | 191 | 190 | 567 |
| Mean (SD) | 1.878 (0.5428) | 1.852 (0.5045) | 1.943 (0.5644) | 1.891 (0.5382) |
| Median | 2.000 | 2.000 | 2.000 | 2.000 |
| Min, Max | 0.000, 3.000 | 0.000, 3.000 | 0.000, 3.000 | 0.000, 3.000 |

| Variable | Placebo IV (N = 187) | Risankizumab 600 mg IV (N = 191) | Risankizumab 1200 mg IV (N = 191) | Total (N = 569) |
|---|---|---|---|---|
| Baseline hs-CRP (mg/L) | | | | |
| N | 187 | 186 | 190 | 563 |
| Mean (SD) | 20.398 (25.6710) | 19.328 (26.2593) | 20.747 (25.2942) | 20.162 (25.7025) |
| Median | 9.400 | 9.330 | 11.650 | 9.580 |
| Min, Max | 0.20, 139.00 | 0.23, 161.00 | 0.20, 167.00 | 0.20, 167.00 |
| Baseline FCP (mg/kg) | | | | |
| n | 146 | 150 | 151 | 447 |
| Mean (SD) | 2648.9 (4831.20) | 2379.2 (3879.64) | 2132.4 (2819.36) | 2383.9 (3915.93) |
| Median | 987.5 | 1367.0 | 1220.0 | 1225.0 |
| Min, Max | 30, 28800 | 30, 28800 | 30, 16877 | 30, 28800 |
| Draining fistulas (yes, no) – n (%) | | | | |
| Yes | 15 (8.0) | 14 (7.3) | 16 (8.4) | 45 (7.9) |
| No | 172 (92.0) | 177 (92.7) | 175 (91.6) | 524 (92.1) |
| Non-draining fistulas (yes, no) – n (%) | | | | |
| Yes | 12 (6.4) | 14 (7.3) | 12 (6.3) | 38 (6.7) |
| No | 175 (93.6) | 177 (92.7) | 179 (93.7) | 531 (93.3) |
| Baseline corticosteroid use (yes, no) – n (%) | | | | |
| Yes | 68 (36.4) | 65 (34.0) | 62 (32.5) | 195 (34.3) |
| No | 119 (63.6) | 126 (66.0) | 129 (67.5) | 374 (65.7) |
| Baseline immunomodulator use (yes, no) – n (%) | | | | |
| Yes | 40 (21.4) | 36 (18.8) | 53 (27.7) | 129 (22.7) |
| No | 147 (78.6) | 155 (81.2) | 138 (72.3) | 440 (77.3) |

CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; FCP = fecal calprotectin; hs-CRP = high sensitivity C-reactive protein; ITT = intent-to-Treat; IV = intravenous; max = maximum; min = minimum; SD = standard deviation; SES-CD = Simple Endoscopic Score for Crohn's disease

Treatment Compliance

Overall, mean treatment compliance during the 12-Week Induction Period was comparable across treatment arms (99.6% in the risankizumab 600 mg arm, 97.9% in the risankizumab 1200 mg arm, and 99.0% in the placebo arm).

***Outcomes and estimation***

Co-Primary Endpoint OUS

The study met the co-primary endpoints of clinical remission and endoscopic response for the risankizumab 600 mg and 1200 mg arms compared to the placebo arm for both the US protocol and the OUS specific protocol.

At Week 12 a statistically significant greater (p-value ≤ 0.001) proportion of subjects in the risankizumab 600 mg and risankizumab 1200 mg arms achieved the co-primary endpoint of clinical remission (defined by CDAI in the US protocol and by SF/APS in the OUS protocol) compared to placebo arm (Table 26 and Table 27).

At Week 12, a statistically significantly greater (p-value < 0.001) proportion of subjects in the risankizumab 600 mg and risankizumab 1200 mg arms achieved endoscopic response, assessed in both the US protocol and the OUS protocol, compared to the placebo arm (Table 28). Overall, numerically similar results were observed for the risankizumab 600 mg arm and the risankizumab 1200 mg arm.

*Table 26 CDAI Clinical Remission at Week 12 (NRI-C) – Total and by Prior Biologics Failed (ITT1A Population)*

| Subgroup Category | | Responder (NRI-C) | | Response Rate Diff Compared to Placebo | | | |
|---|---|---|---|---|---|---|---|
| Treatment | N | n (%) | [95% CI][a] | Diff(%)[b] | Adjusted Diff(%)[b] | [95% CI][c] | P-value[c] |
| All | | | | | | | |
| Placebo IV | 187 | 37 (19.8) | [14.1, 25.5] | | | | |
| Risankizumab 600 mg IV | 191 | 80 (42.0) | [34.9, 49.0] | 22.2 | 22.1 | [13.1, 31.0] | < 0.001 |
| Risankizumab 1200 mg IV | 191 | 77 (40.3) | [33.4, 47.3] | 20.5 | 20.5 | [11.6, 29.5] | < 0.001 |
| Prior Biologics Failed ≤ 1 | | | | | | | |
| Placebo IV | 88 | 18 (20.5) | [12.0, 28.9] | | | | |
| Risankizumab 600 mg IV | 92 | 42 (45.7) | [35.5, 55.8] | 25.2 | | [12.0, 38.4] | |
| Risankizumab 1200 mg IV | 88 | 41 (46.6) | [36.2, 57.0] | 26.1 | | [12.7, 39.5] | |
| Prior Biologics Failed > 1 | | | | | | | |
| Placebo IV | 99 | 19 (19.2) | [11.4, 26.9] | | | | |
| Risankizumab 600 mg IV | 99 | 38 (38.5) | [28.9, 48.1] | 19.3 | | [7.0, 31.7] | |
| Risankizumab 1200 mg IV | 103 | 36 (35.0) | [25.7, 44.2] | 15.8 | | [3.7, 27.8] | |

CDAI = Crohn's Disease Activity Index; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; COVID-19 = coronavirus disease - 2019; ITT = intent-to-Treat; IV = intravenous; NRI-C = Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19

a. 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.

b. Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test.

*Table 27 Clinical Remission (Average Daily SF/APS) at Week 12 (NRI-C) – Total and by Prior Biologics Failed (ITT1A Population)*

| Subgroup Category | | Responder (NRI-C) | | Response Rate Diff Compared to Placebo | | | |
|---|---|---|---|---|---|---|---|
| Treatment | N | n (%) | [95% CI][a] | Diff(%)[b] | Adjusted Diff(%)[b] | [95% CI][c] | P-value[c] |
| All | | | | | | | |
| Placebo IV | 187 | 36 (19.3) | [13.6, 24.9] | | | | |
| Risankizumab 600 mg IV | 191 | 66 (34.6) | [27.8, 41.3] | 15.3 | 15.2 | [6.4, 24.0] | 0.001 |
| Risankizumab 1200 mg IV | 191 | 76 (39.8) | [32.8, 46.7] | 20.5 | 20.4 | [11.5, 29.3] | <0.001 |
| Prior Biologics Failed ≤ 1 | | | | | | | |
| Placebo IV | 88 | 19 (21.6) | [13.0, 30.2] | | | | |
| Risankizumab 600 mg IV | 92 | 37 (40.2) | [30.2, 50.2] | 18.6 | | [5.4, 31.8] | |
| Risankizumab 1200 mg IV | 88 | 37 (42.0) | [31.7, 52.4] | 20.5 | | [7.0, 33.9] | |

| Subgroup Category | | Responder (NRI-C) | | Response Rate Diff Compared to Placebo | | | |
|---|---|---|---|---|---|---|---|
| Treatment | N | n (%) | [95% CI][a] | Diff(%)[b] | Adjusted Diff(%)[b] | [95% CI][c] | P-value[c] |
| Prior Biologics Failed > 1 | | | | | | | |
| Placebo IV | 99 | 17 (17.2) | [9.7, 24.6] | | | | |
| Risankizumab 600 mg IV | 99 | 29 (29.3) | [20.3, 38.3] | 12.1 | | [0.5, 23.8] | |
| Risankizumab 1200 mg IV | 103 | 39 (37.9) | [28.5, 47.2] | 20.7 | | [8.7, 32.6] | |

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; COVID-19 = coronavirus disease - 2019; ITT = intent-to-Treat; IV = intravenous; NRI-C = Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; SF/APS = stool frequency/abdominal pain score

a. 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.

b. Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test.

c. Across the strata, 95% CI for adjusted difference and p-value are calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (Number of prior biologics failed [≤ 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each subgroup, 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

Note: Green color indicates that this co-primary endpoint achieved statistical significance based on the pre-specified graphical testing procedure for the OUS protocol.

*Table 28 Endoscopic Response at Week 12 (NRI-C) – Total and by Prior Biologics Failed (ITT1A Population)*

| Subgroup Category | | | Responder (NRI-C) | | | Response Rate Diff Compared to Placebo | |
|---|---|---|---|---|---|---|---|
| Treatment | N | n (%) | [95% CI][a] | Diff(%)[b] | Adjusted Diff(%)[b] | [95% CI][c] | P-value[c] |
| All | | | | | | | |
| Placebo IV | 187 | 21 (11.2) | [6.7, 15.8] | | | | |
| Risankizumab 600 mg IV | 191 | 55 (28.8) | [22.4, 35.3] | 17.6 | 17.6 | [9.9, 25.4] | <0.001 |
| Risankizumab 1200 mg IV | 191 | 65 (34.2) | [27.4, 40.9] | 22.9 | 23.1 | [15.1, 31.1] | <0.001 |
| Prior Biologics Failed ≤ 1 | | | | | | | |
| Placebo IV | 88 | 14 (15.9) | [8.3, 23.6] | | | | |
| Risankizumab 600 mg IV | 92 | 33 (36.0) | [26.1, 45.8] | 20.1 | | [7.6, 32.5] | |
| Risankizumab 1200 mg IV | 88 | 39 (44.3) | [33.9, 54.7] | 28.4 | | [15.5, 41.3] | |
| Prior Biologics Failed > 1 | | | | | | | |
| Placebo IV | 99 | 7 (7.1) | [2.0, 12.1] | | | | |
| Risankizumab 600 mg IV | 99 | 22 (22.2) | [14.0, 30.4] | 15.2 | | [5.5, 24.8] | |
| Risankizumab 1200 mg IV | 103 | 26 (25.5) | [17.0, 33.9] | 18.4 | | [8.6, 28.2] | |

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; COVID-19 = coronavirus disease - 2019; ITT = intent-to-Treat; IV = intravenous; NRI-C = Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19

a. 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.

b. Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test.

c. Across the strata, 95% CI for adjusted difference and p-value are calculated according to the CHM test adjusted for strata (Number of prior biologics failed [≤ 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each subgroup, 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

Note: Green color indicates that this co-primary endpoint achieved statistical significance based on the pre-specified graphical testing procedure for both the US-specific and OUS protocols.

Key Secondary Endpoints OUS

The key secondary endpoints (i.e., endpoints under the overall type I error control) for the OUS protocols are summarised in Table 29. Overall, both risankizumab arms (600 mg and 1200 mg) have clear treatment effect over placebo for resolution of clinical symptoms, improvements in quality of life (QoL), reduction in mucosal inflammation as measured by endoscopy, and CD-related hospitalizations.

A majority of endpoints were statistically significant for the risankizumab 600 mg arm and the risankizumab 1200 mg arm versus placebo for the OUS protocol.

Overall efficacy rates for the risankizumab 600 mg and 1200 mg arms were numerically similar.

Clinical response and clinical remission, as defined by CDAI and SF/APS, were seen at Week 4, with statistically significant differences observed for risankizumab 600 mg and 1200 mg arms versus placebo. Additionally, clinical response per CDAI and SF/APS were statistically significant for each risankizumab dose versus placebo at Week 12, with greater efficacy and treatment differences relative to those at Week 4.

Other patient reported outcome (PRO) questionnaires that summarize QoL, such as Inflammatory Bowel Disease Questionnaire (IBDQ), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, and SF-36, showed overall numerically higher improvement in the risankizumab arms versus placebo and statistical significance is shown in Table 29.

Endoscopic remission and ulcer-free endoscopy at Week 12 were statistically significant versus placebo in the OUS protocol. The composite endpoint for clinical response (per CDAI and SF/APS) and endoscopic response (i.e., clinical response and endoscopic response in the same patient), were also statistically significant for the risankizumab arms versus placebo.

CD-related hospitalizations were lower in the risankizumab groups versus placebo and met statistical significance. Additionally, while the total number of subjects analyzed was small, there was a trend for reduction in extra-intestinal manifestations (EIMs) for subjects who received risankizumab versus placebo. Due to the small sample size of the number of subjects with draining fistulas at baseline (N = 45), no meaningful conclusions can be drawn and the endpoint did not meet statistical significance.

*Table 29 Summary of Key Secondary Efficacy Endpoints Under the Overall Type I Error Control, Global (Outside-US)-Specific Protocol (NRI-C) (ITT1A Population)*

| | Endpoints | Placebo (N = 187) % (n)[a] or LSMEAN (SE) | Risankizumab 600 mg IV (N = 191) % (n)[a] or LSMEAN (SE) | Risankizumab 1200 mg IV (N = 191) % (n)[a] or LSMEAN (SE) | Adjusted Treatment Difference95% CI[b] | | p-Value[b] | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Risankizumab 600 mg IV – placebo | Risankizumab 1200 mg IV – placebo | Risankizumab 600 mg IV vs. placebo | Risankizumab 1200 mg IV vs. placebo |
| 1 | CDAI clinical remission at Week 12 | 19.8 (37) | 42.0 (80) | 40.3 (77) | 22.1 [13.1, 31.0] | 20.5 [11.6, 29.5] | < 0.001[$] | < 0.001[$] |
| 2 | CDAI clinical response at Week 4 | 20.9 (39) | 36.6 (70) | 32.5 (62) | 15.7 [6.8, 24.6] | 11.8 [3.0, 20.5] | 0.001[$] | 0.008[$] |
| 3 | Clinical remission (SF/APS) at Week 4 | 8.0 (15) | 17.3 (33) | 18.3 (35) | 9.2 [2.6, 15.7] | 10.3 [3.7, 16.8] | 0.006[$] | 0.002[$] |
| 4 | CDAI clinical response at Week 12 | 30.0 (56) | 59.5 (114) | 60.7 (116) | 29.4 [19.8, 39.0] | 30.6 [21.1, 40.1] | < 0.001[$] | < 0.001[$] |
| 5 | Change from baseline in FACIT-Fatigue at Week 12 (MMRM) | N = 144 7.7 (0.87) | N = 168 10.5 (0.81) | N = 172 10.8 (0.81) | 2.8 [0.4, 5.1] | 3.0 [0.7, 5.3] | 0.020[$] | 0.010[$] |
| 6 | Change from baseline in IBDQ total score at Week 12 (MMRM) | N = 144 27.2 (2.76) | N = 168 39.6 (2.60) | N = 172 42.2 (2.60) | 12.4 [5.0, 19.8] | 15.0 [7.7, 22.4] | 0.001[$] | < 0.001[$] |

| | Endpoints | Placebo (N = 187) % (n)[a] or LSMEAN (SE) | Risankizumab 600 mg IV (N = 191) % (n)[a] or LSMEAN (SE) | Risankizumab 1200 mg IV (N = 191) % (n)[a] or LSMEAN (SE) | Adjusted Treatment Difference95% CI[b] | | p-Value[b] | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Risankizumab 600 mg IV – placebo | Risankizumab 1200 mg IV – placebo | Risankizumab 600 mg IV vs. placebo | Risankizumab 1200 mg IV vs. placebo |
| Holm Procedure | Enhanced SF/APS clinical response and endoscopic response at Week 12 | 7.0 (13) | 21.0 (40) | 24.1 (46) | 13.9 [7.1, 20.7] | 17.3 [10.3, 24.2] | < 0.001[S] | < 0.001[S] |
| | Endoscopic remission at Week 12 | 4.3 (8) | 19.4 (37) | 20.4 (39) | 15.0 [8.9, 21.2] | 16.2 [9.9, 22.4] | < 0.001[S] | < 0.001[S] |
| | Enhanced SF/APS clinical response at Week 4 | 31.6 (59) | 45.0 (86) | 38.7 (74) | 13.6 [4.0, 23.3] | 7.1 [-2.4, 16.6] | 0.006[NS] | 0.142[NS] |
| | Ulcer-free endoscopy at Week 12 | N = 186 4.3 (8) | N = 190 13.8 (26) | N = 189 15.4 (29) | 9.4 [3.8, 15.1] | 11.2 [5.3, 17.0] | 0.001[S] | < 0.001[S] |
| | Enhanced SF/APS clinical response at Week 12 | 39.1 (73) | 61.8 (118) | 59.2 (113) | 22.8 [13.0, 32.5] | 20.0 [10.2, 29.9] | < 0.001[S] | < 0.001[S] |
| | Resolution of EIMs at Week 12, in subjects with any EIMs at baseline | N = 97 23.7 (23) | N = 100 29.5 (30) | N = 97 37.1 (36) | 5.6 [-6.8, 17.9] | 13.4 [0.7, 26.1] | 0.377[NS] | 0.039[NS] |

| | Endpoints | Placebo (N = 187) % (n)[a] or LSMEAN (SE) | Risankizumab 600 mg IV (N = 191) % (n)[a] or LSMEAN (SE) | Risankizumab 1200 mg IV (N = 191) % (n)[a] or LSMEAN (SE) | Adjusted Treatment Difference95% CI[b] | | p-Value[b] | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Risankizumab 600 mg IV – placebo | Risankizumab 1200 mg IV – placebo | Risankizumab 600 mg IV vs. placebo | Risankizumab 1200 mg IV vs. placebo |
| Holm Procedure (continued) | CD-related hospitalization through Week 12 (AO) | 11.2 (21) | 3.1 (6) | 2.1 (4) | -8.1 [-13.2, -2.9] | -9.1 [-14.1, -4.2] | 0.002[S] | < 0.001[S] |
| | No draining fistulas at Week 12 in subjects with draining fistulas at baseline | N = 15 13.3 (2) | N = 14 7.1 (1) | N = 16 43.8 (7) | -6.2 [-28.1, 15.7] | 30.4 [0.6, 60.2] | 1.000[NS] | 0.113[NS] |
| | Change from baseline in WPAI-CD overall work impairment at Week 12 (MMRM) | N = 68 -12.253 (3.3683) | N = 73 -19.576 (3.2747) | N = 86 -21.013 (3.0074) | -7.323 [-16.399, 1.753] | -8.759 [17.518, 0.001] | 0.113[NS] | 0.050[NS] |
| | Change from baseline in SF-36 physical component summary score at Week 12 (MMRM) | N = 142 5.237 (0.6166) | N = 167 7.458 (0.5767) | N = 172 7.951 (0.5749) | 2.221 [0.577, 3.865] | 2.714 [1.077, 4.351] | 0.008[NS] | 0.001[S] |

AO = as observed; APS = abdominal pain score; CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EIM = extra-intestinal manifestation; FACIT = Functional Assessment of Chronic Illness Therapy; IBDQ = Inflammatory Bowel Disease Questionnaire; ITT = intent-to-treat; IV = intravenous; LS = least squares; MMRM = mixed effect model repeat measurement; NRI-C = Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; SE = standard error; SF = stool frequency; SF-36 = 36-Item Short Form Health Survey; WPAI-CD = Work Productivity and Impairment Questionnaire – Crohn's disease

a. The % (n) represents the synthesized results from multiple imputation.

b. Adjusted treatment difference, 95% CI and p-values for comparison of binary endpoints between risankizumab and placebo were calculated using CMH test adjusted for randomization stratification factors (the number of prior biologics failed [≤ 1, > 1] and baseline corticosteroid use [yes or no]); 95% CI and p-values for comparison of continuous endpoints between risankizumab and placebo were calculated using MMRM (mixed effect model repeat measurement) with baseline, treatment, visit, treatment by visit interaction and stratification factors in the model.

Note: S, NS: The endpoint achieved (S) or did not achieve (NS), statistical significance based on the pre-specified graphical testing procedure for the OUS protocol. Green color indicates that the endpoint achieved statistical significance based on the pre-specified graphical testing procedure for the OUS protocol.

### *Ancillary analyses*

The MAH has provided data on a range of exploratory endpoints for the ITT1A population. Overall, these endpoints offer supportive data to the co-primary and key secondary endpoints. Symptom improvement as noted (shown by changes over time in clinical remission [per CDAI or SF/APS], mean APS, APS remission, mean SF, SF remission, clinical response [per CDAI, enhanced (SF/APS), or SF/APS], Crohn's Symptom Severity [CSS], resolution of EIMs, PGIC, and PGIS) and QoL improvement (shown by improvements in IBDQ, FACIT-Fatigue, WPAI-CD, EQ- 5D-5L, and SF-36 scores) were

observed over time for the risankizumab arms versus placebo. In addition, changes from baseline in SES-CD at Week 12 were greater in the risankizumab arms versus placebo.

Additionally, decreases in the biomarkers of FCP and hs-CRP were observed as early at Week 4 for the risankizumab arms versus placebo. The decrease of hs-CRP and FCP from baseline in risankizumab arms compared to placebo continued through to Week 12.

The MAH has also provided data from the additional efficacy populations to support the efficacy of RZB, these populations include the ITT1B, ITT2A and ITT2B.

12-Week Induction Period, ITT1B Population

The ITT1B population was used for exploratory efficacy analysis purposes and includes the subjects who were in ITT1 set for the 12-Week Induction Period but did not have baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). These subjects had lower baseline eligible SES-CD than included in the ITT1A population, excluding the narrowing component. Overall, the efficacy results in the ITT1B population were similar to the ITT1A population.

Induction Period 2, ITT2A Population

For subjects who did not achieve SF/APS clinical response at Week 12, defined as a ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score and both not worse than baseline, the proportion who achieved SF/APS clinical response at Week 24 was high and numerically similar across all treatment arms (Table 30).

*Table 30 Clinical Response (SF/APS) at Week 24 among Clinical Non-responders at the Entry of Induction Period 2 (As Observed) (ITT2A Population)*

| | Randomized Treatment Groups | | | Non-Randomized |
|---|---|---|---|---|
| Endpoints | Risankizumab 180 mg SC % (n) | Risankizumab 360 mg SC % (n) | Risankizumab 1200 mg IV % (n) | Placebo/Risankizumab 1200 mg IV % (n) |
| Clinical Response (SF/APS) | (N = 30) 76.7 (23) | (N = 29) 75.9 (22) | (N = 26) 61.5 (16) | (N = 58) 81.0 (47) |

APS = abdominal pain score; ITT = intent-to-treat; IV = intravenous; SC = subcutaneous; SF = stool frequency

Induction Period 2, ITT2B Population

The ITT2B population was used for exploratory efficacy analysis purposes and includes the subjects who were in ITT2 set for Induction Period 2 but did not have baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease) (i.e., had a lower baseline eligible SES-CD).

Overall, the efficacy results in the ITT2B population were supportive of a treatment effect.

**Induction Study M16-006:**

***Sample size***

Sample size calculation is based on the larger sample size needed to detect treatment difference for each of the co-primary endpoints. Since historical data show slightly lower event rate and similar treatment difference versus placebo for the endoscopic response rate than the CDAI clinical remission rate at Week 52, CDAI clinical remission rates at Week 52 are used for power calculation. Assuming the Week 52 CDAI clinical remission rate will be 46% for one of the risankizumab treatment groups and 28% for the placebo group, a sample size of 150 subjects for each of the risankizumab treatment

groups and 150 for the placebo group will have 87% power to detect the treatment difference between risankizumab and placebo using Fisher's exact test at a 0.05 significant level (two-sided). Assuming the Week 52 clinical remission rate will be 38.7% for one of the risankizumab treatment groups and 20% for the placebo group, a sample size of 150 subjects for each of the risankizumab treatment groups and 150 for the placebo group will have 93% power to detect the treatment difference between risankizumab and placebo using Fisher's exact test at a 0.05 significant level (two-sided). Assuming the Week 52 endoscopic response rate will be 32.6% for one of the risankizumab dose groups and 10% for the placebo group, this sample size will have > 95% power to detect the treatment difference between risankizumab and placebo using a Fisher's exact test at a 0.05 significant level (two-sided).

***Randomisation and blinding (masking)***

At baseline, eligible patients were randomized to three parallel groups with 1200 mg IV and 600 mg IV dose of risankizumab treatments or placebo in a 1:1:1 ratio. The 12-Week Induction Period randomization were stratified by number of prior biologics failed (1, > 1), baseline steroid use (Yes, No), and baseline eligible SES-CD (original, alternative), where the stratum of "original" includes the patients with baseline eligible SES-CD of ≥ 6 (or ≥ 4 for subjects with isolated ileal disease), and the stratum of "alternative" includes the patients with baseline eligible SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease.

Subjects with clinical non-response to risankizumab at Week 12 were to be re-randomized in a 1:1:1 ratio to risankizumab 1200 mg IV dose group, risankizumab 360 mg SC dose group, or risankizumab 180 mg SC dose group in the Induction Period 2. Subjects with clinical non-response to placebo at Week 12 blindly received risankizumab 1200 mg IV dose. No stratification was made for the Induction Period 2 randomization.

***Statistical methods***

A statistical analysis plan (SAP) was written and signed off prior to data base lock which included a number of amendments. These amendments are unlikely to have influenced the analyses outcomes for the primary outcome as far as can be ascertained.

The primary hypotheses for the co-primary endpoint were stated as:

(iii) The proportion of subjects achieving clinical remission treated with risakizumab is greater than that treated with placebo at Week 12

(iv) The proportion of subjects achieving endoscopic response treated with risakizumab is greater than that treated with placebo at Week 12

The estimands corresponding to the primary efficacy objective for global protocol outside US were stated to have been defined mainly as a definition of the outcome. Intercurrent events were specified as: 1) premature discontinuation of study drug and 2) initiation or dose escalation of CD-related corticosteroids.

Several analyses populations were defined, with the key one for the purposes of this assessment being the Intent-to-Treat Population (ITT) that included subjects who received at least one dose of study drug; for the 12-Week Induction Period, ITT1 was defined as randomized subjects who received at least one dose of study drug during the 12-Week Induction Period.

For the primary outcome, the Cochran Mantel-Haenszel (CMH) test adjusting for stratification factors was used. If there was a stratum for a treatment group that had no subjects in it, a value of 0.1 was used.

Point estimates and 95% confidence interval (CI)s for the difference in proportions between each of risankizumab treatment groups and placebo were be provided. Construction of CI for the common risk difference was based on the Mantel-Haenszel estimate adjusting for stratification factors.

For analysis of continuous Variables a Mixed-Effect Model Repeated Measurement (MMRM) model was used. A hierarchical Multiplicity approach was adopted that split the initial 5% alpha to each of the two doses (testing each dose at 2.5% level) and then sequentially testing secondary endpoints, after both co-primary endpoints were rejected. A sequential testing approach thereafter was adopted until the last 10 secondary endpoints were reached after which a Bonferroni-Holm procedure was adopted.

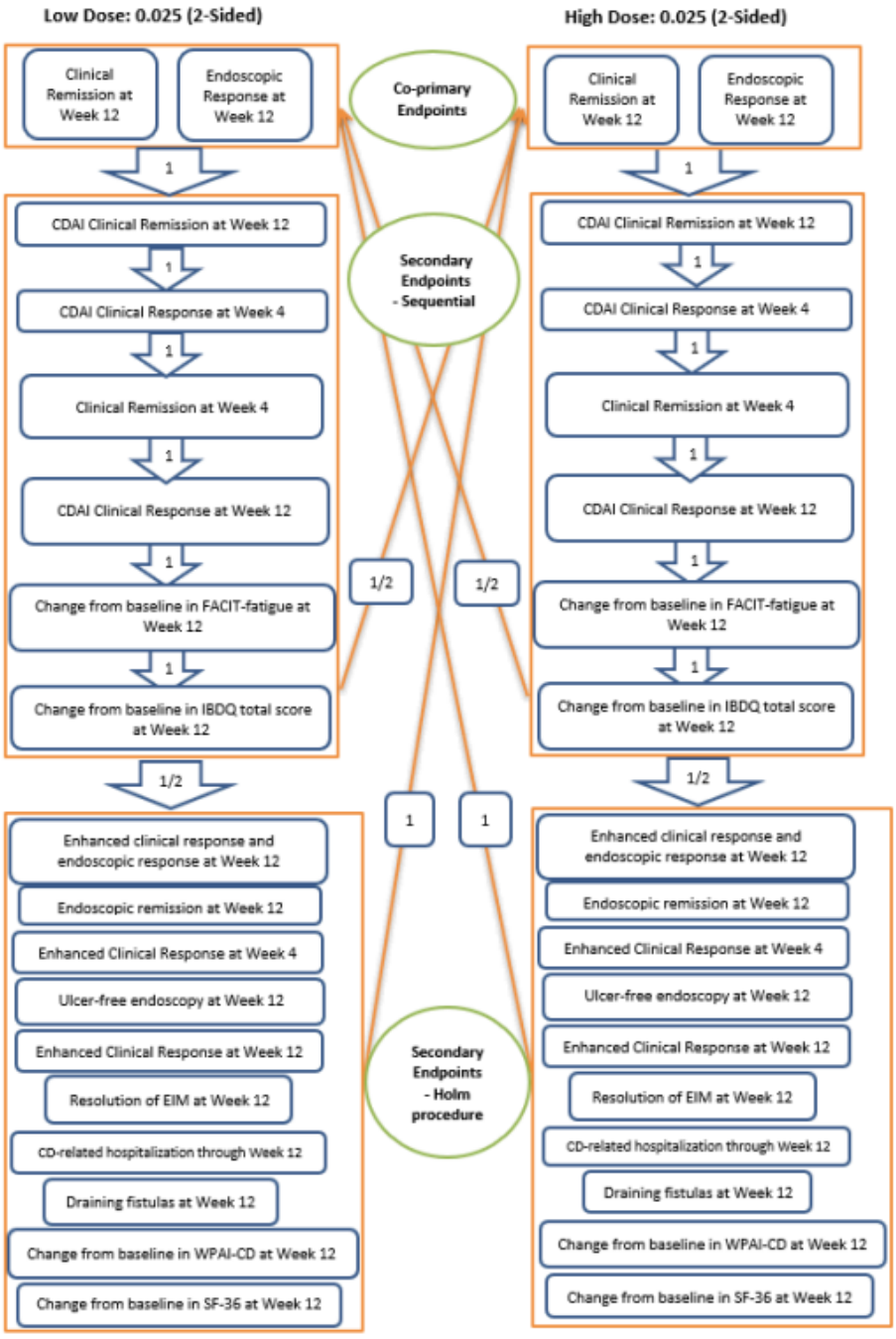
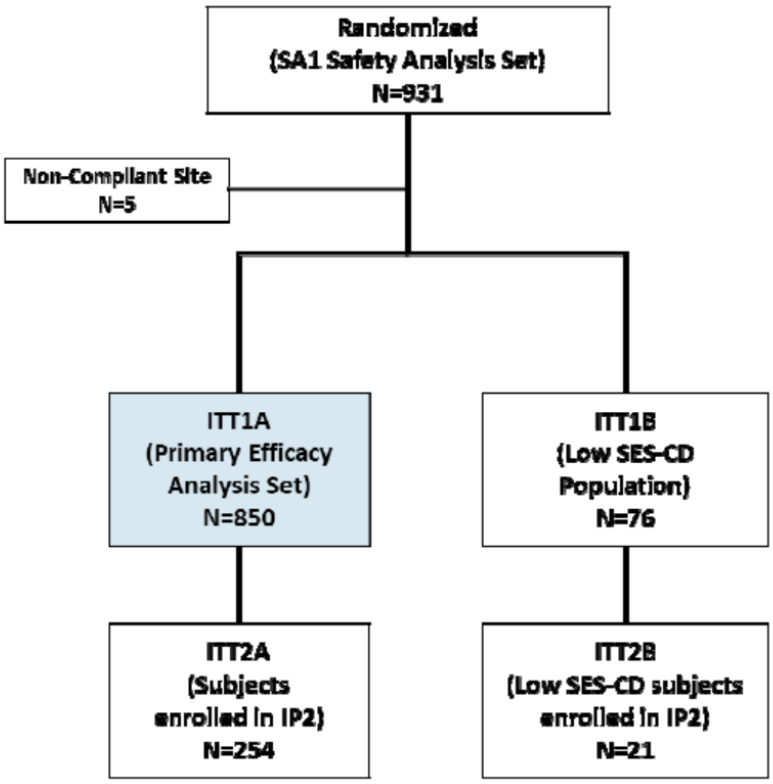



*Figure 18 Graphical Multiple Testing Procedure for Global Protocol Outside US*

**Results**

***Participant Flow***




Intent-to-Treat Population

The ITT population includes subjects who received at least 1 dose of study drug.

*12-Week Induction Period:*

The ITT population for the 12-Week Induction Period (denoted as ITT1) includes randomized subjects who received at least 1 dose of study drug during this period.

- ITT1A: includes the subjects with a baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease); the primary population for the efficacy analysis. N = 850 (336 subjects in the risankizumab 600 mg arm, 339 subjects in the risankizumab 1200 mg arm, and 175 subjects in the placebo arm)
- ITT1B: includes the subjects not included in ITT1A because they did not have baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). These subjects had a lower baseline eligible SES-CD and were used for exploratory efficacy analyses. N = 76 (35 subjects in the risankizumab 600 mg arm, 31 subjects in the risankizumab 1200 mg arm, and 10 subjects in the placebo arm)

Five subjects from a non-compliant site were excluded from the efficacy analyses for 12-Week Induction Period (excluded from ITT1A: 1 subject in the placebo arm, 2 subjects in the risankizumab 600 mg arm, and 2 subjects in the risankizumab 1200 mg arm).

*Induction Period 2:*

The ITT population for the Induction Period 2 (denoted as ITT2) includes subjects who were randomized and received at least 1 dose of risankizumab during the Induction Period 2, and the subjects who received placebo induction treatment during 12-Week Induction Period and entered the Induction Period 2 (denoted as placebo/risankizumab).

The placebo/risankizumab subjects were analyzed as a separate treatment group in the Induction Period 2.

- ITT2A: includes subjects who had baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). N = 254 (65 subjects in the risankizumab 180 mg SC arm, 60 subjects in the risankizumab 360 mg SC arm, 57 subjects in the risankizumab 1200 mg IV arm, and 72 subjects in the placebo IV/risankizumab 1200 mg IV arm)
- ITT2B: includes the subjects who did not have baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). These subjects had a lower baseline eligible SES-CD and were used for exploratory efficacy analysis. N = 21 (1 subject in the risankizumab 180 mg SC arm, 8 subjects in the risankizumab 360 mg SC arm, 9 subjects in the risankizumab 1200 mg IV arm, and 3 subjects in the placebo IV/risankizumab 1200 mg IV arm)

Three subjects from a non-compliant site were excluded from the efficacy analyses for Induction Period 2 (excluded from ITT2A: 1 subject in the risankizumab 180 mg SC arm, no subjects in the risankizumab 360 mg SC arm, 1 subject in the risankizumab 1200 mg IV arm, and 1 subject in the placebo IV/risankizumab 1200 mg IV arm).

For the corresponding ITT populations, subjects were assigned to a treatment group based on the randomization or re-randomization schedule, regardless of the treatment actually received. The demographics/baseline and efficacy analyses were based on the corresponding ITT population.

During the first 12-week Induction Period, a higher percentage of subjects in the risankizumab 600 mg and risankizumab 1200 mg treatment arms compared to placebo completed study drug. The most frequent primary reason for discontinuation of study drug in all treatment arms was an AE, and the number of subjects who discontinued study drug due to AE was numerically higher in the placebo arm compared to either risankizumab arm. The most frequently reported AE that led to discontinuation was Crohn's disease (2 subjects in the risankizumab 600 mg arm, 2 subjects in the risankizumab 1200 mg arm, and 7 subjects in the placebo arm), suggesting a lack of efficacy of study drug in these subjects. Subject final status and reasons for discontinuation of study drug during the first 12-Week Induction Period are shown in Table 31.

*Table 31 Subject Disposition and All Reasons for Study Drug Discontinuation for the 12-Week Induction Period (SA1 Population)*

| | Placebo IV (N = 186) n (%) | Risankizumab 600 mg IV (N = 373) n (%) | Risankizumab 1200 mg IV (N = 372) n (%) | Total (N = 931) n (%) |
|---|---|---|---|---|
| Completed induction period study drug | 163 (87.6) | 365 (97.9) | 366 (98.4) | 894 (96.0) |
| Discontinuation due to (primary reason) | | | | |
| Any reason | 23 (12.4) | 8 (2.1) | 6 (1.6) | 37 (4.0) |
| AE | 13 (7.0) | 4 (1.1) | 3 (0.8) | 20 (2.1) |
| Lack of efficacy | 3 (1.6) | 0 | 1 (0.3) | 4 (0.4) |
| Withdrawal by subject | 4 (2.2) | 3 (0.8) | 0 | 7 (0.8) |
| Covid-19 logistical restrictions | 2 (1.1) | 0 | 0 | 2 (0.2) |
| Other | 1 (0.5) | 1 (0.3) | 2 (0.5) | 4 (0.4) |
| Discontinuation due to (all reasons)[a] | | | | |
| Any reason | 23 (12.4) | 8 (2.1) | 6 (1.6) | 37 (4.0) |
| AE | 14 (7.5) | 5 (1.3) | 4 (1.1) | 23 (2.5) |
| Lack of efficacy | 4 (2.2) | 0 | 2 (0.5) | 6 (0.6) |
| Withdrawal by subject | 4 (2.2) | 3 (0.8) | 0 | 7 (0.8) |
| Covid-19 logistical restrictions | 2 (1.1) | 0 | 1 (0.3) | 3 (0.3) |
| Other | 1 (0.5) | 1 (0.3) | 3 (0.8) | 5 (0.5) |

AE = adverse event; COVID-19 = coronavirus disease - 2019; IV = intravenous; SA = safety population

a. Subjects may have reported more than 1 reason for discontinuation.

Protocol Deviations

For the ITT1A population a summary of the major protocol deviations is shown below.

Protocol deviations were defined in accordance with the ICH guidelines and included, but were not limited to, the following: inclusion/exclusion criteria violation (75 [8.8%] total subjects), receipt of wrong treatment or incorrect dose of study drug (4 [0.5%] total subjects), development of withdrawal criteria without being withdrawn (no subjects), and use of prohibited concomitant medications (35 [4.1%] total subjects).

According to the MAH the protocol deviations were not considered to have affected the study or interpretation of study results or conclusions.

TABLE 14.1 1.4

Summary of Major Protocol Deviations
(ITT1A Population)

| Protocol Deviation@ | Placebo IV (N=175) n (%) | Risankizumab 600 mg IV (N=336) n (%) | Risankizumab 1200 mg IV (N=339) n (%) | Total (N=850) n (%) |
|---|---|---|---|---|
| Subjects who had at least one protocol deviation | 31 (17.7) | 35 (10.4) | 43 (12.7) | 109 (12.8) |
| Subject entered into the study even though did not satisfy entry criteria | 17 (9.7) | 24 (7.1) | 34 (10.0) | 75 (8.8) |
| Inclusion criteria | | | | |
| 2 | 0 | 0 | 1 (0.3) | 1 (0.1) |
| 3 | 6 (3.4) | 11 (3.3) | 17 (5.0) | 34 (4.0) |
| 4 | 2 (1.1) | 0 | 3 (0.9) | 5 (0.6) |
| 5 | 4 (2.3) | 9 (2.7) | 16 (4.7) | 29 (3.4) |
| 7 | 2 (1.1) | 1 (0.3) | 2 (0.6) | 5 (0.6) |
| Any inclusion criteria not met | 13 (7.4) | 18 (5.4) | 32 (9.4) | 63 (7.4) |
| Exclusion criteria | | | | |
| 11 | 0 | 3 (0.9) | 0 | 3 (0.4) |
| 14 | 1 (0.6) | 0 | 0 | 1 (0.1) |
| 23 | 2 (1.1) | 2 (0.6) | 0 | 4 (0.5) |
| 24 | 1 (0.6) | 0 | 0 | 1 (0.1) |
| 30 | 0 | 2 (0.6) | 2 (0.6) | 4 (0.5) |
| Any exclusion criteria met | 4 (2.3) | 6 (1.8) | 2 (0.6) | 12 (1.4) |
| Subject received wrong treatment or incorrect dose | 0 | 3 (0.9) | 1 (0.3) | 4 (0.5) |

Note: ITT1A Population includes randomized subjects who received at least one dose of study drug during the 12-Week Induction Period, and had baseline eligible SES-CD of >= 6 (>= 4 for isolated ileal disease).
Percentages calculated based on N in the header.
@ Only 4 ICH major protocol deviations were included this analysis. A subject may have more than one deviation.

| Protocol Deviation@ | Placebo IV (N=175) n (%) | Risankizumab 600 mg IV (N=336) n (%) | Risankizumab 1200 mg IV (N=339) n (%) | Total (N=850) n (%) |
|---|---|---|---|---|
| Subject received excluded concomitant treatment | 18 (10.3) | 8 (2.4) | 9 (2.7) | 35 (4.1) |
| Subject developed withdrawal criteria during the study and was not withdrawn | 0 | 0 | 0 | 0 |

Note: ITT1A Population includes randomized subjects who received at least one dose of study drug during the 12-Week Induction Period, and had baseline eligible SES-CD of >= 6 (>= 4 for isolated ileal disease).
Percentages calculated based on N in the header.
@ Only 4 ICH major protocol deviations were included this analysis. A subject may have more than one deviation.

**Recruitment**

The First Subject First Visit was 10 May 2017 and the Last Subject Last Visit: 14 Apr 2021.

Database Lock: 18th May 2021

**Conduct of the Study**

Protocol Amendments

The original protocol (17 February 2017) had 6 global amendments, 3 country-specific amendments, and 1 administrative change.

The substantial, global amendments, number of subjects enrolled under each amendment, and major changes to the protocol were summarised as follows:

- Amendment 1 (substantial) (05 July 2017, 4 subjects). Addition of CDAI criteria to the inclusion criteria; update to instructions on which haematocrit (Hct) value to use in calculating the CDAI for inclusion; addition of "psychological or psychiatric cause" to Exclusion Criterion 29; updated information on discontinuation of individual subjects for subjects who were not responders at Week 12; updated contraception recommendations and criteria; clarification of the blind-breaking process; updated latent tuberculosis (TB) requirements; updated pregnancy

reporting timing; addition of assent information for subjects less than 18 years old, clarification of stratification criteria.

- Amendment 2 (substantial) (29 September 2017, 141 subjects). Addition of an anaphylaxis adjudication committee; revisions to allow for local regulations for the difference in minimum age for adults; update of Inclusion Criterion 6 for immunomodulators (IMM) use; update of Exclusion Criterion 18 for CD related complications; update of prohibited medications; addition of international normalized ratio (INR) and anaphylaxis testing; addition of details for additional hepatitis testing and anaphylaxis testing; addition of endoscopic remission to ranked secondary endpoints and Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) to non-ranked secondary endpoints; addition of clinical and endoscopic remission over time as endpoints; updated criteria for discontinuation of individual subjects; revisions to reduce redundancy; revisions to algin with Common Toxicity Criteria for Adverse Events (CTCAE) grading criteria for adverse events (AEs); revisions to allow for additional types of anaphylactic reactions and to provide Investigators with guidance on reporting of events; updates for alignment with template requirements and for consistency across the risankizumab programs; clarifications of sample size calculations; update to reflect the most recent subject diary entries and addition of patient-reported outcome (PRO) for collection; updates in the schedule of activities to reflect changes made in the body of the protocol; addition of information on the sample collection schedule; revision to align with regulatory agency feedback.
- Amendment 3 (substantial) (09 July 2018, 132 subjects). Extension of the AE collection period duration, final follow-up call, and period for prohibition of vaccines; modified benefits and risks to align with the IB; addition of blood collection for tryptase following a suspected drug administration hypersensitivity reaction; addition of "worsening" CD to common AEs associated with underlying disease; addition of "intramuscular" as possible route of administration for prohibited anti-infectives; exclusion of subjects who receive exclusive enteral nutrition to treat CD; clarification and explanation of inclusion requirements for oral locally acting steroids, IV or oral systemic steroids; addition of height measurement for pediatric subjects; prohibition of local, routine testing for fecal calprotectin and high-sensitivity C-reactive protein; modification of contraception language; modification of statistical methods for secondary endpoints to align with regulatory feedback; removal of stool sample collection for fecal-calprotectin (FCP) at screening; clarified repeat screening tests and the qualifications for a screening period extension.
- Amendment 4 (substantial) (22 February 2019, 476 subjects). Documentation of the DMC opinion to continue the trial and enroll 16-17 year-olds; addition of language to allow single repeat testing of transient exclusionary laboratory values during the screening period; clarification of the types of prohibited corticosteroids; modification to permit enrollment of not more than 20% subjects with prior exposure, including intolerance or inadequate response, to ustekinumab; specification that enrollment of subjects with Baseline SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or Baseline SES-CD of 3 for isolated ileal disease would be no more than 10% of the total population; addition of stratification factor of Baseline SES-CD; update definitions of endoscopic remission and endoscopic response; revision to allow a commercially available assay to determine approved biologic washout; clarification that TB prophylaxis is permissible; revision of the order and addition of ranked secondary endpoints, update of ranked secondary endpoints to non-ranked secondary endpoints, and addition of non-ranked secondary endpoint; addition of CTCAE version; clarification of timing of database lock (DBL); update of statistical assumptions for sample size determination; addition of details

of multiplicity adjustment and subgroup analysis for Bio-IR and non-Bio-IR population; update of the missing imputation methodology to remove last observation carried forward (LOCF).

- Amendment 5 (substantial) (19 December 2019, 89 subjects). Specifying the total N of 855 for the primary intent-to-treat (ITT) population used for efficacy analysis, that the number of subjects with lower SES-CD will be no more than 85, and that data collected from subjects with the lower SES-CD will be analyzed as an exploratory efficacy analysis; specifying that Hct from the preceding visit may be used to calculate the CDAI if there are technical issues; revision of definition of endoscopic remission; revision of the term "endoscopic healing" to "ulcer-free endoscopy"; update of secondary endpoint ranking and combining and adding new ranked secondary endpoints; clarification of timing of DBL; removing the missing imputation method OC from the sensitivity analysis of the continuous efficacy variables; addition of missing data handling methods; clarification of the way continuous laboratory and vital signs would be summarized; removed Fisher's exact test for risankizumab treatment group differences versus placebo for AEs; addition of "Optional Blood Sample for Biologic Drug Level."
- Amendment 6 (substantial) (28 July 2020, 4 subjects). Additions/revisions due to the Coronavirus disease – 2019 (COVID-19) pandemic, including benefit and risk, criteria to exclude subjects with active COVID-19, addition of COVID-19 AE data collection process, modification of study visits/protocol specified procedures impacted by changes in local regulations, protocol deviations, missing data, data monitoring, and COVID-19 testing; addition of language regarding site responsibility; and clarification of HIV results language.

**Baseline Data**

12-Week Induction Period ITT1A Population

Key baseline demographics were generally balanced between the three treatment arms (Table 32). Overall, the majority of subjects were white, not Hispanic or Latino, were between the ages of 18 and < 40, and were normal weight according to body mass index (BMI).

*Table 32 Baseline Demographic Characteristics of Subjects for 12-Week Induction Period (ITT1A Populations)*

| Variable | Placebo IV (N = 175) | Risankizumab 600 mg IV (N = 336) | Risankizumab 1200 mg IV (N = 339) | Total (N = 850) |
|---|---|---|---|---|
| Sex – n (%) | | | | |
| Female | 87 (49.7) | 147 (43.8) | 156 (46.0) | 390 (45.9) |
| Male | 88 (50.3) | 189 (56.3) | 183 (54.0) | 460 (54.1) |
| Age (years) | | | | |
| n | 175 | 336 | 339 | 850 |
| Mean (SD) | 37.1 (13.36) | 38.3 (13.33) | 37.0 (13.19) | 37.5 (13.28) |
| Median | 34.0 | 37.0 | 34.0 | 34.0 |
| Min, Max | 16, 74 | 16, 79 | 16, 74 | 16, 79 |
| Age category – n (%) | | | | |
| < 18 | 2 (1.1) | 2 (0.6) | 4 (1.2) | 8 (0.9) |
| [18, 40) | 115 (65.7) | 191 (56.8) | 212 (62.5) | 518 (60.9) |
| [40, 65) | 50 (28.6) | 130 (38.7) | 109 (32.2) | 289 (34.0) |
| ≥ 65 | 8 (4.6) | 13 (3.9) | 14 (4.1) | 35 (4.1) |
| Race – n (%) | | | | |
| White | 134 (76.6) | 258 (76.8) | 247 (72.9) | 639 (75.2) |
| Black or African American | 9 (5.1) | 9 (2.7) | 13 (3.8) | 31 (3.6) |
| Asian | 31 (17.7) | 65 (19.3) | 74 (21.8) | 170 (20.0) |
| Native Hawaiian or Other Pacific Islander | 1 (0.6) | 0 | 1 (0.3) | 2 (0.2) |
| Multiple | 0 | 4 (1.2) | 4 (1.2) | 8 (0.9) |
| Ethnicity – n (%) | | | | |
| Hispanic/Latino | 10 (5.7) | 11 (3.3) | 14 (4.1) | 35 (4.1) |
| Non-Hispanic/Latino | 165 (94.3) | 325 (96.7) | 325 (95.9) | 815 (95.9) |
| Body weight (kg) | | | | |
| n | 175 | 336 | 339 | 850 |
| Mean (SD) | 70.370 (18.1740) | 69.920 (17.6775) | 69.811 (19.5329) | 69.969 (18.5185) |
| Median | 70.000 | 67.400 | 67.000 | 67.500 |
| Min, Max | 38.00, 145.15 | 32.00, 145.60 | 38.00, 158.50 | 32.00, 158.50 |

| Variable | Placebo IV (N = 175) | Risankizumab 600 mg IV (N = 336) | Risankizumab 1200 mg IV (N = 339) | Total (N = 850) |
|---|---|---|---|---|
| BMI ($kg/m^2$) | | | | |
| n | 175 | 336 | 339 | 850 |
| Mean (SD) | 24.29 (5.786) | 24.09 (5.643) | 23.87 (6.148) | 24.04 (5.873) |
| Median | 23.43 | 23.30 | 22.65 | 23.04 |
| Min, Max | 14.9, 51.7 | 13.0, 49.7 | 13.7, 58.2 | 13.0, 58.2 |
| BMI category – n (%) | | | | |
| Underweight [< 18.5 $kg/m^2$] | 18 (10.3) | 45 (13.4) | 47 (13.9) | 110 (12.9) |
| Normal [≥ 18.5 and < 25 $kg/m^2$] | 89 (50.9) | 164 (48.8) | 182 (53.7) | 435 (51.2) |
| Overweight [≥ 25 and < 30 $kg/m^2$] | 46 (26.3) | 81 (24.1) | 69 (20.4) | 196 (23.1) |
| Obese [≥ 30 $kg/m^2$] | 22 (12.6) | 46 (13.7) | 41 (12.1) | 109 (12.8) |

BMI = body mass index; ITT = intent-to-Treat; IV = intravenous; max = maximum; min = minimum; SD = standard deviation

Use of any prior Crohn's disease-related medication was reported by 99.3% of subjects (Table 33). The most frequently reported prior CD-related medications used by the treatment groups were azathioprine (55.6% of subjects) and mesalazine (52% of subjects).

*Table 33 Prior Crohn's Disease-Related Biologics, Immunomodulators, and Steroids (ITT1A Population)*

| Generic Name (WHO 2018Q1) | Placebo IV (N = 175) n (%) | Risankizumab 600 mg IV (N = 336) n (%) | Risankizumab 1200 mg IV (N = 339) n (%) | Total (N = 850) n (%) |
|---|---|---|---|---|
| CD-related medications | 174 (99.4) | 333 (99.1) | 337 (99.4) | 844 (99.3) |
| **Biologic/Small Molecule Medications** | | | | |
| **Anti-TNFs** | | | | |
| Adalimumab | 76 (43.4) | 134 (39.9) | 131 (38.6) | 341 (40.1) |
| Infliximab | 75 (42.9) | 143 (42.6) | 160 (47.2) | 378 (44.5) |
| Certolizumab | 2 (1.1) | 4 (1.2) | 3 (0.9) | 9 (1.1) |
| Certolizumab pegol | 6 (3.4) | 5 (1.5) | 1 (0.3) | 12 (1.4) |
| Golimumab | 2 (1.1) | 3 (0.9) | 1 (0.3) | 6 (0.7) |
| **Anti-integrins** | | | | |
| Natalizumab | 0 | 1 (0.3) | 1 (0.3) | 2 (0.2) |
| Vedolizumab | 28 (16.0) | 67 (19.9) | 62 (18.3) | 157 (18.5) |
| Etrolizumab | 2 (1.1) | 0 | 3 (0.9) | 5 (0.6) |
| **Anti-p40s** | | | | |
| Ustekinumab | 24 (13.7) | 47 (14.0) | 50 (14.7) | 121 (14.2) |

| Generic Name (WHO 2018Q1) | Placebo IV (N = 175) n (%) | Risankizumab 600 mg IV (N = 336) n (%) | Risankizumab 1200 mg IV (N = 339) n (%) | Total (N = 850) n (%) |
|---|---|---|---|---|
| **Other Biologics** | | | | |
| Interleukin inhibitors | 0 | 1 (0.3) | 0 | 1 (0.1) |
| **Small Molecule** | | | | |
| Tofacitinib | 0 | 0 | 1 (0.3) | 1 (0.1) |
| Upadacitinib | 0 | 1 (0.3) | 1 (0.3) | 2 (0.2) |
| Filgotinib | 0 | 1 (0.3) | 2 (0.6) | 3 (0.4) |
| **Immunomodulators** | | | | |
| Tacrolimus | 1 (0.6) | 4 (1.2) | 1 (0.3) | 6 (0.7) |
| Thalidomide | 1 (0.6) | 8 (2.4) | 10 (2.9) | 19 (2.2) |
| Tioguanine | 1 (0.6) | 2 (0.6) | 2 (0.6) | 5 (0.6) |
| Mercaptopurine | 11 (6.3) | 28 (8.3) | 32 (9.4) | 71 (8.4) |
| Methotrexate | 32 (18.3) | 60 (17.9) | 52 (15.3) | 144 (16.9) |
| Azathioprine | 92 (52.6) | 202 (60.1) | 179 (52.8) | 473 (55.6) |
| **Corticosteroids (any route of administration)** | | | | |
| Beclometasone | 1 (0.6) | 5 (1.5) | 4 (1.2) | 10 (1.2) |
| Betamethasone | 0 | 2 (0.6) | 1 (0.3) | 3 (0.4) |
| Budesonide | 48 (27.4) | 88 (26.2) | 83 (24.5) | 219 (25.8) |
| Dexamethasone | 1 (0.6) | 2 (0.6) | 2 (0.6) | 5 (0.6) |
| Hydrocortisone | 5 (2.9) | 5 (1.5) | 2 (0.6) | 12 (1.4) |
| Methylprednisolone | 17 (9.7) | 49 (14.6) | 43 (12.7) | 109 (12.8) |
| Prednisolone | 27 (15.4) | 55 (16.4) | 48 (14.2) | 130 (15.3) |
| Prednisone | 50 (28.6) | 87 (25.9) | 81 (23.9) | 218 (25.6) |
| **Aminosalicylates** | | | | |
| Balsalazide | 2 (1.1) | 2 (0.6) | 0 | 4 (0.5) |
| Mesalazine | 98 (56.0) | 169 (50.3) | 175 (51.6) | 442 (52.0) |
| Sulfasalazine | 5 (2.9) | 23 (6.8) | 19 (5.6) | 47 (5.5) |

CD = Crohn's disease; IMM = immunomodulators; ITT = intent-to-Treat; IV = intravenous; Q1 = first quarter; TNF = tumor necrosis factor; WHO = World Health Organization

Note: This table includes Crohn's disease-related biologics, IMMs, and steroids with a start date before the first study drug dose date.

Baseline disease characteristics were generally well balanced among treatment arms (Table 34). In the ITT1A population, there were 491 subjects in the Bio-IR population and 359 subjects in the non-Bio-IR population; 28.1% of subjects failed 1 biologic and 29.6% of subjects failed more than 1 biologic. In the Bio-IR population, 95.1% subjects failed 1 or more anti-TNF and 28.9% failed vedolizumab.

The most common CD location per SES-CD was in the ileal-colonic region (49.6% of all subjects).

Overall, approximately 30% and approximately 24% of subjects were on concomitant corticosteroids and/or immunomodulators at baseline, respectively.

*Table 34 Baseline Disease Characteristics, Selective Variables (ITT1A Population)*

| Variable | Placebo IV (N = 175) | Risankizumab 600 mg IV (N = 336) | Risankizumab 1200 mg IV (N = 339) | Total (N = 850) |
|---|---|---|---|---|
| Crohn's disease duration (years) | | | | |
| n | 175 | 336 | 339 | 850 |
| Mean (SD) | 8.220 (7.1025) | 9.036 (8.8378) | 8.934 (8.4151) | 8.827 (8.3336) |
| Median | 6.431 | 6.153 | 6.437 | 6.341 |
| Min, Max | 0.077, 37.949 | 0.068, 38.995 | 0.268, 52.624 | 0.068, 52.624 |
| Biologics failure history (0, 1, > 1) – n (%) | | | | |
| 0 | 78 (44.6) | 141 (42.0) | 140 (41.3) | 359 (42.2) |
| 1 | 41 (23.4) | 100 (29.8) | 98 (28.9) | 239 (28.1) |
| > 1 | 56 (32.0) | 95 (28.3) | 101 (29.8) | 252 (29.6) |

| Variable | Placebo IV (N = 175) | Risankizumab 600 mg IV (N = 336) | Risankizumab 1200 mg IV (N = 339) | Total (N = 850) |
|---|---|---|---|---|
| Baseline CDAI | | | | |
| n | 175 | 336 | 339 | 850 |
| Mean (SD) | 319.22 (59.388) | 311.24 (62.430) | 311.46 (68.445) | 312.97 (64.311) |
| Median | 314.00 | 303.95 | 302.20 | 306.55 |
| Min, Max | 179.1, 471.0 | 134.4, 550.5 | 76.0, 634.0 | 76.0, 634.0 |
| Average daily stool frequency | | | | |
| N | 175 | 336 | 339 | 850 |
| Mean (SD) | 6.081 (2.7881) | 5.761 (2.7124) | 5.633 (2.8396) | 5.776 (2.7809) |
| Median | 5.857 | 5.286 | 5.286 | 5.429 |
| Min, Max | 0.143, 16.000 | 0.143, 20.286 | 0.000, 24.143 | 0.000, 24.143 |
| Average daily abdominal pain score | | | | |
| n | 175 | 336 | 339 | 850 |
| Mean (SD) | 1.943 (0.5621) | 1.873 (0.5665) | 1.888 (0.5247) | 1.893 (0.5492) |
| Median | 2.000 | 2.000 | 2.000 | 2.000 |
| Min, Max | 0.000, 3.000 | 0.000, 3.000 | 0.000, 3.000 | 0.000, 3.000 |
| Baseline SES-CD | | | | |
| n | 175 | 336 | 339 | 850 |
| Mean (SD) | 13.8 (6.77) | 14.7 (7.67) | 13.4 (6.53) | 14.0 (7.07) |
| Median | 13.0 | 13.0 | 12.0 | 12.0 |
| Min, Max | 4, 35 | 4, 45 | 4, 36 | 4, 45 |
| CD location per SES-CD – n (%) | | | | |
| Ileal only | 19 (10.9) | 52 (15.5) | 54 (15.9) | 125 (14.7) |
| Colonic only | 70 (40.0) | 115 (34.2) | 118 (34.8) | 303 (35.6) |
| Ileal-colonic | 86 (49.1) | 169 (50.3) | 167 (49.3) | 422 (49.6) |
| Baseline hs-CRP (mg/L) | | | | |
| N | 175 | 333 | 338 | 846 |
| Mean (SD) | 16.326 (21.3370) | 18.135 (26.9099) | 16.230 (21.9175) | 17.000 (23.8890) |
| Median | 8.360 | 7.290 | 7.605 | 7.695 |
| Min, Max | 0.24, 118.00 | 0.20, 181.00 | 0.20, 161.00 | 0.20, 181.00 |

| Variable | Placebo IV (N = 175) | Risankizumab 600 mg IV (N = 336) | Risankizumab 1200 mg IV (N = 339) | Total (N = 850) |
|---|---|---|---|---|
| Baseline fecal calprotectin (mg/kg) | | | | |
| N | 141 | 284 | 282 | 707 |
| Mean (SD) | 2499.3 (4308.76) | 1767.3 (2272.65) | 2322.3 (3988.31) | 2134.7 (3489.69) |
| Median | 1200.0 | 960.0 | 1045.0 | 1045.0 |
| Min, Max | 30, 26786 | 30, 14690 | 30, 28800 | 30, 28800 |
| Draining fistulas (yes, no) – n (%) | | | | |
| Yes | 9 (5.2) | 18 (5.4) | 24 (7.1) | 51 (6.0) |
| No | 165 (94.8) | 318 (94.6) | 314 (92.9) | 797 (94.0) |
| Missing | 1 | 0 | 1 | 2 |
| Non-draining fistulas (yes, no) – n (%) | | | | |
| Yes | 18 (10.3) | 30 (8.9) | 25 (7.4) | 73 (8.6) |
| No | 156 (89.7) | 306 (91.1) | 313 (92.6) | 775 (91.4) |
| Missing | 1 | 0 | 1 | 2 |
| Baseline corticosteroid use (yes, no) – n (%) | | | | |
| Yes | 50 (28.6) | 102 (30.4) | 101 (29.8) | 253 (29.8) |
| No | 125 (71.4) | 234 (69.6) | 238 (70.2) | 597 (70.2) |
| Baseline immunomodulator use (yes, no) – n (%) | | | | |
| Yes | 42 (24.0) | 88 (26.2) | 73 (21.5) | 203 (23.9) |
| No | 133 (76.0) | 248 (73.8) | 266 (78.5) | 647 (76.1) |

CDAI = Crohn's Disease Activity Index; hs-CRP = high sensitivity C-reactive protein; ITT = intent-to-Treat; IV = intravenous; max = maximum; min = minimum; SD = standard deviation; SES-CD = Simple Endoscopic Score for Crohn's disease

Treatment Compliance 12-Week Induction Period

Overall mean treatment compliance during the 12-Week Induction Period was comparable across treatment arms (99.4% in the risankizumab 600 mg arm, 98.3% in the risankizumab 1200 mg arm, and 98.7% in the placebo arm).

***Outcomes and estimation***

The study met the co-primary endpoints of clinical remission and endoscopic response for the risankizumab 600 mg and 1200 mg arms compared to the placebo arm for both the US protocol and the OUS protocol. At Week 12, a statistically significantly greater (p-value < 0.001) proportion of subjects in the risankizumab 600 mg and risankizumab 1200 arms achieved the co-primary endpoint of clinical remission (as defined by the CDAI in the US protocol and by the SF/APS in the OUS protocol) compared to the placebo arm (Table 35 and Table 36).

At Week 12, a statistically significantly greater (p-value < 0.001) proportion of subjects in the risankizumab 600 mg and risankizumab 1200 mg arms achieved endoscopic response, assessed in both the US protocol and the OUS protocol, compared to the placebo arm (Table 37).

In addition, a clear treatment effect was demonstrated in the key subgroup populations of non-Bio-IR and Bio-IR for all co-primary endpoints, with higher efficacy and effect size noted in the non-Bio-IR population. Overall, numerically similar results were observed for the risankizumab 600 mg arm and the risankizumab 1200 mg arm in the overall population as well as both subgroup populations.

*Table 35 CDAI Clinical Remission at Week 12 (NRI-C) – Total and by Prior Biologics Failure (ITT1A Population)*

| Subgroup Category Treatment | N | Responder (NRI-C) n (%) | [95% CI][a] | Response Rate Diff Compared to Placebo Diff (%)[b] | Adjusted Diff (%)[b] | [95% CI][c] | P-value[c] |
|---|---|---|---|---|---|---|---|
| All | | | | | | | |
| Placebo IV | 175 | 43 (24.6) | [18.2, 31.0] | | | | |
| Risankizumab 600 mg IV | 336 | 152 (45.2) | [39.9, 50.5] | 20.6 | 20.7 | [12.4, 29.0] | < 0.001 |
| Risankizumab 1200 mg IV | 339 | 141 (41.6) | [36.3, 46.8] | 17.0 | 16.7 | [8.5, 24.9] | < 0.001 |
| Prior Biologic Failure | | | | | | | |
| Yes | | | | | | | |
| Placebo IV | 97 | 25 (25.8) | [17.1, 34.5] | | | | |
| Risankizumab 600 mg IV | 195 | 83 (42.5) | [35.5, 49.4] | 16.7 | | [5.5, 27.8] | |
| Risankizumab 1200 mg IV | 199 | 75 (37.7) | [31.0, 44.4] | 11.9 | | [0.9, 22.9] | |
| No | | | | | | | |
| Placebo IV | 78 | 18 (23.1) | [13.8, 32.5] | | | | |
| Risankizumab 600 mg IV | 141 | 69 (48.9) | [40.7, 57.2] | 25.8 | | [13.3, 38.3] | |
| Risankizumab 1200 mg IV | 140 | 66 (47.1) | [38.9, 55.4] | 24.0 | | [11.5, 36.5] | |

CDAI = Crohn's Disease Activity Index; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; COVID-19 = coronavirus disease - 2019; ITT = intent-to-Treat; IV = intravenous; NRI-C = Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19

a. 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.

b. Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test.

c. Across the strata, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (Number of prior biologics failed [0, 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each stratum, 95% CI for difference calculated using normal approximation to the binomial distribution. 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.

Note: Green color indicates that this co-primary endpoint achieved statistical significance based on the pre-specified graphical testing procedure for the US-specific protocol.

*Table 36 Clinical Remission (SF/APS) at Week 12 (NRI-C) – Total and by Prior Biologics Failed (ITT1A Population)*

| Subgroup Category Treatment | N | Responder (NRI-C) n (%) | [95% CI][a] | Response Rate Diff Compared to Placebo Diff (%)[b] | Adjusted Diff (%)[b] | [95% CI][c] | P-value[c] |
|---|---|---|---|---|---|---|---|
| All | | | | | | | |
| Placebo IV | 175 | 38 (21.7) | [15.6, 27.8] | | | | |
| Risankizumab 600 mg IV | 336 | 146 (43.5) | [38.2, 48.8] | 21.7 | 21.9 | [13.8, 29.9] | <0.001 |
| Risankizumab 1200 mg IV | 339 | 139 (41.0) | [35.8, 46.2] | 19.3 | 18.8 | [10.8, 26.8] | <0.001 |
| Prior Biologic Failure | | | | | | | |
| Yes | | | | | | | |
| Placebo IV | 97 | 22 (22.7) | [14.3, 31.0] | | | | |
| Risankizumab 600 mg IV | 195 | 79 (40.5) | [33.6, 47.4] | 17.8 | | [7.0, 28.6] | |
| Risankizumab 1200 mg IV | 199 | 77 (38.7) | [31.9, 45.5] | 16.0 | | [5.3, 26.7] | |
| No | | | | | | | |
| Placebo IV | 78 | 16 (20.6) | [11.6, 29.5] | | | | |
| Risankizumab 600 mg IV | 141 | 67 (47.5) | [39.3, 55.8] | 27.0 | | [14.8, 39.2] | |
| Risankizumab 1200 mg IV | 140 | 62 (44.3) | [36.1, 52.5] | 23.7 | | [11.6, 35.9] | |

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; COVID-19 = coronavirus disease - 2019; ITT = intent-to-Treat; IV = intravenous; NRI-C = Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; SF/APS = stool frequency/ abdominal pain score

a. 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.

b. Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test.

c. Across the strata, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (Number of prior biologics failed [0, 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each stratum, 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

Note: Green color indicates that this co-primary endpoint achieved statistical significance based on the pre-specified graphical testing procedure for the OUS protocol.

*Table 37 Endoscopic Response at Week 12 (NRI-C) – Total and by Prior Biologics Failure (ITT1A Population)*

| Subgroup Category Treatment | N | n (%) | Responder (NRI-C) [95% CI][a] | Diff (%)[b] | Adjusted Diff (%)[b] | Response Rate Diff Compared to Placebo [95% CI][c] | P-value[c] |
|---|---|---|---|---|---|---|---|
| All | | | | | | | |
| Placebo IV | 175 | 21 (12.0) | [7.2, 16.8] | | | | |
| Risankizumab 600 mg IV | 336 | 135 (40.3) | [35.0, 45.6] | 28.2 | 28.3 | [21.2, 35.4] | < 0.001 |
| Risankizumab 1200 mg IV | 339 | 109 (32.1) | [27.1, 37.1] | 20.1 | 20.3 | [13.6, 27.1] | < 0.001 |
| Prior Biologic Failure | | | | | | | |
| Yes | | | | | | | |
| Placebo IV | 97 | 11 (11.4) | [5.0, 17.7] | | | | |
| Risankizumab 600 mg IV | 195 | 64 (32.9) | [26.2, 39.5] | 21.5 | | [12.3, 30.7] | |
| Risankizumab 1200 mg IV | 199 | 47 (23.8) | [17.9, 29.8] | 12.5 | | [3.8, 21.1] | |
| No | | | | | | | |
| Placebo IV | 78 | 10 (12.8) | [5.4, 20.2] | | | | |
| Risankizumab 600 mg IV | 141 | 71 (50.5) | [42.2, 58.8] | 37.7 | | [26.5, 48.8] | |
| Risankizumab 1200 mg IV | 140 | 61 (43.9) | [35.6, 52.1] | 31.1 | | [20.0, 42.2] | |

CI = confidence interval; COVID-19 = coronavirus disease - 2019; ITT = intent-to-Treat; IV = intravenous; NRI-C = Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19

a. 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.

b. Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test.

c. Across the strata, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (Number of prior biologics failed [0, 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each stratum, 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

Note: Green color indicates that this co-primary endpoint achieved statistical significance based on the pre-specified graphical testing procedure for both the US-specific and OUS protocols.

The key secondary endpoints (i.e., endpoints under the overall Type I error control) for the OUS protocols are summarised in Table 38.

Overall, both risankizumab arms (600 mg and 1200 mg) demonstrated clear treatment effects over placebo for resolution of clinical symptoms, improvements in quality of life (QoL), reduction in mucosal inflammation as measured by endoscopy, and CD-related hospitalizations. A majority of endpoints were statistically significant for the risankizumab 600 mg arm and the risankizumab 1200 mg arm versus placebo (this was the case for both the US and OUS protocols). Overall efficacy rates for the risankizumab 600 mg and 1200 mg arms were numerically similar.

Clinical response and clinical remission, as defined by CDAI and SF/APS, were seen at Week 4, with statistically significant differences observed for the risankizumab 600 mg and 1200 mg arms versus placebo.

Additionally, clinical response per CDAI and SF/APS were statistically significant for each risankizumab arm versus placebo at Week 12, with greater efficacy and treatment differences relative to those at Week 4. Other patient reported outcome (PRO) questionnaires that summarize QoL, such as Inflammatory Bowel Disease Questionnaire (IBDQ), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, Work Productivity and Impairment Questionnaire – Crohn's disease (WPAI-CD), and SF-36, showed overall numerically better improvement in the risankizumab arms versus placebo.

*Table 38 Summary of Key Secondary Endpoints Under the Overall Type I Error Control, OUS Protocol (NRI-C) (ITT1A Population)*

| | Endpoints | Placebo (N = 175) % (n)[a] or LSMEAN (SE) | Risankizumab 600 mg IV (N = 336) % (n)[a] or LSMEAN (SE) | Risankizumab 1200 mg IV (N = 339) % (n)[a] or LSMEAN (SE) | Adjusted Treatment Difference 95% CI[b] | | p-Value[b] | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Risankizumab 600 mg IV – Placebo | Risankizumab 1200 mg IV – Placebo | Risankizumab 600 mg IV vs. Placebo | Risankizumab 1200 mg IV vs. Placebo |
| 1 | CDAI clinical remission at Week 12 | 24.6 (43) | 45.2 (152) | 41.6 (141) | 20.7 [12.4, 29.0] | 16.7 [8.5, 24.9] | < 0.001[S] | < 0.001[S] |
| 2 | CDAI clinical response at Week 4 | 25.2 (44) | 40.8 (137) | 37.2 (126) | 15.4 [7.2, 23.7] | 11.2 [3.1, 19.2] | < 0.001[S] | 0.007[s] |
| 3 | Clinical remission (SF/APS) at Week 4 | 9.1 (16) | 21.0 (71) | 21.2 (72) | 11.5 [5.4, 17.5] | 11.7 [5.7, 17.8] | < 0.001[S] | < 0.001[S] |
| 4 | CDAI clinical response at Week 12 | 36.7 (64) | 59.7 (201) | 64.9 (220) | 23.1 [14.2, 31.9] | 27.7 [19.0, 36.4] | < 0.001[S] | < 0.001[S] |
| 5 | Change from baseline in FACIT-Fatigue at Week 12 (MMRM) | (N = 134) 6.0 (0.86) | (N = 302) 11.2 (0.59) | (N = 310) 10.1 (0.58) | 5.2 [3.2, 7.2] | 4.1 [2.1, 6.1] | < 0.001[S] | < 0.001[S] |
| 6 | Change from baseline in IBDQ total score at Week 12 (MMRM) | (N = 134) 23.6 (2.72) | (N = 302) 44.3 (1.87) | (N = 310) 43.0 (1.85) | 20.7 [14.3, 27.1] | 19.4 [13.1, 25.8] | < 0.001[S] | < 0.001[S] |

| | Endpoints | Placebo (N = 175) % (n)[a] or LSMEAN (SE) | Risankizumab 600 mg IV (N = 336) % (n)[a] or LSMEAN (SE) | Risankizumab 1200 mg IV (N = 339) % (n)[a] or LSMEAN (SE) | Adjusted Treatment Difference 95% CI[b] | | p-Value[b] | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Risankizumab 600 mg IV – Placebo | Risankizumab 1200 mg IV – Placebo | Risankizumab 600 mg IV vs. Placebo | Risankizumab 1200 mg IV vs. Placebo |
| Holm Procedure (continued) | CD-related hospitalization through Week 12 (AO) | 12.0 (21) | 3.3 (11) | 1.8 (6) | -8.7 [-13.9, -3.5] | -10.2 [-15.2, -5.2] | < 0.001[S] | < 0.001[S] |
| | No draining fistulas at Week 12 in subjects with draining fistulas at baseline | (N = 9) 22.2 (2) | (N = 18) 27.8 (5) | (N = 24) 29.2 (7) | 5.6 [-28.6, 39.7] | 6.9 [-25.7, 39.6] | 1.00[NS] | 1.00[NS] |
| | Change from baseline in WPAI-CD Overall Work Impairment at Week 12 (MMRM) | (N = 65) -8.344 (3.5640) | (N = 156) -17.930 (2.3446) | (N = 162) -20.485 (2.3112) | -9.586 [-17.890, -1.282] | -12.141 [-20.390 - 3.892] | 0.024[NS] | 0.004[S] |
| | Change from baseline in SF-36 Physical Component Summary score at Week 12 (MMRM) | (N = 134) 5.482 (0.5985) | (N = 302) 8.394 (0.4107) | (N = 309) 8.756 (0.4071) | 2.913 [1.512, 4.313] | 3.275 [1.877, 4.672] | < 0.001[S] | < 0.001[S] |

| | Endpoints | Placebo (N = 175) % (n)[a] or LSMEAN (SE) | Risankizumab 600 mg IV (N = 336) % (n)[a] or LSMEAN (SE) | Risankizumab 1200 mg IV (N = 339) % (n)[a] or LSMEAN (SE) | Adjusted Treatment Difference 95% CI[b] | | p-Value[b] | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Risankizumab 600 mg IV – Placebo | Risankizumab 1200 mg IV – Placebo | Risankizumab 600 mg IV vs. Placebo | Risankizumab 1200 mg IV vs. Placebo |
| Holm Procedure | Enhanced SF/APS clinical response and endoscopic response at Week 12 | 8.0 (14) | 30.9 (104) | 23.2 (79) | 23.2 [16.8, 29.6] | 15.2 [9.3, 21.2] | < 0.001[S] | < 0.001[S] |
| | Endoscopic remission at Week 12 | 9.1 (16) | 24.2 (81) | 23.9 (81) | 15.1 [9.0, 21.2] | 15.4 [9.4, 21.4] | < 0.001[S] | < 0.001[S] |
| | Enhanced SF/APS clinical response at Week 4 | 31.0 (54) | 46.0 (155) | 43.4 (147) | 14.9 [6.2, 23.5] | 11.8 [3.2, 20.3] | 0.001[S] | 0.007 |
| | Ulcer-free endoscopy at Week 12 | (N = 173) 7.6 (13) | (N = 336) 21.0 (71) | (N = 338) 16.4 (55) | 13.7 [7.9, 19.5] | 9.1 [3.7, 14.5] | < 0.001[S] | 0.001[S] |
| | Enhanced SF/APS clinical response at Week 12 | 41.9 (73) | 62.8 (211) | 64.3 (218) | 21.0 [12.2, 29.9] | 21.6 [12.8, 30.4] | < 0.001[S] | < 0.001[S] |
| | Resolution of EIMs at Week 12, in subjects with any EIMs at baseline | (N = 64) 20.5 (13) | (N = 140) 38.1 (53) | (N = 158) 43.7 (69) | 14.6 [2.1, 27.0] | 23.7 [11.1, 36.3] | 0.022[NS] | < 0.001[S] |

AO = as observed; APS = abdominal pain score; CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EIM = extra-intestinal manifestation; FACIT = Functional Assessment of Chronic Illness Therapy; IBDQ = Inflammatory Bowel Disease Questionnaire; ITT = intent-to-treat; IV = intravenous; LS = least squares; MMRM = mixed effect model repeat measurement; NRI-C = Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; SE = standard error; SF = stool frequency; SF-36 = 36-Item Short Form Health Survey; WPAI-CD = Work Productivity and Impairment Questionnaire – Crohn's disease

a. The % (n) represents the synthesized results from multiple imputation.

b. Adjusted treatment difference, 95% CI and p-values for comparison of binary endpoints between risankizumab and placebo were calculated using CMH test adjusted for randomization stratification factors (the number of prior biologics failed [0, 1, > 1] and baseline corticosteroid use [yes or no]); 95% CI and p-values for comparison of continuous endpoints between risankizumab and placebo were calculated using MMRM with baseline, treatment, visit, treatment by visit interaction and stratification factors in the model.

Note: S, NS: The endpoint achieved (S) or did not achieve (NS), statistical significance based on the pre-specified graphical testing procedure for the OUS protocol. Green color indicates that the endpoint achieved statistical significance based on the pre-specified graphical testing procedure for the OUS protocol.

Additional Efficacy Variables

The MAH has provided data on a range of exploratory endpoints for the ITT1A population.

Overall, these endpoints offer supportive data to the co-primary and key secondary endpoints. Symptom improvement (shown by changes over time in clinical remission [per CDAI or SF/APS], mean APS, APS remission, mean SF, SF remission, clinical response [per CDAI, enhanced (SF/APS), or SF/APS], Crohn's Symptom Severity [CSS], resolution of EIMs, PGIC, and PGIS) and QoL improvement (shown by improvements in IBDQ, FACIT-Fatigue, WPAI-CD, EQ-5D-5L, and SF-36 scores) were

observed over time for the risankizumab arms versus placebo. Changes from baseline in SES-CD at Week 12 were greater in the risankizumab arms versus placebo.

Additionally, decreases in the biomarkers of hs-CRP and FCP were observed as early as Week 4 and were sustained at Week 12 for the risankizumab 600 mg and 1200 mg arms versus placebo. The decreases in mean hs-CRP for the risankizumab 600 mg and 1200 mg treatment arms were numerically larger than the placebo arm at Week 4, Week 8, and Week 12 (nominal p-value < 0.001 in each risankizumab treatment arm at all 3 timepoints). The differences in mean FCP for the risankizumab 600 mg and 1200 mg treatment arms were numerically larger than placebo at Week 4 (risankizumab 600 mg nominal p-value < 0.001; risankizumab 1200 mg nominal p-value = 0.003) and at Week 12 (nominal p-value < 0.001 in each risankizumab treatment arm).

12-Week Induction Period, ITT1B Population

The ITT1B population was used for exploratory efficacy analysis purposes and includes the subjects who were in ITT1 set for the 12-Week Induction Period but did not have baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). These subjects had lower baseline eligible SES-CD than included in the ITT1A population, excluding the narrowing component. Overall, the efficacy results in the ITT1B population were similar to the ITT1A population.

Induction Period 2 ITT2A Population

Subjects in the risankizumab treatment arms who did not achieve SF/APS clinical response (defined as a ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily APS and both not worse than baseline) at Week 12 were then randomized 1:1:1 into Induction Period 2 and subjects in the placebo arm who did not achieve SF/APS clinical response at Week 12 received risankizumab 1200 mg IV during Induction Period 2.

For these subjects baseline demographics and disease characteristics were generally balanced between the three treatment arms.

The proportion who achieved SF/APS clinical response at Week 24 was high and numerically similar across all treatment arms (Table 39).

*Table 39 Clinical Response (SF/APS) at Week 24 among Clinical Non-responders at the Entry of Induction Period 2 (As Observed) (ITT2A Population)*

| | Randomized Treatment Groups | | | Placebo/ |
|---|---|---|---|---|
| | Risankizumab 180 mg SC | Risankizumab 360 mg SC | Risankizumab 1200 mg IV | Risankizumab 1200 mg IV |
| | N | N | N | N |
| Endpoints | n (%) | n (%) | n (%) | n (%) |
| Clinical Response (SF/APS) | 45<br>39 (86.7) | 51<br>37 (72.5) | 42<br>34 (81.0) | 58<br>49 (84.5) |

APS = abdominal pain score; ITT = intent-to-treat; IV = intravenous; SC = subcutaneous; SF = stool frequency

Induction Period 2, ITT2B Population

The ITT2B population was used for exploratory efficacy analysis purposes and includes the subjects who were in ITT2 set for Induction Period 2 but did not have baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease) (i.e., had a lower baseline eligible SES-CD). Overall, the efficacy results in the ITT2B population were supportive of a treatment effect.

***Maintenance Study M16-000 Sub-Study 1***

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 Crohn's Disease

Study M16-000 consists of three sub-studies. Only the randomised portion of M16-000 Sub-Study 1, as pivotal, is discussed below.

- Sub-Study 2, also a 52-week maintenance study, is an ongoing randomized study with the objective of evaluating 2 methods of dose-escalation for subjects with loss of response during maintenance treatment.
- Sub-Study 3 is an ongoing open-label (OL) extension with the objective of collecting long-term safety data.

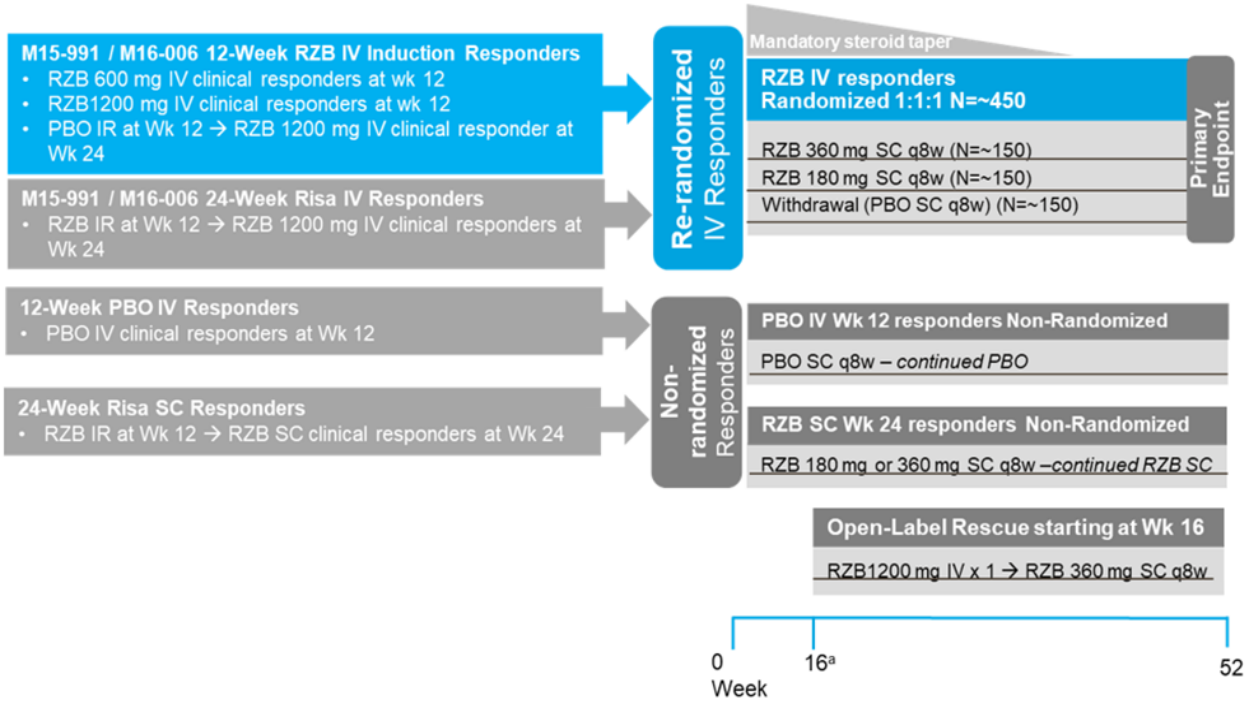
***Methods***

M16-000 Sub-Study 1 was a Phase 3, multi-centre, 52-week maintenance study with a 20-week Follow-Up period, consisting of a randomized (pivotal) and non-randomized portion. The randomized portion was a re-randomized responder withdrawal design, double blind and placebo controlled.

Subjects from M15-998 and M16-006, with SF/APS clinical response and a Baseline induction eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease) excluding the narrowing component after 12 weeks of RZB IV induction (600 mg or 1200 mg), were re-randomized 1:1:1 to continue receiving RZB 180 mg SC q8w or RZB 360 mg SC q8w, or to have RZB treatment withdrawn (via administration of blinded PBO Sc). Study duration was approximately 68 weeks.

Dose selection was based on data from the dose-ranging Phase 2 Study M15-993 and preliminary PK/pharmacodynamic modeling, which suggested doses higher than Phase 2 tested doses could be evaluated to further define the dose/exposure-response relationship. In Study M15-993, which tested RZB 180 mg SC q8w for 26 weeks in subjects who achieved clinical remission to RZB induction treatment, approximately 30% of subjects lost clinical remission and a majority did not achieve endoscopic remission or deep remission endpoints.

In the schematic, blue boxes identify the primary efficacy analysis set.




IR = induction response; IV = intravenous; PBO = placebo; q8w = every 8 weeks; RZB = risankizumab; SC = subcutaneous; Wk = week

Starting at Week 16, subjects who demonstrated loss of response during Sub-Study 1 based upon increased symptom activity and confirmation with objective markers of inflammation were eligible to receive OL risankizumab rescue therapy (risankizumab 1200 mg IV for one dose followed by risankizumab 360 mg SC q8w).

***Study participants***

Subjects were enrolled from M150991 or M16-006 into Sub-Study 1 if they achieved SF/APS clinical response to RZB (either at Week 12 of the 12-Week Induction Period or at Week 24 after Induction Period 2 (placebo up to Week 12).

For subjects receiving concomitant CS, tapering was mandatory starting at Week 0/re-randomisation. Initiation of, increase in dose, or decrease in dose of other concomitant CD-medications (i.e., ASA, oral locally acting CS, or IMM) was prohibited during the 52-Week maintenance period.

Starting at Week 16, subjects with loss of response were eligible to receive open label RZB rescue therapy - RZB 1200 mg IV x one dose, then RZB 360 mg SC q8w.

Subjects who initiated new or had a dose escalation of CS, or who received OL rescue treatment were categorized as non-responders for primary efficacy analyses of co-primary endpoints.

The target for enrolment was 450 subjects, with enrolment duration extended to include ≤ 15% more subjects to mitigate against potential missed visits due the onset of the Covid-19 pandemic.

***Treatments***

Subjects were randomized 1:1:1 to receive either RZB 360 mg SC *or* RZB 180 mg SC *or* PBO.

PBO was matched (IV and SC) to maintain blinding.

Dosing occurred every 8 weeks: Week 0, 8, 16, 24, 32, 40 and 48.

***Objectives***

To evaluate the efficacy and safety of continuing RZB as maintenance therapy vs. withdrawing RZB treatment in subjects with moderately to severely active CD who responded to intravenous RZB IV induction treatment in study M16-006 or M15-991 and who had a Baseline of induction eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease).

### *2.6.5.3. Outcomes/endpoints*

**Co-primary endpoint at Week 52**

The co-primary endpoint, at week 52, was similar to that of the induction studies:

- the achievement of clinical remission (SF/APS) and
- the achievement of endoscopic response.

(For the US protocol co-primary endpoints were CDAI clinical remission at Week 52 and the proportion of subjects with endoscopic response at Week 52.)

**Key secondary endpoints at/by Week 52**

Most key secondary endpoints at or by Week 52 were similar to the induction studies, with differing rank order. There was no endpoint for fistula or EIMS evaluation; there were 4 new endpoints based on SF/APS.

**Key Secondary Endpoints for Phase 3 Efficacy Studies for OUS Protocol**

| **Induction Studies M15-991 and M16-006** | **Maintenance Study M16-000** |
|---|---|
| **OUS Protocol** | **OUS Protocol** |
| CDAI remission at Week 12 | CDAI clinical remission at Week 52 |
| CDAI clinical response at Week 4 | Maintenance of SF/APS clinical remission at Week 52 |
| SF/APS clinical remission at Week 4 | Ulcer-free endoscopy at Week 52 |
| CDAI clinical response at Week 12 | Endoscopic remission at Week 52 |
| Change from baseline in FACIT- Fatigue at Week 12 | Change from baseline of induction in IBDQ total score at Week 52 |
| Change from baseline in IBDQ at Week 12 | Change from baseline of induction in FACIT-Fatigue at Week 52 |
| Enhanced SF/APS clinical response and endoscopic response at Week 12 | Corticosteroid-free SF/APS clinical remission at Week 52 |
| Endoscopic remission at Week 12 | CDAI clinical response at Week 52 |
| Enhanced SF/APS clinical response at Week 4 | SF/APS clinical remission and endoscopic response at Week 52 |
| Ulcer-free endoscopy at Week 12 | Enhanced clinical response at Week 52 |
| Enhanced SF/APS clinical response at Week 12 | Deep remission (SF/APS) at Week 52 |

Endpoint definitions as per protocol:

| | |
|---|---|
| Clinical remission | average daily SF ≤ 2.8 and not worse than Baseline of the induction study AND average daily AP score ≤ 1 and not worse than Baseline of the induction study |

| | |
|---|---|
| Enhanced clinical response | ≥ 60% decrease in average daily SF and/or ≥ 35% decrease in average daily AP score and both not worse than Baseline of the induction study, and/or clinical remission |
| Clinical response | ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score and both not worse than Baseline of the induction study |
| Endoscopic response | decrease in SES-CD > 50% from Baseline of the induction study (or for subjects with isolated ileal disease and an SES-CD of 4 at Baseline of the induction study, at least a 2 point reduction from Baseline of the induction study), as scored by central reviewer |
| Ulcer-free endoscopy | SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore ≥ 1 at Baseline of the induction study, as scored by a central reviewer |
| Endoscopic remission | SES-CD ≤ 4 and at least a 2point reduction versus baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer |
| Deep remission | CDAI clinical remission and endoscopic remission |
| CDAI clinical response | reduction of CDAI ≥ 100 points from baseline of the induction study |
| CDAI clinical remission | CDAI < 150 |
| SF remission | average daily SF ≤ 2.8 and not worse than baseline |
| AP remission | average daily AP score ≤ 1 and not worse than baselinens as per protocol: |

There were additional endpoints to evaluate efficacy, PK & immunogenicity and safety evaluations. Exposure adjusted occurrence of CD-related hospitalisations from Week 0 to Week 52 was assessed. Endpoints were, in the main, similar to the induction studies and are not further discussed here.

#### *2.6.5.4. Sample size*

For sample size calculations it was assumed that the Week 52 rate of clinical remission (SF/APS) would be 38.7% for one of the RZB arms vs. 20% in the PBO arm. A sample size of 150 subjects per arm was determined to have 93% power to detect treatment differences between one of the RZB arms and PBO, using Fisher's exact test at an alpha of 0.05 (two-sided).

Using this sample size (n=150 per arm), assuming the Week 52 endoscopic response rate would be 32.6% for one of the RZB arms vs. 10% in the PBO arm, power would be >95% to detect a treatment difference between the RZB arms and PBO, using Fisher's exact test at an alpha of 0.05 (two-sided).

#### *2.6.5.5. Randomisation*

All subjects were to maintain the unique identification number assigned at the Screening visit of M16-006 or M15-991 and were to be centrally re-randomised by web-based IRT for Sub-Study 1.

Enrolled subjects, re-randomized into 2 RZB dose arms or PBO arm 1:1:1 (150 subjects per arm), were stratified by endoscopic response (per local read), clinical remission status from the last visit of M16-006 or M15-998 and RZB induction dose (600 mg or 1200mg IV).

#### *2.6.5.6. Blinding (masking)*

Participants, those administering interventions and those assessing outcomes were blinded to group assignment. PBO and RZB (IV or SC) presentations were identical in match to maintain blinding.

Applicant personnel with direct oversight of the conduct and management of the study, the Investigators, blinded study site personnel and subjects were to remain blinded to study treatment throughout the blinded period of the study. The Investigator was able to access the IRT system to break the blind in case of a medical emergency.

#### *2.6.5.7. Statistical methods*

*Efficacy*

The comparisons between each of the RZB dose arms vs. PBO for the primary efficacy variable were performed using the Cochran-Mantel-Haenszel (CMH) test adjusted by M16-000 Week 0 SF/APS clinical remission status and M16-000 Week 0 endoscopic response status (per central read), and last RZB induction dose.

A multiple testing procedure was used to provide strong control of the Type I error rate at alpha = 0.05 (2 sided) across analyses comparing each RZB dose arm to PBO with respect to the co primary endpoints and key secondary endpoints. A CMH based two-sided 95% confidence interval (CI) for the difference between treatment arms was calculated.

Continuous secondary efficacy variables collected at only one post-Week 0 visit were analyzed using an analysis of covariance (ANCOVA) model including treatment, stratification factors, and measurements at both induction Baseline and Week 0.

The primary analysis was conducted in the Intent-to-Treat (ITT) 1A population, which included the randomized subjects in the ITT1 set (subjects who received at least 1 dose of study drug) who had eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease) at Baseline of the induction study and received RZB IV for only 1 period of 12 weeks in the induction study.

*Results*

**Participant flow**

Sub-study 1 enrolled 712 subjects from the induction studies, across 273 sites worldwide (ITT1).

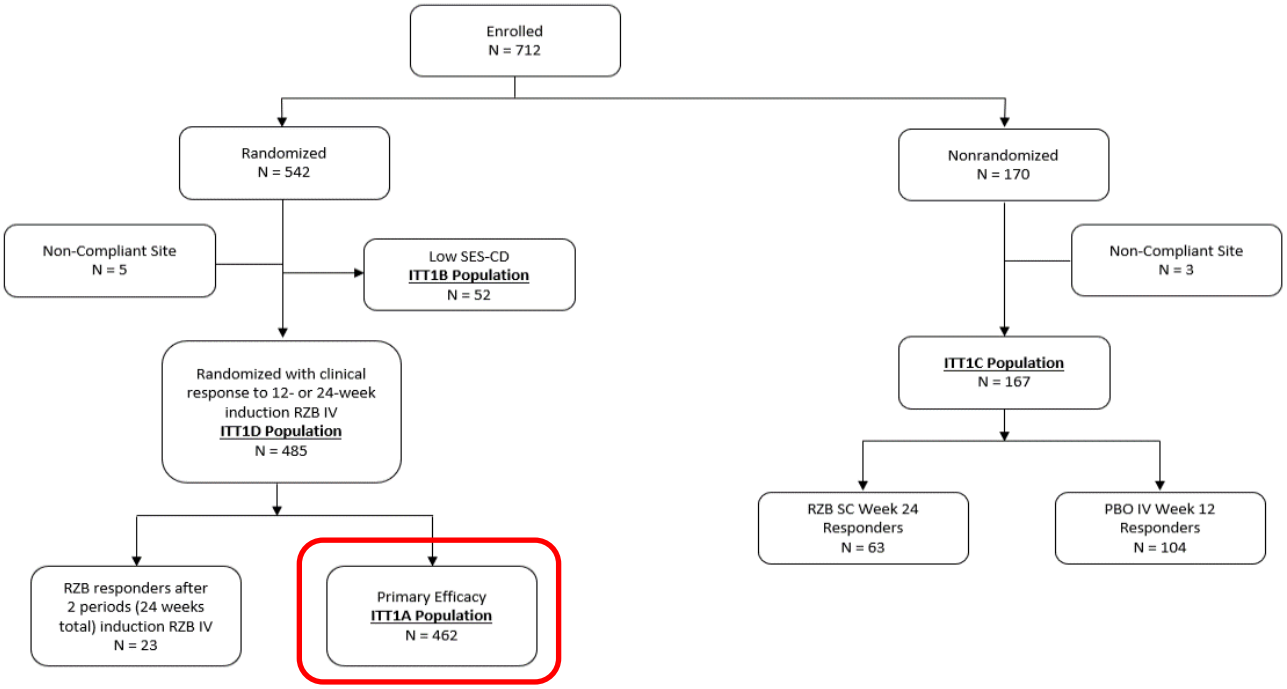
Of these, 542 subjects entered the randomised group.

Of these, 52 subjects were found to have a low SES-CD score and were excluded from primary analysis (ITT1B). In addition, the data of 5 subjects was excluded from efficacy analysis prior to DBL, due to identified site non-compliance.

Of 485 subjects remaining, 23 subjects were excluded from primary analysis as their treatment response came after 24 weeks of RZB induction treatment, rather than 12 weeks.

The remaining 462 subjects (outlined in red in the diagram below) form the ITT1A population, the primary population for efficacy analysis in Sub-Study 1. ITT1A randomized subjects had eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease) at Baseline of the study and received IV risankizumab for only 1 period of 12 weeks in the induction studies M15-991 or M16-006.

**M16-000 Sub-Study 1 ITT1 Population**




ITT1A subjects were re-randomised to the RZB 180 mg SC arm (n=157) or the RZB 360 mg SC arm (n=141) or the Withdrawal/Placebo SC arm (n=164).

As shown in the table below, a similar percentage (87-92%) completed study drug across the 3 arms.

TABLE 14.1__2.1

Subject Final Status and All Reasons for Study Discontinuation
(ITT1A Population)

| | Placebo SC (N=164) n (%) | Risankizumab 180 mg SC (N=157) n (%) | Risankizumab 360 mg SC (N=141) n (%) | Total (N=462) n (%) |
|---|---|---|---|---|
| COMPLETED STUDY | 144 (87.8) | 144 (91.7) | 124 (87.9) | 412 (89.2) |
| DISCONTINUATION DUE TO (PRIMARY REASON) | | | | |
| ANY REASON | 20 (12.2) | 13 (8.3) | 17 (12.1) | 50 (10.8) |
| ADVERSE EVENT | 3 (1.8) | 2 (1.3) | 4 (2.8) | 9 (1.9) |
| LACK OF EFFICACY | 9 (5.5) | 5 (3.2) | 6 (4.3) | 20 (4.3) |
| LOST TO FOLLOW-UP | 0 | 2 (1.3) | 2 (1.4) | 4 (0.9) |
| WITHDRAWAL BY SUBJECT | 2 (1.2) | 2 (1.3) | 0 | 4 (0.9) |
| COVID-19 INFECTION | 0 | 0 | 0 | 0 |
| COVID-19 LOGISTICAL RESTRICTIONS | 0 | 0 | 1 (0.7) | 1 (0.2) |
| OTHER | 6 (3.7) | 2 (1.3) | 4 (2.8) | 12 (2.6) |
| DISCONTINUATION DUE TO (ALL REASONS) [A] | | | | |
| ANY REASON | 20 (12.2) | 13 (8.3) | 17 (12.1) | 50 (10.8) |
| ADVERSE EVENT | 4 (2.4) | 2 (1.3) | 5 (3.5) | 11 (2.4) |
| LACK OF EFFICACY | 9 (5.5) | 5 (3.2) | 6 (4.3) | 20 (4.3) |
| LOST TO FOLLOW-UP | 0 | 2 (1.3) | 3 (2.1) | 5 (1.1) |
| WITHDRAWAL BY SUBJECT | 3 (1.8) | 2 (1.3) | 1 (0.7) | 6 (1.3) |
| COVID-19 INFECTION | 0 | 0 | 0 | 0 |
| COVID-19 LOGISTICAL RESTRICTIONS | 1 (0.6) | 0 | 1 (0.7) | 2 (0.4) |
| OTHER | 6 (3.7) | 2 (1.3) | 4 (2.8) | 12 (2.6) |
| SUBJECTS RECEIVING RESCUE MEDICATION | 66 (40.2) | 38 (24.2) | 30 (21.3) | 134 (29.0) |

Note: ITT1A Population includes the randomized subjects in the intent-to-treat population who received IV risankizumab for only one period of 12 weeks in the induction study M16-006 or M15-991 and at least one dose of study drug in the sub-study 1, and had eligible SES-CD of >= 6 (>= 4 for isolated ileal disease) at baseline of induction study.
Percentages calculated on N in the header.
[A] Subjects who discontinued study were counted under each reason given for discontinuation, therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.

Mean treatment compliance among randomized subjects was reported as > 99.0% across treatment arms.

The most common primary reason for discontinuation was:

- RZB 180 mg SC - lack of efficacy (5/157; 3.2%); AE, lost to follow-up, subject withdrawal or another reason (each 2/157; 1.3%)
- RZB 360 mg SC arm - lack of efficacy (6/141; 4.3%); AE or another reason (each 4/141; 2.8%).
- PBO arm - lack of efficacy (9/164; 5.5%); another reason (6/164; 3.7%); AE (3/164; 1.8%).

No subjects were discontinued due to Covid-19; 1 subject (RZB 360 mg SC arm) discontinued due to Covid 19 logistical restrictions (<1%).

The number of subjects who received rescue medication was:

RZB 180 mg SC (38/157; 24.2%) vs. RZB 360 mg SC (30/141; 21.3%) vs. PBO (66/164; 40.2%)

**Protocol Deviations**

The data of 5 subjects was excluded from efficacy analysis prior to data base lock, in line with the pre-specified SAP, due to investigator non-compliance.

For the remaining ITT1A population (n=462) similar rates of subjects with at least one protocol deviation were reported across treatment arms (14.6-15.3%), most commonly receiving excluded concomitant treatment (9.2-13.4%) followed by inclusion criteria deviations (1.8-5.0%).

The protocol deviations were not considered to have affected the study or interpretation of study results or conclusions.

TABLE 14.1 4

Summary of Major Protocol Deviations
(ITT1A Population)

| Protocol Deviation@ | Placebo SC (N=164) n (%) | Risankizumab 180 mg SC (N=157) n (%) | Risankizumab 360 mg SC (N=141) n (%) | Total (N=462) n (%) |
|---|---|---|---|---|
| Subjects who had at least one protocol deviation | 24 (14.6) | 24 (15.3) | 21 (14.9) | 69 (14.9) |
| Subject entered into the study even though did not satisfy entry criteria | 3 (1.8) | 5 (3.2) | 7 (5.0) | 15 (3.2) |
| Inclusion criteria | | | | |
| 1 | 0 | 0 | 2 (1.4) | 2 (0.4) |
| 2 | 3 (1.8) | 5 (3.2) | 3 (2.1) | 11 (2.4) |
| Any inclusion criteria not met | 3 (1.8) | 5 (3.2) | 5 (3.5) | 13 (2.8) |
| Exclusion criteria | | | | |
| 1 | 0 | 0 | 2 (1.4) | 2 (0.4) |
| Any exclusion criteria met | 0 | 0 | 2 (1.4) | 2 (0.4) |
| Subject received wrong treatment or incorrect dose | 1 (0.6) | 3 (1.9) | 1 (0.7) | 5 (1.1) |
| Subject received excluded concomitant treatment | 22 (13.4) | 16 (10.2) | 13 (9.2) | 51 (11.0) |
| Subject developed withdrawal criteria during the study and was not withdrawn | 0 | 0 | 0 | 0 |

**Recruitment**

First subject first visit: 09 April 2018; Last subject last visit: 26 April 2021; Database lock 15 May 2021

Enrolment duration was extended to include up to 15% more subjects to mitigate against potential missed visits due the onset of the Covid-19 pandemic.

**Conduct of the study**

According to the protocol dated 26 April 2021, 9 amendments were made to the original protocol dated 17 February 2017. Some amendment aspects were discussed under SA with regulatory authorities e.g. sample size and endpoint definitions and rankings (see Clinical AR for detail).

None of the approved amendments were considered to have affected the interpretation of the M16-000 Sub-Study 1 analysis and all were approved before data base lock for Sub-Study 1 on 15 May 2021.

Significant non-compliance was identified at one investigational site  before the database lock. As was pre-specified in the final SAP, for the subjects (n=8) enrolled at this investigational site efficacy data was excluded and safety data included in statistical analyses.

**Baseline data**

***Intent-to-Treat (ITT) 1A population***

Key baseline demographics were generally balanced across the 3 treatment arms. Overall, the majority of subjects were white, not Hispanic or Latino, aged 18 to < 40 years and of normal weight (BMI).

*Table 40 Baseline demographics of ITT1A population*

| Variable | Withdrawal (Placebo SC)[a] (N = 164) | Risankizumab 180 mg SC (N = 157) | Risankizumab 360 mg SC (N = 141) | Total (N = 462) |
|---|---|---|---|---|
| Sex – n (%) | | | | |
| Female | 75 (45.7) | 89 (56.7) | 60 (42.6) | 224 (48.5) |
| Male | 89 (54.3) | 68 (43.3) | 81 (57.4) | 238 (51.5) |
| Age (years) | | | | |
| N | 164 | 157 | 141 | 462 |
| Mean (SD) | 38.0 (12.95) | 39.1 (14.76) | 37.0 (12.81) | 38.1 (13.55) |
| Median | 37.0 | 37.0 | 35.0 | 35.5 |
| Min, Max | 17, 76 | 16, 75 | 16, 71 | 16, 76 |
| Age category – n (%) | | | | |
| < 18 | 1 (0.6) | 2 (1.3) | 2 (1.4) | 5 (1.1) |
| [18, 40) | 95 (57.9) | 88 (56.1) | 86 (61.0) | 269 (58.2) |
| [40, 65) | 62 (37.8) | 54 (34.4) | 47 (33.3) | 163 (35.3) |
| ≥ 65 | 6 (3.7) | 13 (8.3) | 6 (4.3) | 25 (5.4) |
| Race – n (%) | | | | |
| White | 126 (76.8) | 127 (80.9) | 111 (78.7) | 364 (78.8) |
| Black or African American | 10 (6.1) | 4 (2.5) | 8 (5.7) | 22 (4.8) |
| Asian | 28 (17.1) | 22 (14.0) | 20 (14.2) | 70 (15.2) |
| American Indian/Alaska Native | 0 | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 (0.6) | 0 | 1 (0.2) |
| Multiple | 0 | 3 (1.9) | 2 (1.4) | 5 (1.1) |
| Ethnicity – n (%) | | | | |
| Hispanic/Latino | 7 (4.3) | 8 (5.1) | 7 (5.0) | 22 (4.8) |
| Non-Hispanic/Latino | 157 (95.7) | 149 (94.9) | 134 (95.0) | 440 (95.2) |
| Geographic region – n (%) | | | | |
| North America | 50 (30.5) | 39 (24.8) | 38 (27.0) | 127 (27.5) |
| South/Central America | 2 (1.2) | 4 (2.5) | 0 | 6 (1.3) |
| Western Europe | 52 (31.7) | 55 (35.0) | 46 (32.6) | 153 (33.1) |
| Eastern Europe | 22 (13.4) | 27 (17.2) | 30 (21.3) | 79 (17.1) |
| Asia | 26 (15.9) | 21 (13.4) | 20 (14.2) | 67 (14.5) |
| Other | 12 (7.3) | 11 (7.0) | 7 (5.0) | 30 (6.5) |
| Body weight (kg) | | | | |
| N | 164 | 157 | 141 | 462 |
| Mean (SD) | 71.759 (19.1794) | 69.230 (16.2090) | 70.411 (17.5205) | 70.488 (17.7006) |
| Median | 67.500 | 67.000 | 68.600 | 67.850 |
| Min, Max | 36.60, 147.50 | 38.10, 126.70 | 39.00, 140.00 | 36.60, 147.50 |
| Body weight category - n(%) | | | | |
| < 60 kg | 49 (29.9) | 48 (30.6) | 40 (28.4) | 137 (29.7) |
| ≥ 60 kg | 115 (70.1) | 109 (69.4) | 101 (71.6) | 325 (70.3) |
| BMI (kg/m²) | | | | |
| N | 164 | 157 | 141 | 462 |
| Mean (SD) | 24.79 (6.287) | 24.35 (5.358) | 23.85 (5.374) | 24.35 (5.710) |
| Median | 23.85 | 23.04 | 22.54 | 23.46 |
| Min, Max | 13.0, 54.1 | 15.5, 41.5 | 15.1, 46.2 | 13.0, 54.1 |
| BMI category - n(%) | | | | |
| Underweight [< 18.5 kg/m²] | 19 (11.6) | 17 (10.8) | 16 (11.3) | 52 (11.3) |
| Normal [≥ 18.5 and < 25 kg/m²] | 83 (50.6) | 81 (51.6) | 80 (56.7) | 244 (52.8) |
| Overweight [≥ 25 and < 30 kg/m²] | 36 (22.0) | 34 (21.7) | 29 (20.6) | 99 (21.4) |
| Obese [≥ 30 kg/m²] | 26 (15.9) | 25 (15.9) | 16 (11.3) | 67 (14.5) |

*Table 41 Disease characteristics at Baseline of Induction study and Week 0 of Sub-Study 1(ITT1A)*

| | Variable | Withdrawal (PBO SC)[a] (N = 164) | RZB 180 mg SC (N = 157) | RZB 360 mg SC (N = 141) | Total (N = 462) |
|---|---|---|---|---|---|
| Induction Study Baseline | CD duration in years, n | 164 | 157 | 141 | 462 |
| | Mean (SD) | 9.613 (8.7694) | 10.768 (10.2375) | 9.296 (8.0708) | 9.909 (9.1014) |
| | Median (Min, Max) | 7.498 (0.068, 52.624) | 7.055 (0.151, 47.567) | 6.598 (0.416, 47.622) | 7.102 (0.068, 52.624) |
| | Biologics failure history | | | | |
| | 0, n (%) | 41 (25.0) | 44 (28.0) | 39 (27.7) | 124 (26.8) |
| | 1, n (%) | 60 (36.6) | 42 (26.8) | 51 (36.2) | 153 (33.1) |
| | > 1, n (%) | 63 (38.4) | 71 (45.2) | 51 (36.2) | 185 (40.0) |
| | Baseline CDAI, n | 164 | 157 | 141 | 462 |
| | Mean (SD) | 307.38 (64.860) | 323.21 (67.586) | 308.92 (61.130) | 313.23 (64.960) |
| | Median (Min, Max) | 296.90 (179.3, 550.5) | 315.00 (220.3, 623.8) | 307.30 (131.9, 445.0) | 305.70 (131.9, 623.8) |
| | Average Daily SF, n | 164 | 157 | 141 | 462 |
| | Mean (SD) | 5.751 (2.6943) | 6.054 (3.2268) | 5.868 (2.6008) | 5.890 (2.8567) |
| | Median (Min, Max) | 5.143 (0.000, 20.286) | 5.429 (0.143, 24.143) | 5.571 (0.429, 17.836) | 5.429 (0.000, 24.143) |
| | Average Daily AP, n | 164 | 157 | 141 | 462 |
| | Mean (SD) | 1.875 (0.5169) | 2.006 (0.4611) | 1.848 (0.5437) | 1.911 (0.5108) |
| | Median (Min, Max) | 2.000 (0.286, 3.000) | 2.000 (0.429, 3.000) | 2.000 (0.000, 3.000) | 2.000 (0.000, 3.000) |
| | Baseline SES-CD, n | 164 | 157 | 141 | 462 |
| | Mean (SD) | 14.0 (7.10) | 14.7 (7.05) | 14.3 (7.36) | 14.3 (7.16) |
| | Median (Min, Max) | 13.0 (4, 34) | 13.0 (4, 36) | 12.0 (4, 37) | 13.0 (4, 37) |

| | Variable | Withdrawal (PBO SC)[a] (N = 164) | RZB 180 mg SC (N = 157) | RZB 360 mg SC (N = 141) | Total (N = 462) |
|---|---|---|---|---|---|
| Induction Study Baseline | Baseline hs-CRP (mg/L), n | 162 | 156 | 140 | 458 |
| | Mean (SD) | 17.153 (25.4597) | 17.041 (21.4348) | 22.782 (28.6244) | 18.836 (25.3037) |
| | Median (Min, Max) | 7.670 (0.26, 181.00) | 8.415 (0.39, 151.00) | 10.050 (0.25, 129.00) | 8.470 (0.25, 181.00) |
| | Baseline FCP (mg/kg), n | 140 | 120 | 114 | 374 |
| | Mean (SD) | 1640.7 (2055.69) | 2829.3 (4700.09) | 2182.5 (2471.67) | 2187.2 (3273.84) |
| | Median (Min, Max) | 794.5 (30, 11378) | 1561.0 (30, 28800) | 1543.0 (30, 14649) | 1293.5 (30, 28800) |
| | Baseline corticosteroid use | | | | |
| | Yes, n (%) | 51 (31.1) | 51 (32.5) | 42 (29.8) | 144 (31.2) |
| | No, n (%) | 113 (68.9) | 106 (67.5) | 99 (70.2) | 318 (68.8) |
| | Baseline immunomodulator use | | | | |
| | Yes, n (%) | 40 (24.4) | 41 (26.1) | 40 (28.4) | 121 (26.2) |
| | No, n (%) | 124 (75.6) | 116 (73.9) | 101 (71.6) | 341 (73.8) |
| Sub-Study 1 Wk 0 | CDAI, n | 163 | 157 | 138 | 458 |
| | Mean (SD) | 133.58 (80.643) | 132.83 (75.776) | 137.22 (67.701) | 134.42 (75.119) |
| | Median (Min, Max) | 126.00 (0.0, 380.0) | 121.00 (0.0, 377.0) | 140.25 (0.0, 302.3) | 129.20 (0.0, 380.0) |
| | Average Daily SF, n | 163 | 157 | 139 | 459 |
| | Mean (SD) | 1.820 (1.8383) | 2.163 (1.9917) | 2.080 (1.7701) | 2.016 (1.8742) |
| | Median (Min, Max) | 1.429 (0.000, 11.143) | 2.000 (0.000, 11.857) | 1.857 (0.000, 8.571) | 1.714 (0.000, 11.857) |

| | Variable | Withdrawal (PBO SC)[a] (N = 164) | RZB 180 mg SC (N = 157) | RZB 360 mg SC (N = 141) | Total (N = 462) |
|---|---|---|---|---|---|
| Sub-Study 1 Wk 0 | Average Daily AP, n | 163 | 157 | 139 | 459 |
| | Mean (SD) | 0.746 (0.5830) | 0.716 (0.6367) | 0.728 (0.5848) | 0.730 (0.6013) |
| | Median (Min, Max) | 0.857 (0.000, 2.143) | 0.714 (0.000, 3.000) | 0.857 (0.000, 2.286) | 0.857 (0.000, 3.000) |
| | SES-CD, n | 162 | 151 | 136 | 449 |
| | Mean (SD) | 7.6 (6.61) | 7.9 (6.44) | 8.5 (7.34) | 8.0 (6.78) |
| | Median (Min, Max) | 6.0 (0, 32) | 7.0 (0, 33) | 7.0 (0, 32) | 7.0 (0, 33) |
| | hs-CRP (mg/L), n | 164 | 157 | 141 | 462 |
| | Mean (SD) | 6.945 (8.8451) | 6.480 (7.7915) | 10.457 (26.2484) | 7.859 (16.1384) |
| | Median (Min, Max) | 4.070 (0.20, 53.40) | 3.730 (0.20, 47.90) | 3.900 (0.20, 258.00) | 3.830 (0.20, 258.00) |
| | FCP (mg/kg), n | 158 | 150 | 136 | 444 |
| | Mean (SD) | 1126.8 (3107.67) | 1121.7 (2712.06) | 1065.9 (1716.87) | 1106.4 (2606.83) |
| | Median (Min, Max) | 307.0 (30, 28013) | 412.5 (30, 28800) | 424.0 (30, 14804) | 363.5 (30, 28800) |

PBO = placebo; RZB = risankizumab; % calculated on non-missing values

The clinical characteristics were generally similar and balanced across arms at Baseline of Induction and at Week 0 of Sub-Study 1, apart from a higher hs-CRP in the RZB 360 mg SC arm.

At Baseline of induction CS use (PBO 31.1%; RZB 180 mg SC 32.5%; RZB 360 mg SC 29.8%) and IMM use (PBO 24.4%; RZB 180 mg SC 26.1%; RZB 360 mg SC 28.4%) were similar.

At Baseline of the Induction study, overall approximately 27% had not failed a biologic, approximately 33% had failed 1 prior biologic and approximately 40% had failed >1 prior biologic (see table below).

Number of Prior Crohn's Disease-Related Biologics Failed of the Induction Study per Subject (ITT1A Population)

| Number of Prior Crohn's Disease-Related Biologics Failed of the Induction Study | Placebo SC (N=164) n (%) | Risankizumab 180 mg SC (N=157) n (%) | Risankizumab 360 mg SC (N=141) n (%) | Total (N=462) n (%) |
|---|---|---|---|---|
| 0 | 41 (25.0) | 44 (28.0) | 39 (27.7) | 124 (26.8) |
| 1 | 60 (36.6) | 42 (26.8) | 51 (36.2) | 153 (33.1) |
| 2 | 36 (22.0) | 43 (27.4) | 27 (19.1) | 106 (22.9) |
| 3 | 22 (13.4) | 19 (12.1) | 17 (12.1) | 58 (12.6) |
| 4 | 4 (2.4) | 6 (3.8) | 7 (5.0) | 17 (3.7) |
| 5 | 0 | 3 (1.9) | 0 | 3 (0.6) |
| 6 | 1 (0.6) | 0 | 0 | 1 (0.2) |
| Subjects with > 1 Prior CD-Related Biologics Failed | 63 (38.4) | 71 (45.2) | 51 (36.2) | 185 (40.0) |

Note: ITT1A Population includes the randomized subjects in the intent-to-treat population who received IV risankizumab for only one period of 12 weeks in the induction study M16-006 or M15-991 and at least one dose of study drug in the sub-study 1, and had eligible SES-CD of >= 6 (>= 4 for isolated ileal disease) at baseline of induction study.
This table includes all Crohn's disease-related biologics use with a start date before the first study drug dose date of M15-991 or M16-006.
Biologics failed includes inadequate response or intolerance.
Percentages calculated based on N in the header.

Mean treatment compliance among randomized subjects was reported as > 99.0% across the RZB 180 mg SC, RZB 360 mg SC and PBO arms.

As detailed in the table 42, the use of concomitant CD-related medication at Baseline of the induction studies was reported by 66.2% of ITT1A subjects, most commonly CS (31.2%), IMM (26.2%) and, individually, mesalazine (26.2%) and azathioprine (20.8%).

*Table 42 CD-related medications reported at Baseline of Induction (ITT1A)*

| Generic Name (WHO 2018Q1) | Withdrawal (PBO SC)[a] (N = 164) n (%) | RZB 180 mg SC (N = 157) n (%) | RZB 360 mg SC (N = 141) n (%) | Total (N = 462) n (%) |
|---|---|---|---|---|
| **Any CD-Related Medication** | 107 (65.2) | 103 (65.6) | 96 (68.1) | 306 (66.2) |
| **Aminosalicylates** | 48 (29.3) | 37 (23.6) | 45 (31.9) | 130 (28.1) |
| Mesalazine | 47 (28.7) | 35 (22.3) | 39 (27.7) | 121 (26.2) |
| Sulfasalazine | 1 (0.6) | 2 (1.3) | 6 (4.3) | 9 (1.9) |
| **Corticosteroids** | 51 (31.1) | 51 (32.5) | 42 (29.8) | 144 (31.2) |
| Beclometasone | 0 | 1 (0.6) | 0 | 1 (0.2) |
| Budesonide | 11 (6.7) | 9 (5.7) | 10 (7.1) | 30 (6.5) |
| Meprednisone | 1 (0.6) | 1 (0.6) | 0 | 2 (0.4) |
| Methylprednisolone | 11 (6.7) | 6 (3.8) | 3 (2.1) | 20 (4.3) |
| Prednisolone | 12 (7.3) | 12 (7.6) | 11 (7.8) | 35 (7.6) |
| Prednisone | 16 (9.8) | 22 (14.0) | 18 (12.8) | 56 (12.1) |
| **Immunomodulators** | 40 (24.4) | 41 (26.1) | 40 (28.4) | 121 (26.2) |
| Azathioprine | 33 (20.1) | 31 (19.7) | 32 (22.7) | 96 (20.8) |
| Mercaptopurine | 2 (1.2) | 4 (2.5) | 3 (2.1) | 9 (1.9) |
| Methotrexate | 5 (3.0) | 6 (3.8) | 5 (3.5) | 16 (3.5) |

| | | | | |
|---|---|---|---|---|
| **Antibiotics** | 5 (3.0) | 4 (2.5) | 1 (0.7) | 10 (2.2) |
| Ciprofloxacin | 2 (1.2) | 3 (1.9) | 0 | 5 (1.1) |
| Co-Trimoxazole | 0 | 1 (0.6) | 0 | 1 (0.2) |
| Levofloxacin | 1 (0.6) | 0 | 1 (0.7) | 2 (0.4) |
| Metronidazole | 1 (0.6) | 0 | 0 | 1 (0.2) |
| Rifaximin | 1 (0.6) | 0 | 0 | 1 (0.2) |
| **Anti-Diarrheal** | 15 (9.1) | 15 (9.6) | 8 (5.7) | 38 (8.2) |
| Bismuth | 1 (0.6) | 0 | 0 | 1 (0.2) |
| Codeine | 1 (0.6) | 0 | 0 | 1 (0.2) |
| Lomotil | 1 (0.6) | 1 (0.6) | 2 (1.4) | 4 (0.9) |
| Loperamide | 13 (7.9) | 14 (8.9) | 6 (4.3) | 33 (7.1) |
| Racecadotril | 1 (0.6) | 0 | 0 | 1 (0.2) |

**Outcomes and estimation**

The ITT1A efficacy analysis set, described below, contained 462 subjects in 3 arms: PBO (n=164) vs RZB 180mg SC (n=157) vs. RZB 360 mg SC (n=141).

*Maintenance Intent-to-Treat Efficacy Analysis Set ITT1A*

| Analysis Population | Study | Definition | Objective |
|---|---|---|---|
| **ITT1A** | M16-000 Sub-Study 1 | Subjects who were randomized and received at least one dose of study drug in Sub-Study 1 and received 12-weeks of risankizumab IV for only one period of induction and had a baseline SES-CD excluding the narrowing component of ≥ 6, or ≥ 4 for isolated ileal disease, confirmed by a blinded central reviewer; excludes subjects from a non-compliant site | **Primary efficacy population for the 52-week maintenance study**<br>Evaluate the efficacy of risankizumab SC maintenance treatment versus withdrawal (placebo SC) in subjects who responded to 12-weeks of risankizumab IV induction treatment |

*Results and Analysis*

*Table 43 - Primary Efficacy Results of Pivotal Maintenance Phase 3 Study M16-000*

| | Randomized Subjects | | | Adjusted Treatment Difference | |
|---|---|---|---|---|---|
| | **WD (PBO) SC N = 164 n (%)** | **RZB 180 mg SC N = 157 n (%)** | **RZB 360 mg SC N = 141 n (%)** | **Δ RZB 180 mg SC – PBO (95% CI)** | **Δ RZB 360 mg SC – PBO (95% CI)** |
| US Protocol | | | | | |
| CDAI clinical remission at Week 52[a] | 67 (40.9) | 87 (55.4) | 74 (52.2) | 14.7 (5.0, 24.5) **S | 14.6 (4.3, 25.0) **S |
| Endoscopic response at Week 52[b] | 36 (22.0) | 74 (47.1) | 66 (46.5) | 26.0 (17.2, 34.7) ***S | 27.8 (18.7, 37.0) ***S |
| OUS Protocol | | | | | |
| SF/APS clinical remission at Week 52[c] | 65 (39.6) | 73 (46.5) | 73 (51.8) | 7.7 (-2.1, 17.5) NS | 15.2 (4.9, 25.4) **S |
| Endoscopic response at Week 52[b] | 36 (22.0) | 74 (47.1) | 66 (46.5) | 26.0 (17.2, 34.7) ***NS | 27.8 (18.7, 37.0) ***S |

a. CDAI clinical remission: CDAI < 150.

b. Endoscopic response: decrease in SES-CD > 50% from baseline (or for subjects with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), as scored by central reviewer.

c. SF/APS clinical remission: average daily SF ≤ 2.8 and not worse than baseline and average daily APS ≤ 1 and not worse than baseline.

S, NS The endpoint achieved or did not achieve, statistical significance based on the pre-specified graphical testing procedure.

** P value ≤ 0.01; *** P value < 0.001.

In Sub-Study 1, the co-primary endpoints of clinical remission (SF/APS) and endoscopic response were met at Week 52 for RZB 360 mg SC vs. PBO.

- For the endpoint of clinical remission, the difference in favour of RZB treatment, 15.2%, was statistically significant (p=0.004, 95% CI 4.9-25.4%).
- For the endpoint of endoscopic response, the difference in favour of RZB treatment, 27.8%, was statistically significant (p<0.001, 95% CI 18.7-37%).

By Week 52, 51.8% (73/141) of patients on RZB 360 mg SC maintenance treatment achieved clinical remission (SF/APS) vs 39.6% (65/164) PBO; 46.5% (66/141) of patients on RZB 360 mg SC maintenance treatment achieved endoscopic response vs 22.0% (36/164) PBO.

The co-primary endpoint of clinical remission (SF/APS) was not met at 52 weeks for RZB 180 mg SC vs. PBO - the difference in favour of RZB treatment, 7.7%, was not statistically significant (95% CI -2.1-17.5%). As per the pre-defined graphical testing procedure for the OUS protocol, testing was halted and therefore no secondary endpoints achieved statistical significance. Therefore, results for the key secondary endpoints are presented with nominal *P* values.

As noted in table above, for the US protocol, the study met the co-primary endpoints of CDAI clinical remission and endoscopic response for the RZB 180 mg SC and RZB 360 mg SC arms vs. PBO (*P* values ≤ 0.01 for both endpoints).

*Table 44 CSE Table – Key Secondary Endpoints for M16-001 Sub-Study 1 ITT1A (OUS)*

| | WD (PBO SC) | | RZB 180 mg SC | | RZB 360 mg SC | | Adjusted Treatment Difference[a] | |
|---|---|---|---|---|---|---|---|---|
| Secondary Endpoints[b] | N | n (%) or LSMean (SE) | N | n (%) or LSMean (SE) | N | n (%) or LSMean (SE) | Δ RZB 180 mg SC – PBO (95% CI) | Δ RZB 360 mg SC – PBO (95% CI) |
| CDAI clinical remission at Week 52 | 164 | 67 (40.9) | 157 | 87 (55.4) | 141 | 74 (52.2) | 14.7 (5.0, 24.5) **NS | 14.6 (4.3, 25.0) **NS |
| SF/APS clinical remission at Week 52 among subjects with clinical remission at Week 0 | 91 | 46 (50.5) | 92 | 59 (64.1) | 72 | 50 (69.2) | 14.4 (0.5, 28.3) *NS | 21.0 (6.5, 35.5) **NS |
| Ulcer-free endoscopy at Week 52 | 162 | 17 (10.5) | 157 | 38 (24.2) | 141 | 43 (30.5) | 13.9 (6.6, 21.2) ***NS | 22.0 (14.3, 29.7) ***NS |
| Endoscopic remission at Week 52 | 164 | 21 (12.8) | 157 | 47 (29.9) | 141 | 55 (39.1) | 17.2 (9.3, 25.0) ***NS | 28.5 (19.9, 37.0) ***NS |
| Change from Baseline of induction study in IBDQ total score at Week 52 | 93 | 56.4 (2.62) | 117 | 60.9 (2.33) | 104 | 62.2 (2.43) | 4.5 (–2.3, 11.3) NS | 5.8 (–1.2, 12.8) NS |
| Change from Baseline of induction study in FACIT-Fatigue at Week 52 | 93 | 15.0 (0.85) | 117 | 15.5 (0.76) | 104 | 15.4 (0.80) | 0.5 (–1.7, 2.7) NS | 0.4 (–1.9, 2.7) NS |
| Corticosteroid-free use for 90 days and SF/APS clinical remission at Week 52 among subjects taking steroids at Baseline of induction study | 51 | 12 (23.5) | 51 | 22 (43.1) | 42 | 14 (34.0) | 19.3 (3.3, 35.2) *NS | 11.4 (-3.3, 26.1) NS |
| CDAI clinical response at Week 52 | 164 | 79 (48.2) | 157 | 105 (66.9) | 141 | 87 (61.6) | 18.8 (8.8, 28.8) ***NS | 16.2 (5.7, 26.6) **NS |
| SF/APS Clinical remission and endoscopic response at Week 52 | 164 | 27 (16.5) | 157 | 50 (31.8) | 141 | 49 (35.1) | 16.1 (8.1, 24.1) ***NS | 21.6 (12.8, 30.4) ***NS |
| Enhanced clinical response at Week 52 | 164 | 81 (49.4) | 157 | 97 (61.8) | 141 | 84 (59.5) | 12.9 (2.7, 23.1) *NS | 12.8 (2.2, 23.3) *NS |
| SF/APS Clinical remission and endoscopic remission at Week 52 | 164 | 16 (9.8) | 157 | 35 (22.3) | 141 | 39 (27.7) | 12.7 (5.4, 20.0) **NS | 20.2 (12.3, 28.2) ***NS |
| Exposure-adjusted CD-related hospitalizations from Week 0 through Week 52 | 164 | 8 (0.0580)[c] | 157 | 5 (0.0343)[c] | 141 | 9 (0.0711)[c] | –2.37 (–7.3931, 2.6526) NS | 1.31 (–4.8364, 7.4541) NS |
| Change from BL of induction study in SF-36 Physical Component Summary score at Week 52 | 92 | 11.3 (0.62) | 117 | 11.9 (0.56) | 103 | 12.0 (0.58) | 0.6 (–1.0, 2.2) NS | 0.6 (–1.1, 2.3) NS |

*Note: nominal p-values.*

As detailed in the table above, while not statistically significant, the following were in favour of RZB 360 mg SC over RZB 180 mg SC vs. PBO at Week 52:

- SF/APS clinical remission among subjects with clinical remission at Week 0
- Ulcer-free endoscopy
- Endoscopic remission
- Change from Baseline of induction study in IBDQ total score

- SF/APS Clinical remission and endoscopic response
- SF/APS Clinical remission and endoscopic remission
- Change from BL of induction study in SF-36 Physical Component Summary score

The following key secondary endpoints were in favour of RZB 180 mg SC over RZB 360 mg SC vs PBO at Week 52:

- CDAI clinical remission
- Change from Baseline of induction study in FACIT-Fatigue
- CS-free use for 90 days & SF/APS clinical remission among subjects taking steroids at Baseline of induction study
- CDAI clinical response
- Enhanced clinical response
- Exposure-adjusted CD-related hospitalizations from Week 0 through Week 52

Overall, the symptomatic endpoints showed a degree of efficacy for both RZB regimens vs. PBO.

Regarding mucosal healing, for the results of endoscopic and composite endpoints, dose response was observed, with numerically higher efficacy for RZB 360 mg SC vs. RZB 180 mg SC arm vs. PBO.

The proportion of subjects with endoscopic remission in the RZB 360 mg SC arm increased over time, from 28.7% at Week 0 to 39.1% at Week 52; the proportion in the RZB 180 mg SC arm remained stable (29.1% at Week 0; 29.9% at Week 52); the proportion in the PBO arm decreased (28.4% at Week 0; 12.8% at Week 52).

Similar trends were observed for other endoscopic endpoints e.g. ulcer-free endoscopy (Table 45).

*Table 45 Endoscopic Response, Endoscopic Remission, CDAI Deep Remission, and SF/APS Deep Remission at Week 0 and Week 52 (ITT1A Population)*

| | Withdrawal (PBO SC) | | RZB 180 mg SC | | RZB 360 mg SC | | Adjusted Treatment Difference[a] | |
|---|---|---|---|---|---|---|---|---|
| Endpoint[b] Timepoint | N | n (%) | N | n (%) | N | n (%) | Δ RZB 180 mg SC – PBO (95% CI) | Δ RZB 360 mg SC – PBO (95% CI) |
| Endoscopic response | | | | | | | | |
| Week 0 | 162 | 73 (45.1) | 151 | 66 (43.7) | 136 | 55 (40.4) | -- | -- |
| Week 52 | 164 | 36 (22.0) | 157 | 74 (47.1) | 141 | 66 (46.5) | 26.0(17.2, 34.7) *** | 27.8 (18.7, 37.0) *** |
| Endoscopic remission | | | | | | | | |
| Week 0 | 162 | 46 (28.4) | 151 | 44 (29.1) | 136 | 39 (28.7) | -- | -- |
| Week 52 | 164 | 21 (12.8) | 157 | 47 (29.9) | 141 | 55 (39.1) | 17.2 (9.3, 25.0) *** | 28.5(19.9, 37.0) *** |
| CDAI deep remission | | | | | | | | |
| Week 0 | 164 | 31 (18.9) | 153 | 29 (19.0) | 137 | 22 (16.1) | -- | -- |
| Week 52 | 164 | 17 (10.4) | 157 | 40 (25.5) | 141 | 41 (29.1) | 14.9 (7.6, 22.3) *** | 21.2 (13.1, 29.4) *** |
| SF/APS deep remission | | | | | | | | |
| Week 0 | 164 | 31 (18.9) | 153 | 30 (19.6) | 136 | 20 (14.7) | -- | -- |
| Week 52 | 164 | 16 (9.8) | 157 | 35 (22.3) | 141 | 39 (27.7) | 12.7 (5.4, 20.0) ** | 20.2 (12.3, 28.2) *** |

a. Risk difference = (risankizumab - placebo). Adjusted risk difference was calculated based on the CMH test.
b. For definitions of endpoints, refer to Table 2.
* P value ≤ 0.05; ** P value ≤ 0.01; *** P value < 0.001.

CS-free clinical remission (SF/APS), for subjects who took CS at baseline of induction, was numerically in favour of RZB 180 mg SC (27/51, 52.9%) vs. RZB 369 mg SC (11/42, 25.6%) vs. PBO (12/51, 23.5%).

Regarding QoL, the results were numerically similar across treatment arms.

The incidence rate of CD-related hospitalizations reported through Week 52 was low in all groups: RZB 180 mg SC (5) vs. RZB 360 mg SC (9) vs. PBO (8).

For non-ranked secondary inflammatory markers (i.e., hs-CRP and FCP), SES-CD and serum IL-22 levels decreased in subjects in the RZB arms over 52 weeks. These markers stayed the same as at Week 0 or increased in subjects in the PBO arm over 52 weeks.

*Placebo (PBO) response*

Prolonged efficacy is apparent in the PBO/withdrawal arm and the magnitude of PBO responses for some endpoints is noted. Similar rates of clinical remission and clinical response were observed through Week 16 between the RZB SC and PBO arms, with rates decreasing thereafter in the PBO arm.

Both observed and population PK model-predicted RZB PK profiles during the maintenance period indicated prolonged RZB residual exposures from the previous induction treatment in PBO arm, up to at least Week 16. Also, prolonged suppression of IL-22 was observed in the PBO arm at Week 52 compared to the Baseline of Induction.

*Subgroup Analyses*

Bio-IR & Non-Bio-IR Subgroups

The range of proportion of subjects across the randomized arms were 72-75% BIO-IR vs 25-28% non-BIO-IR.

At Week 52, as shown in the following table, higher response rates were reported in the non-Bio-IR and Bio-IR subjects for both induction doses vs PBO.

For the BIO-IR group, the response rate difference to PBO was greater for the RZB 360 mg dose vs the RZB 180 mg dose for the co-primary endpoints (clinical remission (SF/APS) 14.0% (95% CI 1.1, 26.8) vs 6.6 % (95% CI -5.8, 18.9) respectively; endoscopic response 23.4 % (95% CI 11.4, 35.4) vs 20.4% (95 % CI 8.9, 31.9) respectively).

For the non-BIO-IR group, the response rate difference to PBO for the co-primary endpoint of clinical remission (SF/APS) was similar for RZB 180 mg, 5.3% (95% CI -15.7, 26.2) and RZB 360 mg, 5.4% (95% CI -16.1, 27.0). The response rate difference to PBO for the co-primary endpoint of endoscopic response was greater for the RZB 180 mg dose, 36.8% (95% CI 17.2, 56.5) vs. the RZB 360 mg dose, 27.0% (95% CI 6.3, 47.7).

The PBO (withdrawal) response rates are noted, as are the small number of subjects in the non-BIO-IR groups shown.

*Table 46. Primary Efficacy Results of Study M16-000 Sub-Study 1 for Subjects Who Were Bio-IR and Non-Bio-IR at Baseline of Induction Studies (NRI-C, ITT1A Population)*

| | **Bio-IR[a]** | | | | | **Non-Bio-IR[b]** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Randomized Subjects** | | | **Response Rate Difference[c]** | | **Randomized Subjects** | | | **Response Rate Difference[c]** | |
| | **WD (PBO) SC N = 123 n (%)** | **RZB 180 mg SC N = 113 n (%)** | **RZB 360 mg SC N = 102 n (%)** | **Δ RZB 180 mg SC – PBO (95% CI)** | **Δ RZB 360 mg SC – PBO (95% CI)** | **WD (PBO) SC N = 41 n (%)** | **RZB 180 mg SC N = 44 n (%)** | **RZB 360 mg SC N = 39 n (%)** | **Δ RZB 180 mg SC – PBO (95% CI)** | **Δ RZB 360 mg SC – PBO (95% CI)** |
| CDAI clinical remission at Week 52[d] (US) | 43 (35.0) | 55 (48.7) | 49 (47.6) | 13.7 (1.2, 26.2) | 12.7 (-0.2, 25.6) | 24 (58.5) | 32 (72.7) | 25 (64.1) | 14.2 (-5.8, 34.2) | 5.6 (-15.7, 26.9) |
| SF/APS clinical remission at Week 52[e] (OUS) | 42 (34.1) | 46 (40.7) | 49 (48.1) | 6.6 (-5.8, 18.9) | 14.0 (1.1, 26.8) | 23 (56.1) | 27 (61.4) | 24 (61.5) | 5.3 (-15.7, 26.2) | 5.4 (-16.1, 27.0) |
| Endoscopic response at Week 52[f] (US and OUS) | 25 (20.3) | 46 (40.7) | 45 (43.7) | 20.4 (8.9, 31.9) | 23.4 (11.4, 35.4) | 11 (26.8) | 28 (63.6) | 21 (53.8) | 36.8 (17.2, 56.5) | 27.0 (6.3, 47.7) |

Induction Dose Subgroups (RZB 600 mg versus 1200 mg IV)

The range of proportion of subjects across the randomized arms were 44-46% with RZB 600 mg induction completed and 54-56% with RZB 1200mg induction completed.

For the RZB 600 mg induction group, the response rate difference to PBO was greater for the RZB 360 mg maintenance dose vs the RZB 180 mg dose for the co-primary endpoints (clinical remission

(SF/APS) 3.2% (95% CI -13.5, 19.8) vs -1.6 % (95% -13.5, 19.8) respectively; endoscopic response 23.0% (95 % CI 7.0, 38.9) vs. 14.1 % (95% CI -1.4, 29.7) respectively).

For the RZB 1200 mg induction group, the response rate difference to PBO for the co-primary endpoint of clinical remission (SF/APS) was higher for the RZB 360 mg dose, 19.8% (95% CI 4.9, 34.7) vs. RZB 180 mg, 14.0% (95% CI -0.3, 28.3). The response rate difference to PBO for the co-primary endpoint of endoscopic response was greater for the RZB 180 mg dose, 34.3% (95% CI 21.4, 47.2) vs. the RZB 360 mg dose, 25.8% (95% CI 12.4, 39.3).

On interpretation, the PBO (withdrawal) response rates are noted, as are the wide ranging CI and CI crossing unity reported.

*Table 47. Primary Efficacy Results of Study M16-000 Sub-Study 1 for the Rizankizumab Induction Last Dose Subgroup (NRI-C, ITT1A Population)*

| | **RZB 600 mg IV Induction Dose** | | | | | **RZB 1200 mg IV Induction Dose** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Randomized Subjects** | | | **Response Rate Difference[a]** | | **Randomized Subjects** | | | **Response Rate Difference[a]** | |
| | **WD (PBO) SC N = 75 n (%)** | **RZB 180 mg SC N = 69 n (%)** | **RZB 360 mg SC N = 65 n (%)** | **Δ RZB 180 mg SC – PBO (95% CI)** | **Δ RZB 360 mg SC – PBO (95% CI)** | **WD (PBO) SC N = 89 n (%)** | **RZB 180 mg SC N = 88 n (%)** | **RZB 360 mg SC N = 76 n (%)** | **Δ RZB 180 mg SC – PBO (95% CI)** | **Δ RZB 360 mg SC – PBO (95% CI)** |
| CDAI clinical remission at Week 52[b] (US) | 38 (50.7) | 36 (52.2) | 34 (51.9) | 1.5 (-14.8, 17.8) | 1.2 (-15.4, 17.9) | 29 (32.6) | 51 (58.0) | 40 (52.4) | 25.4 (11.2, 39.6) | 19.8 (4.9, 34.7) |
| SF/APS clinical at Week 52[c] (OUS) | 36 (48.0) | 32 (46.4) | 33 (51.2) | -1.6 (-17.9, 14.7) | 3.2 (-13.5, 19.8) | 29 (32.6) | 41 (46.6) | 40 (52.4) | 14.0 (-0.3, 28.3) | 19.8 (4.9, 34.7) |
| Endoscopic response at Week 52[d] (US and OUS) | 22 (29.3) | 30 (43.5) | 34 (52.3) | 14.1 (-1.4, 29.7) | 23.0 (7.0, 38.9) | 14 (15.7) | 44 (50.0) | 32 (41.6) | 34.3 (21.4, 47.2) | 25.8 (12.4, 39.3) |

a. Risk difference = (risankizumab – placebo). 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

Adolescent Subjects ≥ 16 to < 18 Years of Age at Week 52

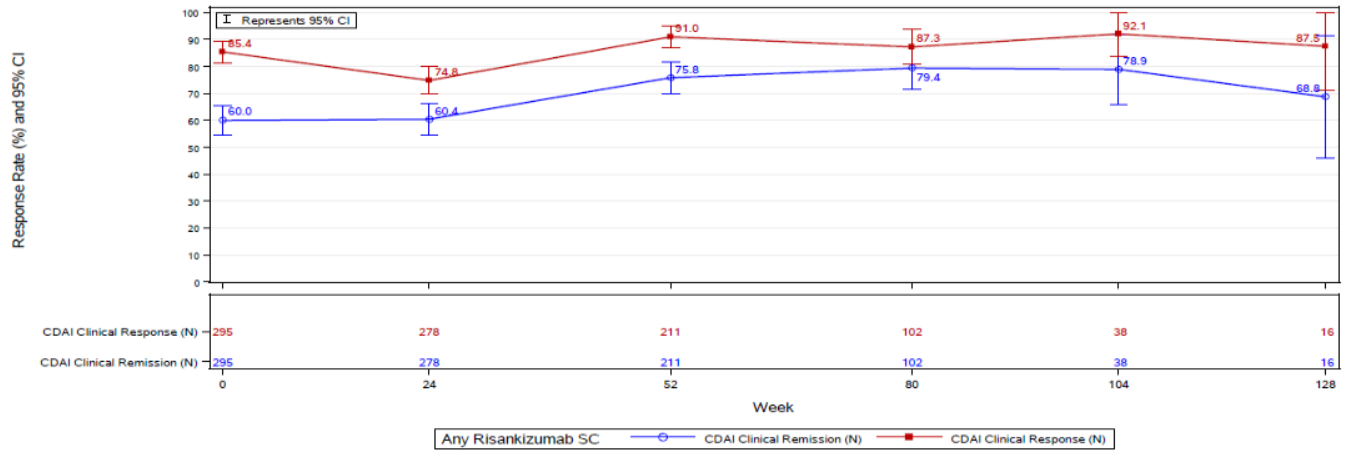
The adolescent population subset was small (n = 5), with 2 subjects in the RZB 360 mg arm, 2 in the RZB 180 arm mg, and 1 on PBO. One (1/5) subject in the RZB 180 mg arm achieved the co-primary endpoints of clinical remission (per CDAI or SF/APS) and endoscopic response.

No conclusions on the limited amount of data can be drawn.

*M16-000 Sub-Study 1 & Sub-Study 3 Integrated maintenance data up to Week 104*

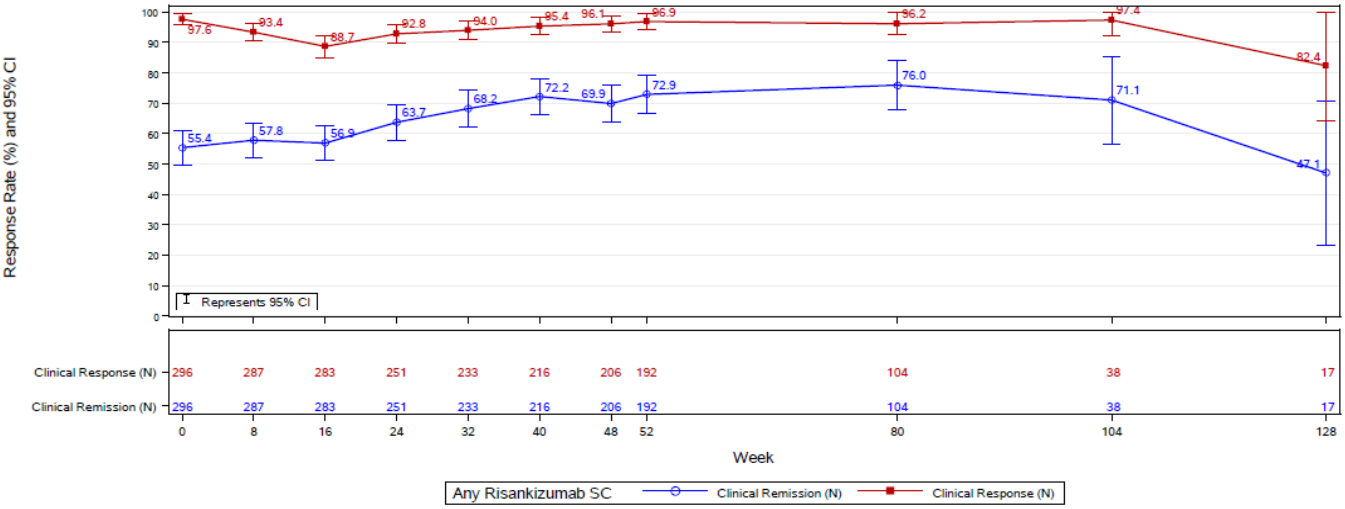
Sub-Study 3 is ongoing. On integration of Sub-Study 1 and available Sub-Study 3 observed data (ISE3A), the number of subjects who have completed to Week 104 is small, however trends in the proportion of subjects who achieved clinical remission (per CDAI or SF/APS) and clinical response (per CDAI or SF/APS) increased during the maintenance study and there is some evidence of maintenance of effect over time as per the following figures.

*Figure 19.* *CDAI Clinical Remission and CDAI Clinical Response at Scheduled Visits (ISE3A Population)*




CDAI clinical remission: CDAI < 150. CDAI clinical response: CDAI ≥ 100-points from baseline.

*Figure 20.* *SF/APS Clinical Remission and SF/APS Clinical Response at Scheduled Visits (ISE3A Population)*




SF/APS clinical remission: average daily SF ≤ 2.8 & not worse than baseline + average daily APS ≤ 1 & not worse than baseline.

SF/APS clinical response: ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily APS & both not worse than baseline.

## 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).

*Summary of Efficacy for Study M15-991 (induction)*

| |
|---|
| **Title:** A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study to Assess the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease Who Failed Prior Biologic Treatment |

| | | | |
|---|---|---|---|
| Study identifier | M15-991 | | |
| Design | The study consists of a Screening Period (approximately 35 days), 12-Week Induction Period, Induction Period 2, and 20-week Follow-up Period.<br><br>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 IV, RISA 600 mg IV or placebo (PBO) in 1:1:1 ratio through Week 12 and dosing in 12-Week Induction Period were at Week 0, Week 4, and Week 8.<br><br>Induction Period 2 is a 12-week randomized, double-blinded, 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 360 mg IV or RISA 180 mg IV in 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 the Induction Period 2. | | |
| | Duration of main phase: | | 12 weeks (12-Week Induction Period: double-blind period) |
| | Duration of Run-in phase: | | not applicable |
| | Duration of Extension phase: | | not applicable |
| Hypothesis | Superiority of RISA vs. PBO at Week 12 | | |
| Treatment groups | 12-Week Induction Period | RISA 1200 mg IV | RISA 1200 mg IV at Week 0, 4 and 8 |
| | | RISA 600 mg IV | RISA 600 mg IV at Week 0, 4 and 8 |
| | | PBO | PBO at Week 0, 4 and 8 |
| Endpoints and definitions | Co-Primary | Clinical remission (SF/APS) at Week 12 | The achievement of clinical remission (SF/APS) at Week 12 |
| | | Endoscopic response at Week 12 | The achievement of endoscopic response at Week 12 |
| Database lock | 20 May 2021 | | |
| Analysis population | The Intent-to-Treat population (ITT1A) includes all randomized subjects who received at least one dose of study drug in the 12-Week Induction | | |

| | | | | |
|---|---|---|---|---|
| and time point description | Period and had baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). The ITT1A was the primary population for efficacy analysis of the 12-Week Induction Period. Subjects were included in the analysis according to the treatment groups that they were randomized to. | | | |
| **Results and Analysis** | | | | |
| **Analysis description** | **Primary and Secondary Analysis** | | | |
| Effect estimate per comparison | Clinical remission (SF/APS) at Week 12 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 20.4% | 15.2% |
| | | 95% CI | [11.5%, 29.3%] | [6.4%, 24.0%] |
| | | P-value | < 0.001 | 0.001 |
| | Endoscopic response at Week 12 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 23.1% | 17.6% |
| | | 95% CI | [15.1%, 31.1%] | [9.9%, 25.4%] |
| | | P-value | < 0.001 | < 0.001 |
| | Clinical remission (CDAI) at Week 12 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 20.5% | 22.1% |
| | | 95% CI | [11.6%, 29.5%] | [13.1%, 31.0%] |
| | | P-value | <0.001 | < 0.001 |
| | CDAI clinical response at Week 4 (NRI-C) | Comparison groups | RISA 1200 | RISA 600 mg |

| | | | | |
|---|---|---|---|---|
| | | | mg IV vs PBO | IV vs PBO |
| | | Difference | 11.8% | 15.7% |
| | | 95% CI | [3.0%, 20.5%] | [6.8%, 24.6%] |
| | | P-value | 0.008 | 0.001 |
| | Clinical remission (SF/APS) at Week 4 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 10.3% | 9.2% |
| | | 95% CI | [3.7%, 16.8%] | [2.6%, 15.7%] |
| | | P-value | 0.002 | 0.006 |
| | CDAI clinical response at Week 12 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 30.6% | 29.4% |
| | | 95% CI | [21.1%, 40.1%] | [19.8%, 39.0%] |
| | | P-value | <0.001 | < 0.001 |
| | FACIT-Fatigue at Week 12 (MMRM) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 3.0 | 2.8 |
| | | 95% CI | [0.7, 5.3] | [0.4, 5.1] |
| | | P-value | 0.01 | 0.02 |
| | IBDQ at Week 12 (MMRM) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 15.0 | 12.4 |
| | | 95% CI | [7.7, 22.4] | [5.0, 19.8] |

| | | | | |
|---|---|---|---|---|
| | | P-value | < 0.001 | 0.001 |
| | Enhanced clinical response and endoscopic response at Week 12 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 17.3% | 13.9% |
| | | 95% CI | [10.3%, 24.2%] | [7.1%, 20.7%] |
| | | P-value | < 0.001 | < 0.001 |
| | Endoscopic remission at Week 12 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 16.2% | 15.0% |
| | | 95% CI | [9.9%, 22.4%] | [8.9%, 21.2%] |
| | | P-value | < 0.001 | < 0.001 |
| | Enhanced clinical response at Week 4 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 7.1% | 13.6% |
| | | 95% CI | [-2.4%, 16.6%] | [4.0%, 23.3%] |
| | | P-value | 0.142 | 0.006 |
| | Ulcer-free endoscopy at Week 12 (NRI-C)[a] | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 11.2% | 9.4% |
| | | 95% CI | [5.3%, 17.0%] | [3.8%, 15.1%] |
| | | P-value | < 0.001 | 0.001 |

| | | | | |
|---|---|---|---|---|
| | Enhanced clinical response at Week 12 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 20.0% | 22.8% |
| | | 95% CI | [10.2%, 29.9%] | [13.0%, 32.5%] |
| | | P-value | < 0.001 | < 0.001 |
| | Resolution of EIMs at Week 12 (NRI-C)[b] | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 13.4% | 5.6% |
| | | 95% CI | [0.7%, 26.1%] | [-6.8%, 17.9%] |
| | | P-value | 0.039 | 0.377 |
| | CD-related hospitalization through Week 12 (AO) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | -9.1% | -8.1% |
| | | 95% CI | [-14.1%, -4.2%] | [-13.2%, -2.9%] |
| | | P-value | < 0.001 | 0.002 |
| | Resolution of draining fistulas at Week 12 (NRI-NC)[c] | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 30.4% | -6.2% |
| | | 95% CI | [0.6%, 60.2%] | [-28.1%, 15.7%] |
| | | P-value | 0.113 | 1.0 |
| | WPAI-CD at Week 12 (MMRM) | Comparison groups | RISA 1200 | RISA 600 mg |

| | | | | |
|---|---|---|---|---|
| | | | mg IV vs PBO | IV vs PBO |
| | | Difference | -8.759 | -7.323 |
| | | 95% CI | [-17.518, -0.001] | [-16.399, 1.753] |
| | | P-value | 0.05 | 0.113 |
| | SF-36 PCS at Week 12 (MMRM) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 2.714 | 2.221 |
| | | 95% CI | [1.077, 4.351] | [0.577, 3.865] |
| | | P-value | 0.001 | 0.008 |
| Notes | Treatment differences presented above were adjusted for the stratification factors of the number of prior biologics failed (<= 1, > 1) and baseline corticosteroid use (yes or no) at baseline.<br>a. For subjects with SES-CD ulcerated surface subscore ≥ 1 at baseline.<br>b. For subjects with any EIM at baseline.<br>c. For subjects with draining fistulas at baseline. | | | |

*Summary of Efficacy for Study M16-006 (induction)*

| **Title:** A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease | |
|---|---|
| Study identifier | M16-006 |
| Design | The study consists of a Screening Period (approximately 35 days), 12-Week Induction Period, Induction Period 2, and 20-week Follow-up Period.<br>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 IV, RISA 600 mg IV or placebo (PBO) in 2:2:1 ratio through Week 12 and dosing in 12-Week Induction Period were at Week 0, Week 4, and Week 8.<br>Induction Period 2 is a 12-week randomized, double-blinded, 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 360 mg IV or RISA 180 mg IV in 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 the Induction Period 2. | | |
| | Duration of main phase: | | 12 weeks (12-Week Induction Period: double-blind period) |
| | Duration of Run-in phase: | | not applicable |
| | Duration of Extension phase: | | not applicable |
| Hypothesis | Superiority of RISA vs. PBO at Week 12 | | |
| Treatment groups | 12-Week Induction Period | RISA 1200 mg IV | RISA 1200 mg IV at Week 0, 4 and 8 |
| | | RISA 600 mg IV | RISA 600 mg IV at Week 0, 4 and 8 |
| | | PBO | PBO at Week 0, 4 and 8 |
| Endpoints and definitions | Co-Primary | Clinical remission (SF/APS) at Week 12 | The achievement of clinical remission (SF/APS) at Week 12 |
| | | Endoscopic response at Week 12 | The achievement of endoscopic response at Week 12 |
| Database lock | May 18 2021 | | |
| Analysis population and time point description | The Intent-to-Treat population (ITT1A) includes all randomized subjects who received at least one dose of study drug in the 12-Week Induction Period and had baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). The ITT1A was the primary population for efficacy analysis of the 12-Week Induction Period. Subjects were included in the analysis according to the treatment groups that they were randomized to. | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary and Secondary Analysis** | | |

| | | | | |
|---|---|---|---|---|
| Effect estimate per comparison | Clinical remission (SF/APS) at Week 12 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 18.8% | 21.9% |
| | | 95% CI | [10.8%, 26.8%] | [13.8%, 29.9%] |
| | | P-value | < 0.001 | < 0.001 |
| | Endoscopic response at Week 12 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 20.3% | 28.3% |
| | | 95% CI | [13.6%, 27.1%] | [21.2%, 35.4%] |

| | | | | |
|---|---|---|---|---|
| | | P-value | < 0.001 | < 0.001 |
| | Clinical remission (CDAI) at Week 12 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 16.7% | 20.7% |
| | | 95% CI | [8.5%, 24.9%] | [12.4%, 29.0%] |
| | | P-value | < 0.001 | < 0.001 |
| | CDAI clinical response at Week 4 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 11.2% | 15.4% |
| | | 95% CI | [3.1%, 19.2%] | [7.2%, 23.7%] |
| | | P-value | 0.007 | < 0.001 |
| | Clinical remission (SF/APS) at Week 4 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 11.7% | 11.5% |
| | | 95% CI | [5.7%, 17.8%] | [5.4%, 17.5%] |
| | | P-value | < 0.001 | < 0.001 |
| | CDAI clinical response at Week 12 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 27.7% | 23.1% |
| | | 95% CI | [19.0%, 36.4%] | [14.2%, 31.9%] |
| | | P-value | < 0.001 | < 0.001 |
| | FACIT-Fatigue at Week 12 (MMRM) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 4.1 | 5.2 |
| | | 95% CI | [2.1, 6.1] | [3.2, 7.2] |
| | | P-value | < 0.001 | < 0.001 |
| | IBDQ at Week 12 (MMRM) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |

| | | | | |
|---|---|---|---|---|
| | | Difference | 19.4 | 20.7 |
| | | 95% CI | [13.1, 25.8] | [14.3, 27.1] |
| | | P-value | < 0.001 | < 0.001 |
| | Enhanced clinical response and endoscopic response at Week 12 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 15.2% | 23.2% |
| | | 95% CI | [9.3%, 21.2%] | [16.8%, 29.6%] |
| | | P-value | < 0.001 | < 0.001 |
| | Endoscopic remission at Week 12 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 15.4% | 15.1% |
| | | 95% CI | [9.4%, 21.4%] | [9.0%, 21.2%] |
| | | P-value | < 0.001 | < 0.001 |
| | Enhanced clinical response at Week 4 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 11.8% | 14.9% |
| | | 95% CI | [3.2%, 20.3%] | [6.2%, 23.5%] |
| | | P-value | 0.007 | 0.001 |
| | Ulcer-free endoscopy at Week 12 (NRI-C)[a] | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 9.1% | 13.7% |
| | | 95% CI | [3.7%, 14.5%] | [7.9%, 19.5%] |
| | | P-value | 0.001 | < 0.001 |
| | Enhanced clinical response at Week 12 (NRI-C) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 21.6% | 21.0% |
| | | 95% CI | [12.8%, 30.4%] | [12.2%, 29.9%] |

| | | | | |
|---|---|---|---|---|
| | | P-value | < 0.001 | < 0.001 |
| | Resolution of EIMs at Week 12 (NRI-C)[b] | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 23.7% | 14.6% |
| | | 95% CI | [11.1%, 36.3%] | [2.1%, 27.0%] |
| | | P-value | < 0.001 | 0.022 |
| | CD-related hospitalization through Week 12 (AO) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | -10.2% | -8.7% |
| | | 95% CI | [-15.2%, -5.2%] | [-13.9%, -3.5%] |
| | | P-value | < 0.001 | < 0.001 |
| | Resolution of draining fistulas at Week 12 (NRI-NC)[c] | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 6.9% | 5.6% |
| | | 95% CI | [-25.7%, 39.6%] | [-28.6%, 39.7%] |
| | | P-value | 1.00 | 1.00 |
| | WPAI-CD at Week 12 (MMRM) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | -12.141 | -9.586 |
| | | 95% CI | [-20.390, -3.892] | [-17.890, -1.282] |
| | | P-value | 0.004 | 0.024 |
| | SF-36 PCS at Week 12 (MMRM) | Comparison groups | RISA 1200 mg IV vs PBO | RISA 600 mg IV vs PBO |
| | | Difference | 3.275 | 2.913 |
| | | 95% CI | [1.877, 4.672] | [1.512, 4.313] |
| | | P-value | < 0.001 | < 0.001 |

| | |
|---|---|
| Notes | Treatment differences presented above were adjusted for the stratification factors of the number of prior biologics failed (0, 1, > 1) and baseline corticosteroid use (yes or no) at baseline.<br>a. For subjects with SES-CD ulcerated surface subscore ≥ 1 at baseline.<br>b. For subjects with any EIM at baseline.<br>c. For subjects with draining fistulas at baseline. |

*Summary of Efficacy for Study M16-000 Sub-Study 1 (maintenance)*

| **Title:** A Multicenter, Randomized, Double-Blind, Placebo-Controlled 52-Week Maintenance and an Open-Label Extension Study of the Efficacy and Safety of RZB in Subjects with Crohn's Disease | | | |
|---|---|---|---|
| Study identifier | M16-000 Sub-Study 1 | | |
| Design | Maintenance period: 52 weeks, randomized, double-blind, placebo-controlled trial. Eligible subjects with clinical response to induction treatment with intravenous RZB were randomized to RZB 360 mg SC, RZB 180 mg SC or placebo (PBO) in 1:1:1 ratio through Week 52 and dosing at Week 0, 8, 16, 24, 32, 40 and 48.<br>Follow up period: 20 weeks. | | |
| | Duration of maintenance & follow up | | 68 weeks |
| Hypothesis | Superiority of RZB vs. PBO at Week 52 | | |
| Treatment groups | 52-Week maintenance period | RZB 360 mg SC | Q8W |
| | | RZB 180 mg SC | Q8W |
| | | PBO | Q8W |
| Endpoints and definitions | Co-primary | | |
| | Clinical remission (SF/APS) at Week 52 | | Proportion with average daily SF ≤ 2.8 and not worse than Baseline AND average daily APS ≤ 1 and not worse than Baseline |
| | Endoscopic response at Week 52 | | Proportion with a decrease in SES CD > 50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2-point reduction from Baseline), as scored by central reviewer |
| | Ranked Secondary at/through Week 52 | | |
| | Clinical remission (CDAI) | | |
| | Maintenance of clinical remission (SF/APS) | | |
| | Ulcer-free endoscopy | | |
| | Endoscopic remission | | |
| | IBDQ | | |
| | FACIT-Fatigue | | |
| | Corticosteroids-free clinical remission (SF/APS) | | |
| | CDAI clinical response | | |

| | | | |
|---|---|---|---|
| | Clinical remission (SF/APS) and endoscopic response | | |
| | Enhanced clinical response | | |
| | Deep remission (SF/APS) | | |
| | CD-related hospitalizations | | |
| | SF-36 PCS | | |
| Database lock | May 15 2021 | | |
| Analysis population and time point description | Sub-Study 1 ITT1A - Intent-to-Treat population at Week 52, analysed according to the treatment allocation at randomisation. | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis**<br>The results for the RZB 360mg SC arm vs. placebo, which were statistically significant are shown here. The results for the RZB 180mg SC arm were not statistically significant. | | |
| Effect estimate per comparison | Clinical remission (SF/APS) at Week 52 (NRI-C) | Comparison groups | RZB 360 mg SC vs PBO |
| | | Difference | 15.2% |
| | | 95% CI | [4.9%, 25.4%] |
| | | P-value | 0.004 |
| | Endoscopic response at Week 52 (NRI-C) | Comparison groups | RISA 360 mg SC vs PBO |
| | | Difference | 27.8% |
| | | 95% CI | [18.7%, 37.0%] |
| | | P-value | < 0.001 |
| The results for secondary endpoints were not statistically significant. Only descriptive statistics are shown for secondary endpoint analysis here. | | | |
| Descriptive statistics and estimate variability | Treatment group (n) | RZB 360 mg SC n=141 | PBO n=164 |
| | **Primary Analysis at Week 52 (NRI-C), n/N (%)** | | |
| | Clinical remission (SF/APS) | 73/141 (51.8%) | 65/164 (39.6%) |
| | Endoscopic response | 66/141 (46.5%) | 36/164 (22.0%) |
| | **Secondary Analysis at/through Week 52 (NRI-C), n/N (%)** | | |
| | Clinical remission (CDAI) | 74/141 (52.2%) | 67/164 (40.9%) |
| | Maintenance of clinical remission (SF/APS) | 50/72 (69.2%) | 46/91 (50.5%) |
| | Ulcer-free endoscopy | 43/141 (30.5%) | 17/162 (10.5%) |
| | Endoscopic remission at Week 52 | 55/141 (39.1%) | 21/164 (12.8%) |

| | | | |
|---|---|---|---|
| | IBDQ (ANCOVA), LS-Mean Change from Baseline [95% CI] | 62.2 [57.4, 67.0] | 56.4 [51.3, 61.6] |
| | FACIT-Fatigue (ANCOVA), LS-Mean Change from Baseline [95% CI] | 15.4 [13.8, 17.0] | 15.0 [13.3, 16.6] |
| | Steroids-free clinical remission (SF/APS) | 14/42 (34.0%) | 12/51 (23.5%) |
| | CDAI clinical response | 87/141 (61.6%) | 79/164 (48.2%) |
| | Clinical remission (SF/APS) and endoscopic response | 49/141 (35.1%) | 27/164 (16.5%) |
| | Enhanced clinical response | 84/141 (59.5%) | 81/164 (49.4%) |
| | Deep remission (SF/APS) | 39/141 (27.7%) | 16/164 (9.8%) |
| | CD-related hospitalizations, n/PYS (%) | 9/126.54 (7.1%) | 8/137.85 (5.8%) |
| | SF-36 PCS (ANCOVA), LS-Mean Change from Baseline [95% CI] | 12.0 [10.8, 13.1] | 11.3 [10.1, 12.6] |

### *2.6.5.8. Clinical studies in special populations*

**Number of Subjects with CD Grouped by Age in Phase 2 and 3 Clinical Studies**

| Trials | Number of Subjects in Age Group | | | | Total Number of Subjects |
|---|---|---|---|---|---|
| | Age < 65 | Age 65 to 74 | Age 75 to 84 | Age 85+ | |
| M15-993/M15-989 | 110 | 5 | 0 | 0 | 115 |
| M15-991 | 451 | 22 | 0 | 0 | 473 |
| M16-006 | 768 | 32 | 4 | 0 | 804 |
| M16-000 Sub-study 1 | 352 | 21 | 2 | 0 | 375 |

### *2.6.5.9. In vitro biomarker test for patient selection for efficacy*

Not applicable.

### *2.6.5.10. Analysis performed across trials (pooled analyses and meta-analysis)*

Not applicable.

### *2.6.5.11. Supportive study(ies)*

Not applicable.

## 2.6.6. Discussion on clinical efficacy

The MAH has presented the clinical development program in support of the marketing authorization of risankizumab in patients 16 years and older who have moderately to severely active Crohn's Disease (CD). Risankizumab (RZB) has been investigated in two phase 2 studies (M15-993, M15-989) and three pivotal Phase 3 studies (M15-991, M16-006, M16-000, Sub-Study 1).

The clinical development plan consists of a standard clinical package for a new product for the treatment of Crohn's Disease, in line with the Guideline on the Development of New Medicinal Products for the Treatment of Crohn's Disease (CPMP/EWP/2284/99 Rev. 2). The pivotal clinical studies are standard randomised controlled trials. The studies are agreed with respect to study design, duration, patient population, placebo comparator and clinical endpoints. The MAH received EU scientific advice which was followed in general or otherwise justified.

The co-primary endpoints of clinical remission (SF/APS) and endoscopic response are justified as clinically relevant and of importance in providing an objective facet, reflective of developments in the scientific literature and clinical guidance regarding CD.

The results of the Phase 2 dose-finding Study M15-993 (1311.6) indicated a dose dependent response, supporting the higher RZB dose (600 mg) for induction and at least a dose of RZB 180 mg SC for maintenance of effect but an upper dose-response limit, for induction or maintenance, was not deduced.

Phase 2 study M15-989, (1311.20), an open label extension study was terminated by the sponsor so that subjects could roll over into Phase 3 Study M16-000 Sub-study 3 OLE, which is ongoing. The descriptive results supported the safety and tolerability of RZB 180 mg SC as a long term treatment in patients with moderately to severely active CD, who showed a clinical response, or remission, on previous treatment with RZB.

**Study M15-991 and Study M16-006 (induction studies)**

The Phase 3 induction studies (Study M15-991 and Study M16-006) were multi-centre, randomised, double-blind, placebo-controlled evaluations of risankizumab (risankizumab 600 mg IV or 1200 mg IV at Weeks 0, 4, and 8) in subjects 16 years and older with moderately to severely active CD defined as a CDAI of 220 to 450, a daily average stool frequency (SF) of ≥ 4 and/or average daily abdominal pain score (APS) ≥2, and a Simple Endoscopic Score (SES) – CD (excluding the narrowing component) of ≥ 6, or ≥ 4 for isolated ileal disease, confirmed by central review.

Subjects with a SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease while still meeting the symptomatic criteria for moderate-severe disease activity were enrolled as an exploratory population. This exploratory analyses in a limited subset of patients with SES-CD scores of 3, 4 or 5 is considered relevant to the wider CD population.

The definition of moderately to severely active Crohn's disease, the trial design and dosing regimens are considered acceptable to determine the efficacy of RZB as an induction therapy in CD.

The co-primary endpoints were discussed under scientific advice and they are accepted as reflecting clinically important targets for the treatment of CD. The RZB induction studies also included a number of controlled secondary endpoints representing clinically meaningful parameters, including measurements of improvements in mucosal inflammation, including endoscopic response, endoscopic remission, and ulcer-free endoscopy and QoL.

For both inductions studies no issues of concern were identified in relation to protocol amendments. However, the MAH was asked to provide more detailed discussion on protocol deviations and how it was concluded that there was no impact on the results, given the number and type described. The

MAH provided further clarity as requested and it is agreed that protocol deviations had no impact on study results.

Induction Study M15-991

Study M15-991 enrolled subjects who had a documented inadequate response or intolerance to use of an approved biologic agent (Bio-IR), such as infliximab, adalimumab, certolizumab, natalizumab, ustekinumab and/or vedolizumab. The number of subjects with prior exposure to ustekinumab was capped at 20% of the total population.

The baseline data presented by the MAH demonstrated that the study populations were well characterised in terms of disease extent, duration, disease activity and prior treatment. Patients were between 16-80 years. 4 patients in total were under 18 (i.e., either 16 or 17 years) with 2 patients under 18 treated in the RZB treated groups.

The demographic and baseline disease characteristics for subjects were similar across the treatment groups in the induction study and are reflective of a subject population with moderately to severely active CD. In addition, there was good compliance with treatment, balanced across the groups.

Use of any prior Crohn's disease related medication was reported by 100% of subjects. The most frequently reported prior CD-related medications used by the treatment groups were adalimumab (71.4% of subjects) and infliximab (65.2% of subjects). Patients had also exposure to vedolizumab (33.7%) and ustekinumab (20.4%). In general, the exposure to prior medications was balanced between all groups.

This study recruited subjects with failure to prior biologic therapy and in the ITT1A group 47.1% had 1 biologic failure with 52.9 experiencing >1 biologic failure. One subject in the 1200 mg IV group had 7 prior failures and across all groups there were patients who had failed up to 5 prior therapies.

The majority of subjects were recorded as having a loss of response or intolerance/medical complication to their therapy. However, in number of instances the recorded reason of 'other' is high; notably Infliximab 18.5%, Adalimumab 29.0%, Vedolizumab 9.3%, Ustekinumab 8.1%. The high rate of 'unknowns' was addressed by the MAH and it is confirmed that the population in Study M15-991 is 100% source verified as having IR to and/or intolerance to at least one prior biologic.

The study met the co-primary endpoints of clinical remission and endoscopic response for the risankizumab 600 mg and 1200 mg arms compared to the placebo arm for both the US protocol and the OUS specific protocol.

At Week 12 a statistically significant greater (p-value ≤ 0.001) proportion of subjects in the risankizumab 600 mg and risankizumab 1200 mg arms achieved the co-primary endpoint of clinical remission (defined by CDAI in the US protocol and by SF/APS in the OUS protocol) compared to placebo arm.

At Week 12, a statistically significantly greater (p-value < 0.001) proportion of subjects in the risankizumab 600 mg and risankizumab 1200 mg arms achieved endoscopic response, assessed in both the US protocol and the OUS protocol, compared to the placebo arm. Overall, numerically similar results were observed for the risankizumab 600 mg arm and the risankizumab 1200 mg arm.

For the key secondary endpoints (i.e., endpoints under the overall type I error control) for the OUS protocol both risankizumab arms (600 mg and 1200 mg) have clear treatment effect over placebo for resolution of clinical symptoms, improvements in quality of life (QoL), reduction in mucosal inflammation as measured by endoscopy, and CD-related hospitalizations.

A majority of endpoints were statistically significant for the risankizumab 600 mg arm and the risankizumab 1200 mg arm versus placebo and the overall efficacy rates for the risankizumab 600 mg and 1200 mg arms were numerically similar.

Clinical response and clinical remission, as defined by CDAI and SF/APS, were seen at Week 4, with statistically significant differences observed for risankizumab 600 mg and 1200 mg arms versus placebo. Additionally, clinical response per CDAI and SF/APS were statistically significant for each risankizumab dose versus placebo at Week 12, with greater efficacy and treatment differences relative to those at Week 4.

Other patient reported outcome (PRO) questionnaires that summarize QoL, such as Inflammatory Bowel Disease Questionnaire (IBDQ), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, and SF-36, showed overall numerically higher improvement in the risankizumab arms versus placebo and reached statistical significance.

Endoscopic remission and ulcer-free endoscopy at Week 12 were statistically significant versus placebo in the OUS protocol. The composite endpoint for clinical response (per CDAI and SF/APS) and endoscopic response (i.e., clinical response and endoscopic response in the same patient), were also statistically significant for the risankizumab arms versus placebo.

CD-related hospitalizations were lower in the risankizumab groups versus placebo and met statistical significance.

For a number of parameters, namely the proportion of subjects with enhanced SF/APS clinical response at Week 4, the proportion of subjects with resolution of extra-intestinal manifestations (EIMs) at Week 12, in subjects with any EIMs at Baseline, the proportion of subjects without draining fistulas at Week 12 in subjects with draining fistulas at Baseline and the change from baseline in Work Productivity and Impairment Questionnaire – Crohn's disease (WPAI-CD) overall work impairment at Week 12 significance was not meet versus placebo for either 600 mg IV or 1200 mg IV doses. In addition, the endpoint of change from baseline in 36-Item Short Form Health Survey (SF-36) physical component summary score at Week 12 was not meet for subjects treated with the 600 mg IV dose.

For the ITT2A population (these were subjects who did not achieve SF/APS clinical response at Week 12, defined as a ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score and both not worse than baseline), the proportion who achieved SF/APS clinical response at Week suggested a trend towards improvement in symptoms but no firm conclusions can be ascertained from this exploratory analysis.

For the exploratory analysis in the ITT1B and ITT2B populations, i.e., those subjects who did not have baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease) there is a trend towards treatment benefit following RZB however the exploratory nature of these groups mean that no efficacy conclusions can be determined.

Induction Study M16-006

Study M16-006 enrolled subjects who were Bio-IR or subjects who were Non-Bio-IR. The non-bio-IR population included subjects who had an IR or intolerance to conventional therapy, but not biologic therapy.

Conventional therapy was defined as one or more of the following: aminosalicylates, oral locally acting steroids (e.g., budesonide, beclomethasone), systemic corticosteroids (prednisone or equivalent), or immunomodulators. This population also included subjects who received biologic therapy in the past but stopped therapy based on reasons other than IR or intolerance (e.g., change in reimbursement coverage, well-controlled disease). The number of subjects with prior exposure to ustekinumab was capped at 20% of the total population.

The study populations were well characterised in terms of disease extent, duration, disease activity and prior treatment. Patients were between 16-79 years. Eight patients in total were under 18 (i.e., either 16 or 17 years) with 6 patients in the RZB treated groups.

The demographic and baseline disease characteristics for subjects were similar across the treatment groups in the induction study and are reflective of a subject population with moderately to severely active CD. In addition, there was good compliance with treatment, balanced across the groups.

Study M16-006 included both Bio-IR and non-Bio-IR patients. Of the 850 patients in the ITT1A group 28.1% had 1 biologic failure with 29.6% experiencing >1 biologic failure. 42.2% of patients with no biologic failure.

Of the subjects with >1 prior biologic failure most had failure to 2 agents with a small number of subjects having ≥ 4 (5.1%). Most common prior treatment was Infliximab (44.5%) followed by Adalimumab (40.0%), Vedolizumab (18.5%) and Ustekinumab (14.2%).

RZB was superior to placebo, meeting the co-primary endpoints of clinical remission (SF/APS) (CDAI) and endoscopic response for the risankizumab 600 mg and 1200 mg IV arms compared to the placebo arm for both the US and the OUS protocols (P values < 0.001).

In addition, a clear treatment effect was demonstrated in the key subgroup populations of non-Bio-IR and Bio-IR for all co-primary endpoints with numerically similar results were observed for the risankizumab 600 mg and 1200 mg IV arms.

A majority of key secondary endpoints, including reduction in mucosal inflammation, resolution of clinical symptoms, improvements in QoL, and reduction in CD-related hospitalizations, under the overall Type I error control were statistically significant for both risankizumab arms versus placebo.

The population for this study includes Bio-IR subjects and Non-Bio-IR subjects. The non-bio-IR population included subjects who had an IR or intolerance to conventional therapy, but not biologic therapy.

There are improvements in responder rates observed whether, or not subjects had prior failure to biologic treatment across all co-primary endpoints. Although the data from the subgroups are not controlled for Type 1 error it is clear that there is a consistent pattern of effect in favour of treatment with RZB.

The non-bio-IR population also included subjects who received biologic therapy in the past but stopped therapy based on reasons other than IR or intolerance (e.g., change in reimbursement coverage, well-controlled disease). The MAH has provided results of an ad-hoc subgroup analysis which was conducted to compare the efficacy of subjects in the non-Bio-IR stratum with no prior exposure to biologics (i.e., bio-naïve; N=314) with the subjects in the total non-Bio-IR stratum (N=359). The results indicate a consistency in results for the efficacy endpoints of clinical remission and endoscopic response. Inclusion of subjects who received biologic therapy in the past but stopped therapy based on reasons other than IR or intolerance is unlikely to have any impact on observed efficacy results.

The baseline characteristics were well balanced across all treatment arms in each population, there was no impact of non-Bio-IR nor Bio-IR subgroups on the overall efficacy.

For the ITT2A population (these were subjects who did not achieve SF/APS clinical response at Week 12, defined as a ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score and both not worse than baseline), the proportion who achieved SF/APS clinical response at Week 24 suggested a trend towards improvement in symptoms, but no firm conclusions can be ascertained from this exploratory analysis.

For the exploratory analysis in the ITT1B and ITT2B populations, i.e those subjects who did not have baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease) there is a trend towards treatment benefit following RZB however the exploratory nature of these groups mean that no efficacy conclusions can be determined.

Choice of RZB 600 mg IV as the Induction Dose

The co-primary endpoints in both induction studies were met for the two RZB doses investigated (600mg IV and 1200mg IV) and there did not appear to be any benefit for patients in receiving the higher dose.

Across the range of ranked secondary endpoints, the 1200 mg IV dose performs marginally better in terms of statistical significance over placebo for a number of endpoints compared to 600 mg IV however, while it appears that there is no clear evidence of a benefit in terms of efficacy for either dose over the other. While there are slight differences in the point estimates for various endpoints between the risankizumab arms, the variability is within that expected in clinical trials, the 95% CIs are highly overlapping, and the totality of data does not indicate a dose-response and demonstrates a flat exposure-response relationship for the relevant clinical endpoints.

**M16-000 Sub-Study 1 (maintenance)**

This was a randomized, double blind, 52-Week study to assess the safety and efficacy of RZB for maintenance in moderately to severely active CD. The trial population, emanating from the induction studies M15-991 and M16-001, included a mixed population of approximately 75% Bio-IR and 25% non-BIO IR subjects. The baseline demographic and disease characteristics were similar to those reported in other studies for the condition under study. The population is accepted as representative of patients with moderate to severe CD requiring maintenance systemic therapy based on CD status, in the context of the proposed indication.

The maintenance study endpoints, assessing clinical signs, symptoms, mucosal healing and QoL aspects of CD, were justified by the MAH. The co-primary endpoints were discussed under scientific advice; they are accepted as reflecting clinically important targets for symptomatic, clinical and endoscopic response to long term treatment. Achieving endoscopic endpoints has been associated with improved long-term outcomes.

While the drug substance and drug product used in the pivotal trials are the to-be-marketed forms of RZB, the to-be-marketed SC presentation is an on-person device has not been studied at Phase 3. However, comparability data demonstrates that these products are comparable and no significant differences are expected to occur.

Enrolment duration was extended to include up to 15% more subjects to mitigate against potential missed visits due the onset of the Covid-19 pandemic, which is accepted. A slight imbalance in subject numbers per arm (placebo arm n=164/462; 35.5%) is not expected to influence results.

No issues of concern were identified in relation to protocol amendments.

Overall, superiority of RZB compared to PBO for maintenance treatment was seen for the co-primary endpoints at week 52. Patients in the RZB 360 mg arm demonstrated a statistically significant improvement in OUS (and US) co-primary data sets. The RZB 360 mg SC maintenance dose was statistically significantly superior to treatment with placebo over 52 weeks with regard to the co-primary endpoints of clinical remission (SF/APS) and endoscopic response; the RZB 180 mg SC dose did not reach statistical significance.

A strong placebo response in the randomised withdrawal arm is noted, with prolonged efficacy from induction, which was lost compared to treatments arms by week 52. This is most likely accounted for

by for by residual exposure from induction treatment lasting for approximately 16 to 24 weeks in Sub-Study 1.

The MAH stated that: "Each of the co-primary efficacy endpoints will be tested at two-sided significance level of 0.05 for 360 mg risankizumab SC dose versus placebo, followed by testing each of the co-primary endpoints at two-sided significance level of 0.05 for risankizumab 180 mg SC dose versus placebo. If both co-primary endpoints achieve statistical significance for both dose levels, continued testing of the ranked secondary endpoints for risankizumab SC 360 mg and 180 mg versus placebo will follow the multiplicity adjustment using graphic alpha spending methodology. The overall type I error rate of efficacy evaluation based on the co-primary and ranked secondary endpoints for the two doses will be strongly controlled at 0.05 (2-sided) level. Specifically, the testing will utilise the sequence of hypothesis testing for the co-primary endpoints for both doses, as stated above, followed by the ranked secondary endpoints in the order as specified in Section 3.1. If both co-primary endpoints for each dose achieve statistical significance in the hierarchical order specified above at alpha=0.05 (2-sided), continued testing will follow a prespecified weight of α allocation between the single hypothesis within the family, as well as between the families of hypotheses across the doses (denoted as node). [ SAP Risankizumab (ABBV-066) M16-000 Sub-Study 1 – Statistical Analysis Plan Version 2.0 – 30 April 2021]"

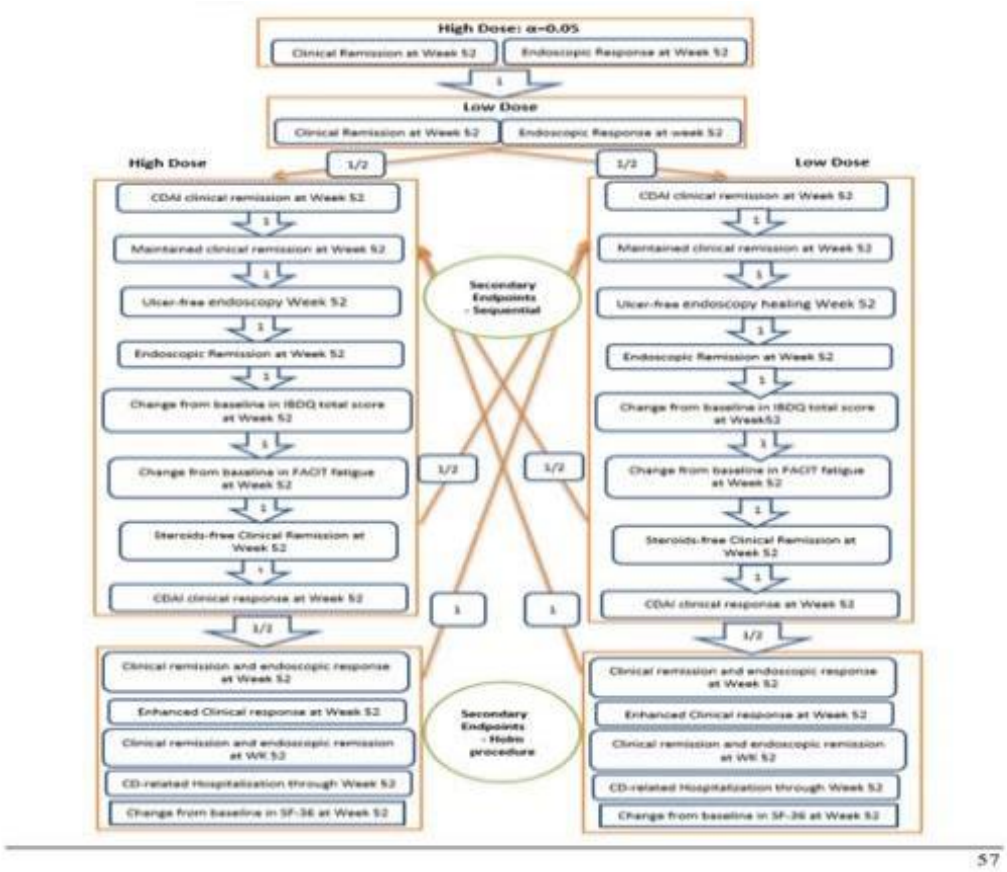



*Figure 21 Graphical Multiple Testing Procedure for Global Protocol Outside US*

The acceptance of an initially raised 'major objection' relates to clarification of the multiplicity question. The reading of the above text in the SAP stated that both doses for both (co) primary endpoints should reach statistical significance, otherwise all secondary endpoints could not be tested, or considered as confirmatory. This was considered to be important as it is not the same as some secondary endpoints passing and others failing. The statistical evidence for all secondary endpoints failing to achieve type I error control, versus some secondary endpoints failing to achieving type I error control is important,

regardless of whether one or both doses passed. In this case, the MO was raised precisely because it was felt that not a single secondary efficacy endpoint could be considered as confirmatory, despite having nominal significance. The CHMP guidelines on multiplicity while acknowledging that secondary endpoints need not be subject to type I error control, also recognises that the evidence from these endpoints without type I error control may nevertheless be unreliable and could not normally be considered confirmatory.

There is no question that the higher 360mg dose achieved clinical and statistical evidence for the co-primary endpoint. The translation of the multiplicity rule as both DOSES and both co-primary endpoints requiring statistical significance was re-examined outside the context of the secondary endpoints testing. It was subsequently felt that based on statistical evidence, the higher dose of 360mg could be approvable based on the co-primary endpoints despite only nominal significance levels for all thirteen secondary endpoints. Consequently, the CHMP agrees to accept the 360 mg dose as a maintenance treatment in UC.

While only nominally statistically significant, secondary endpoints on endoscopic results are supportive of the efficacy of RZB versus placebo and are clinically relevant. Evaluation of endoscopic endpoints (e.g., endoscopic remission, ulcer-free endoscopy, sustained endoscopic remission, deep remission) demonstrated a dose response, with the RZB 360 mg SC arm having higher efficacy than observed for the RZB 180 mg SC arm versus placebo. Relative rates of improvement in symptomatic endpoints were not demonstrably different between the treatment and PBO arms. Overall, the trends in non-significant secondary endpoints supported the 360 mg dose over the 180 mg dose.

In addition, the MAH was asked to remove the text "or if such therapies are not advisable" from the indication as it was considered to be inappropriate/unnecessary. The revised indication, as proposed by the MAH which referred to "or have medical contraindications to such therapies" was also not agreed.

The indication proposed by CHMP is sufficient to provide prescribers with the necessary information for the appropriate use of risankizumab, in the treatment of CD. The MAH agreed to update the indication to the following:

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

***Assessment of paediatric data on clinical efficacy***

The number of adolescent patients recruited to the Induction and maintenance studies was small (n=15 in total).

No conclusions on the limited amount of data can be drawn. Therefore, as the Paediatric development which enrols patients from 2 years of age to 18 has been deferred until 2026, the indications should be restrict from 18 years of age.

## 2.6.7. Conclusions on the clinical efficacy

The CHMP considers that the MAH has shown statistically significant effects for both co-primary endpoints for risankizumab 600 mg and 1200 mg arms (IV) compared to the placebo arm for induction of CD control. The MAH has also shown statistically significant effects for both co-primary endpoints for risankizumab 360 mg (SC) as a maintenance dosage. The primary endpoints were nominally supported by secondary endpoints. Statistical significance of the secondary endpoints is not considered an essential requirement to conclude an overall positive benefit/risk regarding the highest risankizumab dosage.

Therefore, the CHMP supports the proposed dose of 600 mg administered by intravenous infusion for induction, followed by 360 mgs administered by subcutaneous injection for maintenance.

## 2.6.8. Clinical safety

The clinical development program for risankizumab in Crohn's disease included the following studies:

- One Phase 2 dose-ranging study M15-993
- One Phase 2 open label extension study M15-989
- Two Phase 3 induction studies (Study M15-991 and Study M16-006)
- One Phase 3 randomized withdrawal maintenance study (Study M16-000)

In addition, additional safety and tolerability data are provided from Phase 1 studies in healthy volunteers.

- Four Phase 1 PK and safety studies of single IV or SC doses of risankizumab (Studies M16-533, M16-324, M17-381, and M19-128)
- One non-drug study (Study F20-282) assessed the effectiveness and tolerability of the adhesive for the on-body delivery system (OBDS) device (the intended delivery device for maintenance therapy)

A total of 1,574 subjects received at least 1 dose of risankizumab in the global Phase 2 and Phase 3 CD studies, representing a total of 2,059.2 patient-years (PY) of risankizumab exposure. Of these subjects, 1,405 (89.3%) had exposure to risankizumab for at least 3 months, and 852 (54.1%) had exposure to risankizumab for at least 1 year. For the proposed to-be-marketed doses (which were based primarily on efficacy considerations), 620 subjects received at least 1 dose of risankizumab 600 mg IV, and 233 subjects had exposure to risankizumab 360 mg SC for at least 1 year.

The safety of risankizumab for both induction and maintenance treatment regimens were characterized based on a comprehensive evaluation of multiple analysis sets. The 3 primary analysis sets are summarised below:

- The induction phase of treatment (Week 0 through Week 12).

  The Placebo-Controlled 12-Week Induction Period Safety Analysis Set provided an integrated safety assessment across the placebo-controlled 12-Week Induction Periods of the Phase 2 and Phase 3 studies. This analysis set provides a robust assessment of risankizumab induction treatment, where subjects received doses of risankizumab (600 or 1200 mg) administered by IV infusion

- The maintenance phase of treatment (Week 0 of maintenance up to week 52).

  The Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set provided safety information for subjects who were in the pivotal portion of the placebo-controlled randomized responder-withdrawal Phase 3 maintenance trial, Study M16-000 Sub-Study 1. This analysis set, a subset of the entire safety population of Study M16-000 Sub-Study 1 (denoted as SA1), contained safety data from subjects with clinical response to IV risankizumab induction who were randomized to risankizumab 180 mg or 360 mg SC doses or to a withdrawal (placebo SC) arm. This analysis set provided the most clinically relevant safety results for maintenance treatment with risankizumab as it is the only analysis set that aligns with treatment practice

(i.e., assessment of safety of maintenance treatment in subjects with clinical response to IV risankizumab induction).

- The All Treated Safety Analysis Set

  This integrated set provided an integrated safety assessment for all subjects, both risankizumab-treated and placebo-treated (risankizumab naïve [up to the first dose of risankizumab]), across Phase 2 and 3 induction and maintenance studies; this analysis set provided the largest sample size and PY of exposure for the detection of uncommon and rare events across the entire CD program. This analysis set contains subgroups to further characterize safety, including the any risankizumab IV (ANY RZB IV) and any risankizumab SC (ANY RZB SC) groups to characterize safety for the IV and SC routes of administration of higher and lower doses, respectively; as well as the ANY RZB group, which includes the safety data for all subjects with any treatment of risankizumab.

*Table 48 Primary Safety Analysis Sets*

| 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) | 1629 | Integrated<br>M15-991 / M16-006 12-Week Induction Period;<br>M15-993 Period 1[b] | All subjects who received at least 1 dose of study drug during the studies and treatment periods indicated | RZB 1200 mg IV<br>RZB 600 mg IV<br>PBO IV | Safety of risankizumab as induction treatment[a] |
| Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set | 542 | Not integrated<br>M16-000 Sub-Study 1 | All randomized subjects who received at least 1 dose of study drug in M16-000 SS1 and who had received IV risankizumab induction | RZB 360 mg SC<br>RZB 180 mg SC<br>Withdrawal (PBO) SC | Safety of risankizumab as maintenance treatment in subjects with clinical response to IV risankizumab induction |
| All Treated Safety Analysis Set (ISS4) | 1670 | Integrated<br>M15-993 Period 1, 2, and 3;<br>M15-989;<br>M15-991 / M16-006 12-Week Induction Period, Induction Period 2;<br>M16-000 Sub-Study 1, Sub-Study 2, Sub-Study 3 | All subjects who received at least 1 dose of study drug from all Phase 2 and 3 CD studies | RZB 1200 mg IV<br>RZB 600 mg IV<br>RZB 360 mg SC<br>RZB 180 mg SC<br>Any RZB IV<br>Any RZB SC<br>Any RZB<br>PBO IV/SC (RZB naïve) | Comprehensive overview of safety and exposure to RZB and PBO in all Phase 2 and 3 Studies<br>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) |

IV = intravenous; PBO = placebo; RZB = risankizumab; SC = subcutaneous; SS1 = Sub-Study 1

a. Selected analyses will be performed overall, as well as presented for selected outputs by subjects having Baseline eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease), for the Placebo-controlled 12-week Induction Period Safety Analysis Set.

b. Only the risankizumab 600 mg IV and Placebo IV groups are included for Study M15-993 Period 1 in the Placebo-Controlled 12-Week Induction Period analysis.

The treatment flow for the 3 primary analysis sets are summarised in the Figure 22.

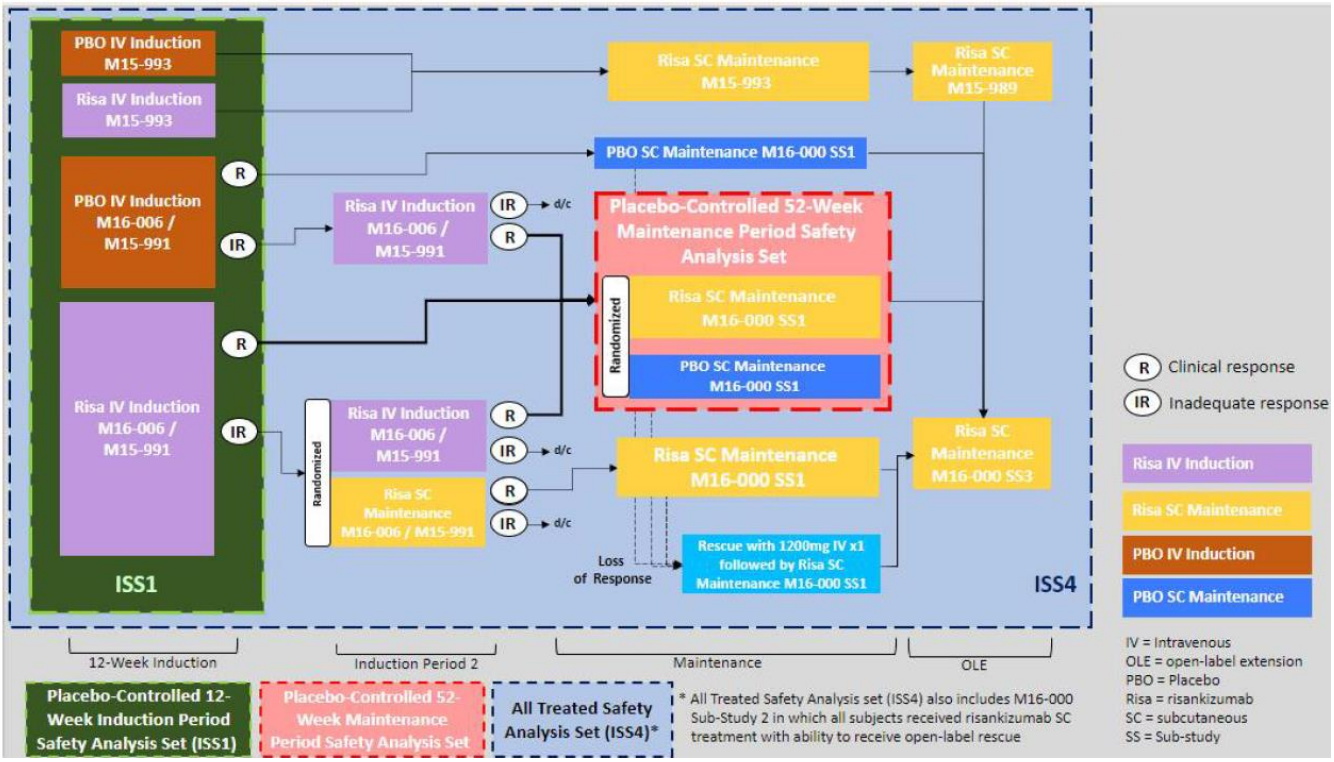



*Figure 22 Treatment Flow for Primary Analysis Sets*

In addition to the 3 primary analysis sets described above, 3 integrated analysis sets characterizing subsets of populations during the induction or maintenance periods are presented as supportive integrated safety analysis. These include:

- 24-Week Induction Period Safety Analysis Set (M15-991 / M16-006 12-Week Induction Period, Induction Period 2)
- Maintenance Treatment Safety 1 Analysis Set (M16-000 Sub-Study 1, Sub-Study 3)
- Maintenance Treatment Safety Analysis Set 2 (M15-991 / M16-006 Induction Period 2; M16-000 Sub-Study 1, Sub-Study 3)

*Table 49 Supportive Integrated Analyses Sets*

| Analysis Sets | N | Pooled Studies / Treatment Periods or Sub-Studies | Study Population | Treatment Groups | Key Analyses or Purpose |
|---|---|---|---|---|---|
| 24-Week Induction Period Safety Analysis Set (ISS2) | 457 | M15-991 / M16-006 12-Week Induction Period, Induction Period 2 | All subjects who received at least 1 dose of study drug in Induction Period 2 | • Induction Period 2 (Weeks 12 - 24):<br>  • RZB 1200 mg IV<br>  • RZB 360 mg SC<br>  • RZB 180 mg SC<br>  • PBO/RZB 1200 mg IV<br>  • RZB Total<br>• 12-Week Induction Period and Induction Period 2 (Weeks 0 - 24):<br>  • RZB IV[a]/1200 mg IV | • Safety of RZB in subjects who did not have clinical response to IV study drug in the 12-Week Induction Period and who entered Induction Period 2<br>• Safety of RZB in subjects who received 24 weeks of IV RZB treatment |
| Maintenance Treatment Safety Analysis Set 1 (ISS3A) | 620 | M16-000 Sub-Study 1, Sub-Study 3 | All subjects who received at least 1 dose of study drug in Study M16-000 SS1 and who received 12 weeks of IV RZB or IV PBO during the induction studies | • Any RZB SC<br>• PBO SC (RZB exposed [i.e., RZB IV responders re-randomized to PBO])<br>• PBO SC (RZB naïve [i.e., PBO IV responders maintained on PBO SC])<br>Note: Only PBO exposure during Study M16-000 Sub-Study 1 is included | • Safety of RZB and PBO SC maintenance treatment among subjects who achieved clinical response to RZB or PBO IV in the 12-Week Induction Period<br>• Safety of RZB and PBO SC maintenance treatment among PBO/1200 mg IV subjects in induction, who received at least 1 dose of PBO or RZB (180 mg or 360 mg) SC in Study M16-000 Sub-Study 1 |

| Analysis Sets | N | Pooled Studies / Treatment Periods or Sub-Studies | Study Population | Treatment Groups | Key Analyses or Purpose |
|---|---|---|---|---|---|
| Maintenance Treatment Safety Analysis Set 2 (ISS3B) | 169 | M15-991 / M16-006 Induction Period 2; M16-000 Sub-Study 1, Sub-Study 3 | • All subjects who received at least 1 dose of RZB SC during Study M16-000 Sub-Study 1 and who were randomized to RZB SC in Induction Period 2; these subjects may have enrolled in Study M16-000 Sub-Study 3<br>• All subjects who received at least 1 dose of PBO SC during Study M16-000 Sub-Study1 and who received IV PBO during the induction studies | • Any RZB SC<br>• PBO SC (RZB naïve) | • Safety of RZB SC maintenance treatment in subjects with delayed clinical response (i.e., subjects who achieved clinical response to RZB SC at Week 24 of induction)<br>• Safety in subjects with clinical response who were naïve to RZB treatment |

a. RZB IV for the 12-Week Induction Period includes RZB 600 mg and 1200 mg groups.

The MAH provided comparison to data from Risankizumab Psoriasis 150 mg SC CCDS and referred to postmaketing safety data from the approved indications of psoriasis and psoriatic arthritis.

The MAH has focused the Summary of Clinical Safety on pooled data and data analysed separately for 3 primary analysis sets; The Placebo-Controlled 12-Week Induction Period Safety Analysis Set, The Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set, The All Treated Safety Analysis Set.

The primary safety analysis sets are considered broadly reasonable. The induction phase set integrates data from the induction phases of M15-991, M16-006 and M15-993, where patients received at least one dose of risankizumab of 600 or 1200 mg at 0,4 and 8 weeks administered by IV infusion (200mg IV dose from period 1 of M15-993 not included). Pooling of this dataset is considered appropriate and it is agreed that the population n=1629 provides for a robust characterisation of safety during induction treatment.

The 52 week maintenance period analysis set includes all randomised subjects to M16-000 who received at least 1 dose of drug in sub study 1 (n= 542, of which n=179 subjects were randomised to risankizumab 180 mg SC, n=179 subjects to risankizumab 360 mg SC, and n=184 subjects to withdrawal [placebo SC] arm). This set includes subjects who had achieved SF/APS clinical response to IV risankizuma and who had previously received IV risankizumab induction. While the MAH outlines

this as the most clinically relevant in terms of characterisation of safety results for maintenance treatment with risankizumab, noteworthy in terms of the proposed to-be-marketed dose and device is the absence of any clinical safety data with the on-body delivery system, see discussion below and related MO.

The all treated safety analysis set includes all subjects across the CD program and all treatment groups with extended exposure beyond Week 52. For subjects receiving placebo, events would be attributed to only placebo exposure (i.e., PBO IV/SC [RZB-naïve] subjects), until their first dose of risankizumab.

A comparison of safety findings to the established safety profile from psoriasis clinical development programme as well as reference to post-marketing experience of safety is provided and of interest.

Analysis of safety

Treatment-emergent AEs are defined as events with onset after the first dose of study drug and within 140 days after the last dose of study drug.

Adverse events are coded using the MedDRA version 23.1, with the same version used for the pivotal study CSRs. Each AE is coded to a SOC and preferred term (PT). A subject with more than 1 AE for the same PT is counted only once for that term. Severity of the AEs was assessed using National Cancer Institute (NCI) Common Terminology Criteria. All AEs presented in this section were treatment-emergent, unless otherwise noted.

Safety was evaluated by monitoring of AEs, including SAEs; evaluation of clinical laboratory values (hematology and clinical chemistry), and physical examination including vital signs. In addition to analysis of all treatment-emergent AEs (TEAEs), Areas of Special Interest (ASI) were defined based on prevalence in the moderately to severely active CD population, customary concerns with injected immunoglobulin products, the immunomodulatory activity of risankizumab, or regulatory interest. These ASIs were identified using standard MedDRA queries (SMQ) and company MedDRA queries (CMQ).

These ASIs included:

- adjudicated CV events (including MACE and extended MACE);
- infections (including serious infections, active TB, opportunistic infections [excluding TB and herpes zoster], and herpes zoster)
- malignancies (including malignant tumours, non-melanoma skin cancer [NMSC]), and malignant tumours (excluding NMSC)
- hypersensitivity reactions (including serious hypersensitivity reactions) and
- adjudicated anaphylactic reactions;
- hepatic events;
- injection site reactions (including infusion-related reactions).

Real-world epidemiology data have been presented as reference benchmarks to contextualize the long-term event rates of ASIs that are rare and of longer latency such as MACE and malignancies.

To adjust for potentially different follow-up times between treatment groups, exposure-adjusted event rate (EAERs) and exposure-adjusted incidence rates (EAIRs) are provided for all AE tables from the integrated analysis sets. The EAER was generally used as the main approach when summarizing long-term AEs, because they capture the complete event information during the entire follow up period. Exposure-adjusted incidence rates were summarized for AEs which typically occur as single instances or for composite endpoints of interrelated events (i.e., deaths, malignancies, and MACE).

For the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set and the All Treated Safety Analysis Set, AE summaries are descriptive and only raw percentages and rates are presented. To appropriately account for differences in study sizes, study-size adjusted (SSA) percentage and rate are provided in-text for the following integrated datasets: Placebo-Controlled 12-Week Induction Period Safety Analysis Set, 24-Week Induction Period Safety Analysis Set, and the Maintenance Treatment

Safety 1 and 2 Analysis Sets.

Subgroup analyses were conducted to evaluate whether demographic characteristics or disease characteristics factors had a differential effect on safety.

Demographic and other Characteristics

12-Week Induction

The demographics for the Placebo-Controlled 12-Week Induction Period Safety Analysis Set are summarized in Table 50.

*Table 50 Demographic Characteristics (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

| Variable | Placebo IV (N = 432) | Risankizumab 600 mg IV (N = 620) | Risankizumab 1200 mg IV (N = 577) | Risankizumab Total (N = 1197) |
|---|---|---|---|---|
| **Age (years)** | | | | |
| Mean (SD) | 38.2 (13.46) | 39.2 (13.34) | 38.3 (13.33) | 38.8 (13.34) |
| Median (min, max) | 35.5 (16, 80) | 37.0 (16, 79) | 36.0 (16, 74) | 37.0 (16, 79) |
| < 18 – n (%) | 5 (1.2) | 4 (0.6) | 5 (0.9) | 9 (0.8) |
| [18, 40) – n (%) | 255 (59.0) | 341 (55.0) | 329 (57.0) | 670 (56.0) |
| [40, 65) – n (%) | 150 (34.7) | 244 (39.4) | 219 (38.0) | 463 (38.7) |
| ≥ 65 – n (%) | 22 (5.1) | 31 (5.0) | 24 (4.2) | 55 (4.6) |
| **Sex – n (%)** | | | | |
| Female | 220 (50.9) | 299 (48.2) | 272 (47.1) | 571 (47.7) |
| Male | 212 (49.1) | 321 (51.8) | 305 (52.9) | 626 (52.3) |
| **Race – n (%)** | | | | |
| American Indian/Alaska Native | 0 | 0 | 0 | 0 |
| Asian | 54 (12.5) | 84 (13.5) | 89 (15.4) | 173 (14.5) |
| Black or African American | 22 (5.1) | 18 (2.9) | 21 (3.6) | 39 (3.3) |
| Native Hawaiian or Other Pacific Islander | 3 (0.7) | 0 | 1 (0.2) | 1 (< 0.1) |
| White | 352 (81.5) | 514 (82.9) | 461 (79.9) | 975 (81.5) |
| Multiple | 1 (0.2) | 4 (0.6) | 5 (0.9) | 9 (0.8) |
| **Ethnicity - n (%)** | | | | |
| Hispanic/Latino | 32 (7.4) | 33 (5.3) | 33 (5.7) | 66 (5.5) |
| Non-Hispanic/Latino | 400 (92.6) | 587 (94.7) | 544 (94.3) | 1131 (94.5) |
| **Geographic region[a] – n (%)** | | | | |
| North America | 131 (30.3) | 153 (24.7) | 150 (26.0) | 303 (25.3) |
| South/Central America | 13 (3.0) | 10 (1.6) | 11 (1.9) | 21 (1.8) |
| Western Europe | 130 (30.1) | 223 (36.0) | 194 (33.6) | 417 (34.8) |
| Eastern Europe | 76 (17.6) | 110 (17.7) | 103 (17.9) | 213 (17.8) |
| Asia | 52 (12.0) | 78 (12.6) | 85 (14.7) | 163 (13.6) |
| Other | 30 (6.9) | 46 (7.4) | 34 (5.9) | 80 (6.7) |

| Variable | Placebo IV (N = 432) | Risankizumab 600 mg IV (N = 620) | Risankizumab 1200 mg IV (N = 577) | Total (N = 1197) |
|---|---|---|---|---|
| **Weight (kg)** | | | | |
| Mean (SD) | 71.502 (18.9414) | 71.197 (18.1931) | 71.398 (19.1798) | 71.294 (18.6677) |
| Median | 70.000 | 68.923 | 68.000 | 68.400 |
| Min, Max | 35.00, 145.15 | 32.00, 145.60 | 38.00, 158.50 | 32.00, 158.50 |
| < 60 kg | 134 (31.0) | 180 (29.0) | 172 (29.8) | 352 (29.4) |
| ≥ 60 kg | 298 (69.0) | 440 (71.0) | 405 (70.2) | 845 (70.6) |
| **Body mass index (kg/m$^2$)** | | | | |
| Mean (SD) | 24.72 (5.873) | 24.63 (5.817) | 24.48 (6.118) | 24.56 (5.962) |
| Median (min, max) | 23.73 (13.6, 51.7) | 23.84 (13.0, 52.4) | 23.39 (13.7, 58.2) | 23.63 (13.0, 58.2) |
| < 18.5 – n (%) | 45 (10.4) | 71 (11.5) | 70 (12.1) | 141 (11.8) |
| [18.5, 25) – n (%) | 205 (47.5) | 288 (46.5) | 292 (50.6) | 580 (48.5) |
| [25, 30) – n (%) | 107 (24.8) | 163 (26.3) | 128 (22.2) | 291 (24.3) |
| ≥ 30 – n (%) | 75 (17.4) | 98 (15.8) | 87 (15.1) | 185 (15.5) |
| **Tobacco/nicotine use – n (%)** | | | | |
| Currently smokes | 97 (22.5) | 141 (22.7) | 119 (20.6) | 260 (21.7) |
| Ex-smoker | 91 (21.1) | 150 (24.2) | 135 (23.4) | 285 (23.8) |
| Never smoked | 243 (56.3) | 328 (52.9) | 322 (55.8) | 650 (54.3) |
| Unknown | 1 (0.2) | 1 (0.2) | 1 (0.2) | 2 (0.2) |
| **Alcohol use – n (%)** | | | | |
| Current drinker | 163 (37.7) | 234 (37.7) | 214 (37.1) | 448 (37.4) |
| Former drinker | 51 (11.8) | 63 (10.2) | 59 (10.2) | 122 (10.2) |
| Non-drinker | 190 (44.0) | 292 (47.1) | 298 (51.6) | 590 (49.3) |
| Unknown | 28 (6.5) | 31 (5.0) | 6 (1.0) | 37 (3.1) |

Maintenance up to 52 Weeks and All Treated Safety Analysis Set

The demographics for Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set are summarized in Table 51.

*Table 51 Demographic Characteristics at Baseline of Induction Study (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set)*

| Variable | Withdrawal (Placebo SC) (N = 184) | Risankizumab 180 mg SC (N = 179) | Risankizumab 360 mg SC (N = 179) | Total (N = 542) |
|---|---|---|---|---|
| **Age (years)** | | | | |
| n | 184 | 179 | 179 | 542 |
| Mean (SD) | 38.3 (13.50) | 39.4 (14.54) | 37.9 (13.02) | 38.5 (13.69) |
| Median (min, max) | 37.0 (17, 76) | 37.0 (16, 75) | 35.0 (16, 71) | 36.0 (16, 76) |
| < 18 | 1 (0.5) | 2 (1.1) | 2 (1.1) | 5 (0.9) |
| [18, 40) | 107 (58.2) | 100 (55.9) | 104 (58.1) | 311 (57.4) |
| [40, 65) | 68 (37.0) | 62 (34.6) | 64 (35.8) | 194 (35.8) |
| ≥ 65 | 8 (4.3) | 15 (8.4) | 9 (5.0) | 32 (5.9) |
| **Sex - n(%)** | | | | |
| Female | 86 (46.7) | 101 (56.4) | 77 (43.0) | 264 (48.7) |
| Male | 98 (53.3) | 78 (43.6) | 102 (57.0) | 278 (51.3) |
| **Race - n(%)** | | | | |
| White | 145 (78.8) | 147 (82.1) | 143 (79.9) | 435 (80.3) |
| Black or African American | 10 (5.4) | 5 (2.8) | 10 (5.6) | 25 (4.6) |
| Asian | 29 (15.8) | 23 (12.8) | 23 (12.8) | 75 (13.8) |
| American Indian/Alaska Native | 0 | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 (0.6) | 0 | 1 (0.2) |
| Multiple | 0 | 3 (1.7) | 3 (1.7) | 6 (1.1) |
| **Ethnicity - n(%)** | | | | |
| Hispanic/Latino | 9 (4.9) | 10 (5.6) | 9 (5.0) | 28 (5.2) |
| Non-Hispanic/Latino | 175 (95.1) | 169 (94.4) | 170 (95.0) | 514 (94.8) |

| Variable | Withdrawal (Placebo SC) (N = 184) | Risankizumab 180 mg SC (N = 179) | Risankizumab 360 mg SC (N = 179) | Total (N = 542) |
|---|---|---|---|---|
| **Geographic region - n(%)** | | | | |
| North America | 57 (31.0) | 47 (26.3) | 47 (26.3) | 151 (27.9) |
| South/Central America | 4 (2.2) | 4 (2.2) | 1 (0.6) | 9 (1.7) |
| Western Europe | 57 (31.0) | 58 (32.4) | 61 (34.1) | 176 (32.5) |
| Eastern Europe | 27 (14.7) | 36 (20.1) | 35 (19.6) | 98 (18.1) |
| Asia | 26 (14.1) | 22 (12.3) | 23 (12.8) | 71 (13.1) |
| Other | 13 (7.1) | 12 (6.7) | 12 (6.7) | 37 (6.8) |
| **Body weight (kg)** | | | | |
| Mean (SD) | 72.006 (18.6827) | 70.471 (17.1678) | 71.159 (18.6777) | 71.219 (18.1719) |
| Median | 67.950 | 68.600 | 68.600 | 68.350 |
| Min, Max | 36.60, 147.50 | 38.10, 126.70 | 39.00, 145.60 | 36.60, 147.50 |
| < 60 kg | 51 (27.7) | 53 (29.6) | 52 (29.1) | 156 (28.8) |
| ≥ 60 kg | 133 (72.3) | 126 (70.4) | 127 (70.9) | 386 (71.2) |
| **Body mass index (kg/m$^2$)** | | | | |
| Mean (SD) | 24.87 (6.222) | 24.65 (5.585) | 24.14 (5.596) | 24.56 (5.810) |
| Median | 23.86 | 23.70 | 22.98 | 23.68 |
| Min, Max | 13.0, 54.1 | 15.1, 44.5 | 15.1, 47.4 | 13.0, 54.1 |
| Underweight [< 18.5 kg/m$^2$] | 20 (10.9) | 18 (10.1) | 21 (11.7) | 59 (10.9) |
| Normal [≥ 18.5 and < 25 kg/m$^2$] | 94 (51.1) | 90 (50.3) | 96 (53.6) | 280 (51.7) |
| Overweight [≥ 25 and < 30 kg/m$^2$] | 40 (21.7) | 41 (22.9) | 40 (22.3) | 121 (22.3) |
| Obese [≥ 30 kg/m$^2$] | 30 (16.3) | 30 (16.8) | 22 (12.3) | 82 (15.1) |
| **Tobacco/nicotine use - n(%)** | | | | |
| Currently smokes | 44 (23.9) | 36 (20.1) | 36 (20.1) | 116 (21.4) |
| Ex-smoker | 41 (22.3) | 47 (26.3) | 35 (19.6) | 123 (22.7) |
| Never smoked | 98 (53.3) | 95 (53.1) | 108 (60.3) | 301 (55.5) |
| Unknown | 1 (0.5) | 1 (0.6) | 0 | 2 (0.4) |

| Variable | Withdrawal (Placebo SC) (N = 184) | Risankizumab 180 mg SC (N = 179) | Risankizumab 360 mg SC (N = 179) | Total (N = 542) |
|---|---|---|---|---|
| **Alcohol use - n(%)** | | | | |
| Current drinker | 74 (40.2) | 72 (40.2) | 67 (37.4) | 213 (39.3) |
| Former drinker | 15 (8.2) | 17 (9.5) | 25 (14.0) | 57 (10.5) |
| Non-drinker | 92 (50.0) | 87 (48.6) | 85 (47.5) | 264 (48.7) |
| Unknown | 3 (1.6) | 3 (1.7) | 2 (1.1) | 8 (1.5) |

a. "Other" geographic region contains Australia, Egypt, Israel, New Zealand, South Africa, and Tunisia.
Notes: Demographics characteristics are summarized at the Baseline of the induction study.
Percentages calculated on non-missing values.

### *2.6.8.1. Patient exposure*

12-Week Induction

The Placebo-Controlled 12-Week Induction Period Safety Analysis Set includes data from 1,629 subjects, of whom 1,197 received at least 1 dose of risankizumab (either 600 mg IV [N = 620] or 1200 mg IV [N = 577]) and 432 received at least 1 dose of placebo. The median duration of exposure for each of the 3 treatment groups was 84.0 days.

TABLE 2.3 1.1.1

Extent of Exposure to Study Drug
(Placebo-Controlled 12-Week Induction Period Safety Analysis Set)

| Exposure to Study Drug | Placebo IV (N=432) | Risankizumab 600 mg IV (N=620) | Risankizumab 1200 mg IV (N=577) | Risankizumab Total (N=1197) |
|---|---|---|---|---|
| Duration interval (days) | | | | |
| >= 1 dose | 432 (100) | 620 (100) | 577 (100) | 1197 (100) |
| > 28 (4 weeks) | 405 (93.8) | 615 (99.2) | 571 (99.0) | 1186 (99.1) |
| > 56 (8 weeks) | 390 (90.3) | 611 (98.5) | 565 (97.9) | 1176 (98.2) |
| > 84 (12 weeks) | 115 (26.6) | 181 (29.2) | 169 (29.3) | 350 (29.2) |
| > 112 (16 weeks) | 0 | 0 | 1 (0.2) | 1 (<0.1) |
| Duration interval (days) | | | | |
| 1 - 28 | 27 (6.3) | 5 (0.8) | 6 (1.0) | 11 (0.9) |
| 29 - 56 | 15 (3.5) | 4 (0.6) | 6 (1.0) | 10 (0.8) |
| 57 - 84 | 275 (63.7) | 430 (69.4) | 396 (68.6) | 826 (69.0) |
| 85 - 112 | 115 (26.6) | 181 (29.2) | 168 (29.1) | 349 (29.2) |
| > 112 | 0 | 0 | 1 (0.2) | 1 (<0.1) |
| Duration (days) | | | | |
| n | 432 | 620 | 577 | 1197 |
| Mean (SD) | 78.9 (15.04) | 83.3 (7.04) | 83.0 (7.98) | 83.1 (7.50) |
| Median | 84.0 | 84.0 | 84.0 | 84.0 |
| Min, Max | 28, 106 | 28, 112 | 28, 154 | 28, 154 |

Note: ISS1 includes all subjects that have received at least one dose of study drug in the 12-week induction Period 1 from the two global Phase 3 studies: M15-991 and M16-006, as well as the subjects from the Phase 2 study M15-993 who received placebo or risankizumab 600mg IV for the 12-week induction period.
Total exposure is defined as last dose date of study drug in induction period + 28 - first dose date of study drug, first dose date of study drug in induction period 2, if applicable - first dose date of study drug, or first dose date of study drug in M16-000, if applicable - first dose date of study drug, whichever is shorter.

Maintenance up to 52 Weeks

The Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set includes data from 358 subjects who received at least 1 dose of risankizumab (N = 179 for each of 180 and 360 mg SC) for a median duration of 390.0 days of maintenance treatment and 184 who received at least 1 dose of placebo for a mean duration of 308.5 days

Extent of Exposure
Among Randomized Subjects
(SA1 Population)

| Exposure to study drug | Placebo SC [A] (N=184) n (%) | Risankizumab 180 mg SC [A] (N=179) n (%) | Risankizumab 360 mg SC [A] (N=179) n (%) | Risankizumab Total [A] (N=358) n (%) | Risankizumab Rescue Therapy [B] (N=150) n (%) |
|---|---|---|---|---|---|
| Duration interval (days) | | | | | |
| 1 - 56 | 0 | 2 (1.1) | 2 (1.1) | 4 (1.1) | 22 (14.7) |
| 57 - 112 | 10 (5.4) | 9 (5.0) | 7 (3.9) | 16 (4.5) | 10 (6.7) |
| 113 - 168 | 23 (12.5) | 13 (7.3) | 19 (10.6) | 32 (8.9) | 25 (16.7) |
| 169 - 224 | 22 (12.0) | 9 (5.0) | 12 (6.7) | 21 (5.9) | 39 (26.0) |
| 225 - 280 | 7 (3.8) | 10 (5.6) | 8 (4.5) | 18 (5.0) | 47 (31.3) |
| 281 - 336 | 8 (4.3) | 2 (1.1) | 4 (2.2) | 6 (1.7) | 7 (4.7) |
| 337 - 392 | 83 (45.1) | 107 (59.8) | 81 (45.3) | 188 (52.5) | 0 |
| > 392 | 31 (16.8) | 27 (15.1) | 46 (25.7) | 73 (20.4) | 0 |
| Duration (days) | | | | | |
| n | 184 | 179 | 179 | 358 | 150 |
| Mean (SD) | 308.5 (109.30) | 334.8 (101.50) | 328.1 (106.59) | 331.4 (103.98) | 185.0 (80.92) |
| Median | 385.5 | 389.0 | 390.0 | 390.0 | 202.5 |
| Min, Max | 105, 402 | 56, 423 | 56, 438 | 56, 438 | 8, 316 |

All Treated Safety Analysis Set

The All Treated Safety Analysis Set includes data from all 1,574 subjects in the Phase 2 and Phase 3 CD studies who received at least 1 dose of risankizumab for a median duration of 390.5 days and a total 2,059.2 PY of exposure. Of these subjects, 852 (54.1%) subjects had exposure to risankizumab for at least 1 year.

A total of 688 subjects received the risankizumab 600 mg IV induction dose. A total of 533 subjects received the risankizumab 360 mg SC maintenance dose, including 333 with at least 6 months of exposure and 233 with at least 12 months of exposure.

Extent of Exposure to Study Drug
(All Treated Safety Analysis Set)

| Exposure to Study Drug | Placebo IV/SC (RZB naive) (N=432) | RZB 180 mg SC (N=1096) | RZB 360 mg SC (N=533) | RZB 600 mg IV (N=688) | RZB 1200 mg IV (N=1023) | Any RZB SC (N=1318) | Any RZB IV (N=1536) | Any RZB (N=1574) |
|---|---|---|---|---|---|---|---|---|
| Duration interval (days) | | | | | | | | |
| >= 1 dose | 432 (100) | 1096 (100) | 533 (100) | 688 (100) | 1023 (100) | 1318 (100) | 1536 (100) | 1574 (100) |
| >= 30 (1 month) | 405 (93.8) | 1090 (99.5) | 525 (98.5) | 683 (99.3) | 956 (93.5) | 1315 (99.8) | 1505 (98.0) | 1550 (98.5) |
| >= 90 (3 months) | 209 (48.4) | 953 (87.0) | 449 (84.2) | 241 (35.0) | 378 (37.0) | 1215 (92.2) | 746 (48.6) | 1405 (89.3) |
| >= 180 (6 months) | 99 (22.9) | 724 (66.1) | 333 (62.5) | 39 (5.7) | 29 (2.8) | 1010 (76.6) | 114 (7.4) | 1234 (78.4) |
| >= 360 (12 months) | 50 (11.6) | 374 (34.1) | 233 (43.7) | 1 (0.1) | 0 | 603 (45.8) | 2 (0.1) | 852 (54.1) |
| >= 540 (18 months) | 0 | 151 (13.8) | 27 (5.1) | 0 | 0 | 268 (20.3) | 0 | 397 (25.2) |
| >= 720 (24 months) | 0 | 88 (8.0) | 5 (0.9) | 0 | 0 | 135 (10.2) | 0 | 190 (12.1) |
| >= 900 (30 months) | 0 | 59 (5.4) | 1 (0.2) | 0 | 0 | 72 (5.5) | 0 | 99 (6.3) |
| >= 1080 (36 months) | 0 | 46 (4.2) | 0 | 0 | 0 | 46 (3.5) | 0 | 54 (3.4) |
| >= 1260 (42 months) | 0 | 45 (4.1) | 0 | 0 | 0 | 45 (3.4) | 0 | 47 (3.0) |
| >= 1440 (48 months) | 0 | 43 (3.9) | 0 | 0 | 0 | 45 (3.4) | 0 | 45 (2.9) |
| >= 1620 (54 months) | 0 | 40 (3.6) | 0 | 0 | 0 | 42 (3.2) | 0 | 44 (2.8) |
| Duration interval (days) | | | | | | | | |
| 1 - 29 | 27 (6.3) | 6 (0.5) | 8 (1.5) | 5 (0.7) | 67 (6.5) | 3 (0.2) | 31 (2.0) | 24 (1.5) |
| 30 - 89 | 196 (45.4) | 137 (12.5) | 76 (14.3) | 442 (64.2) | 578 (56.5) | 100 (7.6) | 759 (49.4) | 145 (9.2) |
| 90 - 179 | 110 (25.5) | 229 (20.9) | 116 (21.8) | 202 (29.4) | 349 (34.1) | 205 (15.6) | 632 (41.1) | 171 (10.9) |
| 180 - 359 | 49 (11.3) | 350 (31.9) | 100 (18.8) | 38 (5.5) | 29 (2.8) | 407 (30.9) | 112 (7.3) | 382 (24.3) |
| 360 - 539 | 50 (11.6) | 223 (20.3) | 206 (38.6) | 1 (0.1) | 0 | 335 (25.4) | 2 (0.1) | 455 (28.9) |
| 540 - 719 | 0 | 63 (5.7) | 22 (4.1) | 0 | 0 | 133 (10.1) | 0 | 207 (13.2) |
| 720 - 899 | 0 | 29 (2.6) | 4 (0.8) | 0 | 0 | 63 (4.8) | 0 | 91 (5.8) |
| 900 - 1079 | 0 | 13 (1.2) | 1 (0.2) | 0 | 0 | 26 (2.0) | 0 | 45 (2.9) |
| 1080 - 1259 | 0 | 1 (<0.1) | 0 | 0 | 0 | 1 (<0.1) | 0 | 7 (0.4) |
| 1260 - 1439 | 0 | 2 (0.2) | 0 | 0 | 0 | 0 | 0 | 2 (0.1) |
| 1440 - 1619 | 0 | 3 (0.3) | 0 | 0 | 0 | 3 (0.2) | 0 | 1 (<0.1) |
| >= 1620 | 0 | 40 (3.6) | 0 | 0 | 0 | 42 (3.2) | 0 | 44 (2.8) |

Note: ISS4 includes all subjects that have received at least one dose of study drug from all Phase 2 and 3 CD studies and associated periods and Sub-studies: M15-993 (Periods 1, 2 and 3), M15-989, M15-991 (Periods 1 and 2), M16-006 (Periods 1 and 2), and M16-000 (Sub-Studies 1, 2 and 3).
Subjects may be represented in more than one treatment group according to treatments received.

Exposure by age across all indications in the clinical development (Psoriasis, Crohn's Disease, Ankylosing Spondylitis, Asthma, Generalized Pustular PsO or Erythrodermic PsO, Psoriatic Arthritis and Ulcerative Colitis studies) and by dose in terms of patient years is outlined in Table 52 and 53.

*Table 52 Exposure by Age Group and Gender*

| | Male | | Female | |
|---|---|---|---|---|
| **Age Group (years)** | **n** | **Patient Years** | **n** | **Patient Years** |
| **Cumulative for All Indications[a]** | | | | |
| < 18 | 10 | 8.4 | 14 | 8.5 |
| 18 to 64 | 3566 | 7825.4 | 2297 | 4054.6 |
| 65 to 74 | 343 | 803.0 | 292 | 522.6 |
| ≥ 75 | 45 | 102.1 | 38 | 47.2 |
| **Indication 1: Psoriasis[b]** | | | | |
| < 18 | 5 | 2.4 | 7 | 3.2 |
| 18 to 64 | 1966 | 6087.9 | 847 | 2487.2 |
| 65 to 74 | 223 | 684.9 | 108 | 324.6 |
| ≥ 75 | 26 | 80.1 | 15 | 23.3 |
| **Indication 2: Crohn's Disease[c]** | | | | |
| < 18 | 5 | 6.0 | 7 | 5.4 |
| 18 to 64 | 767 | 921.6 | 723 | 881.6 |
| 65 to 74 | 29 | 33.7 | 38 | 45.7 |
| ≥ 75 | 4 | 6.9 | 1 | 1.2 |

*Table 53 Exposure by Dose*

| Dose of Exposure | n | Patient Years |
|---|---|---|
| **Cumulative for All Indications[a]** | | |
| Risankizumab 150 mg SC | 3904 | 8581.2 |
| Risankizumab 180 mg SC | 1096 | 1057.5 |
| Risankizumab 360 mg SC | 533 | 408.6 |
| Risankizumab 600 mg IV | 688 | 176.3 |
| Risankizumab 1200 mg IV | 1023 | 249.3 |
| Risankizumab Other Dose | 1168 | 2899.0 |
| **Indication 1: Psoriasis[b]** | | |
| Risankizumab 150 SC | 2374 | 7044.9 |
| Risankizumab Other Dose | 823 | 2648.7 |
| **Indication 2: Crohn's Disease[c]** | | |
| Risankizumab 180 mg SC | 1096 | 1057.5 |
| Risankizumab 360 mg SC | 533 | 408.6 |
| Risankizumab 600 mg IV | 688 | 176.3 |
| Risankizumab 1200 mg IV | 1023 | 249.3 |
| Risankizumab Other Dose | 41 | 10.3 |

*Subject Disposition*

12-Week Induction

In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), 1,629 subjects received at least 1 dose of study drug, with 1,197 subjects treated with risankizumab IV and 432 subjects treated with placebo (Table 54). The percentage of subjects who discontinued study drug during the 12-Week Induction Period was 2.1% each in the risankizumab 600 mg and 1200 mg IV groups and 11.6% in the placebo group. Among the subjects who prematurely discontinued study drug, discontinuation due an AE was the most frequently reported primary reason for the Total RZB and placebo groups, with lower rates in the Total RZB group versus (vs.) placebo (1.0% vs. 6.5%, respectively). The most common AE leading to discontinuation of study drug in each treatment group was worsening of CD. A higher percentage of subjects in the placebo group (2.1%) compared with the Total RZB group (0.3%) reported lack of efficacy as the primary reason for premature discontinuation of study drug. No subjects discontinued due to COVID-19, while 2 subjects in the placebo group discontinued primarily due to COVID-19 logistical restrictions.

*Table 54 Subject Disposition (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

| | | Risankizumab | | |
|---|---|---|---|---|
| | **Placebo IV (N = 432) n (%)** | **600 mg IV (N = 620) n (%)** | **1200 mg IV (N = 577) n (%)** | **Total (N = 1197) n (%)** |
| Completed Induction Period Study Drug | 382 (88.4) | 607 (97.9) | 565 (97.9) | 1172 (97.9) |
| Discontinuation Due to (Primary Reason) | | | | |
| Any Reason | 50 (11.6) | 13 (2.1) | 12 (2.1) | 25 (2.1) |
| Adverse Event | 28 (6.5) | 5 (0.8) | 7 (1.2) | 12 (1.0) |
| Lack of Efficacy | 9 (2.1) | 1 (0.2) | 3 (0.5) | 4 (0.3) |
| Lost to Follow-Up | 2 (0.5) | 0 | 0 | 0 |
| Withdrawal by Subject | 6 (1.4) | 4 (0.6) | 0 | 4 (0.3) |
| Covid-19 | 0 | 0 | 0 | 0 |
| Covid-19 Logistical Restrictions | 2 (0.5) | 0 | 0 | 0 |
| Other | 3 (0.7) | 3 (0.5) | 2 (0.3) | 5 (0.4) |

Maintenance up to 52 Weeks

In the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), 542 subjects received at least 1 dose of study drug, with 358 subjects treated with either risankizumab 180 mg or 360 mg SC and 184 subjects treated in the withdrawal (placebo SC) arm (Table 54). Fewer subjects discontinued study drug in either of the risankizumab treatment arms as compared to the withdrawal (placebo SC) arm.

Across the study, lack of efficacy was the most frequently reported primary reason for discontinuation, with a higher percentage of subjects in the withdrawal (placebo SC) arm (6.0%) compared with the risankizumab 180 mg SC and 360 mg SC arms (1.7% and 3.4%, respectively) reporting lack of efficacy as the primary reason for premature discontinuation of study drug. No subjects in any treatment arms discontinued due to COVID-19 or COVID-19 logistical restrictions.

*Table 55 Subject Disposition (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set)*

| | **Withdrawal (Placebo SC) (N = 184) n (%)** | **Risankizumab 180 mg SC (N = 179) n (%)** | **Risankizumab 360 mg SC (N = 179) n (%)** | **Total (N = 542) n (%)** |
|---|---|---|---|---|
| Completed study | 160 (87.0) | 164 (91.6) | 160 (89.4) | 484 (89.3) |
| Discontinuation due to (primary reason) | | | | |
| Any reason | 24 (13.0) | 15 (8.4) | 19 (10.6) | 58 (10.7) |
| Adverse event | 5 (2.7) | 2 (1.1) | 3 (1.7) | 10 (1.8) |
| Lack of efficacy | 11 (6.0) | 3 (1.7) | 6 (3.4) | 20 (3.7) |
| Lost to follow-up | 0 | 2 (1.1) | 2 (1.1) | 4 (0.7) |
| Withdrawal by subject | 4 (2.2) | 5 (2.8) | 2 (1.1) | 11 (2.0) |
| COVID-19 | 0 | 0 | 0 | 0 |
| COVID-19 logistical restrictions | 0 | 0 | 0 | 0 |
| Other | 4 (2.2) | 3 (1.7) | 6 (3.4) | 13 (2.4) |

All Treated Safety Analysis Set

In the All Treated Safety Analysis Set, 1,670 subjects received at least 1 dose of study drug, with 1,574 subjects treated with risankizumab and 432 subjects treated with placebo IV/SC (RZB naïve). The percentage of subjects who discontinued study drug was 15.1% in the ANY RZB group and 19.0% in the placebo IV/SC (RZB naïve) group. Among the subjects who prematurely discontinued study

drug, adverse event was the most frequently reported primary reason for both the ANY RZB and placebo IV/SC (RZB-naïve) groups (4.3% and 7.9%, respectively).

### *2.6.8.2. Adverse events*

Percentage of subjects with AEs was lower in the risankizumab groups (53.9% in the risankizumab 600 mg IV group, 54.4% in the risankizumab 1200 mg IV group) compared to the placebo group (61.4%) (Table 65). The rates of SAEs, severe AEs, and AEs leading to study drug discontinuation were lower in both risankizumab IV groups compared with the placebo group. One death was reported in the risankizumab 1200 mg IV group, and 2 deaths were reported in the placebo group (discussed further below). Overall, there was no apparent dose-relationship on AE rates between the 600 mg and 1200 mg risankizumab IV doses (Table 56).

*Table 56 Overview of Treatment-Emergent Adverse Events in Percentage and EAER per 100 PY (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

| | Placebo IV (N = 432) (PY = 117.6) | | Risankizumab 600 mg IV (N = 620) (PY = 159.8) | | Risankizumab 1200 mg IV (N = 577) (PY = 143.3) | | Risankizumab Total (N = 1197) (PY = 303.1) | | Treatment Comparison [95% CI][a] for n (%) differences | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Subjects with:** | **n (%) [SSA%]** | **Events (E/100 PY) [SSA E/100 PY]** | **n (%) [SSA%]** | **Events (E/100 PY) [SSA E/100 PY]** | **n (%) [SSA%]** | **Events (E/100 PY) [SSA E/100 PY]** | **n (%) [SSA%]** | **Events (E/100 PY) [SSA E/100 PY]** | **RZB 600 mg IV - PBO IV** | **RZB 1200 mg IV - PBO IV** |
| All TEAEs | 274 (63.4) [61.4] | 876 (744.9) [707.2] | 339 (54.7) [53.9] | 910 (569.5) [551.6] | 312 (54.1) [54.4] | 713 (497.6) [497.3] | 651 (54.4) [54.7] | 1623 (535.5) [540.9] | -7.5 [-13.7, -1.3] | -5.9 [-12.4, 0.5] |
| Any COVID-19 related TEAEs | 3 (0.7) [0.8] | 4 (3.4) [4.0] | 1 (0.2) [0.2] | 1 (0.6) [0.6] | 0 | 0 | 1 (< 0.1) [< 0.1] | 1 (0.3) [0.3] | -0.6 [-1.6, 0.3] | -0.8 [-1.8, 0.1] |
| TEAEs related to study drug per investigator | 91 (21.1) [21.1] | 188 (159.9) [154.5] | 117 (18.9) [18.6] | 213 (133.3) [132.3] | 108 (18.7) [18.7] | 198 (138.2) [137.1] | 225 (18.8) [18.5] | 411 (135.6) [133.4] | -2.6 [-7.6, 2.5] | -2.5 [-7.8, 2.7] |
| Severe TEAEs | 52 (12.0) [11.2] | 93 (79.1) [76.1] | 32 (5.2) [5.0] | 42 (26.3) [25.7] | 30 (5.2) [5.2] | 43 (30.0) [30.6] | 62 (5.2) [5.2] | 85 (28.0) [27.9] | -6.2 [-9.7, -2.8] | -5.4 [-9.0, -1.8] |
| Serious TEAEs | 67 (15.5) [15.0] | 115 (97.8) [93.7] | 41 (6.6) [6.5] | 54 (33.8) [32.7] | 23 (4.0) [4.0] | 30 (20.9) [21.1] | 64 (5.3) [5.4] | 84 (27.7) [27.7] | -8.5 [-12.5, -4.6] | -10.0 [-14.0, -6.1] |
| TEAEs leading to discontinuation of study drug | 37 (8.6) [8.2] | 51 (43.4) [43.7] | 13 (2.1) [2.0] | 16 (10.0) [9.6] | 12 (2.1) [2.1] | 15 (10.5) [10.7] | 25 (2.1) [2.1] | 31 (10.2) [10.3] | -6.2 [-9.0, -3.3] | -5.7 [-8.7, -2.7] |

| Subjects with: | Placebo IV (N = 432) (PY = 117.6) n (%) [SSA%] | Placebo IV (N = 432) (PY = 117.6) Events (E/100 PY) [SSA E/100 PY] | Risankizumab 600 mg IV (N = 620) (PY = 159.8) n (%) [SSA%] | Risankizumab 600 mg IV (N = 620) (PY = 159.8) Events (E/100 PY) [SSA E/100 PY] | Risankizumab 1200 mg IV (N = 577) (PY = 143.3) n (%) [SSA%] | Risankizumab 1200 mg IV (N = 577) (PY = 143.3) Events (E/100 PY) [SSA E/100 PY] | Risankizumab Total (N = 1197) (PY = 303.1) n (%) [SSA%] | Risankizumab Total (N = 1197) (PY = 303.1) Events (E/100 PY) [SSA E/100 PY] | Treatment Comparison [95% CI][a] for n (%) differences RZB 600 mg IV - PBO IV | Treatment Comparison [95% CI][a] for n (%) differences RZB 1200 mg IV - PBO IV |
|---|---|---|---|---|---|---|---|---|---|---|
| TEAEs leading to death | 2 (0.5) [0.6] | 5 (4.3) [5.6] | 0 | 0 | 1 (0.2) [0.2] | 1 (0.7) [0.8] | 1 (< 0.1) [ < 0.1] | 1 (0.3) [0.4] | -0.6 [-1.5, 0.2] | -0.5 [-1.4, 0.5] |
| All deaths | 2 (0.5) [0.6] | 2 (1.7) [2.2] | 0 | 0 | 1 (0.2) [0.2] | 1 (0.7) [0.8] | 1 (< 0.1) [ < 0.1] | 1 (0.3) [0.4] | -0.6 [-1.5, 0.2] | -0.5 [-1.4, 0.5] |
| Deaths occurring ≤ 140 days after last dose of study drug | 2 (0.5) [0.6] | 2 (1.7) [2.2] | 0 | 0 | 1 (0.2) [0.2] | 1 (0.7) [0.8] | 1 (< 0.1) [ < 0.1] | 1 (0.3) [0.4] | -0.6 [-1.5, 0.2] | -0.5 [-1.4, 0.5] |
| Deaths occurring > 140 days after last dose of study drug | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0.0 |
| COVID-19 related deaths | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0.0 |

a. Study-size adjusted risk difference between treatment groups.

Notes: E/100 PY = Events per 100 patient-years.

SSA estimates for 1200 mg IV and the 1200 mg IV - Placebo treatment difference and 95% CI are based on two studies: Studies M15-991 and M16-006. SSA estimates for Placebo, 600 mg IV and treatment difference and 95% CI are based on all 3 studies: Studies M15-993, M15-991 and M16-006.

*Maintenance up to 52 Weeks*

In the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), the rate of AEs was similar between the two risankizumab arms (283.5 E/100 PY in the 180 mg SC arm and 269.3 E/100 PY in the 360 mg SC arm), indicating no dose-dependent pattern in overall AE rate, and similar to the withdrawal (placebo SC) arm (339.7 E/100 PY) (Table 57). The rates of SAEs and AEs leading to discontinuation were generally similar in risankizumab-treated subjects compared to the withdrawal (placebo SC) arm. There were no deaths during the 52-week maintenance period.

*All Treated Safety Analysis Set*

In the ANY RZB SC group of the All Treated Safety Analysis Set, the rate of AEs was 272.0 E/100 PY, the rate of SAEs was 18.1 E/100 PY, and the rate of AEs leading to discontinuation of study drug was 3.7 E/100 PY. The rates of AEs, SAEs, AEs leading to discontinuation of study drug, and deaths of the ANY RZB SC and the RZB 360 mg SC groups were similar to the corresponding rates observed in the Total RZB group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set.

In the ANY RZB group, there were 4 deaths reported (detailed further below).

*Table 57 Overview of Treatment-Emergent Adverse Events EAER per 100 PY (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set and All Treated Safety Analysis Sets)*

| | Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set | | | | | | | | | | All Treated Safety Analysis Set | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Withdrawal (Placebo SC) (N = 184) (PY = 160.4) | | Risankizumab 180 mg SC (N = 179) (PY = 169.3) | | Risankizumab 360 mg SC (N = 179) (PY = 166.4) | | Risankizumab Total (N = 358) (PY = 335.7) | | Treatment Comparison [95% CI][a] for n (%) differences | | RZB 360 mg SC (N = 533) (PY = 442.6) | | Any RZB SC (N = 1318) (PY = 1547.0) | |
| Subjects with: | n (%) | Events (E/100 PY) | n (%) | Events (E/100 PY) | n (%) | Events (E/100 PY) | n (%) | Events (E/100 PY) | RZB 180 mg SC - PBO SC | RZB 360 mg SC - PBO SC | n (%) | Events (E/100 PY) | n (%) | Events (E/100 PY) |
| All TEAEs | 135 (73.4) | 545 (339.7) | 128 (71.5) | 480 (283.5) | 129 (72.1) | 448 (269.3) | 257 (71.8) | 928 (276.5) | -1.9 (-11.1, 7.3) | -1.3 (-10.5, 7.9) | 338 (63.4) | 1217 (275.0) | 876 (66.5) | 4208 (272.0) |
| Any COVID-19 related TEAEs | 1 (0.5) | 1 (0.6) | 1 (0.6) | 1 (0.6) | 4 (2.2) | 4 (2.4) | 5 (1.4) | 5 (1.5) | 0.0 (-1.5, 1.5) | 1.7 (-0.7, 4.1) | 20 (3.8) | 21 (4.7) | 65 (4.9) | 68 (4.4) |
| TEAEs related to study drug per investigator | 46 (25.0) | 91 (56.7) | 49 (27.4) | 102 (60.2) | 45 (25.1) | 91 (54.7) | 94 (26.3) | 193 (57.5) | 2.4 (-6.7, 11.4) | 0.1 (-8.8, 9.1) | 121 (22.7) | 255 (57.6) | 314 (23.8) | 749 (48.4) |
| Severe TEAEs | 23 (12.5) | 33 (20.6) | 12 (6.7) | 15 (8.9) | 21 (11.7) | 26 (15.6) | 33 (9.2) | 41 (12.2) | -5.8 (-11.8, 0.2) | -0.8 (-7.5, 5.9) | 40 (7.5) | 50 (11.3) | 125 (9.5) | 197 (12.7) |
| Serious TEAEs | 23 (12.5) | 31 (19.3) | 22 (12.3) | 33 (19.5) | 24 (13.4) | 35 (21.0) | 46 (12.8) | 68 (20.3) | -0.2 (-7.0, 6.6) | 0.9 (-6.0, 7.8) | 58 (10.9) | 81 (18.3) | 177 (13.4) | 280 (18.1) |

| | Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set | | | | | | | | | | All Treated Safety Analysis Set | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Withdrawal (Placebo SC) (N = 184) (PY = 160.4) | | Risankizumab 180 mg SC (N = 179) (PY = 169.3) | | Risankizumab 360 mg SC (N = 179) (PY = 166.4) | | Risankizumab Total (N = 358) (PY = 335.7) | | Treatment Comparison [95% CI][a] for n (%) differences | | RZB 360 mg SC (N = 533) (PY = 442.6) | | Any RZB SC (N = 1318) (PY = 1547.0) | |
| Subjects with: | n (%) | Events (E/100 PY) | n (%) | Events (E/100 PY) | n (%) | Events (E/100 PY) | n (%) | Events (E/100 PY) | RZB 180 mg SC - PBO SC | RZB 360 mg SC - PBO SC | n (%) | Events (E/100 PY) | n (%) | Events (E/100 PY) |
| TEAEs leading to discontinuation of study drug | 6 (3.3) | 6 (3.7) | 3 (1.7) | 4 (2.4) | 6 (3.4) | 8 (4.8) | 9 (2.5) | 12 (3.6) | -1.6 (-4.8, 1.6) | 0.1 (-3.6, 3.8) | 15 (2.8) | 19 (4.3) | 48 (3.6) | 58 (3.7) |
| TEAEs leading to death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0.0 | 0 | 0 | 2 (0.2) | 2 (0.1) |
| All deaths | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | 0 | 0 | 2 (0.2) | 2 (0.1) |
| Deaths occurring ≤ 140 days after last dose of study drug | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0.0 | 0 | 0 | 2 (0.2) | 2 (0.1) |

*Common Adverse Events*

12-Week Induction

In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), the most frequent AEs by SOC (≥ 14.0% of subjects) in all treatment groups were infections and infestations and gastrointestinal disorders, both of which occurred more frequently in the placebo group compared with the risankizumab 600 mg and 1200 mg IV groups.

The most common AEs (≥ 5.0%) in any risankizumab treatment group were headache and nasopharyngitis, whereas the most common AEs in the placebo group were Crohn's disease, abdominal pain, nausea, and headache (Table 58). Overall, Crohn's disease (worsening of CD) was the most common AE in the placebo group and occurred more frequently than in either risankizumab group. The overall pattern of most commonly reported AEs was generally similar between the risankizumab 600 mg and 1200 mg IV dosing groups.

*Table 58 Most frequent Adverse Events Reported in ≥2% of Subjects in Any Risankizumab Group, by Frequency of PT in Descending Order of Total RZB Group (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

| | | Risankizumab | | |
|---|---|---|---|---|
| MedDRA 23.1 Preferred Term | Placebo IV (N = 432) n (%) [SSA%] | 600 mg IV (N = 620) n (%) [SSA%] | 1200 mg IV (N = 577) n (%) [SSA%] | Total (N = 1197) n (%) [SSA%] |
| Headache | 24 (5.6) [5.1] | 40 (6.5) [6.3] | 30 (5.2) [5.2] | 70 (5.8) [5.9] |
| Nasopharyngitis | 19 (4.4) [3.9] | 32 (5.2) [5.1] | 30 (5.2) [5.1] | 62 (5.2) [5.1] |
| Arthralgia | 19 (4.4) [4.2] | 31 (5.0) [4.7] | 20 (3.5) [3.5] | 51 (4.3) [4.5] |
| Nausea | 25 (5.8) [5.6] | 26 (4.2) [4.0] | 16 (2.8) [2.7] | 42 (3.5) [3.5] |
| Fatigue | 16 (3.7) [3.6] | 22 (3.5) [3.4] | 18 (3.1) [3.0] | 40 (3.3) [3.3] |
| Pyrexia | 18 (4.2) [3.9] | 21 (3.4) [3.2] | 17 (2.9) [2.8] | 38 (3.2) [3.2] |
| Anaemia | 21 (4.9) [4.4] | 19 (3.1) [3.0] | 16 (2.8) [2.8] | 35 (2.9) [3.0] |
| Abdominal pain | 26 (6.0) [5.7] | 17 (2.7) [2.6] | 13 (2.3) [2.2] | 30 (2.5) [2.6] |
| Upper respiratory tract infection | 6 (1.4) [1.3] | 14 (2.3) [2.2] | 16 (2.8) [2.7] | 30 (2.5) [2.4] |
| Crohn's disease | 64 (14.8) [14.5] | 19 (3.1) [3.1] | 10 (1.7) [1.7] | 29 (2.4) [2.5] |
| Dizziness | 8 (1.9) [1.7] | 14 (2.3) [2.1] | 12 (2.1) [2.0] | 26 (2.2) [2.2] |
| Rash | 5 (1.2) [1.2] | 15 (2.4) [2.3] | 8 (1.4) [1.4] | 23 (1.9) [1.9] |
| Vomiting | 14 (3.2) [3.3] | 15 (2.4) [2.3] | 7 (1.2) [1.2] | 22 (1.8) [1.9] |

Maintenance up to 52 Weeks

In the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), the SOC with the most frequently reported AEs was gastrointestinal disorders (35.8% in the risankizumab 180 mg arm, 37.4% in the risankizumab 360 mg arm, and 40.8% in the withdrawal [placebo SC] arm).

The most common AEs (≥ 5.0%) in any risankizumab arm of the Placebo-Controlled 52- Week Maintenance Period Safety Analysis Set were Crohn's disease, nasopharyngitis, arthralgia, headache, abdominal pain, anaemia, and nausea, whereas the most common AEs in the withdrawal (placebo SC) arm were Crohn's disease, nasopharyngitis, arthralgia, headache, abdominal pain, nausea, and diarrhoea (Table 59). Of the AEs reported in > 5.0% of subjects in the risankizumab arms, all were reported more frequently in the withdrawal (placebo SC) arm as compared to either risankizumab arm.

The percentages of subjects (≥ 5.0%) with commonly reported AEs and the overall pattern of commonly reported AEs were generally comparable between the risankizumab 180 mg and 360 mg SC arms.

*Table 59 Most frequent Adverse Events Reported in ≥2% of Subjects in the Risankizumab Total Arm by Frequency of PT in Descending Order (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set)*

| | Withdrawal (Placebo SC) (N = 184) n (%) | Risankizumab | | |
|---|---|---|---|---|
| | | 180 mg SC (N = 179) n (%) | 360 mg SC (N = 179) n (%) | Total (N = 358) n (%) |
| Crohn's disease | 32 (17.4) | 19 (10.6) | 21 (11.7) | 40 (11.2) |
| Nasopharyngitis | 25 (13.6) | 17 (9.5) | 17 (9.5) | 34 (9.5) |
| Arthralgia | 20 (10.9) | 15 (8.4) | 17 (9.5) | 32 (8.9) |
| Headache | 11 (6.0) | 9 (5.0) | 11 (6.1) | 20 (5.6) |
| Abdominal pain | 13 (7.1) | 8 (4.5) | 9 (5.0) | 17 (4.7) |
| Anaemia | 8 (4.3) | 9 (5.0) | 8 (4.5) | 17 (4.7) |
| Pyrexia | 6 (3.3) | 7 (3.9) | 8 (4.5) | 15 (4.2) |
| Injection site erythema | 5 (2.7) | 7 (3.9) | 7 (3.9) | 14 (3.9) |
| Nausea | 13 (7.1) | 9 (5.0) | 4 (2.2) | 13 (3.6) |
| Fatigue | 4 (2.2) | 7 (3.9) | 5 (2.8) | 12 (3.4) |
| Back pain | 4 (2.2) | 3 (1.7) | 8 (4.5) | 11 (3.1) |
| Diarrhoea | 10 (5.4) | 6 (3.4) | 4 (2.2) | 10 (2.8) |
| Upper respiratory tract infection | 7 (3.8) | 7 (3.9) | 3 (1.7) | 10 (2.8) |
| Arthropathy | 6 (3.3) | 2 (1.1) | 7 (3.9) | 9 (2.5) |
| Hypertension | 4 (2.2) | 5 (2.8) | 4 (2.2) | 9 (2.5) |
| Constipation | 7 (3.8) | 7 (3.9) | 1 (0.6) | 8 (2.2) |
| Urinary tract infection | 6 (3.3) | 1 (0.6) | 7 (3.9) | 8 (2.2) |
| Eczema | 4 (2.2) | 5 (2.8) | 2 (1.1) | 7 (2.0) |
| Gastroenteritis | 4 (2.2) | 3 (1.7) | 4 (2.2) | 7 (2.0) |
| Gastroenteritis viral | 6 (3.3) | 5 (2.8) | 2 (1.1) | 7 (2.0) |
| Oral herpes | 2 (1.1) | 4 (2.2) | 3 (1.7) | 7 (2.0) |
| Pruritus | 2 (1.1) | 4 (2.2) | 3 (1.7) | 7 (2.0) |

All Treated Safety Analysis Set

The most common AEs (≥ 5%) in the ANY RZB SC group of the All Treated Safety Analysis Set were Crohn's disease, arthralgia, nasopharyngitis, headache, and abdominal pain. The overall pattern of the most frequently reported AEs in the ANY RZB SC group of the All Treated Safety Analysis Set was consistent with that of the Total RZB group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set (Table 59).

*TEAEs assessed as related*

12-Week Induction

Across treatment groups in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set, AEs assessed by the investigator as having a possible relationship to study drug were most frequently reported (≥ 3.5% in all treatment groups) in the SOCs of infections and infestations and skin and subcutaneous tissue disorders. The AEs most frequently assessed by the investigator as having a possible relationship to study drug in the Total RZB group (≥ 1.5%) were fatigue (2.1%), headache (1.9%), and arthralgia (1.5%). The AEs that were most frequently assessed by the investigator as having a possible relationship to study drug in the placebo group (≥ 1.5%) were Crohn's disease (2.4%) and headache (1.8%).

The most frequent AEs considered by the investigators as having a reasonable possibility of being related to study drug were generally comparable among the placebo, risankizumab 600 mg IV, and risankizumab 1200 mg IV groups.

Maintenance up to 52 Weeks

Across treatment arms in the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), AEs assessed by the investigator as having a possible relationship to study drug were most frequently reported (≥ 5.0%) in the SOCs of gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and skin and subcutaneous tissue disorders. The AEs most frequently assessed by the investigator as having a possible relationship to study drug in the Total RZB group (≥ 2.0%) were injection site erythema (3.6%) and nasopharyngitis (2.2%). The AEs that were most frequently assessed by the investigators as having a possible relationship to study drug in the withdrawal (placebo SC) arm were Crohn's disease (3.3%), injection site erythema (2.2%), and arthralgia (2.2%). The most frequent AEs considered by the investigators as related to study drug were generally comparable among the withdrawal (placebo SC), risankizumab 180 mg SC, and risankizumab 360 mg SC arms.

All Treated Safety Analysis Set

The most common AEs assessed by the investigator as having a possible relationship to study drug in the ANY RZB SC group of the All Treated Safety Analysis Set were consistent with those observed in the Total RZB group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set, both by SOC and PT.

*Severe TEAEs*

12-Week Induction

In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), a higher percentage of subjects in the placebo group (11.2%) had severe AEs compared with the risankizumab 600 mg and 1200 mg IV groups (5.0% and 5.2%, respectively). Severe AEs were most frequently reported in the SOC of gastrointestinal disorders (2.4% and 1.4%) in the risankizumab 600 mg and 1200 mg IV groups, respectively. No individual severe AE was reported at a frequency ≥ 1.0% in either of the risankizumab treatment groups and the rates of severe AEs were generally comparable between the risankizumab 600 mg IV and 1200 mg IV groups. The most frequently reported severe AEs in the Total RZB group (≥ 0.5%) were anaemia (0.5%) and Crohn's disease (0.5%). The most frequently reported severe AEs in the placebo group (≥ 1.0%) were Crohn's disease (5.7%) and abdominal pain (1.2%), which are expected given the indication.

Maintenance up to 52 Weeks

In the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), 6.7%, 11.7%, and 12.5% of subjects in the risankizumab 180 mg SC, risankizumab 360 mg SC, and the withdrawal (placebo SC) arms, respectively, reported severe AEs.

Severe AEs were most frequently reported (≥ 1.5% across treatment arms) in the SOCs of gastrointestinal disorders and infections and infestations. The most frequently reported (≥ 1.0%) severe AEs were anaemia (1.1%) and appendicitis (1.1%) in the risankizumab 180 mg SC arm, viral infection (1.7%), anaemia (1.1%), small intestinal obstruction (1.1%), and back pain (1.1%) in the risankizumab 360 mg SC arm, and Crohn's disease (2.2%) and abdominal pain (1.1%) in the withdrawal (placebo SC) arm. These events are either commonplace in the general population or expected in the indication.

All Treated Safety Analysis Set

The pattern of severe AEs in the ANY RZB SC group of the All Treated Safety Analysis Set was consistent with that observed in the Total RZB group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set, both by SOC and PT.

*Adverse Drug Reactions for Labeling*

The ADRs for risankizumab were identified following the guidelines described in Council for International Organizations of Medical Sciences (CIOMS) Working Groups III and V 'Guidelines for Preparing Core Clinical-Safety Information on Drugs' (CIOMS Working Groups III and V 1999). The AEs included in the submission safety data analysis sets were medically reviewed to determine the ADRs for risankizumab based on the totality of the data. A review of literature for background disease-related events in moderately to severely active CD provided additional context.

In general, the decision to consider an AE as an ADR was based on the totality and levels of evidence taking into account the following considerations: disproportionate number of reports between placebo and risankizumab, observed dose-related effect, consistency of the findings across studies, temporal relationship, dechallenge/rechallenge information for relevant event reports, preclinical data and biological plausibility based on mechanism of action and/or class effect. The identification of similar trends among medically related events was also a factor in classifying an AE as an ADR. Specifically, clinically related PTs were grouped and the disproportionality between risankizumab and placebo was assessed based on the grouped rates.

All AEs by MedDRA coded PTs in the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set) and maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set) were examined regardless of the investigator causality assessment. Adverse events that occurred in ≥ 1% of subjects in the risankizumab 600 mg IV group or risankizumab 360 mg SC arm and at a disproportionally higher rate compared to the respective placebo-treated subjects were identified.

The body of evidence for AEs observed at a frequency of < 1% (uncommon and rare events) that were deemed events of medical importance (serious, fatal/life threatening) or AEs of safety interest was also reviewed. All AEs were examined by MedDRA SOC, SMQ, CMQ, and PTs. In addition, PTs were grouped according to medical concepts and clinical relevance post-hoc for further assessment when indicated.

The frequencies of all currently labeled ADRs (using groupings of clinically related PTs) for the psoriasis program were reviewed against the frequencies observed in the CD development program. Further, dose-response across the 2 risankizumab IV doses (600 mg and 1200 mg) in the induction and the 2 risankizumab SC doses (180 mg and 360 mg) in the maintenance period was taken into consideration for AEs in the ADR determination.

For further assessment of ADRs, additional post-hoc analyses were conducted by grouping PTs representing similar medical concepts and identified in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set and Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set in the following areas:

- Infusion-related reactions (PTs grouped: infusion-related reaction, infusion site bruising, infusion site cellulitis, infusion site erythema, infusion site extravasation, infusion site irritation, infusion site pain, infusion site swelling)
- Lower respiratory infections (PTs grouped: bronchitis, pneumonia, pneumonia mycoplasmal, and tracheitis)
- Rash (PTs grouped: rash, rash erythematous, rash macular, rash maculopapular, rash pruritic, rash pustular, and rash vesicular) and
- Dermatitis (PTs grouped: dermatitis, dermatitis allergic, eczema).

<u>12-Week Induction</u>

Based on the comprehensive review of AEs in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set as outlined above, no new ADRs were identified in the CD patient population . Among the

5 grouped ADRs in current product labeling, 2 grouped adverse reactions (upper respiratory infections and headache) occurred at a marginally higher rate in the risankizumab 600 mg IV group (10.2% for upper respiratory tract infection [URTI] and 6.5% for headache) and 1200 mg IV group (10.1% for upper respiratory infections and 5.2% for headache) than the placebo group (9.0% for upper respiratory infections and 5.1% for headache) during the 12-Week Induction Period of pooled induction studies and were determined to be ADRs for patients with moderate to severe CD during induction treatment. The non-grouped ADR event of folliculitis in the current product labeling remained as an ADR (0.2% in both risankizumab 600 mg and 1200 mg IV groups and 0% in placebo). For other ADRs listed in current product labeling (fatigue and tinea infections), rates for both risankizumab groups were similar compared to placebo. Rates for fatigue were 4.0%, 3.8% and 4.7% for the risankizumab 600 mg IV, risankizumab 1200 mg IV, and placebo groups, respectively; rates for tinea infections were 0.2%, 0% and 0.2%, respectively. Therefore, fatigue and tinea infections were not considered as ADRs for induction treatment. The 2 identified grouped ADRs, URTIs and headache in the placebo-controlled induction studies were observed at similar frequency categories as those in the psoriasis studies in the current labeling. The frequency categories for these 2 ADRs in the CD studies remained unchanged as currently listed ADRs (very common and common, respectively).

Maintenance up to 52 Weeks

Based on the comprehensive review of AEs in the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set, no new ADRs were identified. Among the 5 grouped ADRs listed in current product labeling, 3 grouped adverse reactions (fatigue, tinea infections, and ISRs), occurred at a rate ≥ 1% of subjects in the risankizumab arms, and at a higher rate than the withdrawal (placebo SC) arm during the 52-week maintenance period (Table 60). These 3 events were determined to be ADRs for patients with moderate to severe CD during maintenance treatment. The other 2 grouped events, upper respiratory tract infections and headache, were not considered as ADRs for maintenance as rates in the risankizumab arms were lower than those of the withdrawal (placebo SC) arm. The non-grouped event of folliculitis was not considered an ADR based on the assessment that 1 event each occurred in the risankizumab 180 mg SC and withdrawal (placebo SC) arms and no event occurred in the risankizumab 360 mg SC arm.

Three identified grouped ADRs, fatigue, ISRs, and tinea infections were observed at a rate ≥ 1% to < 10% in the placebo-controlled maintenance study with risankizumab 360 mg SC (Table 60). The rates for these 3 ADRs in the CD studies were classified as a frequency category of common, the same frequency category as currently listed ADRs.

*Table 60 Adverse Drug Reactions Occurring in ≥1% of Subjects in the Risankizumab 180 mg SC, 360 mg SC, and Total RZB Arms with a Higher Rate than Withdrawal (Placebo SC) Arm (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set) Compared to Data from the Risankizumab Psoriasis Program*

| | | | Risankizumab | | |
|---|---|---|---|---|---|
| ADR Group Term | Risankizumab Psoriasis 150 mg SC CCDS[a] n (%) | Withdrawal (Placebo SC) (N = 184) n (%) | 180 mg SC (N = 179) n (%) | 360 mg SC (N = 179) n (%) | Total (N = 358) n (%) |
| Upper respiratory tract infections | 170 (13.0) | 37 (20.1) | 27 (15.1) | 28 (15.6) | 55 (15.4) |
| Headache | 46 (3.5) | 12 (6.5) | 9 (5.0) | 11 (6.1) | 20 (5.6) |
| Fatigue | 33 (2.5) | 5 (2.7) | 8 (4.5) | 7 (3.9) | 15 (4.2) |
| Injection site reactions | 19 (1.5) | 9 (4.9)[b] | 9 (5.0)[b] | 11 (6.1)[b] | 20 (5.6)[b] |
| Tinea infections | 15 (1.1) | 1 (0.5) | 1 (0.6) | 3 (1.7) | 4 (1.1) |

CCDS = company core data sheet

a. Data from CCDS Version 8.0 Section 9.1. 07 July 2021.

b. Search was based on injection site reaction CMQ (not from Study M16-000 Sub-Study 1 CSR

Although the rates of determined ADRs (clinically grouped PTs) in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set and the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set appear to be numerically higher compared to the rates in the currently labeled ADRs, they continued to fall into the same frequency category as the current labeled ADRs from the psoriasis studies. Additionally, caution should be exercised when comparing ADR rates across indications, as studies were conducted in distinct patient populations and had different placebo-controlled treatment durations (16 weeks in psoriasis vs. 52 weeks in the CD maintenance study) and study designs.

Furthermore, based on analyses of post-hoc data presented in Table 61, infusion-related reactions, lower respiratory tract infections, rash, and dermatitis do not warrant inclusion as ADRs, as the rates in the risankizumab IV groups and risankizumab SC arms were similar to the rates in the placebo group and the withdrawal (placebo SC) arm, respectively. Infusion-related reactions, particularly in the risankizumab 1200 mg IV group, were comprised of infusion site events rather than systemic manifestations of infusion-related reactions.

Overall, no new adverse reactions were identified in risankizumab CD studies and the observed rates and severity of the currently labeled ADRs in the CD clinical studies were similar to the psoriasis clinical studies. This is reflected in the SmPC. The ADR profile observed in subjects with CD treated with risankizumab was consistent with the ADR profile observed in subjects with plaque psoriasis.

*Table 61 Post-Hoc Analysis with Grouped Preferred Terms*

| ADR Group Term | Placebo-Controlled 12-Week Maintenance Period Safety Analysis Set | | | | Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set | | | |
|---|---|---|---|---|---|---|---|---|
| | | RZB | | | | RZB | | |
| | PBO IV (N = 432) n (%)[a] | 600 mg IV (N = 620) n (%)[a] | 1200 mg IV (N = 577) n (%)[a] | Total (N = 1197) n (%)[a] | WD (PBO SC) (N = 184) n (%) | 180 mg SC (N = 179) n (%) | 360 mg SC (N = 179) n (%) | Total (N = 358) n (%) |
| Infusion-related reactions | 5 (1.0) | 4 (0.6) | 8 (1.4) | 12 (1.0) | -- | -- | -- | -- |
| Lower respiratory tract infections | 10 (2.5) | 9 (1.4) | 10 (1.7) | 19 (1.5) | 8 (4.3) | 2 (1.1) | 4 (2.2) | 6 (1.7) |
| Dermatitis | 4 (0.8) | 5 (0.9) | 7 (1.2) | 12 (1.0) | 5 (2.7) | 7 (3.9) | 3 (1.7) | 10 (2.8) |
| Rash | 9 (2.1) | 15 (2.3) | 10 (1.8) | 25 (2.1) | 7 (3.8) | 4 (2.2) | 4 (2.2) | 8 (2.2) |

a. Study-size adjusted percentages.

### *2.6.8.3. Serious adverse event/deaths/other significant events*

In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), the percentage of subjects with SAEs was similar between the risankizumab IV dose groups with no dose-dependent pattern (6.5% in the 600 mg group and 4.0% in the 1200 mg group) and lower in both risankizumab IV dose groups compared with the placebo group (15.0%, Table 62 and Figure 23). This was driven by a higher proportion of subjects who reported SAEs attributable to the underlying disease (such as Crohn's disease, abdominal abscess, anal abscess) in the placebo arm.

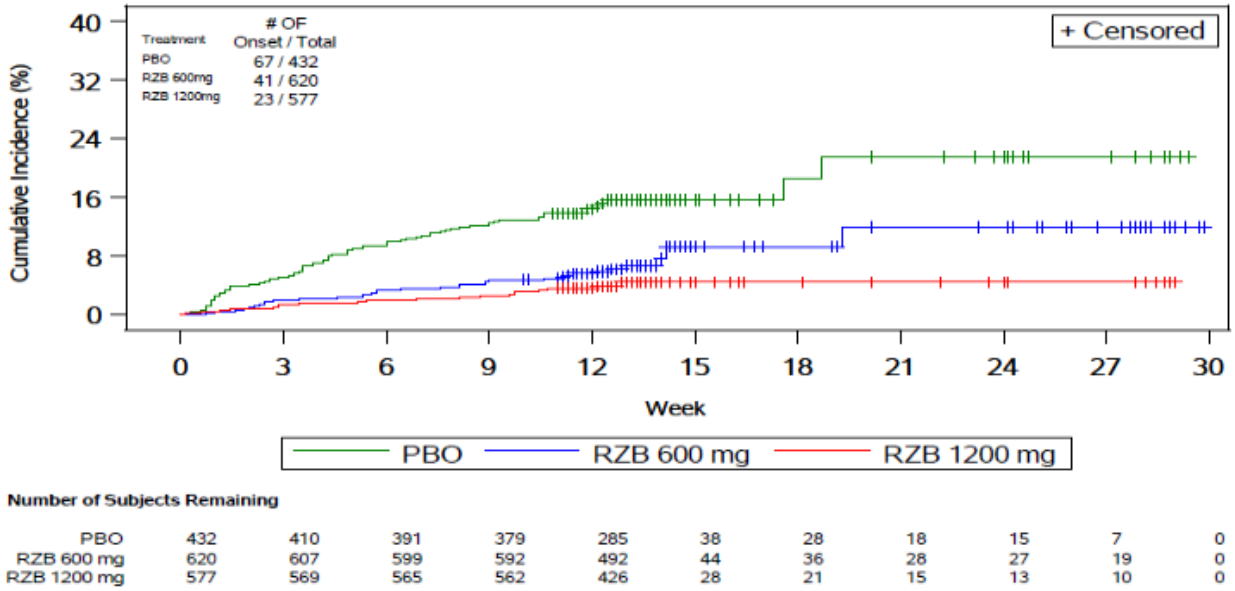



*Figure 23 Cumulative Incidence Plot for Treatment-Emergent Serious Adverse Events (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

The most frequently reported SAE was Crohn's disease (0.8% in the Total RZB group and 8.9% in the placebo group), which, together with the other SAEs in the gastrointestinal disorders SOC, is likely attributable to the underlying disease (Table 62). Serious AEs in the infections and infestations SOC were reported at similar percentages in the risankizumab 600 mg IV group (0.9%) and risankizumab 1200 mg IV group (0.7%) and were reported in a higher percentage in subjects in the placebo group (3.6%) (ASI discussion of serious infections).

The most frequently reported SAEs assessed by the investigator as having a possible relationship to study drug were anaemia in the risankizumab 1200 mg IV group (2 subjects [0.4%]) and Crohn's disease in the placebo group (7 subjects [1.4%]); all other SAEs in the above 2 treatment groups and all SAEs in the risankizumab 600 mg IV group that were assessed by the investigator as having a possible relationship to study drug were reported by 1 subject each. In the risankizumab 600 mg IV, risankizumab 1200 mg IV, and placebo groups, a total of 3 subjects (0.5%), 6 subjects (1.0%), and 28 subjects (5.8%) discontinued study drug due to an SAE, respectively (Table 62).

*Table 62 Treatment-Emergent Serious Adverse Events in Percentage and EAER per 100 PY Occurring in ≥2% Subjects in Any Treatment Group (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

| | | | Risankizumab | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo IV (N = 432) (PY = 117.6) | | 600 mg IV (N = 620) (PY = 159.8) | | 1200 mg IV (N = 577) (PY = 143.3) | | Total (N = 1197) (PY = 303.1) | |
| System Organ Class MedDRA 23.1 Preferred Term | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] |
| **Any adverse event** | **67 (15.5) [15.0]** | **115 (97.8) [93.7]** | **41 (6.6) [6.5]** | **54 (33.8) [32.7]** | **23 (4.0) [4.0]** | **30 (20.9) [21.1]** | **64 (5.3) [5.4]** | **84 (27.7) [27.7]** |
| **Blood and lymphatic system disorders** | **4 (0.9) [0.7]** | **6 (5.1) [4.0]** | **2 (0.3) [0.4]** | **2 (1.3) [1.4]** | **3 (0.5) [0.6]** | **4 (2.8) [2.9]** | **5 (0.4) [0.4]** | **6 (2.0) [2.1]** |
| Anaemia | 3 (0.7) [0.6] | 3 (2.6) [2.1] | 2 (0.3) [0.4] | 2 (1.3) [1.4] | 3 (0.5) [0.6] | 4 (2.8) [2.9] | 5 (0.4) [0.4] | 6 (2.0) [2.1] |
| **Gastrointestinal disorders** | **52 (12.0) [11.5]** | **71 (60.4) [59.3]** | **18 (2.9) [2.8]** | **23 (14.4) [14.2]** | **6 (1.0) [1.0]** | **7 (4.9) [4.7]** | **24 (2.0) [2.0]** | **30 (9.9) [9.6]** |
| Abdominal pain | 3 (0.7) [0.8] | 4 (3.4) [4.0] | 0 | 0 | 0 | 0 | 0 | 0 |
| Crohn's disease | 40 (9.3) [8.9] | 44 (37.4) [35.9] | 7 (1.1) [1.1] | 9 (5.6) [5.3] | 3 (0.5) [0.5] | 3 (2.1) [2.1] | 10 (0.8) [0.8] | 12 (4.0) [3.9] |
| Ileus | 0 | 0 | 3 (0.5) [0.5] | 3 (1.9) [1.9] | 0 | 0 | 3 (0.3) [0.2] | 3 (1.0) [1.0] |
| Intestinal obstruction | 3 (0.7) [0.7] | 3 (2.6) [2.8] | 1 (0.2) [0.2] | 1 (0.6) [0.6] | 0 | 0 | 1 (< 0.1) [< 0.1] | 1 (0.3) [0.3] |
| Intestinal stenosis | 2 (0.5) [0.6] | 2 (1.7) [2.2] | 0 | 0 | 0 | 0 | 0 | 0 |
| Large intestine perforation | 0 | 0 | 1 (0.2) [0.2] | 1 (0.6) [0.6] | 1 (0.2) [0.2] | 1 (0.7) [0.6] | 2 (0.2) [0.2] | 2 (0.7) [0.6] |
| Small intestinal obstruction | 3 (0.7) [0.7] | 3 (2.6) [2.5] | 2 (0.3) [0.3] | 2 (1.3) [1.3] | 1 (0.2) [0.2] | 1 (0.7) [0.6] | 3 (0.3) [0.2] | 3 (1.0) [1.0] |
| **General disorders and administration site conditions** | **3 (0.7) [0.6]** | **3 (2.6) [2.3]** | **0** | **0** | **2 (0.3) [0.4]** | **2 (1.4) [1.4]** | **2 (0.2) [0.2]** | **2 (0.7) [0.7]** |
| Asthenia | 2 (0.5) [0.4] | 2 (1.7) [1.6] | 0 | 0 | 0 | 0 | 0 | 0 |

| | | | Risankizumab | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo IV (N = 432) (PY = 117.6) | | 600 mg IV (N = 620) (PY = 159.8) | | 1200 mg IV (N = 577) (PY = 143.3) | | Total (N = 1197) (PY = 303.1) | |
| System Organ Class MedDRA 23.1 Preferred Term | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] |
| **Infections and infestations** | **16 (3.7) [3.6]** | **20 (17.0) [16.7]** | **6 (1.0) [0.9]** | **6 (3.8) [3.4]** | **4 (0.7) [0.7]** | **4 (2.8) [2.9]** | **10 (0.8) [0.9]** | **10 (3.3) [3.5]** |
| Abdominal abscess | 2 (0.5) [0.3] | 2 (1.7) [1.2] | 0 | 0 | 0 | 0 | 0 | 0 |
| Anal abscess | 2 (0.5) [0.4] | 2 (1.7) [1.6] | 1 (0.2) [0.1] | 1 (0.6) [0.4] | 0 | 0 | 1 (< 0.1) [0.1] | 1 (0.3) [0.4] |
| Pneumonia | 2 (0.5) [0.4] | 2 (1.7) [1.6] | 0 | 0 | 1 (0.2) [0.2] | 1 (0.7) [0.6] | 1 (< 0.1) [< 0.1] | 1 (0.3) [0.3] |
| **Renal and urinary disorders** | **3 (0.7) [0.7]** | **3 (2.6) [2.5]** | **2 (0.3) [0.3]** | **3 (1.9) [1.8]** | **2 (0.3) [0.4]** | **2 (1.4) [1.4]** | **4 (0.3) [0.3]** | **5 (1.6) [1.6]** |
| Nephrolithiasis | 1 (0.2) [0.3] | 1 (0.9) [1.1] | 0 | 0 | 2 (0.3) [0.4] | 2 (1.4) [1.4] | 2 (0.2) [0.2] | 2 (0.7) [0.7] |
| Ureterolithiasis | 0 | 0 | 2 (0.3) [0.3] | 2 (1.3) [1.2] | 0 | 0 | 2 (0.2) [0.2] | 2 (0.7) [0.6] |
| **Respiratory, thoracic and mediastinal disorders** | **1 (0.2) [0.1]** | **1 (0.9) [0.5]** | **1 (0.2) [0.2]** | **1 (0.6) [0.6]** | **3 (0.5) [0.6]** | **3 (2.1) [2.2]** | **4 (0.3) [0.3]** | **4 (1.3) [1.3]** |
| Pulmonary embolism | 0 | 0 | 0 | 0 | 2 (0.3) [0.4] | 2 (1.4) [1.4] | 2 (0.2) [0.2] | 2 (0.7) [0.7] |

| System Organ Class<br>MedDRA 23.1 Preferred Term | Placebo IV<br>(N = 432)<br>(PY = 117.6)<br>n (%)<br>[SSA%] | Placebo IV<br>(N = 432)<br>(PY = 117.6)<br>Events<br>(E/100 PY)<br>[SSA<br>E/100 PY] | Risankizumab<br>600 mg IV<br>(N = 620)<br>(PY = 159.8)<br>n (%)<br>[SSA%] | Risankizumab<br>600 mg IV<br>(N = 620)<br>(PY = 159.8)<br>Events<br>(E/100 PY)<br>[SSA<br>E/100 PY] | Risankizumab<br>1200 mg IV<br>(N = 577)<br>(PY = 143.3)<br>n (%)<br>[SSA%] | Risankizumab<br>1200 mg IV<br>(N = 577)<br>(PY = 143.3)<br>Events<br>(E/100 PY)<br>[SSA<br>E/100 PY] | Risankizumab<br>Total<br>(N = 1197)<br>(PY = 303.1)<br>n (%)<br>[SSA%] | Risankizumab<br>Total<br>(N = 1197)<br>(PY = 303.1)<br>Events<br>(E/100 PY)<br>[SSA<br>E/100 PY] |
|---|---|---|---|---|---|---|---|---|
| **Infections and infestations** | **16 (3.7) [3.6]** | **20 (17.0) [16.7]** | **6 (1.0) [0.9]** | **6 (3.8) [3.4]** | **4 (0.7) [0.7]** | **4 (2.8) [2.9]** | **10 (0.8) [0.9]** | **10 (3.3) [3.5]** |
| Abdominal abscess | 2 (0.5) [0.3] | 2 (1.7) [1.2] | 0 | 0 | 0 | 0 | 0 | 0 |
| Anal abscess | 2 (0.5) [0.4] | 2 (1.7) [1.6] | 1 (0.2) [0.1] | 1 (0.6) [0.4] | 0 | 0 | 1 (< 0.1) [0.1] | 1 (0.3) [0.4] |
| Pneumonia | 2 (0.5) [0.4] | 2 (1.7) [1.6] | 0 | 0 | 1 (0.2) [0.2] | 1 (0.7) [0.6] | 1 (< 0.1) [< 0.1] | 1 (0.3) [0.3] |
| **Renal and urinary disorders** | **3 (0.7) [0.7]** | **3 (2.6) [2.5]** | **2 (0.3) [0.3]** | **3 (1.9) [1.8]** | **2 (0.3) [0.4]** | **2 (1.4) [1.4]** | **4 (0.3) [0.3]** | **5 (1.6) [1.6]** |
| Nephrolithiasis | 1 (0.2) [0.3] | 1 (0.9) [1.1] | 0 | 0 | 2 (0.3) [0.4] | 2 (1.4) [1.4] | 2 (0.2) [0.2] | 2 (0.7) [0.7] |
| Ureterolithiasis | 0 | 0 | 2 (0.3) [0.3] | 2 (1.3) [1.2] | 0 | 0 | 2 (0.2) [0.2] | 2 (0.7) [0.6] |
| **Respiratory, thoracic and mediastinal disorders** | **1 (0.2) [0.1]** | **1 (0.9) [0.5]** | **1 (0.2) [0.2]** | **1 (0.6) [0.6]** | **3 (0.5) [0.6]** | **3 (2.1) [2.2]** | **4 (0.3) [0.3]** | **4 (1.3) [1.3]** |
| Pulmonary embolism | 0 | 0 | 0 | 0 | 2 (0.3) [0.4] | 2 (1.4) [1.4] | 2 (0.2) [0.2] | 2 (0.7) [0.7] |

Maintenance up to 52 Weeks

In the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), the percentage and rate of subjects with SAEs were similar in both risankizumab SC dose arms (12.3%, 19.5 E/100 PY in the risankizumab 180 mg SC arm and 13.4%, 21.0 E/100 PY in the risankizumab 360 mg SC arm) compared with the withdrawal (placebo SC) arm (12.5%, 19.3 E/100 PY), with no evidence of a dose response between the risankizumab 180 mg SC and 360 mg SC arms (Table 63).

Serious adverse events were most frequently reported in the SOC of gastrointestinal disorders in both risankizumab SC arms and the withdrawal (placebo SC) arm. The most frequently reported SAEs in risankizumab-treated subjects were Crohn's disease (1.2 E/100 PY in both the risankizumab 180 mg and 360 mg SC arms), small intestinal obstruction (0.6 E/100 PY in the risankizumab 180 mg SC arm and 1.8 E/100 PY in the risankizumab 360 mg SC arm), and subileus (1.8 E/100 PY in the risankizumab 180 mg SC arm and 0.6 E/100 PY in the risankizumab 360 mg SC arm) (Table 63). All of these PTs are in the gastrointestinal disorder SOC and appear to be attributable to the underlying disease. Serious AEs of Crohn's disease occurred in a higher rate of subjects in the withdrawal (placebo SC) arm (2.5 E/100 PY). All SAEs assessed by the investigator as having a possible relationship to study drug were reported by 1 subject each . A total of 1 subject in the risankizumab 180 mg arm and 4 subjects in the risankizumab 360 mg arm discontinued study drug due to an SAE.

*Table 63 Treatment-Emergent Serious Adverse Events EAER per 100 PY Occurring in ≥2% Events in Any Treatment Arm (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set)*

| System Organ Class<br>MedDRA 23.1 Preferred Term | Withdrawal (Placebo SC)<br>(N = 184)<br>(PY = 160.4)<br>Events<br>(E/100 PY) | Risankizumab<br>180 mg SC<br>(N = 179)<br>(PY = 169.3)<br>Events<br>(E/100 PY) | Risankizumab<br>360 mg SC<br>(N = 179)<br>(PY = 166.4)<br>Events<br>(E/100 PY) | Risankizumab<br>Total<br>(N = 358)<br>(PY = 335.7)<br>Events<br>(E/100 PY) |
|---|---|---|---|---|
| **Any adverse event** | **31 (19.3)** | **33 (19.5)** | **35 (21.0)** | **68 (20.3)** |
| **Gastrointestinal disorders** | **12 (7.5)** | **14 (8.3)** | **13 (7.8)** | **27 (8.0)** |
| Anal fistula | 2 (1.2) | 0 | 3 (1.8) | 3 (0.9) |
| Crohn's disease | 4 (2.5) | 2 (1.2) | 2 (1.2) | 4 (1.2) |
| Ileus | 0 | 1 (0.6) | 2 (1.2) | 3 (0.9) |
| Large intestinal stenosis | 0 | 3 (1.8) | 1 (0.6) | 4 (1.2) |
| Small intestinal obstruction | 0 | 1 (0.6) | 3 (1.8) | 4 (1.2) |
| Subileus | 0 | 3 (1.8) | 1 (0.6) | 4 (1.2) |
| **Infections and infestations** | **8 (5.0)** | **5 (3.0)** | **10 (6.0)** | **15 (4.5)** |
| Abscess limb | 0 | 0 | 2 (1.2) | 2 (0.6) |
| Anal abscess | 2 (1.2) | 0 | 1 (0.6) | 1 (0.3) |
| Appendicitis | 1 (0.6) | 2 (1.2) | 0 | 2 (0.6) |
| Diverticulitis | 3 (1.9) | 0 | 0 | 0 |
| Viral infection | 0 | 0 | 3 (1.8) | 3 (0.9) |
| **Musculoskeletal and connective tissue disorders** | **1 (0.6)** | **0** | **5 (3.0)** | **5 (1.5)** |
| Back pain | 0 | 0 | 3 (1.8) | 3 (0.9) |
| **Respiratory, thoracic and mediastinal disorders** | **3 (1.9)** | **1 (0.6)** | **0** | **1 (0.3)** |
| Chronic obstructive pulmonary disease | 3 (1.9) | 1 (0.6) | 0 | 1 (0.3) |

All Treated Safety Analysis Set

The overall SAE rate (18.1 E/100 PY) and types of SAEs in the ANY RZB SC group of the All Treated Safety Analysis Set were similar to those observed in the Total RZB group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set (20.3 E/100 PY) (Table 63). The SAEs with the highest EAER in the ANY RZB SC group of the All Treated Safety Analysis Set were Crohn's disease (1.6 E/100 PY) and small intestinal obstruction (0.8 E/100 PY). The EAER of SAEs with risankizumab treatment was stable, with no increased risk of experiencing an SAE with longer exposure.

The cumulative incidence plot for SAEs in the All Treated Safety Analysis Set suggests that the risk of subjects experiencing SAEs on risankizumab remained constant over time. The number of subjects exposed to risankizumab at and after Week 144 is too small for any meaningful interpretation.

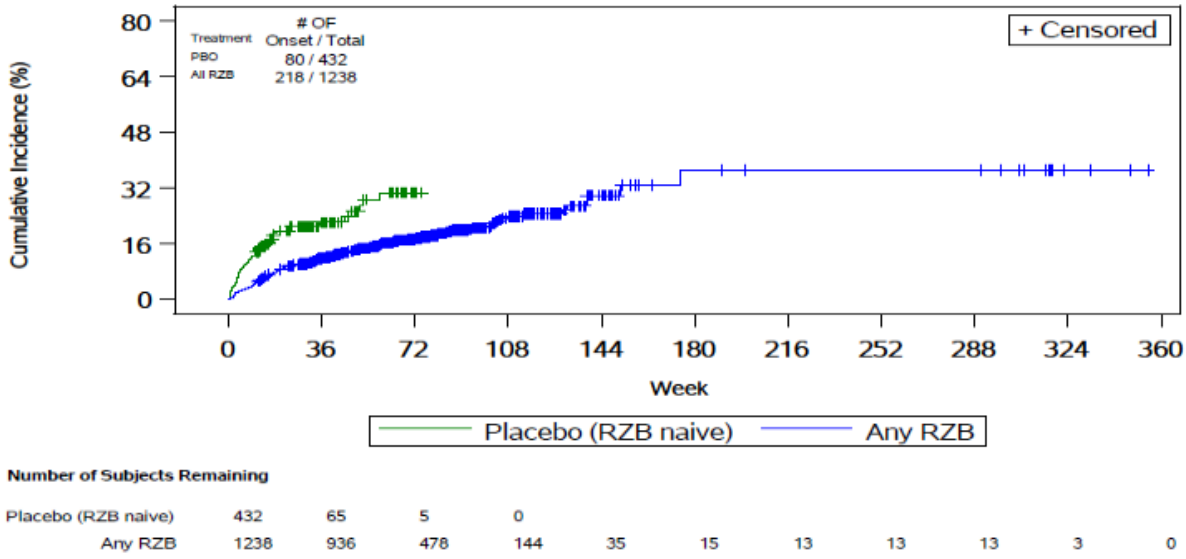



*Figure 24 Cumulative Incidence Plot for Treatment-Emergent Serious Adverse Events (All Treated Safety Analysis Set)*

*AEs in ASI*

12-Week Induction

During the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), the percentages and rates of AEs in the ASI categories, including hepatic events and hypersensitivity reactions, were generally comparable between the Total RZB and placebo groups, with similar percentages observed in the risankizumab 600 mg IV and 1200 mg IV groups (Table 64). Notable differences include a higher rate of serious infection reported in the placebo group and a numerically higher rate of ISRs in the risankizumab 1200 mg IV group as compared to the risankizumab 600 mg IV group.

*Table 64 Overview of Treatment-Emergent Adverse Events in Areas of Safety Interest in Percentage and EAER per 100 PY (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

| | Placebo IV (N = 432) (PY = 117.6) | | Risankizumab 600 mg IV (N = 620) (PY = 159.8) | | Risankizumab 1200 mg IV (N = 577) (PY = 143.3) | | Risankizumab Total (N = 1197) (PY = 303.1) | | Treatment Comparison [95% CI][a] for n (%) differences | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | RZB 600 mg IV - PBO IV | RZB 1200 mg IV - PBO IV |
| Adjudicated MACE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0.0 |
| Adjudicated extended MACE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0.0 |
| Serious infections | 16 (3.7) [3.6] | 20 (17.0) [16.7] | 6 (1.0) [0.9] | 6 (3.8) [3.4] | 4 (0.7) [0.7] | 4 (2.8) [2.9] | 10 (0.8) [0.9] | 10 (3.3) [3.5] | -2.7 [-4.6, -0.7] | -2.5 [-4.5, -0.5] |
| Active tuberculosis | 1 (0.2) [0.3] | 1 (0.9) [1.1] | 1 (0.2) [0.2] | 1 (0.6) [0.6] | 0 | 0 | 1 (< 0.1) [< 0.1] | 1 (0.3) [0.3] | -0.2 [-0.8, 0.5] | -0.3 [-1.0, 0.3] |
| Opportunistic infections excluding tuberculosis and herpes zoster | 3 (0.7) [0.5] | 3 (2.6) [2.0] | 0 | 0 | 1 (0.2) [0.2] | 1 (0.7) [0.6] | 1 (< 0.1) [< 0.1] | 1 (0.3) [0.3] | -0.5 [-1.2, 0.1] | -0.4 [-1.1, 0.3] |
| Herpes zoster | 1 (0.2) [0.2] | 1 (0.9) [0.7] | 2 (0.3) [0.3] | 2 (1.3) [1.2] | 1 (0.2) [0.2] | 1 (0.7) [0.6] | 3 (0.3) [0.2] | 3 (1.0) [0.9] | 0.1 [-0.4, 0.7] | -0.0 [-0.5, 0.5] |
| Malignant tumours | 0 | 0 | 0 | 0 | 1 (0.2) [0.2] | 1 (0.7) [0.8] | 1 (< 0.1) [< 0.1] | 1 (0.3) [0.4] | 0.0 | 0.2 [-0.2, 0.6] |
| Non-Melanoma Skin Cancer (NMSC) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0.0 |

| | Placebo IV (N = 432) (PY = 117.6) | | Risankizumab 600 mg IV (N = 620) (PY = 159.8) | | Risankizumab 1200 mg IV (N = 577) (PY = 143.3) | | Risankizumab Total (N = 1197) (PY = 303.1) | | Treatment Comparison [95% CI][a] for n (%) differences | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | RZB 600 mg IV - PBO IV | RZB 1200 mg IV - PBO IV |
| Malignant tumours excluding NMSC | 0 | 0 | 0 | 0 | 1 (0.2) [0.2] | 1 (0.7) [0.8] | 1 (< 0.1) [< 0.1] | 1 (0.3) [0.4] | 0.0 | 0.2 [-0.2, 0.6] |
| Hypersensitivity | 21 (4.9) [4.3] | 29 (24.7) [21.8] | 30 (4.8) [4.7] | 33 (20.7) [20.2] | 30 (5.2) [5.3] | 30 (20.9) [21.4] | 60 (5.0) [5.1] | 63 (20.8) [20.9] | 0.4 [-2.1, 3.0] | 1.4 [-1.2, 4.1] |
| Serious hypersensitivity | 1 (0.2) [0.1] | 1 (0.9) [0.5] | 1 (0.2) [0.2] | 1 (0.6) [0.6] | 0 | 0 | 1 (< 0.1) [< 0.1] | 1 (0.3) [0.3] | 0.0 [-0.4, 0.4] | 0.0 |
| Adjudicated anaphylactic reactions | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0.0 |
| Hepatic events | 7 (1.6) [1.7] | 7 (6.0) [6.4] | 10 (1.6) [1.6] | 14 (8.8) [8.5] | 8 (1.4) [1.4] | 9 (6.3) [6.1] | 18 (1.5) [1.4] | 23 (7.6) [7.1] | -0.2 [-1.8, 1.5] | -0.3 [-2.0, 1.3] |
| Injection site reactions[b] | 5 (1.2) [1.0] | 6 (5.1) [4.2] | 5 (0.8) [0.8] | 7 (4.4) [4.4] | 12 (2.1) [2.0] | 12 (8.4) [8.2] | 17 (1.4) [1.4] | 19 (6.3) [6.1] | -0.2 [-1.3, 0.9] | 1.1 [-0.3, 2.6] |

Maintenance up to 52 Weeks

During the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), the rates of AEs in the ASI categories were generally comparable between the Total RZB group and the withdrawal (placebo SC) arms, with no dose dependency observed (Table 65).

All Treated Safety Analysis Set

*Table 65 Overview of Treatment-Emergent Adverse Events in Areas of Safety Interest in Percentage and EAER per 100 PY (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set and All Treated Safety Analysis Sets) (continued)*

| | Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set | | | | | | | | | | All Treated Safety Analysis Set | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Withdrawal (Placebo SC) (N = 184) (PY = 160.4) | | Risankizumab 180 mg SC (N = 179) (PY = 169.3) | | Risankizumab 360 mg SC (N = 179) (PY = 166.4) | | Risankizumab Total (N = 358) (PY = 335.7) | | Treatment Comparison [95% CI] for n (%) differences | | RZB 360 mg SC (N = 533) (PY = 442.6) | | Any RZB SC (N = 1318) (PY = 1547.0) | |
| | n (%) | Events (E/100 PY) | n (%) | Events (E/100 PY) | n (%) | Events (E/100 PY) | n (%) | Events (E/100 PY) | RZB 180 mg SC - PBO IV | RZB 360 mg SC - PBO IV | n (%) | Events (E/100 PY) | n (%) | Events (E/100 PY) |
| Malignant tumours | 1 (0.5) | 1 (0.6) | 0 | 0 | 1 (0.6) | 1 (0.6) | 1 (0.3) | 1 (0.3) | -0.5 (-1.6, 0.5) | 0.0 (-1.5, 1.5) | 2 (0.4) | 3 (0.7) | 9 (0.7) | 10 (0.6) |
| Non-Melanoma Skin Cancer (NMSC) | 1 (0.5) | 1 (0.6) | 0 | 0 | 0 | 0 | 0 | 0 | -0.5 (-1.6, 0.5) | -0.5 (-1.6, 0.5) | 0 | 0 | 1 (< 0.1) | 1 (< 0.1) |
| Malignant tumours excluding NMSC | 0 | 0 | 0 | 0 | 1 (0.6) | 1 (0.6) | 1 (0.3) | 1 (0.3) | 0.0 | 0.6 (-0.5, 1.7) | 2 (0.4) | 3 (0.7) | 8 (0.6) | 9 (0.6) |
| Hypersensitivity | 17 (9.2) | 19 (11.8) | 18 (10.1) | 21 (12.4) | 12 (6.7) | 21 (12.6) | 30 (8.4) | 42 (12.5) | 0.8 (-5.3, 6.9) | -2.5 (-8.1, 3.0) | 38 (7.1) | 53 (12.0) | 109 (8.3) | 152 (9.8) |
| Serious hypersensitivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0.0 | 0 | 0 | 1 (< 0.1) | 1 (< 0.1) |
| Adjudicated anaphylactic reactions | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0.0 | 0 | 0 | 0 | 0 |

The rates of AEs in the ASI categories in the ANY RZB SC group of the All Treated Safety Analysis Set were generally comparable to those of the Total RZB group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set (Table 65).

Notable events include 1 AE of active TB in the ANY RZB SC group, which is discussed below.

*MACE and Extended MACE*

12-Week Induction

There were no adjudicated CV events reported during the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set (Table 64).

Maintenance up to 52 Weeks

In the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set, 2 adjudicated MACE were reported, 1 non-fatal myocardial infarction in the risankizumab 360 mg SC arm in a 40-50-year-old subject with a history of dyslipidemia and long term smoker and 1 non-fatal stroke in the withdrawal (placebo SC) treatment arm (Table 66 and Table 67). The incidence rate of MACE in these 2 treatment arms was 0.6/100 PY.

*Table 66 Treatment-Emergent MACE (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set)*

| | | Risankizumab | | |
|---|---|---|---|---|
| Category<br>Adjudicated Term | Withdrawal (Placebo SC)<br>(N = 184)<br>n (%) | 180 mg SC<br>(N = 179)<br>n (%) | 360 mg SC<br>(N = 179)<br>n (%) | Total<br>(N = 358)<br>n (%) |
| **Any adjudicated CV event** | **1 (0.5)** | **0** | **1 (0.6)** | **1 (0.3)** |
| **MACE** | **1 (0.5)** | **0** | **1 (0.6)** | **1 (0.3)** |
| Cardiovascular Death | 0 | 0 | 0 | 0 |
| Non-fatal Myocardial Infarction | 0 | 0 | 1 (0.6) | 1 (0.3) |
| Non-fatal Stroke | 1 (0.5) | 0 | 0 | 0 |

*All Treated Safety Analysis Set*

A total of 4 subjects in the ANY RZB group had an adjudicated MACE including 1 MACE of non-fatal myocardial infarction noted above. The additional 3 subjects had a MACE while on 180 mg risankizumab SC (1 subject during M16-000 Sub-Study 1, and 2 subjects during the Phase 3 OLE [Study M16-000 Sub-Study 3]). All of the subjects who had a MACE had CV risk factors or a history of CV disease. One fatal SAE of sudden cardiac death is detailed in Table 67. None of the non-fatal cardiac events led to study drug discontinuation. The incidence rate of MACE in the ANY RZB group was 0.2/100 PY and was not higher than the background rate for this patient population based on published estimates.

There were no additional cases of extended MACE.

*Table 67 Listing of Subjects with Adjusted MACE in CD Studies*

| Induction Study Number<br>Subject Number<br>Age Range | Study and Treatment at Event Occurrence | AE Onset Day Since First Dose of Study Drug / First Dose of RZB | Previous Induction Treatment | Preferred Term/ Adjudicated Term | Comments |
|---|---|---|---|---|---|
| 1311.0006<br>M16-000<br>40-45 | M16-000 (Sub-Study 3)<br>RZB 180 mg SC | 1709 / 1709 | RZB 200 mg IV | Transient ischaemic attack/<br>Non-fatal stroke | Risk factors: long term smoker<br>, obesity (BMI 33.9), sedentary lifestyle |
| M16-006<br>30-35 | M16-000 (Sub-Study 3)<br>RZB 180 mg SC | 306 / 306 | RZB 1200 mg IV | Sudden cardiac death/<br>Sudden cardiac death | Risk factors: obesity (BMI 35.0), former smoker for 4 years |
| M16-006<br>70-75 | M16-000 (Sub-Study 1),<br>RZB 180 mg SC | 483 / 483 | RZB 600 mg IV (12-Week Induction Period), RZB 180 mg SC (IP2) | Stress cardiomyopathy/<br>Non-fatal myocardial infarction | Risk factors: hypertension, cardiac arrhythmia (atrial fibrillation, atrial flutter), heart murmur, former smoker for 7 years |
| | | 487 / 487 | RZB 600 mg IV (12-Week Induction Period), RZB 180 mg SC (IP2) | Coronary artery disease/<br>Non-fatal myocardial infarction | |
| M16-006<br>45-50 | M16-000 (Sub-Study 1)<br>RZB 360 mg SC | 411 / 411 | RZB 600 mg IV | Acute myocardial infarction/<br>Non-fatal myocardial infarction | Risk factors: dyslipidemia, long term smoker |
| M16-006<br>60-65 | M16-000 (Sub-Study 1)<br>Placebo SC | 420 / 420 / 250 (from first dose of placebo) | RZB 1200 mg IV | Cerebral infarction/<br>Non-fatal stroke | Risk factors: long term smoker<br>, obesity (BMI 33) |

There were no adjudicated CV events reported during the 12-Week Induction Period.

Overall, 4 subjects treated with risankizumab and one subject in the withdrawal (placebo SC) group experienced adjudicated MACE, of whom all had known risk factors for MACE or a history of CV disease. The MACE incidence rate in the ANY RZB treatment group of the All Treated Safety Analysis Set (0.2/100 PY) was not higher than the background rate for this patient population based on published estimates (0.82/100 PY) (Kristensen 2013). Overall, the data did not suggest an increased risk of MACE with risankizumab treatment in subjects with CD.

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

*Overall and Serious Infections*

12-Week Induction

In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), AEs in the infections and infestations SOC were reported at a lower percentage and rate among subjects in the risankizumab groups (19.2%, 83.3 E/100 PY in the 600 mg IV group and 18.3%, 95.6 E/100 PY in the 1200 mg IV group, compared to subjects in the placebo group (24.4%, 117.7 E/100 PY). There was no evidence of dose effect, with similar percentages and rates of infection AEs reported in the risankizumab 600 mg IV and 1200 mg IV groups. The majority of infection AEs reported with risankizumab exposure were not serious were mild or moderate in severity, and none of the infection AEs led to discontinuation of study drug. The most common infections in the Total RZB group (≥ 1% of subjects) were nasopharyngitis (5.1%), upper respiratory tract infection (2.4%), influenza (1.1%), and urinary tract infection (1.0%). The most common infection AEs in the placebo group (≥ 1% of subjects) were nasopharyngitis (3.9%), sinusitis (1.7%), anal abscess (1.6%), gastroenteritis (1.5%), pneumonia (1.4%), upper respiratory tract infection (1.3%), and bronchitis (1.0%).

*Table 68 Treatment-Emergent Serious Infections (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

| System Organ Class<br>MedDRA 23.1 Preferred Term | Placebo IV<br>(N = 432)<br>n (%) [SSA%] | Risankizumab<br>600 mg IV<br>(N = 620)<br>n (%) [SSA%] | Risankizumab<br>1200 mg IV<br>(N = 577)<br>n (%) [SSA%] | Risankizumab<br>Total<br>(N = 1197)<br>n (%) [SSA%] |
|---|---|---|---|---|
| **Infections and infestations** | **16 (3.7) [3.6]** | **6 (1.0) [0.9]** | **4 (0.7) [0.7]** | **10 (0.8) [0.9]** |
| Abdominal abscess | 2 (0.5) [0.3] | 0 | 0 | 0 |
| Abdominal wall abscess | 1 (0.2) [0.3] | 0 | 0 | 0 |
| Abscess intestinal | 1 (0.2) [0.3] | 0 | 0 | 0 |
| Anal abscess | 2 (0.5) [0.4] | 1 (0.2) [0.1] | 0 | 1 (< 0.1) [0.1] |
| Appendicitis | 0 | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| Cellulitis of male external genital organ | 1 (0.2) [0.2] | 0 | 0 | 0 |
| Gastroenteritis | 1 (0.2) [0.3] | 0 | 0 | 0 |
| Gastroenteritis Escherichia coli | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| Leptospirosis | 0 | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| Lower respiratory tract infection | 0 | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| Neutropenic sepsis | 1 (0.2) [0.2] | 0 | 0 | 0 |
| Osteomyelitis | 0 | 1 (0.2) [0.1] | 0 | 1 (< 0.1) [0.1] |
| Perirectal abscess | 1 (0.2) [0.2] | 0 | 0 | 0 |
| Pneumonia | 2 (0.5) [0.4] | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| Pulmonary sepsis | 1 (0.2) [0.3] | 0 | 0 | 0 |
| Pyelonephritis | 1 (0.2) [0.3] | 0 | 0 | 0 |
| Rectal abscess | 1 (0.2) [0.1] | 0 | 0 | 0 |
| Sepsis | 1 (0.2) [0.2] | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| Tonsillitis | 1 (0.2) [0.3] | 0 | 0 | 0 |
| Urinary tract infection | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| Vaginal abscess | 1 (0.2) [0.1] | 0 | 0 | 0 |
| Viral myocarditis | 1 (0.2) [0.2] | 0 | 0 | 0 |
| Viral pharyngitis | 0 | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| Vulval cellulitis | 1 (0.2) [0.3] | 0 | 0 | 0 |

In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), serious infections were reported at a lower percentage and rate among subjects in the risankizumab groups (0.9%, 3.4 E/100 PY in the 600 mg IV group and 0.7%, 2.9 E/100 PY in the 1200 mg group [Table 68 and Table 64]) compared to subjects in the placebo group (3.6%, 16.7 E/100 PY). The higher rate of serious infections in the placebo group was driven primarily by more events of gastrointestinal abscess. There was no evidence of dose-response, with similar percentages and rates of serious infections reported in the risankizumab 600 mg IV and 1200 mg IV groups. None of the serious infections reported in risankizumab subjects were reported in more than one subject and none led to discontinuation of study drug. One subject in the risankizumab 600 mg IV treatment group had an SAE of leptospirosis, which was moderate in severity, resulted in hospitalization/prolonged hospitalization, was considered by the investigator to have no reasonable possibility of being related to study drug. The subject had an occupation-related exposure to rodents. Study drug was not changed due to the infection.

Maintenance up to 52 Weeks

In the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set) the rate of infection-related AEs was lower in both risankizumab treatment arms (51.4 E/100 PY for 180 mg SC, 57.7 E/100 PY for 360 mg SC) compared to the rate in the withdrawal (placebo SC) arm (76.0 E/100 PY). The most common infection AEs in the Total RZB group (≥ 3% of subjects) were nasopharyngitis (12.5%) and upper respiratory tract infection (3.6%), while the most common infection AEs in the withdrawal (placebo SC) arm were nasopharyngitis (18.7%), URTI (4.4%), urinary tract infection (4.4%), gastroenteritis viral (3.7%), and influenza (3.7%).

Most infection-related AEs reported with risankizumab exposure were not serious, were mild or moderate in severity, and few led to discontinuation of study drug.

Treated Safety Analysis Set

The rate of infection in the ANY RZB SC group was 56.6 E/100 PY (All Treated Safety Analysis Set), and similar to the rate of 54.5 E/100 PY in the Total RZB group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set. The majority of infection events in the ANY RZB group were non-serious, mild to moderate in severity, and few (3 events, 0.2%) led to discontinuation of study drug.

Overall, the cumulative incidence plot shows the incidence of infection appeared to be higher during the early stages of treatment which is likely due to infections related to active underlying disease, with no apparent differences between risankizumab or placebo (Figure 25). The small denominators at later time points lend to wide variability in the event rates, reflected in this graph.

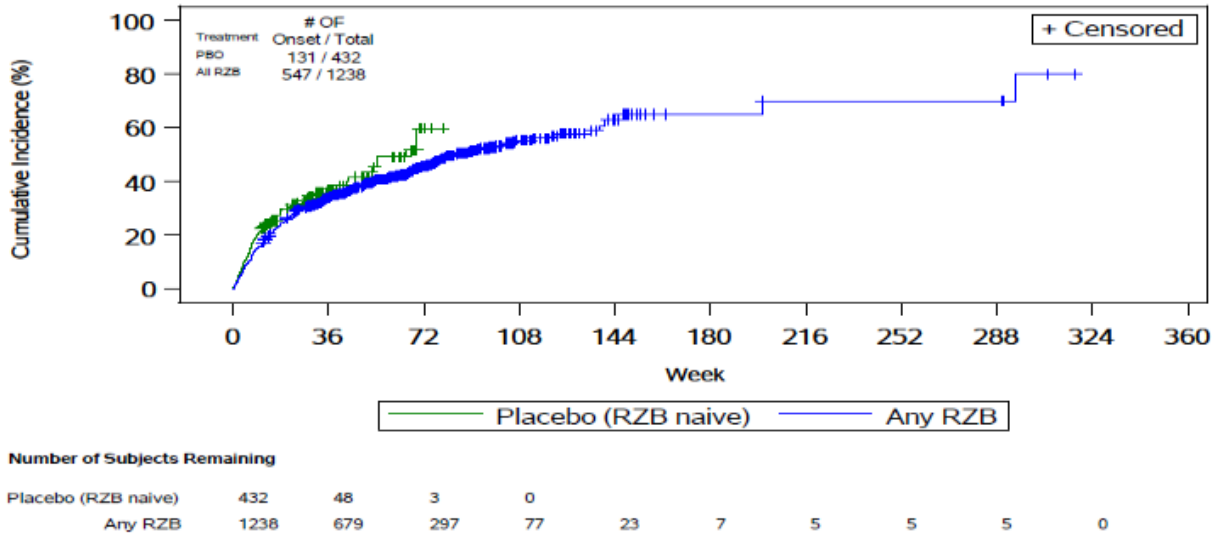



*Figure 25 Cumulative Incidence Plot for Treatment-Emergent Infections (All Treated Safety Analysis Set)*

Upper respiratory tract infections were among the most commonly reported types of infections, which was consistent with findings from a population-based epidemiological study in patients with CD. Upper respiratory tract infections (grouping of clinically related PTs) have been identified as ADRs from the psoriasis clinical development program and are listed in the current ADR table in the product label. Based on this review of both risankizumab IV doses in induction as well as both risankizumab SC doses in long-term maintenance therapy, no additional types of infection were identified as ADRs.

Additionally, no meaningful change in frequency or severity of the currently known ADR for upper respiratory tract infections was identified.

*Opportunistic Infections Excluding TB and Herpes Zoster*

12-Week Induction

In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), opportunistic infections were reported at a similar percentage and rate across treatment groups (0%, 0 E/100 PY in the risankizumab 600 mg IV group, 0.2% [1 event] 0.6 E/100 PY in the risankizumab 1200 mg IV group, and 0.5% [3 events] 2.0 E/100 PY in the placebo group) (Table 64).

The single opportunistic infection reported in the risankizumab 1200 mg IV group was CMV infection, which was reported on Day 15. After the database lock of Study M16-006, follow-up information confirmed the CMV was based on a biopsy obtained during Screening, and the subject was asymptomatic. The event was non-serious, moderate in severity, did not lead to discontinuation of study drug, was considered by the investigator to have no reasonable possibility of being related to study drug. The CMV infection occurred prior to receiving risankizumab and resolved after 22 days.

Maintenance up to 52 Weeks

In the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set) a single event of opportunistic infection was reported in each risankizumab treatment arm (Table 69).

Both events were non-serious, mild in severity, and neither led to discontinuation of study drug nor were considered by the investigator to have a reasonable possibility of being related to study drug.

*Table 69 Treatment-Emergent Opportunistic Infection (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set)*

| | | Risankizumab | | |
|---|---|---|---|---|
| MedDRA 23.1 Preferred Term | Withdrawal (Placebo SC) (N = 184) (PY = 160.4) Events (E/100 PY) | 180 mg SC (N = 179) (PY = 169.3) Events (E/100 PY) | 360 mg SC (N = 179) (PY = 166.4) Events (E/100 PY) | Total (N = 358) (PY = 335.7) Events (E/100 PY) |
| Any adverse event | 0 | 1 (0.6) | 1 (0.6) | 2 (0.6) |
| Aeromonas infection | 0 | 0 | 1 (0.6) | 1 (0.3) |
| Oral fungal infection | 0 | 1 (0.6) | 0 | 1 (0.3) |

*All Treated Safety Analysis Set*

The rate of opportunistic infection in the ANY RZB SC group was 0.5 E/100 PY (8 events, All Treated Safety Analysis Set), which was similar to the rate of the Total RZB group (0.6 E/100 PY) in the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set. Most events were non-serious, mild to moderate in severity, and none led to discontinuation of study drug. The most frequently reported opportunistic infection in this group was non-serious oral fungal infection (0.2 E/100 PY, 3 events).

The incidence rate of opportunistic infection in the ANY RZB SC group (0.5/100 PY) of the All Treated Safety Analysis Set was consistent with the background rate for this patient population based on published estimates.

There were 3 SAEs of opportunistic infection in the ANY RZB group (detailed below) and 1 SAE in the placebo IV/SC (RZB-naïve) group (neutropenic sepsis):

- Disseminated histoplasmosis; A subject (Study M16-000 Sub-Study 1, a 20-30-year-old in the risankizumab 360 mg arm with steroid use (after tapering from 20 mg once a day [QD]) had an SAE of disseminated histoplasmosis (moderate in severity) on Day 460 (Day 369 of Sub-Study 1; 29 days after the last dose of treatment). The diagnosis was based on the findings of a biopsy obtained from the Week 52 colonoscopy required by the protocol. The subject had no symptoms compatible with acute or chronic disseminated histoplasmosis, no cough, and no chest x-ray was performed. The blood fungal culture was negative and there were no skin lesion findings. Galactomannan antigen test result was borderline. The subject had previously received 12 weeks of risankizumab 600 mg IV for induction, was randomized to the risankizumab 360 mg SC arm in M16-000 Sub-Study 1, and on Day 278 received OL rescue with risankizumab (1 dose of risankizumab 1200 mg IV) and subsequently received 3 doses of

risankizumab 360 mg SC q8w) in Substudy 1. For context, disseminated histoplasmosis may present as acute infection or chronic infection. Patients with chronic infection often present with pancytopenia, hepatosplenomegaly and involvement of other sites including GI, skin, brain, and adrenal glands. Patients with acute infection present with fever, fatigue, in addition to manifestations above. However, in this case, the subject had no clinical symptoms compatible with acute or chronic disseminated histoplasmosis. Histoplasmosis in this case was diagnosed via intestinal biopsy performed during protocol guided colonoscopy. The event resolved with itraconazole therapy and did not lead to study drug discontinuation; it was assessed by the investigator as having a reasonable possibility of being related to study drug.

- Bronchopulmonary aspergillosis; A subject, a 60-70-year-old with history as a former short-term smoker and asthma received placebo during the 12-Week Induction Period of Study M15-991, followed by risankizumab 1200 mg IV in Induction Period 2 (subject received 3 IV doses but did not enroll in Study M16-000). The subject was on concomitant medication of methylprednisone 8 mg QD. On Day 167 (during the follow-up period of Induction Period 2), the subject experienced SAEs of staphylococcal pneumonia and acute kidney injury (both of which resolved after 18 days). On Day 189, the subject experienced a severe SAE of bronchopulmonary aspergillosis that resolved after 62 days and did not lead to study drug discontinuation. Both the investigator and sponsor consider the event to have a reasonable possibility of being related to study drug.
- Cytomegalovirus infection; A subject (Study M15-991), a 20-30-year-old with relevant medical history of CD, perirectal abscess drainage, and receiving concomitant methylprednisone 7.5 mg QD, experienced an SAE of CMV infection on Day 93. The subject received placebo IV during the 12-Week Induction Period, followed by risankizumab 1200 mg IV in Induction Period 2. An ileocolonoscopy was performed for the Week 12 visit (Day 85, prior to receiving study drug in Induction Period 2) as part of study activities and a rectal biopsy was performed. On Day 93 the rectal biopsy was positive for CMV. The subject was afebrile and was admitted to the hospital to carry out IV antiviral therapy. The event resolved after 8 days and did not lead to study drug discontinuation. The investigator considered the event to have a reasonable possibility of being related to study drug but the sponsor considered the event to have no reasonable possibility of being related to study drug. The CMV infection was detected prior to the subject receiving their first dose of risankizumab.

The cumulative incidence plot for treatment-emergent opportunistic infections in the All Treated Safety Analysis Set suggests that the risk of subjects experiencing an opportunistic infection on risankizumab remained stable up to Week 108; thereafter the sample sizes were too small for meaningful interpretation.

During the induction period, no subjects developed opportunistic infection post-risankizumab exposure compared to 3 subjects in the placebo group. During the 52-week maintenance period, the event rates of opportunistic infection were the same between the risankizumab 180 mg SC and risankizumab 360 mg SC treatment arms (0.6 E/100 PY) and no events were reported in the withdrawal (placebo SC) arm. The rate of opportunistic infection in the ANY RZB SC treatment group of the All Treated Safety Analysis Set (0.5 E/100 PY) was similar to that of the Total RZB group (0.6 E/100 PY) in the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set. The incidence rate of opportunistic infection in the ANY RZB SC group (0.5/100 PY) of the All Treated Safety Analysis Set was consistent with the background rate for this patient population based on published estimates (0.80/100 PY) (Kirchgesner 2018). There was no specific pattern in type of pathogens observed. Overall, the data did not suggest an increased risk of opportunistic infection with risankizumab treatment in subjects with CD.

*Active Tuberculosis*

12-Week Induction

In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), 1 event (0.6 E/100 PY) of active TB was reported in the risankizumab 600 mg IV group and 1 event was reported in the placebo IV group (1.1 E/100 PY, Table 69). The subject in the risankizumab 600 mg IV group was a 40-50-year-old with a history of active TB that was previously treated with moxifloxacin, isoniazid, pyrazinamide, rifampicin, and ethambutol approximately 7 years prior to study entry. The subject had a positive QuantiFERON-TB Gold test and an episode of pyrexia during Screening. As the Screening chest x-ray was normal, active TB was ruled out by the investigator and no TB prophylaxis was initiated prior to the first dose of study drug. However, due to previous episodes of pyrexia, the subject underwent diagnostic workup. On Day 69, a bronchoalveolar lavage was performed and the results could not exclude TB; on the same day, the subject experienced a non-serious AE of pyrexia and was discontinued from the study after having received 3 risankizumab 600 mg IV doses. Subsequently, a non-serious AE of TB, confirmed via chest x-ray, was reported on Day 155 (Day 100 of the follow-up period [which started on Day 56]). The event of active TB was considered by the investigator to have no reasonable possibility of being related to risankizumab.

Maintenance up to 52 Weeks

In the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), there were no events of active TB reported in any treatment arm.

All Treated Safety Analysis Set

In the ANY RZB group (All Treated Safety Analysis Set), there was 1 additional case of active TB, which was reported in a 30-40-year-old subject with no history of active or latent TB and taking concomitant methotrexate. The subject received 600 mg IV during the 12-Week Induction Period in Study M15-991, then entered Study M16-000 Sub-Study 2 and received 1 dose of risankizumab 180 mg SC. On Day 118, 28 days after the last dose of risankizumab 180 mg SC, the subject experienced an SAE of active TB. The subject had suspected contact with a TB-positive person, and the event led to discontinuation of study drug.

The incidence rate of active TB for the ANY RZB group of the All Treated Safety Analysis Set was 0.097/100 PY.

*Subjects with Latent TB With or Without Prophylaxis*

In the CD studies, subjects with latent TB were eligible for enrollment per local guidelines. If latent TB was established, TB prophylaxis was to be initiated and maintained according to local country guidelines although it was not mandated. Across the risankizumab CD clinical studies, 72 subjects with latent TB were concurrently treated with risankizumab and TB prophylaxis during the study and did not develop active TB during the mean treatment follow-up of 1.4 years; 55 subjects with latent TB who did not receive prophylaxis during the study did not develop active TB during the mean treatment follow-up of 2.0 years.

*Herpes Zoster*

12-Week Induction

In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), herpes zoster was reported at a similar percentage and rate among subjects in the risankizumab groups

(0.3%, 1.2 E/100 PY in the 600 mg IV group and 0.2%, 0.6 E/100 PY in the 1200 mg IV group) and subjects in the placebo group (0.2%, 0.7 E/100 PY) (Table 64). All of the events of herpes zoster reported in risankizumab subjects were mild in severity and none led to discontinuation of study drug.

Maintenance up to 52 Weeks

In the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), the rates of herpes zoster were similar across treatment arms, with1.2 E/100 PY [2 events], 0 events, and 0.6 E/100 PY [1 event] reported in the risankizumab 180 mg SC, risankizumab 360 mg SC, and withdrawal (placebo SC) arms. Both events of herpes zoster in the risankizumab 180 mg SC arm were non-serious, mild to moderate in severity, and resolved. Neither event led to discontinuation of study drug.

All Treated Safety Analysis Set

The rate of herpes zoster in the ANY RZB SC group was 0.8 E/100 PY (12 events, All Treated Safety Analysis Set). None of the events were serious or led to study drug discontinuation and all events were mild to moderate in severity. The incidence rate of herpes zoster in the ANY RZB SC group of the All Treated Safety Analysis Set (0.8/100 PY) was similar to the expected range for this patient population based on published estimates (between 0.9 and 1.0 per 100 PY) (Sandborn 2021, Colombel 2017).

*Malignancies, NMSC, and Malignant Tumours Excluding NMSC*

12-Week Induction

In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set) there was 1 event of malignancy (SAE of squamous cell carcinoma of the lung) reported in a subject in the risankizumab 1200 mg IV group (< 0.1% subjects, 0.4 E/100 PY, Table 68) that started on Day 8 and was not considered related to study drug by the investigator.

Maintenance up to 52 Weeks

In the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), the incidence rates of malignancies were low (0.0/100 PY in the risankizumab 180 mg arm, 0.6/100 PY [1 subject] in the 360 mg arm, and 0.6/100 PY [1 subject] in the withdrawal (placebo SC) arm). The subject in the risankizumab 360 mg arm had HER2-positive breast cancer, and the subject in the withdrawal (placebo SC) arm had basal cell carcinoma; both subjects had risk factors and the events were considered to have no reasonable possibility of being related to study drug by the investigator.

All Treated Safety Analysis Set

The incidence rates of malignancies in the ANY RZB SC and the ANY RZB groups in the All Treated Safety Analysis Set were 0.6/100 PY and 0.5/100 PY, respectively. There were a total of 12 events in the ANY RZB group reported in 11 subjects, of which 9 were serious (Table 70).

Of note, a subject was a 30-40 year-old  who received 12 weeks of risankizumab 1200 mg IV for induction in Study M16-006, 52 weeks of risankizumab 180 mg SC in Study M16-000 Sub-Study 2, and continued receiving risankizumab 180 mg SC in Study M16-000 Sub-Study 3. The subject experienced a severe SAE of papillary thyroid cancer on Day 522 while in Study M16-000 Sub-Study 3. Risk factors included former long-term smoker and concurrent methotrexate use. Study drug was discontinued and the investigator considered the event to have a reasonable possibility of being related to study drug while the sponsor considered the event to have no reasonable possibility of being related to study drug. The event resolved with a thyroidectomy after 30 days. Among all subjects in the All Treated Safety Analysis Set, 3 subjects had a lung malignancy reported and 3 subjects experienced breast cancer. All risankizumab-treated subjects with malignancies had relevant risk factors (such as history

of tobacco use and family history of cancer) and/or the time to event onset suggested an incompatible temporal relationship with risankizumab therapy.

The malignancy reports ranged from Study Days 8 to 2190.

*Table 70 Treatment-Emergent Malignancies EAIR per 100 PY by PT (All Treated Safety Analysis Set)*

| System Organ Class<br>MedDRA 23.1 Preferred Term | Any RZB SC<br>(N = 1318)<br>n/PY (n/100 PY) | Any RZB<br>(N = 1574)<br>n/PY (n/100 PY) |
|---|---|---|
| Any adverse event | 9/1542.5 (0.6) | 11/2049.7 (0.5) |
| Malignant Tumours Excluding NMSC | | |
| Breast cancer | 1/1545.6 (< 0.1) | 1/2057.5 (< 0.1) |
| Gastrointestinal carcinoma | 1/1546.7 (< 0.1) | 1/2058.7 (< 0.1) |
| HER2 positive breast cancer | 1/1545.9 (< 0.1) | 1/2057.9 (< 0.1) |
| Invasive breast carcinoma | 1/1546.8 (< 0.1) | 1/2058.7 (< 0.1) |
| Lung adenocarcinoma | 2/1546.6 (0.1) | 2/2058.2 (< 0.1) |
| Metastases to bone | 1/1546.8 (< 0.1) | 1/2058.7 (< 0.1) |
| Papillary thyroid cancer | 1/1546.6 (< 0.1) | 1/2058.6 (< 0.1) |
| Squamous cell carcinoma of lung | 0/1547.0 | 1/2058.9 (< 0.1) |
| Superficial spreading melanoma stage unspecified | 1/1546.8 (< 0.1) | 1/2058.4 (< 0.1) |
| NMSC | | |
| Basal cell carcinoma | 1/1546.7 (< 0.1) | 2/2056.7 (< 0.1) |

The slope of the cumulative incidence plots for treatment-emergent malignancies excluding NMSC in the All Treated Safety Analysis Set indicated that the event rate was stable through Week 252 (approximately 4.8 years). The apparent increase thereafter is due to a single report of melanoma out of 30 subjects leading to an approximate 3.4% increase from the 1.8% rate preceding that event. The small denominators at later time points lend to wide variability in the event rates.

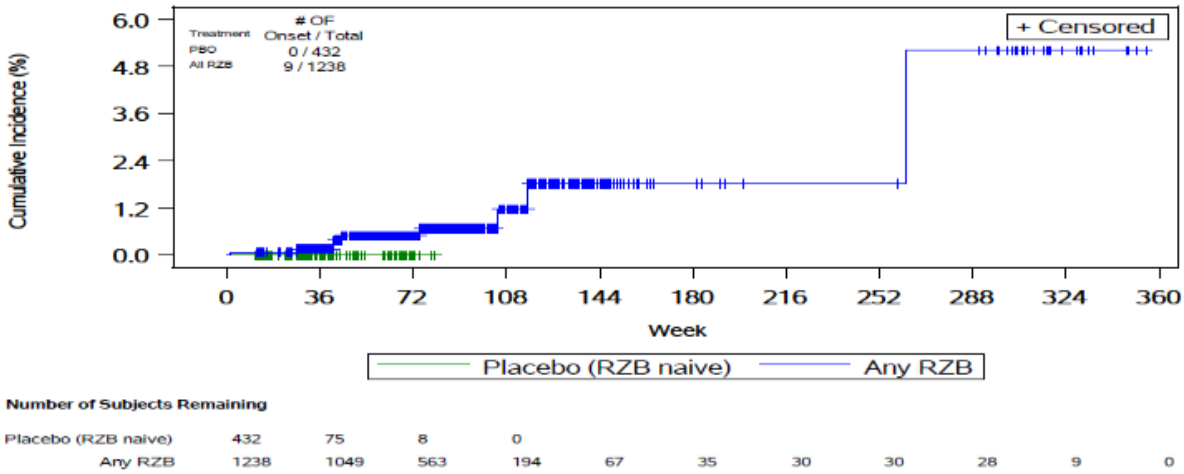



*Figure 26 Cumulative Incidence Plot for Treatment-Emergent Malignant Tumours Excluding NMSC (All Treated Safety Analysis Set)*

In the All Treated Safety Analysis Set, the incidence rate of malignancy was 0.5/100 PY for the ANY RZB group, which was not higher than the background rate for this patient population based on published estimates (1.33/100 PY) (Taborelli 2020). All subjects who reported a malignancy had relevant risk factors and/or the time to event onset after the first dose of risankizumab suggested an incompatible temporal relationship with risankizumab. The types of malignancies reported in the CD program (i.e., breast and lung cancer) were consistent with the most common cancers reported in the

general population (Ferlay 2021, Sung 2021) and do not suggest an increased risk of malignancies with risankizumab treatment. Based on the CD program data, no safety concern was identified with regards to malignancies in subjects with CD exposed to Risankizumab.

*Hepatic Disorder*

12-Week Induction

Analysis of Hepatic Laboratory Data In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), the mean change from Baseline at Week 12 showed the following: an ALT increase of 4.1, 1.0, and 0.0 U/L; an AST increase of 3.0, 2.3, and 0.4 U/L; and a total bilirubin increase of 3.1, 3.1, and 1.9 µmol/L in the risankizumab 600 mg IV, risankizumab 1200 mg IV, and placebo IV groups, respectively. There were no dose-dependent increases in ALT, AST, or total bilirubin values. The mean changes in ALT and AST were not considered clinically meaningful, as small asymptomatic changes in ALT and AST of this magnitude are relatively common in the general population and seen in up to 50% of the IBD population (Dufour 2000, Klein 2020).

Between Baseline and Week 12, the percentage of subjects with Grade 1 values in ALT and AST (> ULN to ≤ 3 × ULN) were similar across the treatment groups (Table 71). The proportions of subjects meeting criteria for liver-related elevations (as defined in Table 71 with the exception of ALT/AST > ULN to ≤ 3 × ULN) in ALT, AST, total bilirubin, and alkaline phosphatase (ALP) values in the risankizumab 600 mg IV and 1200 mg IV treatment groups were low (< 2.5% for all criteria across the treatment groups). There was no meaningful difference between the risankizumab groups and the placebo group in the percentage of subjects with an ALT or AST ≥ 3 × ULN, ALT or AST ≥ 5 × ULN, ALT or AST ≥ 10 × ULN, or ALT or AST ≥ 20 × ULN. Across all categories of aminotransferase, ALP, and bilirubin elevations, no dose-effect was observed.

*Table 71 Summary of Subjects with Liver Tests Higher than Upper Limit of Normal During the Study (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

| | | Risankizumab | | | Treatment Comparison (95% CI)[a] | |
|---|---|---|---|---|---|---|
| Criteria | Placebo IV (N = 432) n/N_OBS (%) [SSA%] | 600 mg IV (N = 620) n/N_OBS (%) [SSA%] | 1200 mg IV (N = 577) n/N_OBS (%) [SSA%] | Total (N = 1197) n/N_OBS (%) [SSA%] | 600 mg IV - Placebo | 1200 mg IV - Placebo |
| ALT > ULN – ≤ 3 × ULN[b] | 44/432 (10.2) [10.7] | 74/620 (11.9) [11.6] | 63/577 (10.9) [10.4] | -- | -- | -- |
| ALT ≥ 3 × ULN | 4/422 (0.9) [0.9] | 9/616 (1.5) [1.4] | 5/573 (0.9) [0.9] | 14/1189 (1.2) [1.1] | 0.5 [-0.7, 1.8] | -0.0 [-1.2, 1.2] |
| ALT ≥ 5 × ULN | 3/422 (0.7) [0.6] | 3/616 (0.5) [0.5] | 2/573 (0.3) [0.3] | 5/1189 (0.4) [0.4] | -0.1 [-0.9, 0.8] | -0.3 [-1.1, 0.5] |
| ALT ≥ 10 × ULN | 0/422 | 2/616 (0.3) [0.3] | 0/573 | 2/1189 (0.2) [0.2] | 0.3 [-0.1, 0.7] | 0.0 |
| ALT ≥ 20 × ULN | 0/422 | 1/616 (0.2) [0.2] | 0/573 | 1/1189 (< 0.1) [< 0.1] | 0.2 [-0.1, 0.5] | 0.0 |

| Criteria | Placebo IV (N = 432) n/N_OBS (%) [SSA%] | Risankizumab 600 mg IV (N = 620) n/N_OBS (%) [SSA%] | Risankizumab 1200 mg IV (N = 577) n/N_OBS (%) [SSA%] | Risankizumab Total (N = 1197) n/N_OBS (%) [SSA%] | Treatment Comparison (95% CI)[a] 600 mg IV - Placebo | Treatment Comparison (95% CI)[a] 1200 mg IV - Placebo |
|---|---|---|---|---|---|---|
| AST > ULN – ≤ 3 × ULN[b] | 25/432 (5.8) [6.2] | 42/620 (6.8) [6.6] | 39/577 (6.7) [6.4] | -- | -- | -- |
| AST ≥ 3 × ULN | 3/423 (0.7) [0.7] | 6/615 (1.0) [1.0] | 4/573 (0.7) [0.7] | 10/1188 (0.8) [0.8] | 0.3 [-0.8, 1.4] | -0.0 [-1.1, 1.0] |
| AST ≥ 5 × ULN | 1/423 (0.2) [0.2] | 3/615 (0.5) [0.5] | 0/573 | 3/1188 (0.3) [0.2] | 0.3 [-0.4, 1.0] | -0.2 [-0.6, 0.2] |
| AST ≥ 10 × ULN | 0/423 | 1/615 (0.2) [0.2] | 0/573 | 1/1188 (< 0.1) [< 0.1] | 0.2 [-0.1, 0.5] | 0.0 |
| AST ≥ 20 × ULN | 0/423 | 1/615 (0.2) [0.2] | 0/573 | 1/1188 (< 0.1) [< 0.1] | 0.2 [-0.1, 0.5] | 0.0 |
| TBL ≥ 2 × ULN | 2/424 (0.5) [0.5] | 9/619 (1.5) [1.3] | 4/572 (0.7) [0.8] | 13/1191 (1.1) [1.1] | 0.8 [-0.3, 2.0] | 0.2 [-0.8, 1.3] |
| ALP ≥ 1.5 × ULN | 10/424 (2.4) [2.1] | 14/619 (2.3) [2.2] | 9/572 (1.6) [1.6] | 23/1191 (1.9) [1.9] | 0.1 [-1.7, 1.9] | -0.4 [-2.1, 1.3] |
| ALT and/or AST ≥ 3 × ULN and TBL ≥ 1.5 × ULN | 0/423 | 4/616 (0.6) [0.6] | 1/572 (0.2) [0.2] | 5/1188 (0.4) [0.4] | 0.6 [0.0, 1.3] | 0.2 [-0.2, 0.6] |
| ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN | 0/423 | 2/616 (0.3) [0.3] | 1/572 (0.2) [0.2] | 3/1188 (0.3) [0.2] | 0.3 [-0.1, 0.7] | 0.2 [-0.2, 0.6] |

TBL = total bilirubin

a. Study size adjusted risk difference between treatment groups.

b. Values in this row based on ISS only includes Grade 1 elevations.

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

Among the Total RZB group, 5 subjects had an ALT elevation > 5 × ULN, and among these 5 subjects, 3 subjects had a concurrent AST elevation > 5 × ULN (Table 71). No additional subject had an isolated AST elevation > 5 × ULN. Thus, 5 unique subjects in the Total RZB group (3 in the risankizumab 600 mg IV group and 2 in the risankizumab 1200 mg IV group) of the Placebo-Controlled 12-Week Induction Period Safety Analysis Set had an ALT and/or AST elevation > 5 × ULN. Among these 5 subjects with an ALT and/or AST elevation > 5 × ULN, 1 subject had an ALT ≥ 10 × ULN and 1 additional subject had an ALT and AST ≥ 10 × ULN (as well as meeting the criteria for a potential Hy's law case).

An additional 2 subjects had values meeting a potential Hy's law case. Subjects with ≥ 10 × ULN elevation in AST/ALT and/or potential Hy's law cases are presented below:

Subjects with ALT and/or AST Elevations ≥ 10 × ULN:

- A subject (Study M16-006): a 30-40 year-old in the risankizumab 600 mg IV treatment group experienced an SAE of leptospirosis on Day 53. The subject was started on ciprofloxacin the same day. Two days later (Day 55), developed > 10 × ULN (Grade 3) ALT and Grade 3 AST elevations (ALT: 492 U/L; AST: 314 U/L) with marginally elevated total bilirubin (21 µmol/L, ULN 17 µmol/L). Of note, ALP remained normal during the event (55 U/L; range: 30 to 125 U/L) and for subsequent risankizumab treatment. Ciprofloxacin was discontinued 2 days later

(Day 57), and meropenem followed by sultamicillin was initiated (Days 61 to 76). Total bilirubin returned to the normal range on Day 56 and the SAE of leptospirosis resolved on Day 65, with normalization of ALT and AST on the same day. Study drug was not discontinued due to this event. Treatment with antibiotics, particularly ciprofloxacin, has been associated with serum enzyme elevations and acute liver injury (time to onset typically 2 days to 2 weeks). Leptospirosis infection can lead to multiple organ involvement including acute liver failure. Further, the normalization of liver enzymes in spite of ongoing risankizumab therapy does not support a causal association with risankizumab.

- A Subject with non-serious AE of rash on Day 55

Subjects with Potential Hy's Law Cases:

- A subject (Study M16-006): a 60-70-year-old in the risankizumab 600 mg IV treatment group, with a non-serious viral infection diagnosed on Day 16, was initiated on amoxicillin-clavulanate (Days 23 through 27) and developed the following laboratory abnormalities on Day 28 (Week 4): ALT 159 U/L (> 3 × ULN), AST 136 U/L (> 3 × ULN), Grade 3 total bilirubin 91 µmol/L (≥ 3 × ULN), Grade 3 ALP (923 U/L, > 5 × ULN) and Grade 4 gamma glutamyl transferase (GGT) (1092 U/L, > 20 × ULN). This subject was receiving concomitant medications of methotrexate and isoniazid (for TB prophylaxis; Days 1 through 36). All 3 drugs (amoxicillin-clavulanate, methotrexate, and isoniazid) are known to be associated with liver toxicity. The laboratory elevations were reported as non-serious AEs (mild blood ALP increased, moderate GGT increased, and severe drug-induced liver injury) and assessed by investigator as having no reasonable possibility of being related to study drug; the study drug dose was not changed. Repeat testing on Day 37, 10 days after amoxicillin-clavulanate was discontinued, showed decreases in these values, with AST in the normal range. On Day 56 (Week 8 assessment), ALT and total bilirubin also returned to normal, with GGT (178 U/L) and ALP (165 U/L) downtrending. Isoniazid was also discontinued. Given the confounding and positive dechallenge with known hepatotoxic medications (amoxicillin-clavulanate and isoniazid), this case was not judged to meet criteria for Hy's law.
- A subject (Study M15-991): a 40-50 year-old in the risankizumab 1200 mg IV treatment group, experienced an SAE of gastroenteritis Escherichia coli on Day 4 and the subject initiated treatment with paracetamol, hydrocodone/acetaminophen, ondansetron, piperacillin/tazobactam, morphine, and prochlorperazine. On the same day of diagnosis (Day 4), laboratory abnormalities of AST > 3 × ULN and Grade 3 total bilirubin were measured (AST: 156 U/L and total bilirubin 82 µmol/L); the ALT value was 117 U/L. The elevations in AST and total bilirubin were not reported as AEs. On Day 6, the paracetamol and hydrocodone/acetaminophen were discontinued and AST and total bilirubin decreased (AST: 78 U/L and total bilirubin: 34 µmol/L). On Day 30, AST and total bilirubin returned to normal range. Alkaline phosphate measurements remained within normal range and ALT never reached > 3 × ULN over the course of the other hepatic laboratory abnormalities. The study drug was not changed and the subject continued in study without further recurrence of liver test abnormalities in ALT, AST, or total bilirubin. This case was not judged to be a Hy's law case as positive dechallenge with paracetamol and acetaminophen, known hepatotoxic agents, provides the more likely alternative etiology.
- A subject (Study M16-006): a 30-40 year-old in the risankizumab 600 mg IV group with a history of hepatic steatosis and concomitant azathioprine (100 mg beginning on Day −567, with dose change to 125 mg on Day −202 and continuing to Day 80), developed a non-serious AE of rash on Day 55 and study drug was withdrawn (next scheduled dose was not given), with the last dose administered on Day 29. The rash resolved on its own after 7 days. On Day 80,

the subject developed an SAE of rash and was hospitalized; concomitant azathioprine was discontinued. On Day 82, the subject experienced an SAE of hepatic function abnormal with Grade 4 ALT (49.15 – 61.6 × ULN), AST (22.5 – 30 × ULN), and bilirubin (2.13 – 2.2 × ULN) elevations (ALP was normal at 114.67 U/L). The subject was treated with methylprednisolone (IV for 5 days, then oral administration) for the rash and medications for liver protection. Autoantibody testing was negative; liver biopsy was not performed. The ALT and AST rapidly declined over the next 3 days, and the total bilirubin also showed a decreasing trend. On Day 87, the subject was discharged from the hospital and on Day 109, the AST and ALT returned to normal range. The event of hepatic function abnormal was considered by the investigator to have a reasonable possibility of being related to study drug. The delayed time to onset of liver enzyme elevation (7 weeks after last study drug dose) and the pattern of rapid resolution of liver enzymes in the setting of long half-life of study drug, is inconsistent with DILI and rather suggestive of an acute insult; consequently the details of this case do not support a causal association of study drug to the events. Therefore, this case was not judged to be a Hy's law case.

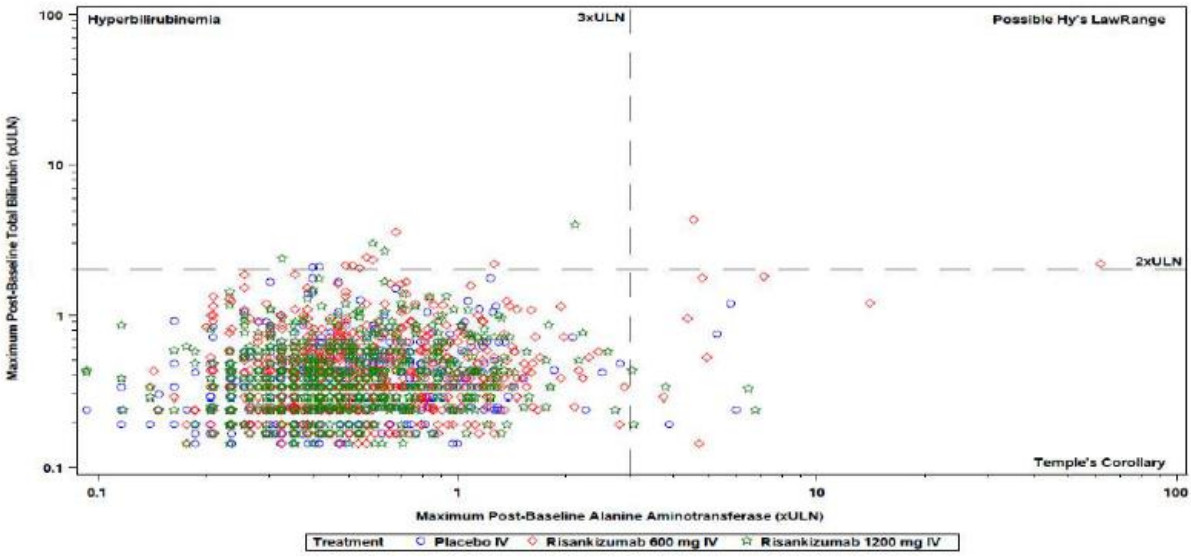



*Figure 27 eDISH Plot of Maximum Postbaseline Total Bilirubin Versus Maximum Postbaseline ALT (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

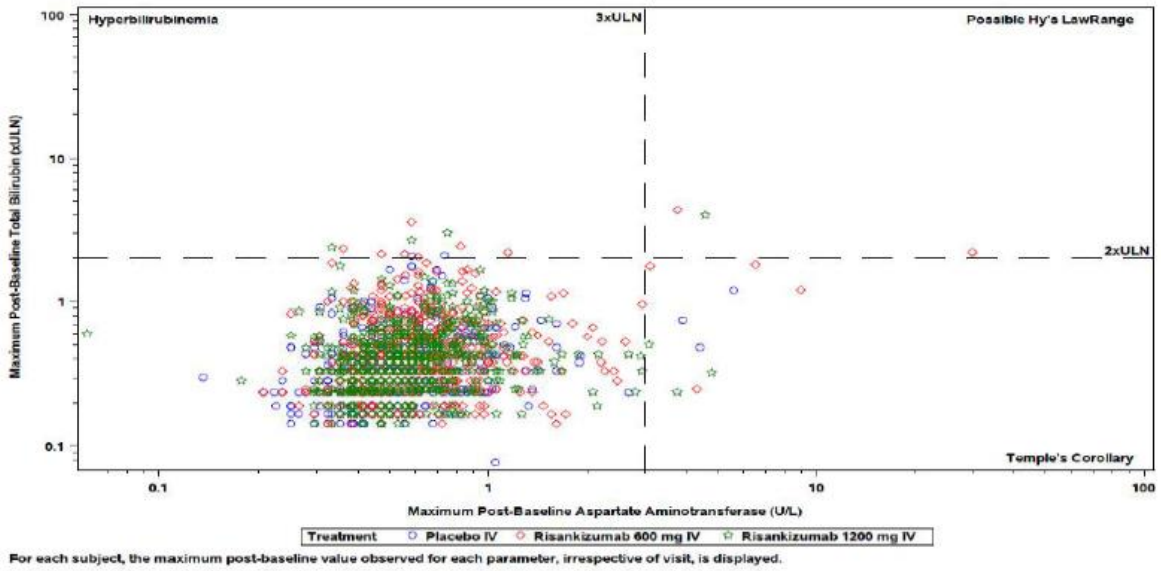



*Figure 28 eDISH Plot of Maximum Postbaseline Total Bilirubin Versus Maximum Postbaseline AST (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

Analysis of Hepatic Events

In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), hepatic events were reported at a similar percentage and rate among subjects in the risankizumab groups and subjects in the placebo group (1.6%, 8.5 E/100 PY in the risankizumab 600 mg IV group; 1.4%, 6.1 E/100 PY in the risankizumab 1200 mg IV group; and 1.7%, 6.4 E/100 PY in the placebo group). The majority of hepatic events reported in the risankizumab groups were liver enzyme increases, non-serious, mild to moderate in severity, and few events led to discontinuation of study drug (0.3% [2 subjects]) in the 600 mg IV treatment group.

A total of 2 subjects reported serious hepatic events:

- A subject  (Study M16-006) had an SAE of severe hepatic function abnormal; details on this case are presented above in the discussion on laboratory abnormalities meeting criteria for a potential Hy's law case.
- A subject (Study M16-006): a 50-60-year-old in the risankizumab 1200 mg IV treatment group taking concomitant azathioprine (Day −182 to Day 3) experienced an SAE of liver disorder (requiring hospitalization) on Day 57. Laboratory testing on Day 57 showed Grade 3 ALT (> 5 × and < 10 × ULN), Grade 2 AST (> 3 × and < 5 × ULN) with total bilirubin in normal range, and ALP (> 2 × and < 3 × ULN). An abdominal ultrasound revealed steatosis and hemangioma. The investigator considered the event to have no reasonable possibility of being related to study drug and attributed to azathioprine taken prior to the event. Study drug was withheld but then continued without further recurrence.

Additionally, 1 subject with a history of elevated liver enzymes (ALT, AST, ALP, and GGT) in the risankizumab 600 mg IV treatment group discontinued study drug as a result of a non-serious hepatic event on Day 23 (AST increased, AST and ALT were 85 U/L and 65 U/L, respectively [Baseline ALT of 91 U/L and AST of 53 U/L]. The event was moderate in severity, resolved, and was not considered to have a reasonable possibility of being related to study drug by the investigator.

While the majority of the hepatic events were representative of laboratory abnormalities and are best assessed by the more comprehensive laboratory data, events reported or coded to the PT of DILI were assessed further and are presented below.

Two subjects in the risankizumab 600 mg IV arm had the AE of drug-induced liver injury (Table 72). The drug-induced liver injury has been described above in the discussion on laboratory abnormalities of ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN. The drug-induced liver injury (reported term: drug hepatitis), who had no relevant medical history, occurred on Day 36 and was non-serious, moderate in severity, and considered by the investigator to have a reasonable possibility of being related to study drug. Alanine aminotransferase and AST were elevated (ALT: 168 U/L; AST: 89 U/L) on Day 36 but returned to normal by Day 57. Study drug dose was not changed and there was no further recurrence of hepatic events. Further details on these cases are provided in the Study M16-006 CSR.

*Table 72 Treatment-Emergent Hepatic Events (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

| | | Risankizumab | | |
|---|---|---|---|---|
| System Organ Class<br>MedDRA 23.1 Preferred Term | Placebo IV<br>(N = 432)<br>n (%) [SSA%] | 600 mg IV<br>(N = 620)<br>n (%) [SSA%] | 1200 mg IV<br>(N = 577)<br>n (%) [SSA%] | Total<br>(N = 1197)<br>n (%) [SSA%] |
| **Any adverse event** | **7 (1.6) [1.7]** | **10 (1.6) [1.6]** | **8 (1.4) [1.4]** | **18 (1.5) [1.4]** |
| **Hepatobiliary disorders** | **1 (0.2) [0.3]** | **6 (1.0) [0.9]** | **3 (0.5) [0.5]** | **9 (0.8) [0.7]** |
| Drug-induced liver injury | 0 | 2 (0.3) [0.3] | 0 | 2 (0.2) [0.2] |
| Hepatic function abnormal | 1 (0.2) [0.3] | 3 (0.5) [0.5] | 1 (0.2) [0.2] | 4 (0.3) [0.3] |
| Hepatosplenomegaly | 0 | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| Hepatotoxicity | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| Liver disorder | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| **Investigations** | **5 (1.2) [1.1]** | **5 (0.8) [0.8]** | **5 (0.9) [0.9]** | **10 (0.8) [0.8]** |
| Alanine aminotransferase increased | 1 (0.2) [0.3] | 0 | 2 (0.3) [0.3] | 2 (0.2) [0.2] |
| Aspartate aminotransferase increased | 0 | 1 (0.2) [0.2] | 1 (0.2) [0.2] | 2 (0.2) [0.2] |
| Blood alkaline phosphatase increased | 0 | 2 (0.3) [0.3] | 0 | 2 (0.2) [0.2] |
| Blood bilirubin increased | 0 | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| Gamma-glutamyltransferase increased | 1 (0.2) [0.1] | 3 (0.5) [0.5] | 1 (0.2) [0.2] | 4 (0.3) [0.3] |
| Hepatic enzyme abnormal | 1 (0.2) [0.2] | 0 | 0 | 0 |
| Hepatic enzyme increased | 1 (0.2) [0.3] | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| Liver function test abnormal | 1 (0.2) [0.2] | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| Transaminases increased | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| **Metabolism and nutrition disorders** | **1 (0.2) [0.3]** | **0** | **0** | **0** |
| Hypoalbuminaemia | 1 (0.2) [0.3] | 0 | 0 | 0 |

Maintenance up to 52 Weeks

Analysis of Hepatic Laboratory Data

In the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), the mean change from Baseline of induction at Week 52 showed the following: an ALT increase of 5.5, 7.1, and 3.8 U/L; an AST increase of 4.9, 6.6, and 4.5 U/L; and a total bilirubin increase of 3.9, 5.0, and 3.3 µmol/L in the risankizumab 180 mg SC, risankizumab 360 mg SC, and withdrawal [placebo SC] arms, respectively. There were no dose-dependent increases in ALT, AST, or total bilirubin values among the treatment arms over time. The mean changes in ALT and AST were not considered clinically meaningful, as small asymptomatic changes in ALT and AST of this magnitude are relatively common in the general population and seen in up to 50% of the IBD population (Dufour 2000, Klein 2020).

Between Week 0 and Week 52 of the maintenance period, the percentage of subjects with Grade 1 values in ALT and AST (> ULN to ≤ 3 × ULN) were similar across treatment arms (Table 73). The proportions of subjects meeting criteria for liver-related elevations (as defined in Table 73 with the exception of ALT/AST > ULN to ≤ 3 × ULN) in ALT, AST, total bilirubin, and ALP values in the risankizumab 180 mg and 360 mg SC arms were low (< 3%, Table 73). There was no meaningful

difference between risankizumab arms and the withdrawal (placebo SC) arm in the percentage of subjects with an ALT or AST ≥ 3 × ULN or ALT or AST ≥ 5 × ULN. No subjects in the risankizumab 180 mg SC arm had an ALT or AST value ≥ 5 × ULN or higher. Few subjects in the risankizumab 360 mg SC arm had an ALT elevation ≥ 5 × ULN (2 subjects) or AST elevation ≥ 5 × ULN (1 subject). None had concurrent AST and ALT elevations ≥ 5 × ULN or ALT and/or AST elevations > 10 × ULN. Of the 4 subjects in the Total RZB group with ALT ≥ 3 × ULN, one discontinued study drug.

There were no subjects who had ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN across treatment groups in the 52-week maintenance period and no Hy's law cases were identified (Table 73).

*Table 73 Summary of Subjects with Liver Tests Higher than Upper Limit of Normal During the Study (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set)*

| | | Risankizumab | | |
|---|---|---|---|---|
| Criteria | Withdrawal (Placebo SC) (N = 184) n/N_OBS (%) | 180 mg SC (N = 179) n/N_OBS (%) | 360 mg SC (N = 179) n/N_OBS (%) | Total (N = 358) n/N_OBS (%) |
| ALT > ULN – ≤ 3 × ULN[a] | 15/184 (8.2) | 19/179 (10.6) | 15/179 (8.4) | 34/358 (9.5) |
| ALT ≥ 3 × ULN | 1/175 (0.6) | 1/172 (0.6) | 3/173 (1.7) | 4/345 (1.2) |
| ALT ≥ 5 × ULN | 0/175 | 0/172 | 2/173 (1.2) | 2/345 (0.6) |
| ALT ≥ 10 × ULN | 0/175 | 0/172 | 0/173 | 0/345 |
| ALT ≥ 20 × ULN | 0/175 | 0/172 | 0/173 | 0/345 |
| AST > ULN – ≤ 3 × ULN[a] | 11/184 (6.0) | 17/179 (9.5) | 9/179 (5.0) | 26/358 (7.3) |
| AST ≥ 3 × ULN | 2/175 (1.1) | 0/171 | 2/173 (1.2) | 2/344 (0.6) |
| AST ≥ 5 × ULN | 1/175 (0.6) | 0/171 | 1/173 (0.6) | 1/344 (0.3) |
| AST ≥ 10 × ULN | 0/175 | 0/171 | 0/173 | 0/344 |
| AST ≥ 20 × ULN | 0/175 | 0/171 | 0/173 | 0/344 |
| TBL ≥ 2 × ULN | 3/176 (1.7) | 1/172 (0.6) | 5/173 (2.9) | 6/345 (1.7) |
| ALP ≥ 1.5 × ULN | 4/176 (2.3) | 1/172 (0.6) | 0/173 | 1/345 (0.3) |
| ALT and/or AST ≥ 3 × ULN and TBL ≥ 1.5 × ULN | 0/175 | 1/172 (0.6) | 0/173 | 1/345 (0.3) |
| ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN | 0/175 | 0/172 | 0/173 | 0/345 |

a. Values in this row based on Study M16-000 Sub-Study 1 CSR only includes Grade 1 elevations.

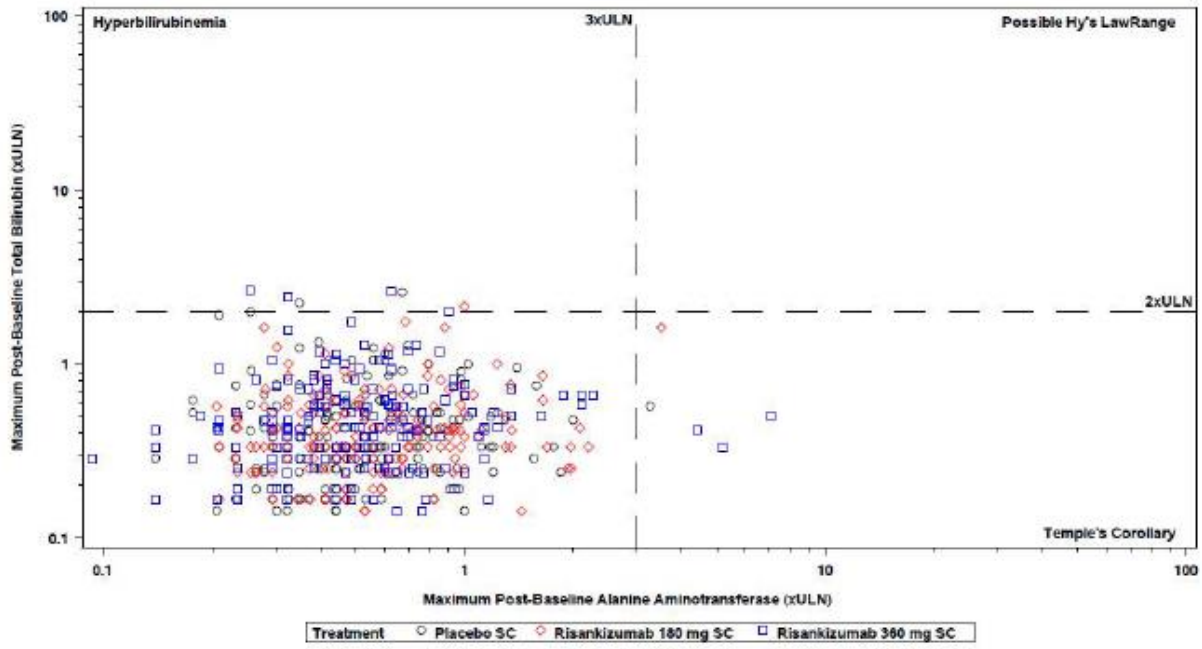



*Figure 29 eDISH Plot of Maximum Postbaseline Total Bilirubin Versus Maximum Postbaseline ALT (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set)*

Analysis of Hepatic Events

In the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), the rates of hepatic events were 4.7 E/100 PY in the risankizumab 180 mg SC arm, 5.4 E/100 PY in the risankizumab 360 mg SC arm, and 2.5 E/100 PY in the withdrawal (placebo SC) arm (Table 74). No dose dependency was observed for hepatic events. The majority of hepatic events were liver enzyme increases, none were serious or severe in severity, and only 1 subject discontinued study drug due to a hepatic event. The subject who discontinued study drug (also mentioned above) was in the risankizumab 180 mg SC arm and had 1 event of ALT increased of mild severity (was not associated with Grade 3 or above liver enzyme tests) with a concurrent moderate event of blood bilirubin increased; neither of the events were considered to have a reasonable possibility of being related to study drug.

*Table 74 Treatment-Emergent Hepatic Events (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set)*

| | | Risankizumab | | |
|---|---|---|---|---|
| MedDRA 23.1 Preferred Term | Withdrawal (Placebo SC) (N = 184) (PY = 160.4) Events (E/100 PY) | 180 mg SC (N = 179) (PY = 169.3) Events (E/100 PY) | 360 mg SC (N = 179) (PY = 166.4) Events (E/100 PY) | Total (N = 358) (PY = 335.7) Events (E/100 PY) |
| Any adverse event | 4 (2.5) | 8 (4.7) | 9 (5.4) | 17 (5.1) |
| Alanine aminotransferase increased | 1 (0.6) | 4 (2.4) | 0 | 4 (1.2) |
| Blood alkaline phosphatase increased | 0 | 0 | 1 (0.6) | 1 (0.3) |
| Blood bilirubin increased | 0 | 1 (0.6) | 0 | 1 (0.3) |
| Hepatic function abnormal | 0 | 1 (0.6) | 0 | 1 (0.3) |
| Hepatic steatosis | 0 | 2 (1.2) | 2 (1.2) | 4 (1.2) |
| Hepatomegaly | 0 | 0 | 1 (0.6) | 1 (0.3) |
| Hyperbilirubinaemia | 1 (0.6) | 0 | 2 (1.2) | 2 (0.6) |
| Hypoalbuminaemia | 0 | 0 | 1 (0.6) | 1 (0.3) |
| Liver function test abnormal | 1 (0.6) | 0 | 0 | 0 |
| Liver function test increased | 1 (0.6) | 0 | 1 (0.6) | 1 (0.3) |
| Urine bilirubin increased | 0 | 0 | 1 (0.6) | 1 (0.3) |

All Treated Safety Analysis Set

Analysis of Hepatic Laboratory Data Across all risankizumab exposure (All Treated Safety Analysis Set), the proportions of subjects meeting criteria for liver-related elevations in ALT, AST, and total bilirubin values (as defined in Table 74 with the exception of ALT/AST > ULN to ≤ 3 × ULN) in the ANY RZB SC group were low (≤ 1.3%).

Of the 8 subjects in the ANY RZB group with ALT elevation > 5 × ULN and 7 subjects in the ANY RZB group with AST elevation > 5 × ULN, 3 of the 15 subjects had concurrent AST and ALT elevations > 5 × ULN. Thus, a total of 12 unique subjects in the All Treated Safety Analysis Set had an ALT and/or AST elevation > 5 × ULN.

No additional subjects beyond those detailed in the 12-Week Induction section above had ALT and/or AST elevations ≥ 10 × ULN. The 3 subjects with ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN (potential Hy's law) in the ANY RZB group of the All Treated Safety Analysis Set were detailed above in the 12-Week Induction Period section (Figure 30 and Figure 31). Overall, no confirmed Hy's law cases were identified.

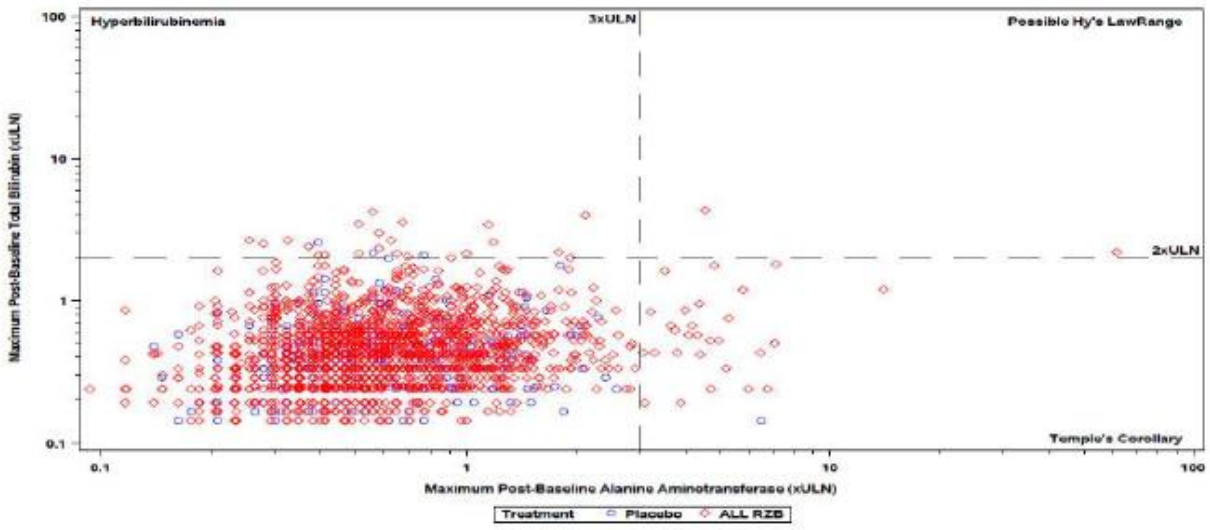



*Figure 30 eDISH Plot of Maximum Postbaseline Total Bilirubin Versus Maximum Postbaseline ALT (All Treated Safety Analysis Set)*

Analysis of Hepatic Events

In the ANY RZB SC group of the All Treated Safety Analysis Set, the rate of hepatic events was 4.1 E/100 PY, similar to the rate (5.1 E/100 PY) of the Total RZB group in the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set. The majority of hepatic events in the ANY RZB SC group were related to liver enzyme increases and are addressed above under laboratory data. The majority of hepatic events were non-serious and mild to moderate in severity, and only 1 subject discontinued study drug due to a hepatic event (< 0.1%).

In the ANY RZB group, there were 2 serious hepatic events (one resulting in study drug discontinuation and the other resulting in study drug being withheld) and both are detailed in the 12-Week Induction section above.

Two additional subjects discontinued study drug due to non-serious hepatic events, one of which is mentioned in the 12-Week Induction section and the other in the Maintenance section above. Overall, a total 3 subjects (0.2%) had hepatic events that led to discontinuation of study drug.

Exploratory Cox proportional hazards models were run to assess treatment group and prespecified baseline predictors for treatment-emergent hepatic events. These were conducted for the Phase 3 subset of the Placebo-Controlled 12-Week Induction Period Safety Analysis Set (data from Studies M15-991 and M16-006 only) and the entire All Treated Safety Analysis Set. No significant treatment effect was observed after adjustment for prespecified significant baseline predictors.

The cumulative incidence plot for treatment-emergent hepatic events in the All Treated Safety Analysis Set suggests that the risk of subjects experiencing hepatic events on risankizumab remained constant over time.

The small denominators at later time points lend to wide variability in the event rates.

The assessment of cases with serious hepatic events, hepatic events leading to discontinuation, potential Hy's law cases, and those with PCS lab elevations were confounded with risk factors including concomitant use of hepatotoxic medications, alcohol use/abuse, and underlying disease such as hepatic steatosis.

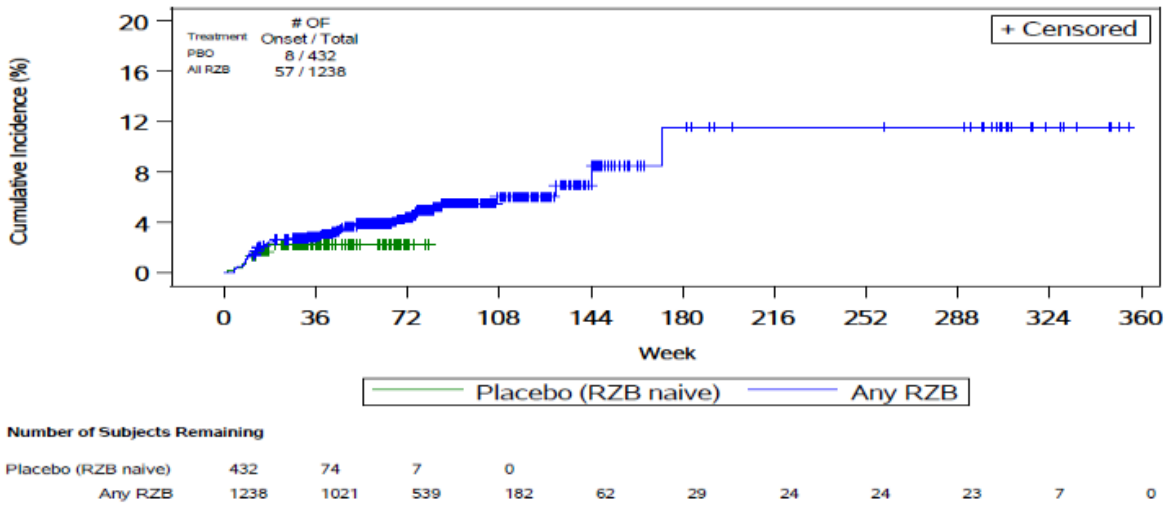



*Figure 31 Cumulative Incidence Plot for Treatment-Emergent Hepatic Events (All Treated Safety Analysis Set)*

No evidence of hepatotoxicity was observed with risankizumab administration in animal studies. In addition, there is no known mechanistic basis for interleukin (IL)-23 inhibition and drug-induced liver injury.

Overall, in the risankizumab CD program, no clinically meaningful changes from Baseline were noted in either the induction or maintenance studies. Further, no dose-dependent increases in liver enzyme tests were observed across IV or SC risankizumab treatments. The majority of enzyme elevations were transient, resolved without any change to study drug, and were asymptomatic (i.e., not accompanied with abdominal pain, jaundice, etc.). The percentage of subjects with PCS laboratory values in ALT, AST, and total bilirubin values were low (< 3%). For subjects with aminotransferase elevations ≥ 5 × ULN, alternative etiologies or confounding factors were identified, or no clear causal association with risankizumab was determined. No confirmed Hy's law cases were identified.

The majority of hepatic AEs were non-serious and related to liver enzyme increases, and 3 subjects (0.2%) in the ANY RZB group discontinued study drug due to a hepatic event.

When considering the totality of the data, no risk of hepatoxicity with risankizumab administration in subjects with CD was observed.

*COVID-19*

The risk of SARS-COV-2 infection and severe outcomes associated with COVID-19 are not yet well characterized for the CD population. Current estimates are difficult to generalize because transmission and disease severity depend on key factors such as geography, distribution of SARS-COV-2, implementation of public health mitigation strategies, COVID-19 testing capacities, demographics, and underlying population health. COVID-19 cases were identified using search terms associated with COVID-19 (MedDRA SMQ Narrow).

<u>12-Week Induction</u>

During the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), the percentage of subjects with COVID-19 related AEs was low in each treatment group (< 1%) and comparable between the risankizumab and placebo treatment groups (Table 56). There was one subject in the risankizumab 600 mg IV treatment group with a COVID-19 related, non-serious AE (COVID-19) that was mild in severity and resolved after 14 days. Study drug was temporarily

withdrawn and the event was considered by the investigator to have no reasonable possibility of being related to study drug.

Maintenance up to 52 Weeks

During the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), the percentage of subjects with COVID-19 related AEs was low in each treatment arm (< 2.5%) and comparable between the treatment arms (Table 57). There were no deaths due to COVID-19 and the single COVID-19 related SAE (which required hospitalization) was mild in severity, did not require medical intervention, and did not lead to discontinuation of study drug.

All Treated Safety Analysis Set

Across the risankizumab CD program, 70 (4.4%) subjects in the ANY RZB group reported COVID-19 related AEs (Table 75). There were no COVID-19 related deaths. There were 2 SAEs of COVID-19 in the ANY RZB group, one of which is detailed above in the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set. The additional subject had an SAE of COVID-19 on Day 578 in Study M16-000 (Sub-Study 3) while in the risankizumab 180 mg SC treatment group. The event required hospitalization and the event was considered severe but did not lead to study discontinuation and resolved after 6 days. The investigator considered it to have reasonable possibility of being related to study drug, but the sponsor did not consider it to have reasonable possibility of being related to study drug as the subject had COVID-19 risk factors of obesity (body mass index [BMI] of 31.4 and former smoker (15 cigarettes/day for 19 years).

*Table 75 Overview of Treatment-Emergent Adverse Events in Exposure-Adjusted Rate per 100 Patient Years by Age (All Treated Safety Analysis Set)*

| | < 18 years | | | |
|---|---|---|---|---|
| | RZB 1200 mg IV (N = 9) | Any RZB SC (N = 11) | Any RZB IV (N = 11) | Any RZB (N = 12) |
| Exposure-adjusted event rate: | (PYs = 2.8) Events (E/100 PYs) | (PYs = 9.0) Events (E/100 PYs) | (PYs = 3.7) Events (E/100 PYs) | (PYs = 12.6) Events (E/100 PYs) |
| All TEAEs | 12 (428.6) | 59 (655.6) | 23 (621.6) | 82 (650.8) |
| TEAEs related to COVID-19 | 0 | 0 | 0 | 0 |
| TEAEs related to study drug according to the investigator | 2 (71.4) | 21 (233.3) | 3 (81.1) | 24 (190.5) |
| Severe TEAEs | 2 (71.4) | 1 (11.1) | 2 (54.1) | 3 (23.8) |
| Serious TEAEs | 0 | 3 (33.3) | 0 | 3 (23.8) |
| TEAEs leading to discontinuation of study drug | 0 | 0 | 0 | 0 |
| TEAEs leading to death | 0 | 0 | 0 | 0 |
| All deaths | 0 | 0 | 0 | 0 |
| Deaths occurring <= 140 days after last dose of study drug | 0 | 0 | 0 | 0 |
| Deaths occurring > 140 days after last dose of study drug | 0 | 0 | 0 | 0 |
| Deaths related to COVID-19 | 0 | 0 | 0 | 0 |

### *2.6.8.4. Laboratory findings*

12-Week Induction

Mean changes from Baseline in hematology parameters and clinical chemistry parameters (excluding liver function tests [LFTs]) in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set were generally small and not considered to be clinically meaningful. There were no clinically relevant or dose-dependent trends in hematology or clinical chemistry parameters in any treatment group over time, with the exception of changes observed in platelet counts. Slight decreases in mean platelet counts were observed in the risankizumab 600 mg IV and 1200 mg IV groups, and mean platelet counts remained within the normal range. The decrease observed in mean platelet count likely reflects

the decreased systemic inflammation observed (e.g., decreased high-sensitivity C-reactive protein [hs-CRP]) in the risankizumab-treated subjects.

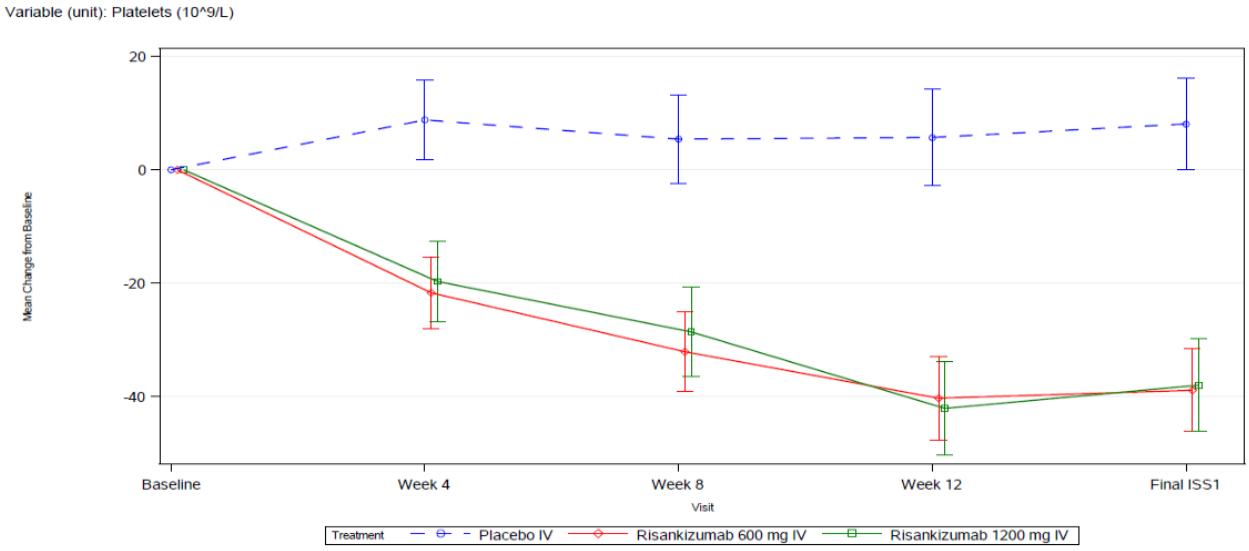



*Figure 32 Plot of Mean Change From Baseline in Laboratory Parameters (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

*Table 76 Hematology during the 12-Week Induction Period (SA1A Population)*

| Variable (unit)<br>Time Point<br>Treatment | N | Mean | SD | Median | Min | Max |
|---|---|---|---|---|---|---|
| Platelets (10^9/L) | | | | | | |
| Baseline | | | | | | |
| Placebo IV | 176 | 346.5 | 123.34 | 323.5 | 96.0 | 899.0 |
| Risankizumab 600 mg IV | 338 | 345.6 | 117.63 | 323.0 | 72.0 | 921.0 |
| Risankizumab 1200 mg IV | 339 | 343.5 | 115.08 | 329.0 | 100.0 | 944.0 |
| Week 4 | | | | | | |
| Placebo IV | 164 | 347.8 | 120.47 | 324.0 | 150.0 | 962.0 |
| Risankizumab 600 mg IV | 327 | 320.3 | 101.61 | 298.0 | 104.0 | 686.0 |
| Risankizumab 1200 mg IV | 327 | 320.9 | 104.69 | 303.0 | 0.4 | 793.0 |
| Week 8 | | | | | | |
| Placebo IV | 153 | 346.7 | 117.87 | 320.0 | 114.0 | 861.0 |
| Risankizumab 600 mg IV | 320 | 308.3 | 96.32 | 293.0 | 0.3 | 784.0 |
| Risankizumab 1200 mg IV | 320 | 311.6 | 98.34 | 294.0 | 0.4 | 782.0 |
| Week 12 | | | | | | |
| Placebo IV | 145 | 339.7 | 107.76 | 326.0 | 67.0 | 687.0 |
| Risankizumab 600 mg IV | 310 | 305.4 | 102.12 | 288.0 | 0.3 | 998.0 |
| Risankizumab 1200 mg IV | 312 | 301.6 | 94.63 | 287.5 | 0.4 | 634.0 |

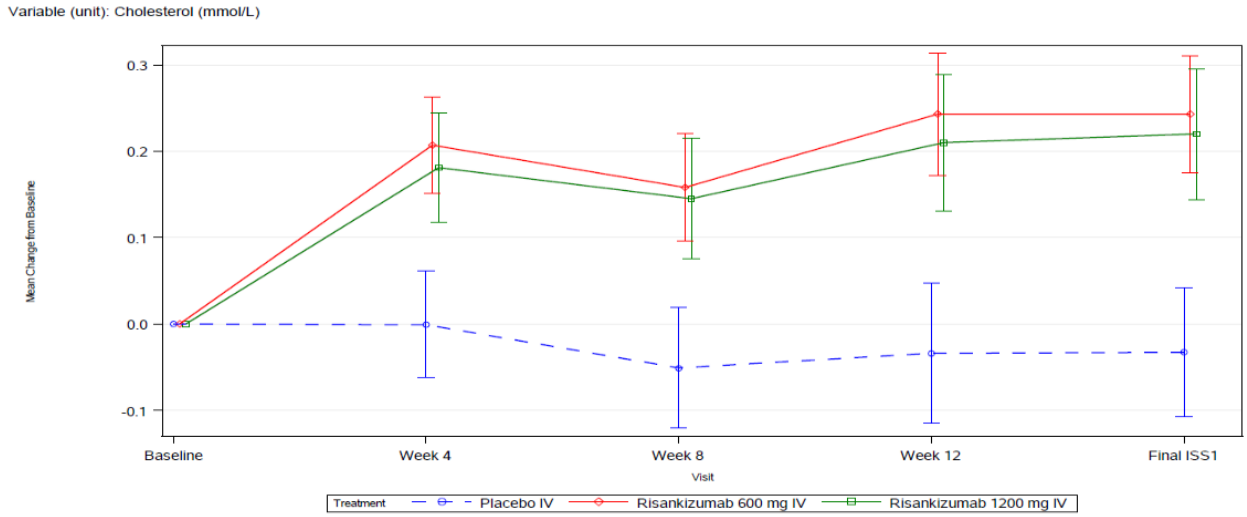



*Figure 33 Plot of Mean Change From Baseline in Laboratory Parameters (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

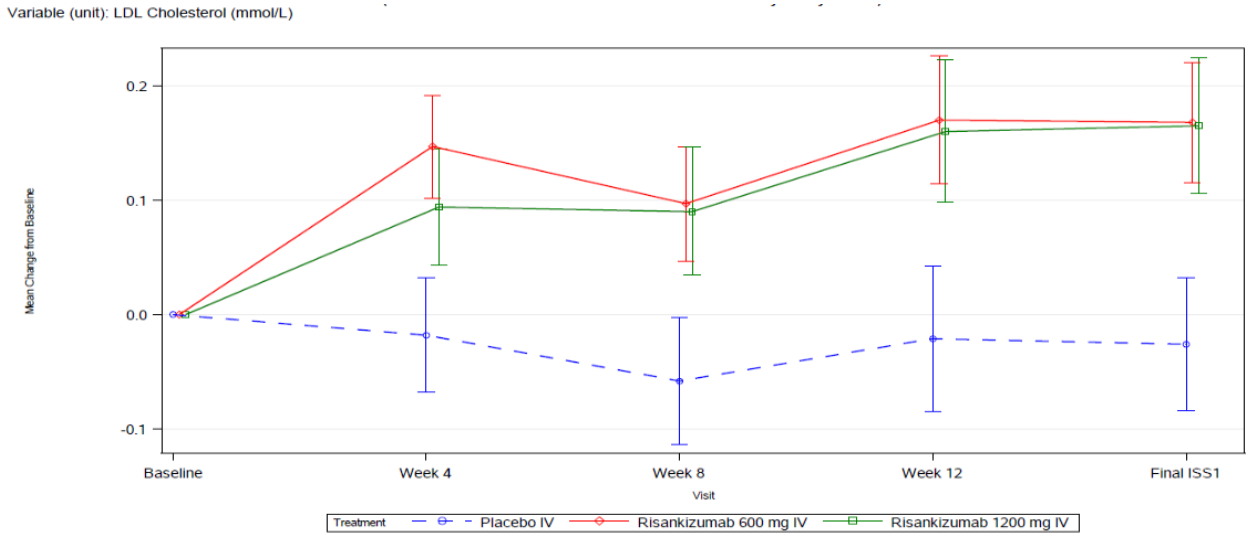



*Figure 34 Plot of Mean Change From Baseline in Laboratory Parameters (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

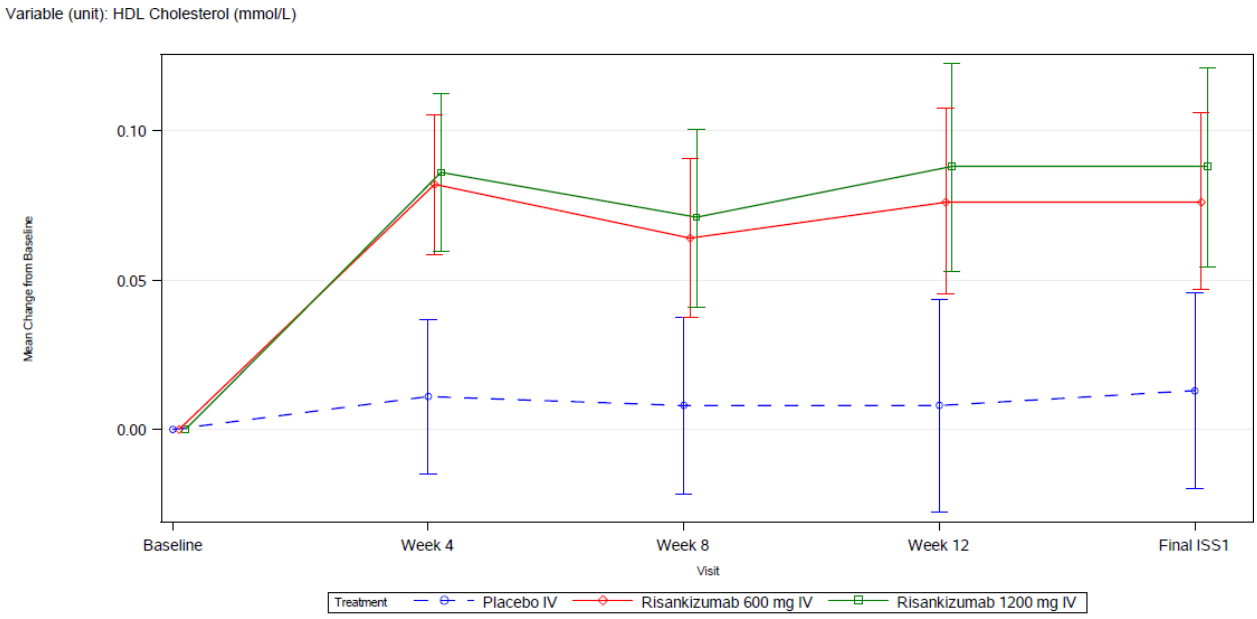



*Figure 35 Plot of Mean Change From Baseline in Laboratory Parameters (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

Maintenance up to 52 Weeks

Mean changes from Week 0 of Sub-Study 1 in hematology parameters and clinical chemistry parameters (excluding LFTs) in the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set) were generally small and not considered to be clinically meaningful. There were no clinically relevant or dose-dependent trends in hematology or clinical chemistry parameters in any treatment group over time, with the exception of changes observed in platelet counts.

Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Significant Values for Laboratory Values (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)

| Category<br>Variable (unit)<br>Criteria | Placebo IV (N = 432)<br>n/N_OBS<br>(%) [SSA %] | Risankizumab 600 mg IV (N = 620)<br>n/N_OBS<br>(%) [SSA %] | Risankizumab 1200 mg IV (N = 577)<br>n/N_OBS<br>(%) [SSA %] | Risankizumab Total (N = 1197)<br>n/N_OBS<br>(%) [SSA %] | Treatment Comparison (95% CI) [A]<br>600 mg IV - Placebo | Treatment Comparison (95% CI) [A]<br>1200 mg IV - Placebo |
|---|---|---|---|---|---|---|
| HEMATOLOGY | | | | | | |
| Hemoglobin (g/L) | | | | | | |
| Grade 3 (< 80.0 g/L) | 12/422 (2.8) [2.8] | 10/618 (1.6) [1.7] | 16/573 (2.8) [2.9] | 26/1191 (2.2) [2.2] | -1.1 [-3.0, 0.8] | -0.0 [-2.2, 2.1] |
| Platelets (10^9/L) | | | | | | |
| Grade 3 (25.0 -< 50.0 x 10^9/L) | 0/422 | 0/618 | 0/571 | 0/1189 | 0.0 | 0.0 |
| Grade 4 (< 25.0 x 10^9/L) | 2/422 (0.5) [0.4] | 1/618 (0.2) [0.2] | 1/571 (0.2) [0.2] | 2/1189 (0.2) [0.2] | -0.2 [-0.8, 0.4] | -0.2 [-0.9, 0.4] |
| >= Grade 3 | 2/422 (0.5) [0.4] | 1/618 (0.2) [0.2] | 1/571 (0.2) [0.2] | 2/1189 (0.2) [0.2] | -0.2 [-0.8, 0.4] | -0.2 [-0.9, 0.4] |

Clinical Chemistry Except LFTs

12-Week Induction

Shifts in clinical chemistry was evaluated for creatinine. Shifts in creatinine values from Grade 0, 1, or 2 at Baseline to Grade 3 or higher during treatment were generally infrequent and no clinically meaningful differences were observed across treatment groups in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set.

Maintenance up to 52 Weeks

Shifts in clinical chemistry (excluding LFT) values from Grade 0, 1, or 2 at Baseline of the induction study to Grade 3 or higher during treatment were generally infrequent and no clinically meaningful

differences were observed across treatment arms in the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set).

*Clinically Significant Abnormalities*

12-Week Induction

Rates of hematology values that met Grade 3 or Grade 4 criteria were low (< 3.5% for each parameter in each risankizumab group) and were generally similar across treatment groups in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set (Table 77). Four risankizumab-treated subjects had hematology values that met Grade 4 criteria. The subject with lymphocyte values that met Grade 4 criteria (on Days 58 and 85) also had lymphocytes values that met Grade 3 criteria at Screening, Baseline, and throughout the study. None of the abnormalities in hematology parameters that met Grade 4 criteria in risankizumab-treated subjects was reported as an AE or led to study drug discontinuation).

Four subjects (0.3%) in the Total RZB group had Grade 3 values in neutrophils compared with no subjects in the placebo IV group (Table 77). Of these 4 subjects, a non-serious AE of neutropenia of moderate severity was reported on Day 92 (in the follow-up period) for 1 subject in the risankizumab 600 mg IV group; the AE was assessed as having a reasonable possibility of being related to the study drug.

Maintenance up to 52 Weeks

Rates of hematology values that met Grade 3 or Grade 4 criteria were low (< 3.0% for each parameter in each risankizumab arm) and were similar across treatment arms in the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set (Table 78).

*Table 77 Summary of Potentially Clinically Significant Hematology Values (Grade ≥3) (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

| Category<br>Variable (unit)<br>Criteria | Placebo IV (N = 432)<br>n/N_OBS<br>(%) [SSA%] | Risankizumab<br>600 mg IV (N = 620)<br>n/N_OBS<br>(%) [SSA%] | Risankizumab<br>1200 mg IV (N = 577)<br>n/N_OBS<br>(%) [SSA%] | Risankizumab<br>Total (N = 1197)<br>n/N_OBS<br>(%) [SSA%] |
|---|---|---|---|---|
| **Hemoglobin (g/L)** | | | | |
| Grade 3 (< 80.0 g/L) | 12/422 (2.8) [2.8] | 10/618 (1.6) [1.7] | 16/573 (2.8) [2.9] | 26/1191 (2.2) [2.2] |
| **Platelets ($10^9$/L)** | | | | |
| Grade 3 (25.0 -< 50.0 × $10^9$/L) | 0/422 | 0/618 | 0/571 | 0/1189 |
| Grade 4 (< 25.0 × $10^9$/L) | 2/422 (0.5) [0.4] | 1/618 (0.2) [0.2][a] | 1/571 (0.2) [0.2][a] | 2/1189 (0.2) [0.2][a] |
| **Leukocytes ($10^9$/L)** | | | | |
| Grade 3 (1.0 -< 2.0 × $10^9$/L) | 1/423 (0.2) [0.1] | 3/618 (0.5) [0.5] | 0/571 | 3/1189 (0.3) [0.2] |
| Grade 4 (< 1.0 × $10^9$/L) | 1/423 (0.2) [0.2] | 0/618 | 0/571 | 0/1189 |
| **Neutrophils ($10^9$/L)** | | | | |
| Grade 3 (0.5 -< 1.0 × $10^9$/L) | 0/421 | 3/618 (0.5) [0.5] | 1/572 (0.2) [0.2] | 4/1190 (0.3) [0.3] |
| Grade 4 (< 0.5 × $10^9$/L) | 1/421 (0.2) [0.2] | 1/618 (0.2) [0.2] | 0/572 | 1/1190 (< 0.1) [< 0.1] |
| **Lymphocytes ($10^9$/L)** | | | | |
| Grade 3 (0.2 - < 0.5 × $10^9$/L) | 12/422 (2.8) [2.8] | 20/618 (3.2) [3.1] | 11/572 (1.9) [2.0] | 31/1190 (2.6) [2.5] |
| Grade 4 (< 0.2 × $10^9$/L) | 1/422 (0.2) [0.2] | 1/618 (0.2) [0.2] | 0/572 | 1/1190 (< 0.1) [< 0.1] |

a. Results on platelets are influenced by extreme values in risankizumab 600 mg IV group (2 records from 1 subject at Weeks 8 and 12) and risankizumab 1200 mg IV group (3 records from 1 subject at Weeks 4, 8, and 12) which have been confirmed to be data entry errors (Study M16-006 CSR

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

Maintenance up to 52 Weeks

Rates of hematology values that met Grade 3 or Grade 4 criteria were low (< 3.0% for each parameter in each risankizumab arm) and were similar across treatment arms in the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set (Table 78).

Among subjects in the risankizumab 180 mg and 360 mg SC arms, no Grade 3 hematology values in platelets, or Grade 4 values in hemoglobin, platelets, leukocytes, or lymphocytes were observed (Table 78. Of the abnormalities in hematology reported as AEs in subjects in the risankizumab 180 mg and 360 mg arms, the majority were assessed by the investigator as having no reasonable possibility of being related to study drug, and none of these AEs led to study drug discontinuation. One subject in the risankizumab 360 mg SC arm had a neutrophil value that met Grade 4 criteria at one time point; the abnormality (0.138 × 109) occurred on Day 343 and was not recorded as an AE. A repeat test taken 2 days later was normal.

*Table 78 Summary of Potentially Clinically Significant Hematology Values Compared to Week 0 of Sub-Study 1 (Grade ≥3) (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set)*

| | | Risankizumab | | |
|---|---|---|---|---|
| Variable (unit)<br>Criteria[a] | Withdrawal/ (PBO SC)<br>(N = 184)<br>n/N_OBS (%) | 180 mg SC<br>(N = 179)<br>n/N_OBS (%) | 360 mg SC<br>(N = 179)<br>n/N_OBS (%) | Total<br>(N = 358)<br>n/N_OBS (%) |
| **Hemoglobin (g/L)** | | | | |
| ≥ Grade 3 | 4/174 (2.3) | 5/171 (2.9) | 3/174 (1.7) | 8/345 (2.3) |
| **Platelets ($10^9$/L)** | | | | |
| ≥ Grade 3 | 0/174 | 0/170 | 0/173 | 0/343 |
| ≥ Grade 4 | 0/174 | 0/170 | 0/173 | 0/343 |
| **Leukocytes ($10^9$/L)** | | | | |
| ≥ Grade 3 | 1/174 (0.6) | 1/171 (0.6) | 0/173 | 1/344 (0.3) |
| ≥ Grade 4 | 0/174 | 0/171 | 0/173 | 0/344 |
| **Neutrophils ($10^9$/L)** | | | | |
| ≥ Grade 3 | 0/174 | 0/171 | 1/173 (0.6) | 1/344 (0.3) |
| ≥ Grade 4 | 0/174 | 0/171 | 1/173 (0.6) | 1/344 (0.3) |
| **Lymphocytes ($10^9$/L)** | | | | |
| ≥ Grade 3 | 3/174 (1.7) | 5/171 (2.9) | 0/173 | 5/344 (1.5) |
| ≥ Grade 4 | 0/174 | 0/171 | 0/173 | 0/344 |

a. Post-Week 0 grade must also have been more extreme (worse) than the Week 0 grade to be included in the numerator. If a subject does not have a Week 0 value then the subject would be counted in the numerator if the subject had at least one post-Week 0 measurement and met the specific criteria.

Notes: Toxicity grading scale is based on NCI Common Terminology Criteria version 4.03.
N_OBS indicates the number of subjects with both Week 0 and post-Week 0 values for the respective parameter.

All Treated Safety Analysis Set

In the ANY RZB SC group of the All Treated Analysis Set, the percentages of subjects who had Grade 3 or 4 hematology values were low (< 2.0% for each parameter). The majority of Grade 3 or 4 values were transient and did not lead to study drug discontinuation.

*Clinical Chemistry Except LFTs*

12-Week Induction

Rates of chemistry values that met Grade 3 or Grade 4 criteria were low (< 2.0% for each parameter for each risankizumab group) and were similar across treatment groups in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set (Table 79).

Two risankizumab-treated subjects in the risankizumab 600 mg IV group had chemistry values that met Grade 4 criteria. One subject had a Grade 4 value in potassium (hypo) that was reported as AEs of hypokalemia and hypophosphataemia, along with a concurrent AE of low magnesium; none of the AEs were considered to have a reasonable possibility of being related to study drug, and study drug was not discontinued.

One subject had a Grade 4 value in triglycerides that was not reported as an AE.

Fasting was not required prior to study visits. No Grade 4 values in glucose (hyper) were reported in any treatment group of the Placebo-Controlled 12-Week Induction Period Safety Analysis Set (Table 79). The percentage of subjects with PCS values in glucose (hyper) in the Total RZB group (0.6%) was similar to that of subjects in the placebo IV group (1.0%). Of the 8 subjects in the Total RZB group with Grade 3 elevations in glucose, 6 subjects had relevant medical history (5 subjects with diabetes mellitus and 1 subject with type 1 diabetes), and 1 subject was diagnosed with diabetes mellitus during the study.

*Table 79 Summary of Potentially Clinically Significant Clinical Chemistry (Except LFTs) Values (Grade ≥3) (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

| | | Risankizumab | | |
|---|---|---|---|---|
| | Placebo IV (N = 432) | 600 mg IV (N = 620) | 1200 mg IV (N = 577) | Total (N = 1197) |
| Category<br>Variable (unit)<br>Criteria | n/N_OBS<br>(%) [SSA%] | n/N_OBS<br>(%) [SSA%] | n/N_OBS<br>(%) [SSA%] | n/N_OBS<br>(%) [SSA%] |
| **Creatinine (µmol/L)** | | | | |
| Grade 3 (3.0 × ULN - < 6.0 × ULN or > 3.0 × Baseline) | 1/424 (0.2) [0.2] | 0/619 | 2/573 (0.3) [0.4] | 2/1192 (0.2) [0.2] |
| Grade 4 (> 6.0 × ULN) | 0/424 | 0/619 | 0/573 | 0/1192 |
| **Calcium Corrected Hypo (mmol/L)** | | | | |
| Grade 3 (1.5 - < 1.75 mmol/L) | 0/422 | 0/618 | 0/571 | 0/1189 |
| Grade 4 (< 1.5 mmol/L) | 0/422 | 0/618 | 0/571 | 0/1189 |
| **Calcium Corrected Hyper (mmol/L)** | | | | |
| Grade 3 (3.1 - < 3.4 mmol/L) | 0/422 | 0/618 | 0/571 | 0/1189 |
| Grade 4 (> 3.4 mmol/L) | 0/422 | 0/618 | 0/571 | 0/1189 |
| **Sodium Hypo (mmol/L)** | | | | |
| Grade 3 (120 - < 130 mmol/L) | 3/424 (0.7) [0.7] | 0/619 | 0/572 | 0/1191 |
| Grade 4 (< 120 mmol/L) | 0/424 | 0/619 | 0/572 | 0/1191 |
| **Sodium Hyper (mmol/L)** | | | | |
| Grade 3 (155 - < 160 mmol/L) | 0/424 | 0/619 | 0/572 | 0/1191 |
| Grade 4 (> 160 mmol/L) | 0/424 | 0/619 | 0/572 | 0/1191 |
| **Potassium Hypo (mmol/L)** | | | | |
| Grade 3 (2.5 - < 3.0 mmol/L) | 2/424 (0.5) [0.4] | 1/616 (0.2) [0.2] | 3/573 (0.5) [0.5] | 4/1189 (0.3) [0.3] |
| Grade 4 (< 2.5 mmol/L) | 1/424 (0.2) [0.2] | 1/616 (0.2) [0.1] | 0/573 | 1/1189 (< 0.1) [0.1] |
| **Potassium Hyper (mmol/L)** | | | | |
| Grade 3 (6.0 - < 7.0 mmol/L) | 2/424 (0.5) [0.4] | 0/616 | 1/573 (0.2) [0.2] | 1/1189 (< 0.1) [< 0.1] |
| Grade 4 (> 7.0 mmol/L) | 0/424 | 0/616 | 0/573 | 0/1189 |

| | | Risankizumab | | |
|---|---|---|---|---|
| | Placebo IV (N = 432) | 600 mg IV (N = 620) | 1200 mg IV (N = 577) | Total (N = 1197) |
| Category<br>Variable (unit)<br>Criteria | n/N_OBS<br>(%) [SSA%] | n/N_OBS<br>(%) [SSA%] | n/N_OBS<br>(%) [SSA%] | n/N_OBS<br>(%) [SSA%] |
| **Glucose Hypo (mmol/L)** | | | | |
| Grade 3 (1.7 - < 2.2 mmol/L) | 0/424 | 0/619 | 0/572 | 0/1191 |
| Grade 4 (< 1.7 mmol/L) | 0/424 | 0/619 | 0/572 | 0/1191 |
| **Glucose Hyper (mmol/L)** | | | | |
| Grade 3 (13.9 - < 27.8 mmol/L) | 5/424 (1.2) [1.0] | 2/619 (0.3) [0.3] | 6/572 (1.0) [1.0] | 8/1191 (0.7) [0.6] |
| Grade 4 (> 27.8 mmol/L) | 0/424 | 0/619 | 0/572 | 0/1191 |
| **Albumin (g/L)** | | | | |
| Grade 3 (< 20 g/L) | 1/424 (0.2) [0.2] | 1/619 (0.2) [0.2] | 0/572 | 1/1191 (< 0.1) [< 0.1] |
| **Cholesterol (mmol/L)** | | | | |
| Grade 3 (10.34 - 12.92 mmol/L) | 0/422 | 0/619 | 0/572 | 0/1191 |
| Grade 4 (> 12.92 mmol/L) | 0/422 | 0/619 | 0/572 | 0/1191 |
| **Triglycerides (mmol/L)** | | | | |
| Grade 3 (5.7 - 11.4 mmol/L) | 2/422 (0.5) [0.6] | 8/619 (1.3) [1.3] | 8/572 (1.4) [1.5] | 16/1191 (1.3) [1.4] |
| Grade 4 (> 11.4 mmol/L) | 0/422 | 1/619 (0.2) [0.2] | 0/572 | 1/1191 (< 0.1) [< 0.1] |

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

The denominator N_OBS is defined as the number of subjects with at least one post-baseline value in Period 1 for the respective parameter.

Maintenance up to 52 Weeks

Rates of chemistry values that met Grade 3 or Grade 4 criteria were low (< 1.5% for each parameter in each risankizumab arm) and were similar across treatment arms in the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set (Table 80).

A single subject in the risankizumab 360 mg arm had chemistry values that met Grade 4 criteria (Table 80). The subject had increased triglycerides on Day 262 (Day 170 of Study M16-000 Sub-Study 1; 12.52 mmol/L, Grade 4), Day 190 of Sub-Study 1 (8.45 mmol/L, Grade 3), and Day 282 of Sub-Study 1 (16.25 mmol/L, Grade 4). A non-serious AE of blood triglycerides increased was reported on Day 172 of Sub-Study 1 and assessed by the investigator of having no reasonable possibility of being related to study drug; the study dose was not changed.

One additional subject in the risankizumab 180 mg SC arm had values that met Grade 3 criteria and was recorded as an AE. This subject had increased triglycerides at 2 different time points. The elevated triglyceride value at the first time point was recorded as a non-serious AE and assessed by the investigator having no reasonable possibility of being related to study drug; the study dose was not changed.

No Grade 4 values in glucose (hyper) were reported in any treatment arm (Table 80). Two subjects in the risankizumab 360 mg SC arm, each with a medical history of diabetes mellitus, had Grade 3 glucose values. The percentage of subjects with Grade 3 glucose values in the RZB group was the same as that of the withdrawal (placebo SC) arm (0.6%).

*Table 80 Summary of Potentially Clinically Significant Clinical Chemistry Values (Except LFTs) Compared to Week 0 of Sub-Study 1 (Grade ≥3) (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set)*

| Variable (unit) Criteria[a] | Withdrawal (PBO SC) (N = 184) n/N_OBS (%) | Risankizumab 180 mg SC (N = 179) n/N_OBS (%) | Risankizumab 360 mg SC (N = 179) n/N_OBS (%) | Risankizumab Total (N = 358) n/N_OBS (%) |
|---|---|---|---|---|
| **Creatinine (µmol/L)** | | | | |
| ≥ Grade 3 | 0/176 | 1/172 (0.6) | 0/173 | 1/345 (0.3) |
| ≥ Grade 4 | 0/176 | 0/172 | 0/173 | 0/345 |
| **Calcium Corrected for Albumin (mmol/L) - Hypo** | | | | |
| ≥ Grade 3 | 0/9 | 0/8 | 0/8 | 0/16 |
| ≥ Grade 4 | 0/9 | 0/8 | 0/8 | 0/16 |
| **Calcium Corrected for Albumin (mmol/L) - Hyper** | | | | |
| ≥ Grade 3 | 0/9 | 0/8 | 0/8 | 0/16 |
| ≥ Grade 4 | 0/9 | 0/8 | 0/8 | 0/16 |
| **Sodium (mmol/L) - Hypo** | | | | |
| ≥ Grade 3 | 2/176 (1.1) | 1/172 (0.6) | 0/173 | 1/345 (0.3) |
| ≥ Grade 4 | 0/176 | 0/172 | 0/173 | 0/345 |
| **Sodium (mmol/L) - Hyper** | | | | |
| ≥ Grade 3 | 0/176 | 0/172 | 0/173 | 0/345 |
| ≥ Grade 4 | 0/176 | 0/172 | 0/173 | 0/345 |
| **Potassium (mmol/L) - Hypo** | | | | |
| ≥ Grade 3 | 0/175 | 0/172 | 0/173 | 0/345 |
| ≥ Grade 4 | 0/175 | 0/172 | 0/173 | 0/345 |
| **Potassium (mmol/L) - Hyper** | | | | |
| ≥ Grade 3 | 0/175 | 0/172 | 0/173 | 0/345 |
| ≥ Grade 4 | 0/175 | 0/172 | 0/173 | 0/345 |
| **Glucose (mmol/L) - Hypo** | | | | |
| ≥ Grade 3 | 0/176 | 0/172 | 0/173 | 0/345 |
| ≥ Grade 4 | 0/176 | 0/172 | 0/173 | 0/345 |
| **Glucose (mmol/L) - Hyper** | | | | |
| ≥ Grade 3 | 1/176 (0.6) | 0/172 | 2/173 (1.2) | 2/345 (0.6) |
| ≥ Grade 4 | 0/176 | 0/172 | 0/173 | 0/345 |
| **Albumin (g/L)** | | | | |
| ≥ Grade 3 | 0/176 | 0/172 | 0/173 | 0/345 |
| **Cholesterol (mmol/L)** | | | | |
| ≥ Grade 3 | 0/160 | 0/160 | 0/157 | 0/317 |
| ≥ Grade 4 | 0/160 | 0/160 | 0/157 | 0/317 |
| **Triglycerides (mmol/L)** | | | | |
| ≥ Grade 3 | 1/160 (0.6) | 2/160 (1.3) | 2/157 (1.3) | 4/317 (1.3) |
| ≥ Grade 4 | 0/160 | 0/160 | 1/157 (0.6) | 1/317 (0.3) |

a. Post-Week 0 grade must also have been more extreme (worse) than the Week 0 grade to be included in the numerator. If a subject does not have a Week 0 value then the subject would be counted in the numerator if the subject had at least one post-Week 0 measurement and met the specific criteria.

All Treated Safety Analysis Set

In the All Treated Analysis Set, the percentages of subjects in the ANY RZB SC group who had Grade 3 or 4 chemistry values were low (< 1.5% for each parameter). The majority of Grade 3 or 4 values were transient and no subject discontinued study drug due to Grade 3 or 4 values in clinical chemistry.

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

During the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), mean changes in vital sign parameters during risankizumab administration were not considered to be clinically meaningful and were comparable to changes observed in the placebo group. The proportion of subjects treated with risankizumab who experienced PCS vital sign abnormalities was low (≤ 2.4% in any treatment group for each parameter).

In the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set, there were no clinically meaningful mean changes from Week 0 in vital sign parameters with risankizumab administration. The proportion of subjects treated with risankizumab who experienced PCS vital sign abnormalities was low (< 6.0% in any treatment arm for each parameter).

Similar results were observed in the ANY RZB SC group of the All Treated Safety Analysis Set, in which < 6.0% of subjects had PCS vital sign abnormalities for each parameter.

*Safety from To-Be-Marketed Presentation On Body Delivery System*

Study M19-128

The combination products used in the Phase 3 CD program are different vs. the planned to-be-marketed combination products. Study M19-128 was conducted to bridge the Phase 3 and to-be-marketed combination products for both induction and maintenance dosing. The main objective of Study M19-128 was to assess the bioequivalence of the Phase 3 CD drug presentations to the to-be-marketed drug presentations in healthy volunteers. Additional objectives were to characterize the safety and tolerability of the to-be-marketed drug presentations with those used in the Phase 3 CD program. The study consisted of 2 sub-studies: Sub-Study 1 assessed the bioavailability (BA) of risankizumab 360 mg delivered by 4 SC injections of 90 mg in a PFS (1 mL, 90 mg/mL) (Phase 3 CD drug presentation) with a single SC injection of 360 mg via an OBDS (2.4 mL, 150 mg/mL) (to-be-marketed drug presentation). Sub-Study 2 assessed the bioequivalence of 1800 mg risankizumab administered by IV infusion using 6 × 300 mg vial (3.33 mL, 90 mg/mL) (Phase 3 CD drug presentation) vs. 3 × 600 mg vial (10 mL, 60 mg/mL) (to-be-marketed drug presentation).

Safety of Sub-Study 1

In Sub-Study 1 evaluating PFS vs OBDS, higher rates of ISRs were reported in the to-be-marketed (risankizumab 360 mg OBDS) drug presentation (45/129 [34.9%] subjects) as compared to the Phase 3 PFS drug presentation (11/127 [8.7%] subjects). All ISRs were mild in severity and a majority (87/100 [87%] events) resolved on the day of onset. The majority of ISRs in the risankizumab 360 mg OBDS arm were related to injection site erythema and/or injection site induration. The rates of ISRs observed in this study are likely due to the nature of Phase 1 study designs involving confinement and closer observation of healthy volunteers.

*Table 81 Overview of Subjects with TEAEs (Substudy 1)*

| | Risankizumab | | | | | |
|---|---|---|---|---|---|---|
| | Substudy 1 | | | | | Total |
| | Group 1 360 mg SC (90 mg PFS × 4) N = 127 | Group 2 360 mg OBDS SC N = 129 | Group 3 180 mg OBDS SC N = 30 | Group 1 360 mg SC (90 mg PFS × 4) (Japanese) N = 8 | Group 2 360 mg OBDS SC (Japanese) N = 8 | N = 286 |
| | n (%) | | | | | n (%) |
| Adverse Events | 39 (30.7%) | 64 (49.6%) | 10 (33.3%) | 5 (62.5%) | 8 (100%) | 113 (39.5%)<br>13 (81.3%) |
| AE with possibility of being related to study drug | 18 (14.2%) | 41 (31.8%) | 6 (20%) | 4 (50%) | 7 (87.5%) | 65 (22.7%)<br>11 (68.8%) |
| AE with possibility of being related to device causality | 1 (0.8%) | 35 (27.1%) | 7 (23.3%) | 0 | 1 (12.5%) | 43 (15.0%)<br>1 (6.3%) |
| Severe AE | 1 (0.8%) | 1 (0.8%) | 0 | 0 | 0 | 2 (0.7%)<br>0 |
| Serious AE | 1 (0.8%) | 0 | 0 | 0 | 0 | 1 (0.3%)<br>0 |
| AE leading to discontinuation of study drug | 0 | 0 | 0 | 0 | 0 | 0 |
| AE results in death | 0 | 0 | 0 | 0 | 0 | 0 |
| Injection site reaction related AE | 11 (8.7%) | 45 (34.9%) | 8 (26.7%) | 4 (50%) | 8 (100%) | 64 (22.4%)<br>12 (75%) |
| Hypersensitivity related AE | 2 (1.6%) | 2 (1.6%) | 0 | | | 4 (1.4%) |
| All Deaths | 0 | 0 | 0 | 0 | 0 | 0 |

Group 1: Risankizumab 90 mg PFS × 4 SC Injections (4 mL of 90 mg/mL formulation)
Group 2: Risankizumab 360 mg OBDS × 1 SC Injection (2.4 mL of 150 mg/mL formulation)
Group 3: Risankizumab 180 mg OBDS × 1 SC Injection (1.2 mL of 150 mg/mL formulation)
Group 1 (Japanese): Risankizumab 90 mg PFS × 4 SC Injections (4 mL of 90 mg/mL formulation)
Group 2 (Japanese): Risankizumab 360 mg OBDS × 1 SC Injection (2.4 mL of 150 mg/mL formulation)

The main SOC contributing the TEAEs across all groups were general disorders and administration site conditions (69/286, 24.1%) and a majority of TEAEs were ISRs. ISRs were reported at a higher rate in Group 2 (360 mg OBDS) and Group 3 (180 mg OBDS) versus Group 1 (90 mg PFS) with the most common PTs reported of "injection site induration" and "injection site erythema" (Table 82).

*Table 82 Number and Percentage of Subjects Reporting Treatment Emergent Adverse Events Identified by Injection Site Reaction CMQ*

| | Group 1, 360 mg SC (90 mg PFS × 4) N = 127 n (%) | Group 2, 360 mg OBDS SC N =129 n (%) | Group 3, 180 mg OBDS SC N = 30 n (%) | Group 1 (Japanese), 360 mg SC (90 mg PFS × 4) N = 8 n (%) | Group 2 (Japanese), 360 mg OBDS SC N = 8 n (%) |
|---|---|---|---|---|---|
| **Injection site reaction** | 11 (8.7%) | 45 (34.9%) | 8 (26.7%) | 4 (50.0%) | 8 (100%) |
| Injection site induration | 0 | 24 (18.6%) | 5 (16.7%) | -- | -- |
| Injection site erythema | 1 (0.8%) | 17 (13.2%) | 1 (3.3%) | 0 | 3 (37.5%) |
| Injection site swelling | 0 | 10 (7.8%) | 2 (6.7%) | 0 | 2 (25.0%) |
| Injection site pain | 7 (5.5%) | 9 (7.0%) | 1 (3.3%) | 4 (50.0%) | 7 (87.5%) |
| Injection site pruritus | 5 (3.9%) | 8 (6.2%) | 0 | 2 (25%) | 2 (25%) |
| Injection site oedema | 0 | 3 (2.3%) | 1 (3.3%) | -- | -- |
| Injection site irritation | 0 | 2 (1.6%) | 0 | -- | -- |
| Administration site extravasation | 0 | 1 (0.8%) | 0 | -- | -- |
| Injection site discomfort | 0 | 1 (0.8%) | 0 | -- | -- |
| Injection site hemorrhage | 0 | 1 (0.8%) | 0 | -- | -- |
| Injection site bruising | 1 (0.8%) | 0 | 0 | -- | -- |

Group 1: Risankizumab 90 mg PFS × 4 SC Injections (4 mL of 90 mg/mL formulation)
Group 2: Risankizumab 360 mg OBDS × 1 SC Injection (2.4 mL of 150 mg/mL formulation)
Group 3: Risankizumab 180 mg OBDS × 1 SC Injection (1.2 mL of 150 mg/mL formulation)
Group 1 (Japanese): Risankizumab 90 mg PFS × 4 SC Injections (4 mL of 90 mg/mL formulation)
Group 2 (Japanese): Risankizumab 360 mg OBDS × 1 SC Injection (2.4 mL of 150 mg/mL formulation)

*Table 83 Subjects with Device Related Adverse Events as Assessed by the Investigator Listed by PT (Listed in Order of Decreasing Frequency per OBDS)*

| | Group 1 360 mg SC (90 mg PFS × 4) N = 127 n (%) | Group 2 360 mg OBDS SC N = 129 n (%) | Group 3 180 mg OBDS SC N = 30 n (%) | Group 1 Japanese 360 mg SC (90 mg PFS × 4) N = 8 n (%) | Group 2 Japanese 360 mg OBDS SC N = 8 n (%) |
|---|---|---|---|---|---|
| Any adverse event related to device | 1 (0.8) | 35 (27.1) | 7 (23.3) | 0 | 1 (12.5) |
| General disorders and administration site conditions | 1 (0.8) | 35 (27.1) | 7 (23.3) | 0 | 1 (12.5) |
| Injection site induration | 0 | 23 (17.8) | 5 (16.7) | 0 | 0 |
| Injection site erythema | 1 (0.8) | 14 (10.9) | 1 (3.3) | 0 | 1 (12.5) |
| Injection site swelling | 0 | 8 (6.2) | 2 (6.7) | 0 | 0 |
| Injection site oedema | 0 | 3 (2.3) | 1 (3.3) | 0 | 0 |
| Injection site irritation | 0 | 2 (1.6) | 0 | 0 | 0 |
| Administration site extravasation | 0 | 1 (0.8) | 0 | 0 | 0 |
| Injection site discomfort | 0 | 1 (0.8) | 0 | 0 | 0 |
| Injection site hemorrhage | 0 | 1 (0.8) | 0 | 0 | 0 |
| Injection site pruritus | 0 | 1 (0.8) | 0 | 0 | 0 |

Notes: Device related AEs were captured using General Disorders and Administration Site Conditions SOC.
Subjects are counted once in each row, regardless of the number of events they may have had. Table depicts the most grade adverse event for each preferred term as assessed for each subject.

Safety Sub-Study 2

For the IV presentations, the safety and tolerability was similar between the Phase 3 CD (risankizumab 300 mg, 90 mg/mL vial) and to-be-marketed (risankizumab 600 mg, 60 mg/mL vial) drug presentations.

*Table 84 Overview of Subjects with TEAEs (Substudy 2)*

| | Risankizumab | | |
|---|---|---|---|
| | Substudy 2 | | Total |
| | Group 4 1800 mg IV (300 mg liquid vial) N = 53 | Group 5 1800 mg IV (600 mg liquid vial) N = 54 | N = 107 |
| Adverse Events | 17 (32%) | 14 (26%) | 31 (29%) |
| AE with possibility of being related to study drug | 3 (6%) | 1 (2%) | 4 (4%) |
| Severe AE | 0 | 0 | 0 |
| Serious AE | 0 | 0 | 0 |
| AE leading to discontinuation of study drug | 0 | 0 | 0 |
| AE results in death | 0 | 0 | 0 |
| Injection site reaction related AE | 0 | 0 | 0 |
| Hypersensitivity related AE | 2 (4%) | 0 | 2 (2%) |
| All deaths | 0 | 0 | 0 |

Group 4: Risankizumab 1800 mg IV infusion – 6 × 300 mg liquid vials (90 mg/mL)
Group 5: Risankizumab 1800 mg IV infusion – 3 × 600 mg liquid vials (60 mg/mL)

Comparison of Hypersensitivity Reactions and Injection-Site Reactions by Treatment-emergent ADA Status Across Treatment Groups in Substudy 1 and Substudy 2 are summarized in Table 85.

*Table 85 Comparison of Hypersensitivity Reactions and Injection-Site Reactions by Treatment-emergent ADA Status Across Treatment Groups in Substudy 1 and Substudy 2*

| | Substudy 1 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1: 360 mg SC Injection (90 mg PFS × 4) | | Group 2: 360 mg OBDS SC Injection (2.4 mL of 150 mg/mL) | | Group 3: 180 mg OBDS SC Injection (1.2 mL of 150 mg/mL) | | Total | |
| | ADA + (N = 7) | ADA - (N = 110) | ADA+ (N = 16) | ADA- (N = 107) | ADA+ (N =1) | ADA- (N =26) | ADA+ (N =24) | ADA- (N =243) |
| hypersensitivity reactions (per SMQ), n (%) | 0 (0%) | 2 (1.8%) | 0 (0%) | 2 (1.9%) | 0 (0%) | 0 (0%) | 0 (0%) | 4 (1.6%) |
| Injection-site reactions (per CMQ), n (%) | 2 (28.6%) | 9 (8.2%) | 6 (37.5%) | 37 (34.6%) | 0 (0%) | 8 (30.8%) | 8 (33.3%) | 54 (22.2%) |
| | Substudy 2 | | | | | |
| | Group 4: 1800 mg IV (6 × 300 mg liquid vials) | | Group 5: 1800 mg IV (3 × 600 mg liquid vials) | | Total | |
| | ADA + (N = 2) | ADA - (N = 46) | ADA + (N = 1) | ADA - (N = 49) | ADA + (N = 3) | ADA - (N = 95) |
| hypersensitivity reactions (per SMQ), n (%) | 0 (0%) | 2 (4.3%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (2.1%) |
| Injection-site reactions (per CMQ), n (%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

Note:

Study F20-282

Study F20-282 in healthy volunteers, which examined the effectiveness and tolerability of the adhesive for the OBDS device (the to-be-marketed combination product for maintenance therapy) demonstrated that the OBDS device was safe and well tolerated in both administration locations (abdomen and upper thigh). Overall, 2 subjects (2/36, 5.6%) who had the OBDS device applied to the abdomen reported

AEs. One subject experienced muscle spasms that were mild and assessed by the investigator as having no reasonable possibility of being related to the OBDS device. The other subject reported paraesthesia and warmth at the site of adhesive that were both mild and assessed by the investigator as having reasonable possibility of being related to the OBDS device. The reported AEs did not impact OBDS device adhesion to the skin. The skin assessment scale reported four subjects (4/36, 11%) who experienced erythema with a numeric score of 1, defined as minimal erythema, barely perceptible post device removal as measured by the FDA transdermal scale (Food and Drug Administration 2018). All product complaints associated with the OBDS device and procedure during the clinical study were reviewed and no new safety risks were identified.

*Studies Results from Supportive Analysis Sets and Phase 1*

Safety Results in Subjects with Delayed Clinical Response to Risankizumab IV

Induction (24-Week Induction Period Safety Analysis Set)

The main objective of this analysis set is to provide an evaluation of the safety of subjects who did not achieve clinical response to IV risankizumab treatment at completion of the 12-Week Induction Period and who were re-randomized in Induction Period 2 to receive risankizumab 1200 mg IV, 180 mg SC, or 360 mg SC. This safety analysis set thus also includes subjects who received placebo IV during the 12-Week Induction Period andrisankizumab 1200 mg IV during Induction Period 2 (Placebo IV/RZB IV) and subjects who received 24 weeks of risankizumab IV induction across both the 12-Week Induction Period and Induction Period 2.

The percentages and rates of subjects with AEs, SAEs, severe AEs, and AEs leading to study drug discontinuation during Induction Period 2 (Table 86) were generally lower than those in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set (Table 56). One death occurred in Induction Period 2 in a subject in the risankizumab 1200 mg IV group; the primary cause of death was sepsis due to fistulizing CD with exacerbation. There was no apparent relationship between risankizumab SC dose and AE rates, and no specific patterns with regards to AEs were observed among risankizumab treatment groups.

The percentages and rates AEs in the ASI categories during Induction Period 2 (Table 87) were generally comparable to those in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set (Table 64). There was no apparent relationship between risankizumab SC dose and ASI rates, and no specific patterns with regards to ASIs were observed among risankizumab treatment groups. Four subjects in the risankizumab 1200 mg IV group had 6 hepatic events; all events were non-serious, mild or moderate in severity, and did not lead to study drug discontinuation.

Continued treatment with risankizumab 180 mg SC, 360 mg SC, or 1200 mg IV for an additional 12 weeks was generally safe and well tolerated. No new safety risks were identified with an additional 12 weeks of induction treatment, and the overall safety profile was consistent with the safety profile of the 12-Week Induction Period.

*Table 86 Overview of Treatment-Emergent Adverse Events in Percentage and EAER per 100 PY (Induction Period 2, 24-Week Induction Period Safety Analysis Set)*

| | Induction Period 2 (Weeks 12 Through 24) | | | | | | | | Total (N = 489) (PY = 154.3) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | RZB 180 mg SC (N = 108) (PY = 33.5) | | RZB 360 mg SC (N = 110) (PY = 34.9) | | RZB 1200 mg IV (N = 109) (PY = 36.2) | | Placebo IV/ RZB 1200 mg IV (N = 162) (PY = 49.6) | | | |
| | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] |
| **Subjects with:** | | | | | | | | | | |
| All TEAEs | 50 (46.3) [46.3] | 113 (337.3) [340.3] | 54 (49.1) [49.0] | 114 (326.6) [325.3] | 59 (54.1) [54.4] | 138 (381.2) [379.8] | 83 (51.2) [51.5] | 188 (379.0) [396.1] | 246 (50.3) [50.3] | 553 (358.4) [358.4] |
| Any COVID-19 related TEAEs | 1 (0.9) [0.8] | 1 (3.0) [2.7] | 0 | 0 | 1 (0.9) [0.8] | 2 (5.5) [5.3] | 2 (1.2) [1.0] | 2 (4.0) [3.2] | 4 (0.8) [0.8] | 5 (3.2) [3.2] |
| TEAEs related to study drug per investigator | 16 (14.8) [15.0] | 25 (74.6) [75.6] | 26 (23.6) [23.8] | 41 (117.5) [119.0] | 13 (11.9) [11.7] | 22 (60.8) [59.5] | 34 (21.0) [21.2] | 59 (119.0) [122.3] | 89 (18.2) [18.2] | 147 (95.3) [95.3] |
| Severe TEAEs | 4 (3.7) [3.8] | 8 (23.9) [24.5] | 4 (3.6) [3.3] | 5 (14.3) [12.7] | 5 (4.6) [4.6] | 10 (27.6) [27.3] | 11 (6.8) [6.8] | 17 (34.3) [32.0] | 24 (4.9) [4.9] | 40 (25.9) [25.9] |
| Serious TEAEs | 5 (4.6) [4.7] | 7 (20.9) [21.8] | 5 (4.5) [4.6] | 6 (17.2) [17.0] | 7 (6.4) [6.5] | 12 (33.1) [32.8] | 13 (8.0) [7.5] | 18 (36.3) [32.7] | 30 (6.1) [6.1] | 43 (27.9) [27.9] |
| TEAEs leading to discontinuation of study drug | 1 (0.9) [1.1] | 1 (3.0) [3.4] | 2 (1.8) [1.9] | 2 (5.7) [6.0] | 1 (0.9) [1.0] | 1 (2.8) [2.9] | 1 (0.6) [0.5] | 1 (2.0) [1.6] | 5 (1.0) [1.0] | 5 (3.2) [3.2] |

| | Induction Period 2 (Weeks 12 Through 24) | | | | | | | | Total (N = 489) (PY = 154.3) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | RZB 180 mg SC (N = 108) (PY = 33.5) | | RZB 360 mg SC (N = 110) (PY = 34.9) | | RZB 1200 mg IV (N = 109) (PY = 36.2) | | Placebo IV/ RZB 1200 mg IV (N = 162) (PY = 49.6) | | | |
| | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] |
| **Subjects with:** | | | | | | | | | | |
| TEAEs leading to death | 0 | 0 | 0 | 0 | 1 (0.9) [1.0] | 1 (2.8) [2.9] | 0 | 0 | 1 (0.2) [0.2] | 1 (0.6) [0.6] |
| All deaths | 0 | 0 | 0 | 0 | 1 (0.9) [1.0] | 1 (2.8) [2.9] | 0 | 0 | 1 (0.2) [0.2] | 1 (0.6) [0.6] |
| Deaths occurring ≤ 140 days after last dose of study drug | 0 | 0 | 0 | 0 | 1 (0.9) [1.0] | 1 (2.8) [2.9] | 0 | 0 | 1 (0.2) [0.2] | 1 (0.6) [0.6] |
| Deaths occurring > 140 days after last dose of study drug | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| COVID-19 related deaths | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

E/100 PY = Events per 100 patient-years.

*Table 87 Overview of Treatment-Emergent Adverse Events in Areas of Safety Interest in Percentage and EAER per 100 PY (24-Week Induction Period Safety Analysis Set)*

| | Induction Period 2 (Weeks 12 Through 24) | | | | | | | | Total (N = 489) (PY = 154.3) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | RZB 180 mg SC (N = 108) (PY = 33.5) | | RZB 360 mg SC (N = 110) (PY = 34.9) | | RZB 1200 mg IV (N = 109) (PY = 36.2) | | Placebo IV/ RZB 1200 mg IV (N = 162) (PY = 49.6) | | | |
| Subjects with | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] |
| Adjudicated MACE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Adjudicated extended MACE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Serious infections | 0 | 0 | 1 (0.9) [0.8] | 1 (2.9) [2.5] | 1 (0.9) [1.0] | 1 (2.8) [2.9] | 4 (2.5) [2.3] | 6 (12.1) [10.6] | 6 (1.2) [1.2] | 8 (5.2) [5.2] |
| Active tuberculosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Opportunistic infections excluding tuberculosis and herpes zoster | 0 | 0 | 0 | 0 | 0 | 0 | 2 (1.2) [1.0] | 2 (4.0) [3.2] | 2 (0.4) [0.4] | 2 (1.3) [1.3] |
| Herpes zoster | 0 | 0 | 1 (0.9) [0.8] | 1 (2.9) [2.5] | 0 | 0 | 1 (0.6) [0.5] | 1 (2.0) [1.6] | 2 (0.4) [0.4] | 2 (1.3) [1.3] |
| Malignant tumours | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.6) [0.7] | 1 (2.0) [2.5] | 1 (0.2) [0.2] | 1 (0.6) [0.6] |
| Non-Melanoma Skin Cancer (NMSC) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.6) [0.7] | 1 (2.0) [2.5] | 1 (0.2) [0.2] | 1 (0.6) [0.6] |

| | Induction Period 2 (Weeks 12 Through 24) | | | | | | | | Total (N = 489) (PY = 154.3) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | RZB 180 mg SC (N = 108) (PY = 33.5) | | RZB 360 mg SC (N = 110) (PY = 34.9) | | RZB 1200 mg IV (N = 109) (PY = 36.2) | | Placebo IV/ RZB 1200 mg IV (N = 162) (PY = 49.6) | | | |
| Subjects with | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] | n (%) [SSA%] | Events (E/100 PY) [SSA E/100 PY] |
| Malignant tumours excluding NMSC | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypersensitivity | 4 (3.7) [3.6] | 4 (11.9) [11.5] | 6 (5.5) [5.8] | 7 (20.1) [22.2] | 9 (8.3) [8.0] | 11 (30.4) [29.9] | 7 (4.3) [5.0] | 8 (16.1) [19.2] | 26 (5.3) [5.3] | 30 (19.4) [19.4] |
| Serious hypersensitivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Adjudicated anaphylactic reactions | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hepatic events | 1 (0.9) [1.1] | 1 (3.0) [3.4] | 1 (0.9) [1.0] | 1 (2.9) [3.4] | 4 (3.7) [3.4] | 6 (16.6) [15.8] | 1 (0.6) [0.7] | 1 (2.0) [2.5] | 7 (1.4) [1.4] | 9 (5.8) [5.8] |
| Injection site reactions | 2 (1.9) [2.1] | 2 (6.0) [6.9] | 3 (2.7) [2.9] | 3 (8.6) [9.4] | 3 (2.8) [2.5] | 3 (8.3) [7.9] | 5 (3.1) [3.5] | 7 (14.1) [15.8] | 13 (2.7) [2.7] | 15 (9.7) [9.7] |

Safety Results in Maintenance Treatment Safety 1 Analysis Set

This analysis set provides an analysis of the safety of risankizumab and placebo SC maintenance treatment among subjects who achieved clinical response to risankizumab IV or placebo IV at completion of the 12-Week Induction Period and received at least 1 dose of risankizumab or placebo in Study M16-000 Sub-Study 1. This set combines the safety from subjects who responded to IV risankizumab and were re-randomized to receive risankizumab 180 mg or 360 mg SC or placebo (i.e., the withdrawal [placebo SC] arm) with the safety of subjects who responded to IV placebo and continued to receive placebo SC during maintenance (i.e., RZB-naïve).

Results from this analysis set were consistent with the primary safety analysis sets and no notable observations were reported. No increases in MACE, malignancies, or infections (including serious infections) were observed as compared to the All Treated Safety Analysis Set.

Safety Results in Maintenance Treatment Safety 2 Analysis Set

This analysis set provides an analysis of the safety of risankizumab SC maintenance treatment among subjects with delayed clinical response to IV risankizumab (i.e., subjects who achieved clinical response to risankizumab SC at Week 24 of Induction) as well as subjects with clinical response to placebo IV induction who received placebo SC during maintenance treatment (i.e., RZB-naïve).

Results from this analysis set were consistent with the primary safety analysis sets and no notable findings were observed.

*Additional Phase 1 and Non-Interventional Studies*

Results from additional healthy volunteer, Phase 1 PK and tolerability Studies M16-533, M16-324, and M17-381 were supportive of the conclusions presented in this CSS for the primary and secondary safety analysis sets. No safety concerns were identified.

### *2.6.8.5. Safety in special populations*

Age

In the Placebo-Controlled 12-Week Induction Period Safety Analysis Set, there were 9 (0.8%) and 5 (1.2%) subjects who were 16 to <18 years, 670 (56.0%) and 255 (59.0%) subjects between the ages of 18 and < 40, 463 (38.7%) and 150 (34.7%) subjects between the ages of 40 and < 65 years, and 55 (4.6%) and 22 (5.1%) subjects ≥ 65 years of age, in the Total RZB and placebo groups, respectively (Table 59). There was no clear pattern with respect to age for any category of AEs or ASIs in the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set. Few subjects ≥ 65 years of age reported AEs in ASI categories in any of the treatment groups. No subjects in the risankizumab 600 mg or 1200 mg IV groups < 18 years or ≥ 65 years of age reported infection-related AEs and the percentages of subjects reporting infection in subjects ≥ 18 and < 65 years of age were generally higher in the placebo IV group compared to the risankizumab IV groups and were comparable between the risankizumab IV groups.

In the All Treated Safety Analysis Set, the ANY RZB group generally did not have any patterns with respect to age for any category of AEs or ASIs with the exception of subjects under 18 years of age who had a numerically higher AE rate overall than subjects above 18 years of age; however, fewer subjects account for greater variability and these differences should be interpreted with caution. Based on the totality data, no new safety findings were identified with regard to risankizumab use and age.

Adolescent Subpopulation (16 to < 18 years old at time of induction Baseline visit)

A total of 14 adolescents (4 subjects in the risankizumab 600 mg IV group, 5 subjects in the risankizumab 1200 mg IV group, and 5 subjects in the placebo group, respectively) enrolled in the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set) (Table 59). Three subjects (64.3%) in the risankizumab 600 mg IV treatment group and 2 subjects (51.8%) in the risankizumab 1200 mg IV treatment group reported AEs. Of subjects aged < 18 years in the risankizumab groups, none reported an SAE, severe AE, or an AE leading to discontinuation. There was no specific pattern with regard to the type of AEs reported by risankizumab-treated subjects under 18 years of age. No subjects < 18 years in a risankizumab treatment group reported an AE in an ASI category. Twelve adolescent subjects received at least 1 dose of risankizumab across the CD studies. Of these, here were no events of an AE leading to discontinuation of study drug and few AEs were serious (23.8 E/100 PY [3 events]) or severe (23.8 E/100 PY [3 events]).

Of the SAEs reported in the ANY RZB group (1 event of suicidal ideation and 1 event of Crohn's disease in the same subject, 1 event of ileal stenosis), none resulted in discontinuation of study drug and only

the event of ileal stenosis was ongoing as of the database lock. The subject with an event of suicidal ideation had an alternate cause listed as "social isolation resulted in increased sadness and anxiety which has led to suicidal ideation" and neither the investigator nor sponsor considered the event to have a reasonable possibility of being related to study drug. The event resolved in 1 day. The SAEs of ileal stenosis was also not considered by the investigator to have a reasonable possibility of being related to study drug while the SAE of Crohn's disease was considered by the investigator to have a reasonable possibility of being related to study drug. Overall, the safety profile in adolescent subjects was consistent with that observed in adult subjects and no dose related effects were observed.

Sex

The gender distribution in the Total RZB group of the Placebo-Controlled 12-Week Induction Period Safety Analysis Set was 52.3% male and 47.7% female and 49.1% male and 50.9% female in the placebo group (Table 59). In general, the percentage of female subjects reporting events across the categories of AEs (including infection AEs) and ASIs in the induction period was higher than the percentage of males across the risankizumab and placebo treatment groups and a similar trend was observed in the rates of AEs and ASIs in the ANY RZB group. Based on the totality of data, no new safety findings were identified with regard to risankizumab use and sex.

Weight

In the Placebo-Controlled 12-Week Induction Period Safety Analysis Set, in the Total RZB group, there were 352 subjects (29.4%) weighing < 60 kg and 845 subjects (70.6%) weighing ≥ 60 kg, compared to 134 subjects (31.0%) weighing < 60 kg and 298 subjects (69.0%) weighing ≥ 60 kg in the placebo group. In general, the percentage of subjects weighing < 60 kg reporting events across the categories of AEs and ASIs in the induction period was higher than the percentage of subjects weighing ≥ 60 kg across the risankizumab and placebo treatment groups, and this difference is likely a manifestation of the higher variability associated with fewer subjects. A similar trend was observed in the rates of AEs and ASIs by weight group in the ANY RZB group of the All Treated Safety Analysis Set. Based on the totality of data, no new safety findings were identified with regard to risankizumab use and weight.

Race

In the Placebo-Controlled 12-Week Induction Period Safety Analysis Set, there were 975 white subjects (81.5%) and 222 non-white subjects (18.5%) in the Total RZB group and 352 white subjects (81.5%) and 80 non-white subjects (18.5%) in the placebo group. In general, the percentage of white subjects reporting events across the categories of AEs and ASIs in the induction period was higher than the percentage of non-white subjects across the Total RZB and placebo groups. A similar trend was observed in the rates of AEs and ASIs with race in the ANY RZB group of the All Treated Safety Analysis Set. Based on the totality of data, no new safety findings were identified with regard to risankizumab use and race.

Geographic Region

The geographic regions with the highest subject enrolment in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set were Western Europe and North America (approximately 30% of subjects each) (Table 59). There was no clear pattern with respect to the subject's geographic region for any category of AEs or ASIs in the induction period. Similarly, there was no clear pattern observed in the rates of AEs and ASIs in the ANY RZB group of the All Treated Safety Analysis Set. Based on the totality of data, there were no notable differences in types of AEs, SAEs, AEs leading to discontinuation, or AEs in ASI categories by geographic region and no new safety findings were identified with regard to risankizumab use and geographic region.

Biologic therapy-intolerant or inadequate responder (BIO-IR) Status

In the Placebo-Controlled 12-Week Induction Period Safety Analysis Set, 71.5% of the subjects in the Total RZB group and 78.9% of the subjects in the placebo group were Bio-IR. There was no clear pattern with respect to Bio-IR status for any category of AEs or ASIs in the induction period In the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set, an examination of ASIs based on Bio-IR status revealed that the rate of serious infection was higher among Bio-IR subjects (9.2 E/100 PY) in the risankizumab 360 mg SC arm vs. Non-Bio-IR subjects (0 events). A similar pattern was also observed in the withdrawal (placebo SC) arm in which the rate of serious infection was higher in Bio-IR subjects (6.2 E/100 PY) compared to Non-Bio-IR subjects (2.1 E/100 PY).

However, in the risankizumab 180 mg SC arm, rate of serious infection was lower in Bio-IR subjects (1.7 E/100 PY) compared to Non-Bio-IR subjects (5.6 E/100 PY). Notably, the rate of serious infection in the Total RZB group (Bio-IR, 5.3 E/100 PY; Non-Bio-IR, 2.7 E/100 PY) was similar to that of the withdrawal (placebo SC) arm regardless of Bio-IR status, suggesting the inconsistent trend in the serious infection rates between Bio-IR and Non-Bio-IR subjects among the treatment groups may be attributed to the low number of events in general and the higher rate of serious infection observed in Bio-IR subjects in the risankizumab 360 mg SC arm was more likely due to Bio-IR status instead of attributable to risankizumab treatment.

Among subjects in the ANY RZB group of the All Treated Safety Analysis Set, rates of AEs, SAEs, and AEs leading to study drug discontinuation were generally higher in the Bio-IR subgroup as compared to the Non-Bio-IR subgroup. For ASI categories, the rates of hypersensitivity were numerically higher in the Bio-IR (14.9 E/100 PY) vs. Non-Bio-IR (8.1 E/100 PY) subgroup. The same pattern was also observed in the placebo IV/SC (RZB naïve) group, in which the rate of hypersensitivity was higher in the Bio-IR subgroup (19.6 E/100 PY) compared to Non-Bio-IR subgroup (10.7 E/100 PY). Nevertheless, the rate of hypersensitivity in the ANY RZB group was lower as compared to the placebo IV/SC (RZB naïve) group in both Bio-IR and Non-Bio-IR subgroups. For the rest of ASIs, the rate was either generally similar or no meaningful comparison could be made due to low number of events between Bio-IR and Non-Bio-IR subjects. The rate of serious infections in the ANY RZB group was comparable between Bio-IR (3.7 E/100 PY) and Non-Bio-IR (3.1 E/100 PY) subjects, further suggesting there is no meaningful difference in the risk of experiencing serious infection with risankizumab treatment between Bio-IR and Non-Bio-IR populations.

Number of Prior Biologics Failed

In the Placebo-Controlled 12-Week Induction Period Safety Analysis Set, 34.7% and 36.5% of the subjects in the Total RZB group and 35.4% and 42.5% of the subjects in the placebo group had previously failed 1 or > 1 biologics. There was no clear pattern with respect to the number of prior biologics failed for any category of AEs or ASIs in the induction period nor was there a clear pattern observed in the rates of AEs and ASIs in the ANY RZB group of the All Treated Safety Analysis Set.

Number of Prior Biolog Baseline Steroid Use

In the Placebo-Controlled 12-Week Induction Period Safety Analysis Set, 32.6% of subjects in the Total RZB group and 33.8% of the subjects in the placebo group were on a concomitant corticosteroid at Baseline. There was no clear pattern with respect to baseline corticosteroid use for any category of AEs or ASIs in the induction period as compared to subjects who were not taking concomitant corticosteroids at Baseline. Similar findings were observed in the ANY RZB group of the All Treated Safety Analysis Set.

Baseline Immunomodulator Use

In the Placebo-Controlled 12-Week Induction Period Safety Analysis Set, 24.6% of the subjects in the Total RZB group and 25.7% of the subjects in the placebo group were on a concomitant immunomodulator (azathioprine, 6-mercaptopurine, methotrexate) at baseline. There was no clear

pattern with respect to baseline immunomodulator use for any category of AEs or ASIs in the induction period as compared to subjects who were not taking concomitant immunomodulators at Baseline. Similar findings were observed in the ANY RZB group of the All Treated Safety Analysis Set.

Use in Pregnancy and Lactation

Twenty maternal exposure pregnancies occurred in the risankizumab CD clinical development program through the cutoff date for this CSS 97.

The pregnancy outcomes are shown in Table 88. One elective termination with fetal defects occurredin a patient < 30 years old at 12 weeks gestation, due to a fetus with a cystic hygroma and fetal hydrops. The subject received risankizumab (180 mg SC Q8 weeks) for six months and then discontinued secondary to the pregnancy. The subject was exposed to risankizumab prior to conception and during the first trimester, and concomitant medications included nortriptyline, paracetamol, and desogestrel. Chromosomal analysis from chorionic villus sampling was normal, and human parvovirus testing was not suggestive of an acute infection. The event was assessed by the investigator with reasonable possibility of relationship to study drug. The sponsor assessed this event with no reasonable possibility of being related to risankizumab based on published data that IgG antibody is actively transported from mother to fetus via Fc receptors on the syncytiotrophoblast that appear after Week 14 of gestation and the active transportation of IgG antibodies starts in the second trimester, increasing throughout the third trimester.

The absence of Fc-receptors in the first trimester indicates that the fetus in this period is not exposed to IgG class monoclonal antibodies during the period of organogenesis (between Weeks 3 and 8) and therefore the risk of mutagenic and teratogenic effects from maternal exposure to an IgG class antibody is negligible (Kane 2009, Ruiz 2014, Weber-Schoendorfer 2015). After discontinuation from Study M15-989, this subject experienced spontaneous abortion from a subsequent pregnancy almost 5 months after last elective termination.

*Table 88 Summary of Pregnancies in Risankizumab CD Clinical Program*

| Maternal Exposure Outcomes (N = 21) | Risankizumab | Placebo | Total |
|---|---|---|---|
| Live birth without congenital anomaly | 3 | 3 | 6 |
| Spontaneous Abortion | 2 | 0 | 2 |
| Elective termination (fetal defects) | 1 | 0 | 1 |
| Elective termination with no fetal defects | 3 | 1 | 4 |
| Ongoing pregnancy | 6 | 0 | 6 |
| Subject lost to follow up | 1 | 0 | 1 |
| **Total** | **16** | **4** | **20** |

Male subjects and their female partners were not required as per the protocols to use contraception. Risankizumab, an immunoglobulin, is not genotoxic and amounts in seminal fluid transferred to the conceptus are negligible. Consequently, male-mediated seminal transfer of large molecule drugs like risankizumab should not present a health risk to the female partner and the drug is not bioavailable to the developing conceptus (Scialli 2015).

One paternal exposure pregnancy was reported in the partner of a male study subject in the risankizumab CD clinical development program. The pregnancy outcome for it is as follows:

- On risankizumab: 1 live birth without congenital anomaly

There are no data on the presence of risankizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Although human IgG is secreted into human milk, published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amount.

#### *2.6.8.6. Immunological events*

12-Week Induction

No cases of adjudicated anaphylactic reactions were reported with risankizumab treatment during the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set).

In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), hypersensitivity reaction was reported at a similar percentage and rate among subjects in the risankizumab and placebo groups (4.7%, 20.2 E/100 PY in the risankizumab 600 mg IV group, 5.3%, 21.4 E/100 PY in the risankizumab 1200 mg IV group, and 4.3%, 21.8 E/100 PY in the placebo IV group) (Table 73). The majority of hypersensitivity reactions reported in the Total RZB group were non-serious, mild to moderate in severity, and few events (2 subjects, 0.3% in the 600 mg IV group and 4 subjects, 0.7% in the 1200 mg group) led to discontinuation of study drug.

Two subjects in the risankizumab 1200 mg IV group had study drug withdrawn due to events of "drug hypersensitivity," both of which were non-serious and considered by the investigator to have a reasonable possibility of being related to study drug.

A subject experienced a moderate AE reported as "allergic response to intraperitoneal (IP) medication" on Day 1 (same day of risankizumab administration), and a subject experienced a severe AE reported as "allergy on IP" on Day 29 (same day of risankizumab administration).

Hypersensitivity reactions with PT of infusion-related reaction led to study drug discontinuation in 3 subjects in the risankizumab arms. One subject in the risankizumab 1200 mg IV group had an infusion-related reaction of moderate severity on Day 6 and discontinued study drug. A subject, also in the risankizumab 1200 mg IV group, had an infusion-related reaction of moderate severity on Day 1 and discontinued study drug. Both events were considered by the investigator to have a reasonable possibility of being related to study drug. One subject in the risankizumab 600 mg IV group had an infusion-related reaction of mild severity on Day 36 and discontinued study drug. The event was considered by the investigator to have a reasonable possibility of being related to study drug. Of note, infusion-related reactions were also reported in 3 subjects in the placebo IV group; for 2 subjects, study dose was not changed, and for 1 subject, study dose was interrupted.

The single SAE in the risankizumab 600 mg IV group was previously described above. The subject developed a non-serious rash on Day 55 and study drug was withdrawn, with the last dose administered on Day 29. The rash resolved on its own after 7 days. On Day 80, the subject developed rash again and was hospitalized. The subject also had an SAE of hepatic function abnormal on Day 82 with increased ALT, AST, and bilirubin. The SAE of rash was considered by the investigator to have a reasonable possibility of being related to study drug. The subject was treated with IV corticosteroids for the rash. Of note, one serious hypersensitivity event occurred in the placebo group.

*Table 89 Treatment-Emergent Hypersensitivity Reactions (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

| System Organ Class<br>MedDRA 23.1 Preferred Term | Placebo IV<br>(N = 432)<br>n (%) [SSA%] | Risankizumab<br>600 mg IV<br>(N = 620)<br>n (%) [SSA%] | Risankizumab<br>1200 mg IV<br>(N = 577)<br>n (%) [SSA%] | Risankizumab<br>Total<br>(N = 1197)<br>n (%) [SSA%] |
|---|---|---|---|---|
| **Any adverse event** | **21 (4.9) [4.3]** | **30 (4.8) [4.7]** | **30 (5.2) [5.3]** | **60 (5.0) [5.1]** |
| **Eye disorders** | **1 (0.2) [0.1]** | **0** | **0** | **0** |
| Swelling of eyelid | 1 (0.2) [0.1] | 0 | 0 | 0 |
| **Immune system disorders** | **4 (0.9) [0.7]** | **2 (0.3) [0.3]** | **3 (0.5) [0.6]** | **5 (0.4) [0.5]** |
| Anaphylactic reaction | 1 (0.2) [0.1] | 0 | 0 | 0 |
| Drug hypersensitivity | 0 | 0 | 2 (0.3) [0.4] | 2 (0.2) [0.2] |
| Hypersensitivity | 3 (0.7) [0.6] | 2 (0.3) [0.3] | 1 (0.2) [0.2] | 3 (0.3) [0.3] |
| **Infections and infestations** | **1 (0.2) [0.1]** | **0** | **0** | **0** |
| Rash pustular | 1 (0.2) [0.1] | 0 | 0 | 0 |
| **Injury, poisoning and procedural complications** | **3 (0.7) [0.6]** | **3 (0.5) [0.5]** | **1 (0.2) [0.2]** | **4 (0.3) [0.3]** |
| Infusion-related reaction | 3 (0.7) [0.6] | 3 (0.5) [0.5] | 1 (0.2) [0.2] | 4 (0.3) [0.3] |
| **Reproductive system and breast disorders** | **0** | **0** | **1 (0.2) [0.2]** | **1 (< 0.1) [< 0.1]** |
| Scrotal dermatitis | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| **Respiratory, thoracic and mediastinal disorders** | **1 (0.2) [0.2]** | **2 (0.3) [0.3]** | **2 (0.3) [0.4]** | **4 (0.3) [0.3]** |
| Allergic bronchitis | 1 (0.2) [0.2] | 0 | 0 | 0 |
| Bronchospasm | 0 | 1 (0.2) [0.2] | 1 (0.2) [0.2] | 2 (0.2) [0.2] |
| Rhinitis allergic | 0 | 1 (0.2) [0.2] | 1 (0.2) [0.2] | 2 (0.2) [0.2] |
| **Skin and subcutaneous tissue disorders** | **15 (3.5) [3.3]** | **23 (3.7) [3.6]** | **23 (4.0) [4.1]** | **46 (3.8) [3.9]** |
| Dermatitis | 1 (0.2) [0.2] | 2 (0.3) [0.4] | 0 | 2 (0.2) [0.2] |
| Dermatitis allergic | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| Dermatitis psoriasiform | 0 | 1 (0.2) [0.1] | 0 | 1 (< 0.1) [0.1] |
| Eczema | 3 (0.7) [0.6] | 3 (0.5) [0.5] | 6 (1.0) [1.0] | 9 (0.8) [0.7] |
| Erythema nodosum | 2 (0.5) [0.3] | 2 (0.3) [0.3] | 3 (0.5) [0.6] | 5 (0.4) [0.4] |
| Rash | 5 (1.2) [1.2] | 15 (2.4) [2.3] | 8 (1.4) [1.4] | 23 (1.9) [1.9] |
| Rash macular | 1 (0.2) [0.3] | 0 | 0 | 0 |
| Rash maculo-papular | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| Rash pruritic | 2 (0.5) [0.5] | 0 | 0 | 0 |
| Rash vesicular | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| Urticaria | 2 (0.5) [0.5] | 1 (0.2) [0.2] | 3 (0.5) [0.6] | 4 (0.3) [0.4] |

Among the subjects who had anti-drug antibody (ADA) tests available in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set, the incidence of hypersensitivity reactions among ADA-positive risankizumab-treated subjects was 7.7% (1/13 subjects, 1 subject with rash) in the risankizumab 600 mg IV group and 0% (0/4 subjects) in the risankizumab 1200 mg IV group. Among ADA-negative risankizumab-treated subjects, the incidence of hypersensitivity reactions was 4.7% (28/596 subjects) in the risankizumab 600 mg IV group and 5.0% (28/561 subjects) in the risankizumab 1200 mg IV group. The rash in the ADA-positive subject was mild and did not lead to study drug discontinuation.

While recognizing that the number of ADA-positive subjects is low, these results suggest that immunogenicity to risankizumab did not have any clinically relevant impact on hypersensitivity reactions.

Maintenance up to 52 Weeks

In the maintenance period (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), there were no adjudicated events of anaphylaxis and the rates of hypersensitivity reactions were similar across all treatment arms (12.4 E/100 PY in the risankizumab 180 mg SC arm, 12.6 E/100 PY in the risankizumab 360 mg SC arm, and 11.8 E/100 PY in the withdrawal (placebo SC) arm (Table 90). All hypersensitivity reactions in the maintenance period were non-serious and mild to moderate in severity. A single event led to study drug discontinuation (urticaria in a subject in the withdrawal [placebo SC] treatment arm).

Of the 4 ADA positive subjects in the risankizumab SC arms, one subject had a hypersensitivity reaction. A subject, <30 years-old in the risankizumab 180 mg SC arm who was also neutralizing antibody (NAb)-positive, experienced a mild AE of dermatitis on Day 183 (Day 15 of Sub-Study 1). The event did not lead to study drug discontinuation and was assessed by the investigator as having no reasonable possibility of being related to study drug.

*Table 90 Treatment-Emergent Hypersensitivity Reactions (Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set)*

| | | Risankizumab | | |
|---|---|---|---|---|
| MedDRA 23.1 Preferred Term | Withdrawal (Placebo SC) (N = 184) (PY = 160.4) Events (E/100 PY) | 180 mg SC (N = 179) (PY = 169.3) Events (E/100 PY) | 360 mg SC (N = 179) (PY = 166.4) Events (E/100 PY) | Total (N = 358) (PY = 335.7) Events (E/100 PY) |
| Any adverse event | 19 (11.8) | 21 (12.4) | 21 (12.6) | 42 (12.5) |
| Allergic oedema | 0 | 0 | 2 (1.2) | 2 (0.6) |
| Conjunctivitis allergic | 0 | 1 (0.6) | 0 | 1 (0.3) |
| Dermatitis | 0 | 1 (0.6) | 1 (0.6) | 2 (0.6) |
| Dermatitis allergic | 1 (0.6) | 1 (0.6) | 0 | 1 (0.3) |
| Dermatitis contact | 2 (1.2) | 1 (0.6) | 0 | 1 (0.3) |
| Eczema | 4 (2.5) | 5 (3.0) | 2 (1.2) | 7 (2.1) |
| Erythema nodosum | 1 (0.6) | 1 (0.6) | 0 | 1 (0.3) |
| Hypersensitivity | 1 (0.6) | 0 | 5 (3.0) | 5 (1.5) |
| Injection site hypersensitivity | 0 | 0 | 3 (1.8) | 3 (0.9) |
| Injection site rash | 0 | 0 | 1 (0.6) | 1 (0.3) |
| Injection site urticaria | 0 | 1 (0.6) | 1 (0.6) | 2 (0.6) |
| Lip swelling | 1 (0.6) | 0 | 0 | 0 |
| Perioral dermatitis | 0 | 1 (0.6) | 0 | 1 (0.3) |
| Rash | 5 (3.1) | 1 (0.6) | 3 (1.8) | 4 (1.2) |
| Rash erythematous | 1 (0.6) | 2 (1.2) | 1 (0.6) | 3 (0.9) |
| Rash pruritic | 1 (0.6) | 1 (0.6) | 0 | 1 (0.3) |
| Rhinitis allergic | 0 | 1 (0.6) | 1 (0.6) | 2 (0.6) |
| Urticaria | 2 (1.2) | 4 (2.4) | 1 (0.6) | 5 (1.5) |

All Treated Safety Analysis Set

No cases across the Phase 3 CD development program were adjudicated as anaphylactic reaction.

The rate of hypersensitivity reaction in the ANY RZB SC group (All Treated Safety Analysis Set) was 9.8 E/100 PY and similar to that of the Total RZB group 12.5 E/100 PY) of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set (Table 74 and 90). The majority of events were non-serious and mild to moderate in severity. No hypersensitivity reaction events in the ANY RZB SC group (All

Treated Safety Analysis Set) led to discontinuation of study drug. A total of 3 serious hypersensitivity reaction events were reported in 2 subjects in the ANY RZB group of the All Treated Safety Analysis Set) (a case of serious rash [detailed in the 12-Week Induction section above] and a case with events of anaphylactic reaction and circulatory collapse). The SAEs of anaphylactic reaction and circulatory collapse occurred in the same subject and are summarized below:

- A subject, a 40-50 year-old in Phase 2 Study M15-993, experienced an SAE of circulatory collapse without loss of consciousness on Day 99 (when receiving OL risankizumab 600 mg IV). Study drug was not interrupted due to this event and no treatment medications were prescribed. The subject later entered OL Phase 2 Study M15-989 and received risankizumab 180 mg SC. On Day 611, this subject experienced an SAE of anaphylactic reaction to IV Ferinject® administration within minutes of starting IV iron therapy. Study drug was not discontinued due to this event and the investigator did not consider the circulatory collapse nor the anaphylactic reaction events to have a reasonable possibility of being related to study drug. Both events resolved the same day.

Adjudication results are not available as Phase 2 studies did not have an adjudication committee.

Among the subjects in the ANY RZB group of the All Treated Safety Analysis Set who had ADA tests available, the incidence of hypersensitivity in ADA-positive subjects was 17.1% (6/35 subjects) compared to 11.1% in ADA-negative subjects (150/1349 subjects). The events in ADA positive subjects were generally mild (none were severe), with 1 event leading to study drug discontinuation. These results suggest that immunogenicity to risankizumab did not have a clinically relevant impact on hypersensitivity reactions.

Considering hypersensitivity SMQ contains PTs covering broad medical concepts, post-hoc clinical grouping of events suggestive of rash and dermatitis and analysis were conducted. The results showed overall, the rates of rash and dermatitis were comparable between risankizumab arms and placebo.

Exploratory Cox proportional hazards models were run to assess treatment group and prespecified baseline predictors for treatment-emergent hypersensitivity reactions. These were conducted for the Phase 3 subset of the Placebo-Controlled 12-Week Induction Period Safety Analysis Set (data from Studies M15-991 and M16-006 only) and the entire All Treated Safety Analysis Set. No significant treatment effect was observed after adjustment for prespecified significant baseline predictors.

The cumulative incidence plot for treatment-emergent hypersensitivity reaction in the All Treated Safety Analysis Set suggests that the risk of subjects experiencing hypersensitivity reaction on risankizumab remained constant over time. The small denominators at later time points lend to wide variability in the event rates.

While the rates of hypersensitivity reactions were similar between the risankizumab and placebo groups in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set, it is noted that 3 patients discontinued due to hypersensitivity infusion-related reactions. One subject in the risankizumab 1200 mg IV group had an infusion-related reaction of moderate severity on Day 6 and discontinued study drug. A subject also in the risankizumabtable 1200 mg IV group, had an infusion-related reaction of moderate severity on Day 1 and discontinued study drug. Both events were considered by the investigator to have a reasonable possibility of being related to study drug. One subject in the risankizumab 600 mg IV group had an infusion-related reaction of mild severity on Day 36 and discontinued study drug. It is noted that infusion reactions is not listed section 4.8 of the SmPC. Infusion reactions are discussed further below. The MAH was requested to outline the rationale for not including infusion as an adverse reactions. In response, the MAH presented the number and percentage of subjects with TEAEs by infusion reaction in the placebo controlled 12 week induction period safety analysis set. It is agreed that given reported infusion-related reactions were observed in

both risankizumab and placebo treatment arms, the rarity of occurrence and lack of a dose-dependent pattern, the totality of data do not point to a causal association with risankizumab treatment.

Serious hypersensitivity reactions are listed as an important potential risk with and evaluation of the rates of serious hypersensitivity reactions is an objective of the proposed long term cohort study listed as additional pharmacovigilance activities.

In the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set the event rates of hypersensitivity reactions were similar across the treatment arms with 12.4 E/100 PY, 12.6 E/100 PY, and 11.8 E/100 PY reported for the risankizumab180 mg SC, risankizumab 360 mg SC, and withdrawal (placebo SC) arms, respectively. No serious hypersensitivity reactions were reported.

The rate of serious hypersensitivity reactions across any risankizumab exposure (<0.1 E/100 PY) was low.

Immunogenicity to risankizumab did not appear to have any clinically relevant impacts on hypersensitivity reactions, though the low number of patient's experiencing ADA precludes any conclusions in this regard.

#### *2.6.8.7. Safety related to drug-drug interactions and other interactions*

The potential for drug-drug interactions between risankizumab and CYP450 enzyme activity, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A using their probe substrates was assessed in the Phase 1 Study M16-007 (1311.36) in subjects with plaque psoriasis which was included and reviewed previously in the risankizumab application for psoriasis. No clinically significant changes in exposure of probe substrates were observed when used concomitantly with risankizumab in subjects with plaque psoriasis.

#### *2.6.8.8. Discontinuation due to adverse events*

12-Week Induction

In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), a lower percentage of subjects discontinued from study drug due to an AE in the risankizumab 600 mg and 1200 mg IV groups (2.0% and 2.1%, respectively) compared with the placebo group (8.2%), with no dose-response between the 2 risankizumab IV dose groups (Table 91). The most common AE leading to discontinuation of study drug in any treatment group was worsening of the underlying disease (Crohn's disease), which was higher in the placebo group (risankizumab 600 mg: 0.5%; risankizumab 1200 mg: 0.5%; placebo: 5.0%). Eight subjects (1.9%) in the placebo group discontinued study drug due to an AE in the SOC of infections and infestations while no subjects in either risankizumab group discontinued study drug due to an AE in the SOC of infections and infestations.

*Table 91 TEAEs Leading to Discontinuation of Study Drug in ≥1 Subject in Any Risankizumab Group (Placebo-Controlled 12-Week Induction Period Safety Analysis Set)*

| System Organ Class<br>MedDRA 23.1 Preferred Term | Placebo IV<br>(N = 432)<br>n (%) [SSA%] | Risankizumab<br>600 mg IV<br>(N = 620)<br>n (%) [SSA%] | Risankizumab<br>1200 mg IV<br>(N = 577)<br>n (%) [SSA%] | Risankizumab<br>Total<br>(N = 1197)<br>n (%) [SSA%] |
|---|---|---|---|---|
| **Any adverse event** | **37 (8.6) [8.2]** | **13 (2.1) [2.0]** | **12 (2.1) [2.1]** | **25 (2.1) [2.1]** |
| **Gastrointestinal disorders** | **29 (6.7) [6.1]** | **4 (0.6) [0.7]** | **5 (0.9) [0.9]** | **9 (0.8) [0.8]** |
| Abdominal mass | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| Colitis | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| Crohn's disease | 24 (5.6) [5.0] | 3 (0.5) [0.5] | 3 (0.5) [0.5] | 6 (0.5) [0.5] |
| Large intestinal stenosis | 0 | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| Large intestinal ulcer | 0 | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| Small intestinal obstruction | 2 (0.5) [0.5] | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| **General disorders and administration site conditions** | **1 (0.2) [0.3]** | **2 (0.3) [0.3]** | **2 (0.3) [0.4]** | **4 (0.3) [0.4]** |
| Disease progression | 0 | 1 (0.2) [0.1] | 0 | 1 (< 0.1) [0.1] |
| Pelvic mass | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| Pyrexia | 1 (0.2) [0.3] | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| Systemic inflammatory response syndrome | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| **Hepatobiliary disorders** | **0** | **1 (0.2) [0.2]** | **0** | **1 (< 0.1) [< 0.1]** |
| Hepatic function abnormal | 0 | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| **Immune system disorders** | **0** | **0** | **2 (0.3) [0.4]** | **2 (0.2) [0.2]** |
| Drug hypersensitivity | 0 | 0 | 2 (0.3) [0.4] | 2 (0.2) [0.2] |
| **Injury, poisoning and procedural complications** | **0** | **1 (0.2) [0.2]** | **1 (0.2) [0.2]** | **2 (0.2) [0.2]** |
| Infusion-related reaction | 0 | 1 (0.2) [0.2] | 1 (0.2) [0.2] | 2 (0.2) [0.2] |
| **Investigations** | **0** | **1 (0.2) [0.2]** | **1 (0.2) [0.2]** | **2 (0.2) [0.2]** |
| Aspartate aminotransferase increased | 0 | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| Hormone level abnormal | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| **Musculoskeletal and connective tissue disorders** | **1 (0.2) [0.2]** | **1 (0.2) [0.2]** | **1 (0.2) [0.2]** | **2 (0.2) [0.2]** |
| Arthralgia | 1 (0.2) [0.2] | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| Fistula | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **0** | **0** | **1 (0.2) [0.2]** | **1 (< 0.1) [< 0.1]** |
| Squamous cell carcinoma of lung | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| **Skin and subcutaneous tissue disorders** | **1 (0.2) [0.3]** | **3 (0.5) [0.4]** | **1 (0.2) [0.2]** | **4 (0.3) [0.3]** |
| Blister | 0 | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| Palmoplantar pustulosis | 0 | 1 (0.2) [0.1] | 0 | 1 (< 0.1) [0.1] |
| Rash | 0 | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |
| Rash maculo-papular | 0 | 0 | 1 (0.2) [0.2] | 1 (< 0.1) [< 0.1] |
| **Surgical and medical procedures** | **0** | **1 (0.2) [0.2]** | **0** | **1 (< 0.1) [< 0.1]** |
| Abortion induced | 0 | 1 (0.2) [0.2] | 0 | 1 (< 0.1) [< 0.1] |

In the 12-week Induction Period safety analysis set, TEAEs leading to discontinuations were 4 times higher in the placebo IV group (8.6%) when compared to the treatment groups (2.1% for 600mg IV and 2.1 for 1200 mg IV group). The imbalance is predominantly driven by AEs in the GI disorder SOC

and those associated with the underlying disease. The MAH was requested to provide the narrative for the event of systemic inflammatory response syndrome.

TEAEs which led to treatment discontinuation were similar for 360mg sc group (3.4%) and placebo/withdrawal group (3.3%) of the placebo-Controlled 52-Week Maintenance Period Safety Analysis Set), though TEAEs which led to discontinuations were lower in the 10 mg sc group (1.7%) due to a lack of GI disorder TEAEs leading to discontinuation in this group.

#### *2.6.8.9. Post marketing experience*

Risankizumab 150 mg (75 mg/0.83 mL × 2 SC injections) administered by SC injection at Week 0, Week 4, and every 12 weeks thereafter was first approved for the treatment of moderate to severe plaque psoriasis in adults on 26 March 2019 (international birth date) in Japan. Risankizumab is also approved in adult patients for the treatment of psoriatic arthritis in Japan, Russia and Europe (14/10/2021). Through 25 March 2021, risankizumab has been approved in 72 countries with estimated cumulative postmarketing patient exposure since first approval of 87,387 patient treatment years across 56 countries. Additionally, a 150 mg/mL formulation in PFS and autoinjector presentations has been approved by FDA and EMA. AbbVie has been continuing to monitor potential new safety signals through its ongoing routine pharmacovigilance that includes weekly review of all postmarketing reports, serious and non-serious, received from all sources (including literature) and SAEs from clinical trials; quarterly review of data mining scores generated from FDA's Adverse Event Reporting System database; periodic reports (Periodic Safety Update Report, development safety update reports, periodic adverse drug experience reports, etc.) with inclusion of sections outlining findings for AEs of interest, per mandated timelines, and postmarketing studies.

The overall safety of risankizumab 150 mg was evaluated through review of postmarketing reports (spontaneous, solicited, literature) received from 26 March 2019 through 25 March 2021. Search of the AbbVie global safety database retrieved 29,696 cases with 58,850 events that were predominantly reported in the psoriasis patients. Overall, 91.6% (27,205/29,696) of the reports were considered non-serious and 95.5% (28,358/29,696) were from a solicited source, which were predominantly collected through patient support programs. The most frequently reported MedDRA SOC (36% of all cases) was general disorders and administration site conditions, in which PTs of drug ineffective, fatigue, and therapeutic response shortened were most frequently reported.

The most commonly reported AEs included psoriasis (8.5%), drug ineffective (3.8%), fatigue (3.6%), pruritus (3.3%), and headache (3%). These events are either labeled for risankizumab or commonly seen in the general population or patients with psoriasis.

Although lack of efficacy (represented by PTs of psoriasis and drug ineffective) is listed as one of the most frequently reported events, it is not unexpected for a product indicated for a chronic condition.

The most commonly reported SAE was death (0.2%). Of the 121 reports of death, 112 were from a solicited postmarketing source, which have known limitations in data quality that preclude a robust analysis. One hundred ten reports contained limited information to establish a causal association with risankizumab and 11 death reports were attributable to the patient's significant comorbidities and natural causes. In 71 of the reports where age was reported, the majority of the deaths occurred in the elderly population with a median age of 69 years. Psoriasis was the most common indication (79%) with the remaining largely unknown (17%). There was 1 death report that occurred in a patient with CD, however, it contained limited information for medical assessment. Psoriasis is associated with multiple comorbidities that could increase the risk of mortality in this population evidenced in a cohort study reporting an increased overall mortality risk (HR, 1.5; 95% CI, 1.3 – 1.7) in patients with severe psoriasis (Gelfand 2007).

COVID-19 was the next most frequently reported SAE (0.17%), followed by hospitalization (0.15%), pneumonia (0.14%), and cerebrovascular accident (0.14%). COVID-19 continues to be monitored through standard surveillance activities and no new safety risks have been identified with COVID-19 and risankizumab use. Considering the ongoing COVID-19 pandemic and improved testing capabilities, the observed increase in the total number of reports received in patients receiving risankizumab is not unexpected.

Though pneumonia and cerebrovascular accident were other most frequently reported SAEs, the events are uncommon. These events as part of serious infections and MACE, continue to be monitored as Important Potential Risks and no safety concerns have been identified. Studies have shown an increased prevalence of CV risk factors including diabetes, hypertension, and obesity in patients with psoriasis (Kimball 2010).

Additionally, patients with moderate to severe psoriasis also have been shown to have an increased risk of MI (Gelfand 2006), stroke (Gelfand 2009), and CV mortality (Mehta 2010).

Given these remaining SAEs were reported in less than 0.2% of the total events, and patients with psoriasis often have comorbidities that could increase the risk of mortality, these findings are not unexpected. Review of the postmarketing reports did not identify any new safety risks for the marketing of risankizumab.

## 2.6.9. Discussion on clinical safety

The MAH has focused the Summary of Clinical Safety on pooled data and data analysed separately for 3 primary analysis sets; The Placebo-Controlled 12-Week Induction Period Safety Analysis Set, The Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set, The All Treated Safety Analysis Set. The primary safety analysis sets are considered broadly reasonable. While the MAH outlines the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set as the most clinically relevant in terms of characterisation of safety results for maintenance treatment with risankizumab, noteworthy in terms of the proposed to-be-marketed dose and device is the absence of clinical safety data with the on-body delivery system.

Patient exposure

With respect to patient exposure, it is noted that Risankizumab is already authorised in the EU for treatment of moderate to severe plaque PsO (2019) as well as psoriatic arthritis in adults (2022) at a dose of 150 mg subcutaneous injection at week 0, week 4, and every 12 weeks thereafter. The MAH has outlined that post-marketing exposure to risankizumab is estimated to be 87,387 patient treatment years (PTY) cumulatively as of 25 March 2021.

Exposure in the intended population to proposed marketed dosing is considered broadly acceptable in the context of ICH E1 and EMA Guideline on the development of new medicinal products for treatment of Crohn's Disease. In the All Treated Safety Analysis Set n=688 subjects received the risankizumab 600 mg IV induction dose and n=533 subjects received the risankizumab 360 mg SC maintenance dose, including 333 with at least 6 months of exposure and 233 with at least 12 months of exposure). However, a number of issues are raised in relation to exposure supporting the application.

Firstly, there is no clinically relevant exposure to the proposed on-body delivery system (OBDS). Given bioequivalence has not been demonstrated for the to-be-marketed SC presentation of 360 mg OBDS compared to the Phase 3 90 mg/mL PFS, extrapolation of findings from the Safety Analysis Sets cannot be made.

Secondly, the MAH seeks an indication from 16 years of age. The number of adolescent patients included in the Crohn's disease program is minimal. A total of n=12 received at least one dose of risankizumab and n=5 adolescent patients went past 52 weeks in maintenance. From data presented, there also appears to very minimal experience from outside of the Crohn's disease program in patients less than 18 years. While the population pharmacokinetics analysis did not identify age as having an independent impact on risankizumab exposures, unexpected age-specific safety issues cannot be ruled out on the basis of data collected in adolescent patients. The MAH excluded adolescents who were not at Tanner stage 5 from the supporting clinical trials, though not all 16 year old adolescents will be Tanner stage 5. The MAH has outlined that all aspects of the Paediatric Investigational Plan are currently differed. As such, the MAH was requested to adjust the indication sought to ≥18 years. The MAH has agreed to restrict the indication to patients ≥ 18 years of age.

Exposure in very elderly patients is (≥75 years) is also extremely limited with n=32 patients aged >65 years in The Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set and just n=5 aged >75 years. The MAH does not consider separate missing information for "use in patients > 65 years" is not warranted in the risankizumab RMP. Given the recommendations outlined in CPMP/EWP/2284/99 Rev. 2 and the potential for safety to differ in these patients due to factors such as increased susceptibility to adverse events (including important potential risks of serious infection), polypharmacy and other physiological differences, the MAH was asked to discuss the need for a warning in section 4.4 in light of the limited exposure in the elderly and the potential for safety to differ in these patients due to factors such as increased susceptibility to adverse events (including important potential risks of serious infection). The MAH discussed this and considered that 'Based on the SmPC guidelines for considerations for Special warnings and precautions for use, since there is no risk identified leading to a precaution for use or which warrants a specific warning for the elderly population, addition of this information to section 4.4 is not warranted.' This was accepted by the CHMP.

Safety Summary

Across the safety data sets, discontinuations for any reason were greatest in the placebo group. Reasons captured by "withdrawal by subject" do not appear to be otherwise described.

In terms of analysis of AEs, in the 12 week induction safety set, there is little difference between the two treatment groups in terms of frequencies observed of all TEAES (54.7% in 600mg group v 54.1% in 1200 mg), severe TEAEs (5.2% in both 600mg IV and 1200 mg groups), serious TEAEs (6.6% in 600mg group v 4% in 1200 mg) and TEAEs leading to discontinuation (2.1% in both 600mg IV and 1200 mg groups). All categories of TEAEs (all TEAEs, related, severe, and serious and TEAES which led to discontinuation) occurred at greater frequency in the placebo group. TEAEs were driving the imbalance relate to indication (predominantly GI events) and are therefore not unexpected.

In the 52 week Maintenance Safety Set TEAEs occurred at a similar overall frequency in both treatment groups when compared to the withdrawal (placebo SC) group with all TEAEs occurring in 71.5 % of the 180 mg SC group, 72% of the 360 mg group and 73.4% of the withdrawal group. There was also little difference in terms of frequencies of TEAES assessed as related or serious TEAEs between treatment groups in the Maintenance Safety Set. Related TEAEs occurred in 27.4% of the 180 mg SC group, 25.1% of the 360 mg group and 25% of the withdrawal group. Serious TEAEs occurring in 12.3% of the 180 mg SC group, 13.4% of the 360 mg group and 12.5% of the withdrawal group.

It is agreed that the All Treated Safety Set the frequencies AEs, SAEs, AEs leading to discontinuation of study drug, and deaths of the ANY RZB SC and the RZB 360 mg SC groups were similar to the corresponding rates observed in the Total RZB group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set.

The most common AEs include those associated with the underlying disease (Crohn's, anaemia and other GI disorders) as well as those AEs already recognised in section 4.8 of the SmpC for Skyrizi including nasopharyngitis (as upper RTI) and headache.

The frequency of TEAEs of Crohn's disease (worsening of CD) during the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set in the treatment groups, while less frequent, is not markedly different when compared to placebo, with 17% of withdrawal/placebo sc group experiencing a worsening of CD event, compared to 10.6% and 11.7% of the 180 mg and 360 mg SC treatment groups. While the difference in follow up time is acknowledged, the MAH was requested to discuss the apparent increase in worsening of CD events/waning of efficacy when compared to the frequencies observed in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set (where a worsening of CD event was reported in 14.8% of placebo IV patients compared to 3.1% and 1.7% of the risankizumab 600 mg and 1200 mg IV groups respectively).

The most frequent AEs considered by the investigators as related to study drug were generally comparable among the treatment and placebo patients across all 3 primary safety sets.

Severe TEAEs were twice as frequent in the placebo group of the 12 week induction safety set, the imbalance driven by GI disorders associated with underlying disease.

The Maintenance up to 52 Weeks analysis set and all Treated Safety Analysis Set demonstrated similar findings for 180mg SC treatment (6.7%) as compared to placebo/withdrawal group (12.5%), though the frequency of severe reactions in the 360mg SC patients (11.7%) was similar to that of the withdraw/placebo SC patients (with Severe AEs in GI and Infection/Infestation SOCs contributing to the majority of cases).

In the 52 week Maintenance Safety Set, a difference in the exposure adjusted rate for injection site reactions (8/100 PYs for placebo SC group compared to 13.8/100 PYs for 360mg sc) is noted, though this is already a listed ADR in section 4.8 of the SmPC with a frequency of common. Also noteworthy is the difference in the exposure adjusted rate for hepatic events (4/100 PYs for placebo SC group compared to 9/100 PYs for 360mg sc).

Deaths

No deaths occurred in the Phase 2 CD studies. As of the data cutoff date for the submission, a total of 6 deaths were reported in the Phase 3 CD studies, 4 in subjects treated with risankizumab and 2 in subjects treated with placebo. All deaths in subjects being treated with risankizumab were treatment-emergent (i.e., occurred within 140 days after the last dose of risankizumab).

Deaths in subjects being treated with risankizumab were due to acute respiratory failure (in a subject with squamous cell lung carcinoma), sepsis (in a subject with fistulizing CD exacerbation), sudden cardiac death (in a subject with a history of positive blood toxicology) and respiratory failure (in a subject with lung adenocarcinoma). None of the deaths were considered related to study drug. On the basis of the data presented the deaths which occurred do not raise particular concern because of known medical history of the subjects.

COVID 19

The MAH presented a summary of COVID-19 cases identified in the primary safety analysis sets. The low number of cases preclude a firm conclusion in terms of the potential for increased risk of infection or poor outcomes but there was no suggestion of same from the data presented.

MACE

The MAH presented a summary of MACE related events. There were 4 cases of relevance in patients exposed to 180mg risankizumab and 1 on the placebo group. It can be agreed that the events

occurred in patients with CV risk factors or a history of CV disease. When compared to the reported rate of MACE for the patient population (0.82/100 PY) (Kristensen 2013), the exposure-adjusted incidence rate observed was not immediately concerning (0.2/100 PY). MACE is listed as an important potential risk in the Summary of Safety Concerns which is agreed. The estimation of the rates of MACE is included as an objective of the cohort study for the Long-Term Prospective Cohort Study in Patients with Crohn's Disease in Real World Setting.

Infections

As outlined by the MAH, patients with CD have been shown to be at increased risk of common infections, viral infections, and GI infections in a population-based cohort study using the Royal College of General Practitioners Research and Surveillance Centre primary care database from 2014 to 2019 (Irving 2021). The most commonly reported infections in CD included upper respiratory tract infection (19.7%), skin infections (16.1%), and acute bronchitis (14.2%). In the Placebo-Controlled 12-Week Induction Period Safety Analysis Set a lower frequency of AEs in the infections and infestations SOC were reported in treatment arms compared to the placebo IV group (19.2% in 600mg IV and 18.3% in the 1200 mg group, compared to subjects in the placebo group 24.4%). Again, in the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set the rate of infection-related AEs was lower in both risankizumab treatment arms (51.4 E/100 PY for 180 mg SC, 57.7 E/100 PY for 360 mg SC) compared to the rate in the withdrawal (placebo SC) arm (76.0 E/100 PY). It can be agreed from the data presented that no meaningful change in frequency or severity of the currently known ADR for upper respiratory tract infections was identified. Upper respiratory infections are currently listed in section 4.8 of the SmPC with a frequency of very common, a term that is denoted to include respiratory tract infection (viral, bacterial, or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis, laryngitis, tracheitis. Updates to this footer propose a change to this footer with replacement of tracheitis by peritonsillar abscess. The MAH was requested to discuss and substantiate that update. The MAH considered that the PT of peritonsillar abscess is part of upper respiratory tract infection grouping and therefore it is appropriate to include this PT in the ADR table under upper respiratory tract infection grouped PTs. Nevertheless, information supporting the addition of peritonsillar abscess was considered limited by the CHMP. The MAH has removed the reference to peritonsillar abscess, and this was considered acceptable.

Opportunistic Infections

In the Placebo-Controlled 12-Week Induction Period Safety Analysis Set there were 3 opportunistic infections in the placebo group. There was a single (asymptomatic) CMV infection in the risankizumab 1200 mg IV group, though this can be discounted as treatment emergent as confirmation of CMV was based on a biopsy obtained during Screening. There were no cases of relevance in the placebo group of the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set. There was a case of Aeromonas and a case of oral fungal infection in the 360mg sc and 180 sc groups respectively. There were 3 SAEs of opportunistic infection in the ANY RZB group (a clinically asymptomatic case of disseminated histoplasmosis, severe SAE of bronchopulmonary aspergillosis that resolved after 62 days and did not lead to study drug discontinuation and a case CMV which resolved after 8 days and did not lead to study drug discontinuation) and 1 SAE in the placebo IV/SC (RZB-naïve) group (neutropenic sepsis). Overall, it is agreed that the data did not demonstrate a greater frequency of opportunistic infection and the incidence rate observed in All Treated Safety Analysis Set (0.5/100 PY in risankizumab patients is consistent with the background rate for this patient population based on published estimates (0.80/100 PY) (Kirchgesner 2018).

Tuberculosis and herpes zoster

The frequencies of active TB were similar in Placebo-Controlled 12-Week Induction Period Safety Analysis Set with a case of active TB in placebo group and a second case in the risankizumab 600 mg

IV group (40-50 year-old subject who had been treated for TB 7 years prior to study entry. There was an additional case of active TB in the All Treated Safety Analysis Set which occurred in a 30-40 year old patient on day 118 following treatment with 600mg IV induction followed by maintenance treatment with 600 mg sc. The patient was reported to have been in contact with a TB positive person. The MAH did not comment on the overall incidence rate of active TB in the All Treated Safety Analysis Set (0.097/100 PY) in terms of the expected rates for the population/ trial site locations. However, in terms of subjects with latent TB, the data was reassuring. Patients with latent TB were enrolled and treated TB prophylaxis (according to local country guidelines). A total of 72 subjects with latent TB were treated with risankizumab and TB prophylaxis during the study and did not develop active TB during the mean treatment follow-up of 1.4 years; 55 subjects with latent TB who did not receive prophylaxis during the study did not develop active TB during the mean treatment follow-up of 2.0 years.

The rates of herpes zoster infection was similar across the safety analysis sets. In the Placebo-Controlled 12-Week Induction Period Safety Analysis Set the was 1 event (0.3%, 1.2 E/100 PY) in the 600 mg IV group, 2 events (0.2%, 0.6 E/100 PY) in the 1200 mg IV group and 1 event in the placebo group (0.2%, 0.7 E/100 PY). In the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set the rates were again similar and the rate of herpes zoster in the ANY RZB SC group was 0.8 E/100 PY (12 events, All Treated Safety Analysis Set). None of the events were serious or led to study drug discontinuation and all events were mild to moderate in severity.

Malignancies, NMSC, and Malignant Tumours Excluding NMSC

In terms of malignancies, NMSC, and malignant tumours excluding NMSC the incidence rates of malignancies were low in Placebo controlled safety analysis sets. In Placebo-Controlled 12-Week Induction Period Safety Analysis Set there was a case of SCC reported on treatment day 8 in 1200mg IV arm which was considered unrelated. In the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set the rates were similar across treatment arms with no events in the risankizumab 180 mg arm, 0.6/100 PY [1 subject] in the 360 mg arm, and 0.6/100 PY [1 subject] in the withdrawal (placebo SC) arm. The subject in the risankizumab 360 mg arm had HER2-positive breast cancer, and the subject in the withdrawal (placebo SC) arm had basal cell carcinoma; both subjects had risk factors and the events were considered to have no reasonable possibility of being related to study drug by the investigator.

Most relevant in terms of malignancies and lag time for occurrence is the All Treated Safety Analysis Set. The MAH presents a cumulative incidence plots for treatment-emergent malignancies excluding NMSC which shows a cumulative incidence that is apparently stable to 252 and then approximately 4.8 years. The MAH outlines that the apparent increase thereafter is due to a single report of melanoma out of 30 subjects leading to an approximate 3.4% increase from the 1.8% rate preceding that event. It can be agreed that the low numbers left in follow up prevents conclusions about the cumulative frequency past 252 weeks. In general though the incidence rate of malignancy was 0.5/100 PY for the ANY RZB group, which is not concerning in terms of the background rate reported for this patient population based on published estimates (1.33/100 PY) (Taborelli 2020).

Hepatic disorder

The MAH has conducted a comprehensive analysis of reported Hepatic Events as well as hepatic laboratory data. The MAH's approach in terms of the assessment of comprehensive laboratory data in addition to PTs of relevance for assessment of this ASI is endorsed. The frequencies of AST and ALT elevation are presented as well as the frequencies of combined elevations of aminotransferases and bilirubin. It is noteworthy that during the Placebo-Controlled 12-Week Induction Period Safety Analysis Set there were no patients in the placebo group who experienced ALT and/or ALT elevations ≥ 3ULN accompanied by elevations in total bilirubin where as in the risankizumab treatment groups there were

5 patients who experienced AST and or ALT elevations ≥ 3 ULN with TBL ≥1.5 ULN, 4 of which were in 600mg IV group (0.6%) and 1 in 1200mg group (0.2%). The MAH was requested to provide a brief summary of these cases to give an understanding of the likely causality in the context of possibly early readings of TBL which may have risen further and in light of the number of cases falling within the Temple's Corollary quadrant of the edish plots provided. While there was an imbalance in cases falling into "Temple's Corollary" for risankizumab patients compared to placebo, The MAH assessment of these 5 cases of AST and or ALT elevations ≥ 3 ULN with TBL ≥1.5 ULN following exposure to risankizumab is accepted. The cases included confounding factors had resolution of the liver test abnormalities or hepatic events with continued risankizumab therapy.

There were also 3 additional patients who experienced AST and or ALT elevations ≥ 3 ULN with TBL ≥2 ULN (criteria for meeting Hys Law if no evidence of biliary obstruction or some other explanation of the injury), 2 of which were in 600mg IV group (0.3%) and 1 in 1200mg group (0.2%). The MAH presented a summary of these 3 cases and outlined that all 3 can be out ruled as Hy's Law cases on the basis of more likely explications. The first case is in a 60-70 year-old subject in the risankizumab 600 mg IV treatment group who experienced ALT 159 U/L (> 3 × ULN), AST 136 U/L (> 3 × ULN), Grade 3 total bilirubin 91 µmol/L (≥ 3 × ULN), Grade 3 ALP (923 U/L, > 5 × ULN) and Grade 4 gamma glutamyl transferase (GGT) (1092 U/L, > 20 × ULN) on treatment day 28 following initiation for amoxicillin-clavulanate (Days 23 through 27). The patient was noted to be on concomitant methotrexate and isoniazid (for TB prophylaxis; Days 1 through 36). It would appear this case fits with hepatocellular-cholestatic injury associated with treatment of older men with amoxicillin-clavulanate and the companies assessment that this case was unlikely related to risankizumab is fully agreed.

Similarly, the case of AST: 156 U/L and total bilirubin 82 µmol/L in a 40-50 year-old subject in the risankizumab 1200 mg IV treatment group on study day 4 following treatment with paracetamol, hydrocodone/acetaminophen, ondansetron, piperacillin/tazobactam, morphine, and prochlorperazine for gastroenteritis is considered likely related to paracetamol toxicity especially in the context of a positive dechallenge when paracetamol was discontinued and maintained treatment with risankizumab.

The case presented in the 30-40 year-old subject in the risankizumab 600 mg IV group with a history of hepatic steatosis and concomitant azathioprine (100 mg beginning on Day –567, with dose change to 125 mg on Day –202 and continuing to Day 80) is considered less clear cut in terms of causality. The patient had their last dose of rizankizumab on day 29 and experienced Grade 4 ALT (49.15 – 61.6 × ULN), AST (22.5 – 30 × ULN), and bilirubin (2.13 – 2.2 × ULN) elevations (ALP was normal at 114.67 U/L) on day 82 in the context of being hospitalised for a rash on day 80. The causality assessment of the investigator was that the hepatic injury had a reasonable possibility of being related to study drug yet the MAH point to the delayed time to onset of liver enzyme elevation (7 weeks after last study drug dose) and the pattern of rapid resolution of liver enzymes in the setting of long half-life of study drug (28 to 29 days). The MAH clarified the duration of liver enzyme derangement for this patient and the issue was considered resolved.

The lack of meaningful difference between risankizumab arms and the withdrawal (placebo SC) arm in Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set in terms of the percentage of subjects with an ALT or AST ≥ 3 × ULN or ALT or AST ≥ 5 × ULN is noted, as is the fact that there were no possible Hy's law cases during this time. During the induction period there were no patients in the placebo group who experienced ALT and/or ALT elevations ≥ 3ULN accompanied by elevations in total bilirubin whereas in the risankizumab treatment groups there were 5 patients who experienced AST and or ALT elevations ≥ 3 ULN with TBL ≥1.5 ULN, 4 of which were in 600mg IV group (0.6%) and 1 in 1200mg group (0.2%). The MAH provided a summary of the 5 cases of AST and or ALT elevations ≥ 3 ULN with TBL ≥1.5 ULN which occurred during the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set on request. While there is an imbalance in cases falling into "Temple's Corollary" for risankizumab patients compared to placebo, the MAH's assessment of these 5

cases of AST and or ALT elevations ≥ 3 ULN with TBL ≥1.5 ULN following exposure to risankizumab is accepted. The cases included confounding factors had resolution of the liver test abnormalities or hepatic events with continued risankizumab therapy. There is insufficient data to conclude a causal relationship between risankizumab treatment and hepatotoxicity.

Hypersensitivity and infusion related reactions

No cases across the risankizumab Phase 3 CD development program were adjudicated as anaphylactic reaction in risankizumab-treated subjects.

While the rates of hypersensitivity reactions were similar between the risankizumab and placebo groups in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set, it is noted that 3 patients discontinued due to hypersensitivity infusion-related reactions. One subject in the risankizumab 1200 mg IV group had an infusion-related reaction of moderate severity on Day 6 and discontinued study drug. Another Subject, also in the risankizumab 1200 mg IV group, had an infusion-related reaction of moderate severity on Day 1 and discontinued study drug. Both events were considered by the investigator to have a reasonable possibility of being related to study drug. One subject in the risankizumab 600 mg IV group had an infusion-related reaction of mild severity on Day 36 and discontinued study drug.

During the induction period, the rates of ISRs (including infusion related reactions) were similar between the risankizumab 600 mg IV, risankizumab 1200 mg IV, and placebo IV groups.

During the 52-week maintenance period, the rate of ISRs were 9.5 E/100 PY, 13.8 E/100 PY, and 8.1 E/100 PY in the risankizumab 180 mg SC, risankizumab 360 mg SC, and withdrawal (placebo SC) arms, respectively. The rate in the any risankizumab treatment SC group of the All Treated Safety Analysis Set was 9.5 E/100 PY.

Serious hypersensitivity reactions are listed as an Important potential risk with and evaluation of the rates of serious hypersensitivity reactions is an objective of the proposed long term cohort study listed as additional pharmacovigilance activities.

In the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set the event rates of hypersensitivity reactions were similar across the treatment arms with 12.4 E/100 PY, 12.6 E/100 PY, and 11.8 E/100 PY reported for the risankizumab180 mg SC, risankizumab 360 mg SC, and withdrawal (placebo SC) arms, respectively. No serious hypersensitivity reactions were reported.

The rate of serious hypersensitivity reactions across any risankizumab exposure (<0.1 E/100 PY) was low.

Immunogenicity to risankizumab did not appear to have any clinically relevant impacts on hypersensitivity reactions, though the low number of patient's experiencing ADA precludes any conclusions in this regard.

Laboratory values and vital signs

Overall, it is agreed that the evaluation of mean changes over time and individual subject changes in haematology and clinical chemistry values, as well as potentially clinically significant abnormalities in hematology and clinical chemistry, does not reveal any dose-dependent patterns or any significant safety concerns with risankizumab treatment. The MAH outlines decreases in mean platelet counts were observed in the 12-Week Induction Safety Analysis Set and Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set). The plotted mean change in platelet values provided by the MAH demonstrates an effect on platelet levels (mean decrease of >40 10^9/L, which the MAH outlines, reflects the decreased systemic inflammation observed). In the excerpt from the analysis of Haematology in the SA1A population there are some very low minimum levels of platelets (highlighted

above). The MAH has confirmed that the findings of very low minimum levels of platelets from the SA1A population identified in the two induction studies were due to data entry errors and that no subjects reported clinically significant low platelet counts during the induction and maintenance studies.

In response to day 120 LOQ the MAH presented a comprehensive summary of the mean change from baseline of lipid following treatment with risankizumab. It is agreed that numerical increases in TC cholesterol and LDL-C in subjects with CD treated with risankizumab were unlikely to be clinically meaningful for the patients included in these trials (the mean values following risankizumab treatment for both total cholesterol (maximum 4.61 mmol/L) and LDL-C (maximum 2.47 mmol/L) at any evaluated time point were below the values of the 50th percentile in the general population) though there is perhaps some uncertainty with respect to use in patients with more borderline or elevated baselines levels.

It can be agreed that mean changes in vital sign parameters during risankizumab administration were not considered clinically meaningful.

Data pertaining to To-Be-Marketed Presentation On Body Delivery System

Clinical data for the proposed to-Be-Marketed Presentation On Body Delivery System comes from study M19-128. The primary objective of substudy 1 of this trial was to assess the relative bioavailability of risankizumab in the to-be-marketed 360 mg OBDS versus the 90 mg PFS used in the Phase 3 studies following a single SC administration at the dose of 360. As this was a single dose study, there is limited value in terms of characterising the safety of the drug device system. Of note, this study failed to demonstrate bioequivalence for Cmax.

It is noted that there were markedly different safety findings observed for the OBDS treatment groups compared to PFS groups in Study M19-128 (related ADRs reported in 0.8% of PFS treated patients compared to 27% of 360 mg OBDS and 23% of subjects reported TEAEs that were related to the OBDS for the 360 mg -Group 2). A fourfold increased frequency of injection site reactions was observed in OBDS treated patients (which occurred in 34.9% of the 360mg treated OBDS patients and 26.7% of the 180mg OBDS treated patients compared to 8.7% of the 360 mg PFS treated patients) when compared to PFS treated patients treated in M19-128 and when compared to patients treated with either 180mg or 360mg SC as part of 52-Week Maintenance in M16-000 Sub-Study 1. The nature of device related ADRS suggests local inflammatory reactions. However, the single dose design of M19-128 limits the interpretation in terms of clinical relevance of this apparent imbalance.

The MAH has demonstrated that there was no trend of increased adverse events with increasing exposure for both Cmax and Cavg metrics and bioequivalence was demonstrated between the OBDS and PFS for AUC. Therefore, the matter is no longer pursued in terms of extrapolation of safety from the findings from the Safety Analysis Sets.

The MAH presents a comparison of hypersensitivity reactions and injection site reactions by ADA status, though the very low number of patients who experienced ADAs or reactions covered by the Hypersensitivity SMQ and CMQ employed preclude any useful analysis. It is nonetheless noted that ADAs are twice as common in the OBDS 360mg group when compared to the PFS 360 mg group. In response to request from the CHMP the MAH showed that, while a higher anti-drug antibody (ADA) incidence was observed in the 360 mg OBDS group (13%) compared to the 90 mg/mL PFS group (6%), the treatment-emergent ADA incidences across all groups were within the range observed in previous Phase 1 single dose studies. There were minimal differences in risankizumab exposure between ADA-positive and ADA-negative groups and comparison of events between 360 OBDS and PFS treatment groups suggest the higher ADA incidence did not drive the difference in immune-related safety events (hypersensitivity reactions and injection-site reactions [ISRs]).

Non-drug study

F20-282 was a non-drug study which enrolled 36 subjects. The primary objective of this study was to gather data on the effectiveness of the OBDS adhesive using qualitative and quantitative measures. One subject out of 36 experiences and AE with reasonable possibility of being related (paresthesia and warmth resolved within 14 minutes and there was no finding or irritation on the adhesive skin assessment at 15- and 30- minutes post-removal). No safety issues are identified from this study.

Elderly

The MAH outlines that there was no clear pattern with respect to age for any category of AEs or ASIs in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set and that overall no new safety findings were identified with regard to risankizumab use and age. For the patients <18 years and those >18 to <65 years, in terms of frequency of TEAEs, the treatment arms are more favourable than the placebo IV group. It is noted though that for patients over 65 years, the number of all TEAEs, severe TEAEs and SAEs are greater for treatment arms than for the placebo IV. The low number of elderly patients exposed (n=32 patients for 600 mg IV and n=24 exposed to 1200 mg IV) add uncertainty to this finding. On request from the CHMP the MAH updated Section 5.2 of the SmPC to note that a total of 5 subjects with CD exposed to risankizumab were 75 years or older. The MAH outlines that greater portion of elderly patients experiencing an SAE (40% of patients ≥75 and 23.9% of patients aged 65-74 years versus 17% of patients <65 years) was largely driven by the imbalance of cardiac disorders and vascular disorders, which the MAH states are expected given the higher prevalence of cardiovascular diseases in the elderly population. The MAH has not explicitly confirmed if the frequencies of events observed are in line with the frequencies expected in the population. The MAH was invited to comment. The MAH was requested to discuss the need for a warning in section 4.4 in light of the limited exposure in the elderly and the potential for safety to differ in these patients due to factors such as increased susceptibility to adverse events (including important potential risks of serious infection). The MAH has discussed this and considers that 'Based on the SmPC guidelines for considerations for Special warnings and precautions for use, since there is no risk identified leading to a precaution for use or which warrants a specific warning for the elderly population, addition of this information to section 4.4 is not warranted.' This was considered acceptable.

Adolescents

The MAH outlines that in the ANY RZB group of the All Treated Safety Analysis Set, subjects under 18 years of age had a numerically higher AE rate overall than subjects above 18 years of age though they outline that these differences should be interpreted with caution give the very low numbers exposed. While the higher overall rates in TEAES are noted in this group, it is agreed that there is no specific pattern in terms of the nature of ARs. Nonetheless, the number of patients aged 16 years to 18 years (n=12 exposed to at least one dose, n=5 exposed to 52 weeks) are considered to be insufficient to have characterised age specific safety effects, if they did exit.

Race wright, geographic region

The MAH has presented safety data to assess differences in frequency and nature of AEs and ASE depending on intrinsic factors of weight, race and geographic region. Based on the totality of data presented it can be agreed that no new safety findings were identified with regard to risankizumab use and weight and race and that while there were differences observed in terms of frequency of some ASIs depending on geographic region, there was no definite trend in terms of the types of AEs, SAEs, AEs leading to discontinuation, or AEs in ASI categories by geographic region.

It is noted that race and body weight did not show a clinically relevant effect on risankizumab PK though Black or African American patients are underrepresented in the safety data set (n=39 in induction period, n=51 in all treated) which adds uncertainty in terms of the characterisation of safety

for these patient. The MAH argued the safety profile in Black or African American subjects was consistent with that observed in the overall population. This issue was not further pursued.

Inconsistent trend in the serious infection rates between Bio-IR and Non-Bio-IR subjects among the treatment groups were observed in the Placebo-Controlled 12-Week Induction Period Safety Analysis Set and All Treated Safety Analysis Set. It is agreed that the low number of events in general result in some uncertainty with respect to effects of Bio-IR status on safety but that the comparable rate of serious infections in the ANY risankizumab group in Bio-IR patients (3.7 E/100 PY) and Non-Bio-IR patients (3.1 E/100 PY) suggests there is no meaningful difference in the risk of experiencing serious infection between Bio-IR and Non-Bio-IR populations.

Pregnancy and lactation

Exposure of pregnant women during the CD development program is limited to 16 patients. At the time of reporting there were 6 ongoing pregnancies and the MAH was invited to provide outcome data if available for these births. The outcomes were reported as 3 live births, 2 spontaneous abortions, 1 elective termination due to foetal defect (foetal cystic hygroma and hydrops at 12 + weeks gestation where the investigator reported there were no obvious risk factors or family history relevant to this event, 3 elective terminations (no foetal defects) and 1 loss to follow up.

Use in pregnancy and lactation is listed as missing information and the MAH proposed a non-interventional cohort study 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. Post authorisation evaluation of safety in pregnancy is endorsed.

The MAH did not propose a change to the current SmPC wording relating to Pregnancy and lactation. This is considered acceptable.

## 2.6.10. Conclusions on the clinical safety

Risankizumab selectively binds with high affinity (< 29 pM) to the p19 subunit of human interleukin 23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor. Risankizumab is authorised for treatment of plaque psoriasis and psoriatic arthritis. Post-marketing exposure to risankizumab is estimated to be 87,387 patient treatment years (PTY) cumulatively as of 25 March 2021.

Data presented for the Crohn’s Disease development program did not demonstrate dose-dependent safety findings between the risankizumab IV induction doses studied (600 mg and 1200 mg) or the risankizumab SC maintenance doses studied (180 mg or 360 mg). Overall, no new safety concerns arise from the CD and the frequency and nature of ARs appear to be in line with the established safety profile. In particular, there is insufficient exposure in adolescents to support the indication initially sought (from 16 years of age) therefore the MAH was requested to amend the indication from 16 years of age to ≥18 years of age. This has been amended.

Uncertainties remain, relating to use in elderly patients and due to limited clinical experience with the OBDS which appears to have a greater potential for injection site reactions.

The CHMP considers the following measures necessary to address issues related to safety: two category 3 PASS studies are agreed for the CD indication on the long-term and pregnancy use.

## *2.7. Risk Management Plan*

### 2.7.1. Safety concerns

| **Summary of Safety Concerns** | |
|---|---|
| Important identified risks | None |
| Important potential risks | • MACE<br>• Serious infections<br>• Malignancies<br>• Serious hypersensitivity reactions |
| Missing information | • Use during pregnancy and lactation<br>• Long-term safety |

### 2.7.2. Pharmacovigilance plan

Table Part III.3: On-going and planned additional pharmacovigilance activities

| **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:<br>• overall malignancy excluding NMSC<br>• NMSC<br>• MACE (defined as a composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death)<br>• serious infections (incl. opportunistic infections)<br>• serious hypersensitivity reactions | 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<br>- Study Progress report: Q3 2023<br>- 1st Interim report of study results (incl. data up to December 2024): December 2026<br>- 2nd Interim report of study results (incl. data up to December 2028): December 2030<br>- End of data collection (incl. data up to December 2032): December 2033<br>- Final report of study results: December 2034 | Final study report: December 2 034 (Protocol v1.3 accepted by EMA Pharmacovi gilance Risk Assessment Committee (PRAC) as of 28 January 2021). |

| 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:<br>- 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).<br>- Evaluate and compare pregnancy outcomes (i.e., live birth, spontaneous abortion, elective abortion, stillbirth) among women exposed to risankizumab versus comparators during pregnancy<br>- 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<br>- Study progress: Q3 2024<br>- End of data collection: Q3 2029<br>- Final study report: Q3 2030 | Final study report: Q3 2030 (Protocol v1.3 accepted by EMA PRAC as of 25 February 2021). |
| **P23-653: Pregnancy Exposure and Outcomes for Women with Crohn's Disease Treated with Risankizumab/ Planned** | **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<br>- Start data collection period: Q2 2024<br>- Progress report: Q3 2027<br>- End data collection period: Q3 2031<br>- Final report: Q1 2032** | **Final report: Q1 2032** |

| Study Name/Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| 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<br>Missing information: long-term safety | Final Report Q2 2024 | Last subject last visit planned for November 2023 |
| **P23-654: Long-Term Comparative Cohort Study in Patients with Crohn's Disease in a Real World Setting/ Planned** | **The clinical trial program was not able to fully characterize the safety profile of risankizumab in the Crohn's disease population. 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, hypersensitivity reactions, and MACE.<br>Missing information: long-term safety** | **- Start data collection period: Q4 2024<br>- Interim report: Q4 2029<br>- End data collection period: Q4 2032<br>- 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<br>Missing information: long-term safety | Final report Q3 2025 | Last subject last visit planned for September 2 024.<br><br>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<br>Missing information: long-term safety | Final report Q3 2025 | Last subject last visit planned for May 2024.<br><br>Final report Q3 2025 |

## 2.7.3. Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern.

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| MACE | Routine risk minimization measures: No specific measures are required for patients receiving risankizumab; standard of care is adequate.<br><br>Other routine risk minimization measures: Prescription-only medicine<br><br>Additional risk minimization measures: None | Pharmacovigilance activities beyond adverse reaction reporting and signal detection.<br>Additional pharmacovigilance activities:<br>• Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting<br>• Risankizumab Psoriasis Long-Term Extension Study LIMMITLESS<br>• Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2<br>• **Long-Term Comparative Cohort Study in Patients with Crohn's Disease in a Real World Setting** |
| Serious infections | Routine risk minimization measures: Product labeling (SmPC Section 4.3, Contraindications and Section 4.4, Special warnings and precautions for use)<br><br>Other routine risk minimization measures: Prescription-only medicine<br><br>Additional risk minimization measures: None | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>Routine pharmacovigilance activities<br>Additional pharmacovigilance activities:<br>• Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting<br>• Risankizumab Psoriasis Long-Term Extension Study LIMMITLESS<br>• Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2<br>• **Long-Term Comparative Cohort Study in Patients with Crohn's Disease in a Real World Setting** |
| Malignancies | Routine risk minimization measures: No specific measures are required for patients receiving risankizumab; standard of care is adequate.<br><br>Other routine risk minimization measures: Prescription-only medicine<br><br>Additional risk minimization measures: None | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>Routine pharmacovigilance activities including follow-up questionnaire for malignancies<br><br>Additional pharmacovigilance activities:<br>• Long-Term Prospective Cohort Study in Psoriasis Patients in Real World Setting<br>• Risankizumab Psoriasis Long-Term Extension Study LIMMITLESS<br>• Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2<br>• **Long-Term Comparative Cohort Study in Patients with Crohn's Disease in a Real World Setting** |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| Serious hypersensitivity reactions | Routine risk minimization measures:<br>SmPC Section 4.3 indicates contraindication if known hypersensitivity to the active substance or to any of the excipients listed in SmPC Section 6.1.<br>SmPC Section 4.4 states if a serious hypersensitivity reaction occurs, administration of risankizumab should be discontinued immediately and appropriate therapy initiated.<br><br>Other routine risk minimization measures: Prescription-only medicine<br><br>Additional risk minimization measures: None | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>Routine pharmacovigilance activities<br>Additional pharmacovigilance activities:<br>• Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting<br>• Risankizumab Psoriasis Long-Term Extension Study LIMMITLESS<br>• Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2<br>• **Long-Term Comparative Cohort Study in Patients with Crohn's Disease in a Real World Setting** |
| Using during pregnancy and lactation | Routine risk minimization measures:<br>SmPC Section 4.6 Fertility, pregnancy, and lactation<br><br>Other routine risk minimization measures: Prescription-only medicine<br><br>Additional risk minimization measures: None | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>Routine pharmacovigilance activities including follow-up questionnaire<br>Additional pharmacovigilance activities:<br>• Pregnancy Exposure and Outcomes for Women with Psoriasis Treated with Risankizumab<br>• **Pregnancy Exposure and Outcomes for Women with Crohn's Disease Treated with Risankizumab** |
| Long-term safety | Routine risk minimization measures:<br>None.<br><br>Other routine risk minimization measures: Prescription-only medicine<br><br>Additional risk minimization measures: None | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>Routine pharmacovigilance activities<br>Additional pharmacovigilance activities:<br>• Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting<br>• Risankizumab Psoriasis Long-Term Extension Study LIMMITLESS<br>• Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2<br>• **Long-Term Comparative Cohort Study in Patients with Crohn's Disease in a Real World Setting** |

## 2.7.4. Conclusion

The CHMP considered that the risk management plan version 4.5 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

The user testing of the PL for risankizumab 360 mg solution for injection in a cartridge (SC) has been presented in a full report. A bridging report for the risankizumab 600 mg solution for injection (IV) as daughter PL to the 360 mg (SC) PL as parent PL has been provided.

The overall quality of the user tested PL is regarded as acceptable. The user testing of the PL is accepted as providing results that indicate it will meet patients' needs such that they will be able to locate important information within the PL, understand it and act upon it safely and correctly.

Bridging the risankizumab 600 mg solution for injection (IV) PL to the 360 mg (SC) PL is acceptable.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Crohn's disease (CD) encompasses a spectrum of clinical and pathological processes manifested by focal asymmetric, transmural, and occasionally granulomatous inflammation that can affect any segment of the gastrointestinal tract and presents with symptoms of fatigue, prolonged diarrhoea with or without gross bleeding, abdominal pain, weight loss, and fever. The disease can affect persons of any age, and its onset is most common in the second and third decades. Females are affected slightly more than males, and the risk for disease is higher in some ethnic groups. The incidence of CD worldwide has increased over the last three decades, particularly in newly industrialized countries. CD incidence is highest in North America and Europe, with estimates of 23.8 and 15 per 100,000 person-years in North America and Europe, respectively. The burden of CD also remains substantial, with the highest prevalence estimates in Europe (322 per 100,000 persons) and North America (319 per 100,000 persons).

The exact cause of CD is still unknown but is hypothesized to be the result of a dysregulated immune system in the context of a genetically susceptible individual. It is thought that a combination of a

patient's genetics, microbiome, immune response, and the environment result in an excessive and abnormal immune response in the gut that results in pathology seen in CD.

The aim of medical treatment in CD has been focused on controlling inflammation and reducing symptoms. In addition to improving symptoms, an emerging goal of therapy is to heal the gut mucosa. Resolution of intestinal ulcers and endoscopic remission have been associated with positive clinical benefits, including higher rates of clinical remission, fewer hospitalizations, and fewer abdominal surgeries. However, improvement of the appearance of the intestinal mucosa may be more difficult to achieve than symptomatic improvement alone.

With this line extension, the new presentations and strengths are indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.

### 3.1.2. Available therapies and unmet medical need

The current standard of medical care for Crohn’s disease involves anti-inflammatory therapeutic approaches, which include 5-aminosalicylic acid (5-ASA) compounds, corticosteroids, immune-modulators including azathioprine (AZA) or its active metabolite 6-mercaptopurine (6-MP) and methotrexate (MTX), and biologic agents including tumour necrosis factor (TNF) antagonist therapies, anti-IL and anti-integrin therapies. Even with combinations of the available therapeutic options, many patients do not attain clinical benefit, cannot tolerate the therapy, or lose response over time.

### 3.1.3. Main clinical studies

M15-991 and M16-006 (induction studies)

The 2 induction studies were randomized, double-blind, placebo-controlled evaluations of risankizumab (risankizumab 600 mg IV or 1200 mg IV at Weeks 0, 4, and 8) in subjects 16 years and older with moderately to severely active CD. Study M15-991 was designed to enrol subjects who had a documented inadequate response or intolerance to use of an approved biologic agent (Bio-IR). Study M16-006 was designed to enroll subjects who were Bio-IR or subjects who were Non-Bio-IR.

M16-000 Sub-Study 1 (maintenance)

This was a randomized, double blind, 52-Week placebo-controlled study to assess the safety and efficacy of RZB for maintenance in moderately to severely active CD. The trial population, emanating from the induction studies M15-991 and M16-001, included a mixed population of approximately 75% Bio-IR and 25% non-BIO IR subjects.

The co-primary endpoints for the 3 studies were discussed under scientific advice; they were accepted as reflecting clinically important targets for symptomatic, clinical and endoscopic response to long term treatment. Achieving endoscopic endpoints has been associated with improved long-term outcomes. The baseline demographic and disease characteristics were similar to those reported in other studies for the condition under study. The population is accepted as representative of patients with moderate to severe CD requiring induction followed by maintenance systemic therapy based on CD status, in the context of the proposed indication.

## *3.2. Favourable effects*

The results of the Phase 2 dose-finding Study M15-993 (1311.6) indicated a dose dependent response, supporting the higher RZB dose (600 mg) for induction and at least a dose of RZB 180 mg SC for

maintenance of effect but an upper dose-response limit, for induction or maintenance, was not deduced.

Induction Study M15-991

The proportion of subjects in clinical remission at Week 12 as per SF/APS criteria (co-primary endpoint) was greater in both the 600 mg IV (34.6) and 1200 mg IV (39.8%) RZB groups than in the placebo group (19.3%; $p < 0.001$ and $p < 0.001$, respectively).

The proportion of subjects in endoscopic response at Week 12 (co-primary endpoint US and OUS protocols) was greater in both the 600 mg IV (28.8%) and 1200 mg IV (34.2%) RZB groups than in the placebo group (11.2%; $p < 0.001$ and $p < 0.001$, respectively).

The proportion of subjects in clinical remission at Week 12 as per CDAI criteria (co-primary endpoint US) was greater in both the 600 mg IV (42.0%) and 1200 mg IV (40.3%) RZB groups than in the placebo group (19.8; $p < 0.001$ and $p < 0.001$, respectively).

Induction Study M16-006

The proportion of subjects in clinical remission at Week 12 as per SF/APS criteria (co-primary endpoint) was greater in both the 600 mg IV (43.5%) and 1200 mg IV (41.0%) RZB groups than in the placebo group (21.7%; $p < 0.001$ and $p < 0.001$, respectively).

The proportion of subjects in endoscopic response at Week 12 (co-primary endpoint US and OUS protocols) was greater in both the 600 mg IV (40.3%8%) and 1200 mg IV (32.1%) RZB groups than in the placebo group (12.0%; $p < 0.001$ and $p < 0.001$, respectively).

The proportion of subjects in clinical remission at Week 12 as per CDAI criteria (co-primary endpoint US) was greater in both the 600 mg IV (44.2%) and 1200 mg IV (41.6%) RZB groups than in the placebo group (24.6; $p < 0.001$ and $p < 0.001$, respectively).

Both induction studies met their co-primary endpoints.

Enhanced SF/APS clinical response and clinical remission were demonstrated to be significant as early as Week 4 in subjects treated with RZB and continued to improve through Week 12.

Additional secondary endpoints measured at Week 12 included the proportion of subjects with enhanced SF/APS clinical response (with ≥60% decrease in average daily SF and/or ≥35% decrease in average daily AP score and both not worse than Baseline, and/or clinical remission), endoscopic remission (SES-CD ≤4 and at least a 2 point reduction versus Baseline and no subscore greater than 1 in any individual variable), mucosal healing (SES-CD ulcerated surface subscore of 0 in subjects with a subscore of >1 at Baseline), a decrease of least 100 points in baseline CDAI, and a CDAI <150 at Week 12. In addition, rates of CD-related hospitalisations through Week 12 were lower in subjects treated with RZB compared to placebo in both induction studies.

In M16-006, a higher proportion of subjects treated with RZB achieved clinical remission per SF/SP score and endoscopic response compared to PBO in groups with and without prior biologic failure.

In addition, a higher portion of subjects also achieved clinical response measured by CDAI<150 compared to placebo

For M16-000, Sub-Study 1 (maintenance), overall, superiority of RZB 360mg compared to PBO for maintenance treatment was seen for the co-primary endpoints at week 52.

Patients in the RZB 360 mg arm demonstrated a statistically significant improvement in OUS (and US) co-primary data sets. However, the 180mg regimen failed to demonstrate superiority over placebo.

While not statistically significant, secondary endpoints on endoscopic results are supportive of the efficacy of RZB versus placebo. Evaluation of endoscopic endpoints (e.g., endoscopic remission, ulcer-free endoscopy, sustained endoscopic remission, deep remission) demonstrated a dose response, with the RZB 360 mg SC arm having higher efficacy than observed for the RZB 180 mg SC arm versus placebo.

**Subgroup analysis**

Results reported for subgroup analysis indicated higher efficacy in BIO-IR subjects compared to non-BIO-IR subjects, with somewhat mixed results for RZB 1200mg IV induction followed by RZB 180 mg SC maintenance versus RZB 600 mg IV induction versus RZB 360 mg SC maintenance regimens.

As supportive data, exposure-response analyses, conducted using Phase 3 maintenance data, show trends of higher response with the higher range exposures associated with RZB 360 mg SC q8w for most of the evaluated efficacy endpoints, particularly for the endoscopic endpoints.

## *3.3. Uncertainties and limitations about favourable effects*

The key uncertainty regarding the favourable effects observed in RZB treatment for CD concerns the fact that, important clinical secondary endpoints were of nominal significance only therefore no confirmatory conclusion on the statistical significance of the reported results can be made. However, it is accepted that the co primary endpoints for maintenance of effect was demonstrated for the higher dose, despite the fact that all thirteen secondary endpoints offer no confirmatory statistical evidence. Although this is consistent with the CHMP guideline on multiplicity adjustments, the guidelines do point out that even though type I error adjustment may not be required for secondary endpoints, it would not automatically mean the evidence may be totally reliable. However, it was felt, on balance, maintenance of clinical efficacy can be concluded for the 360mg dose.

While the drug substance and drug product used in the pivotal trials are the to-be-marketed forms of RZB, the to-be-marketed SC presentation is an on-person device has not been studied at Phase 3.

## *3.4. Unfavourable effects*

No new safety signals arise from the data presented for this extension of indication for Crohn's Disease and the frequency and nature of ARs appear to be in line with the established safety profile. No dose-dependent safety findings between the risankizumab IV induction doses studied (600 mg and 1200 mg) or the risankizumab SC maintenance doses studied (180 mg or 360 mg) were identified.

The most common AEs in the All Treated Safety Analysis include those associated with the underlying disease (Crohn's, anaemia and other GI disorders) as well as those AEs already recognised in section 4.8 of Skyrizi including nasopharyngitis (as upper RTI) and headache. The most frequent AEs considered by the investigators as related to study drug were generally comparable among the treatment and placebo patients across all 3 primary safety sets.

In the 52 week Maintenance Safety Set, a difference in the exposure adjusted rate for injection site reactions (8/100 PYs for placebo SC group compared to 13.8/100 PYs for 360mg sc) is noted, though this is already a listed ADR in section 4.8 of the SmPC with a frequency of common. A greater frequency of injection site reactions was observed in OBDS treated patients (which occurred in 34.9% of the 360mg treated OBDS patients and 26.7% of the 180mg OBDS treated patients in M19-128). The nature of device related ADRS suggests local inflammatory reactions. However, the single dose design of M19-128 limits the interpretation in terms of clinical relevance of this apparent imbalance.

There was a difference in the exposure adjusted rate for hepatic events (4/100 PYs for placebo SC group compared to 9/100 PYs for 360mg SC in the 52 week Maintenance Safety Set. While this imbalance is noted, it is also agreed that the majority of enzyme elevations were transient, resolved without any change to study drug, and were asymptomatic (i.e., not accompanied with abdominal pain, jaundice, etc.). The percentage of subjects with potentially clinically relevant laboratory values in ALT, AST, and total bilirubin values were low (< 3%). For subjects with aminotransferase elevations ≥ 5 × ULN, alternative etiologies or confounding factors were identified, or no clear causal association with risankizumab was determined. No confirmed Hy's law cases were identified. The majority of hepatic AEs were non-serious and related to liver enzyme increases, and 3 subjects (0.2%) in the ANY RZB group discontinued study drug due to a hepatic event.

In terms of important potential risks, there were 4 cases of MACE in patients exposed to 180mg risankizumab and 1 on the placebo group. It can be agreed that the events occurred in patients with CV risk factors or a history of CV disease. When compared to the reported rate of MACE for the patient population (0.82/100 PY) (Kristensen 2013), the exposure-adjusted incidence rate observed is not immediately concerning (0.2/100 PY). MACE is listed as an important potential risk in the Summary of Safety Concerns which is agreed, though it is noted that while the estimation of the rates of MACE is a focus of the cohort study for the Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting it does not appear to be included as an objective for the long-term Prospective Cohort Study in Patients with Crohn's Disease.

The most commonly reported infections in CD included upper respiratory tract infection (19.7%), skin infections (16.1%), and acute bronchitis (14.2%). In the Placebo-Controlled 12-Week Induction Period Safety Analysis Set a lower frequency of AEs in the infections and infestations SOC were reported in treatment arms compared to the placebo IV group (19.2% in 600mg IV and 18.3% in the 1200 mg group, compared to subjects in the placebo group 24.4%). Again, in the Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set the rate of infection-related AEs was lower in both risankizumab treatment arms (51.4 E/100 PY for 180 mg SC, 57.7 E/100 PY for 360 mg SC) compared to the rate in the withdrawal (placebo SC) arm (76.0 E/100 PY). It can be agreed from the data presented that no meaningful change in frequency or severity of the currently known ADR for upper respiratory tract infections was identified. Upper respiratory infections are currently listed 4.8 with a frequency of very common.

In terms of serious opportunistic infections, there were 3 SAEs of opportunistic infection in the ANY RZB group (a clinically asymptomatic case of disseminated histoplasmosis, severe SAE of bronchopulmonary aspergillosis that resolved after 62 days and did not lead to study drug discontinuation and a case CMV which resolved after 8 days and did not lead to study drug discontinuation) and 1 SAE in the placebo IV/SC (RZB-naïve) group (neutropenic sepsis). Overall, it is agreed that the data do not demonstrate a greater frequency of opportunistic infection and the incidence rate observed in All Treated Safety Analysis Set (0.5/100 PY in risankizumab patients is consistent with the background rate for this patient population based on published estimates (0.80/100 PY) (Kirchgesner 2018).

The rate of serious hypersensitivity reactions across any risankizumab exposure (<0.1 E/100 PY) was low.

Immunogenicity to risankizumab did not appear to have any clinically relevant impacts on hypersensitivity reactions, though the low number of patient’s experiencing ADA precludes any conclusions in this regard.

In general, though the incidence rate of malignancy was 0.5/100 PY for the ANY RZB group, which is not concerning in terms of the background rate reported for this patient population based on published estimates (1.33/100 PY).

## 3.5. Uncertainties and limitations about unfavourable effects

The number of adolescent patients included in the Crohn's disease program is minimal. A total of n=12 received at least one dose of risankizumab and n=5 adolescent patients went past 52 weeks in maintenance. From data presented, there also appears to minimal experience from outside of the Crohn's disease program in patients less than 18 years.

While the population pharmacokinetics analysis did not identify age as having an independent impact on risankizumab exposures, unexpected age-specific safety issues cannot be ruled out on the basis of data collected in adolescent patients. The MAH excluded adolescents who were not at Tanner stage 5 from the supporting clinical trials, though not all 16 year old adolescents will be Tanner stage 5. The MAH has outlined that all aspects of the Paediatric Investigational Plan are currently differed. As such, the MAH was requested to adjust the indication sought to ≥18 years. The MAH agreed to adjust the indication sought to ≥18 years.

There remain uncertainties due to limited clinical experience with the OBDS which appears to have a greater potential for injection site reactions, this could potentially result in lack of compliance, however safety and compliance will be monitored for in the post marketing phase.

A fourfold increased frequency of injection site reactions was observed in OBDS treated patients when compared to PFS treated patients treated in M19-128 and when compared to patients treated with either 180mg or 360mg SC as part of 52-Week Maintenance in M16-000 Sub-Study. Treatment emergent ADA incidence was also substantially higher in the 360 mg OBDS group relative to any other group in the CD clinical development programme. Exposure in elderly patients is limited with n=32 patients aged >65 years in The Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set and just n=5 aged >75 years. Given the potential for safety to differ in these patients due to factors such as increased susceptibility to adverse events (including important potential risks of serious infection), polypharmacy and other physiological differences, there is concern in terms of sufficiency of characterisation of safety in these patients. Especially as the data presented do appear to show some differences in observed safety findings, however the low number of elderly patients exposed (n=32 patients for 600 mg IV and n=24 exposed to 1200 mg IV) add uncertainty to this finding.

It is noted that race did not show a clinically relevant effect on risankizumab PK (see section 2 of this AR for discussion) though Black or African American patients are underrepresented in the safety data set (n=39 in induction period, n=51 in all treated) which adds uncertainty in terms of the characterisation of safety for these patients.

## 3.6. Effects Table

*Table 92 Effects Table for Skyrizi (risankizumab in CD (data cut-off: 15 May 2021).*

| Effect | Short Description | Unit | Risankizumab | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |

| Effect | Short Description | Unit | Risankizumab | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Induction M15-991 (12 Weeks)**<br><br>SF/APS clinical remission (OUS) | Av. daily SF ≤2.8, +APS ≤1 and ≤ Baseline | % | **600 mg IV Q4w**<br><br>66/191 (34.6%) | **PBO**<br><br>36/187 (19.3%) | Primary endpoint met<br>P value ≤ 0.01 | Study M15-991 CSR |
| Endoscopic response at Week 12 (US and OUS) | Decrease in SES-CD > 50% from Baseline Induction (if isolated ileal disease + an SES-CD of 4 = ≥2 point reduction) | % | 55/191 (28.8%) | 21/187 (11.2%) | Primary endpoint met<br>P value < 0.001 | " |
| CDAI clinical remission at Week 12 (US) | CDAI < 150 | % | 80/191 (42.0%) | 37/187 (19.8%) | Primary endpoint met<br>P value < 0.001 | " |
| **Induction M16-006 (12 weeks)**<br><br>SF/APS clinical remission (OUS) | Av. daily SF ≤2.8, +APS ≤1 and ≤ Baseline | % | 146/336 (43.5%) | 38/175 (21.7%) | Primary endpoint met<br>P value < 0.001 | Study M16-006 CSR |
| Endoscopic response at Week 12 (US and OUS) | Decrease in SES-CD > 50% from Baseline Induction (if isolated ileal disease + an SES-CD of 4 = ≥2 point reduction) | % | 135/336 (40.3%) | 21/175 (12.0%) | Primary endpoint met<br>P value < 0.001 | " |
| CDAI clinical remission at Week 12 (US) | Proportion of subjects with CDAI < 150 | % | 152/336 (45.2%) | 43/175 (24.6) | Primary endpoint met<br>P value < 0.001 | " |
| **Secondary Endpoints**<br><br>CDAI remission at Week 12 | Proportion of subjects with CDAI < 150 | % | **600 mg IV Q8W**<br><br>Study M15-991 80/191 (42.0%)<br><br>Study M16-006 152/336 (45.2%) | **PBO**<br><br>37/187 (19.8%)<br><br>43/175 (24.6%) | Secondary endpoint met<br>P value < 0.001<br><br>P value < 0.001 | Study M15-991 CSR and Study M16-006 CSR |

| Effect | Short Description | Unit | Risankizumab | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| CDAI clinical response at Week 4 | Proportion of subjects with reduction of CDAI ≥ 100 points from baseline | % | Study M15-991 70/191 (36.6%)<br><br>Study M16-006 137/336 (40.8%) | 39/187 (20.9%)<br><br>44/175 (25.2%) | Secondary endpoint met<br><br>P value ≤ 0.01<br><br>P value < 0.001 | " |
| SF/APS clinical remission at Week 4 | Proportion of subjects with average daily SF ≤ 2.8 and not worse than Baseline AND average daily APS ≤ 1 and not worse than Baseline | | Study M15-991 33/191 (17.3%)<br><br>Study M16-006 71/336 (21%) | 15/187 (8.0%)<br><br>16/175 (9.1%) | Secondary endpoint met<br><br>P value ≤ 0.01<br><br>P value < 0.001 | " |
| CDAI clinical response at Week 12 | Proportion of subjects with reduction of CDAI ≥ 100 points from baseline | | Study M15-991 114/191 (59.5%)<br><br>Study M16-006 201/336 (59.7%) | 56/187 (30.0%)<br><br>64/175 (36.7%) | Secondary endpoint met<br><br>P value < 0.001<br><br>P value < 0.001 | Study M15-991 CSR and Study M16-006 CSR |
| Endoscopic remission at Week 12 | Proportion of subjects with SES-CD ≤ 4 and at least a 2-point reduction versus Baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer | | Study M15-991 37/191 (19.4%)<br><br>Study M16-006 81/336 (24.2%) | 8/187 (4.3%)<br><br>16/175 (9.1%) | Secondary endpoint met<br><br>P value < 0.001<br><br>P value < 0.001 | " |
| **Maintenance (52 Weeks)**<br><br>Clinical remission (SF/APS) | Av. daily SF ≤2.8, +APS ≤1 and ≤ Baseline | % | **360 mg SC Q8w**<br><br>73/141 (51.8%) | 65/164 (39.6%) | Primary endpoint met. p=0.004 | M16-000 Sub-Study 1 CSR |

| Effect | Short Description | Unit | Risankizumab | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| Endoscopic response | Decrease in SES-CD > 50% from Baseline Induction (if isolated ileal disease + an SES-CD of 4 = ≥2 point reduction) | % | 66/141 (46.5%) | 36/164 (22.0%) | Primary endpoint met. P=< 0.001 | " |
| **Secondary Endpoints**<br><br>Clinical Remission CDAI | CDAI <150 | | 74/141 (52.2%) | 67/164 (40.9%) | NS Secondary endpoints | M16-000 Sub Study 1 CSR |
| Maintenance of clinical remission (SF/APS) | Remission at Week 0 + Week 52 | | 50/72 (69.2%) | 46/91 (50.5%) | " | " |
| Ulcer free endoscopy | | | 43/141 (30.5%) | 17/162 (10.5%) | " | " |
| Endoscopic remission | SES-CD ≤ 4 + ≥ 2 point reduction vs baseline + no subscore > 1 in any single variable | % | 55/141 (39.1%) | 21/164 (12.8%) | " | " |
| CS free clinical remission | | % | 14/42 (34.0%) | 12/51 (23.5%) | " | " |
| CDAI clinical response | Reduction ≥100 | % | 87/141 (61.6%) | 79/164 (48.2%) | " | " |
| IBDQ | 32 item validated questionnaire<br><br>LS Mean Change from Baseline [95% CI] | | 62.2 [57.4, 67.0] | 56.4 [51.3, 61.6] | | |
| **Unfavourable Effects** | | | | | | |
| **Placebo-Controlled 12-Week Induction Period Safety Analysis Set** | | % and E/100 PY | **600 mg IV** | **Placebo IV** | **Treatment Comparison [95% CI] for n (%) Differences**<br><br>RZB 600 mg IV - PBO IV | |
| All TEAEs | | | 54.7%, 569.5 E/100 PY | 63.4%, 744.9 E/100 PY | -7.5 [-13.7, -1.3] | |
| Severe TEAEs | | | 5.2% 26.3 E/100 PY | 12.0%, 79.1 E/100 PY | -6.2 [-9.7, -2.8] | |

| Effect | Short Description | Unit | Risankizumab | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| Serious TEAEs | | | 6.6.0%, 33.8 E/100 PY | 15.5% 97.8 E/100 PY | -8.5 [-12.5, -4.6] | |
| TEAEs leading to discontinuation of study drug | | | 2.1% 10E/100 PY | 8.6% 43.4 E/100 PY | -8.5 [-12.5, -4.6] | |
| All deaths | | | 0 | 0.5% 1.7 E/100 PY | -0.6 [-1.5, 0.2] | |
| **Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set** | | % and E/100 PY | **360 SC** | **Placebo SC** | **Treatment Comparison [95% CI] for n (%) Differences**<br><br>RZB 360 mg SC - PBO SC | |
| All TEAEs | | | 72.1%, 283.5 E/100 PY | 73.4%, 339.7 E/100 PY | -1.3 (-10.5, 7.9) | |
| Severe TEAEs | | | 11.7% 15.6 E/100 PY | 12.5%, 20.6 E/100 PY | -0.8 (-7.5, 5.9) | |
| Serious TEAEs | | | 13.4%, 21 E/100 PY | 12.5% 19.3E/100 PY | 0.9 (-6.0, 7.8) | |
| TEAEs leading to discontinuation of study drug | | | 3.4% 4.8 E/100 PY | 3.3% 3.7 E/100 PY | 0.1 (-3.6, 3.8) | |
| All deaths | | | 0 | 0 | 0 | |

Abbreviations: NS – not statistically significant.

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The data from the induction studies show a clear benefit for patients treated with RZB at 12 weeks.

Additional improvements in key measures of clinical and endoscopic importance have also been demonstrated by the MAH in the induction studies.

Statistical and clinically relevant results were demonstrated for the maintenance effect for the co primary endpoints. The secondary endpoints were nominally significant due to the testing strategy however they are considered as providing supportive evidence of efficacy for the 360 mg SC formulation.

No new important risks were identified and no significant differences to the established safety profile were identified during the Crohn's disease program information. There is currently a degree of uncertainty regarding the characterisation of the safety profile however this will be further clarified from post marketing data.

### 3.7.2. Balance of benefits and risks

The CHMP considers that the new presentations, strengths and route of administration for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy, or if such therapies are not advisable is approvable.

## *3.8. Conclusions*

The overall benefit/risk balance of Skyrizi new strength (360mg and 600mg), new pharmaceutical form (concentrate for solution for infusion) and new route of administration (intravenous use) for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy is positive, subject to the conditions stated in section 'Recommendations'.

# 4. Recommendations

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Skyrizi new strength (360mg and 600mg), new pharmaceutical form (concentrate for solution for infusion) and new route of administration (intravenous use) is favourable in the following indication(s):

Skyrizi is indicated for the treatment of adult patients with moderately to severely active Crohn's disease 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).

***Conditions and requirements of the marketing authorisation***

**Periodic Safety Update Reports**

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

***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.