CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761262Orig1s000

INTEGRATED REVIEW

Integrated Review (1 of 2)

Table 1. Administrative Application Information

Category	Application Information
Application type	BLA
Application number(s)	BLA 761262
Priority or standard	Priority
Submit date(s)	9/16/2021
Received date(s)	9/16/2021
PDUFA goal date	6/16/2022
Division/office	Division of Gastroenterology (DG)
Review completion date	6/16/2022
Established/proper name	BI 655066 (Risankizumab-rzaa)
(Proposed) proprietary name	Skyrizi
Pharmacologic class	IL-23 inhibitor
Code name	BI 655066
Applicant	AbbVie, Inc.
Dosage form(s)/formulation(s)	Solution for intravenous infusion
Dosing regimen	600 mg at Week 0, Week 4, and Week 8
Applicant proposed indication(s)/ population(s)	Crohn’s disease
Proposed SNOMED indication	34000006 Crohn's disease (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	600 mg IV at Week 0, 4 and 8
Approved indication(s)/ population(s) (if applicable)	Moderately to severely active Crohn’s disease
Approved SNOMED term for indication (if applicable)	34000006 Crohn's disease (disorder)

Integrated Review (2 of 2)

Table 2. Administrative Application Information

Category	Application Information
Application type	Efficacy Supplement
Application number(s)	BLA 761105 / S-016
Priority or standard	Priority
Submit date(s)	9/16/2021
Received date(s)	9/16/2021
PDUFA goal date	6/16/2022
Division/office	Division of Gastroenterology (DG)
Review completion date	6/16/2022
Established/proper name	Risankizumab-rzaa
(Proposed) proprietary name	Skyrizi
Pharmacologic class	IL-23 inhibitor
Code name	BI 655066
Applicant	AbbVie, Inc.
Dosage form(s)/formulation(s)	Solution for subcutaneous injection
Dosing regimen	360 mg at Week 12, and every 8 weeks thereafter
Applicant proposed indication(s)/ population(s)	Crohn's disease
Proposed SNOMED indication	34000006 Crohn's disease (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	360 mg SC at Week 12, and every 8 weeks thereafter
Approved indication(s)/ population(s) (if applicable)	Moderately to severely active Crohn's disease
Approved SNOMED term for indication (if applicable)	34000006 Crohn's disease (disorder)

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Glossary

ADA	antidrug antibody
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	abdominal pain
APS	abdominal pain score
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BE	bioequivalence
Bio-IR	inadequate response to prior biologic therapy
BLA	biologics license application
BMI	body mass index
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CDC	complement-dependent cytotoxicity
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DB	double-blind
DDLO	Division of Diabetes, Lipid Disorders, and Obesity
DG	Division of Gastroenterology
DILI	drug-induced liver injury
DPMH	Division of Pediatric and Maternal Health
DPV	Division of Pharmacovigilance
ECL	electrochemiluminescence
EIM	extra-intestinal manifestation
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAERS	FDA Adverse Event Reporting System
FCP	fecal calprotectin
FDA	U.S. Food and Drug Administration
GD	gestation day

GI	gastrointestinal
HDL-C	high-density lipoprotein cholesterol
HF	human factor
IFU	Instructions for Use
IgG	immunoglobulin G
IL	interleukin
IND	investigational new drug
IP	intraperitoneally
IR	inadequate response
ISR	injection site reaction
ISS1	primary induction safety database
ITT	intent-to-treat
ITT1A	intent-to-treat primary analysis population
IV	intravenous
LDL-C	low-density lipoprotein cholesterol
LTE	long-term extension
MACE	major adverse cardiovascular events
NISS	Newly Identified Safety Signal
NOAEL	no observed adverse effect level
Non-Bio-IR	no prior biologic therapy
OBDS	on-body delivery system
OBI	on-body injector
OL	open-label
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSIS	Office of Study Integrity and Surveillance
RLHS	real life handing study
PFS	prefilled syringe
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	principal investigator
PD	pharmacodynamic
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PRO	patient-reported outcome
PT	preferred term
Q8W	every 8 weeks
RA	rheumatoid arthritis
SAE	serious adverse event
sBLA	supplemental BLA
SC	subcutaneous
SCID	severe combined immunodeficiency
SD	standard deviation
SES-CD	Simple Endoscopic Score for Crohn’s Disease

SF	stool frequency
SIAQ	Self-Injection Assessment Questionnaire
TBM	to-be-marketed
TEAE	treatment-emergent adverse event
TG	triglyceride
T_{max}	time to maximum concentration
TNF	tumor necrosis factor
ULN	upper limit of normal
VTE	venous thromboembolism

I. Executive Summary

1. Summary of Regulatory Action

AbbVie (Applicant) submitted an original biologics license application (BLA) for the intravenous (IV) induction dosing regimen, and an efficacy supplemental BLA for the subcutaneous (SC) maintenance dosing regimen administered via an on-body injector (OBI) with prefilled cartridge (PFC) for Skyrizi (risankizumab), seeking approval for a proposed indication of "treatment of moderately to severely active Crohn's disease in patients 16 years and older." The BLA and supplemental BLA (sBLA) were reviewed by the multidisciplinary team, and each discipline recommended approval.

The Applicant submitted the results of two phase 3 induction studies (M15-991 and M16-006) and one phase 3 maintenance study (M16-000 Substudy 1) that formed the basis of the substantial evidence of effectiveness. A clinically meaningful and statistically significant benefit was demonstrated on the coprimary endpoints, and multiple key secondary endpoints supported the primary efficacy results in each trial. The safety profile was generally consistent with known adverse reactions for drugs in the class and with the safety profile of risankizumab in other approved indications, with one notable exception of a new hepatotoxicity risk associated with the IV induction dosing regimen for Crohn's disease (CD).

The overall benefit-risk assessment supports approval, and supports the indication originally proposed by the Applicant (described in the Benefit-Risk Framework below). Identified risk will be mitigated through labeling and further monitored through enhanced pharmacovigilance postapproval.

2. Benefit–Risk Assessment

2.1. Benefit–Risk Framework

Table 3. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CD is a chronic, intermittent, relapsing IBD that can affect any portion of the GI tract, and is characterized by transmural infiltration of lymphocytes and macrophages, granulomas, fissuring ulceration, and submucosal fibrosis. • The pathogenesis of CD is thought to be multifactorial including, but not limited to, genetic disposition, triggering event, autoimmune dysregulation, etc. • Clinical manifestations of disease vary and often reflect the site of ongoing GI inflammation including abdominal pain, diarrhea, weight loss, and hematochezia. Extra-intestinal manifestations may include dermatologic (e.g., erythema nodosum, pyoderma gangrenosum), ophthalmologic (e.g., uveitis), orthopedic (e.g., arthralgias, arthritis) involvements. Long-term sequelae due to malabsorption include anemia, poor bone mineral density, nutritional deficiencies and, in pediatrics, growth failure. Some patients may have chronic poor health due to active bowel inflammation, strictures (narrowing) and fistulae between diseased parts of the bowel and adjacent structures, and abscesses. • Assessment of a patient with concern for new-onset CD requires a comprehensive assessment including clinical, radiologic and endoscopic evaluation. Diagnosis of CD is confirmed based on histologic findings obtained during endoscopy. After diagnosis, treatment response is assessed with periodic clinical and endoscopic assessments. Per standard of care, the goal of CD treatment is endoscopic and histologic healing, as ongoing inflammation is linked to long-term sequelae of disease. However, even in CD patients who achieve endoscopic remission, clinical symptoms, such as abdominal pain, may persist due to comorbid condition or intercurrent events.	• CD is a chronic, relapsing disease of the GI tract. If not well controlled, CD can result in significant morbidity and mortality. Patients may experience symptoms that are severe, debilitating, and may lead to major complications or require surgical intervention.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• The overall goal in the treatment and management of CD is to "induce" and "maintain" remission. Current standard of care requires treatment individualization based on disease characteristics including, but not limited to, severity of disease, disease location, and presence of long-term sequelae of disease. • Therapeutic options for treatment include 5-ASA (e.g., mesalamine), corticosteroids, antibiotics, immunomodulators (e.g., AZA, 6-MP, and MTX), biologic therapies (e.g., TNFα blockers, IL-12/23 inhibitors, α4β7 integrin inhibitor), and, in refractory cases, calcineurin inhibitors (e.g., tacrolimus). Corticosteroids are not recommended for long-term use given the toxicities associated with chronic steroid use. Surgical management may be required for patients who fail available therapies or develop complications not amenable to medical management. • Notably, CD patients require long-term maintenance therapy. A subset of patients may be nonresponsive to therapy. Additionally, patients who respond to treatment initially are at risk of developing intolerance to therapy, loss of response to therapy, or adverse reactions that may require discontinuation of therapy.	• Risankizumab is the second anti -IL-23 biologic, following ustekinumab (IL-12/23 inhibitor), proposed for the treatment of moderately to severely active CD. • IL-23 inhibition offers a new mechanism of action as compared to other approved therapies. Despite availability of several therapeutic options for CD patients, many patients require discontinuation of CD treatment due to loss of response, inadequate response, adverse reactions, etc. Thus, there is a need for additional therapies targeting new mechanisms of action to treat CD.
Benefit	• Efficacy of risankizumab was demonstrated in two 12-week induction trials (M16-006 and M15-991), and one 52-week randomized withdrawal maintenance trial (M16-000). • In the induction trials, 1419 subjects with moderately to severely active CD (defined as CDAI score of 220-450 and SES-CD of ≥6) were enrolled, among whom 483 subjects had previously demonstrated inadequate response or intolerance to one or more biologic therapies. Subjects were randomized to receive either intravenous risankizumab 1200 mg, 600 mg, or placebo. • Efficacy was demonstrated on the coprimary endpoints of clinical remission (defined as CDAI <150) at Week 12 and endoscopic response (defined as 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]) at Week 12 for both induction dosages. • The estimated difference in CDAI clinical remission rates between risankizumab and placebo ranged from 16.7% to 22.1% (p<0.001), while the estimated difference in endoscopic response rates between risankizumab and placebo ranged from 17.6% to 28.3% (p<0.001).	• Trials M16-006, M15-991, and M16-000 provided evidence for the effectiveness of risankizumab compared to placebo for both achieving clinical remission (defined as CDAI score of <150) and endoscopic response (defined as a ≥50% change in SES-CD score from baseline) in subjects with moderately to severely active CD. • Efficacy was demonstrated in the induction trials for both the 600 mg and 1200 mg administered at Weeks 0, 4 and 8. The coprimary endpoints of clinical remission and endoscopic response at Week 12 after 3 IV induction doses demonstrated statistical significance. • The higher risankizumab induction dosage of 1200 mg did not demonstrate additional treatment benefit over the 600 mg dosage.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The adjusted treatment difference between risankizumab and placebo were statistically significant for all the multiplicity controlled secondary endpoints for both induction dosages, except for no draining fistulas in subjects with draining fistulas (refer to Section 6.2.1.3). • Subjects who achieved clinical response (defined as ≥30% decrease in average daily SF and/or ≥30% decrease in average daily APS, and both not worse than Baseline) at Week 12 of the induction trials were rerandomized into the maintenance trial to receive 180 mg, 360 mg or placebo for 52 weeks. A total of 440 subjects randomized into the maintenance trial who met the clinical response definition of reduction of CDAI ≥100 points from baseline at the end of induction trial comprised the primary population for efficacy analyses. • Efficacy was demonstrated in the maintenance trial on the coprimary endpoints of clinical remission (defined as CDAI <150) at Week 52 and endoscopic response (defined as 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]) at Week 52 for both maintenance dosages. • The adjusted differences from placebo in CDAI clinical remission rates were 16.9% and 14.2% for the 180-mg and 360-mg doses, respectively. The adjusted differences in endoscopic response rates were 29.9% and 30.6% for the 180-mg and 360-mg doses, respectively. • The first (SF/APS clinical remission) and second (maintenance of CDAI clinical remission) ranked multiplicity-controlled secondary endpoints did not show a statistically significant difference between treatment and placebo arms for 180-mg and 360-mg doses, respectively. Therefore, no other subsequently ranked secondary endpoints could be tested. • While endoscopic remission failed on the multiplicity-controlled testing hierarchy, numerically higher efficacy rates for endoscopic remission at Week 52, in both doses compared to placebo and 360 mg higher than 180 mg, was demonstrated.	• Efficacy was demonstrated in the maintenance trial for both the 180 mg and 360 mg up to 52 weeks. The coprimary endpoints of clinical remission and endoscopic response at Week 52 also demonstrated statistical significance in the overall patient population who achieved clinical response at Week 0 of maintenance. • The equivalent efficacy results of both maintenance dosages support approval of both maintenance doses. While the 180 mg regimen may be considered the lowest effective dosage, the 360 mg dosage may also be appropriate in some patients with more severe or refractory disease. – Induction and maintenance of endoscopic remission is critical for treatment of patients with CD as endoscopic remission reflects quiescent disease and is linked to improved long-term outcomes and decreased morbidity in this patient population. – While the efficacy supplement (sBLA761105-S018) submission containing the complete CMC package is under review to support the 180 mg presentation, 360 mg maintenance dosage will be approved for marketing to provide an additional safe and effective treatment option for patients with moderately to severely active CD, many of whom have refractory disease despite currently available therapies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety profile of induction therapy and maintenance therapy with risankizumab was characterized based on a comprehensive evaluation of the phase 2 and 3 CD placebo-controlled analysis set. – The primary induction safety database included subjects who received risankizumab 1200 mg IV, 600 mg IV, or placebo during the 12-week, placebo-controlled period in studies M16-006, M15-991, and M15-993. – The primary maintenance safety database included subjects who received risankizumab 360 mg SC, 180 mg SC, or placebo in the 52-week, placebo-controlled period of study M16-000 Substudy 1. • The currently approved label contains warnings for hypersensitivity reactions, including anaphylaxis, infections, tuberculosis, and avoidance of live vaccines. • The safety profile of risankizumab in CD was similar to the safety profile previously demonstrated in the plaque psoriasis and psoriatic arthritis populations, except for the following newly identified risks: – **Drug-Induced Liver Injury (DILI) -** One subject treated with risankizumab 600 mg IV induction required hospitalization for a serious adverse reaction of DILI. The subject had normal liver enzymes at baseline, butdeveloped a rash and elevations in liver enzymes (ALT increased to 62-fold ULN, AST increased to 30-fold ULN, and bilirubin increased to 2-fold ULN) by Day 80. Risankizumab was discontinued and methylprednisolone was administered on Day 90 for 5 days. All laboratory elevations decreased to <1 times ULN by Day 150. – Dyslipidemia - Increases in total cholesterol and LDL-C levels were observed during both the induction and maintenance trials. Although the trials were underpowered (based on trial duration and sample size) to reliably assess the association of lipid changes with MACE, no MACE events attributed to risankizumab exposure were reported in the safety database to date. • In general, a higher number of SAEs, TEAEs and AEs leading to study discontinuation were reported in the placebo arm compared to either risankizumab treatment arms in all studies. • Within the maintenance trial, the safety profile for 180 mg versus 360 mg were generally and numerically comparable.	• The overall safety profile supports approval of both maintenance doses. • The observed hepatotoxicity during the induction trial may be attributed to the higher dosage and different route of administration (IV instead of SC) for induction regimen in CD. The one subject with DILI recovered with normalization of liver enzymes after a course of steroid therapy. In the maintenance safety population, subjects who experienced mild elevations of liver enzymes showed evidence of improvement or normalization in liver enzymes despite continuation of study therapy and did not require medical therapy. • The observed dyslipidemia effect did not appear to be dose-dependent. In addition, across all the risankizumab treatment groups, the lipid parameters remained close to or below normal range. • The known and anticipated risks will be managed through labeling, including the following: – The lowest effective IV induction dosing of 600 mg will be labeled. – The indication will be limited to adults with moderately to severely active CD as available data are insufficient to label down to 16 years of age. – Warnings and Precautions section will be updated to include “Hepatotoxicity in Treatment of Crohn’s Disease” to inform patients and prescribers of the risk of hepatotoxicity, particularly during the induction period.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The proposed OBDS was not evaluated in the phase 3 maintenance trial (M16-000), but only in the BE study (M19-128) which reported 8.5% of subjects experiencing dosing failures (wet injections) and an increased risk of injection site reaction (i.e., injection site reaction in 17% and 19% of subjects administered 180 mg and 360 mg dosages, respectively, using the OBDS compared to 0% in subjects using the prefilled syringes). – The root-cause analyses of the dosing failures in the BE study identified potential manufacturing and use error issues with the OBDS. – The same complaints were not observed in the HF study. However, the HF study was conducted in parallel to the BE study, and not all revisions to the IFU were evaluated in the HF study – Interim data from a RLHS conducted in patients with CD over 24 weeks (3 dose administrations) were reassuring as only 5 of 46 subjects reported "minor hazards" related to the OBDS. There were no injection site reactions reported in the RLHS. – Another approved combination product, Repatha (Amgen 2021), utilizes (b) (4) OBDS device, which revealed similar use errors as those seen in the risankizumab BE study. Postmarket data search of Repatha product provided further reassurance of the safety of the proposed OBDS for risankizumab. • (b) (4) – The primary safety database of patients with CD did not reveal a risk of VTE associated with risankizumab exposure. – Postmarket data search to date yielded a small number of cases, but there were insufficient case-level information to determine a true signal of VTE for risankizumab-rzaa exposure. • The size of the safety database was inadequate to fully assess dose-dependence of some adverse events of special interest (including MACE, malignancy, and thrombosis) as these events occur infrequently. • There is insufficient data to inform women of risankizumab use during lactation and pregnancy. • Applicant enrolled pediatric patients 16 to <18 years of age in the phase 3 trials; however, only <1% of the subjects in the submitted safety database	– Section 6.1 Clinical Trial experience will include "Lipid Elevations" as a Specific Adverse Drug Reactions. – The IFU will contain additional diagrams and text instructions regarding the audible "click" for activation of button on the delivery device for the subcutaneous maintenance doses. • The following postapproval safety surveillance strategies and commitments will be issued: – A prospective DILI registry in adult patients with CD. – Enhanced pharmacovigilance for DILI with expedited reportes of liver injury in any indication using detailed questionnaire for follow-up for the reported cases. – OBDS device-related PMC to conduct verification testing related to the audible feedback function of the device – Lactation study and pregnancy registry, both prospective and retrospective studies, as PMRs under 505(o)3 – Pediatric PMC to conduct both a safety and efficacy trial as well as a long-term extension study to evaluate the long-term safety of Skyrizi in pediatric patients 2 to 17 years of age with moderately to severely active CD. – Drug drug interaction PMC to conduct a clinical trial to assess whether Skyrizi alters the metabolism of pharmacokinetics of CYP substrates in patients with CD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	were in the pediatric age group, and the safety data submitted to date are not generalizable to pediatric CD patients 16 to <18 years of age. Only one subject aged 16 to <18 received each TBM dosage. In addition, no patients less than 18 years of age were enrolled in the RLHS evaluating the proposed TBM OBDS device for maintenance therapy administration. • Drug interaction information included in labeling for the plaque psoriasis indication may not be directly applicable for the proposed CD indication because of the differences in two populations, such as inflammatory burden and the proposed higher dosage for CD than the approved dosage for plaque psoriasis and psoriatic arthritis (150 mg SC).	

Abbreviations: 5-ASA, 5-aminosalicylic acid; AE, adverse event; ALT, alanine aminotransferase; APS, abdominal pain score; AZA, azathioprine; BE, bioequivalence; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CMC, chemistry, manufacturing, and controls; CYP, cytochrome p450; DILI, drug-induced liver injury; GI, gastrointestinal; HF, human factor; IBD, inflammatory bowel disease; IFU, instructions for use; IL-23, interleukin 23; IV, intravenous; LDL-C, lower-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MTX, methotrexate; OBDS, on-body delivery system; PMC, postmarketing commitment; PMR, postmarketing requirement; RLHS, real life handling study; SAE, serious adverse event; 6-MP, 6-mercaptopurine; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; TBM, to-be-marketed; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; VTE, venous thromboembolism

2.2. Conclusions Regarding Benefit-Risk

Moderately to severely active CD is a serious disease with associated morbidity and mortality when inadequately treated. Although multiple approved therapies are available, a sizeable portion of these patients are at risk for inadequate response or intolerance to available therapies and would benefit from the availability of additional efficacious therapeutic options.

Risankizumab demonstrated efficacy in inducing clinical remission and endoscopic response at Week 12 after three IV induction doses at Weeks 0, 4 and 8, and in achieving clinical remission and endoscopic response at Week 52 (at both 180 mg and 360 mg). Efficacy was also demonstrated on multiple clinically relevant secondary endpoints with statistical significance at Week 12 and nominally at Week 52. Overall, the results from the analyses of the coprimary and secondary endpoints provided substantial evidence of efficacy for risankizumab in treatment of adult patients with moderately to severely active CD. Thus, the Applicant has met the evidentiary standard required by 21 Code of Federal Regulations (CFR) 314.126 to support approval of risankizumab for the proposed indication. However, limited data collected in pediatric patients 16 to less than 18 years of age are insufficient to support expanding the indication down to pediatric patients 16 years of age. The Applicant agreed to conduct postmarketing commitment (PMC) studies to assess the safety, efficacy, and pharmacokinetics of risankizumab, and evaluate the long-term safety, in pediatric patients 2 to 17 years of age with moderately to severely active CD.

The safety analysis of the 600 mg IV induction dose revealed a concern for hepatotoxicity. Although there was no report of drug-induced liver injury (DILI) in subjects treated with the 1200 mg induction dose, there is a potential dose-dependent hepatotoxicity risk given that the risk has not been identified to date in the other approved indications that utilize a substantially lower dosage of 150 mg administered subcutaneously. A Warnings and Precautions section will be included in labeling to communicate the risk of hepatotoxicity in treatment of CD and an enhanced pharmacovigilance will be required postapproval to mitigate this risk. In addition, the Applicant agreed to conduct a postmarketing observational study to assess the incidence of severe acute liver injury in adults with moderately to severely active CD. As risankizumab 1200 mg induction dosage did not demonstrate additional treatment benefit over the 600 mg dosage, the safety profile supports approval of the 600 mg IV induction dosage as the lowest effective dosage.

The safety profile of the 180 mg and 360 mg were comparable during the 52 weeks of maintenance therapy, and both the 180 mg and 360 mg are considered to be safe and effective dosages as maintenance treatment for moderately to severely active CD. While the 180 mg may represent the lowest effective dosage, given the clinical relevance of the numerically higher efficacy rates for endoscopic remission at Week 52, the 360 mg dosage may confer additional benefit, particularly in some patients with more severe or refractory disease, in whom the benefits are likely to justify the potential increased risks. Of note, the Applicant had initially proposed 360 mg as the only maintenance dosage, and did not include the complete chemistry, manufacturing, and controls (CMC) package to support the 180 mg presentation in the sBLA submission. In recognition of the seriousness and severity of CD, to ensure availability of a safe and effective product without delay, the 360 mg maintenance dosage should be made available to

patients at this time, while the efficacy supplement (sBLA761105-S018; received May 25, 2022) for the 180 mg prefilled cartridge presentation is currently under review to support inclusion of the lower maintenance dosage in labeling.

II. Interdisciplinary Assessment

3. Introduction

With the submission of this biologics license application (BLA) and supplemental BLA (sBLA), AbbVie (the Applicant) seeks to expand the approved indications for Skyrizi (risankizumab) to include adults and pediatric patients 16 years of age and older with moderately to severely active Crohn's disease (CD).

Skyrizi is an interleukin (IL)-23 antagonist indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy, and active psoriatic arthritis in adults. Both of the approved indications use lower dosage of 150 mg subcutaneous (SC) at Week 0, Week 4, and every 12 weeks thereafter, compared to the dosage proposed for CD (i.e., 600 mg intravenous [IV] at Weeks 0, 4, and 8; and 360 mg SC at Week 12, and every 8 weeks thereafter).

The review team identified the following key review issues that have a significant impact on approvability and/or labeling:

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Choice of Induction Dose

- See Section 6.3.1.

3.1.1.2. Choice of Maintenance Dose

- See Section 6.3.2.

3.1.1.3. Bridging Between the TBM Products and the Phase 3 Products

- See Section 6.3.3.

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Drug-Induced Liver Injury

- See Section 7.7.1.

3.1.2.2. Dyslipidemia

- See Section 7.7.2.

3.1.2.3. Subjects Age 16 to Less Than 18 Years

- See Section 7.7.3.

3.1.2.4. On-Body Delivery System

- See Section 7.7.4.

3.2. Approach to the Review

Determination of Efficacy

Induction Period

The primary determination of the short-term (induction period) efficacy was established on the basis of two independently conducted adequate and well-controlled trials (M15-991 and M16-006). The primary analysis was conducted at Week 12, assessing the proportion of subjects who achieved the coprimary endpoints of clinical remission and endoscopic response in each treatment arm (600 mg IV or 1200 mg IV), compared to placebo.

Maintenance Period

Evaluation of efficacy over a longer duration (52 weeks) of treatment was conducted separately. Study M16-000, Substudy 1 was an adequate and well-controlled trial, which enrolled subjects who achieved clinical response at Week 12 (from trials M15-991 and M16-006). The primary analysis assessed the proportion of subjects who achieved the coprimary endpoints of clinical remission and endoscopic response at Week 52 in each treatment arm (risankizumab 180 mg SC or 360 mg SC), compared to placebo.

Determination of Safety

Induction Period

The safety of 12 weeks of treatment with risankizumab 1200 mg IV or 600 mg IV was compared to placebo in the pooled population composed of subjects from the two phase 3, placebo-

controlled trials M15-991 and M16-006, and subjects in the 600 mg IV mg or placebo arms of M15-993 (a 12-week, phase 2, double-blind [DB], randomized, dose-ranging study).

Maintenance Period

The primary analysis of safety focused on the population of subjects who received induction therapy for 12 weeks, achieved clinical response, and then entered the maintenance period (M16-000, Substudy 1; Figure 1) and were rerandomized to receive placebo, 180 mg SC, or 360 mg SC mg for 52 weeks. These controlled data were the basis of the main safety analyses.

Long-Term Extension

Substudies 3 and 4 are open-label (OL), long-term extension (LTE) studies, which are ongoing at the time of this review. Additional analyses were conducted on interim safety data submitted from the LTE studies, including the OL real life handling study (RLHS) portion of M16-000, Substudy 4 (see Section 17.3). These data are descriptive given the uncontrolled nature and various confounding factors, but were reviewed to further assess safety of the proposed to-be-marketed (TBM) device, the on-body delivery system (OBDS), for maintenance therapy in subjects with CD.

Table 4. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Skyrizi (risankizumab)

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
M16-006	Subjects with moderately to severely active Crohn's disease	R, DB, PC, MC, phase 3	Risankizumab 600 mg IV (n=373) Risankizumab 1200 mg IV (n=372) Placebo (n=186)	Coprimary: 1) Proportion of subjects with clinical remission at Week 12 2) Proportion of subjects with endoscopic response at Week 12	Planned: 855 Actual: 931	Centers: 297 Countries: 53
M15-991	Subjects with moderately to severely active Crohn's disease and inadequate response or intolerance to one or more approved biologic agents for Crohn's disease	R, DB, PC, MC, phase 3	Risankizumab 600 mg IV (n=206) Risankizumab 1200 mg IV (n=205) Placebo (n=207) Duration: 12 weeks	Coprimary: 1) Proportion of subjects with clinical remission at Week 12 2) Proportion of subjects with endoscopic response at Week 12	Planned: 579 Actual: 618	Centers: 214 Countries: 53
M16-000	Subjects who achieved clinical response (based on stool frequency or abdominal pain score) at the last visit of induction studies M16-006 or M15-991	R, DB, PC, MC, phase 3	Risankizumab 180 mg SC (n=155) Risankizumab 360 mg SC (n=142) Placebo (n=143) Duration: 52 weeks	Coprimary: 1) Proportion of subjects with clinical remission at Week 52 2) Proportion of subjects with endoscopic response at Week 52	Planned: 1250 Actual: 542 randomized, 170 nonrandomized	Centers: 273 Countries: 53

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
M15-993	Subjects with moderately to severely active Crohn's disease	R, DB, PC, MC, dose-ranging phase 2	Risankizumab 200 mg IV (n=41) Risankizumab 600 mg IV (n=41) Placebo (n=39) Duration: 12 weeks	Primary: Clinical remission, defined as Crohn's Disease Activity Index <150, after 12 weeks of treatment Secondary: Endoscopic response, clinical response, mucosal healing, and deep remission	Planned: 240 Actual: 121	Centers: 36 Countries: 9

Source: Anne Bunner, Ph.D; Clinical Data Scientist

[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

[2] If no randomization, then replace with "Actual Enrolled"

Abbreviations: BID, twice daily; DB, double-blind; ISS1, integrated summary of safety (12-week induction period); IV, intravenous; LTE, long-term extension study; MC, multicenter; N, number of subjects; OL, open-label; PC, placebo-controlled; PG, parallel group; Q4W, every 4 weeks; R, randomized; RZB, risankizumab; SC, subcutaneous; TNF, tumor necrosis factor

4. Patient Experience Data

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		CDAI score, SES-CD, and FACIT-F,SF score, and AP score were used for the primary and/or key secondary endpoints; these instruments incorporate patient and/or clinician reported outcomes (see Section 6).
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☒	Performance outcome	
Other patient experience data submitted in the application		Interim data from Real Life Handling Study M16-000, Substudy 4 (see Section 17.3)
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☒	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	DG participates regularly in public meetings, workshops, and scientific conferences that engage the IBD community.
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☒	Other: (please specify)	

Abbreviations: AP, abdominal pain; CDAI, Crohn's Disease Activity Index; DG, Division of Gastroenterology; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IBD, inflammatory bowel disease SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Table 6. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Interleukin-23 antagonist
Mechanism of action	Risankizumab is a humanized IgG1 mAb that selectively binds to the p19 subunit of human IL-23 and inhibits its interaction with IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. Risankizumab inhibits IL-23 dependent cell signaling and the release of proinflammatory cytokines.
Active moieties	Risankizumab
QT prolongation	No QT prolongation assessment was conducted.
	General Information
Bioanalysis	Risankizumab concentrations in human plasma or serum were quantified using a validated enzyme-linked immunosorbent assay with the sensitivity of 5 ng/mL and a validated bridging electrochemiluminescence (ECL) immunoassay with the sensitivity of 4.34 ng/mL, respectively. The two assays were cross-validated.
Healthy subjects versus patients	Compared to healthy subjects, following SC administration, risankizumab exhibited a higher systemic clearance (0.3 versus 0.23 L/day) and a shorter elimination half-life ($t_{1/2}$) in subjects with active CD (21 versus 28 days). Compared to subjects with psoriasis or psoriatic arthritis, risankizumab exhibited a lower volume of distribution (7.7 versus 11.2 L), SC bioavailability (74% versus 89%) and $t_{1/2}$ in subjects with active CD (21 versus 28 days), although the clearance values of risankizumab were similar among these patient populations. In subjects with active CD treated with 600 mg IV induction doses at Weeks 0, 4, and 8, the median C_{max}, C_{trough}, and $AUC_{8\text{-}12week}$ were estimated to be 156 µg/mL, 38.8 µg/mL, and 2010 µg*day/mL, respectively, after dosing at Week 8. The 360 mg SC maintenance dose started at Week 12 and Q8W thereafter; the steady-state median C_{max}, C_{trough}, and $AUC_{40\text{-}48Week}$ were estimated to be 28 µg/mL, 8.13 µg/mL, and 985 µg*day/mL, respectively, during the maintenance treatment. In the CD phase 3 trials, 360 mg risankizumab was provided by 4 SC injections of 90 mg/mL in the prefilled syringe. For the 180 mg SC maintenance dose provided by 2 SC injections of 90 mg/mL in the prefilled syringe, the steady-state median C_{max}, Ctrough, and $AUC_{40\text{-}48Week}$ were predicted to be 14 µg/mL, 4.07 µg/mL, and 493 µg*day/mL, respectively.

Characteristic	Drug Information
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	Single dose PK: PK parameters after a single SC or IV dosing of risankizumab in healthy subjects is summarized below:

Table 7. Single Dose PK Parameters After a Single SC or IV Dose of Risankizumab in Healthy Subjects

	Geometric Mean (%CV)			
Parameter	**360 mg SC OBDS[1, 2]**	**180 mg SC OBDS[1,2]**	**1800 mg IV[1]**	**600 mg IV[2, 3]**
N	114	28	50	
C_{max} (µg/mL)	42.1 (39)	20.2 (45)	716 (20)	239
AUC_t (µg·day/mL)	1500 (36)	755 (47)	11400 (23)	3800
AUC_{inf} (µg·day/mL)	1640 (37)	902 (50)	12300 (25)	4100
T_{max} (day)[4]	5.0 (2.0-14.0)	5.0 (2.0-28.0)	0.167 (0.125-1.00)	
$T_{1/2}$ (day)[5]	26.2 (5.86)	27.8 (6.26)	28.3 (6.71)	

[1] Observed PK data from Study M19-128
[2] To-be-marketed product
[3] Estimated based on dose-proportionality between 200 mg and 1800 mg (C_{max} or AUC value in 600 mg IV = C_{max} or AUC value in 1800 mg IV ÷ 3)
[4] Median (minimum – maximum)
[5] Harmonic mean (pseudo-standard deviation)

Multiple-dose PK: Risankizumab serum trough concentrations (µg/mL) in subjects with CD following the proposed induction or maintenance dosing regimen are summarized below:

Table 8. Multiple Dose Serum Trough Concentrations Following the Proposed Dosing Regimen in Subjects With CD

		Geometric Mean (%CV) [N]		
Induction Therapy	**Study**	**Week 4**	**Week 8**	**Week 12**
600 mg IV at Weeks 0, 4, and 8	M15-991	20.7 (105) [187]	29.8 (65) [186]	34.8 (106)[184]
	M16-006	23.3 (63) [340]	34.5 (59) [339]	39.4 (48) [332]
Maintenance Therapy at Week 12 then Q8W	**Study**	**Week 16**	**Week 32**	**Week 48**
360 mg SC	M16-000	7.75 (65) [87]	7.93 (48) [60]	7.24 (50) [55]
180 mg SC	M16-000	4.53 (79) [93]	3.75 (52) [75]	3.41 (64) [53]

Source: Reviewer generated based on 2.7.2 Summary of Clinical Pharmacology Studies Table 7 and Table 8

Characteristic	Drug Information
Range of effective dosage(s) or exposure	For induction of remission, IV 600 mg Q4W resulted in better efficacy than IV 200 mg Q4W in phase 2 trial. In phase 3 trial, the induction efficacy at 600 mg IV Q4W was similar to 1200 mg IV Q4W. For maintenance therapy, both SC 360 mg Q8W and 180 mg Q8W showed significant efficacy over placebo on CDAI and endoscopic response (coprimary endpoints) but no dose-response relationship was observed between two doses. The trial was not designed to compare the efficacy between the two maintenance dosing regimens. However, there were trends of numerically higher response in the higher range of exposure (C_{avg}) for several of the evaluated efficacy endpoints, particularly for the endoscopic endpoints such as endoscopic remission and ulcer free endoscopy (exposure-response relationship).
Maximally tolerated dosage or exposure	Maximally tolerated dosage (MTD) was not determined. The highest single and multiple doses evaluated were 1800 mg IV in healthy subjects and 1200 mg IV Q4W up to 24 weeks in subjects with CD, respectively.
Dosage proportionality	Risankizumab showed dose proportional increase in systemic exposure in the dose range of 18-360 mg following single SC administration and 200-1800 following IV administration.
Accumulation	No risankizumab accumulation was observed following multiple IV Q4W or SC Q8W dosing in subjects with CD.
Time to achieve steady-state	In subjects with CD treated with 600 mg IV induction dose at Weeks 0, 4, and 8 followed by 360 mg SC maintenance dose at Week 12 and Q8W thereafter, the steady-state was achieved at Week 16.
Bridge between to-be-marketed and clinical trial formulations	The to-be-marketed (TBM) products are different from the products (formulation+device combination) used in the phase 3 trials. A bridging PK Study M19-128 was conducted in healthy subjects comparing the TBM product for SC injection [360 mg OBSD] versus phase 3 SC product [90 mg/mL PFS x 4 injections]) and the TBM product for IV infusion [60 mg/mL] versus phase 3 IV product [90 mg/mL]). The TBM IV product (60 mg/mL, 600 mg/vial) was bioequivalent to the phase 3 IV product (90 mg/mL, 300 mg/vial). The BE study was conducted using the 1800-mg dose which is 3-fold the proposed dose (i.e., 600 mg). However, since the IV dose was administered under the same infusion duration and PK is dose-proportional following IV infusion from 200 mg to 1800 mg, the results support the bridging between the TBM product and the phase 3 product at the proposed IV dose, i.e., 600 mg. The TBM OBDS 360 mg product (150 mg/mL, 360 mg/2.4mL) met the bioequivalence criteria for AUC but not for C_{max} with the phase 3 product (i.e., 360-mg dose was given by 4 injections of 90 mg/mL in a PFS). The C_{max} values in subjects using the TBM 360 mg OBDS product were ~25% higher than those using the phase 3 PFS product. However, the higher C_{max} with the TBM OBSD product remained lower than that of IV infusion of 600 mg for induction treatment. Therefore, the safety of higher C_{max} with the OBSD is supported by the available safety data associated with multiple doses of 600 mg IV. In addition, AUC is generally considered to be more relevant for assessing the impact on long-term safety than C_{max}. Compared to the TBM OBDS 360 mg product using dose-normalized log-transformed C_{max} and AUC, the OBDS 180 mg product (150 mg/mL, 180 mg/1.2mL) met the bioequivalence criteria for both C_{max} and AUC, demonstrating pharmacokinetic linearity between the two doses. The PK between 180 mg OBDS and 180 mg by 2 injections of 90 mg/mL PFS were not

Characteristic	Drug Information
	directly compared but expected to have similar AUC based on the dose proportionality shown between 180 mg and 360 mg and comparable AUC at 360 mg between OBDS 360 mg and 4 injections of 90 mg/mL PFS. The higher injection site reaction from the TBM SC 360 mg or 180 mg OBSD injection was observed in the PK bridging study. Refer to Section 7.7.4 for discussion on the clinical significance of the injection site reaction.
	Absorption
Bioavailability	74% for SC injection in CD patients based on population PK analyses. Based on the dose-normalized AUC comparison between IV and SC in healthy subjects, 66% (M19-128).
T_{max}	4 hr (1800 mg IV), 5 days (360 mg SC or 180 mg SC)
Food effect (fed/fasted) Geometric least square mean and 90% CI	Not applicable.
	Distribution
Volume of distribution at steady-state	7.7 L (SC)
Plasma protein binding	Plasma protein binding to risankizumab was not assessed.
Drug as substrate of transporters	Not applicable
	Elimination
Mass balance results	No mass balance study was conducted
Clearance	In healthy subjects, 0.15 L/day following IV administration and 0.23 L/day following SC administration (M19-128). In CD patients, 0.3 L/day following SC administration
Half-life	21 days
Metabolic pathway(s)	The metabolic pathway of risankizumab has not been characterized. As a humanized IgG1 mAb, risankizumab is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG
Primary excretion pathways (% dosage)	The renal excretion of risankizumab has not been investigated. As a humanized IgG1 mAb with a molecular weight of approximately 148 kDa, intact risankizumab is unlikely to be filtered by kidney or excreted in urine.

Characteristic	Drug Information
	Intrinsic Factors and Specific Populations
Body weight	Body weight, ranged 32-158.5 kg, did not have a clinically relevant impact on the PK of risankizumab in subjects with CD.
Age	The popPK analysis indicated that age (ranged 16-79 years) was not a significant covariate influencing risankizumab PK in subjects with CD. The population mean clearance (95% confidence interval) (L/day) for 18-65 years old (n=1166), >65 years old (n=52), and <18 years old (n=9) are estimated to be 0.298 (0.291, 0.304), 0.264 (0.242, 0.286), and 0.276 (0.222, 0.330), respectively.
Renal impairment	No dedicated renal impairment study was conducted. The population mean (95% CI) clearance (L/day) for normal renal function (CLCr ≥90 mL/min, n=992), mildly impaired renal function (60≤CLCr <90 mL/min, n=215), and moderately impaired renal function (30≤CLCr <60 mL/min, n=19) are estimated to be 0.304 (0.268, 0.242), 0.297 (0.254, 0.212), and 0.311 (0.282, 0.272), respectively. One patient with severely impaired renal function (CLCr =25.2 mL/min) was included in the PopPK analysis, and the estimated CL was 0.180 L/day.
Hepatic impairment	No dedicated hepatic impairment study was conducted.
	Drug Interaction Liability (drug as perpetrator)
Inhibition/induction of metabolism	Risankizumab at 150 mg SC at Weeks 0, and 4, then Q12W thereafter (dosage recommended for the treatment of plaque psoriasis or psoriatic arthritics and lower than the proposed dosage for CD) has no clinically meaningful effect on the PK of drugs metabolized by cytochrome P450 (CYP)1A2, 2C9, 2C19, 2D6 or 3A. The effect of risankizumab at the proposed dose regimens for the treatment of CD on the activities of CYPs has not been evaluated. A PMC study will be issued to assess the potential CYP-mediated DDI in patients with CD.
Inhibition/induction of transporter systems	Not applicable.
	Immunogenicity
Bioanalysis	Two titer-based ECL bridging ligand binding assays were applied for determination of antidrug antibody (ADA) in human serum (Studies M17-381 and M19-128, and phase 3 studies) or plasma (Studies M16-533 and M16-324 and phase 2 studies). A competitive ligand binding neutralizing antibody (NAb) assay was used in phase 3 studies and a cell-based NAb assay was applied in phase 2 studies.

Characteristic	Drug Information
Incidence	Immunogenicity incidence is summarized below:

Table 9. Immunogenicity Incidence

Therapy	Dose Regimen	Duration	ADA+Incidence	NAb+Incidence
Induction	600 mg IV at Weeks 0,4,8	12 weeks	2.1% (13/607)	0.3% (2/607)
Maintenance	360 mg SC Q8W	52 weeks	0.9% (1/107)	0% (0/107)
	180 mg SC Q8W	52 weeks	2.6% (3/117)	0.9% (1/117)
Induction+ Maintenance (360 mg)	600 mg IV at Weeks 0, 4, 8, followed by 360 mg SC at Week 12, Q8W thereafter	64 Weeks	3.4% (2/58)	0% (0/58)
Induction+ Maintenance (180 mg)	600 mg IV at Weeks 0, 4, 8, followed by 180 mg SC at Week 12, Q8W thereafter	64 Weeks	0% (0/57)	0% (0/58)

Source: Reviewer generated based on R&D/20/1400 Table 2, Table 4, and Table 11.1_2

Clinical impact

The number of ADA+/NAb+ subjects was too small to make a meaningful comparison with ADA-/NAb- subjects.
The median ADA titer values ranged from 10.0 to 65.7 across visits and studies during the 12-week induction period.
The median time to the first appearance of ADA was approximately 4 weeks in the phase 3 induction studies.

Comparisons of hypersensitivity reactions and injection-site reactions by treatment-emergent ADA status over 12-Week induction period or 52-Week maintenance period are summarized below.

Table 10. Hypersensitivity and Injection-Site Reactions by Treatment-Emergent ADA Status Over 12-Week Induction Period or 52-Week Maintenance Period

	Placebo-Controlled 12-Week Induction Period Safety Analysis Set					
	Risankizumab 600 mg IV Induction Dose (N = 609)		Risankizumab 1200 mg IV Induction Dose (N = 565)		All Risankizumab Doses (N = 1174)[a]	
	ADA+ (N = 13)	ADA– (N = 596)	ADA+ (N=4)	ADA– (N=561)	ADA+ (N =17)	ADA– (N =1157)
hypersensitivity reactions (per SMQ), n (%)	1 (7.7%)	28 (4.7%)	0 (0%)	28 (5.0%)	1 (5.9%)	56 (4.8 %)
injection site reactions (per CMQ), n (%)	0 (0%)	5 (0.8%)	0 (0%)	11 (2.0%)	0 (0%)	16 (1.4%)

	Study M16-000			
	Risankizumab 180 mg Q8W Dose (N = 133)		Risankizumab 360 mg Q8W Dose (N = 135)	
	ADA+ (N = 3)	ADA– (N = 130)	ADA+ (N = 1)	ADA– (N = 134)
hypersensitivity reactions (per SMQ), n (%)	1 (33.3%)	15 (11.5%)	0 (0%)	10 (7.4%)
injection site reactions (per CMQ), n (%)	0 (0%)	6 (4.6%)	0 (0%)	9 (6.7%)

Source: R&D/20/1400 Table 8 and Table 10

Characteristic	Drug Information

The incidences of hypersensitivity reactions and injection- or infusion-site reactions in subjects with ADA+ were numerically higher than those with ADA- over up to 248 weeks of exposure for the all-treated analysis set. Refer to Sections 7.6.1.5 and 7.6.2.5 for the clinical significance of the hypersensitivity.

Table 11. Hypersensitivity and Injection-Site Reactions by Treatment-Emergent ADA Status, All Treated Safety Analysis Set

	All Treated Safety Analysis Set									
	600 mg IV at Weeks 0, 4 and 8 (N=677)		Any RZB IV Regimen (N=1384)		360 mg SC Q8W (N=476)		Any RZB SC Regimen (N=1162)		Any RZB (N= 1384)	
	ADA+ (N = 26)	ADA- (N = 651)	ADA+ (N = 35)	ADA- (N =1349)	ADA+ (N = 11)	ADA- (N = 465)	ADA+ (N =28)	ADA- (N = 1134)	ADA+ (N=35)	ADA- (N=1349)
hypersensitivity reactions (per SMQ), n (%)	2 (7.7%)	34 (5.2%)	3 (8.6%)	89 (6.6%)	1 (9.1%)	28 (6.0%)	4 (14.3%)	68 (6.0%)	6 (17.1%)	150 (11.1%)
injection site reactions (per CMQ), n (%)	1 (3.8%)	11 (1.7%)	2 (5.7%)	31 (2.3%)	1 (9.1%)	24 (5.2%)	2 (7.1%)	45 (4.0%)	4 (11.4%)	72 (5.3%)

Source: R&D/20/1400 Table 11

Abbreviations: ADA, antidrug antibody; AUC/AUC_t, area under the concentration-time curve from time 0 to the time of the last measurable concentration; AUC_{inf}, area under the concentration-time curve from time 0 to infinity time; $AUC_{8\text{-}12\ week}$, area under the concentration-time curve from Week 8 to Week 12; $AUC_{40\text{-}48\ week}$, area under the concentration-time curve from Week 40 to Week 48; BE, bioequivalence; C_{avg}, average concentration; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CL, clearance; CL_{Cr}, creatinine clearance; C_{max}, maximum plasma concentration; CMQ, customized MedDRA query; CV, coefficient of variation; C_{trough}, trough concentration; CYP, cytochrome P450; DDI, drug-drug interaction; ECL, electrochemiluminescence; EPC, established pharmacologic class; IgG1 mAb, Immunoglobulin G1 monoclonal antibody; IL-23, interleukin 23; mAb, monoclonal antibody; MTD, maximally tolerated dosage; N, number of patients in treatment group; n, number of patients with given characteristic; Nab, neutralizing antibody; OBDS, on-body delivery system; PFS, prefilled syringe; PK, pharmacokinetics; PMC, postmarketing commitment; popPK, population pharmacokinetics; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; RZB, risankizumab; SC, subcutaneous; SMQ, standardised MedDRA query; TMB, to-be-marketed; T_{max}, time to maximum concentration; $T_{1/2}$, terminal phase elimination half-life; vs, versus

5.1. Nonclinical Assessment of Potential Effectiveness

Risankizumab is a humanized recombinant immunoglobulin G (IgG)1 monoclonal antibody that binds selectively to the p19 subunit of human interleukin 23 (IL-23p19) thus blocking the interaction of IL-23 with the IL-23 receptor. Risankizumab showed high affinity bindings to human IL-23 p19 in vitro, with no detectable binding to human IL-12 or rat IL-23 at the concentration of 1µM. Binding of risankizumab to cynomolgus monkey IL-23 was also high, with a dissociation constant of less than 1pM.

The pharmacodynamic (PD) activity of risankizumab was assessed using a surrogate anti-mouse IL-23p19 antibody (PR-963484) in an anti-CD40-mAb-induced colitis mouse model and a T-cell transfer colitis mouse model. In the anti-CD40-mAb-induced colitis mouse model, PR-963484 was administered intraperitoneally (IP) at a dose of 15 mg/kg twice weekly. A single IP injection of anti-CD40 mAb led to colitis characterized by an increase in endoscopic score and an increase in ionized calcium-binding adapter 1 **(**IBA1+) cells in the colon. The anti-mouse IL-23p19 surrogate antibody to risankizumab, PR-963484, at a dose of 15 mg/kg IP twice per week, significantly ameliorated the anti-CD40-mAb-induced colitis in this mouse model as measured by endoscopy and IBA1+ cell histological analysis. Treatment with PR-963484 did not impact body weight change over 7 days compared to vehicle group nor had an effect on anti-CD40 mAb induced splenomegaly in this mouse model.

The efficacy of PR-963484 was assessed in a mouse model following IP administration of T cells to the severe combined immunodeficiency (SCID) mice to produce colitis. Efficacy was measured by endoscopic evaluation of disease severity (MEDAI sum score) and IBA1+ infiltrating macrophages in the mucosa by histology. PR-963484 was administered IP at a dose of 15 mg/kg twice weekly starting on Day 21 post T-cell transfer. On Day 41, the animals were euthanized and colons were collected for histological analysis. PR-963484 caused a 62% inhibition of disease severity compared to the IgG control group, assessed by endoscopy. Analysis of % of IBA1+ cells in the mucosa also showed a significant (47%) decrease compared to the control group.

In an in vitro study, the ability of risankizumab to trigger antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) were determined by a reporter bioassay and a human serum complement assay. In these assays, risankizumab did not show any effect on ADCC or CDC.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

6.1.1. Induction: Intravenous Infusion

The proposed IV dose for induction treatment is three infusions of 600 mg at Weeks 0, 4, and 8, followed by maintenance treatment with subcutaneous injection every 8 weeks (Q8W) starting at Week 12.

In phase 2 induction trial (Study M15-993), the dose (exposure) dependent increase in response of clinical remission and endoscopic response was shown at Week 12 between 200 mg Q4W and 600 mg Q4W (Table 12). The response rate was numerically greater at 600 mg than 200 mg or placebo, although not statistically significant. Subjects treated with risankizumab showed numerically better endoscopic response rate at both 200-mg and 600-mg doses, compared to placebo. The clinical remission rate, however, was similar between 200 mg and placebo treatment arms with largely overlapping 95% confidence interval although was higher at 600 mg compared to 200 mg and placebo.

Table 12. Induction Efficacy at Week 12 in Phase 2 Trial (Study M15-993) in Response Rate and 95% Confidence Interval

Efficacy Parameter	Placebo N=39	Risankizumab 200 mg IV[c] N=41	Risankizumab 600 mg IV[c] N=41
Clinical remission[a] rate (%)	15.4 (5.9, 30.5)	19.5 (8.8, 34.9)	36.6 (22.1, 53.1)
Endoscopic response[b] rate (%)	12.8 (4.3, 27.4)	26.8 (14.2, 42.9)	36.6 (22.1, 53.1)

Source: Reviewer Generated; Adapted from Table 14 on Page 107 and Table 15 on Page 110 of M15-993 Clinical Study Report R&D/17/0073
[a] Clinical remission: CDAI <150.
[b] Endoscopic response: >50% CDEIS reduction from baseline.
[c] Dosed at Weeks 0, 4 and 8
Abbreviations: IV, intravenous; N, number of patients in treatment group

In phase 3 induction trials, two doses, 600 mg Q4W and 1200 mg Q4W, were studied to further explore the dose/exposure-response relationship. A dose-dependent increase in the response rate was not observed between 600 mg and 1200 mg in two phase 3 induction trials (M15-991 and M16-006) for all efficacy endpoints evaluated, although both doses showed statistically significantly higher response rates for both coprimary endpoints of clinical remission (defined as Crohn's disease activity index [CDAI] <150) and endoscopic response (decrease in Simple Endoscopic Score for Crohn's Disease [SES-CD] >50% from baseline) at Week 12 over placebo. Refer to Efficacy Section 6.2.

6.1.2. Maintenance: Subcutaneous Injection

A dose-ranging phase 2 trial was not conducted to inform the maintenance dosage. In the OL extension period of phase 2 study (M15-993), subjects who achieved clinical remission after the

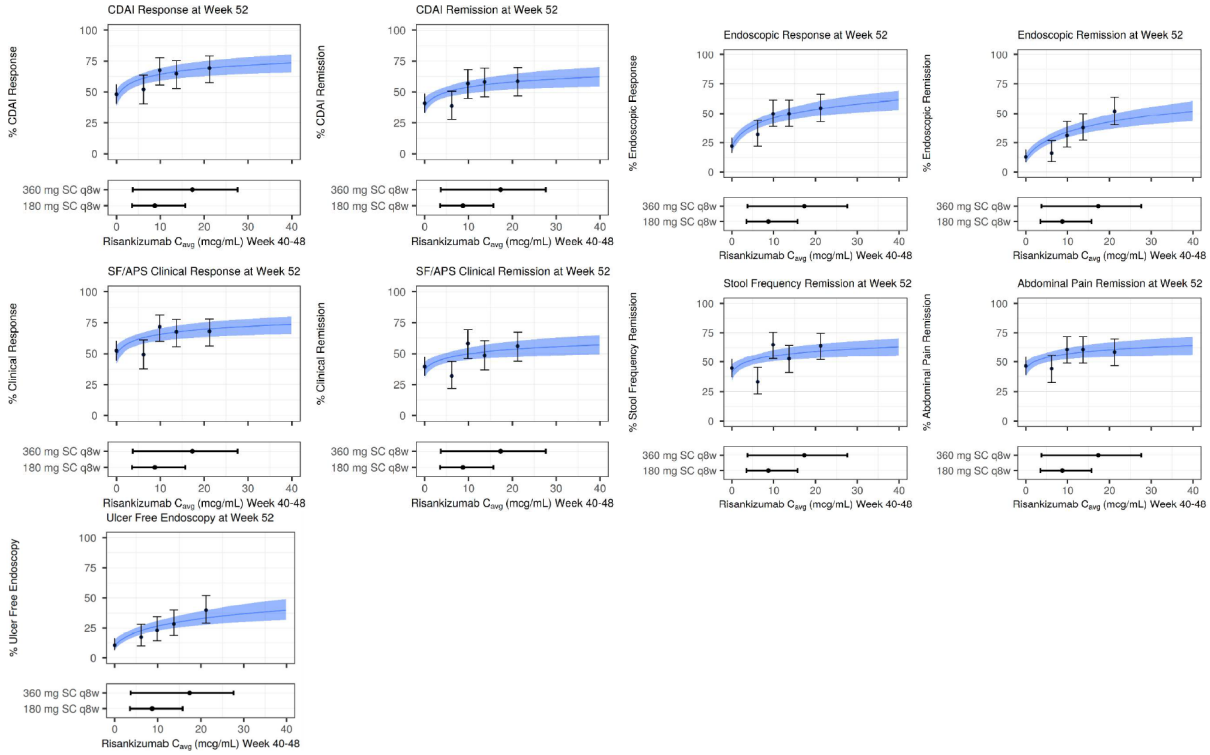
induction treatment were treated with a single dose level of risankizumab 180 mg SC Q8W for 26 weeks. The open-label design of the trial limits interpretability of the results.

The phase 3 randomized withdrawal maintenance study (M16-000) investigated two doses, 180 mg SC Q8W and 360 mg SC Q8W, to further evaluate the dose-response relationship.

In Study M16-000, both SC 180 mg and 360 mg showed significantly higher response rates for both coprimary endpoints, clinical remission and endoscopic response at Week 52, compared to placebo. A dose-response relationship between 180 mg and 360 mg was not observed for coprimary endpoints; however, the 360 mg Q8W regimen showed numerically better results on endoscopic efficacy endpoints.

Similarly, an exposure-response relationship was not apparent for clinical remission, although there were trends of higher response rates in the higher range of exposure (C_{avg}) for the endoscopic remission and "ulcer free endoscopy." See Section 6.2.2.3 for further discussion on efficacy results for the maintenance study.

Figure 1. Exposure-Response Relationship for Maintenance Treatment (Study M16-000)



Source: Figure 11 on Pages 74-76 of Applicant's Exposure-Response Report R&D/20/1614 Titled "Exposure-Response Analyses for Efficacy and Safety of Risankizumab in Subjects with Active Crohn's Disease."
Abbreviations: C_{avg}, average concentration; CDAI, Crohn's Disease Activity Index; SC, subcutaneous; q8w, every 8 weeks

6.2. Clinical Trials Intended to Demonstrate Efficacy

Efficacy was evaluated in two phase 3 induction studies (M16-006 and M15-991) and one maintenance study (M16-000).

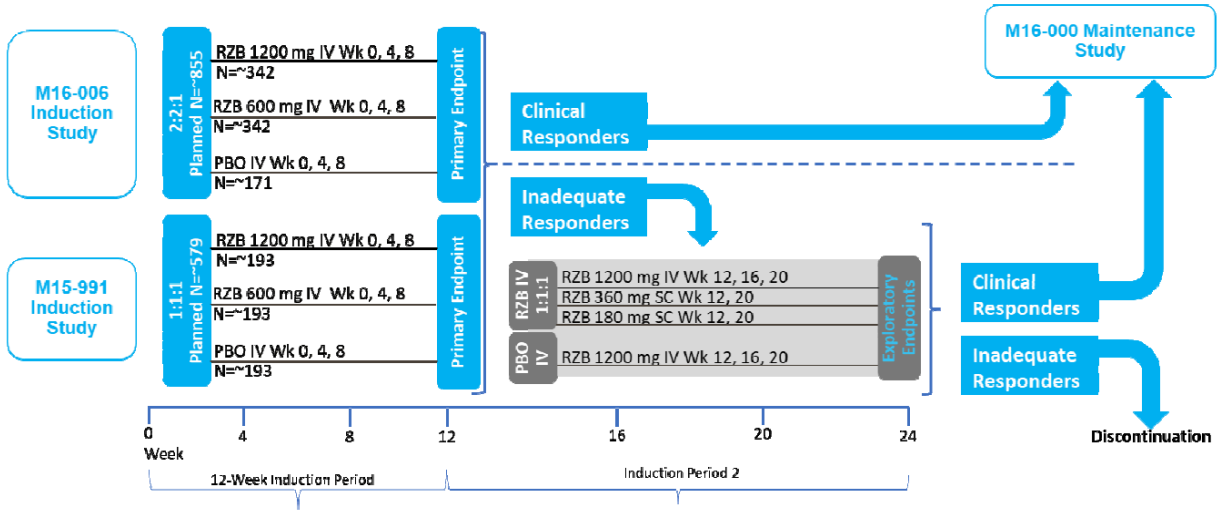
6.2.1. Induction Studies M16-006 and M15-991

6.2.1.1. Design, Studies M16-006 and M15-991

Studies M16-006 and M15-991 were phase 3, multicenter, randomized, DB, placebo-controlled studies that evaluated the efficacy and safety of risankizumab as induction treatment, administered once every 4 weeks (Weeks 0, 4, 8), in subjects 16 to 80 years of age (inclusive) with moderately to severely active CD.

Subjects were eligible to participate in these studies if they had a confirmed diagnosis of CD for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must also have been available. The subjects were required to have a CDAI score of 220 to 450 at Baseline, and endoscopic evidence of mucosal inflammation as documented by a SES-CD of ≥3. All eligible scores exclude the presence of narrowing component and are confirmed by a central reader. (Note that only subjects with SES-CD of ≥6 for ileocolonic or colonic disease or SES-CD of ≥4 for isolated ileal disease were included in the primary efficacy analysis. If a cap of no more than 85 subjects who did not meet the SES-CD criteria for inclusion in the primary efficacy analysis were reached, subsequent enrollees were required to have SES-CD of ≥6 for ileocolonic or colonic disease or SES-CD of ≥4 for isolated ileal disease). Subjects had to have average daily stool frequency (SF) ≥4 and/or average daily abdominal pain score (APS) ≥2 at Baseline, and demonstrated intolerance or inadequate response to one or more of the following categories of drugs: aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), immunomodulators, and/or biologic therapies.

Figure 2. Induction Study Schema for Studies M16-006 and M15-991



Source: BLA761105-S016 Submission. Clinical Overview section 2.5. Pg.16 of 128
Abbreviations: IV, intravenous; N, number of patients in treatment group; PBO, placebo; RZB, risankizumab; SC, subcutaneous; wk, week

Subjects were randomized to receive either risankizumab 1200 mg IV, risankizumab 600 mg IV, or placebo. The randomization ratios in Studies M16-006 and M15-991 were 2:2:1 and 1:1:1,

respectively. Study M16-006 enrolled subjects who had an inadequate response (IR) to prior biologic therapy (Bio-IR) as well as subjects who had no prior biologic therapy (non-Bio-IR), while Study M15-991 only enrolled Bio-IR subjects.

The Bio-IR population was defined as subjects with documented intolerance or inadequate response to one or more of the approved biologics for CD (infliximab, adalimumab, certolizumab, natalizumab, vedolizumab, and/or ustekinumab). The non-Bio-IR population included subjects who had an inadequate response or intolerance to conventional therapy. Conventional therapy was defined as aminosalicylates, oral locally acting steroids (e.g., budesonide, beclomethasone), systemic corticosteroids (prednisone or equivalent), or immunomodulators. This population included subjects who had received biologic therapy in the past but stopped therapy based on reasons other than inadequate response or intolerance (e.g., change in reimbursement coverage, well-controlled disease).

Each of the studies had 2 coprimary endpoints and 15 multiplicity-controlled secondary endpoints.

The coprimary endpoints are CDAI clinical remission (defined as CDAI <150) at Week 12 and endoscopic response (defined as 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) at Week 12.

The first eight multiplicity-controlled secondary endpoints were tested sequentially within doses as follows:

(1) SF/APS clinical remission (defined as an average daily SF ≤2.8 and not worse than baseline AND average daily APS ≤1 and not worse than baseline) at Week 12

(2) CDAI clinical response (defined as a reduction of CDAI ≥100 points from baseline) at Week 4

(3) CDAI clinical response at Week 12

(4) Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) at Week 12

(5) CDAI clinical remission at Week 4

(6) CDAI clinical response and endoscopic response at Week 12

(7) Stool frequency remission (defined as average daily SF ≤2.8 and not worse than baseline) at Week 12

(8) Abdominal pain remission (defined as average daily APS ≤1 and not worse than baseline) at Week 12

The remaining seven secondary endpoints were to be tested if the previous eight secondary endpoints were significant. The following seven secondary endpoints were controlled for multiplicity simultaneously (without a predetermined sequence) using the Holm procedure:

(1) Endoscopic remission (defined as 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) at Week 12

(2) Enhanced clinical response (defined as ≥60% decrease in average daily SF and/or ≥35% decrease in average daily APS and both not worse than baseline, and/or clinical remission) at Week 4

(3) Ulcer-free endoscopy (defined as SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore ≥1 at baseline, as scored by a central reviewer) at Week 12

(4) Enhanced clinical response at Week 12

(5) Resolution of extra-intestinal manifestations (EIMs) at Week 12, in subjects with any EIMs at baseline

(6) CD-related hospitalization through Week 12

(7) No draining fistulas at Week 12, in subjects with draining fistulas at baseline

On April 17, 2020, while the study was ongoing, the Agency recommended that the Applicant change the definition of the coprimary endpoint for clinical remission from SF/APS clinical remission to CDAI clinical remission, and that the Applicant update the ranking of the secondary endpoints to add SF/APS clinical remission. Protocol Amendment 7.01, which implemented this recommended change, was finalized on August 27, 2020.

At Week 12, subjects were evaluated for clinical response based on SF and APS, defined as ≥30% decrease in average daily SF and/or ≥30% decrease in average daily APS and both not worse than baseline.

Subjects who achieved clinical response at Week 12 were eligible for enrollment in Study M16-000. Those who had received placebo continued receiving placebo. Those who had received risankizumab IV were randomized 1:1:1 to either risankizumab 360 mg SC, risankizumab 180 mg SC, or placebo.

Subjects who did not achieve clinical response at Week 12 were randomized to Induction Period 2, a DB, double-dummy 12-week treatment period. Subjects who received risankizumab induction treatment during the first 12-week induction period were randomized 1:1:1 to either risankizumab 1200 mg IV, risankizumab 360 mg SC, or risankizumab 180 mg SC. Subjects who received placebo induction treatment during the first 12-week induction period received risankizumab 1200 mg IV. At Week 24, subjects were again evaluated for clinical response. Those who achieved clinical response were eligible for enrollment in Study M16-000. Those who had received risankizumab SC continued receiving risankizumab SC. Those who had received risankizumab 1200 mg IV were randomized 1:1:1 to either risankizumab 360 mg SC, risankizumab 180 mg SC, or placebo. See Section 16.3.4.

6.2.1.2. Statistical Analysis Plan, Studies M16-006 and M15-991

The primary efficacy results are based on a subset of the Intent-to-Treat (ITT) population, which consisted of randomized subjects who received at least one dose of study drug. The primary analysis was based on the first 12-week Induction Period and excluded results from Induction Period 2. The ITT1 population included randomized subjects who received at least one dose of

study drug during the first 12-week Induction Period. The primary population for efficacy analysis was the ITT1A population, which included subjects in the ITT1 population who had baseline eligible SES-CD of ≥6 (≥4 for isolated ileal disease).

The comparisons between each risankizumab dose versus placebo for the primary efficacy variables were performed based on the normal approximation to the stratified risk difference using Cochran-Mantel-Haenszel (CMH) weights. The stratified risk difference adjusted for the randomization stratification factors of number of prior biologics failed (0, 1, >1) and steroid use at baseline (yes, no). The 95% confidence intervals for the stratified risk differences between treatment groups using CMH weights were also calculated. A multiple testing procedure was used to provide strong control of the type 1 error rate at an overall alpha of 0.05 (2-sided) across analyses comparing each risankizumab dose level to placebo with respect to the coprimary endpoints, and multiplicity-controlled secondary endpoints. Specifically, a graphical testing procedure was used to test coprimary endpoints and secondary endpoints (see Section 16.1 for additional details). Binary secondary endpoints were tested using the same method as the coprimary endpoints. Continuous variables collected longitudinally were analyzed using a Mixed-Effect Model Repeated Measurement (MMRM) model that included categorical fixed effects of treatment, visit and treatment-by-visit interaction, randomization stratification factors, and the continuous fixed covariates of baseline measurements. Continuous efficacy variables that were collected at only one postbaseline visit were analyzed using an Analysis of Covariance (ANCOVA) model.

The estimands corresponding to the primary efficacy objective for U.S.-specific protocol were defined as follows:

- Difference in the percentage of subjects achieving CDAI clinical remission at Week 12 regardless of premature discontinuation of study drug and without initiation or dose escalation of CD-related corticosteroids in each of the risankizumab 1200 mg IV and risankizumab 600 mg IV groups in comparison with the placebo group in the ITT1A population
- Difference in the percentage of subjects achieving endoscopic response at Week 12 regardless of premature discontinuation of study drug and without initiation or dose escalation of CD-related corticosteroids in each of the risankizumab 1200 mg IV and risankizumab 600 mg IV groups in comparison with the placebo group in the ITT1A population.

If a subject prematurely discontinued the study drug, all subsequent data were used. If a subject experienced initiation or dose-escalation of CD-related corticosteroids, the subject was considered a nonresponder.

A nonresponder imputation approach was used to handle missing data due to reasons that were unrelated to coronavirus disease 2019 (COVID-19). Multiple imputation assuming missing at random was used to handle missing data due to COVID-19. As a sensitivity analysis, the nonresponder imputation approach was used to handle all missing data, including for COVID-19.

6.2.1.3. Results of Analyses, Studies M16-006 and M15-991

Table 13 provides details regarding the 1629 subjects included in the primary induction safety database (ISS1), which includes trials M16-006, M15-991, and M15-993. Demographic factors and baseline disease characteristics were generally balanced between the three groups, with the majority being white (81%). The median age was 36 years, with a range of 16 to 80 years of age.

Table 13. Baseline Demographic and Clinical Characteristics, Safety Population, ISS1

Characteristic	RZB 600 mg IV N=620	RZB 1200 mg IV N=577	Placebo IV N=432	Total N=1629
Sex, n (%)				
Female	299 (48.2)	272 (47.1)	220 (50.9)	791 (48.6)
Male	321 (51.8)	305 (52.9)	212 (49.1)	838 (51.4)
Age, years				
Mean (SD)	39.2 (13.3)	38.3 (13.3)	38.2 (13.5)	38.6 (13.4)
Median (min, max)	37 (16, 79)	36 (16, 74)	35.5 (16, 80)	36 (16, 80)
Age group, years, n (%)				
<18 years	4 (0.6)	5 (0.9)	5 (1.2)	14 (0.9)
≥18 years to <40 years	341 (55.0)	329 (57.0)	255 (59.0)	925 (56.8)
≥40 years to <65 years	244 (39.4)	219 (38.0)	150 (34.7)	613 (37.6)
≥65 years	31 (5.0)	24 (4.2)	22 (5.1)	77 (4.7)
Race, n (%)				
Asian	84 (13.5)	89 (15.4)	54 (12.5)	227(13.9)
Black or African American	18 (2.9)	21 (3.6)	22 (5.1)	61 (3.7)
Multiple	4 (0.6)	5 (0.9)	1 (0.2)	10 (0.6)
Native Hawaiian or Other Pacific Islander	0 (0)	1 (0.2)	3 (0.7)	4 (0.2)
White	514 (82.9)	461 (79.9)	352 (81.5)	1327 (81.4)
Ethnicity, n (%)				
Hispanic or Latino	33 (5.3)	33 (5.7)	32 (7.4)	98 (6.0)
Not Hispanic or Latino	587 (94.7)	544 (94.3)	400 (92.6)	1531 (94.0)
Region of participation, n (%)				
Asia	78 (12.6)	85 (14.7)	52 (12.0)	215 (13.2)
Eastern Europe	110 (17.7)	103 (17.9)	76 (17.6)	289 (17.4)
North America	153 (24.7)	150 (26.0)	131 (30.3)	434 (26.6)
Other	46 (7.4)	34 (5.9)	30 (6.9)	110 (6.8)
South/Central America	10 (1.6)	11 (1.9)	13 (3.0)	34 (2.1)
Western Europe	223 (36.0)	194 (33.6)	130 (30.1)	547 (33.6)

Source: Anne Bunner, PhD; Clinical Data Scientist.
Abbreviations: ISS1, integrated summary of safety (12-week induction period); IV, intravenous; N, number of patients in treatment group; n, number of patients with given characteristic; RZB, risankizumab; SD, standard deviation

In M16-006, 55% (512/931) of subjects had failed or were intolerant to treatment with one or more biologic therapies (prior biologic failure). All subjects in M15-991 had prior biologic failure. At baseline, the median CDAI score was 307 (range: 76 to 634) and 307 (range: 72 to 651), and the median SES-CD score was 12 (range: 4 to 45) and 13 (range 4 to 40), in M16-006 and M15-991, respectively. At baseline, 30% and 34% of patients received corticosteroids, 24% and 23% of patients received immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and 31% and 19% of patients received aminosalicylates in M16-006 and M15-991, respectively. See Section 17.1 for further details regarding baseline demographics and clinical characteristics for subjects enrolled in each trial.

A total of 2737 subjects were screened and 1629 subjects were randomized into the trials, and were included in the primary safety database (Table 14).

Table 14. Patient Screening and Enrollment, ISS1

Disposition	ISS1
Patients screened	2737
Screening failures	969
Patients enrolled	1768
Patients randomized	1629

Source: Anne Bunner, PhD; Clinical Data Scientist
Abbreviations: ISS1, integrated summary of safety (12-week induction period)

A higher proportion of subjects randomized to treatment arms completed the study compared to the placebo arm. Additionally, there was a higher rate of study discontinuation observed in the placebo arm (13%) compared to the risankizumab treatment arms (risankizumab 600 mg: 4.2%; risankizumab 1200 mg: 3.5%). A higher rate of treatment discontinuation was observed in the placebo arm (11.6%) compared to the risankizumab treatment arms (2.1% in the risankizumab 600 mg and risankizumab 1200 mg treatment arms). Full details are presented in Table 15.

Table 15. Patient Disposition, ISS1

Disposition Outcome	RZB 600 mg IV N=620 n (%)	RZB 1200 mg IV N=577 n (%)	Placebo IV N=432 n (%)	Risk Difference (%) (95% CI)
Patients randomized	620	577	432	NA
ITT population	614	571	426	NA
ITT1A population	527	530	362	NA
Safety population	620	577	432	NA
Study discontinuation (safety population)				
Discontinued study	26 (4.2)	20 (3.5)	57 (13.2)	-9.0 (-12.6, -5.4)
Adverse event	11 (1.8)	11 (1.9)	31 (7.2)	-5.4 (-8.0, -2.8)
Covid-19 logistical restrictions	1 (0.2)	1 (0.2)	2 (0.5)	-0.3 (-1.0, 0.4)
Lack of efficacy	2 (0.3)	4 (0.7)	14 (3.2)	-2.9 (-4.6, -1.2)
Lost to follow-up	2 (0.3)	1 (0.2)	2 (0.5)	-0.1 (-0.9, 0.6)
Other	4 (0.6)	3 (0.5)	4 (0.9)	-0.3 (-1.4, 0.8)
Withdrawal by subject	8 (1.3)	4 (0.7)	10 (2.3)	-1.0 (-2.7, 0.6)
Treatment discontinuation (safety population)				
Discontinued study drug	13 (2.1)	12 (2.1)	50 (11.6)	-9.5 (-12.7, -6.3)
Adverse event	6 (1)	8 (1.4)	31 (7.2)	-6.2 (-8.8, -3.7)
Covid-19 logistical restrictions	0 (0)	1 (0.2)	2 (0.5)	-0.5 (-1.1, 0.2)
Lack of efficacy	1 (0.2)	4 (0.7)	11 (2.5)	-2.4 (-3.9, -0.9)
Lost to follow-up	(0)	(0)	2 (0.5)	-0.5 (-1.1, 0.2)
Other	3 (0.5)	3 (0.5)	4 (0.9)	-0.4 (-1.5, 0.6)
Withdrawal by subject	4 (0.6)	1 (0.2)	8 (1.9)	-1.2 (-2.6, 0.2)

Source: Anne Bunner, PhD; Clinical Data Scientist Subjects may have reported more than one reason for discontinuation.
Duration is median 84 days (minimum 28, maximum 154, mean 82, standard deviation 10.2 days).
Risk difference (with 95% confidence interval) is shown between 600 mg and placebo groups.
Abbreviations: CI, confidence interval; COVID-19, Coronavirus Disease 2019; ISS1, integrated summary of safety (12-week induction period); IV, intravenous; ITT, intent-to-treat; ITT1A, intent-to-treat primary analysis population; N, number of patients in treatment arm; n, number of patients in specified population or group; NA, not applicable; RZB, risankizumab

Exclusion of Sites/Subjects From the Efficacy Analyses

The Applicant reported that significant noncompliance was identified at an investigational site (Investigator ID 527969), which enrolled 13 subjects (5 subjects in the placebo arm, 4 subjects in the risankizumab 600 mg arm, and 4 subjects in the risankizumab 1200 mg arm) into Trial M15-991 and 5 subjects (1 subject in the placebo arm, 2 subjects in the risankizumab 600 mg arm, and 2 subjects in the risankizumab 1200 mg arm) into Trial M16-006. The following acts of noncompliance were observed, which were attributed to lack of principal investigator (PI) oversight: nonattributable signatures in informed consent forms (ICFs) and essential documents (as confirmed by the PI), termination of the primary study coordinator by the PI for noncompliance and delayed reporting to the Applicant, and significant data challenges (including randomization of subjects who do not meet the eligibility criteria). Therefore, efficacy data for the subjects enrolled at this investigational site were excluded from the statistical analyses.

Efficacy Results

The main analyses for the coprimary endpoints of CDAI clinical remission and endoscopic response by induction study are displayed in Table 16 and Table 17. The results from Studies M15-991 and M16-006 show that subjects who received risankizumab had higher rates of achieving the coprimary endpoints of CDAI clinical remission and endoscopic response than subjects who received placebo. The differences in rates were statistically significant, when comparing risankizumab 600 mg IV to placebo and when comparing risankizumab 1200 mg IV to placebo for both coprimary endpoints. The estimated difference in CDAI clinical remission rates between risankizumab and placebo ranged from 16.7% to 22.1% with all p-values less than 0.001, while the estimated difference in endoscopic response rates between risankizumab and placebo ranged from 17.6% to 28.3% with all p-values less than 0.001 as well.

Table 16. Proportion of Subjects Achieving CDAI Clinical Remission, Studies M16-006 and M15-991

	Study M16-006			Study M15-991		
Parameter	**Placebo (N=175)**	**RZB 600 mg (N=336)**	**RZB 1200 mg (N=339)**	**Placebo (N=187)**	**RZB 600 mg (N=191)**	**RZB 1200 mg (N=191)**
CDAI remission, n (%)[1]	43 (24.6)	152 (45.2)	141 (41.6)	37 (19.8)	80 (42)	77 (40.3)
Missing due to COVID-19	2	2	1	2	1	0
Treatment difference, % [CI[2]]		20.7 [12.4, 29.0]	16.7 [8.5, 24.9]		22.1 [13.1, 31]	20.5 [11.6, 29.5]
p-value		<0.001	<0.001		<0.001	<0.001

Source: Adapted from Tables 12, Clinical Study Reports for M16-006 and M15-99, Pages 105 and 110, respectively, and verified by review team. Datasets: adresp.xpt from M16-006 and M15-991

[1] n represents the average number of subjects who achieved CDAI clinical remission based on multiple imputation model rounded to the nearest integer; % represents the estimated CDAI clinical remission rate based on multiple imputation model

[2] Computed based on stratified risk difference using CMH weights

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; COVID-19, Coronavirus Disease 2019, N, number of patients in treatment arm; n, number of patients in specified population or group; RZB, risankizumab

Table 17. Proportion of Subjects Achieving Endoscopic Response, Studies M16-006 and M15-991

	Study M16-006			Study M15-991		
Parameter	**Placebo (N=175)**	**RZB 600 mg (N=336)**	**RZB 1200 mg (N=339)**	**Placebo (N=187)**	**RZB 600 mg (N=191)**	**RZB 1200 mg (N=191)**
Endoscopic response, n (%)[1]	21 (12.0)	135 (40.3)	109 (32.1)	21 (11.2)	55 (28.8)	65 (34.2)
Missing due to COVID-19	3	14	17	5	9	5
Treatment difference, % [CI[2]]		28.3 [21.2, 35.4]	20.3 [13.6, 27.1]		17.6 [9.9, 25.4]	23.1 [15.1, 31.1]
p-value		<0.001	<0.001		<0.001	<0.001

Source: Adapted from Tables 14, Clinical Study Reports for M16-006 and M15-991, Pages 108 and 113, respectively, and verified by review team. Datasets: adresp.xpt from M16-006 and M15-991

[1] n represents the average number of subjects who achieved endoscopic response based on multiple imputation model rounded to the nearest integer; % represents the estimated endoscopic response rate based on multiple imputation model

[2] Computed based on stratified risk difference using CMH weights

Abbreviations: CI, confidence interval; COVID-19, Coronavirus Disease 2019; N, number of patients in treatment arm; n, number of patients in specified population or group; RZB, risankizumab

The percentage of subjects with missing data for the coprimary endpoints ranged from 16% to 20% in the placebo arms, 4% to 9% in the risankizumab 600 mg IV arm, and 4% to 12% in the risankizumab 1200 mg IV arm. A nonresponder imputation approach was used to handle missing data due to reasons other than COVID-19. The percentage of subjects with missing data due to COVID-19 ranged from 0% to 5% in the risankizumab arms and from 1.1% to 2.7% in the placebo arm. Multiple imputation assuming missing at random was used to handle missing data due to COVID-19. As missing data due to COVID-19 was considered unlikely to be related to treatment outcome, this approach was considered reasonable. In addition, as CD is a chronic condition that generally require long-term maintenance treatment and subjects who discontinued study treatment would not experience a long-term benefit from said treatment without continued treatment, nonresponder imputation was considered appropriate for handling missing data due to dropout. Most of the missing data was due to dropout, with a higher dropout rate in the placebo groups. The placebo groups had much higher rates of dropout due to adverse events, withdrawal by subject, and lack of efficacy (which accounted for the majority of dropout in the placebo groups) compared to the risankizumab group.

The analyses for the ranked secondary endpoints in Study M16-006 and Study M15-991are displayed in Table 18 and Table 19, respectively. The adjusted treatment differences between the risankizumab arms and placebo were statistically significant for the first eight multiplicity-controlled secondary endpoints (tested sequentially) in both Study M16-006 and Study M15-991, with most p-values less than or equal to 0.001 and all p-values less than or equal to 0.023, respectively. In addition, the majority of the seven secondary endpoints that were controlled for multiplicity using the Holm procedure achieved statistical significance. Refer to Section entitled "Discussion of Secondary Endpoints Proposed for Labeling" for further details regarding which endpoints will be included in labeling. The only exceptions were no draining fistulas at Week 12 in subjects with draining fistulas at baseline (which was not significant in both studies for either dose), resolution of EIMs at Week 12 in subjects with any EIMs at baseline (which was only significant for the 1200-mg dose in Study M16-006), and enhanced SF/APS clinical response at Week 4 (which was not significant for the 1200-mg dose in Study M15-991).

Table 18. Secondary Endpoints, Study M16-006

	Endpoints	Parameter	Placebo (N=175)	RZB 600 mg (N=336)	RZB 1200 mg (N=339)	Adjusted Difference, 95% CI (RZB 600 mg vs. Placebo)[1]	Adjusted Difference, 95% CI (RZB 1200 mg vs. Placebo)[1]
1	SF/APS clinical remission at Week 12	%	21.7	43.5	41.0	21.9 [13.8, 29.9] (p<0.001)	18.8 [10.8, 26.8] (p<0.001)
2	CDAI clinical response at Week 4	%	25.2	40.8	37.2	15.4 [7.2, 23.7] (p<0.001)	11.2 [3.1, 19.2] (p=0.007)
3	CDAI clinical response at Week 12	%	36.7	59.7	64.9	23.1 [14.2, 31.9] (p<0.001)	27.8 [19.0, 36.4] (p<0.001)
4	Change in FACIT-F at Week 12	(N) LSMEAN (SE)	(N=134) 6.0 (0.86)	(N=302) 11.2 (0.59)	(N=310) 10.1 (0.58)	5.2 [3.2, 7.2] (p<0.001)	4.1 [2.1, 6.1] (p<0.001)
5	CDAI clinical remission at Week 4	%	10.3	18.4	18.9	7.6 [1.5, 13.7] (p=0.015)	8.4 [2.3, 14.6] (p=0.007)
6	CDAI clinical response and endoscopic response at Week 12	%	5.7	30.0	23.0	24.5 [18.5, 30.5] (p<0.001)	17.3 [11.8, 22.9] (p<0.001)
7	SF remission at Week 12	%	29.8	54.2	54.0	24.2 [15.7, 32.7] (p<0.001)	23.6 [15.1, 32.1] (p<0.001)
8	APS remission at Week 12	%	38.5	59.6	58.1	21.2 [12.4, 30.0] (p<0.001)	19.0 [10.1, 27.8] (p<0.001)
	Endoscopic remission at Week 12[2]	%	9.1	24.2	23.9	15.1 [9.0, 21.2] (p<0.001)	15.4 [9.4, 21.4] (p<0.001)
	Enhanced SF/APS clinical response at Week 4[2]	%	31.0	46.0	43.4	14.9 [6.2, 23.5] (p<0.001)	11.8 [3.2, 20.3] (p=0.007)
	Ulcer-free endoscopy at Week 12[2]	(N) %	(N=173) 7.6	(N=336) 21.0	(N=338) 16.4	13.7 [7.9, 19.5] (p<0.001)	9.1 [3.7, 14.5] (p=0.001)
	Enhanced SF/APS clinical response at Week 12[2]	%	41.9	62.8	64.3	21.0 [12.2, 29.9] (p<0.001)	21.6 [12.8, 30.4] (p<0.001)

Endpoints	Parameter	Placebo (N=175)	RZB 600 mg (N=336)	RZB 1200 mg (N=339)	Adjusted Difference, 95% CI (RZB 600 mg vs. Placebo)[1]	Adjusted Difference, 95% CI (RZB 1200 mg vs. Placebo)[1]
Resolution of EIMs at Week 12, in subjects with any EIMs[2]	(N) %	(N=64) 20.5	(N=140) 38.1	(N=158) 43.7	14.6 [2.1, 27.0] (p=0.022) NS	23.7 [11.1, 36.3] (p<0.001)
CD-related hospitalization[2]	%	12.0	3.3	1.8	-8.7 [-13.9, -3.5] (p<0.001)	-10.2 [-15.2, -5.2] (p<0.001)
No draining fistulas in subjects with draining fistulas[2]	(N) %	(N=9) 22.2	(N=18) 27.8	(N=24) 29.2	5.6 [-28.6, 39.7] (p=1.000)NS	6.9 [-25.7, 39.6] (p=1.000)NS

Source: Table 15, Clinical Study Report for M16-006, Pages 114-115 (verified by review team)
[1] Computed based on stratified risk difference using CMH weights for binary endpoints and MMRM (mixed effect model repeat measurement) for continuous endpoints.
[2] Secondary endpoints were controlled for multiplicity simultaneously (without a predetermined sequence) using the Holm procedure
Abbreviations: APS, abdominal pain score; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; EIM, extraintestinal manifestation; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; LSMEAN, least square means; N, number of patients in treatment arm; n, number of patients in specified population or group; NS, not significant; RZB, risankizumab; SE, standard error; SF, stool frequency

Table 19. Secondary Endpoints, Study M15-991

	Endpoints		Placebo (N=187)	RZB 600 mg (N=191)	RZB 1200 mg (N=191)	Adjusted Difference, 95% CI (RZB 600 mg vs. Placebo)[1]	Adjusted Difference, 95% CI (RZB 1200 mg vs. Placebo)[1]
1	SF/APS clinical remission at Week 12	%	19.3	34.6	39.8	15.2 [6.4, 24.0] (p=0.001)	20.4 [11.5, 29.3] (p<0.001)
2	CDAI clinical response at Week 4	%	20.9	36.6	32.5	15.7 [6.8, 24.6] (p=0.001)	11.8 [3.0, 20.5] (p=0.008)
3	CDAI clinical response at Week 12	%	30.0	59.5	60.7	29.4 [19.9, 39.0] (p<0.001)	30.6 [21.1, 40.1] (p<0.001)
4	Change in FACIT-F at Week 12	(N) LSMEAN (SE)	(N=144) 7.7 (0.87)	(N=168) 10.5 (0.81)	(N=172) 10.8 (0.81)	2.8 [0.4, 5.1] (p=0.020)	3.0 [0.7, 5.3] (p=0.010)
5	CDAI clinical remission at Week 4	%	11.2	20.9	19.4	9.6 [2.3, 16.9] (p=0.010)	8.2 [1.1, 15.3] (p=0.023)
6	CDAI clinical response and endoscopic response at Week 12	%	5.3	20.5	23.0	15.0 [8.5, 21.5] (p<0.001)	17.8 [11.1, 24.5] (p<0.001)
7	SF remission at Week 12	%	28.3	46.1	48.7	17.5 [8.0, 26.9] (p<0.001)	20.3 [10.8, 29.8] (p<0.001)
8	APS remission at Week 12	%	36.4	58.1	59.2	21.8 [12.1, 31.6] (p<0.001)	22.7 [13.0, 32.5] (p<0.001)

Endpoints		Placebo (N=187)	RZB 600 mg (N=191)	RZB 1200 mg (N=191)	Adjusted Difference, 95% CI (RZB 600 mg vs. Placebo)[1]	Adjusted Difference, 95% CI (RZB 1200 mg vs. Placebo)[1]
Endoscopic remission at Week 12[2]	%	4.3	19.4	20.4	15.0 [8.9, 21.2] (p<0.001)	16.2 [9.9, 22.4] (p<0.001)
Enhanced SF/APS clinical response at Week 4[2]	%	31.6	45.0	38.7	13.6 [4.0, 23.3] (p=0.006)	7.1 [-2.4, 16.6] (p=0.142) NS
Ulcer-free endoscopy at Week 12[2]	(N) %	(N=186) 4.3 (8)	(N=190) 13.8 (26)	(N=189) 15.4 (29)	9.4 [3.8, 15.1] (p<0.001)	11.2 [5.3, 17.0] (p<0.001)
Enhanced SF/APS clinical response at Week 12[2]	%	39.1	61.8	59.2	22.8 [13.0, 32.5] (p<0.001)	20.0 [10.2, 29.9] (p<0.001)
Resolution of EIMs at Week 12, in subjects with any EIMs[2]	(N) %	(N=97) 23.7 (23)	(N=100) 29.5 (30)	(N=97) 37.1 (36)	5.6 [-6.8, 17.9] (p=0.377)NS	13.4 [0.7, 26.1] (p=0.039)NS
CD-related hospitalization[2]	%	11.2	3.1	2.1	-8.1 [-13.2, -2.9] (p=0.002)	-9.1 [-14.1, -4.2] (p<0.001)
No draining fistulas in subjects with draining fistulas[2]	(N) %	(N=15) 13.3 (2)	(N=14) 7.1 (1)	(N=16) 43.8 (7)	-6.2 [-28.1, 15.7] (p=1.000)NS	30.4 [0.6, 60.2] (p=0.113)NS

Source: Table 15, Clinical Study Report for M15-991, Pages 118-119 (verified by review team)
[1] Computed based on stratified risk difference using CMH weights for binary endpoints and MMRM (mixed effect model repeat measurement) for continuous endpoints
[2] Secondary endpoints were controlled for multiplicity simultaneously (without a predetermined sequence) using the Holm procedure
Abbreviations: APS, abdominal pain score; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; EIM, extraintestinal manifestation; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; LSMEAN, least square means; N, number of patients in treatment arm; n, number of patients in specified population or group; NS, not significant; RZB, risankizumab; SE, standard error; SF, stool frequency

Discussion of Secondary Endpoints Proposed for Labeling

Endoscopic Endpoints

The results of the ranked secondary endpoints indicate that, in addition to overall clinical remission (based on CDAI score), risankizumab 600 mg IV and 1200 mg IV resulted in improvement in grossly visible endoscopic inflammation, compared to placebo treatment arm. Achievement of resolution of gross inflammation that can be visualized on endoscopy is a clinically relevant outcome of interest, as patients who achieve endoscopic improvement or endoscopic remission have been shown to have better outcomes than those with continued active inflammation (De Cruz et al. 2013; Yzet et al. 2020). Assessment of endoscopic remission based SES-CD score reflects a more comprehensive evaluation of endoscopic response than “ulcer free endoscopy" as it includes assessment of degree of affected surface and presence (or absence) of narrowing, in addition to the extent and size of ulcers. Thus, endoscopic remission will be included in labeling.

CDAI Clinical Response and Remission

(b) (4)

labeling; rather, a descriptive statement regarding the onset of clinical response and remission that occurred as early as Week 4 in a greater proportion of risankizumab-treated subjects compared to placebo will be included to inform prescribers regarding the expected treatment response.

Stool Frequency and Abdominal Pain

Stool frequency and abdominal pain represent important clinical symptoms that impact the quality of life in CD patients. However, these symptoms may be attributed to factors unrelated to underlying CD and/or comorbid conditions (e.g., anxiety, viral gastroenteritis, irritable bowel syndrome, etc.), and should be interpreted with caution.

Since information about general improvement in abdominal pain and stool frequency from baseline may be informative for prescribers and patients with CD, the proportion of subjects in treatment and placebo arms that experienced improvement in these symptoms after induction treatment will be described in the text of the label.

(b) (4)

6.2.1.4. Subgroup Analysis for M16-006, By Prior Biologic Failure

Efficacy results were investigated by prior biologic failure status for important efficacy endpoints in Study M16-006 (Table 20). Study M15-991 was not included in this subgroup analysis as this study only enrolled subjects with prior biologic failure. Although the study was not powered to detect a significant difference for each subgroup, the group without prior biologic failure showed numerically higher clinical remission and endoscopic remission and response

rates compared to the group with prior biologic failure. The risankizumab groups consistently showed higher remission and response rates compared to the placebo across all subgroups.

Table 20. Subgroup Analyses, Study M16-006

Endpoint	RZB 600 mg IV (N=336) %	RZB 1200 mg IV (N=339) %	Placebo IV (N=175) %
Clinical remission at Week 12	45.2%	41.6%	24.6%
Without prior biologic failure	(N=141)	(N=140)	(N=78)
	48.9%	47.1%	23.1%
With prior biologic failure	(N=195)	(N=199)	(N=97)
	42.5%[1]	37.7%	25.8%
Endoscopic response at Week 12	40.3%	32.1%	12.0%
Without prior biologic failure	(N=141)	(N=140)	(N=78)
	50.5%[2]	43.9%	12.8%
With prior biologic failure	(N=195)	(N=199)	(N=97)
	32.9%	23.8%	11.4%
Clinical response at Week 12	59.7%	64.9%	36.7%
Without prior biologic failure	(N=141)	(N=140)	(N=78)
	61.8%	69.3%	40%
With prior biologic failure	(N=195)	(N=199)	(N=97)
	58.3%	61.8%	34.1%
Endoscopic remission at Week 12	24.2%	23.9%	9.1%
Without prior biologic failure	(N=141)	(N=140)	(N=78)
	32%	35.8%	14.1%
With prior biologic failure	(N=195)	(N=199)	(N=97)
	18.5%[3]	15.6%	5.2%

Source: Table 1, Applicant's Response to FDA's January 21, 2022, Request for Information
[1] Percentage is 42.46% and is presented on the label as 42%
[2] Percentage is 50.47% and is presented on the label as 50%
[3] Percentage is 18.48% and is presented on the label as 18%
Abbreviations: IV, intravenous; N, number of patients in the treatment group; RZB, risankizumab

6.2.2. Maintenance Study M16-000, Substudy 1

Study M16-000 evaluated the long-term efficacy and safety of risankizumab in subjects who achieved clinical response in Studies M16-006 and M15-991.

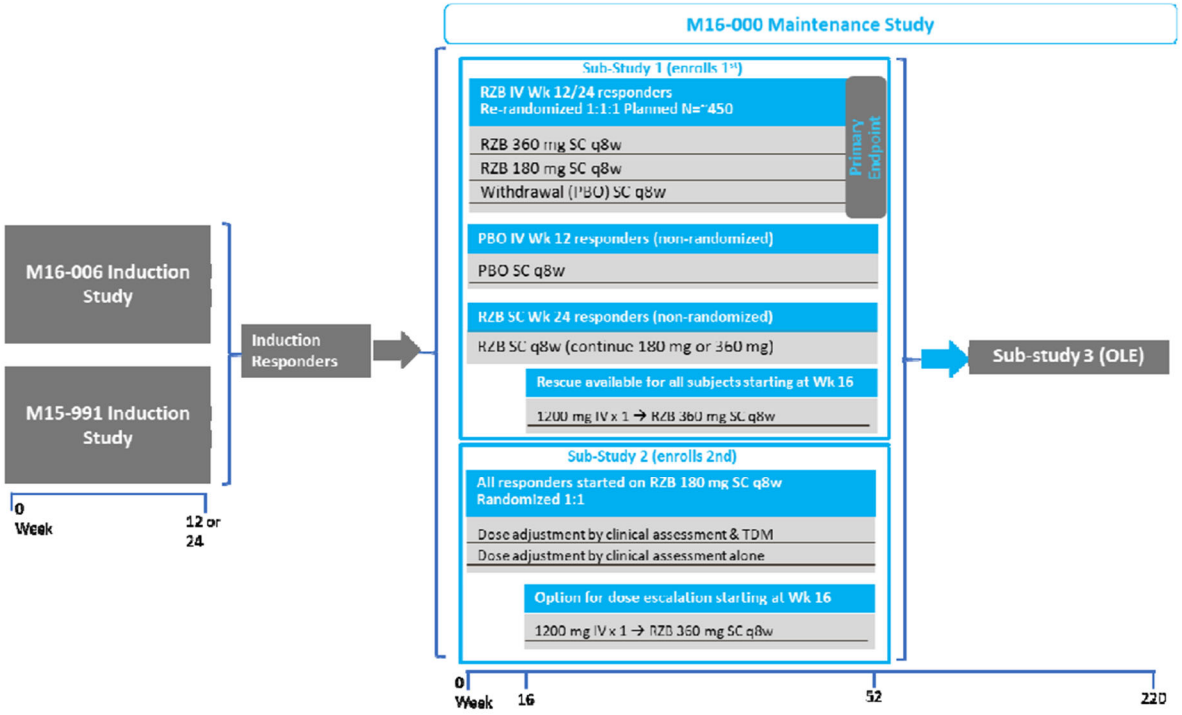
6.2.2.1. Design, Study M16-000

Study M16-000 is a phase 3, multicenter study that enrolled subjects who achieved SF/APS clinical response at the last visit of induction Studies M16-006 or M15-991. Clinical response per SF/APS is defined as ≥30% decrease in average daily SF and/or ≥30% decrease in average daily APS and both not worse than Baseline of the induction study.

Study M16-000 (Figure 3) consists of 3 substudies: Substudy 1 was a 52-week randomized, DB, placebo-controlled maintenance study. Substudy 2, which began after enrollment into Substudy 1 ended, is an ongoing 52-week randomized, exploratory maintenance study of 2 different dosing regimens (therapeutic drug monitoring versus clinical assessment for dose escalation). Substudy 3 is an OL long-term extension to Substudies 1 and 2. Substudy 4 is a RLHS evaluating the OBDS in patients enrolled in Substudy 3 (see Section 17.3).

The results discussed in this review are from Study M16-000, Substudy 1.

Figure 3. Maintenance Study Schema for Study M16-000



Source: BLA761105-S016 Submission. Summary of Clinical Efficacy. Pg.20 of 159
Abbreviations: IV, intravenous; N, number of patients in the treatment group; OLE, open-label extension; PBO, placebo; q8w, every 8 weeks; RZB, risankizumab; SC, subcutaneous; TDM, therapeutic drug monitoring; wk, week

Substudy 1 randomized subjects who met criteria for clinical response (based on stool frequency and abdominal pains cores) after completion of induction trials (M16-006 and M15-991), which included a mixed population of subjects who had an IR or intolerance to prior biologic therapy (Bio-IR) and/or conventional therapy including subjects exposed to biologics but who stopped therapy for reasons other than IR or intolerance (Non-Bio-IR).

Substudy 1 consisted of a randomized portion and a nonrandomized portion. The randomized portion used a rerandomized responder-withdrawal design. Subjects with SF/APS clinical response to IV risankizumab induction (at Week 12 of the induction study or Week 24 of Induction Period 2 in the induction study) and a Baseline induction eligibility SES-CD of ≥6 (≥4 for isolated ileal disease) were rerandomized in a 1:1:1 ratio to receive risankizumab at either 180 mg SC Q8W or 360 mg SC Q8W, or have risankizumab treatment withdrawn (i.e., receive placebo SC Q8W).

Randomized subjects were stratified based on endoscopic response (per local read) and SF/APS clinical remission status at the end of induction, as well as by last risankizumab induction IV dose received. Two of the three stratification factors, endoscopic response and SF/APS clinical remission, were the original coprimary endpoints for the induction study. After Study M16-000 had begun, SF/APS clinical remission was replaced by CDAI clinical remission as a coprimary endpoint (see below for the endpoint definitions). However, the original stratification factor of SF/APS clinical remission status was not changed.

There were subjects who were rerandomized into Study M16-000 but excluded from the primary population for efficacy analysis. This included subjects who achieved SF/APS clinical response to IV risankizumab induction treatment and had a Baseline eligibility SES-CD of <6 (<4 for isolated ileal disease) (i.e., subjects with lower SES-CD) and subjects who achieved SF/APS clinical response to 24 weeks of IV risankizumab induction treatment. The nonrandomized portion of Substudy 1 enrolled subjects with SF/APS clinical response to IV placebo induction treatment and subjects with SF/APS clinical response to SC risankizumab at the end of the induction studies (i.e., subjects who did not respond to the initial IV induction treatment but responded to SC during Induction Period 2). These subjects were assigned by Interactive Response Technology to continue to receive the same blinded study drug, either placebo SC or risankizumab SC, and were also excluded from the primary population for efficacy analysis.

The coprimary endpoints are CDAI clinical remission (defined as CDAI <150) at Week 52 and endoscopic response (defined as 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) at Week 52.

The first nine multiplicity-controlled secondary endpoints were tested sequentially within each dose as follows:

(1) SF/APS clinical remission (defined as an average daily SF ≤2.8 and not worse than baseline AND average daily APS ≤1 and not worse than baseline) at Week 52

(2) CDAI clinical remission at Week 52 among the subjects with CDAI clinical remission at Week 0

(3) Ulcer-free endoscopy at Week 52

(4) Endoscopic remission (defined as 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) at Week 52

(5) Change of FACIT-F at Week 52 from baseline of induction

(6) Discontinuation of corticosteroid use for 90 days and achievement of CDAI clinical remission at Week 52 among subjects taking steroids at baseline of induction

(7) CDAI clinical response (defined as a reduction of CDAI ≥100 points from baseline) at Week 52

(8) Stool frequency remission (defined as average daily SF ≤2.8 and not worse than baseline) at Week 52

(9) Abdominal pain remission (defined as average daily APS ≤1 and not worse than baseline) at Week 52

The remaining three multiplicity-controlled secondary endpoints were to be tested if the previous nine secondary endpoints were significant. The following three secondary endpoints were controlled for multiplicity using the Holm procedure:

(1) CDAI clinical remission and endoscopic response at Week 52

(2) "Deep remission" (defined as subjects who achieve both CDAI clinical remission and endoscopic remission) at Week 52

(3) Exposure-adjusted occurrence of CD-related hospitalizations from Week 0 through 52

6.2.2.2. Statistical Analysis Plan, Study M16-000

The Intent-to-Treat population for the Substudy 1 (denoted as ITT1) includes subjects (randomized and nonrandomized) who received at least one dose of study drug from the Substudy 1.

The primary population for efficacy analyses in Substudy 1 is the ITT1A population. This population includes randomized subjects in the ITT1 population who met the eligibility criterion of SES-CD of ≥6 (≥4 for isolated ileal disease) at baseline of the induction study and received IV risankizumab for only one 12-week period of induction in study M16-006 or M15-991. This included subjects who were randomized to receive placebo during the first 12-week induction period, did not meet the definition of clinical response (defined as ≥30% decrease in average daily SF and/or ≥30% decrease in average daily APS at Week 12), and received risankizumab 1200 mg IV during Induction Period 2. During the review cycle, the Agency sent an information request, asking the Applicant to provide new analyses based on a subset of the study population who met the definition of CDAI clinical response (defined as a reduction of CDAI ≥100 points from baseline) at the end of the induction period. Clinical response based on the CDAI is the currently recommended approach reflected in the U.S. Food and Drug Administration (FDA) draft guidance for industry *Crohn's Disease: Developing Drugs for Treatment* (April 2022). While SF and AP are important symptoms in CD patients, these symptoms represent only two of many clinical manifestations related to CD and may be attributed to factors unrelated to underlying CD and/or comorbid conditions (e.g., anxiety, viral gastroenteritis, irritable bowel syndrome, etc.). Therefore, the individual scores alone inadequately assess clinical response in CD patients, and the primary efficacy analysis utilized the definition of clinical response based on an overall change from baseline CDAI score.

The comparisons between each of the risankizumab dose group versus placebo for the primary efficacy variables was performed using the normal approximation to the stratified risk difference using CMH weights. The stratified risk difference was adjusted for the randomization stratification factors of Study M16-000 Week 0 SF/APS clinical remission status and Study M16-000 Week 0 endoscopic response (Week 12 or 24 of Study M16-006 or Study M15-991) status (per central read), and risankizumab induction dose. 95% confidence intervals for the stratified risk differences between treatment groups using CMH weights were also calculated.

A multiple testing procedure was used to provide strong control of the overall type I error rate at an alpha of 0.05 (2-sided) across analyses comparing each risankizumab dose group to placebo with respect to the coprimary endpoints and ranked secondary endpoints (see Section 16.1 for more details). Binary secondary endpoints were tested using the same method as the coprimary endpoints. The continuous efficacy variable, FACIT-F, was analyzed using an ANCOVA model with strata (endoscopic response at Week 0 (yes or no), SF/APS clinical remission status (based on SF or AP scores) at Week 0 (yes or no), last IV dose during risankizumab induction periods (1200 mg or 600 mg)), and induction baseline FACIT-F and Week 0 FACIT-F.

The estimands corresponding to the primary efficacy objective for U.S.-specific protocol were defined as follows:

- Difference in the percentage of subjects achieving CDAI clinical remission at Week 52 regardless of premature discontinuation of study drug, without initiation or dose escalation of CD-related corticosteroids and without initiation of rescue therapy in each of the risankizumab 360 mg SC and risankizumab 180 mg SC groups in comparison with the placebo group in the ITT1A population
- Difference in the percentage of subjects achieving endoscopic response at Week 52 regardless of premature discontinuation of study drug, without initiation or dose escalation of CD-related corticosteroids and without initiation of rescue therapy in each of the risankizumab 360 mg SC and risankizumab 180 mg SC groups in comparison with the placebo group in the ITT1A population.

If a subject prematurely discontinued the study drug, all subsequent data were used. If a subject experienced initiation or dose-escalation of CD-related corticosteroids, the subject was considered a nonresponder. If a subject initiated rescue therapy, the subject was considered a nonresponder.

A nonresponder imputation approach was used to handle missing data due to reasons not related to COVID-19. Multiple imputation assuming missing at random was used to handle missing data due to COVID-19 in the primary analysis. As a sensitivity analysis, the nonresponder imputation approach was used to handle all missing data, including for COVID-19.

6.2.2.3. Results of Analyses, Study M16-000

Demographic characteristics were generally balanced between treatment groups (Table 21). Review of demographics and subject disposition data revealed no notable differences between the risankizumab treatment and placebo arms.

Table 21. Baseline Demographic and Clinical Characteristics, CDAI Responders in Safety Population, Study M16-000

Characteristic	RZB 180 mg SC Q8W, Responder N=155	RZB 360 mg SC Q8W, Responder N=142	Placebo SC Q8W, Responder N=143
Sex, n (%)			
Female	85 (54.8)	59 (41.5)	66 (46.2)
Male	70 (45.2)	83 (58.5)	77 (53.8)
Age, years			
Mean (SD)	39.4 (14.5)	36.9 (12.9)	38.1 (12.9)
Median (min, max)	37 (16, 75)	34 (16, 71)	37 (17, 76)
Age group, years, n (%)			
<18	1 (0.6)	2 (1.4)	1 (0.7)
18 to <40	89 (57.4)	87 (61.3)	81 (56.6)
40 to <65	52 (33.5)	47 (33.1)	57 (39.9)
≥65	13 (8.4)	6 (4.2)	4 (2.8)

Characteristic	RZB 180 mg SC Q8W, Responder N=155	RZB 360 mg SC Q8W, Responder N=142	Placebo SC Q8W, Responder N=143
Race, n (%)			
Asian	18 (11.6)	18 (12.7)	27 (18.9)
Black or African American	4 (2.6)	7 (4.9)	7 (4.9)
Multiple	3 (1.9)	3 (2.1)	0 (0)
Native Hawaiian or Other Pacific Islander	1 (0.6)	0 (0)	0 (0)
White	129 (83.2)	114 (80.3)	109 (76.2)
Ethnicity, n (%)			
Hispanic or Latino	10 (6.5)	9 (6.3)	6 (4.2)
Not Hispanic or Latino	145 (93.5)	133 (93.7)	137 (95.8)
Region of participation, n (%)			
Asia	17 (11.0)	18 (12.7)	24 (16.8)
Eastern Europe	34 (21.9)	31 (21.8)	22 (15.4)
North America	41 (26.5)	34 (23.9)	45 (31.5)
Other	11 (7.1)	11 (7.7)	8 (5.6)
South/Central America	4 (2.6)	1 (0.7)	1 (0.7)
Western Europe	48 (31.0)	47 (33.1)	43 (30.1)

Source: Anne Bunner, PhD; Clinical Data Scientist
Abbreviations: CDAI, Crohn's disease activity index; N, number of patients in treatment group; n, number of patients with given characteristic; Q8W, every 8 weeks; RZB, risankizumab; SC, subcutaneous; SD, standard deviation

In total, 1288 subjects were eligible for enrollment in Trial M16-000 (Table 22). Of this cohort, 542 subjects met criteria for CDAI clinical response after 12 weeks of induction therapy, and therefore were included in the primary maintenance safety database.

Table 22. Patient Screening and Enrollment, Trial M16-000

Disposition	N
Patients eligible for enrollment[1]	1288
Patients screened[2]	542
Screening failures[2]	0
Patients enrolled[2]	542
Patients randomized[2]	542

Source: ds.xpt and Clinical Study Report for M16-000, adsl.xpt and adresp.xpt for M15-991 and M16-006; Software: R
Source: Anne Bunner, PhD; Clinical Data Scientist
[1] Patients who completed period 1 or 2 in M15-991 or M16-006 and who had SF/APS (stool frequency/abdominal pain score) clinical response at Week 12 or 24 in M15-991 or M16-006 were elig ble for enrollment in M16-000 and are counted here. Only those with M16-000 baseline induction elig bility Simple Endoscopic Score for Crohn's Disease (SES-CD) of ≥6 (≥4 for isolated ileal disease) were eligible for randomization.
[2] 170 nonrandomized subjects not shown in this row.
Abbreviations: N, number of patients in treatment group

A higher proportion of subjects randomized to risankizumab 360 mg SC treatment arm (12.7%) discontinued study compared to the risankizumab 180 mg SC treatment arm (8.4%) and placebo arm (10.5%). Additionally, a higher proportion of subjects treated with risankizumab 360 mg SC (10.6%) discontinued study drug compared to the risankizumab 180 mg SC (7.1%) arm and placebo (9.8%) arm. Higher rate of study discontinuation and treatment discontinuation in the risankizumab 360 mg SC group were attributed to “other” reasons; further clarification regarding reason for discontinuation was not provided in the submission. Additionally, a higher proportion of subjects in the risankizumab 360 mg SC treatment arm discontinued study treatment due to adverse events (AEs) compared to the other treatment or placebo arm(s). The most common reason for treatment discontinuation in the risankizumab 360 mg treatment arm was reported as

"other"; further details were not included in the marketing application. Full details regarding subject disposition are presented in Table 23.

Table 23. Patient Disposition, Responders in Safety Population, Trial M16-000

Disposition Outcome	RZB 180 mg SC Q8W, Responder N=155 n (%)	RZB 360 mg SC Q8W, Responder N=142 n (%)	Placebo SC Q8W, Responder N=143 n (%)	Risk Difference (%) (95% CI)
Patients randomized	155	142	143	
Safety population	155	142	143	
FDA primary efficacy population	135	117	130	
Discontinued study treatment	11 (7.1)	15 (10.6)	14 (9.8)	0.8 (-6.2, 7.8)
Adverse event	2 (1.3)	4 (2.8)	4 (2.8)	0.0 (-3.8, 3.9)
Covid-19 logistical restrictions	0 (0)	2 (1.4)	0 (0)	1.4 (-0.5, 3.3)
Lack of efficacy	2 (1.3)	2 (1.4)	7 (4.9)	-3.5 (-7.5, 0.5)
Lost to follow-up	2 (1.3)	2 (1.4)	0 (0)	1.4 (-0.5, 3.3)
Other	2 (1.3)	6 (4.2)	1 (0.7)	3.5 (-0.1, 7.1)
Withdrawal by subject	4 (2.6)	3 (2.1)	3 (2.1)	0.0 (-3.3, 3.3)
Discontinued study	13 (8.4)	18 (12.7)	15 (10.5)	2.2 (-5.2, 9.6)
Adverse event	2 (1.3)	4 (2.8)	3 (2.1)	0.7 (-2.9, 4.3)
Covid-19 logistical restrictions	0 (0)	1 (0.7)	1 (0.7)	0.0 (-1.9, 1.9)
Lack of efficacy	3 (1.9)	3 (2.1)	7 (4.9)	-2.8 (-7.0, 1.5)
Lost to follow-up	2 (1.3)	3 (2.1)	0 (0)	2.1 (-0.3, 4.5)
Other	3 (1.9)	6 (4.2)	2 (1.4)	2.8 (-1.0, 6.7)
Withdrawal by subject	4 (2.6)	3 (2.1)	3 (2.1)	0.0 (-3.3, 3.3)

Source: Anne Bunner, PhD; Clinical Data Scientist Subjects may have reported more than one reason for discontinuation.
Duration is median 390 days (minimum 56, maximum 438, mean 324, standard deviation 106 days).
Risk difference (with 95% confidence interval) is shown between responder 360 mg treatment and responder placebo groups.
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; N, number of patients in treatment arm; n, number of patients in specified population or group; Q8W, every 8 weeks; RZB, risankizumab; SC, subcutaneous

Exclusion of Sites/Subjects From the Efficacy Analyses

The Applicant reported that significant noncompliance was identified at an investigational site (Investigator ID 527969) before interim database lock. This site had enrolled 8 subjects in Study M16-000, Substudy 1, and had previously enrolled 13 subjects in Study M15-991 and 5 subjects in Study M16-006. The noncompliance was observed in lack of PI oversight (nonattributable signatures in ICFs and essential documents [as confirmed by the PI], termination of primary Study Coordinator by the PI for noncompliance and delayed reporting to the Applicant, and significant data challenges, including subjects randomized without eligibility criteria). As a result of this finding, efficacy data for the subjects enrolled at this investigational site were excluded from the statistical analyses.

Efficacy Results

The Applicant's prespecified primary analysis population was based on randomized subjects who had met the eligibility criterion of SES-CD of ≥6 (≥4 for isolated ileal disease) at baseline of the induction study, received IV risankizumab for 12 weeks in the induction study, and received at least one dose of study drug from the Substudy 1. On October 28, 2021, the Agency sent an information request to the Applicant, asking the Applicant to provide new analyses based on a subset of the study population who met the definition of CDAI clinical response (reduction

of CDAI ≥100 points from baseline) at the end of the induction period, in addition to the eligibility criteria for Study M16-000. The eligibility criteria for Study M16-000 included the achievement of clinical response based on SF and APS during the induction studies, which is defined as ≥30% decrease in average daily SF and/or ≥30% decrease in average daily APS and both not worse than baseline. However, the Agency currently recommends defining clinical response by a change of CDAI score of ≥100 points from baseline (see Section 6.2.2.2).

The Applicant responded to the information request and submitted the updated results on November 8, 2021. The updated results reported by the Applicant were based on reperforming multiple imputation using only the subjects who met the definition of CDAI clinical response at the end of the induction period. The review team performed analyses using the original imputed datasets (which included all subjects from the ITT1A population of Substudy 1 in the imputation) for the subset of subjects who met the definition of CDAI clinical response at the end of the induction period. This resulted in minor differences in the results from the Applicant's analyses and the review team's analyses that did not impact efficacy conclusions. Results presented in this review are based on the review team's analyses; however, the results presented in labeling are based on the Applicant's analyses. Differences that impact the number presented in the label are noted where appropriate.

The results for the protocol-specified analysis are presented in Section 16.2, while the results of the review team's analysis based on CDAI clinical response at the end of induction are presented in Table 24 below. These results show that subjects who received risankizumab had higher rates of CDAI clinical remission and endoscopic response than subjects who received placebo. The differences in rates between the 180-mg dose and placebo and the 360-mg dose and placebo were statistically significant for both coprimary endpoints. The adjusted differences from placebo in CDAI clinical remission rates were 16.9% and 14.3% for the 180-mg and 360-mg doses, respectively; in the protocol-specified analyses, the adjusted differences were 14.7% and 14.6%, respectively. The adjusted differences in endoscopic response rates were 29.9% and 30.5% for the 180-mg and 360-mg doses, respectively. In the protocol-specified analyses, the adjusted differences were 26.0% and 27.8%, respectively.

Table 24. Coprimary Endpoints, Primary Analysis, Study M16-000 Baseline CDAI Clinical Responders

		CDAI Clinical Remission		Endoscopic Response	
Treatment	Sample Size	Remission Rate (%) (95% CI)	Difference in Rate vs. Placebo, 95% CI, and p-Values[1]	Response Rate (%) (95% CI)	Difference in Rate vs. Placebo, 95% CI, and p-Values[1]
Placebo	130	46.2 (37.6, 54.7)	NA	21.5 (14.5, 28.6)	NA
180 mg	135	61.5 (53.3, 69.7)	16.9 (5.9, 27.8) (p=0.003)	50.4 (41.9, 58.8)	29.9 (20.3, 39.5) (p<0.001)
360 mg	117	56.9 (47.9, 65.9)	14.3 (2.8, 25.8) (p=0.015)	48.4 (39.3, 57.5)	30.5 (20.4, 40.6)[2] (p<0.001)

Source: Review team's analysis created from admicdai.xpt and admiendo.xpt
[1] Computed based on stratified risk difference using CMH weights
[2] Lower bound of the 95% confidence interval was 20.57% according to the Applicant's analysis and is reported as 21% in the label
Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; NA, not applicable; vs, versus

For the subset of subjects who achieved CDAI clinical response at the end of the induction period, the percentage of subjects with missing data for the coprimary endpoints ranged from

11% to 14% in the placebo arms, 6% to 9% in the risankizumab 180 mg SC arm, and 15% to 17% in the risankizumab 360 mg SC arm. A nonresponder imputation approach was used to handle missing data due to reasons other than COVID-19. The percentage of subjects with missing data due to COVID-19 was 0% in the placebo and risankizumab 180 mg SC arms, and ranged from 0.9% to 2.6% in the risankizumab 360 mg SC arm. The percentage of subjects who were missing due to dropout (i.e., discontinued from study without utilization of risankizumab rescue therapy or initiation of CD-related corticosteroids) was 3.1% in the placebo arm, 3.7% in the risankizumab 180 mg SC arm, and 7.7% in the risankizumab 360 mg SC arm. The lower missing data rate in the placebo arm may be due to a higher proportion of subjects in the placebo arm requiring rescue therapy, as data from subjects who required risankizumab rescue therapy or initiation of CD-related corticosteroids were not considered missing in the efficacy analyses. Use of rescue therapy generally suggests lack of efficacy from study drug, as such, it is considered appropriate to treat these subjects as nonresponders for the primary analysis. Most missing data were due to study dropout, of which more placebo subjects dropped out due to lack of efficacy or AE compared to the risankizumab arms. Because CD is a chronic condition and subjects who discontinued study treatment would not experience a long-term benefit from said treatment without continued treatment, nonresponder imputation was considered appropriate for handling missing data due to dropout. Furthermore, given the reasons for dropout and the higher rates of rescue therapy usage in the placebo group, it does not appear that the nonresponder imputation used to handle missing data due to reasons other than COVID-19 biased estimates of the treatment effect in favor of the risankizumab arms.

As the coprimary endpoints for both doses met statistical significance versus placebo, the testing procedure continued to the ranked secondary endpoints. For the risankizumab 180-mg dose, the testing procedure was halted at the first ranked secondary endpoint, SF/APS clinical remission (adjusted treatment difference =9.9%, 95% C.I. (-1.4, 21.1), p =0.085). Therefore, no secondary endpoints met statistical significance for this dose. For the risankizumab 360-mg dose, statistical significance was met for the first ranked secondary endpoint, SF/APS clinical remission (adjusted treatment difference =15.9%, 95% C.I. (4.3, 27.4), p =0.007), but not the second ranked secondary endpoint, maintenance of CDAI clinical remission among subjects with CDAI clinical remission at Week 0 (adjusted treatment difference =12.9%, 95% C.I. (-1.4, 27.1), p =0.076). Therefore, only the first ranked secondary endpoint, SF/APS clinical remission, met statistical significance for the 360-mg dose. This secondary endpoint was not included in labeling as stool frequency and abdominal pain are subcomponents assessed in the CDAI score, which is included in the coprimary endpoint,

Table 25 includes details on the efficacy analyses for the multiplicity-controlled, key ranked secondary endpoints. Most of the key ranked secondary endpoint failed to meet statistical significance on the testing hierarchy.

Table 25. Secondary Endpoints, Primary Analysis, Study M16-000 Baseline CDAI Clinical Responders

	180 mg vs. Placebo		360 mg vs. Placebo	
Endpoints	**Adjusted Treatment Difference[1] (95% CI)**	**p-Value**	**Adjusted Treatment Difference[1] (95% CI)**	**p-Value**
SF/APS clinical remission	9.9 (-1.4, 21.1)	0.085	15.9 (4.3, 27.4)	0.007
Maintenance of CDAI clinical remission	14.3 (1.0, 27.6)	0.035[2]	12.9 (-1.4, 27.1)	0.076
Ulcer-free endoscopy	16.0 (8.0, 24.0)	<0.001[2]	25.4 (16.8, 34.0)	<0.001[2]
Endoscopic remission	19.6 (10.7, 28.6)	<0.001[2]	30.5 (20.9, 40.2)	<0.001[2]
Change in FACIT-F	0.0 (-2.3, 2.3)	0.984	0.2 (-2.2, 2.7)	0.846
Discontinuation of corticosteroid use and CDAI clinical remission among subjects with baseline steroid use	26.2 (8.6, 43.7)	0.003[2]	4.4 (-10.5, 19.2)	0.565
CDAI clinical response	20.4 (9.3, 31.4)	<0.001[2]	19.1 (7.6, 30.6)	<0.001[2]
SF remission	9.5 (-1.8, 20.8)	0.098	15.5 (3.9, 27.0)	0.008[2]
AP remission	15.3 (3.9, 26.7)	0.009[2]	16.1 (4.4, 27.8)	0.007[2]
CDAI clinical remission and endoscopic response	26.4 (17.2, 35.5)	<0.001[2]	24.4 (14.4, 34.4)	<0.001[2]
Deep remission	16.5 (8.0, 25.0)	<0.001[2]	23.9 (14.4, 33.3)	<0.001[2]
CD-related hospitalization (incidence rate differences)	-2.47 (-8.3249, 3.3916)	0.409	1.10 (-5.9332, 8.1252)	0.760

Source: Appendix C, Applicant's Response to October 29, 2021, Information Request
[1] Adjusted treatment difference was computed based on stratified risk difference using CMH weights for binary endpoints and ANCOVA model for continuous endpoints
[2] Although the p-values are less than 0.05, the endpoint did not demonstrate statistical significance based on the prespecified multiple testing procedure.
Abbreviations: AP, abdominal pain; APS, abdominal pain score; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; SF, stool frequency; vs, versus

Discussion of Secondary Endpoints Proposed for Labeling: Trial M16-000 Substudy 1

All secondary endpoints, with the exception of the first key secondary endpoint, failed to show a statistically significant difference between treatment and placebo arms. However, the review team recognizes that some of the key secondary endpoints did show numerically higher treatment difference versus placebo arms. Further discussion regarding these endpoints and labeling recommendations are provided below.

(b) (4)

(b) (4)

Endoscopic Remission

While induction of clinical remission is clinically important, induction and maintenance of endoscopic remission is critical for treatment of patients with CD as endoscopic remission reflects quiescent disease and is linked to improved long-term outcomes and decreased morbidity in this patient population. While endoscopic remission could not be tested due to failure of the first and second ranked multiplicity-controlled secondary endpoints in the prespecified testing hierarchy, the efficacy rates were numerically higher in both treatment arms compared to placebo. Endoscopic remission was observed at Week 52 in 41% (48/117) of subjects randomized to the 360 mg dose, 33% (44/135) of subjects randomized to the 180 mg dose, and 13% (17/130) of subjects randomized to placebo. The estimated treatment differences, 95% confidence intervals, and nominal p-values are displayed in Table 25.

Although the 180 mg regimen is considered the lowest effective dosage, given the importance of achieving endoscopic remission in this patient population and numerically higher efficacy rates in the 360 mg treatment group, the 360 mg dosage may provide additional benefit in some patients with more severe and/or refractory disease.

6.2.2.4. Subgroup Analysis for M16-000, By Prior Biologic Failure

Efficacy was assessed by prior biologic failure status for the coprimary efficacy endpoints. Although the study was not powered to detect a significant difference for each subgroup, the response rate differences were consistent with the primary analyses. The group without prior biologic failure showed numerically higher clinical remission and endoscopic response rates compared to the group with prior biologic failure. The risankizumab groups consistently showed higher CDAI clinical remission and endoscopic response rates compared to placebo across subgroups.

Table 26. Subgroup Analyses, Study M16-000

Analysis Parameter	RZB Induction/ Placebo Maintenance[b] (N=130)	RZB Induction/ RZB 180 mg Maintenance (N=135)	RZB Induction/ RZB 360 mg Maintenance (N=117)
Clinical remission[a]	46.2%	61.5%	56.9%
Without prior biologic failure[d]	(N=31) 65%	(N=40) 75%	(N=34) 71%
With prior biologic failure[e]	(N=99) 40%	(N=95) 56%	(N=83) 51%
Endoscopic response[a]	21.5%	50.4%	48.4%
Without prior biologic failure[d]	(N=31) 23%	(N=40) 65%	(N=34) 59%
With prior biologic failure[e]	(N=99) 21%	(N=95) 44%	(N=83) 44%

Source: Clinical reviewer generated table
[a] Coprimary endpoints
[b] The induction-only group consisted of subjects who achieved clinical response (CR-100) to Skyrizi induction therapy and were randomized to receive placebo in the maintenance study (CD-3).
[c] Adjusted treatment difference and 95% CI computed using Cochran Mantel-Haenszel method adjusted for randomization stratification factors
[d] Without prior biologic failure (Non-Bio-IR)
[e] Prior biologic failure was defined as subjects with documented inadequate response or intolerance to at least 1 approved biologic (Bio-IR)
Abbreviations: N, number of patients in treatment groups; RZB, risankizumab

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Choice of Induction Dose

Issue

Determination of the recommended induction dosage for the treatment of moderately to severely active CD in adults.

Background

Studies M16-006 and M15-991 each assessed two treatment arms, the risankizumab 1200 mg IV or risankizumab 600 mg IV, at Weeks 0, 4, and 8, compared to placebo. A higher dose may provide more benefit, but may be associated with increased risk. Primary and key secondary efficacy results by induction dose were reviewed.

Assessment

The results for Studies M16-006 and M15-991 (Table 16 and Table 17) showed that subjects who received risankizumab had higher rates of CDAI clinical remission and endoscopic response than subjects who received placebo. The differences in rates were statistically significant, when comparing risankizumab 600 mg IV to placebo and when comparing risankizumab 1200 mg IV to placebo, for both coprimary endpoints of endoscopic response and CDAI clinical remission, as well as the ranked secondary endpoints.

When comparing risankizumab 600 mg IV to risankizumab 1200 mg IV, the proportions of subjects who achieved CDAI clinical remission were numerically higher among the 600 mg arm (Study M16-006: 45.2%; Study M15-991: 42%) than in the 1200 mg arm (Study M16-006:

41.6%%; Study M15-991: 40.3%), for both studies. For the other coprimary endpoint of endoscopic response (which assesses underlying mucosal inflammation), the proportion of subjects who achieved endoscopic response was numerically higher in the 600 mg arm (40.3%) than in the 1200 mg arm (32.1%) for Study M16-006, but numerically higher in the 1200 mg arm (34.2%) than in the 600 mg arm (28.8%) for Study M15-991.

When comparing risankizumab 600 mg IV to risankizumab 1200 mg IV, the proportion of subjects who achieved CDAI clinical response at Week 12 were numerically higher among the 1200 mg arm (Study M16-006: 64.9%; Study M15-991: 60.7%).) than in the 600 mg arm (Study M16-006: 59.7%; Study M15-991: 59.5%). However, the proportion of subjects who achieved endoscopic remission at Week 12 was numerically higher in the 600 mg arm (24.2%) than in the 1200 mg (23.9%) arm for Study M16-006, but numerically higher in the 1200 mg arm (20.4%) than in the 600 mg arm (19.4%) for Study M15-991.

Conclusion

While efficacy was demonstrated for both induction dosages compared to placebo in Studies M15-991 and M16-006, the efficacy results of the two dosages were numerically similar. The 1200 mg dosage did not demonstrate additional treatment benefit over the 600 mg dosage; therefore, the higher dosage is not recommended over the lower dosage on the basis of efficacy. In addition, the safety review revealed a risk of hepatotoxicity associated with induction therapy. The similar efficacy results and safety concerns associated with induction therapy led the team to conclude that the lower 600 mg dosage (i.e., Applicant-proposed induction dosage) should be recommended as the to-be-marketed induction dosage. Refer to Section 7.6.1 for further information on the safety of the 600 mg and 1200 mg dosages.

6.3.2. Choice of Maintenance Dose

Issue

Determination of the recommended maintenance dose for the treatment of moderately to severely active Crohn's disease in adults.

Background

Study M16-000 was a randomized withdrawal study where induction responders from Studies M16-006 and M15-991 were randomized to receive placebo, risankizumab SC 180 mg, or risankizumab SC 360 mg at Week 12 and every 8 weeks thereafter. The estimated treatment difference for the 360 mg dosage and placebo were similar to the estimated treatment difference for the 180 mg dosage and placebo for the coprimary efficacy endpoints (Section 6.2.2.4). Efficacy results were reviewed to determine which dosage should be recommended for maintenance therapy.

Assessment

The results in Table 24 of Section 6.2.2.3 show that subjects who were rerandomized to risankizumab SC had higher rates of CDAI clinical remission and endoscopic response than subjects who were rerandomized to placebo. The differences in rates between the 180 mg dosage

and placebo and between the 360 mg dosage and placebo were statistically significant for both coprimary endpoints at Week 52. However, the results for all secondary efficacy endpoints were not significant for the 180 mg dosage based on the prespecified multiple testing procedure, whereas for the 360 mg dosage, the results were statistically significant for the first ranked secondary efficacy endpoint, clinical remission based on SF and APS (p=0.007), but not significant for the remaining endpoints based on the prespecified multiple testing procedure. In addition to this endpoint, it is notable that the following key ranked secondary endpoints demonstrated numerically higher treatment difference estimates for the 360 mg dosage compared to the 180 mg dosage at Week 52:

- Ulcer-free endoscopy
- Endoscopic remission
- Change of FACIT-F from baseline of induction
- Stool frequency remission
- Abdominal pain remission
- "Deep remission" (CDAI clinical remission and endoscopic remission)

The 180 mg dosage demonstrated numerically higher treatment difference estimates versus placebo compared to the 360 mg dosage on the remaining 5 endpoints at Week 52, namely:

- Maintenance of CDAI clinical remission (secondary endpoint #2)
- CDAI clinical remission and discontinuation of corticosteroid use among subjects with baseline steroid use (secondary endpoint #6)
- CDAI clinical response (secondary endpoint #7)
- CDAI clinical remission and endoscopic response (unranked secondary endpoint)
- CD-related hospitalization (unranked secondary endpoint)

Sensitivity analyses of the subjects who met criteria for endoscopic response at Week 52 showed that 57%, 62% and 76% of subjects treated with placebo, risankizumab 180 mg and risankizumab 360 mg, respectively, also met criteria for endoscopic remission.

Conclusion

Efficacy was demonstrated for both maintenance dosages for the coprimary endpoints. In addition, most of the key secondary endpoints failed to show statistical significance based on the prespecified multiple testing procedure (though several secondary endpoints were nominally significant). Therefore, both 180 mg and 360 mg are considered to be effective maintenance dosages. While the 180 mg regimen may be considered the lowest effective dosage, the 360 mg dosage may also be appropriate in some patients with more severe or refractory disease based on the numerically higher efficacy rates for the endoscopic remission at Week 52 for the 360 mg dosage compared to the 180 mg dosage. These endpoints are clinically relevant as endoscopic remission represents an important treatment goal to improve long-term outcomes in CD. The added benefit observed with endoscopic findings, in conjunction with a similar safety profile between the two maintenance dosages, supports both 180 mg and 360 mg as the recommended

maintenance dosages. Refer to Section 7.6.2 for further information on the safety of the maintenance dosages.

Of note, the Applicant had initially proposed 360 mg as the maintenance dosage, and did not include the complete chemistry, manufacturing, and controls (CMC) package to support the 180 mg presentation in the sBLA submission. In recognition of the severity of CD, to ensure availability of a safe and efficacious product without delay, the 360 mg maintenance dosage will be labeled at this time, while the efficacy supplement (sBLA761105-S018; received May 25, 2022) for the 180 mg prefilled cartridge presentation is currently under review.

6.3.3. Bridging Between the TBM Products and the Phase 3 Products

Issue

The proposed TBM products for induction treatment (600 mg/vial, 60 mg/mL for IV infusion) and maintenance treatment (360 mg/2.4 mL OBDS for SC injection, 150 mg/mL) are quantitatively and qualitatively different from the products used in the phase 3 trials (300 mg/vial, 90 mg/mL for induction: 4 SC injections x 90 mg/mL in a prefilled syringe (PFS), 90 mg/mL for maintenance).

Background

A bridging pharmacokinetic (PK) Study M19-128 was conducted in healthy subjects to compare:

- The proposed TBM SC products [360 mg OBSD or 180 mg OBDS] versus the phase 3 SC product [4 x 90 mg/mL PFS] (Substudy 1), and
- The proposed TBM IV product [3 x 600 mg/vial] versus the phase 3 IV product [6 x 300 mg/vial] at a dose of 1800 mg (Substudy 2).

The PK bridging study design is summarized in Table 27. A total of 393 of 394 enrolled subjects received a single dose of risankizumab. Serial blood samples were collected predose and at time points after dosing over a period of 113 days for risankizumab PK and immunogenicity assessments. In addition, safety/tolerability assessments were conducted throughout the study.

Table 27. Study M19-128 Design

Design Parameter	Substudy 1 – SC Bridging Study[1]			Substudy 2 – IV Bridging Study	
	Group 1 (Reference[2]) N=127	Group 2 (Test[3]) N=129	Group 3 (Test[3]) N=30	Group 4 (Reference[2]) N=53	Group 5 (Test[3]) N=54
Dose[4]	360 mg	360 mg	180 mg	1800 mg	1800 mg
Formulation (concentration)	90 mg/mL	150 mg/mL	150 mg/mL	90 mg/mL	60 mg/mL
Presentation	PFS	OBDS	OBDS	300 mg/vial	600 mg/vial

Source: Reviewer's independent analysis
[1]SC injection site: abdomen
[2] Reference = the phase 3 SC or IV product,
[3]Test = the proposed TBM SC or IV product (except for 180 mg OBDS/Group 3)
[4]The 1800-mg dose in the IV bridging study is 3-fold higher than the proposed induction therapy dose of 600 mg.
Abbreviations: IV, intravenous; N, number of patients in treatment arm; OBDS, on-body delivery system; PFS, prefilled syringe; SC, subcutaneous

Assessment

A summary of the PK parameters of risankizumab by group following a single SC or IV dose administration in healthy subjects is shown in Table 28 .

IV Formulation Bridging

The proposed TBM IV product (600 mg/vial, 60 mg/mL) was bioequivalent to the phase 3 IV product (300 mg/vial, 90 mg/mL) as the 90% confidence interval (CI) for the ratio of area under the concentration-time curves (AUCs) and maximum plasma concentration (C_{max}) met the bioequivalence criteria of range of 0.80 to 1.25 (Table 28). Although the bioequivalence (BE) study was done at 1800-mg dose, which is 3-fold the proposed dose (i.e., 600 mg), given the IV administration under the same infusion duration and observed dose-proportional PK at the dose range from 200 mg to 1800 mg following single IV infusion, the results support the bridging between the TBM product and the phase 3 product at the proposed dose of 600 mg.

SC Formulation Bridging

The TBM SC 360 mg OBDS (360 mg/2.4 mL, 150 mg/mL) had comparable systemic exposure (AUC) meeting bioequivalence criteria with the phase 3 SC product, in which 360-mg dose was given by 4 injections of 90 mg/mL in a PFS (Table 28). The mean C_{max} in subjects using the TBM SC 360 mg OBDS product was ~25% higher than those using the phase 3 PFS product (Table 28). One of the main reasons that the 90% CI for C_{max} exceeded the upper bound of the 0.8 to 1.25 criteria is probably due to higher variability with the OBDS compared to the PFS product (Figure 4). It should also be noted that the C_{max} with the TBM OBDS product is substantially lower than that of IV infusion of 600 mg for induction treatment (43.1 mcg/mL versus estimated to be 235 mcg/mL). Given the substantially lower concentrations and slow absorption from SC injection site (median T_{max} of 5 days), the systemic safety of 25% higher C_{max} with the OBSD compared to PFS is supported by the available safety data associated with multiple doses of 600 mg IV. In addition, AUC is generally considered to be more relevant for assessing the impact on long-term safety than C_{max}.

On the other hand, the incidence of the injection site reactions in the TBM SC product groups was higher (35% in the 360 mg OBDS group and 27% in the 180 mg OBDS group) than that in

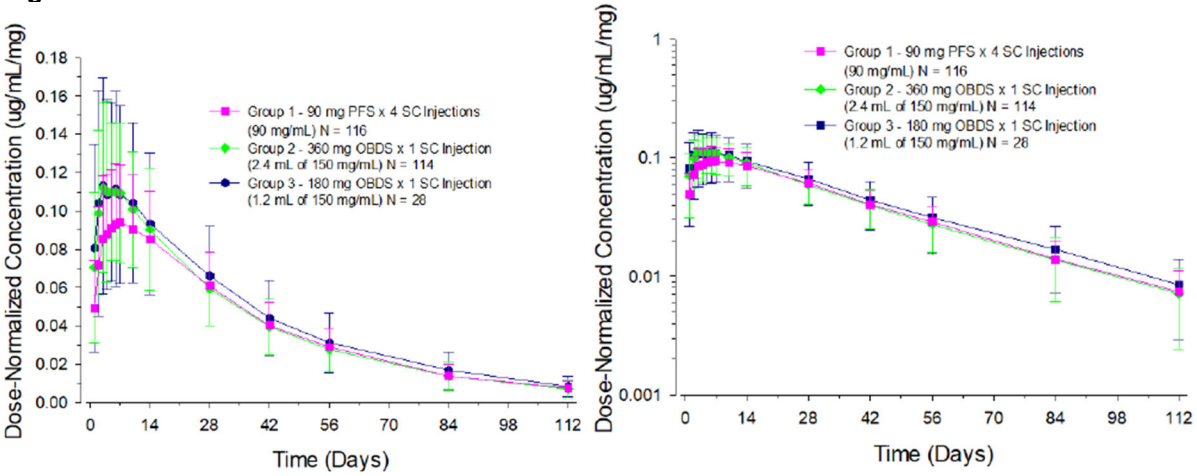
the phase 3 SC product group (9%) in healthy subjects of the PK bridging study. See Section 7.7.4.

Table 28. Relative Bioavailability and 90% Confidence Intervals in Study M19-128

Group (Risankizumab Dose) Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
		Substudy 1			
Group 2 (360 mg OBDS) vs. Group 1 (90 mg PFS × 4 SC injections)	C_{max}	43.1	34.1	1.263	1.184, 1.347
	AUC_t	1555	1461	1.065	1.000, 1.134
	AUC_{inf}	1700	1588	1.070	1.010, 1.134
Group 3 (180 mg OBDS) vs. Group 2 (360 mg OBDS)	C_{max}/Dose	0.110	0.114	0.967	0.861, 1.087
	AUC_t/Dose	4.257	4.225	1.008	0.894, 1.137
	AUC_{inf}/Dose	5.057	4.596	1.100	0.994, 1.218
		Substudy 2			
Group 5 (3 × 600 mg liquid vials) vs. Group 4 (6 × 300 mg liquid vials)	C_{max}	735	736	0.998	0.952, 1.046
	AUC_t	11500	10700	1.079	1.001, 1.164
	AUC_{inf}	12400	11900	1.044	0.976, 1.117

Units for C_{max}, AUC, C_{max}/Dose, and AUC/Dose are µg/mL, µg•day/mL, µg/mL/mg, and µg•day/mL/mg, respectively.
Source: Study M19-128 CSR Table 9, Table 11
Abbreviations: AUC_t, area under the concentration-time curve; AUC_{inf}, area under the concentration-time curve from time 0 to infinity time; C_{max}, maximum concentration; OBDS, on-body delivery system; PFS, prefilled syringe; SC, subcutaneous

Figure 4. Dose-Normalized Mean Risankizumab Serum Concentrations



Source: Study M19-128 CSR Figure 2
Abbreviations: N, number of patients in treatment arm; OBDS, on-body delivery system; PFS, prefilled syringe; SC, subcutaneous

Of note, 13 out of 130 subjects (10%) were excluded from the PK bridging study due to "dosing failure" from OBDS device. Among 13 subjects reported as "dosing failure", 12 (92%) subjects were in the 360 mg OBDS group, and one (8%) subject was in the 180 mg OBDS group. The dosing failures required further review of the OBDS device. See Section 7.7.4

The Office of Study Integrity and Surveillance (OSIS) conducted a remote regulatory assessment or inspection of the clinical portion of Study M19-128. The inspection suggests that the data from Study M19-128 are reliable, although a few objectionable conditions were observed (e.g., lack of filing of financial disclosure forms by subinvestigators, unreported AE and concomitant medications, etc.). See Section 10.

Conclusion

Overall, the PK bridging between the proposed TBM products and the products used in the CD phase 3 trials is considered established.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical safety profile of risankizumab has been established under BLA 761105 for psoriasis. In the current supplement, in vitro primary and secondary pharmacology studies showed that risankizumab has no effect on ADCC or CDC. In vivo studies in mouse models of colitis, a surrogate risankizumab monoclonal antibody showed efficacy when administered intraperitoneally.

In nonclinical studies reviewed previously, intravenous administration of risankizumab to cynomolgus monkeys at doses up to 50 mg/kg/week for 4 weeks had no treatment-related adverse effects on neurological or cardiovascular functions, and no treatment-related effects were observed on the respiratory system in monkeys at subcutaneous doses up to 50 mg/kg/week.

In a 6-month repeat-dose study with a 2-month recovery period, in cynomolgus monkeys, four groups of monkeys were administered subcutaneously with 0 (vehicle, 0.5mM succinic acid, 3.9mM disodium succinate hexadyhydrate, 275mM sorbitol, 0.02% Polysorbate 20, pH 6.0), 5, 20, or 50 mg/kg risankizumab once weekly. There were no treatment-related deaths, clinical signs, neurobehavioral changes, ophthalmology, body weights, body temperature, electrocardiography (ECG), blood pressure, clinical pathology, and macroscopic findings. There was a slight dose dependent change in reticulocytes that did not reverse. Adverse changes in male reproductive organs/tissues were observed in risankizumab-treated males. Upon further analysis it was determined that the male monkeys used in this study were not sexually mature. In a follow-up study in sexually mature male monkeys, subcutaneous administration of risankizumab at 50 mg/kg/week for 26 weeks did not have any treatment related effects on testicular volume, male reproductive hormones (serum testosterone, Luteinizing hormone (LH), and follicle-stimulating hormone (FSH)), semen analysis (sperm count, motility, and morphology; ejaculate volume), gross pathology, organ weights, and histopathological findings including progression of the spermatogenic cycle, cell associations, and cell proportions in the various stages of spermatogenesis. The C_{max} and $AUC_{0\text{-}168h}$ of risankizumab at the 50 mg/kg/week dose at the end of the dosing period were 950 µg/mL and 122,000 µg·h/mL, respectively.

In an enhanced pre- and postnatal toxicity study in cynomolgus monkeys, the animals received subcutaneous doses of risankizumab at 0, 5, or 50 mg/kg once weekly from gestation day (GD) 20 to 22 until parturition, and the infants were evaluated for 6 months after birth. A dose-dependent increase in fetal/infant loss was noted in the risankizumab-treated groups, as compared to the control group. The percent fetal/infant loss was 19%, 32%, and 43% for 0, 5 and 50 mg/kg groups, respectively. The increased fetal/infant loss in the 50 mg/kg dose group was considered related to treatment with risankizumab. The $AUC_{0\text{-}168h}$ values in pregnant monkeys on GD 132 to 134 were 15,700 and 123,000 µg·h/mL at 5 and 50 mg/kg/week, respectively. All infants from the risankizumab-treated groups had dose-dependent increase in serum concentrations of risankizumab up to 91 days postpartum, while no measurable concentrations were observed by Day 180 postpartum. The mean serum concentrations for the infants were approximately 17 to 86% of the respective maternal concentrations. The no observed adverse effect level (NOAEL) for maternal toxicity was identified as 50 mg/kg/week and the NOAEL for developmental toxicity was identified as 5 mg/kg/week.

Genetic toxicology or carcinogenicity studies were not conducted with risankizumab. A carcinogenic risk assessment, based on published literature, revealed that the potential risk for malignancy associated with long-term inhibition of IL-23 following administration of risankizumab is low.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The adverse event profile was reviewed and found to be generally similar to the known safety profile described in the currently approved labeling for risankizumab. Notably, the dosing investigated in CD patients is higher than currently approved dosing in other indications. Additional risks associated with risankizumab exposure in CD patients emerged during the safety review, including risk of hepatotoxicity and dyslipidemia. Refer to Sections 7.7 for further details.

In consideration of the known risks associated with IL-23 inhibitors and similar products (IL-12/23 inhibitors) and FDA's evaluation of the Applicant's submitted safety data, the potential risks of abdominal pain, hypersensitivity reactions including anaphylaxis and local injection site reactions, upper respiratory tract infection, and rash, were identified as AEs of interest during the review. Accordingly, the following grouped queries were conducted to assess risks associated with risankizumab exposure in addition to the evaluation of safety data using the individual preferred terms (PTs):

- Abdominal pain (abdominal pain, abdominal pain upper, abdominal pain lower)
- Hypersensitivity reactions (rash, bronchospasm, rhinitis allergic, dermatitis allergic, drug hypersensitivity, pruritis, rash maculo-papular, rash vesicular, eosinophilia, erythema nodosum, flushing, skin exfoliation, allergic bronchitis, allergy to chemicals, anaphylactic reaction, infusion elated reaction, rash macular, rash pustular, swelling of eyelid, urticaria, hypersensitivity, rash pruritic, seasonal allergy)

- Injection site reaction (injection site erythema, hypersensitivity, rash, swelling, urticaria, warmth, nodule, vesicles, pain, reaction)
- Upper respiratory infections (nasopharyngitis, upper respiratory tract infection, influenza, pharyngitis, respiratory tract infection viral, pharyngitis bacterial, nasal congestion, viral infection, viral pharyngitis, tonsillitis, upper respiratory tract inflammation, viral upper respiratory tract infection, influenza like illness, COVID-19, COVID-19 pneumonia)
- Rash (dry skin, eczema, skin papilloma, dermatitis, acne, rash, skin discoloration, blister, skin exfoliation, papule, skin discoloration, erythema, rosacea, acrochordon, dyshidrotic eczema, erythema induratum, macule, palmoplantar pustulosis, dermatitis allergic, dermatosis, rash maculo-papular, rash popular, rash vesicular, scrotal dermatitis, seborrheic keratosis, xeroderma, lichen sclerosus, rash macular, rash pustular, skin lesion, rash pruritic)

7.3. Potential Safety Concerns Identified Through Postmarket Experience

In support of the marketing application review, the Division of Pharmacovigilance I (DPV-I) was consulted to conduct an analysis of all adverse events associated with risankizumab-rzaa in the FDA Adverse Event Reporting System (FAERS) database and the medical literature. Notably, there were no open Newly Identified Safety Signals (NISSs) for risankizumab-rzaa.

A FAERS search was completed for reporting period April 28, 2020 to October 19, 2021. For the purposes of this review, a case-level analysis was not performed on all reports. DPV reviewed all PTs and reported Designated Medical Events for new potential safety signals, medical literature publications with relevant new safety findings, and unlabeled adverse events with the potential for serious outcomes labeled adverse events with unexpected characteristics, such as an increase in severity. DPV identified an association between risankizumab-rzaa and anaphylaxis (Refer to memo uploaded by Tiffany Kim, PharmD, BCPS on November 19, 2021 under BLA 761105 for full details).

Additionally, DPV conducted a FAERS search for reporting period April 23, 2019 to May 4, 2022, with a specific query for venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism (b) (4) Although the search retrieved a small number of cases of VTE, in general, there were insufficient information to determine a true signal of VTE for risankizumab-rzaa. Refer to memo uploaded by Lisa Wolf, PharmD, BCCCP on May 17, 2022, under BLA 761105 for full details.

Of note, during the review cycle, “Hypersensitivity Reactions” was added to the Warnings and Precautions section of the drug label on January 21, 2022 (at the time of approval for psoriatic arthritis).

(b) (4)

7.4. FDA Approach to the Safety Review

The safety review of this 505(b)(1) application focused primarily on data from the 12-week DB treatment period of the two phase 3 induction trials (M15-991 and M16-006) and the 52-week DB treatment period of the phase 3 trial (Trial M16-000 Substudy 1). See Table 4. M16-000 Substudy 2 and Substudy 3 are currently ongoing, and data were not included in the submission. Additionally, the Applicant submitted data from a phase 2, 12-week induction trial in subjects with moderately to severely active CD (Trial M15-993).

All safety assessments and conclusions are those of the review team unless otherwise specified. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review.

Induction Trials

Safety data from two phase 3 trials, M16-006 and M15-991, and one phase 2 trial, M15-993, were included in the primary induction safety database. The data from each trial were assessed individually and also pooled for the induction trials (M15-991, M16-006, and M15-993) given the similarities in the design of the trials (see Section 6.2.1.1). Analyses of the data from the two phase 3 trials, Trial M16-006 and M15-991, represent events that occurred through the end of the 12-week DB induction treatment period. In Trials M16-006 and M15-991, subjects received 12 weeks of induction therapy with risankizumab 600 mg IV, 1200 mg IV, or placebo. In addition to assessing the safety data from these phase 3 induction trials, the safety review also included evaluation of safety data from a phase 2 trial, Trial M15-993[2] in which subjects were treated with 600 mg or placebo induction therapy. These safety data were included to further inform dose selection and support the safety profile of the induction regimen.

Maintenance Trial

Analyses of Trial M16-000 Substudy 1 represent events that occurred through the end of the 40-week DB maintenance treatment period, at Week 52 of total treatment. Subjects identified by the Applicant as "clinical responders"[3] based on SF and AP scores in Trials M15-991 and M16-006 were randomized into Trial M16-000 to receive DB risankizumab 360 mg SC, 180 mg SC, or placebo every 8 weeks. However, the Division currently recommends rerandomizing subjects who achieve clinical response defined as a change from baseline in CDAI score of ≥100 points (see Section 6.2.2.2). Therefore, the Division requested that the Applicant reanalyze the data using the population that would have been rerandomized into the maintenance study based on the

[2] Trial M15-993 was a phase 2, double-blind, placebo-controlled, 12-week trial investigating the utility of induction therapy 200 mg IV (n=41) and 600 mg IV (n=41) versus placebo (n=39) at Weeks 0, 4 and 8. See Section 14.2.5.

[3] Per the study protocol, subjects were eligible for enrollment in Trial M16-000 if they met criteria "clinical response" based on a Stool Frequency (SF) or Abdominal Pain Score (APS): ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily APS and both not worse than baseline of the induction study.

currently recommended approach. Therefore, the safety analyses for maintenance therapy were conducted using the subjects who met the criteria for clinical response based on CDAI score.[4]

Subpopulations

Further safety analyses were completed based on whether subjects were naïve to biologic therapy (non-Bio-IR) or had a history of intolerance or inadequate response to biologic therapy (Bio-IR) to determine whether the safety profile of risankizumab differs between the two subpopulations. Refer to Section 7.6.3.1. In addition, subgroup analyses based on demographics (sex, age, and race) were conducted to compare the safety profile between risankizumab-treated and placebo-treated subjects. Refer to Section 17.2.

7.5. Adequacy of Clinical Safety Database

The safety database was adequate for a comprehensive safety assessment to support the proposed indication to treat patients with moderately to severely active CD with an induction therapy of risankizumab 600 mg IV at Weeks 0, 4 and 8, followed by a maintenance therapy of risankizumab 180 mg SC or 360 mg SC at Week 12 and every 8 weeks thereafter.

The induction safety database (Trials M16-006, M15-991, and M15-993) included 1197 subjects exposed to risankizumab induction therapy. The maintenance safety database (Trial M16-000 Substudy 1) included 297 subjects exposed to risankizumab maintenance therapy.

The overall safety database includes 620 subjects exposed to the TBM induction dose (risankizumab 600 mg IV) and 142 subjects exposed to the TBM maintenance dose (360 mg SC). Refer to Section 6.2.1.1 for details regarding differences between subjects included in the safety and efficacy analyses.

Table 29 and Table 30 summarize the exposure periods for the induction and maintenance safety population(s), respectively.

[4] A total of 440 of 542 (82%) subjects initially enrolled in Trial M16-000, Sub-study 1 were included in the safety review (risankizumab 180 mg SC: 155 of 179 [87%] subjects; risankizumab 360mg SC: 142 of 179 [79%] subjects; and placebo 143 of 184 [78%] subjects).

Table 29. Induction Period: Duration of Exposure to Risankizumab and Placebo, Safety Population, Integrated Summary of Safety (Trials M16-006, M15-991, and M15-993)

Parameter	RZB 600 mg IV N=620	RZB 1200 mg IV N=577	Placebo IV N=432
Duration of treatment, weeks			
Mean (SD)	11.9 (1)	11.9 (1.1)	11.3 (2.1)
Median (min, max)	12 (4, 16)	12 (4, 22)	12 (4, 15)
Subjects treated, by duration, n (%)			
≥1 dose	620 (100)	577 (100)	432 (100)
<4 weeks	0	0	0
≥4 to <8 weeks	6 (1)	8 (1.4)	37 (8.6)
≥8	614 (99.1)	569 (98.6)	395 (91.4)

Source: Anne Bunner, PhD; Clinical Data Scientist
Abbreviations: IV, intravenous; max, maximum; min, minimum; N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation; RZB, risankizumab

Table 30. Maintenance Period: Duration of Exposure, Safety Population (Trial M16-000 Substudy 1)

Parameter	RZB 180 mg SC Q8W N=155	RZB 360 mg SC Q8W N=142	Placebo SC Q8W N=143
Duration of treatment, weeks			
Mean (SD)	48.7 (14.0)	47.8 (14.4)	44.3 (15.5)
Median (min, max)	55.7 (8, 60)	55.9 (8, 63)	55.1 (15, 57)
Subjects treated, by duration, n (%)			
≥1 dose	155 (100)	142 (100)	143 (100)
<6 months	17 (11)	16 (11.3)	24 (16.8)
≥6 to <10 months	17 (11)	19 (13.4)	25 (17.5)
≥10 months	121 (78.1)	107 (75.4)	94 (65.7)

Source: Anne Bunner, PhD; Clinical Data Scientist
This table includes subjects who responded to 12 weeks of induction therapy (risankizumab 600 mg IV, risankizumab 1200 mg IV or placebo) in trials M16-006 and M15-991 and were rerandomized to placebo, risankizumab 180 mg SC or risankizumab 360 mg SC in trial M16-000.
Abbreviations: max, maximum; min, minimum; N, number of subjects in group; n, number of subjects with given treatment duration; Q8W, every 8 weeks; SC, subcutaneous; SD, standard deviation; RZB, risankizumab

Notably, majority of subjects included in the primary induction safety population had a total duration of exposure ≥8 weeks (risankizumab treatment groups: 98.6 to 99.1%; placebo group: 91.4%) indicating a completed induction dosing regimen. Similarly, approximately three quarters of subjects included in the primary maintenance safety database had a total duration of exposure ≥40 weeks (risankizumab treatment groups: 75.4 to 78.1%; placebo subjects: 65.7%). Given the duration of exposures in the induction and maintenance trials, the safety database is deemed sufficient to support safety of risankizumab in adults with moderately to severely active CD.

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

The following subsections include safety findings and concerns identified during the review of data from the induction population (ISS1), which includes data from Trials M16-006, M15-991, and M15-993 (Section 7.6.1), and maintenance population, Trial M16-000 Substudy 1 (Section 7.6.2). Further safety review was completed for the subpopulations for subjects with inadequate

response to prior biologic therapy (Bio-IR) and subjects who were naïve to the biologics (Non-Bio-IR) (Section 7.6.3.1), and based on demographics (Section 17.2).

7.6.1. Safety Findings and Concerns, Induction

7.6.1.1. Overall Adverse Event Summary, Induction

Table 31 provides a summary of AEs reported in the ISS1 population.

Notably, a greater proportion of placebo subjects reported treatment-emergent adverse events (TEAEs),[5] serious AEs (SAEs), SAEs with fatal outcome, and AEs leading to study drug discontinuation compared to subjects treated with risankizumab.

Table 31. Overview of Treatment-Emergent Adverse Events, Safety Population, ISS1

Event Category	RZB 600 mg IV N=620 n (%)	RZB 1200 mg IV N=577 n (%)	Placebo IV N=432 n (%)	Risk Difference[a] (%) (95% CI)
Any treatment-emergent AE[b]	339 (54.7)	312 (54.1)	274 (63.4)	-8.7 (-14.7, -2.8)
Severe	32 (5.2)	29 (5.0)	50 (11.6)	-6.4 (-9.9, -2.9)
Moderate	128 (20.6)	89 (15.4)	109 (25.2)	-4.6 (-9.8, 0.6)
Mild	177 (28.5)	191 (33.1)	112 (25.9)	2.6 (-2.8, 8.1)
SAE	41 (6.6)	23 (4.0)	67 (15.5)	-8.9 (-12.8, -5.0)
SAEs with fatal outcome	0	1 (0.2)	2 (0.5)	-0.5 (-1.1, 0.2)
AE leading to discontinuation of study drug	13 (2.1)	12 (2.1)	37 (8.6)	-6.5 (-9.3, -3.6)
AE leading to interruption of study drug	0	0	0	0

Source: Anne Bunner, PhD; Clinical Data Scientist
[a] Risk difference (with 95% confidence interval) is shown between 600 mg and placebo groups.
[b] Severity of TEAEs was based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE26) version 4.03.
Abbreviations: AE, adverse event; CI, confidence interval; ISS1, integrated summary of safety (12-week induction period); IV, intravenous; N, number of patients in treatment arm; n, number of patients with at least one event; RZB, risankizumab; SAE, serious adverse event

7.6.1.2. Deaths, Induction

Of subjects included in the primary induction safety database, there were three deaths: one death occurred in the risankizumab 1200 mg arm, no deaths in the risankizumab 600 mg arm, and two deaths in the placebo arm.

The death that occurred in a subject treated with risankizumab 1200 mg IV was reviewed and adjudicated as likely due to a new diagnosis of squamous cell lung carcinoma, and unrelated to study intervention. A brief narrative follows:

- 59-year-old Caucasian female with a history of CD, obstructive sleep apnea, chronic obstructive pulmonary disease, arthritis, colonic polyps, anemia, hypercholesterolemia, hypertension, and former tobacco user enrolled in trial M15-991 was randomized to

[5] Treatment-emergent adverse events defined as events occurring after the first dose of study drug and within 140 days after the last administration of study drug.

receive risankizumab 1200 mg IV induction therapy. On Day 8 (after 1 dose of study drug), the subject developed shortness of breath and chest tightness. A computed tomography (CT) scan and positron emission tomography (PET) scan revealed a 12 mm lung nodule. On Day 32, she underwent partial lung lobectomy and biopsy; findings were consistent with a new diagnosis of squamous cell lung carcinoma. On Day 40, she developed Leriche syndrome and subsequently developed acute respiratory failure and gram-negative bacteremia. On Day 52, she passed away after supportive care was withdrawn.

In addition, there were two deaths in subjects in the placebo arm. Brief narratives follow:

- 49-year-old male with a history of CD enrolled in Trial M16-006 and was randomized to receive placebo induction therapy. During trial enrollment, he required hospitalization for treatment of gastroenteritis and concern for partial intestinal obstruction. During the hospitalization, the subject passed away from complications of septic shock secondary to nosocomial pneumonia.
- 50-year-old male with a history of CD enrolled in Trial M16-006 and was randomized to receive placebo induction therapy. During trial enrollment, he required hospitalization for ileocolonic resection and ileostomy formation for treatment of small bowel stricture secondary to underlying CD. The subject passed away on the day of surgery. Per the autopsy report, the primary cause of death was cardiovascular collapse due to septic shock and secondary cause of death was necrotic peritonitis due to intestinal perforation.

7.6.1.3. Serious Adverse Events, Induction (ISS1)

Table 32 provides an overview of other SAEs that occurred in more than one subject and greater in either treatment arm versus placebo. The SAEs are presented first for the 600 mg treatment group followed by 1200 mg and placebo groups. This facilitates comparing the risankizumab 600 mg arm to placebo first, followed by comparing it to the 1200-mg dose arm, for any dose-dependence in SAEs that occurred in the risankizumab 600 mg and 1200 mg treatment arms. The risk differences are shown for 600 mg treatment group versus placebo because 600 mg is the dose recommended for approval.

The proportion of subjects who reported at least one SAE through Week 12 of the induction study included 41 of 620 subjects (6.6%) in the 600 mg IV arm, 23 of 577 (4%) subjects in the 1200 mg IV arm, and 67 of 432 (15.5%) subjects in the placebo arm. The most frequent SAE reported was CD. The proportion of subjects reporting an SAE of CD in the induction trial was 7 of 620 (1.1%) subjects in the risankizumab 600 mg arm, 3 of 577 (0.5%) subjects in the 1200 mg risankizumab arm, and 40 of 432 (9.3%) subjects in the placebo arm.

Table 32. Serious Adverse Events Reported in More Than One Subject and Greater in Either Treatment Arm Versus Placebo, Safety Population, ISS1

System Organ Class Preferred Term	RZB 600 mg IV N=620 n (%)	RZB 1200 mg IV N=577 n (%)	Placebo IV N=432 n (%)	Risk Difference[a] (%) (95% CI)
Gastrointestinal disorders (SOC)				
Ileus	3 (0.5)	0	0	0.5 (-0.1, 1.0)
Small intestinal obstruction	2 (0.3)	1 (0.2)	3 (0.7)	-0.4 (-1.3, 0.5)
Crohn's disease	7 (1.1)	3 (0.5)	40 (9.3)	-8.1 (-11.0, -5.3)
Renal and urinary disorders (SOC)				
Ureterolithiasis	2 (0.3)	0	0	0.3 (-0.1, 0.8)
Respiratory, thoracic and mediastinal disorders (SOC)				
Pulmonary embolism	0	2 (0.3)	0	0

Source: Anne Bunner, PhD; Clinical Data Scientist
[a] Risk difference (with 95% confidence interval) is shown between 600 mg and placebo groups.
Abbreviations: CI, confidence interval; ISS1, integrated summary of safety (12-week induction period); IV, intravenous; N, number of patients in treatment arm; n, number of patients with adverse event; RZB, risankizumab; SOC, system organ class

Notably, there were a higher proportion of SAEs due to gastrointestinal (GI) disorders reported in the placebo than risankizumab treatment groups. The higher proportion of GI disorders in the placebo group was likely due to poorly controlled underlying CD.

In addition, one subject treated with risankizumab 600 mg IV developed concern for drug-induced liver injury (SAE with PT "hepatic function abnormal"). Refer to Section 7.7.1 for further details.

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, Induction (ISS1)

The proportion of subjects who discontinued treatment due to AEs through Week 12 of the induction study included 13 of 620 (2.1%) subjects in the 600 mg IV arm, 12 of 577 (2.1%) subjects in the 1200 mg IV arm, and 37 of 432 (8.6%) subjects in the placebo arm. The most frequent AE leading to treatment discontinuation reported was CD, which was more frequently reported in the placebo arm (risankizumab 600 mg: 4 of 620 (0.6%) subjects; risankizumab 1200 mg: 3 of 577 (0.5%) subjects; placebo: 24 of 432 (4.6%) subjects). The larger proportion of AEs reported as CD in the placebo arm was attributed to poorly controlled underlying CD.

Table 33 summarizes AEs leading to treatment discontinuation that occurred at a higher proportion in the risankizumab treatment arms compared to placebo arm.

Table 33. Adverse Events Leading to Treatment Discontinuation Reported in at Least One Subject and Greater in Either Risankizumab Treatment Arm Than Placebo, Safety Population, ISS1

System Organ Class Preferred Term	RZB 600 mg IV N=620 n (%)	RZB 1200 mg IV N=577 n (%)	Placebo IV N=432 n (%)	Risk Difference[a] (%) (95% CI)
Gastrointestinal disorders (SOC)				
Large intestinal stenosis	1 (0.2)	0	0	0.2 (-0.2, 0.5)
Large intestinal ulcer	1 (0.2)	0	0	0.2 (-0.2, 0.5)
Abdominal mass	0	1 (0.2)	0	0
Colitis	0	1 (0.2)	0	0

System Organ Class Preferred Term	RZB 600 mg IV N=620 n (%)	RZB 1200 mg IV N=577 n (%)	Placebo IV N=432 n (%)	Risk Difference[a] (%) (95% CI)
Hepatobiliary disorders (SOC)				
Hepatic function abnormal	1 (0.2)	0	0	0.2 (-0.2, 0.5)
Immune system disorders (SOC)				
Drug hypersensitivity	0	2 (0.3)	0	0
Injury, poisoning and procedural complications (SOC)				
Infusion related reaction	1 (0.2)	1 (0.2)	0	0.2 (-0.2, 0.5)
Investigations (SOC)				
Aspartate aminotransferase increased	1 (0.2)	0	0	0.2 (-0.2, 0.5)
Hormone level abnormal	0	1 (0.2)	0	0
Musculoskeletal and connective tissue disorders (SOC)				
Fistula	0	1 (0.2)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)				
Squamous cell carcinoma of lung	0	1 (0.2)	0	0

Source: Anne Bunner, PhD; Clinical Data Scientist.
[a] Risk difference (with 95% confidence interval) is shown between 600 mg and placebo groups.
Abbreviations: CI, confidence interval; ISS1, integrated summary of safety (12-week induction period); IV, intravenous; N, number of patients in treatment arm; n, number of patients with adverse event; RZB, risankizumab; SOC, system organ class

7.6.1.5. Treatment-Emergent Adverse Events, Induction (ISS1)

Table 34 describes the TEAEs in the ISS1 population that occurred in >3% of risankizumab-treated subjects and at a higher rate than placebo through Week 12. Notably, the most common TEAEs observed in subjects treated with risankizumab included upper respiratory tract infections, rash, and headache, which are included as adverse reactions in the previously approved risankizumab drug label. Two new TEAEs, arthralgia and dizziness, were identified during the safety review and the review team recommends inclusion of these AEs in section 6.1 of the label.

Table 34. Adverse Events Occurring in >3% of Risankizumab-Treated Subjects and Higher Than Placebo Through Week 12, Safety Population, ISS1

Preferred Term	RZB 600 mg IV N=620 n (%)	RZB 1200 mg IV N=577 n (%)	Placebo IV N=432 n (%)	Risk Difference[a] (%) (95% CI)
Upper respiratory infections[b,c]	67 (10.8)	63 (10.9)	41 (9.5)	1.3 (-2.4, 5.0)
Headache	40 (6.5)	30 (5.2)	24 (5.6)	0.9 (-2.0, 3.8)
Arthralgia	31 (5.0)	20 (3.5)	19 (4.4)	0.6 (-2.0, 3.2)

Source: Anne Bunner, PhD; Clinical Data Scientist.
[a] Risk difference (with 95% confidence interval) is shown between 600 mg and placebo groups.
[b] Grouping for upper respiratory infections based on Reviewer's assessment: Upper respiratory infections replaces: Influenza like illness, Nasopharyngitis, Influenza, Pharyngitis, Upper respiratory tract infection, Viral upper respiratory tract infection, COVID-19, Nasal congestion, Respiratory tract infection viral, Viral pharyngitis, Tonsillitis, Viral infection, COVID-19 pneumonia, Upper respiratory tract inflammation
[c] Grouped query results included in the drug label excludes the following preferred terms: COVID-19 pneumonia and Viral infection.
Abbreviations: CI, confidence interval; ISS1, integrated summary of safety (12-week induction period); IV, intravenous; N, number of patients in treatment arm; n, number of patients with at least one event; RZB, risankizumab

7.6.1.6. Laboratory Findings, Induction (ISS1)

Review of the chemistry and hematology values that occurred at ≥ level 2 criteria[6] by treatment arm revealed that, in general, the proportion of subjects with abnormal values were similar between the TBM dose (risankizumab 600 mg IV) and placebo. Additionally, there were no notable dose-dependent changes in laboratory values between risankizumab treatment groups.

Table 35 displays the last measured liver biochemistry values which met ≥ level 2 criteria and occurred in a higher proportion in placebo compared to treatment arms. Review of liver biochemistry values revealed no difference between placebo or risankizumab treatment groups. However, concern for transient elevation in liver enzymes (which generally did not meet level 2 criteria) and hepatotoxicity associated with risankizumab exposure emerged during the safety review. Refer to Section 7.7.1 for further details.

Table 35. Proportion of Subjects With Liver Biochemistry Value ≥ Level 2[a] Criteria at Week 12 by Treatment Arm, Safety Population, ISS1

Parameter	RZB 600 mg IV N=620 n/N[c] (%)	RZB 1200 mg IV N=577 n/N [c] (%)	Placebo IV N=432 n/N [c] (%)	Risk Difference[b] (%) (95% CI)
Liver Biochemistry				
Alkaline phosphatase, high (U/L) >2X ULN	2/619 (0.3)	0/572 (0)	3/424 (0.7)	-0.4 (-1.3, 0.5)
Alanine aminotransferase, high (U/L) >5X ULN	1/617 (0.2)	0/573 (0)	2/422 (0.5)	-0.3 (-1.0, 0.4)

Source: Anne Bunner, PhD; Clinical Data Scientist.
[a] Last value on treatment defined as last available lab values while receiving study intervention. Threshold level 2 as defined by the Standard Safety Tables & Figures Integrated Guide.
[b] Risk difference (with 95% confidence interval) is shown between 600 mg and placebo groups.
[c] The denominators shown reflect those subjects with the specific liver biochemistry lab values available.
Abbreviations: CI, confidence interval; ISS1, integrated summary of safety (12-week induction period); IV, intravenous; N, number of patients in treatment arm; n, number of patients meeting criteria; RZB, risankizumab; ULN, upper limit of normal

In addition, a notable imbalance was observed in the proportion of subjects with abnormal lipid values between risankizumab and placebo arms (Table 36). Prior to this review, dyslipidemia was not an established adverse reaction associated with risankizumab exposure. Further safety review was completed in collaboration with the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) to assess the potential risk of dyslipidemia with risankizumab exposure; lipid elevations will be added to the Adverse Reactions section of the risankizumab drug label. Refer to Section 7.7.2.

[6] Threshold level 2 as defined by the Standard Safety Tables & Figures Integrated Guide.

Table 36. Subjects With Last On-Treatment Lipid Value of at Least Level 2[a] Criteria by Treatment Arm, Safety Population, ISS1

Parameter	RZB 600 mg IV N=620 n (%)	RZB 1200 mg IV N=577 n (%)	Placebo IV N=432 n (%)	Risk Difference[a] (%) (95% CI)
Lipids				
Cholesterol, total, high (mg/dL) >210	119/619 (19.2)	99/572 (17.3)	41/422 (9.7)	9.5 (5.3, 13.7)
HDL, males, low (mg/dL) <30	10/321 (3.1)	11/301 (3.7)	11/207 (5.3)	-2.2 (-5.8, 1.4)
HDL, females, low (mg/dL) <40	28/297 (9.4)	26/270 (9.6)	33/215 (15.3)	-5.9 (-11.8, -0.1)
LDL, high (mg/dL) >160	22/614 (3.6)	19/570 (3.3)	5/422 (1.2)	2.4 (0.6, 4.2)

Source: ad b.xpt; Software: R
[a] Last value on treatment defined as last available lab values while receiving study intervention. Threshold level 2 as defined by the Standard Safety Tables & Figures Integrated Guide.
[a] Risk difference (with 95% confidence interval) is shown between 600 mg and placebo groups.
Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; ISS1, integrated summary of safety (12-week induction period); IV, intravenous; LDL, low-density lipoprotein; N, number of patients in treatment arm; n, number of patients meeting criteria; RZB, risankizumab; ULN, upper limit of normal

7.6.2. Safety Findings and Concerns, Maintenance (M16-000 Substudy 1)

7.6.2.1. Overall Adverse Event Summary, Maintenance (M16-000 Substudy 1)

Table 37 provides a summary of AEs reported for the M16-000 Substudy 1 safety population. Notably, the proportion of subjects who reported SAEs was similar across treatment and placebo groups: 17 of 155 (11%) subjects in the risankizumab 180 mg SC arm, 18 of 142 (12.7%) subjects in the risankizumab 360 mg SC arm, and 15 of 143 (10.5%) subjects in the placebo arm. A similar proportion of subjects reported TEAEs, SAEs, and AEs leading to discontinuation across all treatment arms.

Table 37. Overview of Treatment-Emergent Adverse Events, Safety Population, Trial M16-000

Event Category	RZB 180 mg SC Q8W N=155 n (%)	RZB 360 mg SC Q8W N=142 n (%)	Placebo SC Q8W N=143 n (%)	Risk Difference 180 mg vs. Placebo (%) (95% CI)	Risk Difference 360 mg vs. Placebo (%) (95% CI)
Any treatment-emergent AE	107 (69.0)	100 (70.4)	101 (70.6)	-1.6 (-12.0, 8.8)	-0.2 (-10.8, 10.4)
Severe	9 (5.8)	15 (10.6)	14 (9.8)	-4.0 (-10.1, 2.1)	0.8 (-6.2, 7.8)
Moderate	51 (32.9)	38 (26.8)	42 (29.4)	3.5 (-7.0, 14.0)	-2.6 (-13.0, 7.8)
Mild	47 (30.3)	47 (33.1)	45 (31.5)	-1.1 (-11.6, 9.4)	1.6 (-9.2, 12.5)
SAE	17 (11.0)	18 (12.7)	15 (10.5)	0.5 (-6.6, 7.5)	2.2 (-5.2, 9.6)
SAEs with fatal outcome	0	0	0	0	0
AE leading to discontinuation of study drug	3 (1.9)	4 (2.8)	3 (2.1)		0.7 (-2.9, 4.3)
AE leading to interruption of study drug	0	0	0		0

Source: Anne Bunner, PhD; Clinical Data Scientist
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; Q8W, every 8 weeks; RZB, risankizumab; SAE, serious adverse event; SC, subcutaneous; SOC, system organ class; vs, versus

7.6.2.2. Deaths, Maintenance (M16-000 Substudy 1)

There were no deaths that occurred in the primary safety database for trial M16-000 Substudy 1.

7.6.2.3. Serious Adverse Events, Maintenance (M16-000 Substudy 1)

Table 38 provides a summary of SAEs reported for Trial M16-000 Substudy 1 that occurred in more than one subject and greater in either treatment arm versus placebo. In general, a review of the SAEs yielded no meaningful differences between risankizumab treatment groups versus placebo. Notably, the proportions of SAEs were similar across risankizumab treatment groups (placebo: 15 of 143 (10.5%) subjects; risankizumab 180 mg SC: 17 of 155 (11%) subjects; risankizumab 360 mg SC: 18 of 142 (12.7%) subjects).

Table 38. Serious Adverse Events Reported in More Than One Subject and Greater in Either Treatment Arm vs. Placebo, Safety Population, Trial M16-000

System Organ Class Preferred Term	RZB 180 mg SC Q8W N=155 n (%)	RZB 360 mg SC Q8W N=142 n (%)	Placebo SC Q8W N=143 n (%)	Risk Difference 180 mg vs. Placebo (%) (95% CI)	Risk Difference 360 mg vs. Placebo (%) (95% CI)
Gastrointestinal disorders (SOC)					
Anal fistula	0	2 (1.4)	1 (0.7)	-0.7 (-2.1, 0.7)	0.7 (-1.7, 3.1)
Large intestinal stenosis	2 (1.3)	1 (0.7)	0	1.3 (-0.5, 3.1)	0.7 (-0.7, 2.1)
Infections and infestations (SOC)					
Viral infection	0	3 (2.1)	0	0	2.1 (-0.3, 4.5)
Appendicitis	2 (1.3)	0	0	1.3 (-0.5, 3.1)	0

Source: Anne Bunner, PhD; Clinical Data Scientist
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; Q8W, every 8 weeks; RZB, risankizumab; SC, subcutaneous; SOC, system organ class; vs, versus

7.6.2.4. Dropouts and/or Discontinuation Due to Adverse Events, Maintenance (M16-000 Substudy 1)

Table 39 provides a summary of AEs leading to treatment discontinuation for subjects enrolled in Trial M16-000 Substudy 1. Ten subjects discontinued study drug due to AEs: risankizumab 180 mg SC 3 AEs (1.9%), risankizumab 360 mg SC 4 AEs (2.8%), and placebo arm 3 AEs (2.1%). The most commonly reported events were due to GI disorders, of which most events occurred in the risankizumab 360 mg SC group (risankizumab 180 mg: one event; risankizumab 360 mg: four events; placebo: two events). These cases were reviewed (ileus, rectal stenosis, subileus, anal stenosis, Crohn's disease, and colon dysplasia) and many of the events were attributed to long-term sequelae of underlying CD.

Various types of other adverse events led to discontinuation; there was no clustering of one specific event or type of event (Table 39).

Table 39. Adverse Events Leading to Treatment Discontinuation, Safety Population, Trial M16-000

System Organ Class Preferred Term	RZB 180 mg SC Q8W N=155 n (%)	RZB 360 mg SC Q8W N=142 n (%)	Placebo SC Q8W N=143 n (%)	Risk Difference 180 mg vs. Placebo (%) (95% CI)	Risk Difference 360 mg vs. Placebo (%) (95% CI)
Gastrointestinal disorders (SOC)					
Ileus	0	1 (0.7)	0	0	0.7 (-0.7, 2.1)
Rectal stenosis	0	1 (0.7)	0	0	0.7 (-0.7, 2.1)
Subileus	0	1 (0.7)	0	0	0.7 (-0.7, 2.1)
Anal stenosis	1 (0.6)	0	0	0.6 (-0.6, 1.9)	0
Crohn's disease	0	1 (0.7)	1 (0.7)	-0.7 (-2.1, 0.7)	0.0 (-1.9, 1.9)
Colon dysplasia	0	0	1 (0.7)	-0.7 (-2.1, 0.7)	-0.7 (-2.1, 0.7)
General disorders and administration site conditions (SOC)					
Hyperthermia	0	1 (0.7)	0	0	0.7 (-0.7, 2.1)
Infections and infestations (SOC)					
Clostridium difficile infection	0	1 (0.7)	0	0	0.7 (-0.7, 2.1)
Investigations (SOC)					
Alanine aminotransferase increased	1 (0.6)	0	0	0.6 (-0.6, 1.9)	0
Blood bilirubin increased	1 (0.6)	0	0	0.6 (-0.6, 1.9)	0
Psychiatric disorders (SOC)					
Irritability	1 (0.6)	0	0	0.6 (-0.6, 1.9)	0
Skin and subcutaneous tissue disorders (SOC)					
Urticaria	0	0	1 (0.7)	-0.7 (-2.1, 0.7)	-0.7 (-2.1, 0.7)

Source: adae.xpt; Software: Anne Bunner, PhD; Clinical Data Scientist
Two subjects had more than one AEs leading to treatment discontinuation
Recoding note: Ileus replaces: Small intestinal obstruction
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; Q8W, every 8 weeks; RZB, risankizumab; SC, subcutaneous; SOC, system organ class; vs, versus

7.6.2.5. Treatment-Emergent Adverse Events, Maintenance (M16-000 Substudy 1)

Table 37 displays the TEAEs in the Trial M16-000 Substudy 1 that occurred in >3% of risankizumab-treated subjects and higher in either treatment arm than placebo. The proportion of subjects who reported at least one TEAE through Week 52 of the maintenance study included 100 of 155 (69%) subjects in the 180 mg SC arm, 100 of 142 (70.4%) subjects in the 360 mg SC arm, and 101 of 143 (70.6%) of subjects in the placebo arm. The most common TEAEs observed in subjects treated with risankizumab include (b) (4), arthralgia, abdominal pain, and injection site reactions, and these AEs will be included in section 6.1 of the label. Notably, the majority of TEAEs reported occurred in a higher frequency in the risankizumab 360 mg SC versus 180 mg SC dose.

Table 40. Adverse Reactions Reported in More Than 3%[a] of Subjects With Crohn's Disease Treated With Skyrizi in Placebo-Controlled Maintenance Study (CD-3)

Preferred Term	RZB 180 mg SC Q8W N=155 n (%)	RZB 360 mg SC Q8W N=142 n (%)	Placebo SC Q8W N=143 n (%)	Risk Difference 180 mg vs. Placebo (%) (95% CI)	Risk Difference 360 mg vs. Placebo (%) (95% CI)
Arthralgia	13 (8.4)	13 (9.2)	12 (8.4)	0.0 (-6.3, 6.3)	0.8 (-5.8, 7.3)
Abdominal pain[b]	10 (6.4)	12 (8.5)	6 (4.2)	-0.0 (-6.3, 6.3)	4.3 (-1.4, 9.9)
Injection site reaction[c,d]	12 (8.5)	8 (5.6)	4 (2.8)	1.7 (-2.5, 6.0)	2.8 (-1.8, 7.5)
Pyrexia	4 (2.6)	7 (4.9)	4 (2.8)	-0.2 (-3.9, 3.5)	2.1 (-2.3, 6.6)
Anemia	7 (4.5)	7 (4.9)	6 (4.2)	0.3 (-4.3, 5.0)	0.7 (-4.1, 5.6)
Back pain	3 (1.9)	6 (4.2)	3 (2.1)	-0.2 (-3.4, 3.0)	2.1 (-1.9, 6.2)
Urinary tract infection	1 (0.6)	5 (3.5)	4 (2.8)	-2.2 (-5.1, 0.8)	0.7 (-3.3, 4.8)
Arthropathy	1 (0.6)	5 (3.5)	2 (1.4)	-0.8 (-3.1, 1.5)	2.1 (-1.5, 5.7)

Source: Anne Bunner, PhD; Clinical Data Scientist
[a] >3% of subjects treated with Skyrizi 180 mg and/or 360 mg and greater than placebo
[b] Abdominal pain is composed of several similar terms
[c] Grouping for injection site reaction based on Reviewer's assessment: injection site rash, injection site erythema, injection site swelling, injection site urticaria, injection site warmth, injection site pain, injection site hypersensitivity.
[d] This grouped query did not include the term "injection site reaction" and duplicate adverse reaction preferred terms reported in the same subject were counted as a single event. Injection site reaction rates included in the drug label differ from the numbers shown here. The label reports the rate of ADR based on the number of subjects where ADRs are counted only once per subject. A footnote to the table in the label is included to indicate that some subjects had multiple occurrences of injection site reactions.
Treatment-emergent adverse events defined as events that began either on or after the first dose of the study drug in Substudy 1
Abbreviations: CD, Crohn's disease; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; Q8W, every 8 weeks; RZB, risankizumab; SC, subcutaneous; vs, versus

7.6.2.6. Laboratory Findings, Maintenance (M16-000 Substudy 1)

The last on-treatment value that occurred at ≥ level 2 criteria[6] by treatment arm for serum hemoglobin, hematocrit, white blood count absolute lymphocytes, monocytes, neutrophils, eosinophils, platelets, and chemistry including lipid profiles were reviewed in subjects included in the primary maintenance safety population. No clinically meaningful trends were identified between the risankizumab treatment arms and the placebo arm with regard to these hematology and chemistry measurements.

Although liver chemistry values that met ≥ level 2 criteria during maintenance trial did not reveal a difference between placebo and risankizumab treatment groups, the review of induction study safety data raised concern for drug-induced liver injury (DILI) and transient elevations in liver function tests (see Sections 7.6.1.3 and 7.6.1.6). Refer to Section 7.7.1 for further details.

7.6.3. Subpopulations

The Applicant conducted safety analyses for subjects included in the primary safety database with (Bio-IR) and without (non-Bio-IR) history of inadequate response or intolerance to biologic therapy (Section 7.6.3.1).

7.6.3.1. Biologic Naïve Versus Biologic Intolerant

Table 41 and Table 42 show the overall safety profile in subjects who had inadequate response to prior biologic therapy (Bio-IR) and subjects who were naïve to the biologics (Non-Bio-IR) during the induction (M16-006) and maintenance (M16-000 Substudy 1) periods.

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Table 41. Overall AEs in Subjects With and Without Prior TNF Failure, Induction Period

	Non-Bio-IR					Bio-IR				
Event Category	Placebo N=87 n (%)	RZB 600 mg N=167 n (%)	RZB 600 mg vs. Placebo RD (%) (95% CI)	RZB 1200 mg N=165 n (%)	RZB 1200 mg vs. Placebo RD (%) (95% CI)	Placebo N=99 n (%)	RZB 600 mg N=206 n (%)	RZB 600 mg vs. Placebo RD (%) (95% CI)	RZB 1200 mg N=207 n (%)	RZB 1200 mg vs. Placebo RD (%) (95% CI)
Any TEAE	45 (51.7)	84 (50.3)	-1.4 (-14.4, 11.5)	82 (49.7)	-2.0 (-15.0, 11.0)	60 (60.6)	126 (61.2)	0.6 (-11.1, 12.3)	109 (52.7)	-7.9 (-19.7, 3.8)
Any SAE	11 (12.6)	5 (3.0)	-9.6 (-17.1, -2.2)	7 (4.2)	-8.4 (-16.0, -0.8)	17 (17.2)	22 (10.7)	-6.5 (-15.0, 2.1)	7 (3.4)	-13.8 (-21.6, -6.0)
AE leading to discontinuation	6 (6.9)	2 (1.2)	-5.7 (-11.3, -0.1)	4 (2.4)	-4.5 (-10.3, 1.3)	8 (8.1)	7 (3.4)	-4.7 (-10.6, 1.2)	3 (1.4)	-6.6 (-12.2, -1.0)
AE leading to death	1 (1.1)	0	-1.1 (-3.4, 1.1)	0	-1.1 (-3.4, 1.1)	1 (1.0)	0	-1.0 (-3.0, 1.0)	0	-1.0 (-3.0, 1.0)

Source: adae.xpt; Software: R
Abbreviations: AE, adverse event; Bio-IR, prior biologic inadequate response; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; RD, risk difference; RZB, risankizumab; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TNF, tumor necrosis factor; vs, versus

Table 42. Overall AEs in Subjects With and Without Prior TNF Failure, Maintenance Period

	Non-Bio-IR					Bio-IR				
Event Category	Placebo N=50 n (%)	RZB 180 mg N=54 n (%)	RZB 180 mg vs. Placebo RD (%) (95% CI)	RZB 360 mg N=57 n (%)	RZB 360 mg vs. Placebo RD (%) (95% CI)	Placebo N=134 n (%)	RZB 180 mg N=125 n (%)	RZB 180 mg vs. Placebo RD (%) (95% CI)	RZB 360 mg N=122 n (%)	RZB 360 mg vs. Placebo RD (%) (95% CI)
Any TEAE	33 (66.0)	34 (63.0)	-3.0 (-21.4, 15.4)	35 (61.4)	-4.6 (-22.8, 13.6)	102 (76.1)	94 (75.2)	-0.9 (-11.4, 9.5)	94 (77.0)	0.9 (-9.5, 11.3)
Any SAE	4 (8.0)	10 (18.5)	10.5 (-2.3, 23.3)	2 (3.5)	-4.5 (-13.4, 4.4)	19 (14.2)	12 (9.6)	-4.6 (-12.4, 3.3)	22 (18.0)	3.9 (-5.2, 12.9)
AE leading to discontinuation	1 (2.0)	1 (1.9)	-0.1 (-5.4, 5.1)	1 (1.8)	-0.2 (-5.4, 4.9)	5 (3.7)	2 (1.6)	-2.1 (-6.0, 1.8)	5 (4.1)	0.4 (-4.4, 5.1)
AE leading to death	0	0	0	0	0	0	0	0	0	0

Source: adae.xpt; Software: R
Abbreviations: AE, adverse event; Bio-IR, prior biologic inadequate response; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; RD, risk difference; RZB, risankizumab; SAE, serious adverse event; TEAE, treatment emergency adverse event; TNF, tumor necrosis factor; vs, versus

Overall, the safety profile of subjects in the Bio-IR and Non-Bio-IR groups was similar during the induction and maintenance periods. The most common TEAEs occurring in the two subpopulations were generally similar. No clinically meaningful trends were identified in the types of AEs reported in the two groups.

Further safety review was completed to assess the safety profile of the risankizumab 180 mg and 360 mg treatment arms within each subgroup. In the non-Bio-IR group, there was a higher proportion of SAEs reported in the risankizumab 180 mg treatment arm compared to the 360 mg arm. In contrast, in the Bio-IR group, a higher proportion of SAEs were reported in the risankizumab 360 arm compared to 180 mg arm. No additional clinically meaningful trends were identified in the types of AEs reported between the two treatment doses in either subgroup.

The safety profile as demonstrated in both the Bio-IR and Non-Bio-IR groups support approval and labeling of both maintenance dosages.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Drug-Induced Liver Injury

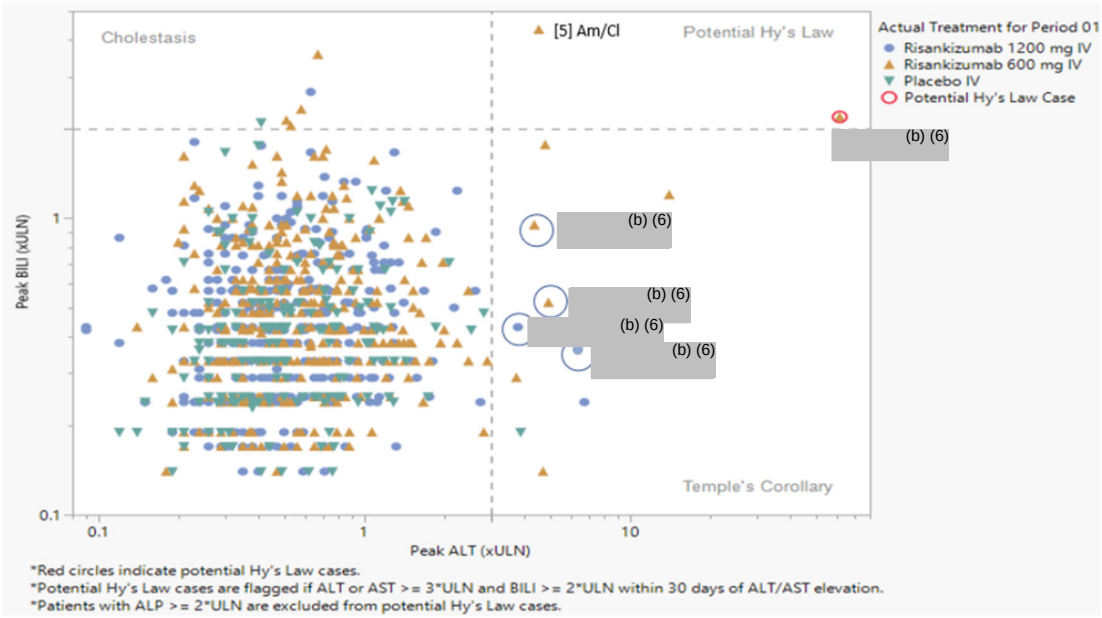
Issue

Hepatotoxicity is not currently included as an adverse event in the approved labeling for risankizumab, or other IL-23 inhibitors. However, a risk of hepatotoxicity related to risankizumab exposure emerged during the safety review of this marketing application that may be attributed to the higher dosage and route of administration proposed for the CD indication.

Assessment

Risankizumab for CD appears to carry a risk of hepatotoxicity, particularly during the proposed induction dosing regimen. Refer to DILI consult review (memo by Paul Hayashi, MD, MPH dated March 21, 2022). Thirty-seven subjects met criteria for Hy's Law, Temple's corollary, and cholestasis quadrants across studies M15-991, M16-006 and M16-000, and these cases were reviewed for potential DILI (Figure 5). The probable DILI cases due to risankizumab were identified in study M16-006.

Figure 5. Study M16-006 eDISH Plot



Source: FDA DILI Team's analysis. A bracketed number three ([3]) indicates probable DILI assessment by the Team.
The bracketed five followed by AM/Cl indicates unlikely DILI due to risankizumab but rather DILI due to amoxicillin-clavulanic acid.
Those subjects without bracketed numbers in Temple's Corollary were either unlikely or poss ble DILI only
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BILI, bilirubin; CI, confidence interval; DILI, drug-induced liver injury; eDISH, evaluation of Drug-Induced Serious Hepatotoxicity; IV, intravenous; ULN, upper limit of normal

Of the 1629 subjects in M16-006, the eDISH plot identified 16 subjects who received risankizumab and were outside the left lower quadrant. Of these, five subjects were assessed as probable DILI attributable to risankizumab and are circled in blue (four in Temple's corollary) or red (one in Hy's Law). Notably, all five of the probable DILIs occurred during induction (three subjects after 600 mg and two subjects after 1200 mg induction doses in M16-006). The other 11 subjects were considered unlikely or only possible DILI due to risankizumab.

Of the two subjects who met criteria for Hy's law, one event occurred in a subject receiving risankizumab 600 mg IV with a concomitant medication, amoxicillin-clavulanate, as the causative agent for DILI. The second case was concerning for DILI related to risankizumab exposure with immunoallergic features with rash after the second dose (further details below).

DILI Case Summary

Patient (b) (6) 30-year-old Asian male, with a history of CD and hepatic steatosis, enrolled in trial M16-006 was randomized to receive risankizumab 600 mg IV. A notable concomitant medication included azathioprine 125 mg daily. The subject's baseline liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin, were normal. On Day 55, he developed a rash (location unknown), which was attributed to study drug and the study drug was discontinued. Rash spontaneously resolved without intervention in 7 days. On Day 80, the subject developed a pruritic rash on his legs, chest, and back, which required hospitalization. On Day 82, the subject was found to have elevated liver

enzymes with ALT 2155 U/L (49.15 to 61.6 × upper limit of normal (ULN)), AST 900 U/L (22.5 to 30 × ULN), and bilirubin 46 (2.13 to 2.2 × ULN). ALP was normal.

During his hospitalization, he was treated with methylprednisolone IV for 5 days and concomitant azathioprine was discontinued. Work up for underlying etiology was negative including Hepatitis A (Hepatitis A IgM), Hepatitis B (surface Ag, core antigen IgM), Hepatitis C (serologies), Hepatitis E (serologies), cytomegalovirus (CMV; IgM, IgG), Epstein-Barr virus (EBV; VCA IgM, VCA IgG, EBNA), HIV antibody, and autoimmune conditions (antinuclear antibodies (ANA), antihepatocyte cytoplasmic antigen type I antibody, antiliver and kidney microsomal antibody, antimitochondrial antibody AMA-M2-3E, antimitochondrial M2-type antibody, and antisoluble liver antigen antibody). Antismooth muscle antibody was not obtained. Abdominal ultrasound and CT scan were performed and reportedly negative; full results and timing of imaging were not provided. Liver biopsy was not performed. The liver enzymes were monitored and downtrending. On Day 87, the subject was discharged from the hospital. On day of discharge, liver enzymes remained elevated, but were downtrending: ALT 432 U/L and AST 45 U/L. On Day 150 (end of trial), AST had normalized and ALT remained slightly elevated (38 U/L).

On review, the development of rash and concurrent elevated liver enzymes with rapid improvement after treatment with corticosteroids is concerning for DILI. The review team notes that liver enzymes were not checked when the rash first occurred at Day 55; the initial elevation in liver enzymes may have occurred at that time (therefore, not at Day 80). Additionally, the subject was receiving concomitant azathioprine; however, the elevation in liver enzymes are unlikely to be secondary to azathioprine because cholestatic injury (not hepatocellular injury) is most commonly seen in hepatotoxicity related to azathioprine therapy. Accordingly, the review team has adjudicated this case as a probable immune mediated DILI related to risankizumab exposure given the narrow latency, the concurrent rash at presentation, and the responsiveness to steroid therapy.

Further review was completed of all subjects enrolled in the maintenance Trial M16-000 Substudy 1. In subjects treated with risankizumab therapy, no subjects met criteria for potential Hy's law, 8 of 368 (2.2%%) subjects met cholestasis criteria (risankizumab 180 mg SC: 1 of 179 subjects; risankizumab 360 mg SC: 7 of 179 subjects) and 2 of 179 (1.1%) subjects met Temple's corollary (risankizumab 180 mg SC therapy: 0 of 179 subjects; risankizumab 360 mg SC: 2 of 179 subjects). All of these subjects developed elevated liver enzymes in the absence of overt clinical symptoms. Two subjects in the 360 mg maintenance arm that met Temple's corollary developed abnormal elevated liver enzymes during trial participation, which cannot be explained by an intercurrent event, comorbid condition, or concomitant medications. During the treatment duration, all subjects showed improvement in liver function enzymes despite continuation of risankizumab therapy and no medical intervention.

In summary, review of the primary safety databases identified a single hepatotoxicity case that may be associated with the induction doses of risankizumab administered intravenously. Transient elevations in liver enzymes were observed with induction and maintenance therapy. Despite this observed risk, it is reassuring that: 1) the subject who developed concern for DILI attributed to risankizumab induction therapy responded well to methylprednisolone treatment,

and 2) of the subjects who developed transient elevation in liver enzymes, liver enzymes normalized without intervention and despite continuation of risankizumab therapy.

A literature review was conducted to assess risk of liver dysfunction related to IL-23 inhibitor exposure in patients with CD diagnosis revealed that risankizumab, and other currently approved IL-23 inhibitors, may be associated with transient elevation in liver enzymes, but not other clinical manifestations of hepatotoxicity. Notably, the proposed dosing regimen for risankizumab proposed for treating CD is much higher and differs in route of administration (IV) compared to the currently approved dosage for plaque psoriasis (BLA 761105) and psoriatic arthritis (BLA 761105/s-14): 150 mg SC at Weeks 0, 4 and every 12 weeks thereafter. In addition, patients with CD may have a lower threshold for immune-mediated DILI because their livers may be exposed to higher amount of endotoxins and pathogen associated molecular patterns (PAMPS), thus altering immune tolerance to drugs. Furthermore, patients with CD are at risk for hepatobiliary extraintestinal manifestations and hepatotoxicity associated with commonly used treatments for CD (i.e., immunomodulators, anti-TNFa therapy, etc.). Therefore, standard of care for patients with CD generally involves routine monitoring of liver function and individualized treatment modification in patients who develop signs and symptoms of liver dysfunction. The hepatotoxicity risk associated with risankizumab therapy in patients with CD may be mitigated by limiting exposure to the lower induction dose (600 mg) and appropriate monitoring during treatment with risankizumab.

Conclusion

Risankizumab may cause transient hepatocellular liver enzyme elevation, but also injury of clinical significance (e.g., hepatocellular injury with jaundice) in susceptible patients during or shortly after induction. Patients and prescribers should be informed of the risk of hepatotoxicity and transient elevation in liver enzymes that may be associated with the higher dosing regimen and route of administration required for treatment of CD patients. A section titled "Hepatotoxicity in Treatment of Crohn's Disease" will be included in the Warnings and Precautions of the prescribing information. In addition, the following additional postmarketing surveillance will be issued at the time of approval: 1) enhanced pharmacovigilance for FAERs reporting for AEs concerning for hepatotoxicity associated with risankizumab exposure and 2) an observational postmarketing requirement (PMR) study to assess the incidence of severe acute liver injury in adults with moderately to severely active CD who are exposed to risankizumab, relative to other therapies used to treat CD.

7.7.2. Dyslipidemia

Issue

The findings of the safety review revealed a potential risk of increase in total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels that may be attributed to risankizumab exposure.

Background

Dyslipidemia is not a known adverse reaction associated with risankizumab exposure or other drugs in the IL-23 antagonist class. Initial review of the primary safety database revealed that

dyslipidemia may be associated with risankizumab exposure. As patients with CD are expected to require long-term maintenance therapy to control the disease, persistent dyslipidemia may place patients at increased risk for associated complications such as major adverse cardiovascular events (MACE) with chronic exposure to risankizumab. Thus, further review was conducted, in collaboration with DDLO, to assess the potential risk of dyslipidemia in subjects enrolled in Trials M16-006, M15-991, and M16-000.

Assessment

Baseline and on-treatment lipid values during the treatment duration were monitored for all subjects included in the primary induction and maintenance safety databases. Of note, all labs were obtained nonfasting, which may lead to increased triglyceride levels compared to fasting levels. In the primary induction safety database, baseline levels of total cholesterol and LDL-C were similar between placebo, risankizumab 600 mg IV, and risankizumab 1200 mg IV treatment groups. Subjects treated with risankizumab 600 mg IV or 1200 mg IV induction therapy developed increases in total cholesterol and LDL-C levels during the 12-week induction treatment period. However, the magnitude of the mean change in LDL-C (6.6 mg/dL increase from baseline at Week 12 for the 600 mg IV induction dose) observed with risankizumab treatment did not vary notably from baseline LDL-C and compared with placebo. Additionally, subjects treated with risankizumab 180 mg SC and 360 mg SC maintenance therapy developed increased levels of LDL-C during the 52-week maintenance treatment compared to placebo subjects. This effect did not appear to be dose dependent, and across all the risankizumab treatment groups (in both induction and maintenance) the LDL-C remained close to or below 100 mg/dL with the fluctuations remaining within a normal range.

At baseline, high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels were similar between placebo and risankizumab treatment groups. In general, small mean increases (2 to 3 mg/dL) in HDL-C levels from baseline and relative to placebo were observed with risankizumab treatment. Additionally, small median increases in TG from baseline at Weeks 12 and 52 were seen in subjects treated with risankizumab 600 mg IV and risankizumab 360 mg SC dose, respectively. These changes were not consistent throughout the study and were not dose-dependent.

Dyslipidemia is a known risk factor for cardiovascular disease and long-term sequelae including stroke and myocardial infarction. Although the trials were underpowered (based on trial duration and sample size) to reliably assess the association of lipid changes with MACE, a review of MACE (defined as nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) was conducted using the available safety data. No MACE were reported in the primary induction safety database. Five MACE were reported in Trial M16-000. Three of five events occurred in Trial M16-000 Substudy 1 and were included in the primary maintenance safety database; one subject treated with risankizumab 180 mg SC (single event was termed as both “stress cardiomyopathy and “non-fatal myocardial infarction”), one subject treated with risankizumab 360 mg SC (acute myocardial infarction), and one subject treated with placebo (cerebral infarction). In addition, two MACE occurred in subjects treated with risankizumab 180 mg SC enrolled in Trial M16-000 Substudy 3 (transient ischemic attack; sudden cardiac death). All cases were reviewed and adjudicated as unrelated to study intervention (see Section 17.4).

Conclusion

In the primary safety database, risankizumab exposure was associated with small increases in lipid parameters, including total cholesterol and LDL-C, which did not appear to be of clinical significance, and unlikely to impact overall cardiovascular disease risk. However, prescribers and patients should be aware of the increased risk of dyslipidemia, that may be associated with risankizumab therapy in patients with CD. Thus, the risk of dyslipidemia will be included in the Adverse Reactions section of the prescribing information.

7.7.3. Subjects Age 16 to Less Than 18 Years

Issue

The Applicant enrolled pediatric patients 16 to <18 years of age in the phase 3 trials, and proposes an indication for moderately to severely active CD in patients 16 years and older. However, the available data in subjects 16 to less than 18 years of age were insufficient to support the safety and efficacy of risankizumab in this subgroup.

Background

In general, trials intended to support approval of therapies for treating pediatric CD should enroll a sufficient number of pediatric subjects that adequately represent the target pediatric patient population to establish safety of the investigational drug for pediatric CD. Additionally, the Division previously recommended (and the Applicant agreed) to expand enrollment criteria to include pediatric subjects 12 to 15 years of age, if preliminary data from their phase 3 trials supported inclusion of this younger cohort (refer to Meeting Minutes from End of Phase 2 meeting on March 2, 2017 [IND 118701]). Enrollment criteria was not expanded during the phase 3 clinical development program and enrollment criteria for Trials M16-006, M15-991 and M16-000 were limited to pediatric subjects 16 to less than 18 years of age.

Assessment

Of the 1629 subjects included in the primary induction safety database, only 14 (<1%) subjects were 16 to less than 18 years of age; specifically, 4 of 620 (0.6%) subjects received risankizumab 600 mg IV, 5 of 577 (0.9%) subjects received risankizumab 1200 mg IV, and 5 of 432 (1.2%) subjects received placebo in the two induction Trials M16-006 and M15-991. Furthermore, of the subjects who achieved CDAI clinical response during the induction studies and continued in the maintenance Trial M16-000 Substudy 1, only 4 of the 542 (0.7%) enrolled subjects were less than 18 years old. In this cohort, only 3 of the 384 (0.7%) subjects treated with risankizumab (risankizumab 180 mg SC: 1 of 179 [1.1%]; risankizumab 360 mg SC: 2 of 179 [1.1%]) and 1 of 184 (0.5%) placebo subjects were less than 18 years old. Importantly, only two subjects age 16 to less than 18 years exposed to risankizumab 600 mg IV continued on to receive risankizumab maintenance therapy; one subject was treated with 360 mg SC dose and one subject was treated with 180 mg SC at Week 12 and every 8 weeks thereafter. Additionally, no subjects less than 18 years of age were enrolled in Trial M16-000 Substudy 4, a RLHS evaluating the proposed to-be-marketed OBDS device for maintenance therapy administration (Section 17.3).

The number of subjects age 16 to less than 18 years included in the primary safety database was too small to provide meaningful data to allow comparison of safety profiles between adult and pediatric subjects; however, the TEAEs reported in this limited number of subjects were generally mild and the type of TEAEs reported were overall similar to the TEAEs reported in adults.

Based on review of the information submitted in the marketing application, it is unclear whether pediatric patients may require dose adjustment based on body weight to account for potential differences in dose-response or exposure-response. In addition, pediatric CD carries a risk of growth delay and/or malnutrition. Therefore, a review of baseline growth and developmental parameters of enrolled subjects aged 16 to less than 18 years was completed to determine whether data generated from this small cohort is representative and generalizable to pediatric CD patients in the age group, who may present with varying baseline growth parameters. In the primary induction safety database, subjects less than 18 years had a mean (standard deviation [SD]) weight of 53.52 kg (8.79 kg) and mean body mass index (BMI) (SD) of 19.6 kg/m^2 (2.68 kg/m^2). Subjects less than 18 years included in the primary maintenance safety population had a mean baseline weight (SD) of 50.92 kg (10.92 kg) and mean baseline BMI (SD) of 19.90 kg/m^2 (3.93 kg/m^2). The baseline weight and height for all subjects less than 18 years were plotted on Center for Disease Control and Prevention growth charts (2017), which revealed that the weight-for-age and stature-for-age for these subjects was close to maximum or "adult" growth.

Additionally, eligibility criteria for trial(s) enrollment required adolescent subjects to have evidence of Tanner stage 5 pubertal development, which is equivalent to adult pubertal development. The growth parameters and pubertal development of the subjects included in the primary safety database most accurately represent "mature" adolescent subjects who are near adult size and pubertal development. However, adolescent patients with CD age 16 to less than 18 years oftentimes vary in size and pubertal development. Importantly, pediatric patients with CD are at risk of disease-related sequelae, such as malnutrition and growth delay, which may lead to impaired growth or pubertal delay. Accordingly, the subjects age 16 to less than 18 years included in the primary safety database do not adequately represent pediatric CD patients in this age range.

At the time of this review, two biologic therapies are FDA-approved for treatment of pediatric CD, infliximab (Janssen Biotech 2021)[7] and adalimumab (AbbVie 2021).[8] A review of the pediatric clinical development programs completed to support the approval of these drugs was

[7] Infliximab: BLA103772/S-5138 submitted in support of the pediatric CD indication included data from an open-label, randomized, multicenter trial in which 112 pediatric subjects (mean age 13.3 years, SD +/- 2.5 years) were enrolled. The Clinical Study Report did not provide details regarding the percentage of enrolled subjects who were 16 to less than 18 years. However, it is estimated that 15 subjects aged 16 to less than 18 years received induction therapy, of which 14 subjects continued on to received maintenance therapy during the trial.

[8] Adalimumab: BLA 125057/s-356 submitted in support of the pediatric CD indication included data from a randomized, double-blind, multicenter trial from which 93 pediatric subjects (mean age 13.6 years, SD +/- 2.5 years) were included in the primary safety database. Of these subjects, 40 subjects age 16 to less than 18 years were treated with adalimumab induction therapy and 32 subjects continued on to receive maintenance therapy (placebo: 6 subjects; adalimumab treatment: 26 subjects).

completed. A single, phase 3, multicenter, randomized trial was completed for each clinical development program, which enrolled pediatric subjects between 6 to less than 18 years of age. In the infliximab trial, 112 subjects were exposed to induction therapy, of which 103 subjects continued onto maintenance therapy. The review team estimates that only 15 of 112 (13.4%) subjects were age 16 to less than 18 years; however, inclusion of pediatric patients across a wide age range increased the robustness of data generated to support the utility of infliximab in pediatric patients with CD. In the adalimumab trial, 167 subjects were included in the primary safety analyses; of which 77 of 167 (46%) subjects were 16 to less than 18 years. The large sample size and the broad age range of enrolled subjects included in these trials allowed for generation of sufficient safety and efficacy data in support of the respective therapies for treatment of pediatric CD. In contrast, subject enrollment in the risankizumab clinical development program is limited to subjects 16 to less than 18 years of age, and the number of subjects in this age cohort included in the primary safety database to support the CD indication was less than the number of subjects age 16 to less than 18 years enrolled in the pediatric CD clinical development programs for infliximab or adalimumab.

Conclusion

Data submitted in support of BLA 761262 and sBLA 761105 are not generalizable to pediatric CD patients 16 to less than 18 years of age. First, the risankizumab clinical development program included a small number of subjects age 16 to less than 18 years, and review of growth and pubertal development of enrolled subjects revealed these subjects were close to adult development. Therefore, enrolled subjects do not adequately represent pediatric patients with CD, who are oftentimes at risk for malnutrition and/or growth delay due to underlying disease. Finally, data generated from this trial is limited due to small sample size and limited number of subjects exposed to the TBM dose compared to previous clinical development trials conducted in support of pediatric CD indications, due to smaller sample size and limited age range of enrolled subjects. Thus, data generated from these trials are insufficient to support the indication for treatment of moderately to severely active CD patients age 16 to less than 18 years. See Division of Pediatric Maternal Health, Pediatric Consult Review by Dr. Mona Khurana, finalized in the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) on February 11, 2022.

Postmarketing commitment (PMC) studies will be issued at the time of approval to assess the safety, efficacy, and pharmacokinetics of risankizumab, and evaluate the long-term safety, in pediatric patients 2 to 17 years of age with moderately to severely active CD. Data submitted in this marketing application, in conjunction with data from Trials M15-993, M16-006, and M16-006, may provide additional supportive safety data for risankizumab for the treatment of CD patients 2 to 17 years of age.

7.7.4. On-Body Delivery System

Issue

The safety review revealed concerns for device performance that impact both efficacy (administration failures) and safety (injection site reactions [ISRs]) of the proposed to-be-marketed OBDS, which is intended for risankizumab maintenance therapy administration.

Background

The on-body injector (OBI) delivery device proposed for risankizumab is a [redacted] OBDS developed by and obtained from [redacted] The OBDS is a sterile, single use, electromechanical OBI that administers a fixed dose of drug product from a prefilled cartridge (PFC) into the subcutaneous tissue of the abdomen or thigh, and is intended for use by patients or caregivers in a nonhealthcare environment or by healthcare professionals in a clinical setting. The device has an integrated adhesive patch for adhesion to the patient's skin. When activated, the device inserts the 29 gauge needle to a nominal 5 mm depth and begins drug delivery over approximately 5 minutes at a constant delivery rate. The device contains mechanical, electrical, and software elements. Refer to Center for Device and Radiological Health (CDRH) review (Refer to the device product review for BLA761105/016 by Kyran Gibson in SalesForce for the full CDRH intercenter consult review, ICC2100802, dated March 22, 2022). Of note, [redacted] OBDS is currently approved for Repatha[9] (evolocumab (Amgen 2021)) drug-device combination as a single-dose Pushtronex system (on-body infusor with prefilled cartridge).

The Applicant did not evaluate the proposed OBDS in the phase 3 maintenance trial (M16-000 Substudy1), but only in the BE PK study M19-128. In the BE study, approximately 10% of the 130 subjects reported device-related complaints and dosing failures. The Applicant conducted root cause analyses and implemented changes to the manufacturing process and revised the Instruction for Use (IFU) to address the use errors identified. However, the human factor (HF) study was conducted in parallel to the BE study, and did not evaluate the final intend-to-market user interface (e.g., packaging, labeling, device(s)) (memo by Matthew Barlow, RN, BSN in DARRTS dated April 22, 2022). Given the deficiencies noted during the review cycle, the Applicant submitted interim data from an ongoing RLHS, M16-000 Substudy 4, to further support the safety of the OBDS for administration of maintenance therapy (risankizumab 180 mg or 360 mg every 8 weeks) (see Section 17.3). The review team requested the Office of Surveillance and Epidemiology (OSE) to perform a review of the FAERS reports for Repatha OBDS to evaluate the postmarket performance of a highly similar delivery device (Refer to memo uploaded by Suprat Saely, PharmD, BCPS, FCCM on March 16, 2022, under BLA 761105).

Assessment

Dosing Failures

The 14 dosing failure complaints reported from 11 of 130 (8.5%) subjects who received the SC maintenance doses using the OBDS in the BE study are shown in Table 43. The root cause analyses of the dosing errors identified 1 manufacturing issue, 11 use errors, and 2 unconfirmed causes.

[9] Repatha (BLA125522) is a proprotein convertase subtilisin kexin type 9 inhibitor antibody approved on August 27, 2015, for hyperlipidemia indication.

Table 43. Root Cause Analyses and Proposed Mitigations for the Dosing Failure Complaints in Study M19-128

Complaint	Number of Complaints	Root Cause	Mitigations
Device did not activate upon removal of green adhesive liner tab	1	Glue blooming residue on battery interrupted power supply	(b) (4)
Device stopped upon applying device to skin (error alarm)	1	Use error (device applied to site more than 30 minutes after activation – "Time Out" alarm	Changes to Step 3C in IFU[1]
Device stopped after pressing start button (error alarm)	4	Use error (safety latch open, device not properly applied to the skin)	Changes to Steps 3C and 3D in IFU[1]
Device stopped approximately 1 minute into injection (error alarm)	1	Use error (safety latch open, device not properly applied to the skin)	Changes to Steps 3C and 3D in IFU[1]
Device stopped immediately after pressing start button (error alarm)	1	Use error (start button not fully pressed)	Changes to Step 4A in IFU[2]
Leakage observed coming from right side of OBDS during injection	1	Use error (start button not fully pressed)	Changes to Step 4A in IFU[2]
Continuous leakage from injection site approximately 2-3 minutes into injection (error alarm)	1	Use error (start button not fully pressed)	Changes to Step 4A in IFU[2]
Error alarm after 5 minutes, 80% drug injected, white plunger was not fully advanced, intermittent stopping and restarting of pumping sounds	1	Use error (start button not fully pressed)	Changes to Step 4A in IFU[2]
Error alarm near completion	1	Use error (insertion of PCA not per IFU)	Changes to step 2D in IFU[2]
Alarm immediately after injection completion	2	Unable to confirm root cause – likely a fluid path obstruction	Changes to step 2D in IFU[2]

Source: Applicant Information Request response dated January 10, 2022
[1] The changes steps 3C and 3D/E in IFU occurred prior to the HF study.
[2] The changes to steps 2D and 4A in IFU occurred after the HF study.
Abbreviations: IFU, instructions for use; OBDS, on-body delivery system; PCA, patient-controlled analgesia

The manufacturing changes and the revisions to the IFU appear reasonably adequate to mitigate the risks associated with the identified manufacturing and use error issues. Although the proposed revisions to the IFU section 2D and 4A were not evaluated in the HF study, it is reassuring that the complaints that warranted the changes to 2D and 4A were not observed in the HF study.

In the two cases of postinjection alarms for which a root cause was not confirmed, the manufacturer attributed the device error to "fluid path obstruction" within the cartridge causing

the plunger to be unable to advance and deliver the remaining amount of drug. In both cases, the device operated as intended by alerting the user that the device was unable to complete injection.

In addition, in the BE study, there were 4 device issues noted as use errors in which the Activation Button was not fully pressed and the needle did not lock out fully. Of these 4 complaints, there were 2 "wet injections" (i.e., leaking) due to the needle not being fully extended and only one case of the device erroring out prior to injection. Further review attributed these wet injections and full injections to interruptions to the optical sensor, where the activation button remained partially pressed and injection was initiated without the needle locked in position.

The mechanics of how the activation button may remain partially pressed to interrupt the optical sensor and, subsequently, initiate injection was clarified and determined to be acceptable through interaction with the Applicant, given that the same optical sensor activation button mechanism is commonly used in other cleared and marketed devices. In addition to the revisions to the IFU to highlight the audible "click," CDRH recommends postmarketing commitment from the Applicant to conduct verification testing or establish acceptance criteria related to the audible feedback (click, timing, correlation with dose delivery, click decibels) used to indicate the activation button has been fully pressed, and implement activation force release testing essential performance requirement for review prior to commercialization and distribution of the OBDS device.

Furthermore, review of interim results from the RLHS of the OBDS device conducted in the intended patient population with CD over 24 weeks (3 dose administrations) was reassuring as only 5 of 46 subjects reported minor hazards related to the OBDS (see Section17.3). Overall, there were 3 dosing failures, all related to use error. The single case of wet injection was attributed to use error where the device adhesive was not secured to skin during the injection. Baseline CDAI scores were similar at Week 0 and 16 (after three doses), which supports long-term efficacy of maintenance therapy administered via OBDS device. Lastly, the FAERS search conducted for the approved Repatha OBDS device retrieved only 59 reports of leakage issues with the OBDS device since initial approval in August 2015 to February 2022. The leakages related to Repatha and "activation button not fully pressed" accounted for 4.7% and <1% of total reported device issues, respectively; and the available root cause analyses identified similar use errors as those seen in the risankizumab BE study. (Refer to memo uploaded to DARRTS by Suprat Saely, PharmD, BCPS on March 16, 2022 under BLA 761105 for full details.)

Injection Site Reactions

There was a substantially higher incidence of ISRs, i.e., erythema (13%), induration (19%), swelling (8%), pain (7%) and pruritis (6%), reported in subjects receiving the proposed subcutaneous maintenance doses using the OBDS compared to the PFS (Table 44) in the BE study.

Table 44. Injection Site Reactions Reported in Study M19-128

Injection Site Reactions	360 mg 4 x 90 mg/mL PFS (N=127) n (%)	360 mg 360 mg/2.4mL OBDS (N=129) n (%)	180 mg 180 mg/1.2mL OBDS (N=30) n (%)
Injection site bruising	1 (0.8)	0	0
Injection site discomfort	0	1 (0.8)	0
Injection site erythema	1 (0.8)	17 (13.2)	1 (3.3)
Injection site haemorrhage	0	1 (0.8)	0
Injection site induration	0	24 (18.6)	5 (16.7)
Injection site irritation	0	2 (1.6)	0
Injection site edema	0	3 (2.3)	1 (3.3)
Injection site pain	7 (5.5)	9 (7.0)	1 (3.3)
Injection site pruritus	5 (3.9)	8 (6.2)	0
Injection site swelling	0	10 (7.8)	2 (6.7)

Source: Study M19-128 R&D/21/0311, Table 14.3 1.2.1
Some subjects had more than one Injection Site Reactions.
Abbreviations: N, number of patients in treatment arm; n, number of patients with given characteristic; OBDS, on-body delivery system; PFS, prefilled syringe

The OBDS product presentation delivers both a higher concentration (150 mg/mL) and higher injection volume (1.2mL or 2.4mL) at a single site compared to that used in the CD phase 3 trials (4 subcutaneous injections of a 90 mg/mL of risankizumab in prefilled syringes administered across 4 different injection sites) which raised the concern for the observed increased risk of ISR. However, the ISRs observed with the OBDS in Study M19-128 were of mild severity and self-limiting with resolution within 72 hours. The most common ISRs were related to the device adhesive (erythema due to skin irritation and/or pulling) and injection volume (induration and swelling at the injection site). Furthermore, the interim data from the RLHS did not include any report of ISRs in patients with CD, and similar types and rates of ISRs were observed from both premarket (phase 1) and postmarket experience with the Repatha OBDS.

As a potential mitigation of ISRs related to the OBDS, the Applicant's proposed labeling (b) (4)
However, the BE study evaluated a single dosing of risankizumab injected in the abdomen exclusively; thus, risk mitigation by (b) (4) (b) (4) from chronic multiple dosing with the OBDS product was not assessed. However, the RLHS evaluated both the abdomen and thigh as injections sites with approximately 30% of the injections administered in the thigh, and as noted above, there were no ISRs reported in the RLHS.

Conclusion

The Applicant has provided a response to all components requested to determine the impact of the activation button use errors on functionality. CDRH recommends issuing a PMC for design verification of the audible "click" heard once the activation button has been fully pressed.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Age

The Applicant proposed no dose adjustment for geriatric patients (aged 65 years and older), and the review team is in agreement that no dose adjustment is warranted.

In PK/exposure analysis, neither age (continuous) nor age category (≥65 years old versus <65 years old) was associated with significant difference in risankizumab exposure.

Within the primary safety population, subjects 65 years and older accounted for 18% of the induction and 17% of the maintenance safety populations. This included 77 subjects in induction (22 placebo, 31 risankizumab 600 mg, 24 risankizumab 1200 mg) and 32 subjects in maintenance (8 placebo, 15 risankizumab 180 mg, 9 risankizumab 360 mg) studies over 12 and 52 weeks, respectively. Although the rates of TEAEs, SAEs, and other events of interest were comparable between arms across age groups, there were too few subjects per arm to draw meaningful conclusions regarding differential safety of induction and maintenance therapy across age groups.

Hepatic Impairment

The Applicant did not conduct a dedicated hepatic impairment study with the proposed product. The approved labeling and the proposed labeling submitted by the Applicant do not include specific information for patients with hepatic impairment in sections 8 and 12.3.

Disease Specific Risk

A risk of hepatotoxicity associated with risankizumab exposure emerged during the safety review, with clinical manifestations that ranged from transient elevation of liver enzymes to concern for DILI. While IL-23 inhibitor exposure has been associated with transient elevation in liver enzymes previously, there is concern that the risk of hepatotoxicity (and the degree of severity of related clinical manifestations) associated with risankizumab exposure may be increased in CD patients due to disease-specific risk factors (see Section 7.7.1). Thus, a section on “Hepatotoxicity in Treatment of Crohn’s Disease” will be added to section 5 Warnings and Precautions of the prescribing information. The providers should obtain liver enzymes and bilirubin prior to initiation of Skyrizi. During induction and up to at least 12 weeks of treatment, the providers should monitor laboratory parameters and monitor more frequently if patients develop elevations and/or symptoms of liver dysfunction. Routine laboratory monitoring of liver enzymes and bilirubin should be continued during maintenance treatment.

8.2. Drug Interactions

Cytochrome P450 Substrates

No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), metoprolol (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with risankizumab-rzaa 150 mg administered subcutaneously at Weeks 0, 4, 8 and 12 (more frequent than the approved recommended dosing frequency) in subjects with plaque psoriasis.

Potential effects of risankizumab on PK of other drugs were not evaluated at the doses proposed for CD. A PMC study will be issued to address the effects of risankizumab in subjects with CD on concomitant medications.

8.3. Plans for Pediatric Drug Development

This clinical development program was granted Orphan Drug Designation in November 2016 and is therefore exempt from Pediatric Research Equity Act (PREA) requirements. Nevertheless, pediatric subjects age 16 to less than 18 years were included in trials M15-991, M16-006 and M16-000, and the Applicant proposes an indication for moderately to severely active CD in patients 16 years and older. The review team concluded that data submitted in support of the marketing application was insufficient to support an indication in CD patients age 16 to less than 18 years (see Section 7.7.3). The Applicant agreed to conduct the following PMCs:

PMC 4294-5 Conduct a one-year, randomized, trial to evaluate the safety, efficacy, and pharmacokinetics of Skyrizi (risankizumab) in pediatric patients 2 to 17 years of age with moderately to severely active Crohn's disease.

Draft Protocol Submission: *10/2022*
Final Protocol Submission: *03/2023*
Trial Completion: *03/2029*
Final Report Submission: *12/2029*

PMC 4294-5 Conduct a LTE study to evaluate the long-term safety of Skyrizi (risankizumab) in pediatric patients 2 to 17 years of age with moderately to severely active Crohn's disease who participated in postmarketing commitment study 4294-5. This study can be conducted as part of postmarketing commitment study 4294-5.

Draft Protocol Submission: *12/2022*
Final Protocol Submission: *03/2023*
Trial Completion: *03/2033*
Final Report Submission: *09/2033*

8.4. Pregnancy and Lactation

Animal Data

Fertility and early embryonic developmental studies were not conducted with risankizumab. However, the potential effects of risankizumab-rzaa on male fertility were assessed in sexually mature cynomolgus monkeys as part of the 26-week repeat dose toxicity study. No effects on male fertility parameters were observed in male monkeys dosed weekly for 26 weeks with 50 mg/kg risankizumab-rzaa. The 50 mg/kg dose in monkeys provides approximately 1.3 times the exposure (AUC) in humans administered the 600 mg induction regimen, and 3.1 times the exposure in humans administered the 360 mg maintenance regimen for CD.

The reproductive toxicity of risankizumab-rzaa was assessed in an enhanced pre- and postnatal developmental toxicity study in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered subcutaneous doses of risankizumab-rzaa at 5 and 50 mg/kg/week from gestation day 20 to parturition, and the monkeys (mother and infants) were monitored for 6 months after delivery. No maternal toxicity was observed in this study. No treatment-related effects on growth and development, malformations, developmental immunotoxicology, or neurobehavioral development were observed in this study. However, a dose-dependent increase in fetal/infant loss was noted in the risankizumab-rzaa-treated groups (32% and 43% in the 5 mg/kg and 50 mg/kg groups, respectively) compared with the vehicle control group (19%). The increased fetal/infant loss in the 50 mg/kg group was considered to be related to risankizumab-rzaa treatment. The NOAEL for maternal toxicity was identified as 50 mg/kg and the NOAEL for developmental toxicity was identified as 5 mg/kg. The 5 mg/kg dose in pregnant monkeys resulted in approximately 0.16 times the exposure (AUC) in humans administered the 600 mg induction regimen and 0.4 times the exposure (AUC) in humans administered the 360 mg maintenance dose. In the infants, mean serum concentrations increased in a dose-dependent manner and were approximately 17% to 86% of the respective maternal concentrations. Following delivery, most adult females and all infants from the risankizumab-rzaa-treated groups had measurable serum concentrations of risankizumab-rzaa up to 91 days postpartum. Serum concentrations were not detectable at 180 days postpartum.

Human Data

Pregnancy

Review of available human data of risankizumab exposure during pregnancy from clinical trials and the Applicant's pharmacovigilance database are insufficient to establish a risk of spontaneous abortion, congenital anomaly or maternal or fetal adverse reactions. Risankizumab is a typical IgG1 monoclonal antibody that should behave similarly to endogenous IgG1. Therefore, similar to the Agency's approach to labeling for other monoclonal antibodies, labeling will include information under section 8.1 Risk Summary and Clinical Considerations about the active transport of monoclonal antibodies across the placenta, the potential for immunosuppression in the in-utero exposed infant and the risks and benefits that should be considered prior to administration of live vaccines. Live vaccines should be delayed for a minimum 5 months (half-life of 28 days x5) after birth.

Upon initial approval, the Applicant was issued two PMRs for pregnancy related studies with risankizumab. One study is a pregnancy registry (PMR 3494-2) and the other a database study. The first interim annual report for both studies is expected in June 2022. With the approval in the CD population, two new pregnancy study PMRs will be issued to identify an unexpected serious risk for adverse pregnancy, fetal, or infant outcomes from the use of risankizumab during pregnancy in females regardless of indication. The first PMR requires a registry for prospective collection of detailed clinical information about pregnancy exposures and outcomes. The second PMR requires a complementary retrospective cohort study in an appropriate database in order to offset the typically slow accrual to pregnancy registries.

Lactation

There are no available animal data with regards to risankizumab-rzaa exposure and breastfeeding. There were cases reported to the Applicant's pharmacovigilance database of drug exposure during breastfeeding; however, upon review there are no data on the presence of risankizumab-rzaa in human milk, the effects on the breastfed infant, or the effects on milk production among the reports. The molecular weight for risankizumab is 146,000 Daltons, and according to breastfeeding experts, the amount in human milk, if any, is expected to be very low. Risankizumab is a typical IgG1 monoclonal antibody that should behave similarly to endogenous IgG1. Therefore, similar to the Agency's approach to labeling for other monoclonal antibodies, labeling will include information under 8.2 that notes: "Maternal IgG and monoclonal antibodies are known to be present in human milk."

A PMR for a clinical lactation study (May 2019) with risankizumab is recommended to inform labeling. Risankizumab is used in females of reproductive age, and there are no current data available to inform women of risankizumab use during breastfeeding.

Females and Males of Reproductive Potential

Upon review of available nonclinical fertility data, as well as review of cases reported to the Applicant's pharmacovigilance database, there are no available data at this time to demonstrate an increased risk in adverse effects related to fertility; thus, section 8.3 Females and Males of Reproductive Potential will be omitted from labeling.

Refer to Division of Pediatric and Maternal Health (DPMH) Review uploaded by Carrie Ceresa, Pharm D., MPH in DARRTS under BLA761262 and BLA 761105/S016 on January 31, 2022 for further discussion and labeling recommendations.

9. Product Quality

The Office of Pharmaceutical Quality Review team has assessed BLA 761262 for the 600 mg induction dose and BLA761105/016 for the 360 mg maintenance dose with respect to CMC and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such OPQ recommends approval of 600 mg (60 mg/mL) intravenous infusion and the 360 mg (150 mg/mL) from a quality perspective. Refer to Quality Executive Summary memo uploaded to BLA761262 in DARRTS by Riley Myers on February 23, 2022.

Of note, Division recommends approval of both 180 mg and 360 mg maintenance dosages. The Applicant initially had not included a complete CMC package to support the 180 mg presentation in the sBLA submission; however, the efficacy supplement (sBLA761105-S018) for the 180 mg (150 mg/mL) prefilled cartridge presentation was submitted on May 25, 2022, and is currently under review.

9.1. Device or Combination Product Considerations

See Section 7.7.4.

Refer to the device product review for BLA 761105/016 by Kyran Gibson in SalesForce for the full CDRH consult review.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

Site Inspections

Six clinical site inspections were conducted to support the review of this application. The final assessment of the inspections is that the studies were conducted adequately, and the data generated are suitable to evaluate the proposed indication. See Section 20 for detailed inspection findings.

Financial Disclosures

Although there were multiple investigators involved in the trials who received financial compensation, the Applicant has provided the appropriate documentation of methods taken to minimize bias and ensure integrity of data for trials M15-991, M16-006, and M16-000.

Additionally, the remote regulatory assessment completed by OSIS for the clinical portion of Study M19-128 revealed failure of two subinvestigators to file the required financial disclosure forms. Refer to memo uploaded by Melkamu Getie Kebtie on March 8, 2022, under BLA 761105 for full details. The Applicant provided clarification that the contracted subinvestigators were AbbVie employees, and submitted an updated employee list documentation in lieu of financial disclosure forms. The review team concluded this did not impact the integrity of the study. See Section 23.

11. Advisory Committee Summary

An advisory committee was not held for this application.

III. Appendices

12. Summary of Regulatory History

Table 45. Summary of Regulatory History

Date	Activity
August 12, 2013	Type B, pre-IND meeting was held between Boehringer Ingelheim (BI) and FDA to discuss the adequacy of the nonclinical data to support the conduct of the proposed phase 2 trial 1311.6, acceptability of the overall trial design with specific attention to clinical endpoints and safety procedures, and acceptability of the trial as proof-of-concept trial for subsequent pivotal phase 3 trials in patients with CD for both TNF-naïve and TNF nonresponders
September 27, 2013	IND 118701 was submitted by BI in the United States for the treatment of CD
December 18, 2013	Type C, CMC meeting was held to discuss the methodology for selection of production cell lines and the subsequent testing that ensures clonality, and the sufficiency of this testing
October 17, 2016	IND 118701 was transferred from BI to AbbVie
November 29, 2016	Orphan-drug designation was granted for the "treatment of pediatric Crohn's disease"
March 2, 2017	Type B, End of Phase 2 meeting was held to discuss the Sponsor's phase 3 clinical development plan to support the proposed indication for the treatment of CD in patients 16 years and older
September 21, 2017	Type C, Guidance meeting was held to discuss the Sponsor's proposed strategy to bridge the 90 mg/mL formulation in prefilled syringes (PFS) used in the phase 3 clinical trials to a 150 mg/mL formulation in an OBDS under development
July 20, 2018	Type C, Guidance meeting was held to discuss the development strategy for the proposed patient-reported outcomes of the Crohn's Symptom Severity (CSS) questionnaire and the (b) (4) the risankizumab (b) (4) inflammatory bowel disease programs
December 2, 2018	Type C, Guidance meeting was held to discuss revisions to the Sponsor's proposed OBDS program
June 27, 2019	Type C, Guidance meeting was held to discuss proposed revisions to the SES-CD inclusion criterion for induction studies M16-006 and M15-991, and anticipated updates to the maintenance protocol M16-000
October 11, 2019	Type C, Guidance meeting was held to discuss proposed revisions for both the IV induction and SC maintenance dosing regimens and the adequacy of the device development program for an OBDS
October 22, 2019	Type C, Guidance meeting to discuss the proposed cutoffs used to define IBDQ-related endpoints
April 17, 2020	Type C, Guidance meeting to discuss the statistical analysis plan for the phase 3 studies
September 14, 2020	Type C, Guidance meeting to discuss the adhesion study and test method for the OBDS to be used in a future marketing application
October 16, 2020	Type C, CMC meeting to discuss the CMC development strategy for risankizumab drug substance and drug product to be used for the treatment of moderately to severely active CD in subjects aged 16 years and older

Date	Activity
October 20, 2020	Type C, Guidance meeting to discuss strategies for the Sponsor's Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), and the planned dossier structure for a future submission of an original non-NME BLA and efficacy supplement (sBLA) to the risankizumab psoriatic arthritis (PsO) BLA 761105 for the treatment of moderately to severely active CD in subjects aged 16 years and older.
May 4, 2021	Type B, Pre-BLA Meeting (WRO Questions)
May 20, 2021	Type B, Pre-BLA Meeting (TCON Questions)
September 16, 2021	BLA/sBLA submission with two Priority Review vouchers
January 5, 2022	The proprietary name of Skyrizi was found conditionally acceptable for BLA 761262
February 24, 2022	Major amendment submissions resulted in extension of the review goal date to June 16, 2022

Abbreviations: CD, Crohn's disease; CMC, chemistry, manufacturing, and controls; IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous; OBDS, on-body delivery system; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumor necrosis factor

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

No new nonclinical studies were submitted under investigational new drug (IND).

13.2. Individual Reviews of Studies Submitted to the NDA

Pharmacology

IL-23/IL-23 Receptor Interaction – Mechanism of Inhibition by Risankizumab (ABBV-066) R&D/18/1302

The potential for ABBV-066 to bind to interleukin (IL)-23 captured by its receptor on cells was investigated on preformed complex of IL-23 captured on IL-23Rα by surface plasmon resonance. The anti-IL-23R antibody 20E5 was covalently immobilized on carboxy methyl dextran matrix of the CM5 biosensor chip via amino groups using an amine coupling kit. Carboxyl groups of the dextran matrix on the chip were activated with 100mM NHS (N-hydroxysulfosuccinimide) and 400mM EDC (1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide Hydrochloride), and IL-23R antibody 20E5, diluted in 10mM sodium acetate, pH 4.5, was injected for 420 s across the activated surface. Human IL-23R protein, at a concentration of 100nM, was injected for 60 s over the IL-23R antibody coated surface, and human IL-23 was injected for 60 s and allowed to bind to the captured IL-23Rα.

ABBV-066 or the negative control immunoglobulin G (IgG) did not bind to IL-23 captured by immobilized IL-23Rα indicating that ABBV-066 is a competitive inhibitor of IL-23Rα. Thus, ABBV-066 binds to the p19 subunit of human IL-23 and inhibits the binding of IL-23 to IL-23Rα. However, ABBV-066 does not bind to IL-23 captured on immobilized IL-23Rα. The results of this study suggest that ABBV-066 would not be able to bind to the cell-surface IL-23/IL-23Rα complex, and thus the risk of mediating cell-targeting effects, such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), or modifying IL-23/IL-23Rα initiated intracellular effects is considered low.

Efficacy of Anti-IL-23p19 mAb PR-963484 in CD40-Induced Colitis in C.B-17 SCID Mice R&D/20/0680

In this study, the efficacy of anti-IL-23p19 mAb PR-963484 was determined in an anti-CD40 mAb-induced colitis mouse model. PR-963484 is a blocking monoclonal antibody that recognizes the p19 subunit of murine IL-23 (interleukin 23). Anti-CD40 mAb (FGK45, r-anti-m-CD40) was injected to C.B-17 severe combined immunodeficiency (SCID) mouse to generate colitis. Anti-IL-23p19 mAb PR-963484 or PBS was injected intraperitoneally (IP) to the mice on Day -1 and 3 at a dose of 15 mg/kg. On Day 0, both groups were injected with agonistic anti-CD40 mAb at 5 mg/kg by IP injections.

A single IP injection of agonistic anti-CD40 mAb led to colitis characterized by an increase in endoscopic score and an increase in IBA1+ cells in the colon associated with a pattern of weight loss characterized by an initial drop in weight followed by recovery and eventual progressive weight loss. IP administration of PR-963484 at a dose of 15 mg/kg 2 times/week significantly ameliorated colitis as measured by endoscopy and IBA1+ cell histological analysis. Treatment with PR-963484 did not impact body weight change over 7 days compared to vehicle control group. In addition, PR-963484 did not have a significantly impact on the anti-CD40 mAb induced splenomegaly.

Efficacy of Anti-p19 mAb, PR-963484, in T-Cell Transfer (TCT) Colitis in SCID Mice

This study was conducted to determine the efficacy of intraperitoneally administered PR-963484 in the TCT model of colitis. The animals were dosed with PR-963484 2 times per week at a dose of 15 mg/kg beginning 3 weeks post T cell transfer. At 6 weeks post transfer, the animals were given a terminal endoscopy and colons were collected for histology. Efficacy was measured by endoscopic evaluation of disease severity (MEDAI sum score) and IBA1+ infiltrating macrophages in the mucosa by histology. PR-963484 was administered IP at 15 mg/kg twice weekly starting on Day 21 post T cell transfer. On Day 41 mice received a terminal endoscopy and on Day 42, the animals were euthanized, and colons collected for histological assessment.

No adverse effects of treatment were observed in the PR-963484 treatment group. Treatment with PR-963484 caused a significant (62%) reduction of disease severity compared to the IgG control group, as assessed by endoscopy. Analysis of % of IBA1+ cells in the mucosa by histology shows a significant (47%) decrease compared to the IgG Control group.

In Vitro Assessment of ADCC and CDC Activity of Risankizumab (ABBV-066)

This study was conducted to characterize the ability of risankizumab to trigger ADCC and CDC activities. Risankizumab and risankizumab/IL-23 complexes were tested in an ADCC

mechanism of action reporter bioassay using as target cells a HEK293 cell line that expresses the IL-23 receptor complex, and the ability of plate-bound risankizumab to activate human serum complement was evaluated through detection of iC3b by enzyme-linked immunosorbent assay (ELISA). Risankizumab was tested at concentrations of 15 µg/mL (100nM) or 1.5 µg/mL (10nM) either alone or in the presence of human IL-23 at 300 ng/mL (5nM).

The results show that risankizumab alone or in the presence of human IL-23 did not activate FcγRIIIa signaling in an ADCC bioassay in which IL-23R expressing target cells and FcγRIIIa expressing effector cells were used. In addition, risankizumab did not show a potential to activate complement in human serum using the iC3b detection assay. These data indicate that the risk of ADCC and/or CDC by risankizumab is minimal.

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

No new in vitro studies were submitted. Please see the Clinical Pharmacology sections of Unireview of original biologics license application (BLA 761105) dated April 23, 2019, in the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS).

14.2. In Vivo Studies

14.2.1. M19-128: A Pivotal PK Bridging Study

Study Design

Study M19-128 was a phase 1, single-dose, randomized, open-label (OL), multicenter study, comprised of two substudies, in healthy subjects.

Substudy 1 was designed to bridge the to-be-marketed (TBM) on-body delivery system (OBDS) and the prefilled syringe (PFS) used in the phase 3 trials. Substudy 1 assessed the relative bioavailability of 360 mg risankizumab given subcutaneously (SC) in the TBM product (2.4 mL of 150 mg/mL risankizumab in a prefilled cartridge with an OBDS; 2.4 mL x 150 mg/mL =360 mg) versus the product used in the phase 3 Crohn's disease (CD) trials, called the phase 3 SC product thereafter (4 SC injections of 90 mg/mL risankizumab in a PFS; 4 x 90 mg =360 mg). Additionally, Substudy 1 assessed the pharmacokinetics (PK) of risankizumab in a 180 mg OBDS following a single SC administration of 1.2 mL of 150 mg/mL risankizumab (1.2 mL x 150 mg/mL =180 mg). The OBDS and the PFS was injected at the abdomen.

Substudy 2 was to compare the TBM intravenous (IV) product with the product used in the phase 3 trials. Substudy 2 was designed to assess the relative bioavailability of 1800 mg risankizumab in the TBM IV product (3 x 600 mg/10 mL in a single vial, 60 mg/mL) versus the phase 3 IV product (6 x 300 mg/3.33 mL in a single vial, 90 mg/mL) following a single IV infusion.

In Substudy 1, study population include healthy U.S. subjects and Japanese subjects. Non-Japanese subjects were randomized in a 4:4:1 ratio into Groups 1 (phase 3 SC product, Reference), 2 (TBM SC product, Test), and 3 (180 mg SC product, Test), respectively (Table 46). The first 16 Japanese subjects who were enrolled into Substudy 1 were randomized in a 1:1 ratio to Groups 1 and 2. The additional Japanese subjects who were enrolled were randomized in a 4:4:1 ratio into the three groups. All subjects enrolled into Substudy 2 were randomized in a 1:1 ratio. A total of 393 subjects received a single dose of risankizumab as summarized in Table 46.

Table 46. Study Design

	Substudy 1 – SC Bridging Study*			Substudy 2 – IV Bridging Study	
Design Parameter	**Group 1 (Reference) N=127****	**Group 2 (Test) N=129****	**Group 3 (Test) N=30**	**Group 4 (Reference) N=53**	**Group 5 (Test) N=54**
Dose***	360 mg	360 mg	180 mg	1800 mg	1800 mg
Formulation (concentration)	90 mg/mL	150 mg/mL	150 mg/mL	90 mg/mL	60 mg/mL
Presentation	PFS	OBDS	OBDS	300 mg/vial	600 mg/vial

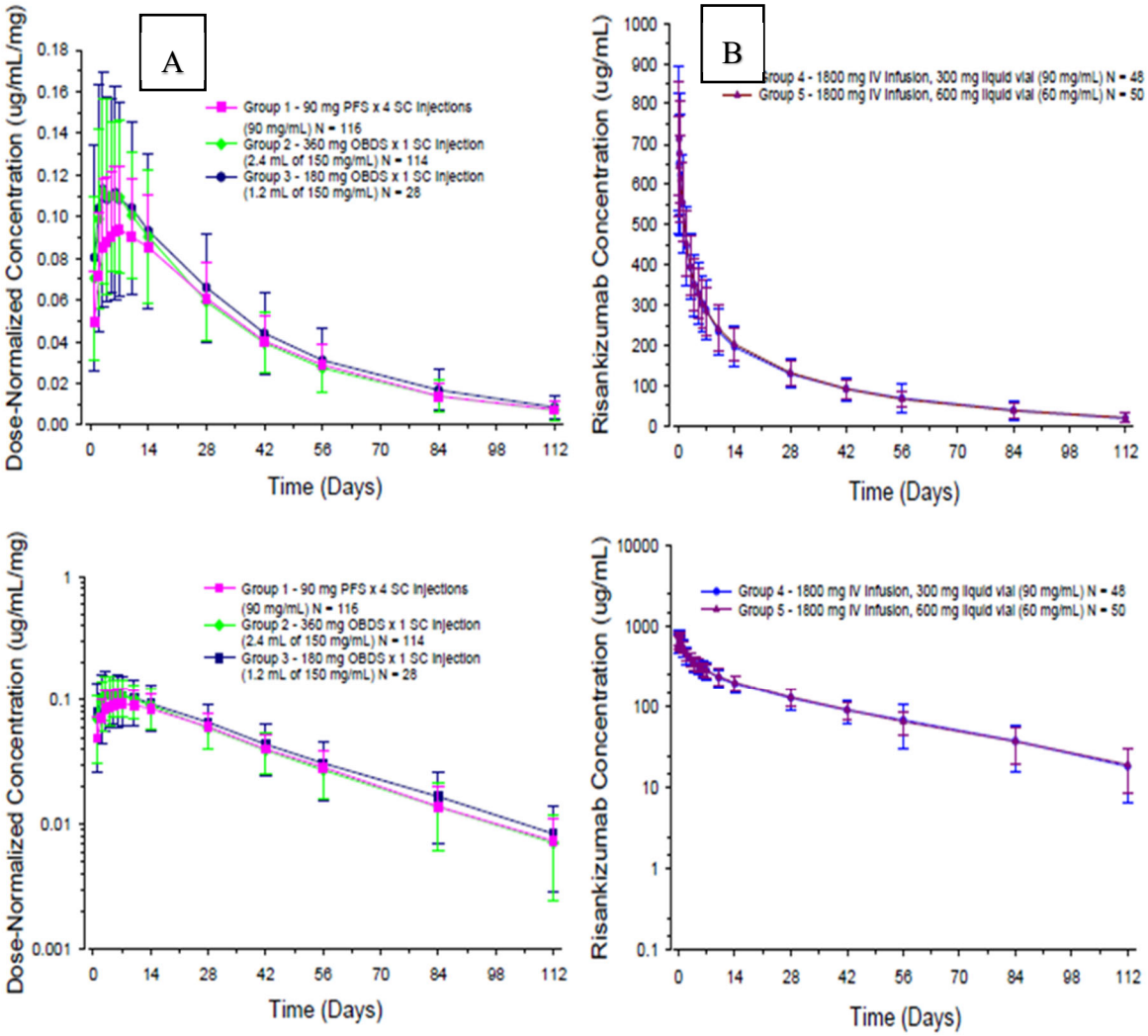
Source: Reviewer generated based on Study M19-128 CSR
N = number of subjects, Reference = the phase 3 SC or IV product, Test = the proposed TBM SC or IV product (except for 180 mg OBDS/Group 3)
*SC injection site: abdomen
**including N=8 Japanese
***The 1800-mg dose in the IV bridging study is 3-fold higher than the proposed induction therapy dose of 600 mg.
Abbreviations: IV, intravenous; SC, subcutaneous; TBM, to-be-marketed

Serial blood samples were collected predose and at time points after dosing over a period of 113 days for risankizumab PK and immunogenicity assessments. In addition, safety/tolerability assessments were conducted throughout the study.

Pharmacokinetics

Risankizumab serum concentration-time profiles from substudies 1 and 2 are presented in Figure 6A, and Figure 6B, respectively. A summary of the PK parameters of risankizumab by group following a single SC or IV dose administration in healthy subjects is shown in Table 47.

Figure 6. Risankizumab Serum Concentrations (Group Mean ± SD) Following a Single SC Dose of 360 mg or 180 mg (A) or a Single IV Dose of 1800 mg (B) in Healthy Subjects



Source: Study M19-128 CSR, Figure 2 and Figure 3
Abbreviations: IV, intravenous; OBDS, on-body delivery system; PFS, prefilled syringe; SC, subcutaneous; SD, standard deviation

Table 47. Geometric Mean (Mean, %CV) Risankizumab PK Parameters Following a Single SC or IV Dose Administration in Healthy Subjects

	Risankizumab SC Administration (Substudy 1)				
				Japanese	
Pharmacokinetic Parameters (units)	Group 1 90 mg PFS × 4 N = 116	Group 2 360 mg OBDS N = 114	Group 3 180 mg OBDS N = 28	Group 1 90 mg PFS × 4 N = 7	Group 2 360 mg OBDS 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)
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)	1640 (1730, 37)	902 (983, 50)	1820 (1930, 37)	1870 (1920, 25)
$t_{1/2}$[b] (day)	27.0 (5.54)	26.2 (5.86)	27.8 (6.26)	26.6 (6.44)	29.5 (6.93)

	Risankizumab IV Administration (Substudy 2)	
Pharmacokinetic Parameters (units)	Group 4 6 × 300 mg liquid vials N = 48	Group 5 3 × 600 mg liquid vials N = 50
C_{max} (µg/mL)	723 (742, 25)	716 (730, 20)
T_{max}[a] (day)	0.2 (0.1 – 0.5)	0.2 (0.1 – 1.0)
AUC_t (µg•day/mL)	10700 (11100, 30)	11400 (11700, 23)
AUC_{inf} (µg•day/mL)	12000 (12500, 29)	12300 (12700, 25)
$t_{1/2}$[b] (day)	27.1 (6.15)	28.3 (6.71)

AUC_{inf} = area under the serum concentration-time curve from time 0 to infinite time; AUC_t = area under the serum concentration-time curve from time 0 to the last measurable concentration; C_{max} = maximum observed serum concentration; T_{max} = time to maximum observed serum concentration

a. Median (minimum through maximum).

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

Source: Study M19-128 CSR Table 8 and Table 10
AUC_t =112 day
Abbreviations: CV, coefficient of variation; IV, intravenous; OBDS, on-body delivery system; PFS, prefilled syringe; PK, pharmacokinetic; SC, subcutaneous

The relative bioavailability of the risankizumab 360 mg OBDS (the TBM SC product) compared to the four injections of 90 mg PFS (the phase 3 SC product), and risankizumab 600 mg liquid vial (the TBM IV product) compared to the 300 mg liquid vial (the phase 3 IV product) based on C_{max}, AUC_t, and AUC_{inf} are presented in Table 48.

The relative bioavailability of risankizumab 180 mg OBDS compared to the 360 mg OBDS based on dose normalized C_{max}, AUC_t, and AUC_{inf} are also presented in Table 48.

In summary, following a single SC administration of 360 mg risankizumab with the TBM SC product compared to the phase 3 SC product, the 90% confidence interval (CI) for the ratio of area under the concentration-time curve (AUC) met the bioequivalence criteria of range of 0.8 to 1.25, but the upper bound of the 90% CI for the ratio of maximum plasma concentration (C_{max}) exceeded the upper limit of bioequivalence (BE) criteria, 1.25, with a range of 1.184 to 1.347 and a point estimate of 1.263 (Table 47 and Table 48).

Following a single IV administration of 1800 mg risankizumab in healthy subjects, PK bioequivalence was demonstrated between the TBM IV product and the phase 3 IV product.

Table 48. Relative Bioavailability and 90% Confidence Intervals for the Bioavailability Assessment

Group (Risankizumab Dose) Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
		Substudy 1			
Group 2 (360 mg OBDS) vs. Group 1 (90 mg PFS × 4 SC injections)	C_{max}	43.1	34.1	1.263	1.184, 1.347
	AUC_t	1555	1461	1.065	1.000, 1.134
	AUC_{inf}	1700	1588	1.070	1.010, 1.134
Group 3 (180 mg OBDS) vs. Group 2 (360 mg OBDS)	C_{max}/Dose	0.110	0.114	0.967	0.861, 1.087
	AUC_t/Dose	4.257	4.225	1.008	0.894, 1.137
	AUC_{inf}/Dose	5.057	4.596	1.100	0.994, 1.218
		Substudy 2			
Group 5 (3 × 600 mg liquid vials) vs. Group 4 (6 × 300 mg liquid vials)	C_{max}	735	736	0.998	0.952, 1.046
	AUC_t	11500	10700	1.079	1.001, 1.164
	AUC_{inf}	12400	11900	1.044	0.976, 1.117

Units for C_{max}, AUC, C_{max}/Dose, and AUC/Dose are µg/mL, µg•day/mL, µg/mL/mg, and µg•day/mL/mg, respectively.

Source: Study M19-128 CSR Table 9 and Table 11
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; OBDS, on-body delivery system; PFS, prefilled syringe; SC, subcutaneous

Immunogenicity

The treatment-emergent antidrug antibody (ADA) incidence ranged from 2% to 13% across all treatment groups and is summarized in Table 49. The potential impact of ADA on risankizumab exposure and safety was evaluated and no marked impact of ADA on risankizumab exposure and safety was observed in this study.

Table 49. Summary of Treatment-Emergent ADA Incidences

	Substudy 1 – SC Bridging Study			Substudy 2 – IV Bridging Study	
Parameter	Group 1 (Reference) 4 x 90 mg PFS	Group 2 (Test) 360 mg OBDS	Group 3 (Test) 180 mg OBDS	Group 4 (Reference) 1800 mg 6 x 300 mg	Group 5 (Test) 1800 mg 3 x 600 mg
ADA incidence, n/N (%)*	7/117 (6%)	16/123 (13%)	1/27 (4%)	2/48 (4%)	1/50 (2%)
Time to appearance of ADA	Day 29-113	Day 13-114	Day 15	Day 15-56	Day 29
ADA titers	10-5880	10-1330	10-23	10-423	10-87

Source: Reviewer generated based on Study M19-128 CSR Table 12
N = number of total subjects, n = number of subjects with ADA+, Reference = the phase 3 product, Test = the proposed to-be-marketed product (except for 180 mg OBDS/Group 3)
*Incidence of ADA (treatment-emergent) to risankizumab was defined when a subject was (1) ADA- or missing assessment at baseline (prior to the first risankizumab dose) and became ADA+ at one or more time points postbaseline; or (2) ADA+ at baseline and showed a ≥4-fold increase in titer values relative to baseline
Abbreviations: ADA, antidrug antibody; IV, intravenous; OBDS, on-body delivery system; PFS, prefilled syringe; SC, subcutaneous

Treatment-Emergent Adverse Events

In Substudy 1, a total of 113/286 (40%) subjects experienced treatment-emergent adverse events (TEAEs). There were no adverse events (AEs) that led to discontinuation of the study or that led to death. Overall, rates of AEs that were related to study drug, related to the device, and injection-site reactions (ISRs) were higher in Group 2 (360 mg OBDS SC product) and Group 3 (180 mg OBDS SC product) as compared to Group 1 (the phase 3 SC product). Rates of serious AEs and severe AEs were low (0 to 1 event per arm) and were neither related to study drug nor device per investigator opinion (Table 50).

Table 50. Overview of Subjects With TEAEs (Substudy 1)

	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%) 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%) 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%) 1 (6.3%)
Severe AE	1 (0.8%)	1 (0.8%)	0	0	0	2 (0.7%) 0
Serious AE	1 (0.8%)	0	0	0	0	1 (0.3%) 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%) 12 (75%)
Hypersensitivity related AE	2 (1.6%)	2 (1.6%)	0			4 (1.4%)
All Deaths	0	0	0	0	0	0

Source: Study M19-128 CSR Table 15
Abbreviation: AE, adverse event; OBDS, on-body delivery system; PFS, prefilled syringe; SC, subcutaneous; TEAE, treatment-emergent adverse event

Hypersensitivity reactions occurred in two subjects in the phase 3 SC product group (Group 1) and two subjects in the 360 mg OBDS SC product group (Group 2). In the 360 mg OBDS SC product group, the main symptoms of ISRs were, reported in the frequency order, injection site

induration (19%), erythema (13%), swelling (8%), pain (7%), and pruritus (6%), which were not reportedly associated with other serious adverse events. In the 180 mg OBDS SC product group, the main symptoms of ISRs were, reported in the frequency order, injection site induration (17%), swelling (7%), erythema (3%), edema (3%), and pain (3%). Refer to Section 7.4.

In Substudy 2, a total of 31/107 (29%) subjects experienced TEAEs. There are no fatal, serious, or severe AEs and no AEs that led to discontinuation of the study. Hypersensitivity events were low and reported by two subjects in the reference arm (the phase 3 IV product). All TEAEs resolved by the end of the study.

Table 51. Overview of Subjects With TEAEs (Substudy 2)

	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

Source: Study M19-128 CSR Table 16
Abbreviations: AE, adverse event; IV, intravenous; TEAE, treatment-emergent adverse event

14.2.2. M16-324: A PK Study for SC Product Development

Study M16-324 was a phase 1, single-dose, OL, randomized, parallel-group study in healthy subjects. The results of the study were used to inform the development of the TBM drug presentations for SC administration. The study consisted of four arms comprising of 12 subjects each and enrollment was stratified by body weight at the beginning of confinement. Each subject received a single dose of risankizumab administered using 90 mg/mL risankizumab liquid formulation as specified per arm.

- Arm 1: 3 SC injections of 0.8 mL each in a prepared syringe over 10 seconds (3 x 90 mg/mL x 0.8 mL =216 mg, Reference)
- Arm 2: 1 SC injection of 2.4 mL in a syringe pump over 3 minutes (1 x 90 mg/mL x 2.4 mL =216 mg, Test)

- Arm 3: 1 SC injection of 2.4 mL in a syringe pump over 6 minutes (1 x 90 mg/mL x 2.4 mL =216 mg, Test)
- Arm 4: 1 SC injection of 2 mL in a prepared syringe over 10 seconds (1 x 90 mg/mL x 2 mL =180 mg, Test)

Blood samples were collected on Day 1 (predose) and up to Day 140 for PK and immunogenicity assessment. Overall PK profiles of risankizumab following a single dose SC administration were generally comparable across all four arms. Baseline and treatment-emergent ADA incidence ranged from 8% to 25% and 0% to 50%, respectively, across all treatment arms.

14.2.3. M16-533: A PK Study in Japanese and Caucasians for IV Administration

Study M16-533 was a phase 1, double-blind (DB), randomized, placebo-controlled, single-center study in healthy Japanese and Caucasian subjects. Eligible subjects were randomized to receive a single IV infusion of 1800 mg risankizumab or placebo in a 6:2 ratio. The results indicate that following a single IV infusion of 1800 mg risankizumab, systemic exposure of risankizumab in Japanese subjects (n=6) was similar to that in Caucasian subjects (n=6). Body weight was not found to be a statistically significant covariate in Study M16-533. However, the earlier clinical studies and popPK analysis identified body weight as a significant covariate affecting risankizumab concentrations. The observed discrepancy is probably due to small sample size (n=6 for each group) and/or relative narrow body weight bands (Japanese versus Caucasian: 69.3±5.34 kg versus 81.3±4.74 kg) studied in Study M16-533. The treatment-emergent ADA incidences were 17% (1/6) in Japanese and 33% (2/6) in Caucasians.

14.2.4. M17-381: A PK Study in Healthy Chinese Subjects for SC and IV Administration

Study M17-381 was a phase 1, OL, single-center study in healthy Chinese subjects. The study consisted of three arms comprising 10 subjects each. Subjects were enrolled and received a single IV dose of 1800 mg risankizumab or a single SC dose of 150 mg or 360 mg risankizumab. Following administration of a single SC dose of risankizumab 150 or 360 mg in healthy Chinese subjects, risankizumab serum concentrations peaked in approximately 3 days on average, with dose-dependent increase in exposure. Risankizumab exposures (AUC) were dose-proportional between the 150 and 360 mg SC doses. Mean terminal $t_{1/2}$ was approximately 29 days

Following administration of the single 1800 mg IV dose, risankizumab serum concentration declined in a biphasic manner with the terminal phase decline in parallel with the SC dosing arms and a mean $t_{1/2}$ 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.

14.2.5. M15-993: A Proof-of Concept Study

Study M15-993 was a proof-of-concept, multicenter, randomized, DB, placebo-controlled, parallel-group, phase 2, dose-ranging study of risankizumab in subjects with moderately to severely active CD. The primary objective was to evaluate the efficacy of risankizumab in inducing clinical remission after 12 weeks of treatment. The secondary objectives were to evaluate the efficacy of risankizumab in inducing endoscopic response, clinical response, mucosal healing, and deep remission, to evaluate the safety of risankizumab, and to explore the PK and pharmacodynamics (PD) of risankizumab in CD. The study is in total 73 weeks, consisted of a screening period of up to a maximum of 4 weeks, a 12-week DB IV period (Period 1), a 14-week OL IV/wash-out period (Period 2), a 26-week SC therapy period (Period 3), and a 15-week follow-up period.

Subjects were men or women 18 to 75 years of age (inclusive) with a diagnosis of CD for at least 3 months prior to Visit 1 confirmed by endoscopic or imaging examination. Subjects were to have moderate to severe CD at Visit 1.1, defined as Crohn's disease activity index (CDAI) ≥220 and ≤450, and mucosal ulcers in at least 1 segment of the ileum or colon along with a Crohn's Disease Endoscopic Index of Severity (CDEIS) ≥7 (for subjects with isolated ileitis ≥4), as assessed by ileocolonoscopy and confirmed by central independent reviewer(s) before randomization. Subjects who were naïve or experienced to 1 or more tumor necrosis factor (TNF) antagonists (infliximab, adalimumab, or certolizumab pegol) at a dose approved for CD were eligible. In Period 1, approximately 120 subjects were randomized in a ratio of 1:1:1 to 1 of the 3 treatment groups: placebo, 200 mg, or 600 mg IV infusion (3 infusions separated by 4 weeks). In Period 3, the SC dose was 180 mg per injection with a total of 4 injections separated by a dose interval of 8 weeks.

The results at Week 12 indicated that treatment with risankizumab, a selective IL-23p19 inhibitor, was able to achieve clinical remission and response (based on CDAI) as shown in Table 52; endoscopic remission, response, and "mucosal healing" (based on CDEIS); "deep remission" as shown in Table 53; biomarker endpoints (c-reactive protein and fecal calprotectin); and quality of life endpoints (IBDQ). Of note, the study was not powered to demonstrate statistically significant difference. Based on these results, treatment with risankizumab 600 mg IV for induction therapy was selected for phase 3 trials. Interestingly, 600 mg IV did not achieve statistical significance over placebo, which may have been at least partially attributed to the small sample size. Treatment with 1200 mg IV of risankizumab was also selected for induction treatment in phase 3 trials.

Table 52. 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)	[B vs. A]	4.1 (–12.4, 20.6)	0.6278
200 mg IV (B)	8/41	19.5 (8.8, 34.9)	[C vs. A]	20.9 (2.6, 39.2)	0.0252
600 mg IV (C)	15/41	36.6 (22.1, 53.1)	[D vs. A]	12.6 (–2.2, 27.5)	0.0955
200+600 mg IV (D)	23/82	28.0 (18.7, 39.1)	[C vs. B]	16.8 (–2.0, 35.6)	0.0799

Source: Table 14 on Page 103 of M15-993 CSR R&D/17/0073
[a] Exact 95% CI by Clopper and Pearson.
[b] Statistics for the difference are calculated using the Cochran-Mantel-
Abbreviations: CDAI, Crohn's disease activity index; CI, confidence interval; FAS, full analysis set; IV, intravenous; NRI, nonresponder imputation

Table 53. Summary of Secondary Endpoints at Week 12 (NRI; FAS-P1)

Treatment	Response n/N	Response Rate (%) (95% CI)[a]	Comparison	Response Rate Diff (%) (95% CI)[b]	P-value
CDAI clinical response					
Placebo (A)	9/39	23.1 (11.1, 39.3)	[B vs. A]	8.6 (–10.7, 27.8)	0.3832
200 mg IV (B)	13/41	31.7 (18.1, 48.1)	[C vs. A]	17.8 (–1.6, 37.2)	0.0725
600 mg IV (C)	17/41	41.5 (26.3, 57.9)	[D vs. A]	13.4 (–3.3, 30.1)	0.1151
200+600 mg IV (D)	30/82	36.6 (26.2, 48.0)	[C vs. B]	9.2 (–10.9, 29.2)	0.3702
CDEIS remission					
Placebo (A)	1/39	2.6 (0.1, 13.5)	[B vs. A]	7.2 (–2.4, 16.9)	0.1429
200 mg IV (B)	4/41	9.8 (2.7, 23.1)	[C vs. A]	16.8 (3.9, 29.7)	0.0107
600 mg IV (C)	8/41	19.5 (8.8, 34.9)	[D vs. A]	12.0 (3.5, 20.6)	0.0057
200+600 mg IV (D)	12/82	14.6 (7.8, 24.2)	[C vs. B]	10.2 (–5.0, 25.3)	0.1883
CDEIS response					
Placebo (A)	5/39	12.8 (4.3, 27.4)	[B vs. A]	14.1 (–2.8, 30.9)	0.1012
200 mg IV (B)	11/41	26.8 (14.2, 42.9)	[C vs. A]	23.5 (5.5, 41.5)	0.0106
600 mg IV (C)	15/41	36.6 (22.1, 53.1)	[D vs. A]	18.7 (4.4, 33.0)	0.0104
200+600 mg IV (D)	26/82	31.7 (21.9, 42.9)	[C vs. B]	9.6 (–10.5, 29.6)	0.3493
Mucosal healing					
Placebo (A)	1/39	2.6 (0.1, 13.5)	[B vs. A]	–0.1 (–7.0, 6.7)	0.9699
200 mg IV (B)	1/41	2.4 (0.1, 12.9)	[C vs. A]	4.9 (–4.6, 14.3)	0.3108
600 mg IV (C)	3/41	7.3 (1.5, 19.9)	[D vs. A]	2.4 (–4.5, 9.2)	0.4977
200+600 mg IV (D)	4/82	4.9 (1.3, 12.0)	[C vs. B]	5.0 (–4.3, 14.3)	0.2915
Deep remission					
Placebo (A)	0/39	0 (0.0, 9.0)	[B vs. A]	2.4 (–2.3, 7.1)	0.3110
200 mg IV (B)	1/41	2.4 (0.1, 12.9)	[C vs. A]	12.4 (2.3, 22.5)	0.0164
600 mg IV (C)	5/41	12.2 (4.1, 26.2)	[D vs. A]	7.4 (1.7, 13.0)	0.0107
200+600 mg IV (D)	6/82	7.3 (2.7, 15.2)	[C vs. B]	10.0 (–1.2, 21.1)	0.0794

Source: Table 15 on Pages 110 and 111 of M15-993 CSR R&D/17/0073
[a] Exact 95% CI by Clopper and Pearson.
[b] Statistics for the difference are calculated using the Cochran-Mantel-Abbreviations: CDAI, Crohn's disease activity index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CI, confidence interval; FAS, full analysis set; IV, intravenous; NRI, nonresponder imputation

Upon entry to an OL Period 2, all subjects who were not in "deep remission" received additional 3 doses of IV risankizumab 600 mg every 4 weeks. Re-induction with 600 mg risankizumab during Period 2 in those subjects who did not achieve "deep remission" in Period 1 achieved greater clinical remission rates at Week 26 compared to those observed at Week 12. Switching from placebo to 600 mg risankizumab led to a clinical remission rate of 54.5%, consistent with

the efficacy of risankizumab 600 mg IV observed with blinded treatment during Period 1. Extended treatment with 600 mg risankizumab in subjects who received 200 mg or 600 mg during Period 1 led to a clinical remission rate of 52.9%, indicating some subjects may benefit from extended induction treatment (Table 53). All six subjects who entered the washout arm in Period 2 remained in clinical remission at Week 26, suggesting a durable PD effect of risankizumab.

Treatment during Period 3 with risankizumab SC was effective as therapy for maintaining clinical remission. The greatest rates of achievement of endoscopic endpoints at Week 52 (CDEIS remission, CDEIS response, and mucosal healing) were observed in the subjects who received risankizumab 600 mg IV during Period 1, suggesting that a higher drug exposure during induction is necessary to achieve endoscopic resolution of disease activity.

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 regimen of 180 mg SC dose every 8 weeks starting at Week 26, near steady state levels were achieved by Week 42.

Treatment-emergent ADA-positive responses were observed in 8% of the subjects who received at least 1 dose of risankizumab (9 out of 108 subjects). 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. The majority of the ADA-positive responses were transient. 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 does not appear to be any impact of ADA on risankizumab plasma concentrations.

In this study, risankizumab was generally safe and well-tolerated as evidenced by the results of assessment of TEAEs, serious adverse events (SAEs), and AEs of special interest as well as laboratory, physical examinations, and vital signs assessments. The most frequently reported AEs were infections, nasopharyngitis in particular. The occurrences of opportunistic infections, tuberculosis, and fungal infections were few during the study. No significant, unexpected safety issues were observed.

In summary, the findings in this proof-of-concept phase 2 study supported the dose selection for induction treatment in phase 3 trial. The phase 2 study also showed a potential benefit of reinduction treatment in some patients and maintenance treatment at 180 mg SC although the OL nature of the study and the small sample size limited the interpretation of the results. Approximate dose-proportional increases in risankizumab plasma trough concentrations were observed and there did not appear to be any impact of ADA on risankizumab plasma concentrations. Risankizumab was generally safe and well-tolerated, and no new safety signals were identified.

14.3. Immunogenicity Assessment

14.3.1. Bioanalytical Methods

Determination of Risankizumab Concentrations

The samples from phase 1 studies M16-533 and M16-324 and phase 2 CD studies M15-993 and M15-989 were analyzed for risankizumab concentrations in plasma using ligand binding assays previously validated and submitted in the psoriasis application.

For phase 1 studies M19-128 (the pivotal PK bridging study), and M-17-381 and pivotal phase 3 CD studies M15-991, M16-006, and M16-000, a bridging electrochemiluminescence (ECL) assay was employed to determine risankizumab concentrations in human serum samples. While this assay is based on the same ligand binding assay principles as the previous risankizumab assay used for the earlier phase 1 and phase 2 studies, it uses serum instead of plasma as well as new critical reagents compared to the previous assay. Main parameters of the assays used are outlined in Table 54.

Of note, the ECL assay was applied in the risankizumab formulation/presentation development (BLA 751105/s009 and s010) and the pivotal phase 3 trials for the treatment of active psoriatic arthritis (BLA 761105/s014).

Table 54. Comparison of Risankizumab Assays

Studies	Original Application Pivotal Psoriasis Studies and Phase I and Phase 2 CD Studies	Pivotal CD Studies and Biopharmaceutics Bridging Study M19-128
Test Site Location	(b) (4)	AbbVie Ludwigshafen, Germany (b) (4)
Test Principle	Enzyme-linked immunosorbent assay (ELISA)	Bridging electrochemiluminescence (ECL) immunoassay
Capture and Detection Reagents	Polyclonal anti-risankizumab antibody and biotinylated anti-idiotypic risankizumab antibody	Biotinylated anti-idiotypic risankizumab antibody and SulfoTag™ labelled anti-idiotypic risankizumab antibody
Matrix	Plasma	Serum
MRD	1:10	1:10
Sensitivity (LLOQ)	5.00 ng/mL	4.34 ng/mL
Assay Range	5.00 to 100 ng/mL	4.34 to 1670 ng/mL

LLOQ = lower limit of quantitation; MRD = minimal required dilution

Source: Summary of biopharmaceutical studies and associated analytical methods, Table 2
Abbreviations: CD, Crohn's disease; LLOQ, lower limit of quantitation; MRD, minimal required dilution

Determination of ADAs and Neutralizing Antibody (Nabs) Against to Risankizumab

Compared to the original BLA immunogenicity assays, a new titer-based acid dissociation bridging ECL immunoassay and a new cell-based NAb assay were used for determination of ADA and NAb in the current supplemental BLA, respectively. Both new assays were previously applied in BLA 761105/s009, s010, and s014.

Briefly, the main difference between the original BLA immunogenicity assays and the new immunogenicity assays is that the serum samples replaced plasma samples which were used in the original BLA immunogenicity assays.

Of note, both ADA and NAb assays applied in the phase 1 studies (M16-533 and M16-324) and phase 2 CD studies (M15-993 and M15-989) were the same assays used in the original psoriasis submission. The new ADA and NAb assays were only applied in the phase 1 studies M17-381 and M19-128 (the pivotal PK bridging study) and phase 3 CD studies M15-991, M16-006, and M16-000.

Refer to the Product Quality Review for more information regarding the performance and validation of the immunogenicity assays. Overall, the new immunogenicity assay is suitable for the intended use in the analysis of clinical samples (see DARRTS dated April 23, 2021, section 6.3.4).

14.3.2. Incidence of Treatment-Emergent ADA and NAb

The summary of the incidence of ADA and NAb to risankizumab across the first 12 weeks (Week 0 to 12) in the phase 2 study M15-993 and phase 3 induction studies M15-991 and M16-006, and across 24 weeks in the phase 3 induction studies (M15-991 and M16-006) are presented in Table 55 and Table 56, respectively. 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 M16-000 is presented in Table 57.

Table 55. Incidence of 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.

Cross reference: Study M15-993 CSR (R&D/20/0073)[1] Table 14.2 4.5.2, Table 14.2 4.3.1.1, Table 14.2 4.3.1.2; Study M15-991 CSR (R&D/20/0587)[3] Table 14.2 4.3; Study M16-006 CSR (R&D/20/1216)[4] Table 14.2 4.3

Source: Immunogenicity Report, R&D/20/1400 Table 2
Abbreviations: ADA, antidrug antibody; IV, intravenous; NAb, neutralizing ant body

Table 56. Incidence of ADA and NAb to Risankizumab Over 24 Weeks of Treatment in Subjects Who Underwent Treatment During Induction Period 2 in Phase 3 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.

Cross reference: Study M15-991 CSR (R&D/20/0587)[3] Table 14.2 4.3; Study M16-006 CSR (R&D/20/1216)[4] Table 14.2 4.3

Source: Immunogenicity Report, R&D/20/1400 Table 3
Abbreviations: ADA, antidrug antibody; IV, intravenous; NAb, neutralizing antibody; SC, subcutaneous

Table 57. Incidence of ADA and NAb 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.

Cross reference: Study M16-000 CSR (R&D/21/0085)[5] Table 14.2 7.3

Source: Immunogenicity Report, R&D/20/1400 Table 4
Abbreviations: ADA, antidrug antibody; Nab, neutralizing antibody; Q8W, every 8 weeks; SC, subcutaneous

The overall ADA and NAb incidence to risankizumab was low (≤5%) in the subjects with CD and comparable between the subjects who received risankizumab induction of either 600 mg IV or 1200 mg IV at Weeks 0, 4, and 8 and the subjects who received risankizumab maintenance regimen of either 180 mg SC every 8 weeks (Q8W) or 360 mg SC Q8W.

In the subjects with CD 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, the incidence of ADA and NAb to risankizumab was 3.4% (2/58) and 0% (0/58), respectively, over 64 weeks of exposure. In the subjects with CD who received the proposed induction dose of 600 mg IV at Weeks 0, 4, and 8, followed by the proposed SC maintenance dose of 180 mg SC at Week 12 and Q8W thereafter up to Week 52, both incidences of ADA and NAb to risankizumab were 0% (0/57) over 64 weeks of exposure.

14.3.3. Effect of Immunogenicity on Risankizumab PK, Safety, and Efficacy

Effect of Immunogenicity on Risankizumab Pharmacokinetics

A summary of risankizumab serum trough concentrations by visit up to 64 weeks of induction and maintenance treatment in all subjects and by ADA status (positive or negative) using pooled data across the phase 3 studies are presented in Table 58 and Table 59, or Figure 7 and Figure 8, respectively. Overall, ADA or NAb status did not have a significant effect on risankizumab exposure based on the popPK analyses.

Table 58. Risankizumab Trough Concentrations (µg/mL) by ADA Status During the First 12-Week Induction Period in Pooled Phase 3 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.

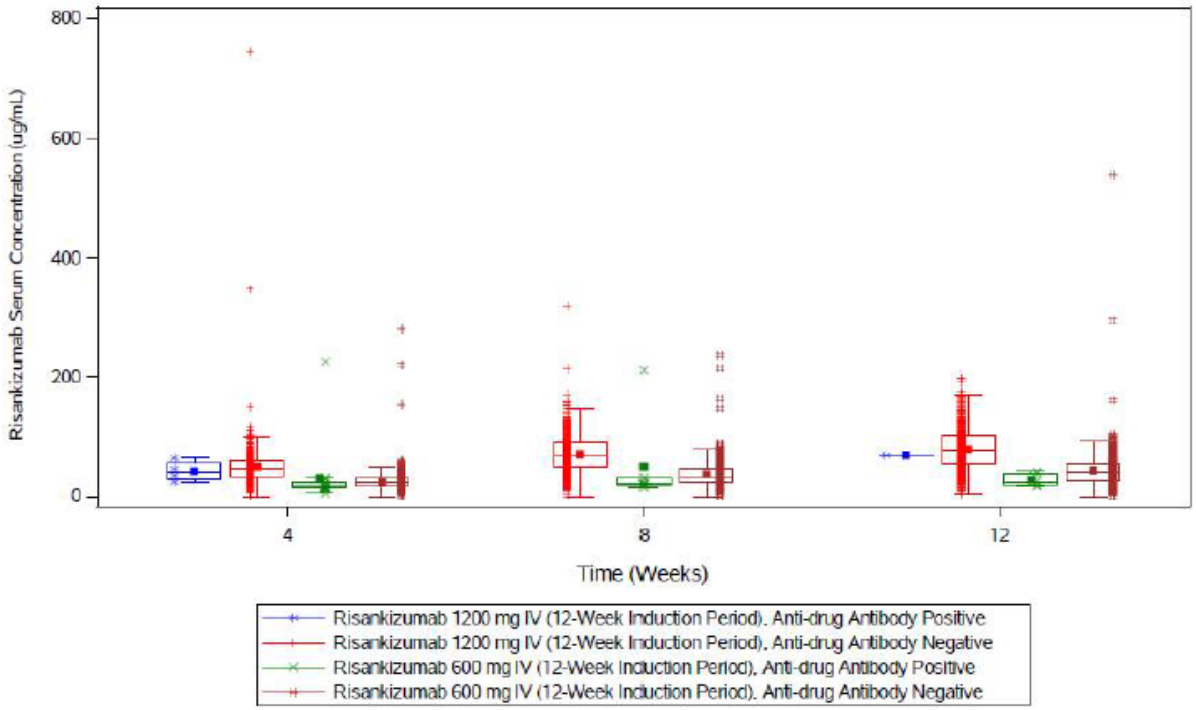
Notes: Subjects who had both risankizumab serum concentration and ADA assessment at each visit are included in this summary.

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

Cross reference: Table 11.1__1

Source: Immunogenicity Report, R&D/20/1400 Table 5
Abbreviations: ADA, antidrug antibody; CD, Crohn's disease; %CV, coefficient of variation; IV, intravenous

Figure 7. Comparison of Risankizumab Trough Concentrations by ADA Status Following IV Induction Doses at Weeks 0, 4, and 8 in Phase 3 Studies



Source: Immunogenicity Report R&D/20/1400, Figure 1
Note: In the box plots, solid square and horizontal bar within each box represents geometric mean and median values, respectively. The other symbols (*, +, x, #) represent risankizumab concentration values from individual subjects
Abbreviations: ADA, antidrug antibody; IV, intravenous

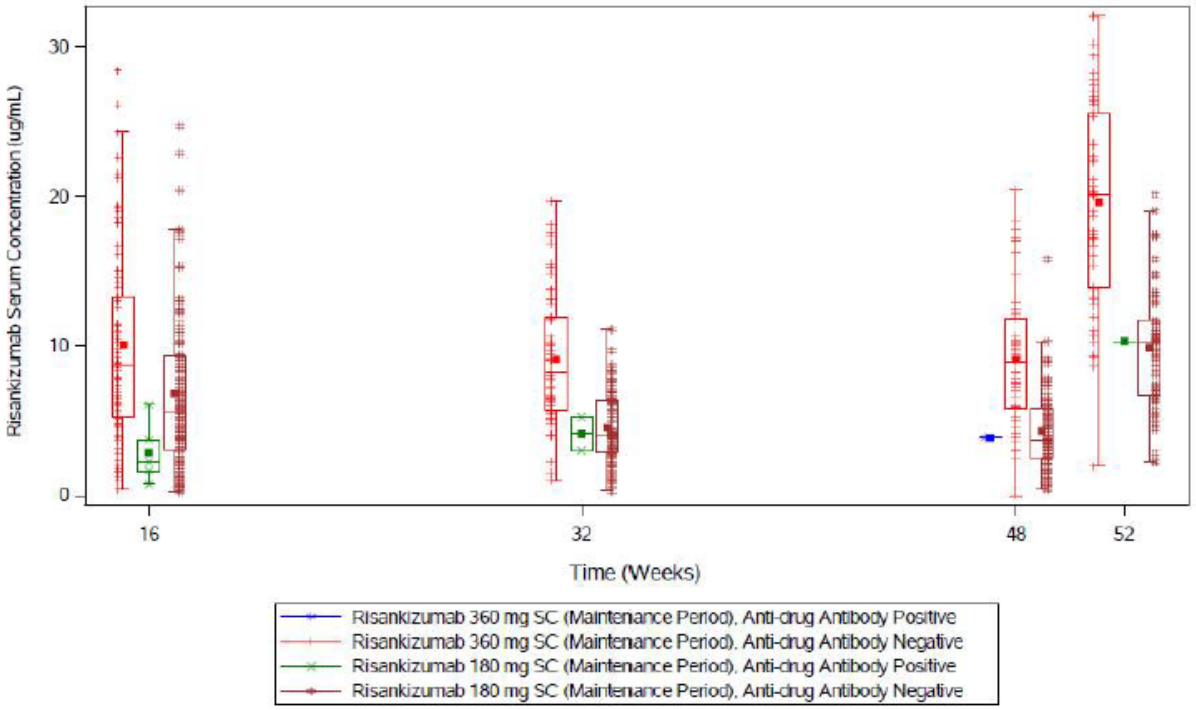
Table 59. Risankizumab Trough Concentrations (µg/mL) by ADA Status Across 52 Weeks of Maintenance Treatment From Phase 3 Maintenance Study

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.
Cross reference: Study M16-000 CSR (R&D/21/0085)[5] Table 14.2__7.1

Source: Immunogenicity Report, R&D/20/1400 Table 7
Abbreviations: ADA, antidrug antibody; %CV, coefficient of variation; Q8W, every 8 weeks; SC, subcutaneous

Figure 8. Comparison of Risankizumab Trough Concentrations by ADA Status Across 52 Weeks of Maintenance Treatment From Phase 3 Maintenance Study



Source: Immunogenicity Report R&D/20/1400, Figure 3
Note: In the box plots, solid square and horizontal bar within each box represents geometric mean and median values, respectively. The other symbols (*, +, x, #) represent risankizumab concentration values from individual subjects
Abbreviations: ADA, antidrug antibody; SC, subcutaneous

Effect of Immunogenicity on Risankizumab Efficacy

The comparison of CDAI clinical remission, stool frequency (SF)/abdominal pain score (APS) clinical remission and endoscopic response endpoints by ADA and NAb status using pooled data from the phase 3 induction or maintenance studies are presented in Table 60, and Table 61, respectively.

As shown in Table 60 and Table 61, the number of ADA/NAb positive subjects was too small to make a meaningful comparison with ADA/NAb negative subjects. Overall, totality of these data and analyses indicate that immunogenicity to risankizumab has no clinically relevant impact on the efficacy in subjects with active moderate to several CD.

Table 60. Risankizumab Efficacy by ADA and NAb Status at Week 12 in 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.

Cross reference: ISE (R&D/20/1144) Table 1.2 1.1.5, Table 1.2 1.2.5, Table 1.2 1.3.5

Source: Immunogenicity Report, R&D/20/1400 Table 12
Abbreviations: ADA, antidrug antibody; APS, abdominal pain score; CDAI, Crohn's disease activity index; NAb, neutralizing antibody; IV, intravenous; Q4W, every 4 weeks; SF, stool frequency

Table 61. Risankizumab Efficacy by ADA and NAb Status at Week 52 From 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

Cross reference: Study M16-000 CSR (R&D/21/0085)[5] Table 14.2 5.30, Table 14.2 5.31, Table 14.2 5.32

Source: Immunogenicity Report, R&D/20/1400 Table 13
Abbreviations: ADA, antidrug antibody; APS, abdominal pain score; CDAI, Crohn's disease activity index; NAb, neutralizing antibody; Q8W, every 8 weeks; SC, subcutaneous; SF, stool frequency

Effect of Immunogenicity on Risankizumab Safety

A comparison of hypersensitivity reactions and injection-site reactions (including infusion-site reactions) over the Induction Period 1 (Weeks 0 to 12), Induction Period 2 (Weeks 12 to 24) or over the 52 weeks of maintenance treatment by ADA status is presented in Table 62, Table 63,

and Table 64, respectively. Additionally, a comparison of hypersensitivity reactions and injection-site reactions (including infusion-site reactions) for the All-Treatment Safety Analysis Set (Excluding data from Substudies 2 and 3 of Study M16-000) by treatment-emergent ADA status is presented in Table 65.

Hypersensitivity Reactions

In the All-Treated Safety Analysis Set, the incidence of hypersensitivity in subjects with ADA+ (17.1%, 6/35) was numerically higher than that with ADA- (11.1%, 150/1349) (Table 65).

Injection and Infusion Site Reactions

In the All-Treated Safety Analysis Set, the incidence of injection or infusion stie reactions in subjects with ADA+ (11.1%, 4/35) was numerically higher than that with ADA- (5.3%, 72/1349) (Table 65).

Of note, the SC and IV products used in the pivotal phase 3 studies are not the TBM products.

Table 62. Comparison of Hypersensitivity Reactions and Injection-Site Reactions by ADA Status in Induction Period 1 (Weeks 0-12)

	Placebo-Controlled 12-Week Induction Period Safety Analysis Set					
	Risankizumab 600 mg IV Induction Dose (N = 609)		Risankizumab 1200 mg IV Induction Dose (N = 565)		All Risankizumab Doses (N = 1174)[a]	
	ADA+ (N = 13)	ADA– (N = 596)	ADA+ (N=4)	ADA– (N=561)	ADA+ (N =17)	ADA– (N =1157)
hypersensitivity reactions (per SMQ), n (%)	1 (7.7%)	28 (4.7%)	0 (0%)	28 (5.0%)	1 (5.9%)	56 (4.8 %)
injection site reactions (per CMQ), n (%)	0 (0%)	5 (0.8%)	0 (0%)	11 (2.0%)	0 (0%)	16 (1.4%)

ADA = anti-drug antibody, IV = intravenous

a. 'All Risankizumab Doses' only includes subjects who had treatment emergent anti-drug antibody (TEADA) information: 1174/1197.

Note: Risankizumab exposure from all subjects that have received at least one dose of risankizumab in the 12-week induction Period 1 from the two global Phase 3 studies: Studies M15-991 and M16-006, as well as the subjects from the Phase 2 Study M15-993 who received placebo or risankizumab 600 mg IV for the 12-week induction period.

Cross reference: ISS (R&D/20/1177) Table 2.4 1.1.7.11, Table 2.4 1.1.7.10

Source: Immunogenicity Report, R&D/20/1400 Table 8
Abbreviations: ADA, antidrug antibody; IV, intravenous; SMQ, standardised MedDRA query

Table 63. Comparison of Hypersensitivity Reactions and Injection-Site Reactions by ADA Status Over Induction Period 2 (Weeks 12-24)

	24-Week Induction Period Safety Analysis Set							
	Risankizumab 1200 mg IV at Weeks 12, 16 and 20 (N = 108)		Risankizumab 180 mg SC at Weeks 12 and 20 (N = 106)		Risankizumab 360 mg SC at Weeks 12 and 20 (N = 110)		All Risankizumab Doses[a] (N = 450)	
	ADA + (N = 0)	ADA- (N = 108)	ADA+ (N = 2)	ADA- (N = 104)	ADA + (N = 3)	ADA- (N = 107)	ADA + (N = 5)	ADA - (N = 455)
hypersensitivity reactions (per SMQ), n (%)	0 (0%)	9 (8.3%)	0 (0%)	4 (3.8%)	0 (0%)	6 (5.6%)	0 (0%)	26 (5.7%)
injection site reactions (per CMQ), n (%)	0 (0%)	3 (2.8%)	0 (0%)	2 (1.9%)	0 (0%)	3 (2.8%)	0 (0%)	13 (2.9%)

ADA = anti-drug antibody, IV = intravenous; SC = Subcutaneous

a. 'All Risankizumab Doses' only includes subjects who had TEADA information: 450/479.

Note: For these subjects, ADA status has been determined over the entire 24-week induction period (including the 12-Week Induction and Induction Period 2). Risankizumab exposure is from all subjects that have received at least one dose of risankizumab in Induction Period 2 from Studies M15-991 and M16-006. Treatment-emergent adverse events are events occurring after the first dose of study drug in Induction Period 2 and within 140 days after the last administration of study drug in Induction Period 2, or until the first dose of study drug in Study M16-000.

Cross reference: ISS (R&D/20/1177) Table 2.4 1.2.6.14, Table 2.4 1.2.6.13

Source: Immunogenicity Report, R&D/20/1400 Table 9
Abbreviations: ADA, antidrug antibody; IV, intravenous; SC, subcutaneous; SMQ, standardised MedDRA query

Table 64. Comparison of Hypersensitivity Reactions and Injection-Site Reactions by ADA Status Over the 52-Week Maintenance Period

	Study M16-000			
	Risankizumab 180 mg Q8W Dose (N = 133)		Risankizumab 360 mg Q8W Dose (N = 135)	
	ADA+ (N = 3)	ADA– (N = 130)	ADA+ (N = 1)	ADA– (N = 134)
hypersensitivity reactions (per SMQ), n (%)	1 (33.3%)	15 (11.5%)	0 (0%)	10 (7.4%)
injection site reactions (per CMQ), n (%)	0 (0%)	6 (4.6%)	0 (0%)	9 (6.7%)

ADA = anti-drug antibody, Q8W = every 8 weeks

Note: Risankizumab exposure from all randomized subjects in Study M16-000 (Sub-Study 1).

Cross reference: Study M16-000 CSR (R&D/21/0085)[5] Table 14.3 2.1.7.5, Table 14.3 2.1.10.3

Source: Immunogenicity Report, R&D/20/1400 Table 10
Abbreviations: ADA, antidrug antibody; Q8W, every 8 weeks; SMQ, standardised MedDRA query

Table 65. Comparison of Hypersensitivity Reactions and Injection-Site Reactions by ADA Status Over up to 248 Weeks of Exposure for the All-Treated Safety Analysis Set

	All Treated Safety Analysis Set									
	600 mg IV at Weeks 0, 4 and 8 (N=677)		Any RZB IV Regimen (N=1384)		360 mg SC Q8W (N=476)		Any RZB SC Regimen (N=1162)		Any RZB (N= 1384)	
	ADA+ (N = 26)	ADA- (N = 651)	ADA+ (N = 35)	ADA- (N =1349)	ADA+ (N = 11)	ADA- (N = 465)	ADA+ (N =28)	ADA- (N = 1134)	ADA+ (N=35)	ADA- (N=1349)
hypersensitivity reactions (per SMQ), n (%)	2 (7.7%)	34 (5.2%)	3 (8.6%)	89 (6.6%)	1 (9.1%)	28 (6.0%)	4 (14.3%)	68 (6.0%)	6 (17.1%)	150 (11.1%)
injection site reactions (per CMQ), n (%)	1 (3.8%)	11 (1.7%)	2 (5.7%)	31 (2.3%)	1 (9.1%)	24 (5.2%)	2 (7.1%)	45 (4.0%)	4 (11.4%)	72 (5.3%)

ADA = anti-drug antibody, IV = intravenous; SC = subcutaneous

Note: Risankizumab exposure from 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: 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-Study 1).

Cross reference: ISS (R&D/20/1177) Table 2.4 1.5.7.13, Table 2.4 1.5.7.12

Source: Immunogenicity Report, R&D/20/1400 Table 11

Abbreviations: ADA, antidrug antibody; IV, intravenous; Q8W, every 8 weeks; RZB, risankizumab; SC, subcutaneous; SMQ, standardised MedDRA query

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

14.3.4. Pharmacodynamics of Risankizumab in Subjects With CD

PD effect of risankizumab on serum levels of IL-22, high sensitivity C-reactive protein (hs-CRP), and fecal calprotectin (FCP) were assessed in a subset of subjects from phase 3 CD studies, M15-991 (n=122), M16-006 (n=123), and M16-000 (n=92). The Applicant postulated that IL-22 is induced by IL-23 and selective inhibition of IL-23 with risankizumab may reduce the levels of IL-22. However, the scientific hypothesis has not been validated in the clinical setting.

Bioanalytical Methods

Commercially available assay kits were used to measure IL-23, hs-CRP, and fecal calprotectin. IL-23 was determined in serum using a quantitative fluorescent sandwich immunoassay (SMC™ Human High Sensitivity Immunoassay kits from EMD Millipore), hs-CRP was determined using the Roche Diagnostic CRPHs particle-enhanced immunoturbidimetric assay, and FCP was determined using the Buhlman quantitative sandwich enzyme immunoassay (ELISA). No interference from risankizumab was noted from the quantitation of IL-23, hs-CRP or FCP.

Baseline Characteristics and Results

Demographics and baseline characteristics in subset of subjects with PD evaluation from Study M15-991, M-16-006, and M16-000 are summarized in Table 66, Table 67, and Table 68, respectively.

Table 66. Demographics and Baseline Characteristics for M15-991 PD Study

Mean (SD) or N (%)	Placebo IV (N=21)	Risankizumab 600 mg IV (N=50)	Risankizumab 1200 mg IV (N=51)	p-value
Male (%)	9 (42.9%)	30 (60.0%)	25 (49.0%)	0.34
Age (years)	41.0 (13.7)	40.5 (13.0)	40.2 (13.3)	0.98
Weight (kg)	72.1 (20.5)	71.9 (18.0)	77.7 (18.2)	0.25
BMI (kg/m^2)	25.1 (6.92)	24.4 (5.21)	27.0 (6.36)	0.09
Disease Duration (years)	13.6 (11.1)	11.3 (8.56)	13.7 (10.6)	0.44
Disease Location (Colonic only/Ileal only/Ileal-colonic)	11/1/9	22/10/18	20/6/25	0.36
CDAI	296 (71.0)	317 (67.5)	311 (60.7)	0.46
SES-CD	16.6 (8.89)	13.3 (7.99)	14.1 (7.54)	0.30
CRP (mg/L)	14.9 (13.3)	23.4 (32.3)	15.2 (14.7)	0.16
Calprotectin (mg/kg)	2200 (2770)	2500 (4540)	1530 (1490)	0.76*
Baseline Immunomodulator Use =YES (%)	4 (19.0%)	6 (12.0%)	10 (19.6%)	0.55
Prior anti-TNF Use =YES (%)	20 (95.2%)	46 (92.0%)	49 (96.1%)	0.66

Note * Calprotectin data are not normally distributed. Data is normally distributed after transformation.

We report the p-value based on log10 transformed data. Without transformation, the p-value is 0.46.

Source: R&D/21/0761 or R&D/21/0911, Table 1
Abbreviations: BMI, body mass index; CDAI, Crohn's disease activity index; CRP, C-reactive protein; IV, intravenous; PD, pharmacodynamic; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumor necrosis factor

Table 67. Demographics and Baseline Characteristics for M16-006 PD Study

Mean (SD) or N (%)	Placebo IV (N=21)	Risankizumab 600 mg IV (N=51)	Risankizumab 1200 mg IV (N=51)	p-value
Male (%)	11 (52.38)	27 (52.94)	25 (51.22)	0.92
Age (years)	37.10 (14.615)	41.25 (13.086)	36.78 (12.819)	0.20
Weight (kg)	65.79 (12.394)	78.06 (21.112)	72.60 (20.068)	0.05
BMI (kg/m^2)	22.80 (3.676)	26.62 (6.941)	24.41 (5.724)	0.03
Disease Duration (years)	8.65 (8.731)	10.72 (9.566)	11.05 (10.597)	0.63
Disease Location (Colonic only/ Ileal only/Ileal-colonic)	7/1/13	15/10/26	17/10/24	0.55
CDAI	313.88 (70.139)	311.81 (65.083)	300.48 (70.345)	0.62
SES-CD	12.62 (4.706)	12.80 (7.029)	11.47 (6.777)	0.57
CRP (mg/L)	10.17 (9.042)	15.76 (27.554)	12.45 (18.423)	0.56
Calprotectin (mg/kg)	1229.24 (994.055)	1522.61 (2719.548)	3248.22 (5380.149)	0.05*
Baseline Immunomodulator Use =YES (%)	6 (28.57)	15 (29.41)	14 (27.45)	0.98
Prior anti-TNF Use =YES (%)	8 (38.10)	27 (52.94)	26 (50.98)	0.50

Note * Calprotectin data are not normally distributed. Data is normally distributed after transformation.

We report the p-value based on log10 transformed data. Without transformation, the p-value is 0.043.

Source: R&D/21/0761 or R&D/21/0911, Table 2
Abbreviations: BMI, body mass index; CDAI, Crohn's disease activity index; CRP, C-reactive protein; IV, intravenous; PD, pharmacodynamic; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumor necrosis factor

Table 68. Demographics and Baseline Characteristics for M16-000 PD Study

Mean (SD) or N (%)	True PBO (N=18)	Withdrawal PBO (N=22)	Risankizumab 180mg (N=24)	Risankizumab 360mg (N=28)	p-value
Male (%)	8 (44.4%)	12 (54.5%)	9 (37.5%)	15 (53.6%)	0.60
Age (years)	41.7 (13.3)	36.8 (14.8)	39.0 (15.8)	41.1 (14.6)	0.69
Weight (kg)	73.3 (18.9)	71.8 (18.4)	70.0 (19.9)	77.7 (21.0)	0.53
BMI (kg/m^2)	25.3 (6.08)	24.1 (4.96)	24.8 (5.42)	26.0 (6.05)	0.68
Disease Duration (years)	11.0 (10.4)	12.4 (7.82)	12.5 (11.3)	9.90 (9.72)	0.75
Disease Location (Colonic only/Ileal only/Ileal-colonic)	7/3/8	8/3/11	11/2/11	11/4/13	0.98
CDAI	303 (55.9)	304 (45.0)	314 (58.4)	295 (56.0)	0.63
SES-CD	13.6 (6.26)	11.5 (6.72)	16.4 (7.22)	12.3 (7.26)	0.08
CRP (mg/L)	10.5 (10.5)	17.1 (23.9)	16.4 (19.9)	17.1 (20.5)	0.68
Calprotectin (mg/kg)	908 (870)	1070 (884)	2870 (3660)	1680 (1990)	0.12*
Baseline Immunomodulator Use =YES (%)	5 (27.8%)	4 (18.2%)	6 (25.0%)	9 (32.1%)	0.72
Prior anti-TNF Use =YES (%)	5 (27.8%)	7 (31.8%)	8 (33.3%)	8 (28.6%)	0.97

Note * Calprotectin data are not normally distributed. Data is normally distributed after transformation.
We report the p-value based on log10 transformed data. Without transformation, the p-value is 0.04.

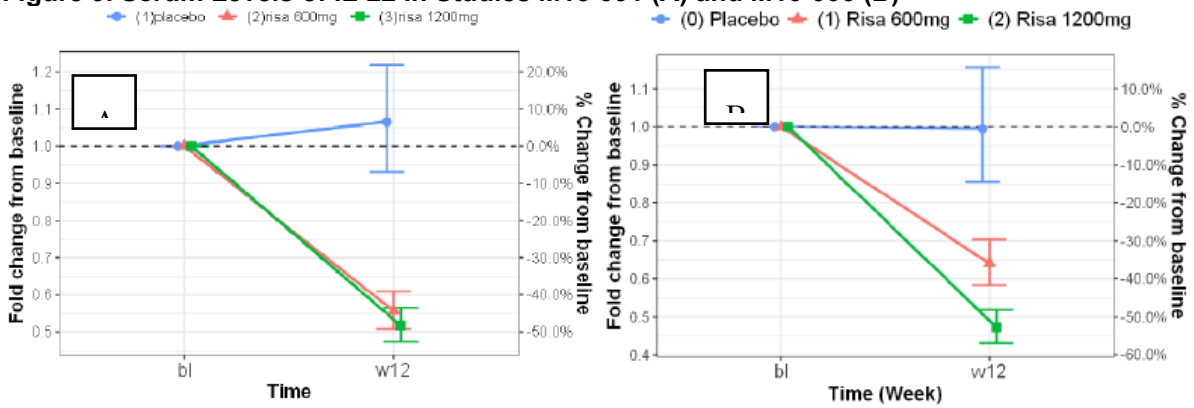
Source: R&D/21/0761 or R&D/21/0911, Table 3
Abbreviations: BMI, body mass index; CDAI, Crohn's disease activity index; CRP, C-reactive protein; PBO, placebo; PD, pharmacodynamic; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumor necrosis factor

Change From Baseline in Serum Levels of IL-22

Induction Study

By Week 12, serum levels of IL-22 were significantly reduced from baseline in CD subjects treated with risankizumab 600 mg (mean: -36% to -44%; $p \leq 0.0001$) or 1200-mg dose regimen (mean: -48% to -53%; $p \leq 0.0001$) in Studies M15-991 (Figure 9A) and M16-006 (Figure 9B). Compared to placebo group, IL-22 levels at Week 12 in all treatment groups were significantly lower ($p \leq 0.0001$ or $p \leq 0.01$). Compared to risankizumab 600 mg group, significant reduction of IL-23 at Week 12 in risankizumab 1200 mg group was only observed in Study M16-006 ($p \leq 0.05$), but not in Study M15-991.

Figure 9. Serum Levels of IL-22 in Studies M15-991 (A) and M16-006 (B)

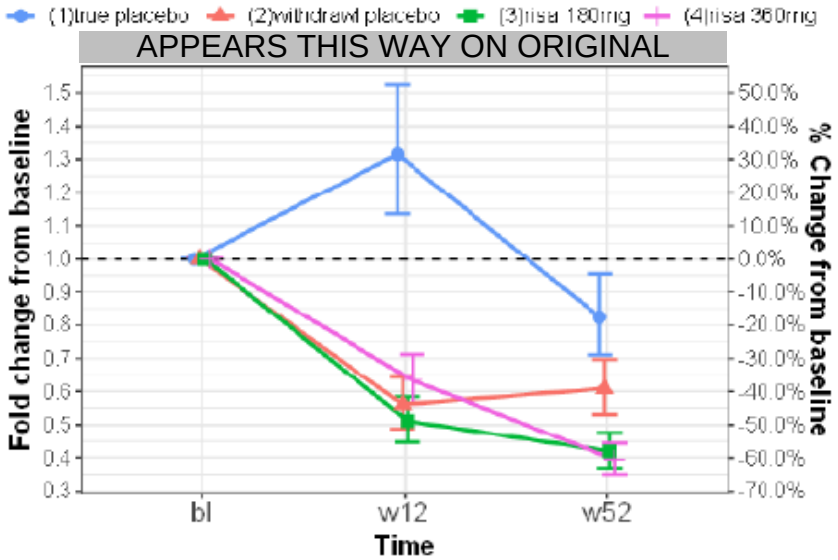


Source: R&D/21/0761, Figure 1 and Figure 2

Maintenance Study

Serum levels of IL-22 were significantly reduced from baseline of induction in the patients who were randomized to placebo after risankizumab induction treatment (withdrawal placebo), risankizumab 180 mg- and 360 mg-treatment subjects at both Week 12 and Week 52 in Study M16-000 (Figure 10 and Table 69). However, clinical relevance of these biomarker findings is unknown.

Figure 10. Serum Levels of IL-22 in Study M16-000



Source: R&D/21/0761, Figure 3

Table 69. Change From Baseline in IL-23 at Week 12 and Week 52 in M16-000

Biomarker	Treatment	Time (week)	Ratio to Baseline	% Chg from baseline	p-value	Sig	Bonf. Adj. p-value	Bonf. Adj. sig
IL-22	True placebo	12	1.32	31.5%	0.064		0.13	
IL-22	True placebo	52	0.82	-17.5%	0.19		0.38	
IL-22	Withdrawl placebo	12	0.56	-43.9%	5.3E-05	****	1E-04	***
IL-22	Withdrawl placebo	52	0.61	-39.1%	0.00037	***	7E-04	***
IL-22	Risankizumab 180 mg	12	0.51	-48.8%	1.2E-06	****	2E-06	****
IL-22	Risankizumab 180 mg	52	0.42	-58.0%	2.2E-10	****	4E-10	****
IL-22	Risankizumab 360 mg	12	0.63	-36.6%	0.00017	***	3E-04	***
IL-22	Risankizumab 360 mg	52	0.39	-60.5%	6.5E-13	****	1E-12	****

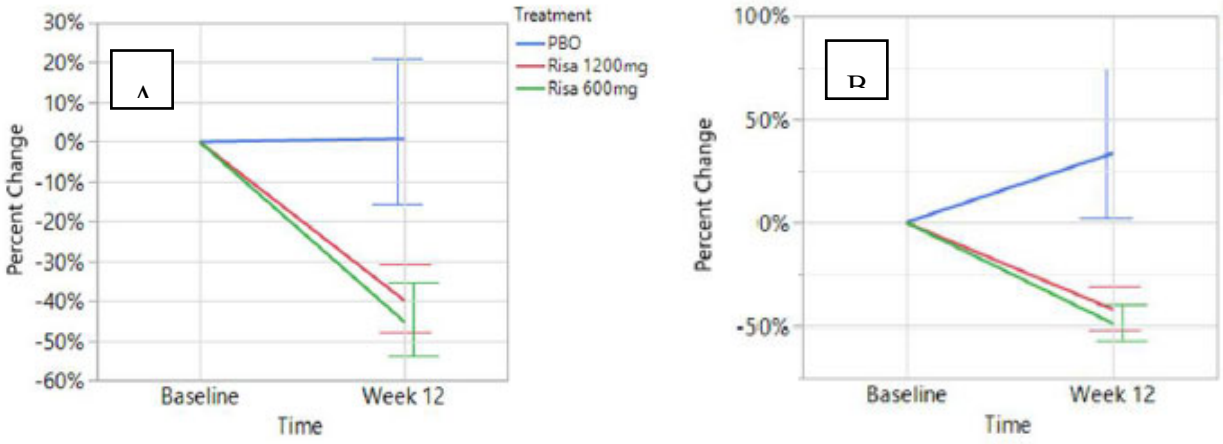
Source: R&D/21/0761, Table 8
***p≤0.001, ****p≤0.0001

Change From Baseline in Serum Levels of CRP

Induction Study

CRP levels decreased by 40% to 49% from baseline at Week 12 in CD subjects treated with risankizumab 600 mg or 1200-mg dose regimen in Studies M15-991 (Figure 11A) and M16-006 (Figure 11B). Compared to placebo group, CRP levels in all risankizumab treatment groups were significantly lower at Week 12 in M15-991 and M16-006.

Figure 11. Serum Levels of CRP in Studies M15-991 (A) and M16-006 (B)



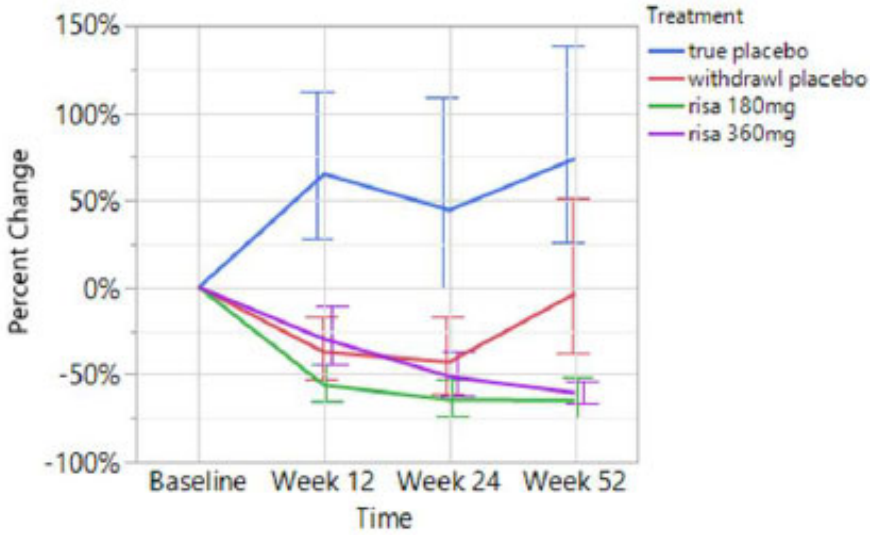
Source: R&D/21/0911, Figure 1 and Figure 3
Abbreviations: CRP, C-reactive protein; PBO, placebo

Maintenance Study

CRP levels decreased from baseline in the patients who were randomized to placebo after risankizumab induction treatment (withdrawal placebo), risankizumab 180 mg- and 360 mg-treatment subjects at Weeks 12, 24 and 52 in Study M16-000 (Figure 12 and Table 70). Compared to true placebo- and withdrawal placebo groups, CRP levels were significantly lower

in both risankizumab treatment groups up to Week 52. However, clinical relevance of these findings remains unknown.

Figure 12. CRP Levels Over Time in Study M16-000



Source: R&D/21/0911, Figure 5
Abbreviations: CRP, C-reactive protein

Table 70. Change From Baseline in CRP at Week 12 and Week 52 in M16-000

Biomarker	Treatment	Percent Change Baseline	Percent Change Week 12	Percent Change Week 24	Percent Change Week 52
CRP	True placebo	0.0%	65.1%	44.5%	73.8%
CRP	Withdrawal placebo	0.0%	-37.4%	-43.0%	-3.7%
CRP	Risankizumab 180 mg	0.0%	-56.2%	-64.7%	-64.8%
CRP	Risankizumab 360 mg	0.0%	-29.8%	-51.3%	-60.6%

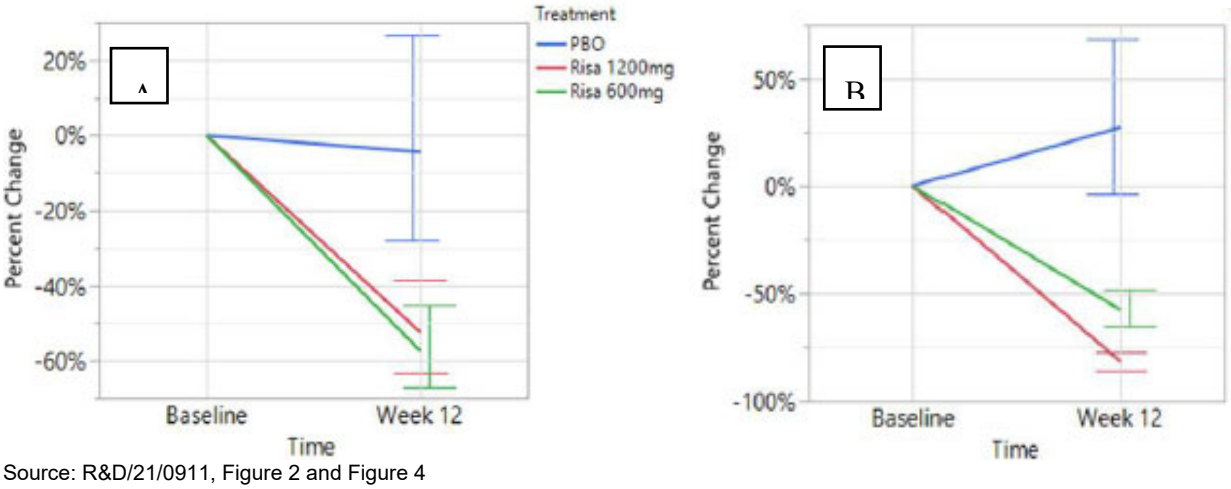
Source: R&D/21/0911, Table 12
Abbreviations: CRP, C-reactive protein

Change From Baseline in Serum Levels of FCP

Induction Study

Up to 82% reduction of FCP from baseline was observed at Week 12 in CD subjects treated with risankizumab 600-mg or 1200-mg dose regimen in Studies M15-991 (Figure 13A) and M16-006 (Figure 13B). Compared to placebo group, significant reduction of FCP was only observed in both risankizumab-treated groups of Study M16-006, but not in Study M15-991.

Figure 13. Serum Levels of FCP in Studies M15-991 (A) and M16-006 (B)

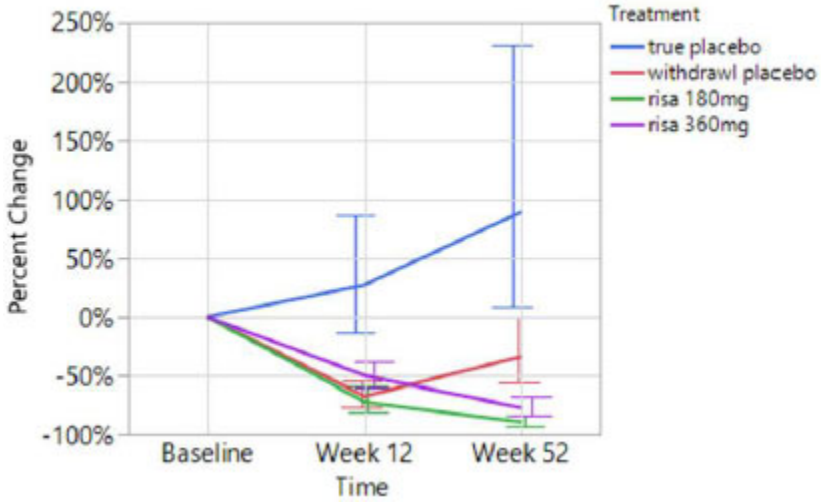


Source: R&D/21/0911, Figure 2 and Figure 4
Abbreviations: FCP, fecal calprotectin; PBO, placebo

Maintenance Study

FCP levels decreased from baseline in the patients who were randomized to placebo after risankizumab induction treatment (withdrawal placebo), risankizumab 180 mg- and 360 mg-treatment subjects at Weeks 12 and 52 in Study M16-000 (Figure 14 and Table 71). Compared to true placebo- and withdrawal placebo groups, FCP levels were significantly lower in both risankizumab treatment groups up to Week 52. However, clinical relevance of these findings remains unknown.

Figure 14. FCP Levels Over Time in Study M16-000



Source: R&D/21/0911, Figure 6
Abbreviations: FCP, fecal calprotectin

Table 71. Change From Baseline in FCP Over Time in M16-000

Biomarker	Treatment	Percent Change Baseline	Percent Change Week 12	Percent Change Week 52
CALPRO	True placebo	0.0%	27.5%	89.6%
CALPRO	Withdrawal placebo	0.0%	-67.4%	-34.0%
CALPRO	Risankizumab 180 mg	0.0%	-72.1%	-89.5%
CALPRO	Risankizumab 360 mg	0.0%	-50.0%	-77.0%

Source: R&D/21/0911, Table 14
Abbreviations: FCP, fecal calprotectin

Overall, the PD activities assessed in the subset of subjects from Study M15-991, M-16-006, and M16-000 are considered exploratory as analytical and/or clinical validation for these PD activities have not been established.

14.4. Pharmacometrics Review

14.4.1. Applicant's Population Pharmacokinetics Analysis

Objective

To characterize the population pharmacokinetics of risankizumab in subjects with moderately to severely active CD.

Data

Risankizumab serum concentrations from subjects with moderately to severely active CD (N=1392) in phase 2 Studies (M15-993 and M15-989), phase 3 Induction Studies (M15-991and M16-006), and phase 3 Maintenance Study (M16-000) (N=375) and healthy volunteers in phase 1 Study M16-533 (N=12) who received at least one dose of risankizumab treatment and who had at least one measurable risankizumab concentration were included in the population PK analyses. An overview of the study designs is provided in Table 72.

Table 72. Summary of Studies Included in the Population Pharmacokinetic Analyses

Study ($N_{treated}/N_{total}$)	Phase, Population	Risankizumab Regimen	Study Design & PK Sample
M16-533 (N=12/16)	Phase 1/ Healthy male Japanese and Caucasian subjects	Single dose 1800 mg IV	Double-blind, randomized, placebo-controlled, single dose study. PK samples on Days 1, 2, 3, 4, 8, 15, 29, 57, 85, and 137.
M15-993 (N=82/121)	Phase 2/Subjects with moderately to severely active CD who are naïve to or were previously treated with anti-TNF therapy	Period 1: placebo or RZB 200 or 600 mg IV at Weeks 0, 4, and 8 Period 2: RZB 600 mg IV at Weeks 14, 18, and 22 or washout Period 3: RZB 180 mg SC at Weeks 26, 34, 42, and 50	Double-blind, placebo-controlled, parallel-group; predose PK samples at Weeks 0, 2, 4, 8 and 12 (Period 1); Weeks 12, 14, 18, 22 (Period 2); and Weeks 26, 34, 42, 50, 52 and 65/EOT (Period 3).

Study ($N_{treated}/N_{total}$)	Phase, Population	Risankizumab Regimen	Study Design & PK Sample
M15-989 (N=65/65)	Phase 2/ Subjects with active CD who have successfully completed Study M15-993	Subjects with clinical response or remission at the end of Study M15-993 or at Screening: RZB 180 mg SC Q8W Subjects who had lost clinical remission at the EOT visit of Study M15-993, or at screening of Study M15-989: Open-label re-induction of RZB with 3 infusions of 600 mg IV Q4W, when clinical response or remission was achieved, subjects were switched to maintenance treatment of RZB 180 mg SC Q8W.	Open-label long-term extension; predose PK samples at Weeks 0, 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188 and 204 (for subjects rolling-over at Week 26 from Study M15-993), Weeks 0, 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190 and 206 (for subjects rolling over at Week 52 from Study M15-993), and Weeks 0, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200 and 216 (for subjects who lost response after completing Study M15-993
M15-991 (N=411/618 in the 12-Week Induction Period)	Phase 3, subjects with moderately to severely active CD (failed prior biologic treatment [Bio-IR])	12-Week Induction Period: RZB 600 mg IV, RZB 1200 mg IV, or placebo Q4W Induction Period 2: RZB IV non responders Group 1: RZB 1200 mg IV Group 2: RZB 360 mg SC Group 3: RZB 180 mg SC Placebo IV non responders Group 4: RZB 1200 mg IV	Double-blind, placebo-controlled, predose PK samples drawn at Weeks 4, 8, 12, 24
M16-006 (N=745/931 in the 12-Week Induction Period)	Phase 3/ Subjects with moderately to severely active CD; study population (Bio-IR had minimum of ~540 subjects; did not fail prior biologic treatment (non-Bio-IR) had minimum of ~315 subjects)	12-Week Induction Period: RZB 600 mg IV, RZB 1200 mg IV or placebo Q4W Induction Period 2: RZB IV nonresponders Group 1: RZB 1200 mg IV Group 2: RZB 360 mg SC Group 3: RZB 180 mg SC Placebo IV nonresponders Group 4: RZB 1200 mg IV	Double-blind, placebo-controlled, predose PK samples drawn at Weeks 4, 8, 12, 24. For subjects who consented to optional intensive PK, additional samples were drawn at Week 8 (immediately at the end of infusion and 2 h post the end of infusion) and at Weeks 9, 10, 11.
M16-000 (N=712, 358/542 randomized subjects who were RZB IV responders, 64/170 non-randomized subjects who were RZB SC responders)	Phase 3/Subjects with moderately to severely active CD who completed Study M16-006 or Study M15-991 and achieved clinical response.	Substudy 1: RZB 180 mg SC, RZB 360 mg SC, or PBO Q8W (RZB IV responders); PBO Q8W (PBO IV responders); RZB 180 mg SC, RZB 360 mg SC (RZB SC responders); RZB 1200 mg IV+RZB 360 mg SC Q8W (Rescue)	Only Substudy 1 data were included in the analyses. Substudy 1: randomized, double-blind, placebo-controlled maintenance. Predose PK samples drawn at Weeks 16, 32, 48, 52 and at the Rescue Visit.

Source: Table 1 of Applicant's population PK report
Abbreviations: CD, Crohn's disease; EOT, end of treatment; IV, intravenous; PBO, placebo; PK, pharmacokinetic; Q4W, every 4 weeks; Q8W, every 8 weeks; RZB, risankizumab; SC, subcutaneous; TNF, tumor necrosis factor

A summary of the demographic data for the subjects available for the population pharmacokinetic analyses is presented in Table 73.

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Table 73. Demographic and Baseline Characteristics of Healthy Subjects and Subjects With Crohn's Disease Included in the Risankizumab Population Pharmacokinetic Analyses

Demographic Parameter	Phase 1 Healthy Subjects M16-533 (N=12)	Phase 2 M15-993/M15-989 (N=115)	Phase 3 M15-991 (N=473)	Phase 3 M16-006 (N=804)	Phase 3 M16-000 (N=375)	Subjects in Phase 3 Studies (N=1277) [a]	Crohn's Disease Subjects (N=1392)
Age at baseline (years)							
Mean (SD)	36.5 (6.37)	38.4 (13.4)	39.7 (13.1)	38.2 (13.5)	38.4 (13.6)	38.7 (13.4)	38.7 (13.4)
Median	36	35	38	35	36	37	37
Min-max	23, 46	19, 74	16, 74	16, 79	16, 76	16, 79	16, 79
Body weight at baseline (kg)							
Mean (SD)	75.3 (7.91)	67.7 (16.6)	73.5 (18.9)	70.4 (18.7)	71.1 (18.1)	71.6 (18.8)	71.2 (18.7)
Median	77.2	65.8	70.8	67.5	67.8	68.5	68.0
Min-max	64.2, 90.0	35.0, 125	35.0, 145	32.0, 159	36.6, 148	32.0, 159	32.0, 159
BMI (kg/m^2) at baseline							
Mean (SD)	23.8 (2.15)	23.8 (5.35)	25.5 (6.04)	24.2 (5.87)	24.5 (5.91)	24.7 (5.96)	24.6 (5.92)
Median	23.7	22.7	24.5	23.4	23.5	23.7	23.7
Min-max	20.3, 28.7	13.6, 37.3	14.5, 52.4	13.0, 58.2	13.0, 54.1	13.0, 58.2	13.0, 58.2
CD activity index score at baseline							
Mean (SD)	--	304 (76)	311 (63.1)	310 (64.0)	312 (63.1)	310 (63.6)	310 (64.7)
Median	--	297	302	304	305	303	303
Min-max	--	109, 518	132, 526	76.0, 634	132, 624	76.0, 634	76.0, 634
CRP high sensitivity at baseline (mg/L)							
Mean (SD)	0.53 (0.27)	21.1 (26.5)	19.1 (24.5)	16.4 (23.8)	18.9 (25.0)	17.4 (24.1)	17.7 (24.3)
Median	0.45	10.0	9.41	7.27	8.47	8.00	8.10
Min-max	0.30, 1.20	0.22, 146	0.20, 167	0.20, 181	0.25, 151	0.20, 181	0.20, 181
Fecal calprotectin at baseline (mg/kg)							
Mean (SD)	22.0 (0.00)	2620 (4040)	1890 (2930)	1820 (3060)	1960 (2850)	1850 (3010)	1910 (3120)
Median	22.0	1300	1050	960	1050	977	991
Min-max	22.0, 22.0	40.0, 25300	30.0, 28800	30.0, 28800	30.0, 28800	30.0, 28800	30.0, 28800
Total bilirubin at baseline (mcmol/L)							
Mean (SD)	10.4 (5.90)	6.42 (5.77)	6.04 (3.70)	6.67 (4.09)	6.54 (4.19)	6.44 (3.96)	6.43 (4.14)
Median	8.55	5.00	5.00	5.13	5.13	5.13	5.13
Min-max	3.42, 22.2	3.00, 38.0	3.00, 41.0	3.00, 39.0	3.00, 39.0	3.00, 41.0	3.00, 41.0
Baseline albumin (g/L)							
Mean (SD)	46.3 (1.91)	36.9 (4.65)	40.8 (4.61)	41.8 (4.47)	40.9 (4.71)	41.4 (4.55)	41.1 (4.72)
Median	46.0	37.0	41.0	42.0	42.0	42.0	42.0
Min-max	43.0, 49.0	24.0, 46.0	18.0, 54.0	24.0, 55.0	23.0, 52.0	18.0, 55.0	18.0, 55.0

Demographic Parameter	Phase 1 Healthy Subjects M16-533 (N=12)	Phase 2 M15-993/M15-989 (N=115)	Phase 3 M15-991 (N=473)	Phase 3 M16-006 (N=804)	Phase 3 M16-000 (N=375)	Subjects in Phase 3 Studies (N=1277) [a]	Crohn's Disease Subjects (N=1392)
Creatinine at baseline (mcmol/L)							
Mean (SD)	73.7 (7.85)	70.7 (16.5)	70.7 (17.2)	71.2 (16.7)	70.0 (15.9)	71.0 (16.9)	71.0 (16.8)
Median	70.7	68.0	70.0	70.7	70.0	70.7	70.0
Min-max	61.9, 88.4	41.0, 145	32.0, 167	35.4, 168	35.4, 168	32.0, 168	32.0, 168
Calculated creatinine clearance (mL/min)							
Mean (SD)	131 (14.3)	111 (31.8)	121 (35.1)	118 (34.7)	121 (36.8)	119 (34.9)	118 (34.7)
Median	132	108	117	114	118	115	115
Min-max	111, 153	39.3, 235	35.1, 268	25.2, 291	43.2, 291	25.2, 291	25.2, 291
Aspartate aminotransferase at baseline (U/L)							
Mean (SD)	18.2 (3.43)	20.0 (15.7)	16.4 (6.76)	17.4 (9.81)	16.8 (9.73)	17.1 (8.82)	17.3 (9.60)
Median	17.5	16.0	15.0	16.0	15.0	15.0	16.0
Min-max	13.0, 25.0	6.00, 155	6.00, 78.0	4.00, 144	5.00, 107	4.00, 144	4.00, 155
Alanine aminotransferase at baseline (U/L)							
Mean (SD)	18.6 (8.84)	19.9 (14.9)	16.9 (10.0)	17.7 (15.1)	17.2 (14.2)	17.4 (13.4)	17.6 (13.6)
Median	17.5	15.0	14.0	14.0	14.0	14.0	14.0
Min-max	8.00, 35.0	4.00, 81.0	4.00, 73.0	4.00, 214	4.00, 202	4.00, 214	4.00, 214
Sex, n (%)							
Male	12 (100)	45 (39)	233 (49)	433 (54)	200 (53)	666 (52)	711 (51)
Female	--	70 (61)	240 (51)	371 (46)	175 (47)	611 (48)	681 (49)
Race, n (%)							
Non-Asian	6 (50)	98 (85)	448 (95)	651 (81)	310 (83)	1099 (86)	1197 (86)
Asian	6 (50)	17 (15)	25 (5)	153 (19)	65 (17)	178 (14)	195 (14)
Treatment-emergent ADA, n (%)							
Negative	9 (75)	106 (92)	466 (99)	794 (99)	369 (98)	1260 (99)	1366 (98)
Positive	3 (25)	9 (8)	7 (1)	10 (1)	6 (2)	17 (1)	26 (2)
Treatment-emergent neutralizing ADA, n (%)							
Negative	--	115 (100)	472 (100)	803 (100)	375 (100)	1275 (100)	1390 (100)
Positive	--	--	1 (0)	1 (0)	--	2 (0)	2 (0)
CMC manufacturing process, n (%)							
CMC1	--	115 (100)[b]	--	--	--	--	115 (8)
CMC2	12 (100)	--	473 (100)	804 (100)	375 (100)	1277 (100)	1277 (92)

Demographic Parameter	Phase 1 Healthy Subjects M16-533 (N=12)	Phase 2 M15-993/M15-989 (N=115)	Phase 3 M15-991 (N=473)	Phase 3 M16-006 (N=804)	Phase 3 M16-000 (N=375)	Subjects in Phase 3 Studies (N=1277) [a]	Crohn's Disease Subjects (N=1392)
Country, n (%)							
USA/Canada	12 (100)	13 (11)	158 (33)	182 (23)	110 (29)	340 (27)	353 (25)
Europe	--	88 (7)	243 (51)	406 (51)	179 (48)	649 (51)	737 (53)
China	--	--	--	65 (8)	5 (1)	65 (5)	65 (5)
Japan	--	--	--	67 (8)	36 (10)	67 (5)	67 (5)
Other Asian countries	--	14 (12)	21 (4)	17 (2)	23 (6)	38 (3)	52 (4)
Rest of Word	--	--	51 (11)	67 (8)	22 (6)	118 (9)	118 (8)

Source: Table 3 of Applicant's population PK report.
[a] Study M16-000 is the maintenance study extension for induction Studies M15-991 and M16-006. All subjects from both induction studies who are clinical responders went into the maintenance study. Therefore, the total number of Phase 3 subjects is 1277 (473+804).
[b] Sixty-five (65) subjects rolled over from Study M15-993 to the open-label extension Study M15-989. Forty-six (46), 70% of them went during the open-label study from CMC1 to CMC2.
Abbreviations: ADA, antidrug antibody; BMI, body mass index; CD, Crohn's disease; CMC, chemistry, manufacturing, and controls; CRP, C-reactive protein; SD, standard deviation

Methods

The risankizumab population PK model was developed using nonlinear mixed-effects modeling based on NONMEM (Version 7.4.4). A previously developed two-compartment population PK model with first order absorption and elimination that described risankizumab PKs in patients with moderate to severe plaque psoriasis and CD served as the starting model for the analyses. The analyses described in this report focused on confirming the adequacy of the model, refining it as necessary and evaluating additional potential covariate-parameter relationships relevant to the CD population.

Interindividual variability on PK parameters was assumed to follow a log-normal distribution. Residual unexplained variability was explored using additive, proportional or a combined additive and proportional error model structures.

The covariates included in the previously developed starting model (body weight and baseline albumin) were tested to confirm their statistical significance. Subsequently, the rest of the covariates were tested for inclusion in the population pharmacokinetic model one step at a time based on forward selection (α=0.01) and backward elimination (α =0.001) process using Stepwise Covariate Model building tool implemented in Perl Speaks NONMEM (PsN Version 4.8.1). Power models were used to characterize relationships of continuous covariate, whereas for categorical covariates a proportional difference was estimated for each category of interest relative to the typical population estimate assigned to the most frequent category. Covariates that impacted the stability of the model by causing errors in minimization or in the covariance step were excluded from the final model.

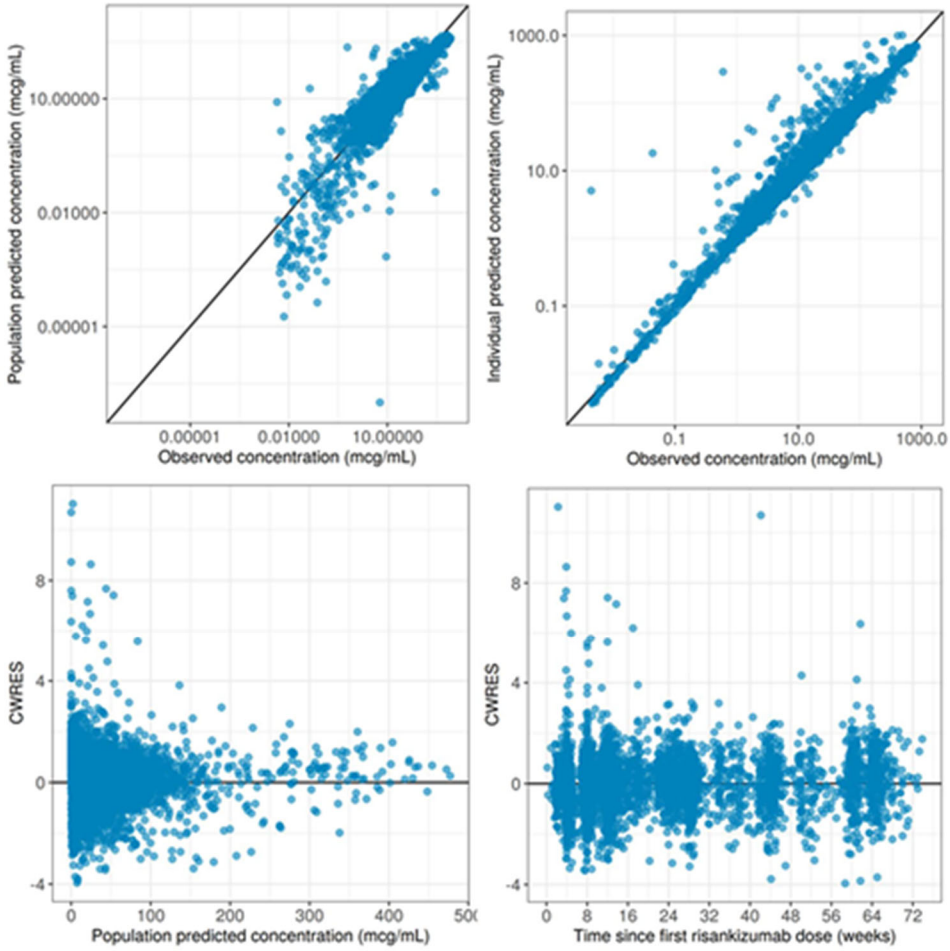
Model Evaluation

Methods used in model evaluation included goodness-of-fit plots, bootstrapping analyses, and visual predictive checks.

After identifying statistically significant covariates for risankizumab PK parameters, simulations were carried out to evaluate their clinical relevance or impact on risankizumab concentration (C_{trough}) at the end of 12 weeks, and AUC over 12 weeks, with induction dosing at Week 0, 4, and 8. A similar analysis was also conducted for the maintenance dosing regimen of 360 mg SC Q8W with dosing on Week 0, 8, 16, 24, 32 and, 40 and evaluating the impact of these covariates on risankizumab trough concentration and AUC over an 8-week period from Weeks 40-48.

Results: A two-compartment model with a first-order absorption for SC administration and first-order elimination adequately described risankizumab PKs (Figure 15).

Figure 15. Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model



Source: Figure 5 of Applicant's population PK report

Results

The estimated PK parameter values and their associated variability for the selected final PK model are presented in Table 74.

Table 74. Parameter Estimates for Risankizumab Final Population Pharmacokinetic Model

Parameter	Estimate (SE)	%RSE[a]	95% CI
Clearance (CL; L/day)	0.296 (0.00460)	1.55	(0.287, 0.305)
Central volume of distribution (Vc; L)	4.98 (0.187)	3.76	(4.61, 5.35)
Intercompartmental clearance (Q; L/day)	0.255 (0.0107)	4.20	(0.234, 0.276)
Peripheral volume of distribution (Vp; 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 (Vc)	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)

Parameter	Estimate (SE)	%RSE[a]	95% CI
Exponent for the effect of baseline calprotectin on risankizumab clearance (CL)	0.0482 (0.00656)	13.6	(0.0353, 0.0611)
Time varying corticosteroid comedication 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)
Interindividual and residual variability			
Variance of interindividual variability in CL, %CV[b], exponential error model	0.109, 33.9	3.17	(0.102, 0.116)
Variance of interindividual variability in Vc, %CV[b], exponential error model	0.345, 64.2	7.10	(0.297, 0.393)
Variance of interindividual variability in Ka, %CV[b], exponential error model	1.03, 134	7.51	(0.878, 1.18)
Variance of covariance between interindividual variability in CL and Vc, %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)

Source: Table 6 of Applicant's population PK report.
[a] Residual standard error
[b] Coefficient of variation
Abbreviations: CI, confidence interval; CL, clearance; %CV, coefficient of variation; SE, standard error

The parameters of the final population PK model were estimated with good precision (%RSE ranging from approximately 1% to 21%). Model evaluation using goodness-of-fit plots and visual predictive checks indicated that the model adequately described risankizumab pharmacokinetics. Risankizumab pharmacokinetic parameter estimates are consistent with previously reported estimates for typical IgG1 monoclonal antibodies, and parameter estimates in subjects with moderate to severe chronic plaque psoriasis and psoriatic arthritis.

Effect of covariates on risankizumab pharmacokinetics:

- Age, race (Asian versus Non-Asian), and liver function markers did not impact risankizumab exposures.
- Body weight was correlated with risankizumab clearance and apparent central volume of distribution but did not have a clinically relevant impact on risankizumab PK.
- Model-predicted risankizumab exposures were similar between adolescents aged 16 to 17 years old versus adults.
- Simulations conducted using the population pharmacokinetic model showed that subjects with low baseline serum albumin (<38 g/L) 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, rather than trough concentrations, which was within the 0.8 to 1.25 reference range.
- Baseline fecal calprotectin, corticosteroid use, sex and creatinine clearance were statistically correlated to risankizumab clearance. However, none of them had a clinically meaningful impact (risankizumab exposures were well within the default 0.8 to 1.25

equivalence boundaries over the range of covariate values observed in subjects with moderate to severe CD).

- ADAs and neutralizing antibodies (Nabs) were not identified as significant covariate for risankizumab clearance.

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 75.

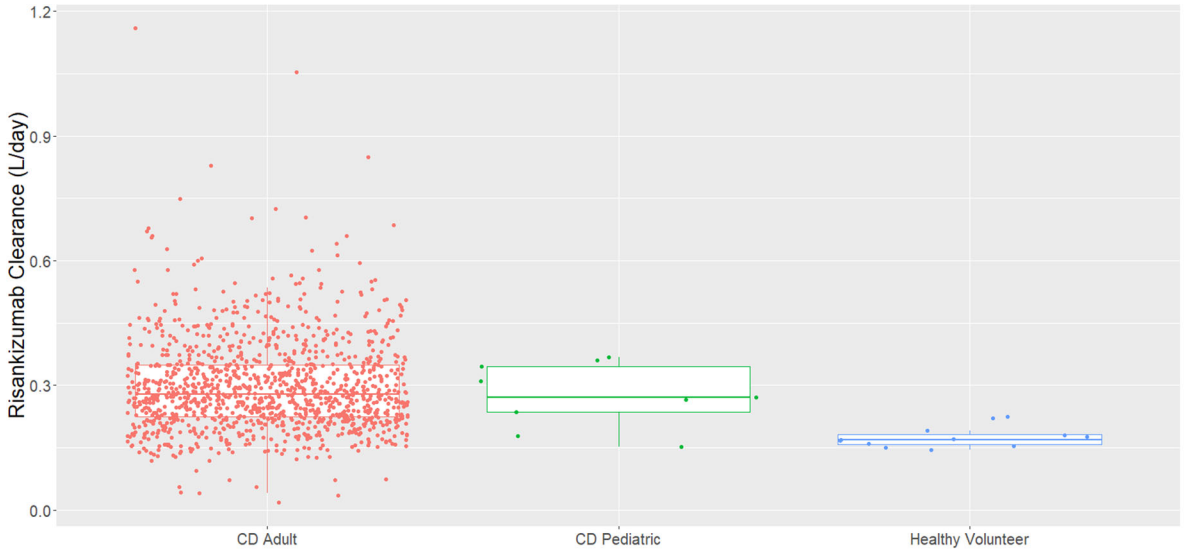
Table 75. Model-Predicted Risankizumab Exposures in Subjects With Moderate to Severe CD During the 12-Week Induction Period at the Proposed Induction Dosing Regimen of Three Doses of 600 mg IV Q4W and During Maintenance Period at the Proposed Maintenance Dosing Regimen of 360 mg SC Q8W Starting at Week 12

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

Source: Table 8 of Applicant's population PK report
Abbreviations: AUC, area under the concentration-time curve; CD, Crohn's disease; $C_{average}$, average plasma concentration; C_{max}, maximum plasma concentration; C_{trough}, trough concentration; IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SD, standard deviation

Reviewer's Comments: *The Applicant's PopPK analysis is acceptable for describing the PK of risankizumab in healthy subjects and patients with CD. Age was not identified as a covariate on PK parameters. The reviewer conducted further exploration to compare the PK of risankizumab between adults and adolescents (≥16 years of age) included in the analysis and confirmed that the estimated clearance values in the 9 adolescent subjects were comparable to that in adults (Figure 16).*

Figure 16. Comparison of Risankizumab Clearance Between Adult and Adolescent Ages 16-17



Source: FDA reviewer's analysis.
Abbreviations: CD, Crohn's disease

14.4.2. Applicant's Exposure-Response Analysis

Objectives

To characterize the relationships between risankizumab systemic exposures and efficacy in subjects with moderately to severely active CD; and to characterize the relationships between risankizumab systemic exposures and safety parameters in subjects with moderately to severely active CD.

Data

Exposure and efficacy/safety 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 Substudy 1 (N=462) who received placebo or at least one dose of risankizumab were included in the efficacy exposure-response analyses.

Exposure and efficacy/safety 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.

Table 76. Summary of Studies Included in the Exposure-Response Analyses

Study ($N_{treated}/N_{total}$)	Efficacy and Safety Data for Exposure-Response Analysis
Phase 2 Study M15-993 (N=82/121)	Double-blind, randomized, placebo-controlled, single dose study. PK samples on Days 1, 2, 3, 4, 8, 15, 29, 57, 85, and 137. Efficacy: The following efficacy variables were evaluated at Week 12: CDAI clinical remission CDAI clinical response SF/APS clinical remission SF/APS clinical response Endoscopic response Endoscopic remission Safety: Not applicable (Exposure-response analyses for safety focused on safety data from the Phase 3 studies, M15-991, M16-006 and M16-000 [Substudy 1]).
Phase 3 Study M15-991 (N=411/618 in the 12-Week Induction Period)	Efficacy: Evaluated at Week 12 (end of Induction Period 1) and Week 24 (end of Induction Period 2): CDAI clinical remission CDAI clinical response SF/APS clinical remission SF/APS clinical response Endoscopic response Endoscopic remission Abdominal pain remission Stool frequency remission Ulcer free endoscopy Safety: Evaluated over 12- and 24-weeks induction and re- induction periods, respectively: AE, SAE, Infection, Serious Infection
Phase 3 Study M16-006 (N=745/931 in the 12-Week Induction Period)	Efficacy: Evaluated at Week 12 (end of Induction Period 1) and Week 24 (end of Induction Period 2): CDAI clinical remission CDAI clinical response SF/APS clinical remission SF/APS clinical response Endoscopic response Endoscopic remission Abdominal pain remission Stool frequency remission Ulcer free endoscopy Safety: Evaluated over 12- and 24-weeks induction and re- induction periods, respectively: AE, SAE, Infection, Serious Infection
Phase 3 Study M16-000 (N=712, 358/542 randomized subjects who were RZB IV responders, 64/170 non-randomized subjects who were RZB SC responders)	Only Substudy 1 data are planned to be included in these analyses. Efficacy endpoints at Week 52: CDAI clinical remission CDAI clinical response SF/APS clinical remission SF/APS clinical response Endoscopic response Endoscopic remission Abdominal pain remission Stool frequency remission Ulcer free endoscopy Safety: AE, SAE, Infection, Serious Infection by Week 52

Source: Table 1 of Applicant's exposure-response report.
Abbreviations: AE, adverse event; APS, abdominal pain score; CDAI, Crohn's disease activity index; IV, intravenous; PK, pharmacokinetic; RZB, risankizumab; SAE, serious adverse event; SC, subcutaneous; SF, stool frequency

Methodology

Exposure-Response Analyses for Efficacy

The relationships between the efficacy endpoints (CDAI clinical remission, CDAI clinical response, SF/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).

Graphical Analyses

Subjects who received risankizumab were grouped into quartiles based on their individual exposures, and subjects who received placebo were binned together (Week 12 and Week 52). Graphical plots were generated for all efficacy endpoints to explore the exposure-response efficacy trends.

Logistic Regression Analyses

Logistic regression models were developed to characterize the exposure- response relationships for the efficacy endpoints at Weeks 12 and 52. Linear, linear-log, and maximum efficacy response (E_{max}) functions were compared for the best description of the effect of risankizumab exposure on achieving the endpoint evaluated. A model that better fits the data was selected based on model selection criteria (Akaike Information Criterion) and visual inspection. The logistic regression models developed were used to conduct simulations to predict the probabilities of achieving the efficacy endpoints at Weeks 12 and 52.

Exposure-Response Analyses for Safety

The proportions of subjects who experienced any of the key safety variables of interest (any AE, any 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 Substudy 1), were determined among subjects who received placebo (Week 12 and Week 52) and in each observed risankizumab exposure quartile. These analyses were graphically shown for visual inspection of any exposure safety relationships.

Results

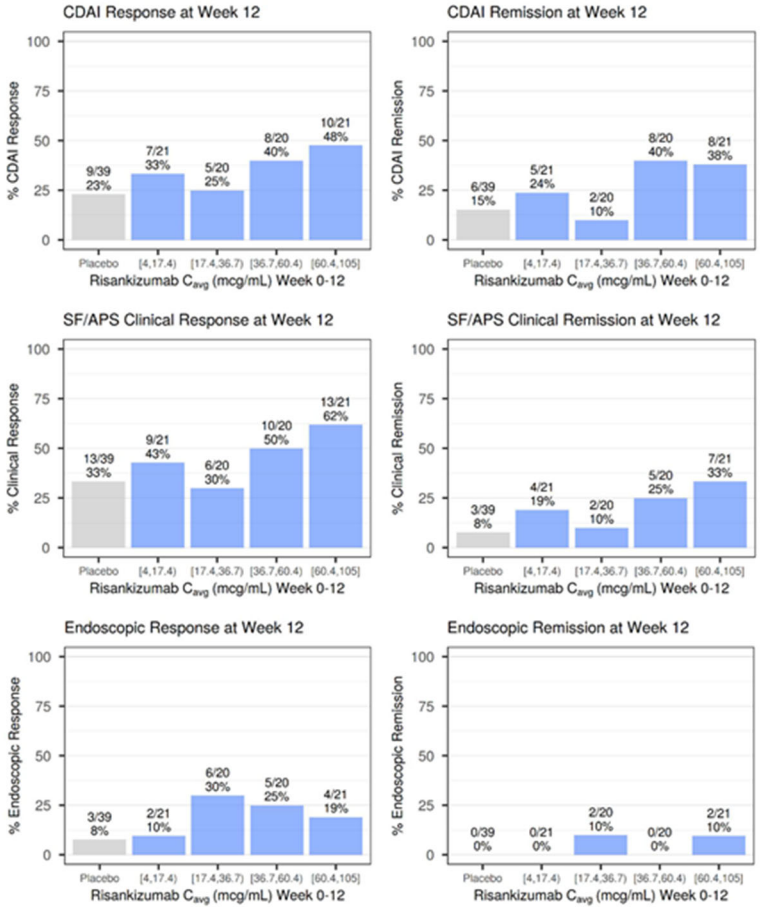
Exposure-Response Analyses for Efficacy

Phase 2 Induction

Exposure-response graphical analyses demonstrated that exposures associated with 600 mg risankizumab IV at Weeks 0, 4 and 8 as an induction regimen rendered favorable 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 (Figure 17). Endoscopic endpoints showed no conclusive exposure-response trends, yet subjects treated with risankizumab showed favorable efficacy compared to placebo. Results from the phase 3 induction studies showed that exposures associated with 600 mg risankizumab IV administered at Weeks 0, 4, and 8, achieved a near maximal effect for all endpoints evaluated, with no added benefit from the 1200 mg IV induction regimen as shown on the left panel of Figure 18.

Figure 17. Relationship Between Risankizumab Predicted $C_{avg,Week0-12}$ and Responses at Week 12 in Phase 2 Study (Study-M15-993)



Source: Figure 4 of Applicant's exposure-response report.
Note: Predicted median and 90% CI of C_{avg} of Week 0-12 are 17.4 (6.53 to 29.3) and 60.5 (37.0 to 104) mg/L for IV 200 mg and 600 mg Q4W, respectively.
Abbreviations: APS, abdominal pain score; C_{avg}, average plasma concentration; CDAI, Crohn's disease activity index; SF, stool frequency

Phase 3 Induction Treatment

As shown on the right panel of Figure 18, logistic regression models adequately described the exposure-response relationships for the efficacy endpoints evaluated at Week 12 for the data available from the phase 3 Studies. Model predictions together with observed data indicated that the efficacy may have reached a plateau at 600 mg IV induction regimen with no substantial added benefit from the 1200 mg IV induction regimen.

Figure 18. Relationship Between Risankizumab Predicted $C_{avg,Week0-12}$ and Responses at Week 12 After 600 and 1200 mg Q4W in Phase 3 Study (Studies M15-991 and M16-006)

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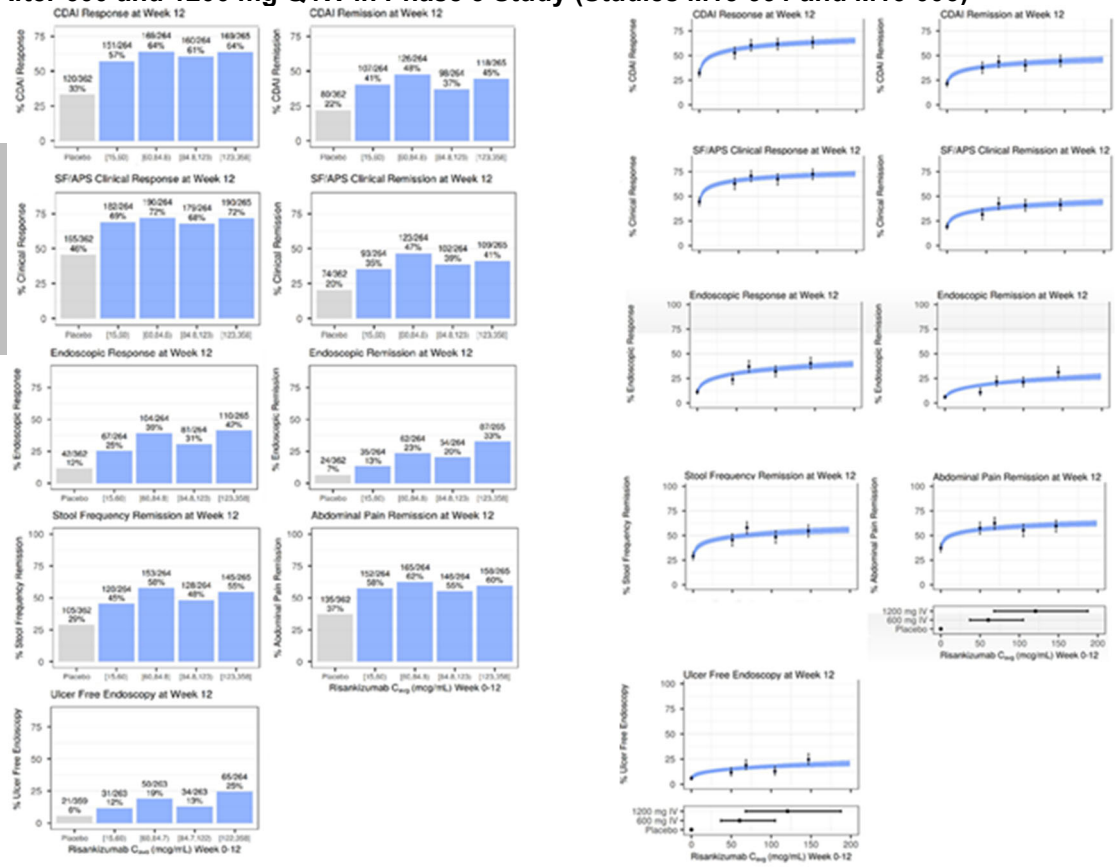

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Source: Figures 5 and 6 of applicant's exposure-response report.
Note: Predicted median and 90% CI C_{avg} of Week 0-12 are 17.4 (6.53 to 29.3), 60.5 (37.0 to 104), and 121 (67.9 to 187) mg/L for IV 600, and 1200 mg Q4W, respectively.
Abbreviations: APS, abdominal pain score; C_{avg}, average plasma concentration; CDAI, Crohn's disease activity index; Q4W, every 4 weeks; SF, stool frequency

Phase 3 Maintenance Treatment

Graphical analyses at Week 52 showed trends of higher response in the higher range of exposure 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. Model predictions from the developed logistic regression models at Week 52 indicated that the response rates for the endoscopic endpoints are about 3 to 7% higher with the 360 mg SC Q8W maintenance regimen (Figure 19).

Figure 19. Relationship Between Risankizumab Predicted $C_{avg,Week40-48}$ and Responses at Week 52 in Maintenance Period (Study M16-000)

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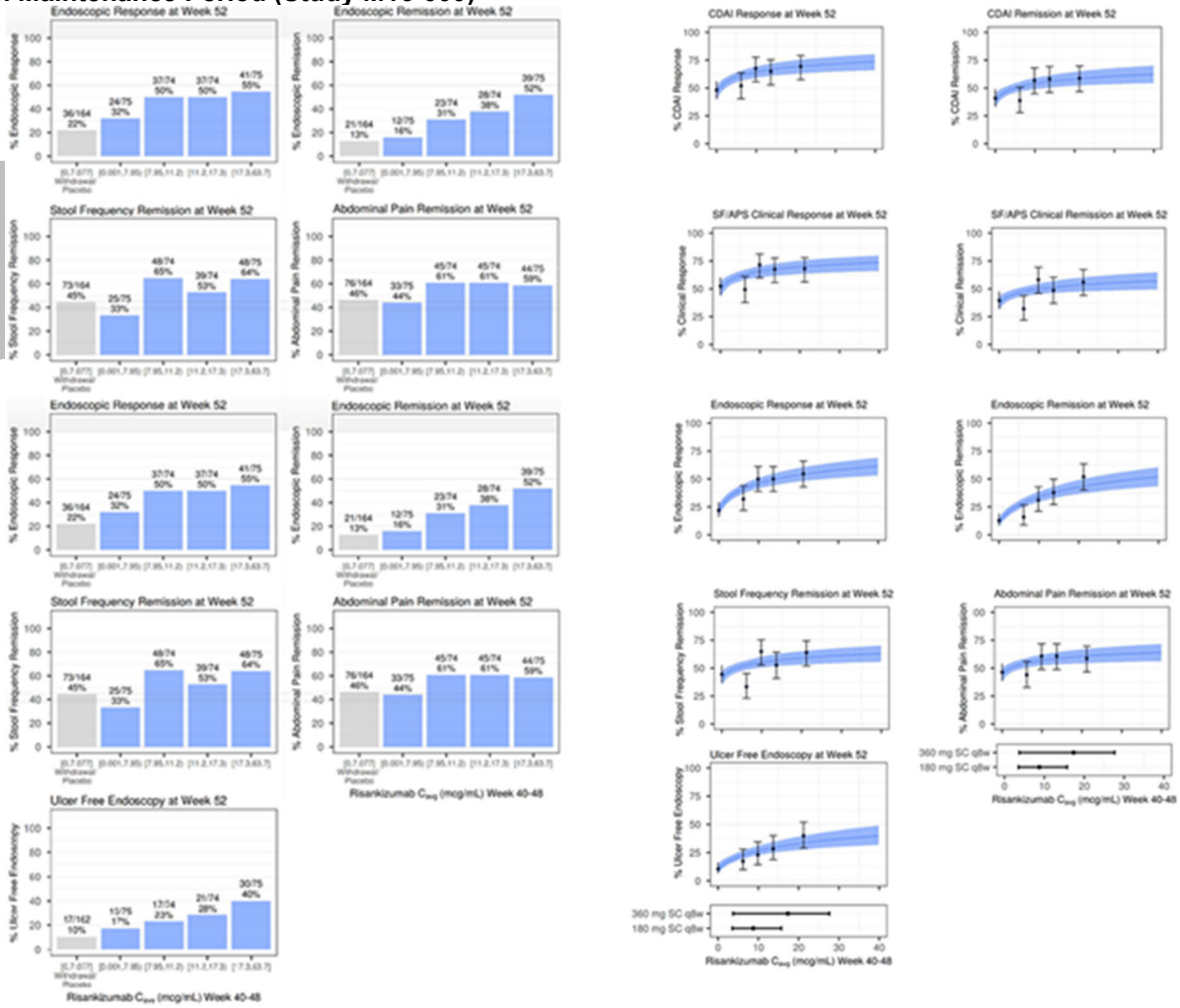

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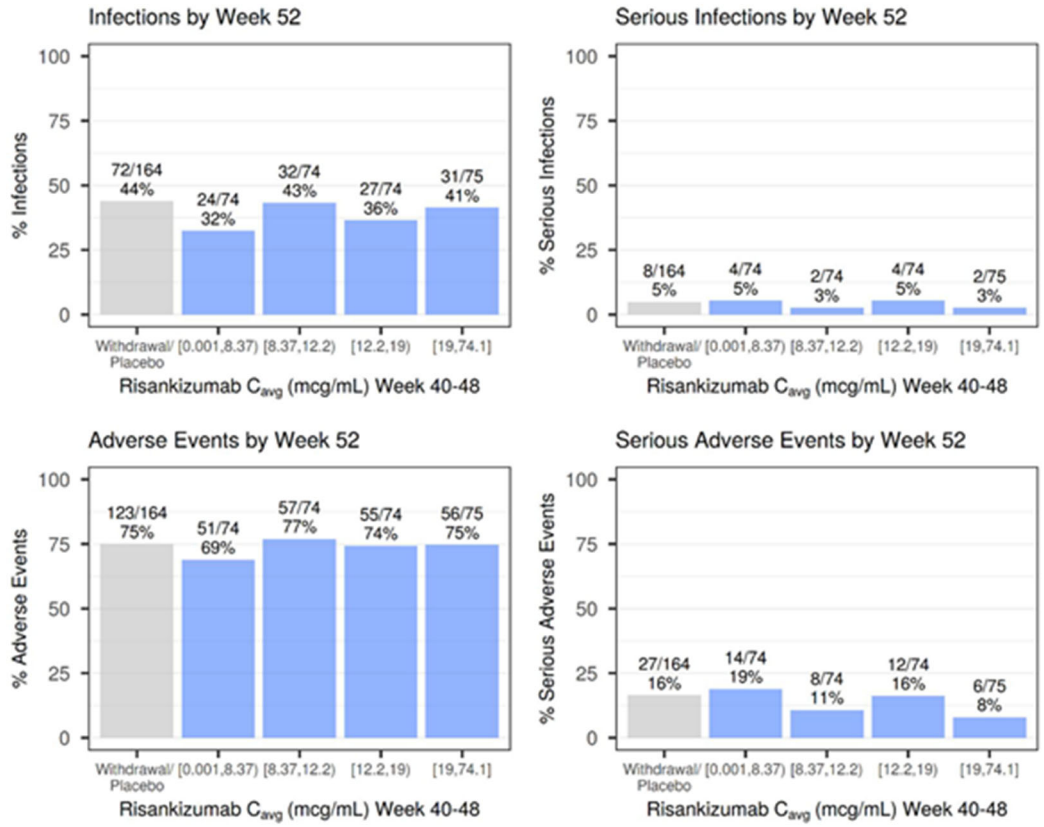
Source: Figures 10 and 11 of Applicant's exposure-response report.
Note: Predicted median and 90% CI C_{avg} of Week 40-48 are 9.62 (3.96 to 29.6) and 17.3 (0.691 to 30.0) mg/L for SC 180 mg and 360 mg Q8W, respectively.
Abbreviations: APS, abdominal pain score; C_{avg}, average plasma concentration; CDAI, Crohn's disease activity index; SF, stool frequency

Exposure-Response Analyses for Safety

Analyses of the key safety variables of interest indicated no apparent relationship between risankizumab exposure and any AE, SAE, infection, or serious infection over the 12 or 24 weeks of induction, or over 52 weeks of maintenance treatment. The relationships between model-predicted risankizumab $C_{avg,Week40-48}$, and percentage of subjects who experienced any AE, SAE, infection, or serious infection over 52 weeks of maintenance treatment are presented in Figure 20.

Figure 20. Exposure-Response Relationships Between Risankizumab C_{avg} and Safety Events of Interest in Maintenance Period (Study M16-000)

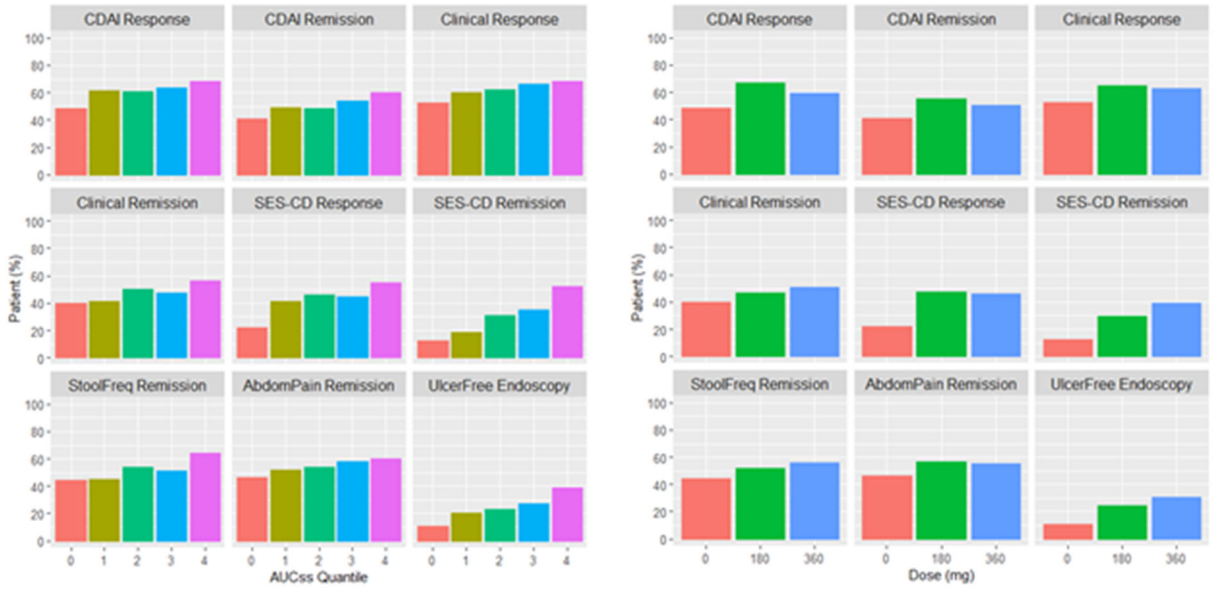


Source: Figure 12 of Applicant's exposure-response report.
Note: Predicted median and 90% CI C_{avg} of Week 40-48 are 9.62 (3.96 to 29.6) and 17.3 (0.691 to 30.0) mg/L for SC 180 and 360 mg Q8W, respectively.

The Applicant's E-R analyses results are generally consistent with observed dose-response (D-R) relationships for induction as well as maintenance of remission in clinical trials. To evaluate the appropriateness of the proposed maintenance dosage of 360 mg Q8W versus 180 mg Q8W, the reviewer conducted further analysis to explore the E-R relationships for efficacy at Week 52 in Study M16-000 using the estimated steady state AUC (AUC_{ss}) as exposure metrics.

The results are shown in the left panel of Figure 21. There was no significant trend of E-R for the evaluated efficacy endpoints at Week 52, except for Simple Endoscopic Score for Crohn's Disease (SES-CD) remission and ulcer free endoscopy, where higher response rates were observed at higher exposure levels. These trends were also consistent with the observed D-R relationships as shown in the right panel of Figure 21.

Figure 21. Exposure-Response (Left) and Dose-Response (Right) Relationships for Efficacy Endpoints at Week 52 (Study M16-000)



Source: Reviewer's analysis.
Note: AUC_{ss} was calculated from risankizumab maintenance dose divided by clearance. The Quartile of 0 represents placebo; The boundaries of Quartiles of 1-4 are 217, 663, 867, 1349, and 4372 mg*d/L respectively.
Abbreviations: AUC_{SS}, area under the curve at steady state; CDAI, Crohn's disease activity index; SES-CD, Simple Endoscopic Score for Crohn's Disease

15. Trial Design: Additional Information and Assessment

15.1. Schedule of Assessments

Figure 22. Induction Studies (M16-006 and M15-991): Study Activities for Efficacy, Safety, and PK/PD

	Screening Period (35 Days)[a]	12-Week Double-Blind Induction				Induction Period 2			Unsch[b]	140-Day Follow-Up[c]
Activity	Screening	Baseline	Week 4	Week 8	Week 12/PD	Week 16	Week 20	Week 24		
Informed consent	X									
Inclusion/Exclusion	X	X[d]								
Medical/Surgery History	X	X[d]								
Previous and Concomitant Medication	X	X[d]	X	X	X	X	X	X	X	
Physical Exam[e]/Vital Signs[f]	X	X	X	X	X	X	X	X	X	
Adverse Event Assessment[g]	X	X	X	X	X	X	X	X	X	X
TB Screening[h]	X[y]									
ECG[i]	X[y]									
Hepatitis B, Hepatitis C Screening[j], and HIV Test[l]	X[y]				X[k]			X[k]		
C. difficile toxin	X[x]									
Urinalysis[m,n]	X[x]	X[o]			X			X		
Pregnancy Test[p]	X[x]	X	X	X	X	X	X	X		
Chemistry and Hematology[n]	X[x]	X[o]	X	X	X	X	X	X		
Optional Blood Sample for Biologic Drug Level	X									
COVID-19 Assessment[z]	X									
hs-CRP[n]		X	X	X	X			X		
Serum Risankizumab[q]			X	X	X			X	X	

	Screening Period (35 Days)[a]	12-Week Double-Blind Induction				Induction Period 2			Unsch[b]	140-Day Follow-Up[c]
Activity	Screening	Baseline	Week 4	Week 8	Week 12/PD	Week 16	Week 20	Week 24		
Serum Anti-Drug Antibody (ADA)[q,w] and Neutralizing Anti-Drug Antibodies (nAb)[q]		X	X	X	X			X	X	
Fecal calprotectin (FCP)[n, r]		X	X		X			X		
Crohn's Disease Activity Index (CDAI)		X[t]	X	X	X	X	X	X	X	
Endoscopy/SES-CD[u]	X				X			X		
Intestinal Biopsies[v]	X				X			X		
Dispense Subject Diary[s]	X									
Subject Diary Review		X	X	X	X	X	X	X	X	
Subject Questionnaire: CSS		X	X	X	X	X	X	X	X	
Subject Questionnaire: PGIC and PGIS		X (PGIS only)	X	X	X	X	X	X	X	
Subject Questionnaires: EQ-5D-5L FACIT-F IBDQ SF-36 WPAI-CD		X	X		X			X		
Study Drug Administration[w]		X	X	X	X[w]	X	X			

a. The Screening period should be a minimum of 4 days, preferably 7 days for CDAI calculation, (refer to Section 5.3.1.1). The Baseline CDAI will be calculated using the data collected during the Screening period. Baseline visit date will serve as the reference for all subsequent visits. A ± 7 day window is permitted around all study visits.

b. Visits to retest a lab will not be considered an Unscheduled visit. Unscheduled visits according to this table are for purposes when the subject is coming in a visit for evaluation and assessment.

c. Subjects will be contacted 140 days following last dose of study drug for an assessment of any new or ongoing AEs, except those subjects who roll-over into Study M16-000 after the end of study participation.

d. Update inclusion/exclusion, prior and concomitant therapy, and medical/surgical history information to assure subject eligibility.

e. Physical examinations are full physical examinations at Screening and Week 12 and Week 24 if the subject receives treatment in Induction Period 2. Physical examinations at all other visits (including unscheduled visits) are symptom based and should include the assessment of EIMs and a count of the number of cutaneous fistulas as part of calculating the CDAI.

f. Blood pressure, pulse rate, temperature, respiratory rate and weight should be performed before blood draws are performed. Height will be measured at Screening only (with shoes off and then adding 1 inch or 2.5 cm) for subjects ≥ 18 years of age. Height will be re-measured at Week 12 and Week 24 (if applicable) for subjects < 18 years of age at Baseline.

g. Collection of SAEs and protocol-related nonserious AEs begins the day the subject signs the informed consent.

h. Subjects with negative QuantiFERON-TB Gold test and/or PPD test within 90 days of Screening will not require a repeat test (documentation must be available). PPD skin test is to be read 48 to 72 hours after placement. In case of positive PPD/positive or repeat indeterminate IGRA testing, subjects may participate in the study if further work up (according to local practice/guidelines) is negative for active TB.

i. For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided source documentation is available. Subjects can have a repeat ECG at any time during the study as warranted based on the opinion of the Investigator.

j. Subjects will be tested for the presence of the HBV and HCV at Screening. A positive result for the hepatitis B surface antigen (HBs Ag) or hepatitis C (HCV RNA detectable in any subject with anti-HCV Ab) will be exclusionary. For subjects who are negative for HBs Ag but are positive for core antibodies (HBc Ab), HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary.

k. For Japan only: for subjects with HBs Ab (+) and/or HBc Ab (+) at Screening, the HBV-DNA PCR test should be performed again at Week 12 and Week 24. Retesting at Week 12 and Week 24 is not necessary with subjects that have a history of HBV vaccine and are HBs Ab (+).

l. HIV testing will be performed at the central laboratory, which will report the results directly to the sites. AbbVie will not receive results from the testing.

m. Dipstick urinalysis will be completed by the sites at required visits. A microscopic analysis will be performed by the central laboratory, in the event the dipstick results show leukocytes, nitrite, protein, ketones or blood greater than negative or glucose greater than normal.

n. Urinalysis, chemistry and hematology, hs-CRP, and FCP may be collected at other scheduled and unscheduled visits than indicated in the table if they are warranted by the Investigator.

o. Lab assessments will only need to be repeated at Baseline if the time between Screening and Baseline is greater than 14 days, or if the subject's health status has changed to warrant a repeat test.

p. Serum pregnancy test will be performed on all WOCBP at Screening. Urine pregnancy test will be performed locally as indicated in the table for all WOCBP. The urine pregnancy test must be negative to receive study drug. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. FSH will be performed in all female subjects < 55 years old with no menses for 12 months.

q. Serum risankizumab concentrations and ADA will be determined from samples collected just prior to dosing at every visit. The date and time of sample collection will be captured on the eCRF. If the subject consented to the optional intensive PK sampling, refer to Appendix H.

r. Stool sample will be collected at each time point indicated in the table. For the visit when endoscopy will be conducted, stool sample should be collected prior to bowel prep and should be returned to the site per the instructions provided outside of this protocol. If a sample cannot be obtained during the site visit, the site will give instructions and a stool sample supply kit.

s. Subjects should also be dispensed the patient information card.

t. Diary information collected during Screening will serve to calculate Baseline CDAI. During screening, subjects will be instructed on how to calculate the number of very soft and liquid stools, including a visual depiction. CDAI should be completed at the Baseline visit, just prior to randomization.

u. Endoscopy at/during the screening period or within 45 days of the Baseline visit will be used to calculate the SES-CD score at Baseline. Endoscopic evaluations using SES CD confirmed by central reader will be done at Screening. Endoscopies completed at Week 12 and Week 24, for those subjects who receive treatment in Induction Period 2, will use the local reader results for stratification for Study M16-000.

v. Biopsies may be done when performing the endoscopy to confirm CD diagnosis (if appropriate documentation for confirmation of the diagnosis does not exist), and/or to rule out dysplasia and colon cancer at the Investigator's discretion. These samples will be processed and assessed locally. Histology report should be available in the subject's source records.

w. Administration of drug will be performed after all assessments and examinations scheduled for that day have been completed, including endoscopy. Completion of PROs are permitted during administration of study drug. At Week 12, study drug will only be administered for subjects who are to receive treatment in Induction Period 2. Subjects will also be dispensed a patient information card. In the event of a suspected systemic post-dose hypersensitivity reaction, serum risankizumab, ADA, and nAb should be collected once within 24 hours of the reaction. In addition, tryptase sample should be obtained between 15 minutes to 3 hours of symptom onset, and no later than 6 hours, and another sample is requested a minimum of 2 weeks after the recorded event or at the next study visit. Also, plasma histamine sample should be obtained within 5 to 15 minutes of the onset of symptoms and no later than 1 hour.

x. For Rescreening, if a subject is being rescreened within 14 days (≤ 14 days have passed) from the collection date of the previous screening testing, it is not required to repeat Screening testing for chemistry/hematology, urinalysis, serum pregnancy, and C. *difficile* provided that the subject's health status has not changed to warrant a repeat test.

y. For Rescreening, if the subject had a complete initial screening evaluation including the TB test, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and electrocardiogram (ECG), these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met and no more than 90 days have passed since the collection date of the testing.

z. Assessment for signs/symptoms of COVID-19 infection. If the investigator suspects the possibility of COVID-19 based on the signs, symptoms and medical complaint (chief complaint, history of exposure, etc.), local laboratory testing must be completed to confirm negative for infection.

Source: Pages 120 – 133; Protocol M16-006, Amendment 6.01; included in marketing application submitted September 16, 2021 under BLA 761105 (SDN: 875)

Figure 23. Maintenance Study (M16-000 Substudy 1): Study Activities

Activity	52-Week Maintenance SS1 and SS2								Unscheduled Visit[b,c]	Rescue Visit	140 Days Follow-Up[d]
	Week 0	Week 8	Week 16	Week 24	Week 32	Week 40	Week 48	Week 52/ PD			
Informed Consent	X										
Inclusion/Exclusion	X[e]										
Medical/Surgery History	x[a]										
Previous and Concomitant Medication	x[a]	X	X	X	X	X	X	X	X	X	
Physical Exam[f]/Vital Signs[g]	x[a]	X	X	X	X	X	X	X	X	X	
Adverse Event Assessment	x[a]	X	X	X	X	X	X	X	X	X	X
Hepatitis B Screening[t]	x[a]			X			X				
Annual TB Testing[h]		X									
ECG[i]		X						X			
Urinalysis[i,j]	x[a]							X			
Pregnancy Tests[i,k]	x[a]	X	X	X	X	X	X	X		X	
Chemistry and Hematology[i]	x[a]			X				X	X	X	
hs-CRP[c,i]	x[a]			X				X	X[c]		
Serum risankizumab[l]	x[a]	X[m]	X	X[m]	X	X[m]	X	X	X	X	
Serum anti-drug antibodies (ADA)[l,s] and neutralizing antibodies (nAb)[l]	X	X[m]	X	X[m]	X	X[m]	X	X	X	X	
Fecal calprotectin (FCP)[c,i,n]	x[a]							X	X[c]		

Activity	52-Week Maintenance SS1 and SS2								Unscheduled Visit[b,c]	Rescue Visit	140 Days Follow-Up[d]
	Week 0	Week 8	Week 16	Week 24	Week 32	Week 40	Week 48	Week 52/ PD			
Crohn's Disease Activity Index (CDAI)[o]	x[a]			X				X	X	X	
Endoscopy/SES-CD[p]	x[a]							X	X		
Intestinal Biopsies[q]	x[a]							X	X		
Subject Diary Review[r]	x[a]	X	X	X	X	X	X	X	X	X	
Subject questionnaire: CSS	x[a]							X	X	X	
Subject questionnaire: PGIC and PGIS	x[a]	X	X	X	X	X	X	X	X	X	
Subject Questionnaires: EQ-5D-5L FACIT-F IBDQ SF-36 WPAI-CD	x[a]							X			
Study Drug Administration[s]	X	X	X	X	X	X	X			X	

a. The final visit of Study M16-006 or Study M15-991 (Week 12 or Week 24) will be considered as the Week 0 visit for Study M16-000. Information from the activities completed at the final visit of Study M16-006 or Study M15-991 will be carried over to the Week 0 visit and will serve as the reference for all subsequent visits. A ± 7-day window is permitted around all study visits.

b. Visits to retest a lab will not be considered an Unscheduled Visit. Unscheduled Visits according to this table are for purposes when the subject is coming in for a visit for evaluation and assessment.

c. hs-CRP and FCP may be collected at unscheduled visits if they are needed for risankizumab rescue therapy.

d. Subjects will be contacted 140 days following study drug discontinuation for an assessment of any new or ongoing AEs, except subjects who enter SS 3.

e. Inclusion/exclusion, prior and concomitant therapy, and medical/surgical history information will be assessed to assure subject eligibility.

f. A full physical examination will be performed at Week 0 and Week 52/Premature Discontinuation Visit. Physical examinations at all other visits may be symptom based and include an assessment of extra-intestinal manifestations (EIMs), including the number of cutaneous fistulas.

g. Blood pressure, pulse rate, temperature, respiratory rate and weight should be performed before blood draws are performed. For subjects ≥ 18 years of age, height will be measured at the Screening Visit of Study M16-006 or Study M15-991 only (with shoes off). For subjects < 18 years of age, where locally permitted, height will be measured at the Screening Visit of Study M16-006 or Study M15-991 (with shoes off), as well as at Study M16-000 Weeks 0 and 52/PD (with shoes off) of SS 1.

h. All subjects will be tested for TB at Week 8. Subjects with a negative QuantiFERON-TB Gold (and/or PPD) test at Screening of the preceding Study M16-006, or Study M15-991, or another AbbVie risankizumab Crohn's disease study will be tested annually for TB by either the QuantiFERON-TB Gold Test (or equivalent) or a TB Skin Test Purified Protein Derivative (PPD). If PPD and/or the QuantiFERON-TB Gold test (or Interferon gamma release assay [IGRA] equivalent) is positive, or if there is a repeat indeterminate (note: the first indeterminate results must be repeated) QuantiFERON-TB Gold test (or IGRA equivalent) upon retesting, patients may continue their participation in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. Refer to Section 5.3.1.1 for further details.

i. ECG, urinalysis, pregnancy test, chemistry and hematology, hs-CRP, and FCP may be collected at other scheduled and unscheduled visits than indicated in the table if they are warranted by the Investigator.

j. Dipstick urinalysis will be completed by the sites at the scheduled visits. A microscopic analysis will be performed by the central laboratory, in the event the dipstick results shows abnormal results.

k. Urine pregnancy test will be performed at all visits where a dose is being received for all WOCBP. Urine pregnancy test will be performed locally as indicated in the table for all WOCBP. The urine pregnancy test must be negative prior to receiving study drug. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. Refer to Section 5.3.1.1 for further details.

l. Serum risankizumab concentrations, ADA, and nAB will be determined from samples collected just prior to dosing at visit. The date and time of sample collection will be captured. Serum for subjects in the TDM arm of SS 2, all risankizumab samples should be shipped the same day they are collected to ensure adequate processing time to determine serum concentration levels needed for dosing adjustments.

m. Subjects in SS 2 only will have additional serum risankizumab concentrations, ADA and nAB collected at Week 8, 24, 40. Serum for subjects in the TDM arm of SS 2, all risankizumab samples should be shipped the same day they are collected to ensure adequate processing time to determine serum concentration levels needed for dosing adjustments.

n. Stool sample will be collected at each time point indicated in the table. For the visit when endoscopy will be conducted, stool sample should be collected prior to bowel prep and should be returned to the site per instructions provided outside of this protocol. If a sample cannot be obtained during the site visit, the site will give instructions and a stool sample supply kit.

o. At Week 0 subjects will be instructed on how to calculate the number of very soft and liquid stools, including a visual depiction.

p. An endoscopy may be performed at unscheduled visits to confirm inadequate response if hs-CRP and FCP are not elevated. Endoscopies used to confirm IR criteria will use the local read at the time of visit to receive risankizumab rescue therapy (if subject meets criteria).

q. Biopsy may be done when performing the endoscopy. Biopsies to rule out dysplasia and colon cancer may be taken at the Investigator's discretion. These samples will be processed and assessed locally. Histology report should be available in the subject's source records.

r. Subjects will be dispensed a patient information card at Week 0. Stool frequency and abdominal pain will be captured at every visit and will be recorded on the appropriate eCRF.

s. Administration of drug will be performed after all assessments and examinations scheduled for that day have been completed. Completion of PROs are permitted during administration of study drug. In the event of an anaphylactic reaction, or other suspected systemic hypersensitivity reaction, blood samples will be drawn 1 hour, 3 hours and 24 hours after the onset of the reaction for assessment, which may include but is not limited to histamine and tryptase. A blood sample for ADA assessment will also be collected along with 1 hour blood samples for above assessments.

t. For Japan only: For subjects who are positive for hepatitis B surface antibody (HBs Ab) and/or are positive for hepatitis B core antibody (HBc Ab) at screening in the induction studies, HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary.

Source: Pages 138 – 141; Protocol M16-000, Amendment 7.01.01.01.01; included in marketing application submitted September 16, 2021 under BLA 761105 (SDN: 875)

15.1.1. Crohn's Disease Activity Index

Figure 24. Crohn's Disease Activity Index (CDAI)

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	__+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	×	2	
2. Abdominal pain rating: 0 = none, 1 = mild, 2 = moderate, 3 = severe	__+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	×	5	
3. General well-being: 0 = generally well, 1 = slightly underpar, 2 = poor, 3 = very poor, 4 = terrible	__+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	×	7	
4. Number of 6 listed categories the subject now has **Check all items that apply:** ☐ Arthritis/arthralgia ☐ Iritis/uveitis ☐ Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis ☐ Fissure, abscess and/or anal fistula (draining/non-draining) ☐ Other cutaneous fistula (draining/non-draining) Fistula ☐ Fever over 100°F (37.8°C) during past week	_____ _____ Record "0" if no categories checked	×	20	
5. Taking Lomotil/Imodium/ Loperamide/opiates for diarrhea 0 = no, 1 = yes	_____	×	30	
6. Abdominal mass 0 = none, 2 = questionable, 5 = defined	_____	×	10	
7. Hematocrit: ___.__	Male: (47 – hematocrit) = Female: (42 – hematocrit) = Subtotal If hematocrit > normal, enter "0"	×	6	
8. Body weight: ___.__(kg) Standard weight: ___.__(kg)	100 × [1 – (Body wt/Standard wt)] = Percent below standard weight: _____ If body wt > std. wt, enter "0"	×	1	
			Total	

Source: Page 136; Protocol M16-006, Amendment 6.01; included in marketing application submitted September 16, 2021 under BLA 761105 (SDN: 875)

15.1.2. Simple Endoscopic Score for Crohn's Disease

Figure 25. Simple Endoscopic Score for Crohn's Disease (SES-CD)

	Rectum	Sigmoid and Left Colon	Transverse Colon	Right Colon	Ileum	Total
Size of Ulcers Enter: 0 if none 1 if aphthous ulcers (Ø 0.1 to 0.5 cm) 2 if large ulcers (Ø 0.5 to 2 cm) 3 if very large ulcers (Ø > 2 cm)						
Ulcerated Surface Enter: 0 if none 1 if < 10% 2 if 10% – 30% 3 if > 30%						
Affected Surface Enter: 0 if unaffected segments 1 if < 50% 2 if 50% – 75% 3 if > 75%						
Presence of Narrowing Enter: 0 if none 1 if single, can be passed 2 if multiple, can be passed 3 if cannot be passed						
					TOTAL =	

Source: Page 135; Protocol M16-006, Amendment 6.01; included in marketing application submitted September 16, 2021 under BLA 761105 (SDN: 875)

16. Efficacy: Additional Information and Assessment

16.1. Multiple Testing Procedure for Induction and Maintenance Trials

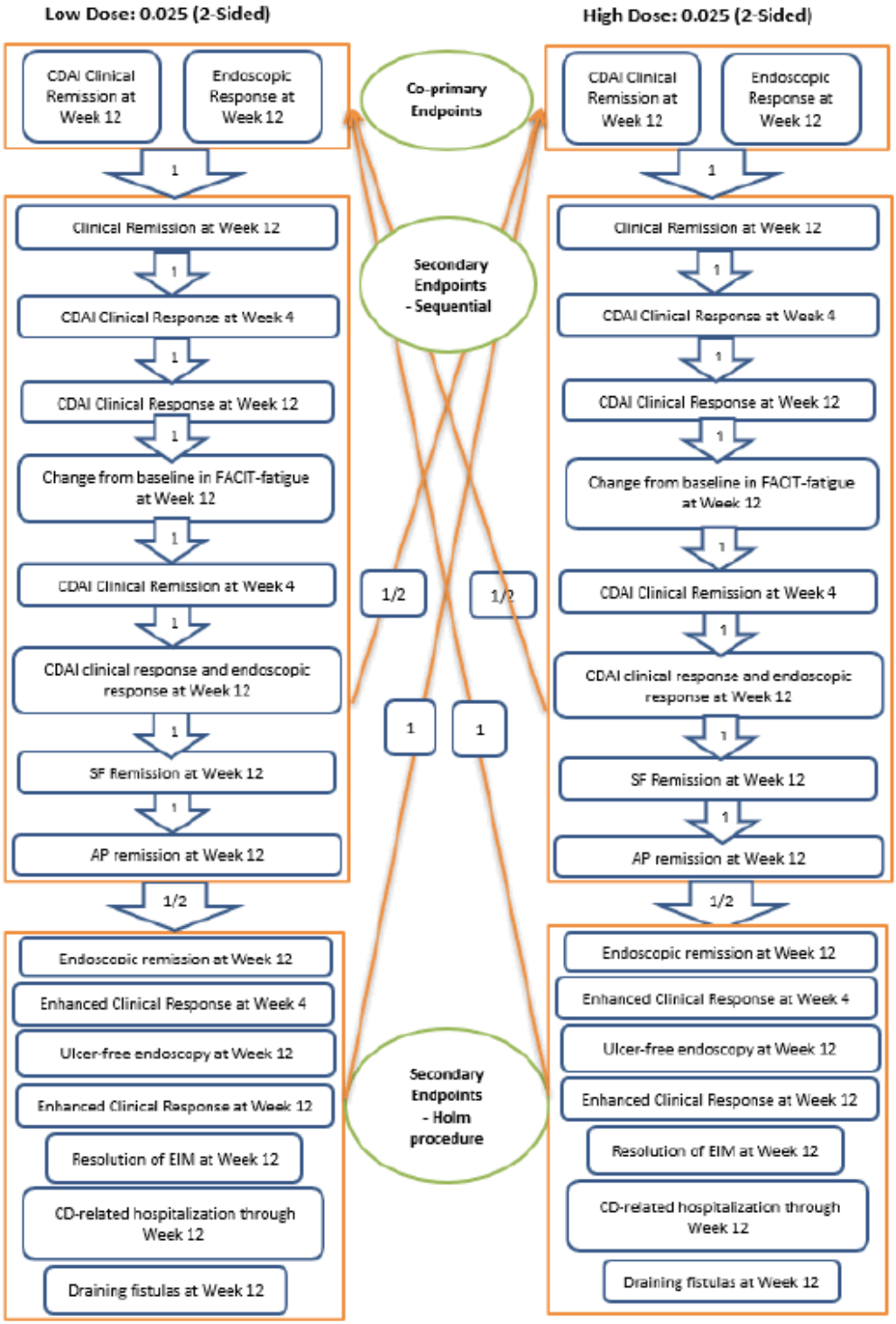
A multiple testing procedure was used to provide strong control of the type 1 error rate at an overall alpha of 0.05 (2-sided) across analyses comparing each risankizumab dose level to placebo with respect to the coprimary endpoints and ranked secondary endpoints. Specifically, a

graphical testing procedure was used to test coprimary endpoints and ranked secondary endpoints.

For the induction studies, the alpha was initially split across the two doses with each of the coprimary endpoints tested at an alpha of 0.025 (2-sided) compared to placebo within each dose. If both coprimary endpoints achieved statistical significance within a dose level, continued testing followed a prespecified weight of alpha allocation between the single hypothesis within the family, as well as between the families of hypotheses across the doses. Secondary endpoints were grouped into two families. Endpoints within the first family were tested sequentially and endpoints within the second family were tested using the Holm procedure.

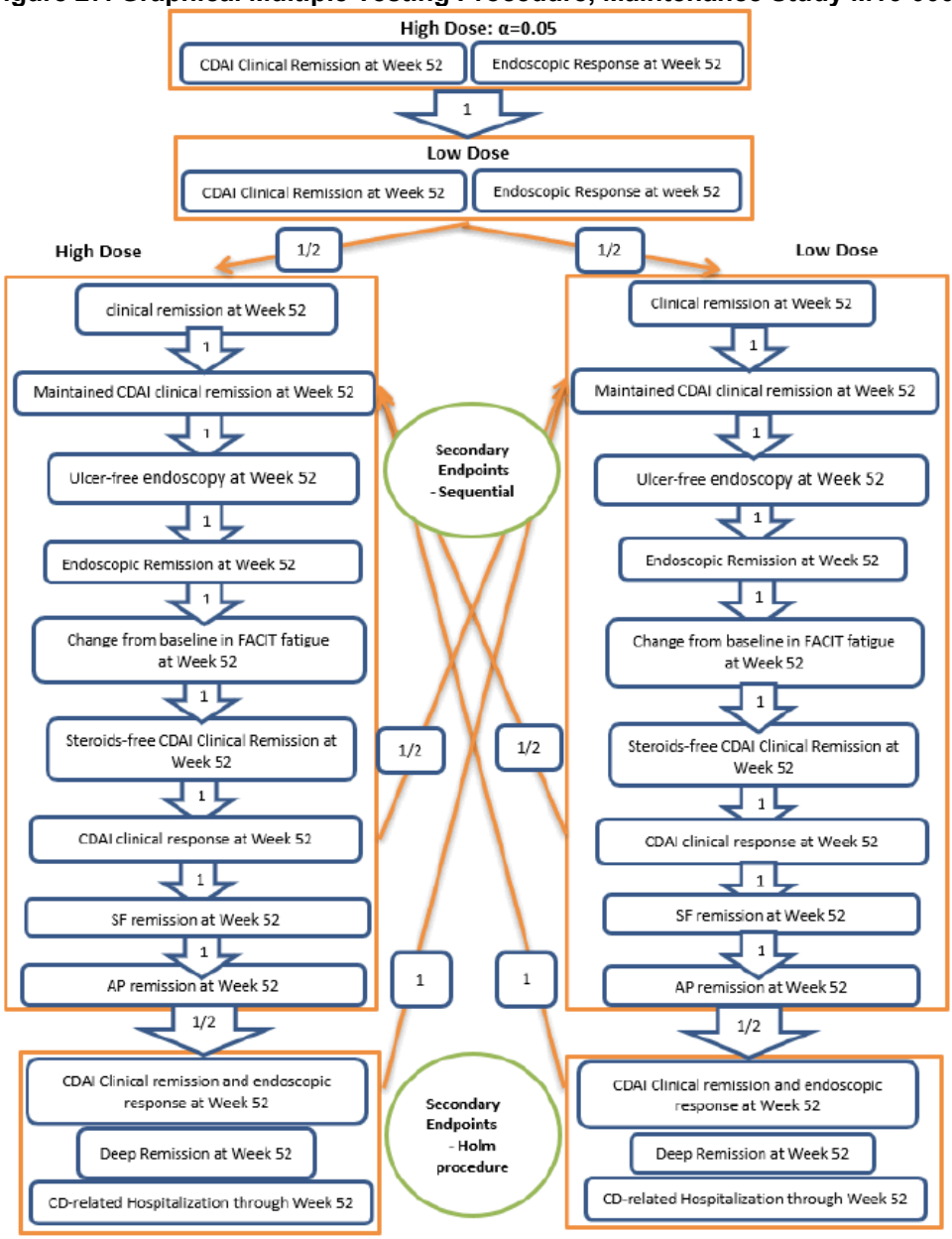
For the maintenance study, each of the coprimary efficacy endpoints was first tested at two-sided significance level of 0.05 for risankizumab 360 mg SC dose versus placebo, followed by testing each of the coprimary endpoints at two-sided significance level of 0.05 for risankizumab 180 mg SC dose versus placebo. If both coprimary endpoints achieved statistical significance for both dose levels, continued testing followed a prespecified weight of alpha allocation between the single hypothesis within the family, as well as between the families of hypotheses across the doses. Secondary endpoints were grouped into two families. Endpoints within the first family were tested sequentially and endpoints within the second family were tested using the Holm procedure.

Figure 26. Graphical Multiple Testing Procedure for Induction, Studies M16-006 and M15-991



Source: Figures 2, Statistical Analysis Plan for Studies M16-006 and M15-991, Pages 53 and 54 respectively
Abbreviations: AP, abdominal pain; CD, Crohn's disease; CDAI, Crohn's disease activity index; EIM, extra-intestinal manifestation; FACIT, Functional Assessment of Chronic Illness Therapy; SF, stool frequency

Figure 27. Graphical Multiple Testing Procedure, Maintenance Study M16-000



Source: Figure 3, Statistical Analysis Plan for Study M16-000, Page 56
Abbreviations: AP, abdominal pain; CD, Crohn's disease; CDAI, Crohn's disease activity index; FACIT, Functional Assessment of Chronic Illness Therapy; SF, stool frequency

16.2. Maintenance Study Results: Protocol-Specified Analysis Population Versus FDA Preferred Analysis Population

Background

The Applicant used clinical response based on stool frequency and abdominal pain score (SF/APS clinical response) as an inclusion criterion for enrollment into Study M16-000 (the maintenance study). Their initial analyses were based on this protocol-specified analysis population. On October 28, 2021, the Agency sent an information request to the Applicant, asking the Applicant to provide new analyses based on a subset of the study population who met the definition of CDAI clinical response (defined as reduction of CDAI ≥100 points from baseline) at the end of induction period. The maintenance population size decreased as a result. The primary efficacy analysis was based on this new U.S. Food and Drug Administration (FDA)-preferred analysis population (see Section 6.2.2.3). The following tables show the protocol-specified (clinical responders defined by SF/APS) and FDA-preferred (clinical responders defined by CDAI score reduction) analyses results for the coprimary endpoints of CDAI clinical remission and endoscopic response in Study M16-000.

Coprimary Endpoints: Protocol-Specified versus FDA-Preferred Analysis

Overall, the clinical remission rates increased for all 3 arms (placebo, 180 mg, and 360 mg) using the FDA-preferred analysis population. The adjusted difference in rate for 180 mg versus placebo increased, while the adjusted difference in rate for 360 mg versus placebo decreased slightly. However, the efficacy conclusions for CDAI clinical remission did not change between the protocol-specified and FDA-preferred analyses. The endoscopic response rates decreased slightly among placebo subjects and increased among treated subjects, leading to an increase in the adjusted differences in rates for 360 mg versus placebo and 180 mg versus placebo.

Table 77. CDAI Clinical Remission, Study M16-000

	SF/APS Clinical Responders at the End of the Induction Period			CDAI Clinical Responders at the End of the Induction Period		
Treatment	Sample Size	Remission Rate (%) (95% CI)	Difference in Rate vs. Placebo (95% CI) p-Values	Sample Size	Remission Rate (%) 95% CI	Difference in Rate vs. Placebo (95% CI) p-Values
Placebo	164	40.9 (33.3, 48.4)	NA	130	46.2 (37.6, 54.7)	NA
180 mg	157	55.4 (47.6, 63.2)	14.7 (5.0, 24.5) (p=0.003)	135	61.5 (53.3, 69.7)	16.9 (5.9, 27.8) (p=0.003)
360 mg	141	52.2 (43.9, 60.5)	14.6 (4.3, 25.0) (p=0.005)	117	56.8 (47.7, 65.8)	14.2 (2.6, 25.7) (p=0.016)

Source: Table 8, Clinical Study Report, Study M16-000, and Table 14.2_2.1.1_R1, Appendix C, Applicant's Response to October 29, 2021, Information Request
Abbreviations: APS, abdominal pain score; CDAI, Crohn's disease activity index; CI, confidence interval; NA, not applicable; SF, stool frequency

Table 78. Endoscopic Response, Study M16-000

	SF/APS Clinical Responders at the End of the Induction Period			CDAI Clinical Responders at the End of the Induction Period		
Treatment	Sample Size	Response Rate (%) (95% CI)	Difference in Rate vs. Placebo (95% CI) p-Values	Sample Size	Response Rate (%) (95% CI)	Difference in Rate vs. Placebo (95% CI) p-Values
Placebo	164	22.0 (15.6, 28.3)	NA	130	21.5 (14.5, 28.6)	NA
180 mg	157	47.1 (39.3, 54.9)	26.0 (17.2, 34.7) (p<0.001)	135	50.4 (41.9, 58.8)	29.9 (20.3, 39.5) (p<0.001)
360 mg	141	46.5 (38.3, 54.8)	27.8 (18.7, 37.0) (p<0.001)	117	48.5 (39.4, 57.6)	30.6 (20.6, 40.7) (p<0.001)

Source: Table 8, Clinical Study Report, Study M16-000, and Table 14.2_2.2.1_R1, Appendix C, Applicant's Response to October 29, 2021, Information Request
Abbreviations: APS, abdominal pain score; CDAI, Crohn's disease activity index; CI, confidence interval; NA, not applicable; SF, stool frequency

16.2.1. Sensitivity Analyses for Missing Data Due to COVID-19

Multiple imputation assuming missing at random was used to handle missing data due to coronavirus disease 2019 (COVID-19) in the primary analysis. While this approach was considered reasonable for the primary analysis, a sensitivity analysis using nonresponder imputation to handle all missing data, including missing data due to COVID-19, was performed to assess the impact of the assumption of missing at random. The response rate for the risankizumab 360 mg, which had the highest amount of missing data due to COVID-19, was affected the most by this sensitivity analysis. Results for the coprimary endpoints were still statistically significant, though borderline in the case of CDAI clinical remission for the risankizumab 360 mg (p =0.047). However, this analysis is likely conservative in this case. It should also be noted that the study was not designed to demonstrate significance for the subset of subjects who achieved CDAI clinical response at the end of the induction study. This analysis produced more favorable results when using the Applicant's protocol-specified primary analysis population with (p =0.017).

Table 79. Coprimary Endpoints, Sensitivity Analysis, Study M16-000 Baseline CDAI Clinical Responders

		CDAI Clinical Remission		Endoscopic Response	
Treatment	Sample Size	Remission Rate (%) (95% CI)	Difference in Rate vs. Placebo (95% CI) p-Values	Response Rate (%) (95% CI)	Difference in Rate vs. Placebo (95% CI) p-Values
Placebo	130	46.2 (37.6, 54.7)	NA	21.5 (14.5, 28.6)	NA
180 mg	135	61.5 (53.3, 69.7)	16.9 (5.9, 27.8) (p=0.003)	50.4 (41.9, 58.8)	29.9 (20.3, 39.5) (p<0.001)
360 mg	117	54.7 (45.7, 63.7)	11.8 (0.2, 23.3) (p=0.047)	47.9 (38.8, 56.9)	29.9 (19.7, 40.0) (p<0.001)

Source: Adapted from Appendix A, Applicant's Response to FDA Information Requested dated February 10, 2022
Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; NA, not applicable

16.3. Additional Efficacy Analyses/Assessment

16.3.1. Efficacy Analyses by Demographic Subgroups in M16-006 and M15-991

Subgroup analyses were conducted to assess the potential for differences in the treatment effect for various demographics. Overall, the treatment effect of risankizumab compared to placebo appeared consistent across demographic subgroups of age, gender, and race. Risankizumab showed better clinical remission and endoscopic response rates compared to placebo for all subgroups.

16.3.1.1. Sex

Table 80. CDAI Remission Rate at Week 12: Analysis of Subgroup: Sex

	Study M15-991			Study M16-006		
Parameter	Placebo	RZB 600 mg	RZB 1200 mg	Placebo	RZB 600 mg	RZB 1200 mg
Male						
N	99	92	102	88	189	183
CDAI remission, n (%)[1]	23 (23.2)	42 (45.8)	43 (42.2)	25 (28.4)	84 (44.4)	73 (39.9)
Treatment diff., % [CI]		22.6 [9.4, 35.7]	18.9 [6.2, 31.6]		16.0 [4.2, 27.8]	11.4 [-0.4, 23.2]
Female						
N	88	99	89	87	147	156
CDAI remission, n (%)[1]	14 (15.9)	38 (38.4)	34 (38.2)	18 (20.7)	68 (46.1)	68 (43.6)
Treatment diff., % [CI]		22.5 [10.2, 34.7]	22.3 [9.6, 35.0]		25.4 [13.7, 37.2]	22.9 [11.4, 34.4]

Source: Table 14.2_1.2.1.4, Clinical Study Report for M15-991, Page 759, and Table 14.2_1.2.1.4, Clinical Study Report for M16-006, Page 869

[1] Average number of subjects who achieved CDAI clinical remission based on multiple imputation model rounded to the nearest integer; % represents the estimated CDAI clinical remission rate based on multiple imputation model

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; diff, difference; n, number of patients in specified population or group; RZB, risankizumab

Table 81. Endoscopic Response Rate at Week 12: Analysis of Subgroup: Sex

	Study M15-991			Study M16-006		
Parameter	Placebo	RZB 600 mg	RZB 1200 mg	Placebo	RZB 600 mg	RZB 1200 mg
Male						
N	99	92	102	88	189	183
Endoscopic response, n (%)[1]	8 (8.1)	27 (29.4)	29 (28.7)	6 (6.9)	75 (39.6)	62 (34.1)
Treatment diff., % [CI]		21.3 [10.6, 32.1]	20.6 [10.3, 30.9]		16.0 [4.2, 27.8]	11.4 [-0.4, 23.2]
Female						
N	88	99	89	87	147	156
Endoscopic response, n (%)[1]	13 (14.8)	28 (28.3)	36 (40.4)	15 (17.2)	60 (41.1)	47 (29.8)
Treatment diff., % [CI]		13.5 [2.0, 25.1]	25.7 [13.1, 38.3]		23.9 [12.6, 35.2]	12.6 [1.9, 23.3]

Source: Table 14.2_1.2.3.3, Clinical Study Report for M15-991, Page 829, and Table 14.2_1.2.3.3, Clinical Study Report for M16-006, Page 947
[1] Average number of subjects who achieved endoscopic response based on multiple imputation model rounded to the nearest integer; % represents the estimated endoscopic response rate based on multiple imputation model
Abbreviations: CI, confidence interval; diff, difference; n, number of patients in specified population or group; RZB, risankizumab

16.3.1.2. Age

Table 82. CDAI Remission Rate at Week 12: Analysis of Subgroup: Age

	Study M15-991			Study M16-006		
Parameter	Placebo	RZB 600 mg	RZB 1200 mg	Placebo	RZB 600 mg	RZB 1200 mg
18≤age <40						
N	104	100	97	115	191	212
CDAI remission, n (%)[1]	18 (17.3)	41 (41.1)	38 (39.2)	30 (26.1)	98 (51.2)	95 (44.8)
Treatment diff., % [CI]		23.8 [11.7, 35.9]	21.9 [9.7, 34.0]		25.1 [14.4, 35.8]	18.7 [8.2, 29.2]
(40≤age <65)						
N	71	78	87	50	130	109
CDAI remission, n (%)[1]	16 (22.5)	33 (42.3)	36 (41.4)	12 (24.0)	49 (37.7)	37 (33.9)
Treatment diff., % [CI]		19.8 [5.1, 34.4]	18.8 [4.6, 33.0]		13.7 [-0.8, 28.2]	9.9 [-4.9, 24.7]

Source: Table 14.2_1.2.1.4, Clinical Study Report for M15-991, Page 758, and Table 14.2_1.2.1.4, Clinical Study Report for M16-006, Page 868
[1] Average number of subjects who achieved CDAI clinical remission based on multiple imputation model rounded to the nearest integer; % represents the estimated CDAI clinical remission rate based on multiple imputation model
Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; diff, difference; n, number of patients in specified population or group, N, number of patients in treatment arm; RZB, risankizumab

Table 83. Endoscopic Response Rate at Week 12: Analysis of Subgroup: Age

	Study M15-991			Study M16-006		
Parameter	Placebo	RZB 600 mg	RZB 1200 mg	Placebo	RZB 600 mg	RZB 1200 mg
18≤age <40						
N	104	100	97	115	191	212
Endoscopic response, n (%)[1]	12 (11.5)	32 (32.0)	35 (36.1)	12 (10.4)	77 (40.2)	70 (32.8)
Treatment diff., % [CI]		20.5 [9.5, 31.5]	24.5 [13.2, 35.9]		29.7 [20.8, 38.7]	22.4 [14.0, 30.9]
40≤age <65						
N	71	78	87	50	130	109
Endoscopic response, n (%)[1]	7 (9.9)	21 (27.0)	28 (32.5)	9 (18.1)	57 (43.5)	33 (30.5)
Treatment diff., % [CI]		17.1 [5.1, 29.2]	22.6 [10.5, 34.7]		25.4 [11.7, 39.1]	12.4 [-1.4, 26.2]

Source: Table 14.2_1.2.3.3, Clinical Study Report for M15-991, Page 828, and Table 14.2_1.2.3.3, Clinical Study Report for M16-006, Page 946
[1] Average number of subjects who achieved endoscopic response based on multiple imputation model rounded to the nearest integer; % represents the estimated endoscopic response rate based on multiple imputation model
Abbreviations: CI, confidence interval; diff, difference; n, number of patients in specified population or group, N, number of patients in treatment arm; RZB, risankizumab

16.3.1.3. Race

Table 84. CDAI Remission Rate at Week 12: Analysis of Subgroup: Race

	Study M15-991			Study M16-006		
Parameter	Placebo	RZB 600 mg	RZB 1200 mg	Placebo	RZB 600 mg	RZB 1200 mg
White						
N	162	176	168	134	258	247
CDAI remission, n (%)[1]	31 (19.1)	72 (41.0)	64 (38.1)	35 (26.1)	112 (43.3)	101 (40.9)
Treatment diff., % [CI]		21.8 [12.4, 31.3]	19.0 [9.4, 28.5]		17.2 [7.6, 26.8]	14.7 [5.1, 24.4]
Nonwhite						
N	25	15	23	41	78	92
CDAI remission, n (%)[1]	6 (24.0)	8 (53.3)	13 (56.5)	8 (19.5)	40 (51.3)	40 (43.5)
Treatment diff., % [CI]		29.3 [-1.0, 59.6]	32.5 [6.2, 58.8]		31.8 [15.3, 48.2]	24.0 [8.2, 39.8]

Source: Table 14.2_1.2.1.4, Clinical Study Report for M15-991, Page 760, and Table 14.2_1.2.1.4, Clinical Study Report for M16-006, Page 870
[1] Average number of subjects who achieved CDAI clinical remission based on multiple imputation model rounded to the nearest integer; % represents the estimated CDAI clinical remission rate based on multiple imputation model
Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; diff, difference; n, number of patients in specified population or group, N, number of patients in treatment arm; RZB, risankizumab

Table 85. Endoscopic Response Rate at Week 12: Analysis of Subgroup: Race

	Study M15-991			Study M16-006		
Parameter	Placebo	RZB 600 mg	RZB 1200 mg	Placebo	RZB 600 mg	RZB 1200 mg
White						
N	162	176	168	134	258	247
Endoscopic response, n (%)[1]	20 (12.3)	52 (29.6)	55 (32.9)	16 (12.0)	97 (37.7)	74 (29.9)
Treatment diff., % [CI]		17.3 [8.8, 25.7]	20.5 [11.8, 29.3]		25.7 [17.6, 33.9]	17.9 [10.0, 25.9]

	Study M15-991			Study M16-006		
Parameter	Placebo	RZB 600 mg	RZB 1200 mg	Placebo	RZB 600 mg	RZB 1200 mg
Nonwhite						
N	25	15	23	41	78	92
Endoscopic response, n (%)[1]	1 (4.0)	3 (20.0)	10 (43.5)	5 (12.2)	38 (48.7)	35 (38.0)
Treatment diff., % [CI]		16.0 [-5.7, 37.7]	39.5 [17.8, 61.1]		36.5 [21.6, 51.5]	25.8 [11.8, 39.9]

Source: Table 14.2_1.2.3.3, Clinical Study Report for M15-991, Page 830, and Table 14.2_1.2.3.3, Clinical Study Report for M16-006, Page 948
[1] Average number of subjects who achieved endoscopic response based on multiple imputation model rounded to the nearest integer; % represents the estimated endoscopic response rate based on multiple imputation model
Abbreviations: CI, confidence interval; diff, difference; n, number of patients in specified population or group, N, number of patients in treatment arm; RZB, risankizumab

16.3.2. Efficacy Analyses by Demographic Subgroups in M16-000

Further subgroup analyses were conducted to assess potential differences in treatment effect for sex, age, and race compared to matched-placebo controls. While efficacy rates for clinical remission and endoscopic response at Week 52 were higher in the risankizumab treatment arms compared to placebo, slight differences in efficacy were observed within each subgroup.

16.3.2.1. Sex

Table 86. CDAI Remission Rate at Week 52: Analysis of Subgroup: Sex

	Study M16-000		
Parameter	Placebo	RZB 180 mg	RZB 360 mg
Male			
N	72	62	67
CDAI remission, n (%)[1]	40 (55.6)	39 (62.9)	42 (62.4)
Treatment diff., % [CI]		7.3 [-9.3, 24.0]	6.9 [-9.4, 23.2]
Female			
N	58	73	50
CDAI remission, n (%)[1]	20 (34.5)	44 (60.3)	25 (49.5)
Treatment diff., % [CI]		25.8 [9.2, 42.4]	15.0 [-3.5, 33.5]

Source: Statistical reviewer generated table, created from admicdai.xpt
[1] Average number of subjects who achieved CDAI clinical remission based on multiple imputation model rounded to the nearest integer; % represents the estimated CDAI clinical remission rate based on multiple imputation model
Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; diff, difference; n, number of patients in specified population or group, N, number of patients in treatment arm; RZB, risankizumab

Table 87. Endoscopic Response Rate at Week 52: Analysis of Subgroup: Sex

	Study M16-000		
Parameter	**Placebo**	**RZB 180 mg**	**RZB 360 mg**
Male			
N	72	62	67
Endoscopic response, n (%)[1]	18 (25.0)	26 (41.9)	32 (47.2)
Treatment diff., % [CI]		16.9 [1.1, 32.8]	22.2 [6.6, 37.8]
Female			
N	58	73	50
Endoscopic response, n (%)	10 (17.2)	42 (57.5)	25 (50.0)
Treatment diff., % [CI]		40.3 [25.4, 55.2]	32.8 [15.8, 49.7]

Source: Statistical reviewer generated table, created from admiendo.xpt
[1] Average number of subjects who achieved endoscopic response based on multiple imputation model rounded to the nearest integer; % represents the estimated endoscopic response rate based on multiple imputation model
Abbreviations: CI, confidence interval; diff, difference; n, number of patients in specified population or group, N, number of patients in treatment arm; RZB, risankizumab

16.3.2.2. Age

Table 88. CDAI Remission Rate at Week 52: Analysis of Subgroup: Age

	Study M16-000		
Parameter	**Placebo**	**RZB 180 mg**	**RZB 360 mg**
18≤age <40			
N	73	75	74
CDAI remission, n (%)[1]	35 (47.9)	51 (68.0)	43 (57.5)
Treatment diff., % [CI]		20.1 [4.5, 35.6]	9.6 [-6.5, 25.6]
40≤age <65			
N	52	47	37
CDAI remission, n (%)	23 (44.2)	23 (48.9)	22 (59.5)
Treatment diff., % [CI]		4.7 [-15.0, 24.4]	15.2 [-5.6, 36.0]

Source: Statistical reviewer generated table, created from admicdai.xpt
[1] Average number of subjects who achieved CDAI clinical remission based on multiple imputation model rounded to the nearest integer; % represents the estimated CDAI clinical remission rate based on multiple imputation model
Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; diff, difference; n, number of patients in specified population or group, N, number of patients in treatment arm; RZB, risankizumab

Table 89. Endoscopic Response Rate at Week 52: Analysis of Subgroup: Age

	Study M16-000		
Parameter	**Placebo**	**RZB 180 mg**	**RZB 360 mg**
18≤age <40			
N	73	75	74
Endoscopic response, n (%)[1]	16 (21.9)	37 (49.3)	37 (49.5)
Treatment diff., % [CI]		27.4 [12.6, 42.2]	27.5 [12.7, 42.4]
40≤age <65			
N	52	47	37
Endoscopic response, n (%)	12 (23.1)	26 (55.3)	18 (48.6)
Treatment diff., % [CI]		32.2 [14.0, 50.5]	25.6 [5.8, 45.3]

Source: Statistical reviewer generated table, created from admiendo.xpt
[1] Average number of subjects who achieved endoscopic response based on multiple imputation model rounded to the nearest integer; % represents the estimated endoscopic response rate based on multiple imputation model
Abbreviations: CI, confidence interval; diff, difference; n, number of patients in specified population or group, N, number of patients in treatment arm; RZB, risankizumab

16.3.2.3. Race

Table 90. CDAI Remission Rate at Week 52: Analysis of Subgroup: Race

	Study M16-000		
Parameter	Placebo	RZB 600 mg	RZB 1200 mg
White			
N	97	111	93
CDAI remission, n (%)[1]	41 (42.3)	67 (60.4)	52 (55.4)
Treatment diff., % [CI]		18.1 [4.7, 31.5]	13.2 [-0.9, 27.3]
Nonwhite			
N	33	24	24
CDAI remission, n (%)	19 (57.6)	16 (66.7)	15 (62.5)
Treatment diff., % [CI]		9.1 [-16.2, 34.4]	4.9 [-20.8, 30.6]

Source: Statistical reviewer generated table, created from admicdai.xpt
[1] Average number of subjects who achieved CDAI clinical remission based on multiple imputation model rounded to the nearest integer; % represents the estimated CDAI clinical remission rate based on multiple imputation model
Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; diff, difference; n, number of patients in specified population or group, N, number of patients in treatment arm; RZB, risankizumab

Table 91. Endoscopic Response Rate at Week 52: Analysis of Subgroup: Race

	Study M16-000		
Parameter	Placebo	RZB 600 mg	RZB 1200 mg
White			
N	97	111	93
Endoscopic response, n (%)[1]	16 (16.5)	52 (46.8)	48 (51.2)
Treatment diff., % [CI]		30.4 [18.5, 42.2]	34.7 [22.1, 47.2]
Nonwhite			
N	33	24	24
Endoscopic response, n (%)	12 (36.4)	16 (66.7)	9 (37.5)
Treatment diff., % [CI]		30.3 [5.3, 55.3]	1.1 [-24.3, 26.5]

Source: Statistical reviewer generated table, created from admiendo.xpt
[1] Average number of subjects who achieved endoscopic response based on multiple imputation model rounded to the nearest integer; % represents the estimated endoscopic response rate based on multiple imputation model
Abbreviations: CI, confidence interval; diff, difference; n, number of patients in specified population or group, N, number of patients in treatment arm; RZB, risankizumab

16.3.3. Subgroup Analysis, Trial M16-000, By Prior Induction Dose

While the results of subgroup analyses by prior induction dose of maintenance study data do not show nominally statistically significant results for the coprimary endpoint of CDAI clinical remission, overall subjects who received 600 mg IV during induction had higher observed rates of achieving the coprimary endpoints during the maintenance study than subjects who received 1200 mg IV induction (Table 92). This difference was mainly due to the higher response rates among placebo patients who received the 600 mg IV induction dose.

Table 92. M16-000 Subgroup Analyses, Coprimary Endpoints, by Prior Induction Dose

	RZB 600 mg IV Induction Dose			RZB 1200 mg IV Induction Dose		
Treatment	N	Rates (%) and 95% CI	Rate Differences	N	Rates (%) and 95% CI	Rate Differences
CDAI clinical remission						
Placebo	61	55.7 (43.3, 68.2)	NA	69	37.7 (26.2, 49.1)	NA
180 mg	56	60.7 (47.9, 73.5)	5.0	79	62.0 (51.3, 72.7)	24.3
360 mg	55	57.5 (45.1, 71.2)	1.8	62	56.1 (44.1, 68.8)	18.5
Endoscopic response						
Placebo	61	26.2 (15.2, 37.3)	NA	69	17.4 (8.4, 26.3)	NA
180 mg	56	51.8 (38.7, 64.9)	25.6	79	49.4 (38.3, 60.4)	32.0
360 mg	55	56.4 (43.3, 69.5)	30.1	62	41.5 (29.2, 53.8)	21.4

Source: Adapted from Table 14.2_2.1.1_R1, Appendix C, Applicant's Response to October 29, 2021, Information Request
Abbreviations: CDAI, Crohn's Disease Activity Index; IV, intravenous; N, number of patients in treatment arm; NA, not applicable; RZB, risankizumab

16.3.4. Subgroup Analysis, Trial M16-000, Initial Induction Nonresponders

Subjects treated with 12 weeks of induction therapy (risankizumab or placebo subjects) in Study M16-006 and M15-991 who did not achieve SF/APS clinical response at Week 12 (termed clinical nonresponders) were eligible to enter Induction Period 2, during which risankizumab clinical nonresponders were randomized to continue risankizumab therapy: risankizumab 1200 mg IV at Weeks 12, 16, and 20, risankizumab 180 mg SC at Weeks 12 and 20, or risankizumab 360 mg SC at Weeks 12 and 20. At Week 24, subjects who met criteria for "clinical response" were eligible to enroll in Trial M16-000.

Additional analyses to assess the efficacy of risankizumab among initial clinical nonresponders (based on SF/APS) at Week 12 who were randomized to receive risankizumab 180 mg SC or 360 mg SC at Week 12 (Induction Period 2) through Week 76 of the Study M16-000 are shown in Table 93 and Table 94. The CDAI remission and endoscopic response rates were generally lower among initial clinical nonresponders than clinical responders, with the exception of the CDAI remission rates in the 360 mg SC group, where the clinical remission rate was higher among clinical nonresponders than clinical responders. However, the sample size of the initial nonresponder group is relatively smaller, and although the maintenance results of the initial induction nonresponders who received maintenance SC dosing for 64 weeks may show comparable nominal 2efficacy, given the exploratory nature of these subgroup analyses, this information will not be included in the label.

Table 93. CDAI Remission at the End of the Maintenance Study Based on SF/APS Response and CDAI Clinical Response at the End of the Induction Period, and Maintenance Dose

	SF/APS Clinical Responders at the End of the Induction Period		SF/APS Clinical Nonresponders at the End of the First Induction Period	
Treatment	Sample Size	Remission Rate (%) 95% CI	Sample Size	Remission Rate (%) 95% CI
180 mg	157	55.4 (47.6, 63.2)	30	53.3 (35.5, 71.2)
360 mg	141	52.2 (43.9, 60.5)	33	66.7(50.6, 82.8)

Source: Tables 8 and 15, Clinical Study Report, Study M16-000, and Table 14.2_2.1.1_R1, Appendix C, Applicant's Response to October 29, 2021, Information Request
Abbreviations: APS, abdominal pain score; CDAI, Crohn's Disease Activity Index; CI, confidence interval; SF, stool frequency

Table 94. Endoscopic Response at the End of the Maintenance Study Based on SF/APS Response and CDAI Clinical Response at the End of the Induction Period, and Maintenance Dose

	SF/APS Clinical Responders at the End of the Induction Period		SF/APS Clinical Nonresponders at the End of the First Induction Period	
Treatment	Sample Size	Remission Rate (%) 95% CI	Sample Size	Remission Rate (%) 95% CI
180 mg	157	47.1 (39.3, 54.9)	30	36.7 (19.4, 53.9)
360 mg	141	46.5 (38.3, 54.8)	33	45.5 (28.5, 62.4)

Source: Table 8, Clinical Study Report, Study M16-000, and Table 14.2_2.2.1_R1, Appendix C, Applicant's Response to October 29, 2021, Information Request
Abbreviations: APS, abdominal pain score; CDAI, Crohn's Disease Activity Index; CI, confidence interval; SF, stool frequency

17. Clinical Safety: Additional Information and Assessment

17.1. Baseline Demographics of Induction Studies (M16-006 and M15-991)

Table 95 and Table 96 provides details regarding the 931 subjects and 618 subjects included in the primary safety database for trials M16-006 and M15-991, respectively. Demographic factors and baseline disease characteristics were generally balanced between the three groups in each trial.

17.1.1. Study M16-006

Table 95. Baseline Demographic and Clinical Characteristics, Safety Population, Trial M16-006

Characteristic	RZB 600 mg IV Per 1 N=373	RZB 1200 mg IV Per 1 N=372	Placebo IV Per 1 N=186
Sex, n (%)			
Female	168 (45.0)	173 (46.5)	93 (50.0)
Male	205 (55.0)	199 (53.5)	93 (50.0)
Age, years			
Mean (SD)	38.5 (13.2)	37.6 (13.5)	37.5 (13.5)
Median (min, max)	37 (16, 79)	34 (16, 74)	34 (16, 74)
Age group, years, n (%)			
<18 years	3 (0.8)	4 (1.1)	2 (1.1)
≥18 years to <40 years	209 (56.0)	226 (60.8)	119 (64.0)
≥40 years to <65 years	146 (39.1)	124 (33.3)	56 (30.1)
≥65 years	15 (4.0)	18 (4.8)	9 (4.8)
Race, n (%)			
Asian	68 (18.2)	75 (20.2)	32 (17.2)
Black or African American	10 (2.7)	13 (3.5)	9 (4.8)
Multiple	4 (1.1)	4 (1.1)	0 (0)
Native Hawaiian or Other Pacific Islander	0 (0)	1 (0.3)	1 (0.5)
White	291 (78.0)	279 (75.0)	144 (77.4)

Characteristic	RZB 600 mg IV Per 1 N=373	RZB 1200 mg IV Per 1 N=372	Placebo IV Per 1 N=186
Ethnicity, n (%)			
Hispanic or Latino	13 (3.5)	18 (4.8)	10 (5.4)
Not Hispanic or Latino	360 (96.5)	354 (95.2)	176 (94.6)
Country of participation, n (%)			
Australia	3 (0.8)	1 (0.3)	0 (0)
Austria	2 (0.5)	3 (0.8)	2 (1.1)
Belarus	1 (0.3)	0 (0)	0 (0)
Belgium	28 (7.5)	33 (8.9)	7 (3.8)
Bosnia and Herzegovina	1 (0.3)	1 (0.3)	0 (0)
Brazil	3 (0.8)	6 (1.6)	5 (2.7)
Bulgaria	0 (0)	2 (0.5)	2 (1.1)
Canada	21 (5.6)	33 (8.9)	11 (5.9)
Chile	2 (0.5)	0 (0)	0 (0)
China	30 (8.0)	34 (9.1)	11 (5.9)
Croatia	8 (2.1)	4 (1.1)	2 (1.1)
Czech Republic	8 (2.1)	7 (1.9)	3 (1.6)
Estonia	1 (0.3)	2 (0.5)	0 (0)
Germany	33 (8.8)	29 (7.8)	12 (6.5)
Greece	7 (1.9)	2 (0.5)	3 (1.6)
Israel	9 (2.4)	8 (2.2)	5 (2.7)
Italy	13 (3.5)	17 (4.6)	8 (4.3)
Japan	31 (8.3)	28 (7.5)	16 (8.6)
Latvia	1 (0.3)	0 (0)	1 (0.5)
Malaysia	0 (0)	1 (0.3)	0 (0)
Mexico	0 (0)	2 (0.5)	0 (0)
Netherlands	3 (0.8)	4 (1.1)	1 (0.5)
New Zealand	1 (0.3)	3 (0.8)	2 (1.1)
Norway	1 (0.3)	7 (1.9)	2 (1.1)
Poland	22 (5.9)	26 (7.0)	15 (8.1)
Portugal	1 (0.3)	8 (2.2)	5 (2.7)
Romania	3 (0.8)	1 (0.3)	2 (1.1)
Russia	11 (2.9)	9 (2.4)	5 (2.7)
Serbia	11 (2.9)	6 (1.6)	6 (3.2)
Singapore	0 (0)	1 (0.3)	0 (0)
Slovakia	2 (0.5)	5 (1.3)	1 (0.5)
South Africa	14 (3.8)	9 (2.4)	4 (2.2)
South Korea	6 (1.6)	8 (2.2)	4 (2.2)
Spain	9 (2.4)	6 (1.6)	3 (1.6)
Sweden	7 (1.9)	3 (0.8)	0 (0)
Switzerland	1 (0.3)	1 (0.3)	2 (1.1)
Ukraine	4 (1.1)	7 (1.9)	6 (3.2)
United Kingdom	16 (4.3)	6 (1.6)	3 (1.6)
United States	59 (15.8)	49 (13.2)	37 (19.9)

Source: Anne Bunner, PhD; Clinical Data Scientist.
Abbreviations: IV, intravenous; N, number of patients in treatment group; n, number of patients with given characteristic; Per, period; RZB, risankizumab; SD, standard deviation

17.1.2. Study M15-991

Table 96. Baseline Demographic and Clinical Characteristics, Safety Population, Trial M15-991

Characteristic	RZB 600 mg IV Per 1 N=206	RZB 1200 mg IV Per 1 N=205	Placebo IV Per 1 N=207
Sex, n (%)			
Female	106 (51.5)	99 (48.3)	104 (50.2)
Male	100 (48.5)	106 (51.7)	103 (49.8)
Age, years			
Mean (SD)	40.4 (13.5)	39.6 (12.9)	39.4 (13.3)
Median (min, max)	38 (17, 74)	39 (16, 74)	37 (17, 80)
Age group, years, n (%)			
<18 years	1 (0.5)	1 (0.5)	3 (1.4)
≥18 years to <40 years	109 (52.9)	103 (50.2)	112 (54.1)
≥40 years to <65 years	82 (39.8)	95 (46.3)	81 (39.1)
≥65 years	14 (6.8)	6 (2.9)	11 (5.3)
Race, n (%)			
Asian	9 (4.4)	14 (6.8)	16 (7.7)
Black or African American	8 (3.9)	8 (3.9)	12 (5.8)
Multiple	0 (0)	1 (0.5)	1 (0.5)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	2 (1.0)
White	189 (91.7)	182 (88.8)	176 (85.0)
Ethnicity, n (%)			
Hispanic or Latino	16 (7.8)	15 (7.3)	22 (10.6)
Not Hispanic or Latino	190 (92.2)	190 (92.7)	185 (89.4)
Country of participation, n (%)			
Argentina	3 (1.5)	2 (1.0)	2 (1.0)
Australia	2 (1.0)	0 (0)	2 (1.0)
Austria	0 (0)	2 (1.0)	1 (0.5)
Belarus	1 (0.5)	0 (0)	0 (0)
Belgium	4 (1.9)	3 (1.5)	5 (2.4)
Bosnia and Herzegovina	1 (0.5)	1 (0.5)	0 (0)
Bulgaria	0 (0)	2 (1.0)	2 (1.0)
Canada	18 (8.7)	21 (10.2)	24 (11.6)
Chile	1 (0.5)	0 (0)	6 (2.9)
China	0 (0)	0 (0)	1 (0.5)
Columbia	1 (0.5)	1 (0.5)	0 (0)
Croatia	5 (2.4)	0 (0)	2 (1.0)
Czech Republic	4 (1.9)	7 (3.4)	8 (3.9)
Denmark	7 (3.4)	4 (2.0)	3 (1.4)
Egypt	6 (2.9)	9 (4.4)	7 (3.4)
Estonia	1 (0.5)	0 (0)	0 (0)
France	18 (8.7)	25 (12.2)	20 (9.7)
Germany	7 (3.4)	10 (4.9)	9 (4.3)
Greece	7 (3.4)	2 (1.0)	1 (0.5)
Ireland	2 (1.0)	1 (0.5)	0 (0)
Israel	6 (2.9)	3 (1.5)	5 (2.4)
Italy	8 (3.9)	6 (2.9)	3 (1.4)
Latvia	1 (0.5)	0 (0)	0 (0)
Lithuania	1 (0.5)	2 (1.0)	0 (0)
Netherlands	1 (0.5)	3 (1.5)	1 (0.5)
New Zealand	3 (1.5)	0 (0)	4 (1.9)

Characteristic	RZB 600 mg IV Per 1 N=206	RZB 1200 mg IV Per 1 N=205	Placebo IV Per 1 N=207
Poland	2 (1.0)	4 (2.0)	3 (1.4)
Portugal	5 (2.4)	8 (3.9)	0 (0)
Romania	4 (1.9)	4 (2.0)	1 (0.5)
Russia	5 (2.4)	1 (0.5)	6 (2.9)
Serbia	4 (1.9)	6 (2.9)	4 (1.9)
Singapore	1 (0.5)	1 (0.5)	0 (0)
Slovakia	6 (2.9)	6 (2.9)	6 (2.9)
South Africa	2 (1.0)	1 (0.5)	1 (0.5)
South Korea	4 (1.9)	8 (3.9)	9 (4.3)
Spain	6 (2.9)	4 (2.0)	5 (2.4)
Switzerland	3 (1.5)	1 (0.5)	1 (0.5)
Taiwan	1 (0.5)	4 (2.0)	5 (2.4)
United Kingdom	5 (2.4)	6 (2.9)	7 (3.4)
United States	50 (24.3)	47 (22.9)	53 (25.6)

Source: Anne Bunner, PhD; Clinical Data Scientist.
Abbreviations: IV, intravenous; N, number of patients in treatment group; n, number of patients with given characteristic; Per, period; RZB, risankizumab; SD, standard deviation

17.2. Safety Analyses by Demographic Subgroups

Safety analyses for the demographic subgroup was focused on overall TEAEs, SAE, and discontinuation of the study drug due to AEs.

17.2.1. Sex

In the primary induction safety database, male subjects represented 212/432 (49.1%), 321/620 (51.8%), and 305/577 (52.9%) in the placebo, risankizumab 600 mg IV, and risankizumab 1200 mg IV treatment arms, respectively, and female subjects represented 220/432 (50.9%), 299/620 (48.2%), and 272/577 (47.1%) in the placebo, risankizumab 600 mg IV, and risankizumab 1200 mg IV treatment arms, respectively.

In the primary maintenance safety database, male subjects represented 77/143 (53.8%), 70/155 (45.2%), and 83/142 (58.5%) in the placebo, risankizumab 180 mg SC, and risankizumab 360 mg SC treatment arms, respectively, and female subjects represented 66/143 (46.2%), 85/155 (54.8%), and 59/142 (41.5%) in the placebo, risankizumab 180 mg SC, and risankizumab 360 mg SC treatment arms, respectively.

Table 97 and Table 98 show an overview of the proportion of males and females who reported any TEAEs, SAEs, AEs leading to discontinuation of the study drug across treatment arms during the induction and maintenance treatment periods, respectively.

Table 97. Number and Percentage of Subjects With TEAEs by Sex, Safety Population, ISS1

	Female					Male				
Event Category	Placebo N=220 n (%)	RZB 600 mg N=299 n (%)	Risk Difference RZB 600 mg vs. Placebo (%)	RZB 1200 mg N=272 n (%)	Risk Difference RZB 1200 mg vs. Placebo (%)	Placebo N=212 n (%)	RZB 600 mg N=321 n (%)	Risk Difference RZB 600 mg vs. Placebo (%)	RZB 1200 mg N=305 n (%)	Risk Difference RZB 1200 mg vs. Placebo (%)
Any AE	144 (65.5)	181 (60.5)	-4.9	170 (62.5)	-3.0	130 (61.3)	158 (49.2)	-12.1	142 (46.6)	-14.8
Any SAE	35 (15.9)	23 (7.7)	-8.2	17 (6.2)	-9.7	32 (15.1)	18 (5.6)	-9.5	6 (2.0)	-13.1
AE leading to discontinuation	16 (7.3)	10 (3.3)	-3.9	8 (2.9)	-4.3	21 (9.9)	3 (0.9)	-9.0	4 (1.3)	-8.6
AE leading to interruption of study drug	0	0	0	0	0	0	0	0	0	0
AE leading to death	0	0	0	1 (0.4)	0.4	2 (0.9)	0	-0.9	0	-0.9

Source: Anne Bunner, PhD; Clinical Data Scientist
Abbreviations: AE, adverse event; ISS1, primary induction safety database; N, number of patients in treatment arm; n, number of patients with at least one event; RZB, risankizumab; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Table 98. Number and Percentage of Subjects With TEAEs by Sex, Safety Population, Trial M16-000

	Female					Male				
Event Category	Placebo N=86 n (%)	RZB 180 mg N=101 n (%)	Risk Difference RZB 180 mg vs. Placebo (%)	RZB 360 mg N=77 n (%)	Risk Difference RZB 360 mg vs. Placebo (%)	Placebo N=98 n (%)	RZB 180 mg N=78 n (%)	Risk Difference RZB 180 mg vs. Placebo (%)	RZB 360 mg N=102 n (%)	Risk Difference RZB 360 mg vs. Placebo (%)
Any AE	68 (79.1)	76 (75.2)	-3.8	63 (81.8)	2.7	67 (68.4)	52 (66.7)	-1.7	66 (64.7)	-3.7
Any SAE	10 (11.6)	13 (12.9)	1.2	12 (15.6)	4.0	13 (13.3)	9 (11.5)	-1.7	12 (11.8)	-1.5
AE leading to discontinuation	4 (4.7)	2 (2.0)	-2.7	3 (3.9)	-0.8	2 (2.0)	1 (1.3)	-0.8	3 (2.9)	0.9
AE leading to interruption of study drug	0	0	0	0	0	0	0	0	0	0
AE leading to death	0	0	0	0	0	0	0	0	0	0

Source: Anne Bunner, PhD; Clinical Data Scientist
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event; RZB, risankizumab; SAE, serious adverse event; TEAE, treatment-emergent adverse event

No clinically meaningful trends were identified in the types of AEs reported between males and females treated with risankizumab compared to respective sex-matched placebo cohorts. The most common TEAEs occurring in male and female subjects in either risankizumab arm when compared to males and females on placebo, respectively, were generally similar to the types of TEAEs observed in the overall study population for the induction trial.

17.2.2. Age

In the primary induction safety database, subjects <65 years of age represented 412/432 (95%), 589/620 (95%), and 553/577 (96%) in the placebo, risankizumab 600 mg IV, and risankizumab 1200 mg IV treatment arms, respectively; and subjects ≥65 years of age represented 22/432 (5.1%), 31/620 (5%), and 24/577 (4.2%) in the placebo, risankizumab 600 mg IV, and risankizumab 1200 mg IV treatment arms, respectively.

In the primary maintenance safety database, subjects <65 years of age represented 139/143 (97%), 142/155 (92%), and 136/142 (96%) in the placebo, risankizumab 180 mg SC, and risankizumab 360 mg SC treatment arms, respectively; and subjects ≥65 years of age represented 4/143 (2.8%), 13/155 (8.4%), and 6/142 (4.2%) in the placebo, risankizumab 180 mg SC, and risankizumab 360 mg SC treatment arms, respectively.

Table 99 and Table 100 show overall TEAEs, SAEs, and AEs leading to discontinuation of the study drug in subjects, based on age of <65 years and ≥65, in the different treatment arms during the induction and maintenance treatment periods.

Table 99. Number and Percentage of Subjects With TEAEs by Age, Safety Population, ISS1

	<65 Years					≥65 Years				
Event Category	Placebo N=410 n (%)	RZB 600 mg N=589 n (%)	Risk Difference RZB 600 mg vs. Placebo (%)	RZB 1200 mg N=553 n (%)	Risk Difference RZB 1200 mg vs. Placebo (%)	Placebo N=22 n (%)	RZB 600 mg N=31 n (%)	Risk Difference RZB 600 mg vs. Placebo (%)	RZB 1200 mg N=24 n (%)	Risk Difference RZB 1200 mg vs. Placebo (%)
Any AE	262 (63.9)	321 (54.5)	-9.4	297 (53.7)	-10.2	12 (54.5)	18 (58.1)	3.5	15 (62.5)	8.0
Any SAE	66 (16.1)	39 (6.6)	-9.5	23 (4.2)	-11.9	1 (4.5)	2 (6.5)	1.9	0	-4.5
AE leading to discontinuation	37 (9.0)	13 (2.2)	-6.8	12 (2.2)	-6.9	0	0	0	0	0
AE leading to interruption of study drug	0	0	0	0	0	0	0	0	0	0
AE leading to death	2 (0.5)	0	-0.5	1 (0.2)	-0.3	0	0	0	0	0

Source: Anne Bunner, PhD; Clinical Data Scientist
Abbreviations: AE, adverse event; ISS1, primary induction safety database; N, number of patients in treatment arm; n, number of patients with at least one event; RZB, risankizumab; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Table 100. Number and Percentage of Subjects With TEAEs by Age, Safety Population, Trial M16-000

	<65 Years					≥65 Years				
Event Category	Placebo N=176 n (%)	RZB 180 mg N=164 n (%)	Risk Difference RZB 180 mg vs. Placebo (%)	RZB 360 mg N=170 n (%)	Risk Difference RZB 360 mg vs. Placebo (%)	Placebo N=8 n (%)	RZB 180 mg N=15 n (%)	Risk Difference RZB 180 mg vs. Placebo (%)	RZB 360 mg N=9 n (%)	Risk Difference RZB 360 mg vs. Placebo (%)
Any AE	128 (72.7)	114 (69.5)	-3.2	123 (72.4)	-0.4	7 (87.5)	14 (93.3)	5.8	6 (66.7)	-20.8
Any SAE	22 (12.5)	18 (11.0)	-1.5	23 (13.5)	1.0	1 (12.5)	4 (26.7)	14.2	1 (11.1)	-1.4
AE leading to discontinuation	5 (2.8)	2 (1.2)	-1.6	6 (3.5)	0.7	1 (12.5)	1 (6.7)	-5.8	0	-12.5
AE leading to interruption of study drug	0	0	0	0	0	0	0	0	0	0
AE leading to death	0	0	0	0	0	0	0	0	0	0

Source: Anne Bunner, PhD; Clinical Data Scientist
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event; RZB, risankizumab; SAE, serious adverse event; TEAE, treatment-emergent adverse event

In the induction and maintenance periods, the overall AE profile was generally similar between age groups. Note that the number of subjects in the ≥65 year age group are small, which precludes a clear determination regarding whether there is an increased risk of adverse events by age.

17.2.3. Race

In the primary induction safety database, of the subjects who received risankizumab 600 mg IV, 514/620 (82.9%) subjects were white and 106/620 (17%) subjects were nonwhite, and of the subjects who received risankizumab 1200 mg IV, 461/577 (79.9%) subjects were white and 116/577 (20%) subjects were nonwhite. Of the subjects who received placebo, 352/432 (81.5%) subjects were white and 80/432 (18.5%) were nonwhite.

In the primary maintenance safety database, of the subjects who received risankizumab 180 mg SC, 129/155(83.2%) subjects were white and 26/155 (17%) subjects were nonwhite, and of the subjects who received risankizumab 360 mg SC, 114/142 (80.3%) subjects were white and 28/142 (20%) subjects were nonwhite. Of the subjects who received placebo, 109/143 (76.2%) subjects were white and 34/143 (24%) were nonwhite.

Table 101 and Table 102 show the proportion of subjects who reported any TEAEs, SAEs, and AEs leading to discontinuation and interruption of the study drug by race across treatment arms, during the induction and maintenance treatment periods.

Table 101. Number and Percentage of Subjects With TEAEs by Race, Safety Population, ISS1

	White					Nonwhite				
Event Category	Placebo N=352 n (%)	RZB 600 mg N=514 n (%)	Risk Difference RZB 600 mg vs. Placebo (%)	RZB 1200 mg N=461 n (%)	Risk Difference RZB 1200 mg vs. Placebo (%)	Placebo N=80 n (%)	RZB 600 mg N=106 n (%)	Risk Difference RZB 600 mg vs. Placebo (%)	RZB 1200 mg N=116 n (%)	Risk Difference RZB 1200 mg vs. Placebo (%)
Any AE	226 (64.2)	290 (56.4)	-7.8	253 (54.9)	-9.3	48 (60.0)	49 (46.2)	-13.8	59 (50.9)	-9.1
Any SAE	50 (14.2)	33 (6.4)	-7.8	23 (5.0)	-9.2	17 (21.2)	8 (7.5)	-13.7	0	-21.2
AE leading to discontinuation	29 (8.2)	11 (2.1)	-6.1	12 (2.6)	-5.6	8 (10.0)	2 (1.9)	-8.1	0	-10.0
AE leading to interruption of study drug	0	0	0	0	0	0	0	0	0	0
AE leading to death	2 (0.6)	0	-0.6	1 (0.2)	-0.4	0	0	0	0	0

Source: Anne Bunner, PhD; Clinical Data Scientist
Abbreviations: AE, adverse event; ISS1, primary induction safety set; N, number of patients in treatment arm; n, number of patients with at least one event; RZB, risankizumab; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Table 102. Number and Percentage of Subjects With TEAEs by Race, Safety Population, Trial M16-000

	White					Nonwhite				
Event Category	Placebo N=145 n (%)	RZB 180 mg N=147 n (%)	Risk Difference RZB 180 mg vs. Placebo (%)	RZB 360 mg N=143 n (%)	Risk Difference RZB 360 mg vs. Placebo (%)	Placebo N=39 n (%)	RZB 180 mg N=32 n (%)	Risk Difference RZB 180 mg vs. Placebo (%)	RZB 360 mg SC N=36 n (%)	Risk Difference RZB 360 mg vs. Placebo (%)
Any AE	107 (73.8)	107 (72.8)	-1.0	104 (72.7)	-1.1	28 (71.8)	21 (65.6)	-6.2	25 (69.4)	-2.4
Any SAE	16 (11.0)	21 (14.3)	3.3	16 (11.2)	0.2	7 (17.9)	1 (3.1)	-14.8	8 (22.2)	4.3
AE leading to discontinuation	4 (2.8)	3 (2.0)	-0.7	5 (3.5)	0.7	2 (5.1)	0	-5.1	1 (2.8)	-2.4
AE leading to interruption of study drug	0	0	0	0	0	0	0	0	0	0
AE leading to death	0	0	0	0	0	0	0	0	0	0

Source: Anne Bunner, PhD; Clinical Data Scientist
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event; RZB, risankizumab; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event

In the primary induction safety database, SAEs, and AEs leading to discontinuation occurred more often in placebo than risankizumab treatment arms in white and nonwhite subjects. In white subjects, TEAEs occurred more often in the risankizumab 1200 mg IV treatment arms compared to placebo. In nonwhite subjects, TEAEs occurred more often in risankizumab 1200 mg IV treatment arm compared to placebo.

In the primary maintenance safety database, in white subjects, the proportion of subjects who reported TEAEs, SAEs and AEs leading to discontinuation were similar between placebo and treatment arms. In nonwhite subjects, a higher proportion of subjects reported SAEs in the risankizumab treatment arm compared to placebo. TEAEs and AEs leading to study discontinuation were similar between treatment and placebo arms. However, the number of nonwhite subjects enrolled included in the maintenance trial were few in number, which precludes a clear determination regarding whether there is an increased risk of adverse events in this cohort.

17.3. Real Life Handling Study: M16-000 Substudy 4

Background

In the phase 3 clinical development program, the Applicant investigated two doses for maintenance therapy, risankizumab 180 mg SC and risankizumab 360 mg SC administered every 8 weeks. A PFS, which contained a 90 mg/mL formulation, was used in the phase 3 trials; two and four PFS were required for the 180 mg or 360 mg SC doses, respectively. However, in the marketing application, the Applicant proposes a new combination product, the OBDS, as the TBM device for risankizumab maintenance therapy administration. At the time of this review, a real-life-handling study (RLHS), M16-000 Substudy 4, investigating the safety of the OBDS device in CD patients is ongoing. The Applicant submitted interim data from the RLHS to support the safety of the OBDS device for risankizumab maintenance therapy administration in patients with CD.

Brief Overview: M16-000 Substudy 4 Real-Life Handling Study

M16-000 Substudy 4[10] is an OL, long-term extension (LTE) study in which enrolled subjects continue risankizumab maintenance therapy. Eligibility criteria require that the enrolled subjects have been on a stable risankizumab maintenance dose (180 mg or 360 mg SC every 8 weeks) for at least 16 weeks prior to trial enrollment. The first 16 weeks of this trial includes a RLHS, which assesses safety of risankizumab maintenance therapy administered via the OBDS device at Weeks 0, 8 and 16. Subjects enrolled in the RLHS continue baseline risankizumab dosing, which is self-administered via the OBDS device. The Week 0 and 16 self-administrations occur at the study site under observation of study staff and the Week 8 dose is self-administered at the subject's home.

[10] A clinical review of protocol M16-000, Amendment 7.01.01.01.01, Substudy 4 was completed in parallel with this review. Refer to the memo uploaded by Suruchi Batra, MD under IND 118701 for further details.

Training

Training for study staff was completed virtually as travel was limited due to the ongoing COVID-19 pandemic. First, study staff observed an instructional video. Subsequently, a live demonstration based on the Instructions for Use (IFU) was completed by the AbbVie OBDS product development team, during which site staff were encouraged to follow along with supplies provided in advance of the training.

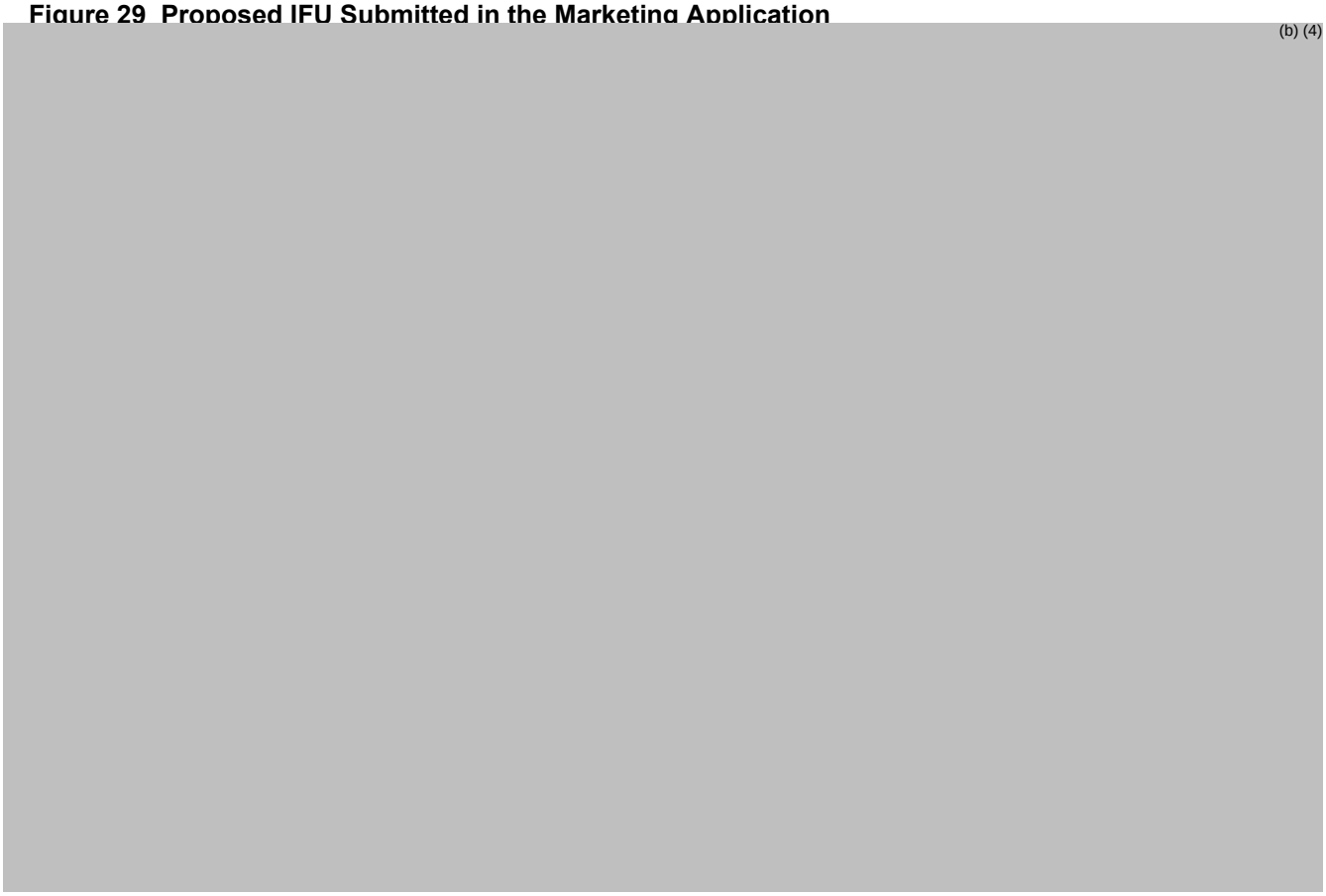
At Week 0, enrolled subjects presented to a study site to receive in person training conducted by site staff prior to self-administration of the Week 0 dose. Training for enrolled subjects was structured similarly to training completed for study staff: subjects first watched an instructional video, then completed a live demonstration with the OBDS device. Per the study protocol, no further training was provided to enrolled subjects. However, subjects may request "additional training" from study staff as needed during the RLHS.

Of note, the IFU used in the RLHS (IFU DN4976V3) differs from the proposed IFU for the TBM OBDS device (IFU DN4976V5). Additional verbal training was completed for study staff and enrolled subjects to communicate the information not included on IFU DN4976V3.

(b) (4)

Figure 29 Proposed IFU Submitted in the Marketing Application

(b) (4)



Device Assessment

Safety of the device was assessed via questionnaires completed by the observer (study staff) and patient-reported outcome (PRO) assessment completed by enrolled subjects. Specifically, at Weeks 0 and 16, observers documented the subject's ability to successfully administer a dose (via the "Observer OBI IFU Checklist Assessment") and recorded any potential device hazards (via the "Use Hazards Checklist"). In addition, all enrolled subjects completed a PRO assessment (Self-Injection Assessment Questionnaire [SIAQ]). See Section 19.1.

The RLHS endpoints are as follows:

- Proportion of subjects with an observer rating of successful subject self-administration, defined as any subject who successfully completed the sequence of critical steps in the IFU without errors to administer study drug via the on-body injector (OBI) at Week 0 and 16.
- Proportion of subjects who had no potential hazards as measured by an observer on the possible use-related hazards checklist for self-administration with OBI at Week 0 and Week 16.
- Subject rating of acceptability using SIAQ at Weeks 0, 8, and 16.
- Proportion of subjects in CDAI clinical remission at Week 0 and 16.

Clinical Review: Real Life Handling Study and Data Quality

Further details were received from the Applicant regarding inconsistencies between the IFUs used in the RLHS and the final proposed IFU, additional OBDS device training provided to enrolled subjects, and number of enrolled subjects who required rescue therapy or rescue medication during the RLHS. The differences in the IFUs do not appear to impact the integrity of safety data generated from this trial in support of the OBDS device. The Applicant clarified that no subjects in the RLHS requested additional training on the OBDS device. Additionally, while a single subject required a short prednisone course to treat disease flare during the RLHS, no subjects required rescue risankizumab therapy, which was reassuring. The information reviewed appears reasonable and the review team agrees that data generated from this trial is sufficient to support safety of the OBDS device.

Real Life Handling Study: Interim Results

At the time of this review, study enrollment has completed, and the study is currently ongoing. The last subject visit is planned for May 19, 2022, and final database lock is planned for June 6, 2022. The Applicant submitted interim data from the RLHS to support safety of the OBDS device for risankizumab maintenance therapy, with a database cut off of February 15, 2022.

Demographics

Forty-six subjects were enrolled (risankizumab 180 mg: 31 subjects; risankizumab 360 mg: 15 subjects). Of the data submitted, 7/46 (15.2%) subjects have data that was reported as missing (study visit was completed, but data were not entered in case report form [CRF]) and 5/46 (10.9%) subjects have datapoints that were not available (visit not yet completed). The mean age of enrolled subjects was 41.7 years (standard deviation [SD] 13.68), 24/46 (52.2%) were males, and the majority were of Caucasian race (38 of 46 subjects or 82.6%). No subjects <18 years were included. Mean body mass index (BMI) was 28.62 kg/m^2 (SD: 7.96 kg/m2) and 29/46 (63%) subjects met BMI criteria for overweight or obese. A review of demographics revealed that adult subjects of varying age, body habitus, and gender were adequately represented.

Injection Site

Enrolled subjects were prompted to rotate injection sites between abdomen and thighs. Injection sites included all four quadrants of the abdomen and both thighs.

Treatment Compliance

Treatment compliance for the combined treatment groups was 100% at Week 0, 89.2% at Week 8 and 97.1% at Week 16.

Safety

No deaths were reported. There was one SAE that led to permanent discontinuation of study drug, which was unrelated to study drug or device (acute pancreatitis, which required hospitalization). No further details regarding the SAE were included in the interim data submitted by the Applicant. The majority of AEs were mild in severity (risankizumab 180 mg: 7/12 [22.6%] adverse events; risankizumab 360 mg: 3/4 [75%] adverse events) and similar to AEs reported in trial M16-000 Substudy 1. No injection site reactions were reported.

Endpoint Assessment

As of the database cutoff, observers reported that 100% of subjects successfully self-administered at Weeks 0 (n=46 subjects) and 8 (n=33 subjects) as indicated by the Observer OBI IFU Checklist Assessment. Additionally, observers reported potential hazards in 2/46 (4.3%) subjects at Weeks 0 via the Potential Hazards Checklist (refer to "Hazards & Product Complaints" section below). No potential hazards were reported at Week 16. Finally, 37/45 (82.2%) of subjects at Week 0 and 26/27 (96.3%) of subjects were in clinical remission (CDAI <150) at Weeks 0, and 16 respectively.

Hazards & Product Complaints

Two hazards were reported at Week 0 (2 of 46 subjects or 4.3%):

- Subject (b) (6) (risankizumab 360 mg) reported three dosing hazards at Week 0. In brief, when the subjected attempted to self-administer risankizumab using the OBDS device, he noted that administration was delayed due to device malfunction, "door could not open/was damaged," and administration was not completed because of delivery notification. He was subsequently given a replacement device with which he successfully self-administered the medication with the OBDS. He completed all critical steps of the IFU, and the PRO assessment was favorable. The subject completed the trial, but further information for the Week 8 or 16 assessments were not recorded at the time of interim data submission.
- Subject (b) (6) (risankizumab 360 mg) device reported one hazard at Week 0 (wet injection). Per the site report, the subject successfully completed self-administration of the OBDS device (completed all critical steps of the IFU) and the OBDS status light changed to flashing green. Soon after initiation the subject reported dampness at the location of the OBDS, and inspection by the site staff revealed that the adhesive was not securely attached to the skin and there was slight dampness around the adhesive. During this time the OBDS status light remained flashing green. Site staff determined that the subject did not attach the device securely to the skin. The subject continued in the trial and self-administered with the OBDS at Week 8 and Week 16 (successfully self-administered based on completion of all critical steps of the IFU).

Six product complaints were reported, 3 of which were due to use error/dosing failure:

- Subject (b) (6) This subject experienced one event related to dosing failure due to device malfunction, which was reported as both a hazard and a product complaint. See Hazards & Product Complaints section above.
- Subject (b) (6) (risankizumab 360 mg): At Week 0, the subject reported that the OBDS was attached to the skin (right lower quadrant of abdomen) and after pushing the start button the status light was a flashing green. No drug was injected and after 5 seconds, the status light was a flashing red. The subject received a replacement device and successfully self-administered (completed all critical steps of the IFU). Root cause analysis confirmed that this was due to incomplete cartridge insertion. The subject continued and completed the trial; all subsequent injections were successfully self-administered, without additional dosing errors, product complaints or reported AEs.

- Subject (b) (6) (risankizumab 180 mg): At Week 8, the subject reported an error notification (flashing red status light) after pushing the OBDS start button. Specifically, the subject reported that the prefilled cartridge loaded correctly, and the status light was flashing blue which indicates correct device function. When the subject pushed the button to deliver the medicine, the OBDS did not initiate injection. Root cause analysis concluded that the subject pushed the OBDS start button prior to attaching to the skin, then applied the OBDS to the skin and pushed the OBDS start button again that resulted in a device error notification (red flashing status light). The subject contacted the study site and was supplied with a replacement device, which the subject reports he self-administered and did not receive a device error notification.

Three of the 6 reported product complaints were associated with AEs:

- Subject (b) (6) (risankizumab 360 mg OBDS): At Week 8, the subject reported a red and itchy area, which was also reported as an AE of dermatitis contact (reported term topical adhesive reaction). Event was rated as moderate in severity and resolved 9 days later. The subject took Benadryl for 4 days after AEs. The investigator reported this event as related to the OBDS and not related to study drug.
- Subject (b) (6) (risankizumab 180 mg OBDS): At Week 0, the subject reported a product complaint of redness on skin where tape adhered, which was also reported as an AE (reported term, tropical adhesive reaction). Specifically, the tape was adhered to the site of injection, the left lower quadrant of the abdomen. The event was mild and resolved on the next day without intervention. The investigator reported this event as related to device and unrelated to study drug. The subject completed the study without further reported product complaints, or AES.
- Subject (b) (6) (risankizumab 180 mg OBDS): At Week 8, the subject reported a product complaint of mild pain and discomfort from pulling the hair and mild skin redness. In addition, the subject reported a mild AE of pain and erythema, which was due to tape adhering to the right lower quadrant of the abdomen. This event resolved within one hour. No further AEs were reported.

Conclusions

It is reassuring that there were no deaths or injection site reactions reported. The majority of TEAEs reported were mild in severity and similar to the safety profile of the primary induction and maintenance safety database. One SAE was reported which led to treatment discontinuation, which was deemed unrelated to study intervention. In addition, all subjects successfully self-administered the device at Weeks 0 and 16. It is reassuring that only 2 hazards and 6 product complaints were reported for all three time points. In addition, while there were three product complaints associated with AEs, the AEs reported were mild in severity and all were associated with adhesive, not the OBDS device. The interim RLHS data submitted supports safety of risankizumab 360 mg and 180 mg maintenance doses administered via OBDS device.

17.4. Safety Review: Major Adverse Cardiovascular Events

A concern for dyslipidemia that may be associated with risankizumab exposure in patients with CD emerged during the safety review of this marketing application. Further safety review revealed that small incremental changes in baseline low-density lipoprotein (LDL) and triglycerides (TGs) was seen at Weeks 12 and 52 in enrolled subjects exposed to risankizumab therapy (Section 7.7.2). A case review of all reported major adverse cardiovascular events (MACE) was completed to determine whether this increase in LDL-C or TGs may predispose to long-term outcomes related to dyslipidemia. No MACE were reported in the induction trials (M16-006 and M15-995). A case review of all MACE reported in trial M16-000 is provided in Table 103.

All MACE were reviewed and adjudicated as unlikely to be related to study intervention or due to multifactorial etiology. At the time of this review, there are insufficient data to support that risankizumab exposure in patients with CD may increase risk of long-term outcomes associated with dyslipidemia. The risk of dyslipidemia will be included in the Clinical Studies section of the label, and the review team recommends routine monitoring of lipid parameters for CD patients treated with risankizumab therapy (Section 7.7.2).

Table 103. Case Review: Major Adverse Cardiovascular Events, Trial M16-000

Subject ID	Trial	Adverse Event	Study Drug Details	Case Details
			Maintenance Trial (M16-000 Substudy 1)	
(b) (6)	M16-000 (Substudy 1)	Stress cardiomyopathy, nonfatal myocardial infarction. Coronary artery disease, nonfatal myocardial infarction	Treatment during event: Risankizumab 180 mg SC Previous treatment: Risankizumab 600 mg IV (IP 1) Risankizumab 180 mg SC (IP 2) This event occurred 483 days after first dose of study drug. Study drug was continued.	75-year-old male with history of CD (s/p bowel resection), hypertension, osteoarthritis, migraines, anxiety, pernicious anemia, GERD, obsessive compulsive disorder, atrial flutter, atrial fibrillation, hypokalemia, and former smoker developed myocardial infarction. Concomitant medications included alprazolam, multivitamin, folic acid, methotrexate, fish oil, ibuprofen, citalopram, omeprazole, loperamide, tilactase, losartan, prazosin, metoprolol, hydrochlorothiazide, warfarin, potassium, ketoconazole. On Day 482, the subject developed a seizure at home. He was transported to the emergency room via EMS. He was treated with abortive medications for seizure and hospitalized. CT scan was remarkable for chronic changes without evidence of acute changes. Lumbar puncture was completed and not consistent with meningitis. An EEG was obtained, results of which were abnormal. On the day of hospital admission, the subject developed non-ST elevation MI in the context of worsening hypokalemia, acute respiratory failure systemic inflammatory response syndrome, sepsis, hypomagnesemia, and pyuria. He was diagnosed with stress induced cardiomyopathy on (b) (6) and coronary artery disease on (b) (6) Details regarding how this latter diagnosis was made and treated were not provided. During his hospitalization, he was initiated on antiepileptic therapy for new diagnosis of seizure disorder, and was treated for non-ST elevation MI. He was discharged from the hospital on Day 493. Study drug was continued. Adverse event was categorized as severe. The Investigator and Applicant deemed the event had no reasonable possibility of being related to study drug. *Reviewer comments: A 79-year-old male with CD and complicated medical history, including known cardiovascular disease, developed a seizure, requiring hospitalization for medical stabilization and further work up of underlying etiology. During his hospitalization, he developed stress induced cardiomyopathy and experienced a non-ST elevated myocardial infarction.*

Subject ID	Trial	Adverse Event	Study Drug Details	Case Details
				On review, it is most likely these events were due to acute medical illness, and unrelated to study intervention.
(b) (6)	M16-000 (Substudy 1)	Acute myocardial infarction	Treatment during event: Risankizumab 360 mg SC Previous treatment: Risankizumab 600 mg IV This event occurred 411 days after first dose of study drug. Study drug was continued.	49-year-old male with history of CD, trigeminal neuralgia, humerus fracture, dyslipidemia, s/p appendectomy and known smoker developed an acute myocardial infarction, which required hospitalization. Concomitant medications included calcium carbonate, cholecalciferol, acetylsalicylic acid, clopidogrel, esomeprazole, ezetimibe, metoprolol, ramipril, rosuvastatin. On Day 411, the subject presented to an emergency department for symptoms of chest pain. He was found to have non-ST elevated MI and was hospitalized for further care. On Day 412, he underwent percutaneous coronary intervention revascularization procedure during which a stent was placed in his lateral anterior descending artery. He was discharged from the hospital on Day 415. Study drug was continued. Adverse event was categorized as severe. The Investigator and Applicant deemed the event had no reasonable possibility of being related to study drug. *Reviewer comments: Notably, this subject had a history of dyslipidemia and was treated with medications clopidogrel and betablockers, which are commonly prescribed for underlying conditions that may put individuals at risk for CVD. Accordingly, this event is likely multifactorial, and unrelated to study intervention.*
(b) (6)	M16-000 (Substudy 1)	Cerebral Infarction	Treatment during event: Placebo Previous treatment: Risankizumab 1200 mg IV during IP1 and IP2 This event occurred 420 days after first dose of study intervention and	61-year-old female with history of CD (s/p bowel resection), hypothyroidism, osteoarthritis, glaucoma, hypothyroidism, joint pain, hemorrhoids, uterine bleeding, history of c-sections, s/p hysterectomy, and known smoker developed an infarction of her right middle cerebral artery, which required hospitalization Concomitant medications included calcium, fish oil, multivitamin, cyanocobalamin, levothyroxine, paracetamol, timolol, and potassium. On Day 420, the subject awoke feeling unwell and found that her left side was “not working.” She was evaluated in the emergency department for facial droop, slurred speech, confusion, difficulty using left side. The subject was

Subject ID	Trial	Adverse Event	Study Drug Details	Case Details
			250 days from first dose of placebo. Study intervention was continued.	found to have a middle cerebral artery due to a carotid arterial stenosis; she was hospitalized for further care. She underwent extracranial stent placement, thrombectomy, and carotid stenting. She remained hospitalized for rehabilitation and was ultimately discharged on Day 445. During her hospitalization, she was treated with aspirin, clopidogrel and tinzaparin. AE was categorized as severe. The Investigator and Applicant deemed the event had no reasonable possibility of being related to study drug. The Applicant and the investigator attributed this event to underlying obesity and pre-existing CD, which may increase risk of VTE. *Reviewer comments: Given the presence of multiple underlying risk factors for VTE, the underlying cause of this event is likely multifactorial.*
			M16-000 Substudy 3 (Long-term Extension Study)	
(b) (6)	M16-000 (Substudy 3)	Transient Ischemic Attack	Treatment during event: Risankizumab 180 mg SC Previous treatment: Enrolled in Trial M15-993: Risankizumab 200 mg IV every 4 weeks x 3 doses Risankizumab 600 mg IV every 4 weeks x 3 doses This event occurred 1709 days after first dose of study intervention. Study intervention was continued.	42-year-old obese female with history of CD, (s/p bowel resection and colostomy and subsequent colostomy take down), cholecystectomy, asthma, right ovarian cyst, postmenopausal, hypothyroidism, depression, anxiety, goiter, cataracts, sinus tachycardia, chronic renal insufficiency, pancreatitis, keratitis, and insomnia and known smoker was admitted to the hospital with a transient ischemic attack. Concomitant medications included lormetazepam, trazodone, hyaluronic acid, paracetamol, loperamide, calcium, vitamin D, bisoprolol, estradiol, venlafaxine, ketoprofen, salbutamol, probiotic, progesterone, domperidone, ultracet, sulfasalazine, montelukast, trazodone, racecadotril, tannic acid, and ultracet. The subject developed decreased motor and sensory loss of her entire left side of her body, as well as aphasia, dysphagia, dysarthria, and left retro-orbital pain. She was hospitalized and diagnosed with a transient ischemic attack. She remained hospitalized for 7 days, during which symptoms slightly improved. Further details regarding treatment provided during hospitalization and after discharge were not provided. Study drug was continued. AE was categorized as severe. The Investigator and Applicant deemed the event had no reasonable possibility of being related to study drug. The Applicant and the investigator attributed this event to underlying obesity, sedentary lifestyle, and pre-existing CD, which may increase risk of VTE.

Subject ID	Trial	Adverse Event	Study Drug Details	Case Details
				Reviewer comments: Given the presence of multiple underlying conditions (including CD, obesity, history of renal insufficiency, etc.) and administration of multiple concomitant medications, the underlying cause of this event is likely multifactorial.
(b) (6)	M16-000 (Substudy 3)	Sudden cardiac death	Treatment during event: Risankizumab 180 mg SC Previous treatment: Risankizumab 1200 mg IV (IP1 and IP2) This event occurred 306 days after first dose of study drug, 9 days after last dose of study intervention. Study drug was continued.	34-year-old male with history of CD, CD-related peripheral arthropathy, obesity (BMI 37.7), hiatal hernia, opioid abuse, allergies, and pneumonia. Concomitant medications included bismuth, omeprazole, and diphenhydramine. On Day 306, the subject became unresponsive while speaking with his father over the phone. Subsequently, the subject's father checked on the subject and found him nonresponsive. The subject's father administered Narcan, initiated CPR, and called emergency medical providers. On arrival, EMS providers noted that the subject was nonresponsive, felt "cool," and was noted to be in asystole. An airway was placed and "multiple rounds of advanced cardiovascular life support was performed without return of spontaneous and perfusing rhythm." The subject was transported to the emergency department. CPR was continued and he was treated with naloxone, sodium bicarbonate and epinephrine. Blood toxicology screen was positive for THC. Despite treatment, he was unable to be resuscitated and was pronounced dead. An autopsy confirmed cause of death as dysrhythmia and sudden cardiac death. Relevant excerpt from autopsy: "CV: The heart weighs 470 grams. The intimal surface of the aorta is free of significant atherosclerosis. The aorta and its major branches and the great veins are normally distributed and unremarkable. The pulmonary arteries contain no thromboemboli. The pericardium, epicardium, and endocardium are smooth, glistening, and unremarkable. The right ventricle is dilated. There are no thrombi in the atria or ventricles. The coronary arterial system is free of significant atherosclerosis. The atrial and ventricular septa are intact. The cardiac valves are unremarkable. The myocardium is dark red-brown and firm, without focal abnormalities. The right, left, and septal ventricular walls are 0.3 cm, 1.2 cm, and 1.2 cm thick, respectively."

Subject ID	Trial	Adverse Event	Study Drug Details	Case Details
				Adverse event was categorized as severe. The Investigator and Applicant deemed the event had no reasonable possibility of being related to study drug. *Reviewer comments: This subject had history of obesity, which are known risk factors for cardiac arrhythmia, and was known to take illegal drugs (documented opioid use). Blood toxicology results were notable for THC. Autopsy results were notable for dilation of right ventricle with no evidence of pre-existing atherosclerotic disease or thromboemboli. While limited data are available, it is likely the underlying cause of this event is multifactorial and may be unrelated to study intervention.*

Source: Reviewer Generated
Abbreviations: AE, adverse event; BMI, body mass index; CD, Crohn's disease; CPR, cardiopulmonary resuscitation; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; EEG, electroencephalogram; EMS, emergency medical services; GERD, gastroesophageal reflux disease; IP, induction period; IV, intravenous; MI, myocardial infarction; SC, subcutaneous; THC, tetrahydrocannabinol; VTE, venous thromboembolism

17.5. Safety Review: Risk of Venothromboembolic Events Associated With Risankizumab Exposure

Clinical Background

During the review cycle, [redacted] (b) (4) safety review was completed to assess whether there may be a risk of VTE associated with risankizumab exposure in CD patients.

Grouped Query: Venothromboembolic Events

A grouped query to assess risk of VTE in the primary induction (ISS1) and maintenance trial (M16-000 Substudy 1) safety databases were completed. Preferred terms included in the grouped query were deep vein thrombosis, thrombosis, cerebral infarction, and transient ischemic attack, and pulmonary embolism. A summary of the grouped query results for the primary induction and maintenance safety databases are presented in Table 104 and Table 105, respectively.

Table 104. TEAEs Associated With Venothromboembolic Events, Primary Safety Population, ISS1

Preferred Term	RZB 600 mg IV N=620 n (%)	RZB 1200 mg IV N=577 n (%)	Placebo IV N=432 n (%)	RZB 600 mg IV vs. Placebo IV Risk Difference (%) (95% CI)
Deep vein thrombosis	0	1 (0.2)	1 (0.2)	-0.2 (-0.7, 0.2)
Pulmonary embolism	0	2 (0.3)	0	0

Source: Adapted from table provided by Anne Bunner, PhD (Clinical Data Scientist)
Abbreviations: CI, confidence interval; ISS1, primary induction safety database; IV, intravenous; RZB, risankizumab; SC, subcutaneous; TEAE, treatment-emergent adverse event

[redacted] (b) (4)

Table 105. TEAEs Associated With Venothromboembolic Events, Primary Safety Population, Maintenance Trials (M16-000)

Preferred Term	RZB 180 mg SC Q8W N=179 n (%)	RZB 360 mg SC Q8W N=179 n (%)	Placebo SC Q8W N=184 n (%)	RZB 360 mg SC Q8W vs. Placebo SC Q8W Risk Difference (%) (95% CI)
Deep vein thrombosis	0	0	1 (0.5)	-0.5 (-1.6, 0.5)
Thrombosis	0	0	1 (0.5)	-0.5 (-1.6, 0.5)
Cerebral infarction	0	0	1 (0.5)	-0.5 (-1.6, 0.5)

Source: Adapted from table provided by Anne Bunner, PhD (Clinical Data Scientist)
Abbreviations: CI, confidence interval; IV, intravenous; Q8W, every 8 weeks; RZB, risankizumab; SC, subcutaneous; TEAE, treatment-emergent adverse event

A case review of all individuals that reported TEAEs associated with VTE was completed (Table 106). This case review included interim data submitted from M16-000 Substudy 3, an LTE study that was ongoing at the time of marketing application submission.

Table 106. Case Review of Subjects Who Reported Venothromboembolic Events (Trials M15-991, M16-006, M16-000)

Subject ID	Trial	Adverse Event	Study Intervention	Case Details
			Primary Induction Safety Database (ISS1)	
(b) (6)		Deep Vein Thrombosis and Pulmonary Embolism	Risankizumab 1200 mg IV This event occurred 21 days after first dose of study intervention. Study intervention was continued.	47-year-old female with history of CD, obesity (BMI of 42.3 kg/m2), dyspnea, cholelithiasis, osteoarthritis, latent tuberculosis, deep vein thrombosis (DVT), and pulmonary embolism (PE) after an eventration repair surgery, and former smoker developed DVT and PE that required hospitalization Concomitant medications included oral contraceptive (gestodene and ethinylestradiol), olmesartan, omeprazole, and loperamide. The subject was randomized to receive risankizumab 1200 mg IV and received her first dose on D1. On Day 22, she presented to a general practitioner for symptoms of shortness of breath, “heavy legs,” and difficulty walking short distances for 3 days. She was referred to the emergency department and CT scan was notable for DVT and bilateral PE for which she was admitted to the hospital on Day 24. She was treated with rivaroxaban. On Day 31, she was discharged, and the event was reported as resolved. The subject remained enrolled in the induction trial. Her second induction dose (Week 4 dose) was delayed due to hospitalization; she resumed study intervention on Day 45. She did not meet criteria for clinical response at the end of Induction Period (IP) 1 and was continued into IP2 during which she received an additional three doses of risankizumab 1200 mg IV therapy (Days 90, 108 and 140). She discontinued trial participation after IP2. AE was categorized as severe. The investigator and Applicant deemed the event had no reasonable possibility of being related to study drug. The Applicant and the investigator attributed this event to underlying obesity, CD, history of VTE, concomitant oral contraceptives, and history of smoking. *Reviewer comments: Given the presence of multiple underlying risk factors for VTE, the underlying cause of this event is likely multifactorial.*

Subject ID	Trial	Adverse Event	Study Intervention	Case Details
(b) (6)	M15-991	Pulmonary Embolism	Risankizumab 1200 mg IV This event occurred prior to administration of first dose of study intervention. Study intervention was continued.	47-year-old white female with history of CD and asthma was diagnosed with bilateral PE and ovarian vein thrombosis, which required hospitalization. Concomitant medications included prednisone 10 mg daily. The subject was randomized to receive risankizumab 1200 mg IV therapy. Prior to administration of risankizumab therapy on Day 1, the subject endorsed difficulty breathing and pain (location was not specified). An abdominal CT was completed, which was notable for bilateral PE and left ovarian vein thrombosis. Per report, the subject was hospitalized and received first dose of risankizumab therapy on the same day (Day 1). The subject was treated with enoxaparin, rivaroxaban, and nefopam. The hospitalization as complicated by development of colitis, for which she was treated with trimebutine, metronidazole, and ciprofloxacin. On Day 7, the event was reported as resolved and she was discharged from the hospital. There was no change in study drug. The subject completed IP1 and continued onto IP2 during which she was treated with risankizumab 180 mg SC therapy. After completion of IP2, she continued onto maintenance trial M16-000 and continued risankizumab 180 mg SC therapy. The AE of pulmonary embolism was categorized as serious, ovarian vein thrombosis as nonserious. AE was categorized as severe. The Investigator and Applicant deemed the event had no reasonable possibility of being related to study drug as symptoms and diagnosis occurred prior to administration of first dose of study drug. *Reviewer Comments: Event onset occurred prior to administration of first dose of risankizumab therapy and is unlikely related to study intervention.*

Subject ID	Trial	Adverse Event	Study Intervention	Case Details
Primary Maintenance Safety Database (Trial M16-000)				
(b) (6)	M16-000 (Substudy 1)	Thrombosis	<u>Treatment during event:</u> Placebo <u>Previous treatment:</u> Risankizumab 1200 mg IV during IP1 This event occurred 452 days after first dose of study intervention and 368 days from first dose of placebo. Study intervention was continued.	44-year-old white female diagnosed with history of CD, "widespread arthralgia," and former smoker developed DVT that required anticoagulant therapy. Concomitant medications including mesalamine, acetaminophen, and pantoprazole. The subject was randomized to receive risankizumab 1200 mg IV induction therapy and did not report any AEs in the induction trial. On Day 85, she continued onto the maintenance trial and was randomized to receive placebo therapy. On Day 453 of the maintenance trial, the subject developed a DVT of her right leg. No symptoms or diagnostic procedures completed to make the diagnosis were provided. She was treated with enoxaparin. On Day 463, the event was reported as resolved and enoxaparin was discontinued. There was no report of oral anticoagulant therapy. The subject continued placebo therapy in the maintenance trial. AE was categorized as mild. The investigator and Applicant deemed the event had no reasonable possibility of being related to study drug. The Applicant attributed this event to underlying CD, history of smoking and noted this event occurred over a year after risankizumab therapy was discontinued. *Reviewer comments: The subject has multiple underlying risk factors for VTE and this event occurred over 400 days after she received her last dose of risankizumab therapy. This event is unlikely related to study intervention.*

Subject ID	Trial	Adverse Event	Study Intervention	Case Details
(b) (6)	M16-000 (Substudy 1)	Deep Vein Thrombosis	Treatment during event: Placebo Previous treatment: Risankizumab 600 mg IV This event occurred 147 days after first dose of study intervention and 117 days from first dose of placebo. Study intervention was continued.	62-year-old white male with history of CD, IgM monoclonal gammopathy, hypertension, hyperlipidemia, left bundle branch block, angina, left anterior descending artery stenosis, coronary artery disease, mitral regurgitation, dilated cardiomyopathy, and former smoker developed deep vein thrombosis that required anticoagulation therapy. Concomitant medications including aspirin, atorvastatin, isosorbide mononitrate, glyceryl trinitrate sublingual spray, perindopril, and bisoprolol. The was randomized to receive risankizumab 600 mg IV induction therapy and did not report any AEs in the induction trial. On Day 85, she continued onto the maintenance trial and was randomized to receive placebo therapy. During the maintenance trial, the subject experienced several AEs. First, she developed an SAE of cardiac failure, which required hospitalization on Days 98-100. In addition, she developed shingles (Days 151-160), common cold (Days 182-188), and pneumonia (Days 185-203). On Day 204, she was reported to have a nonserious AE of left leg DVT, for which she was treated with rivaroxaban. No further details regarding preceding symptoms, diagnosis, or therapy were provided. The event was reported as resolved on Day 218. On Day 260, the subject developed pneumonia and was treated with antibiotics. Finally, on Day 290, she was diagnosed with left lung adenocarcinoma, after which she discontinued from the study. AE of DVT was categorized as moderate. The investigator and Applicant deemed the event had no reasonable possibility of being related to study drug. The Applicant attributed this event to underlying CD, smoking history, monoclonal gammopathy, cardiovascular disease and newly diagnosed lung cancer. *Reviewer comments: Given the presence of multiple underlying risk factors for VTE, the underlying cause of this event is likely multifactorial.*

Subject ID	Trial	Adverse Event	Study Intervention	Case Details
(b) (6)	M16-000 (Substudy 1)	Pulmonary Embolism	Treatment during event: Risankizumab 360 mg SC Previous treatment: Placebo induction therapy Placebo maintenance therapy Risankizumab rescue therapy (1200 mg IV x 1) This event occurred 159 days after risankizumab rescue therapy. Study intervention was continued.	47-year-old white female with history of CD, obesity, and family history of DVT diagnosed with PE that required hospitalization. The subject was enrolled in the induction trial and randomized to receive placebo. She was in clinical response after 12 weeks of induction therapy and continued into the maintenance therapy during which she continued placebo therapy. During the maintenance trial, she received risankizumab rescue therapy (risankizumab 1200 mg IV) on Day 274 and continued risankizumab 360 mg SC every 8 weeks from Day 317 onwards. On Day 433, she developed shortness of breath and was hospitalized for further evaluation. She underwent a pulmonary angiogram that was notable for pulmonary embolism and mild lower lobe consolidation. A subsequent echocardiogram was notable for a dilated right ventricle, dilated right atrium, tricuspid regurgitation, moderate pulmonary hypertension, and trace pericardial effusion. Details regarding treatment during hospitalization was not provided. She was discharged on Day 436, and rivaroxaban was initiated on Day 437. The subject continued in the trial without change in risankizumab study drug schedule. AE was categorized as serious. The investigator and Applicant deemed the event had no reasonable possibility of being related to study drug. The investigator reported that the cause of the event of pulmonary embolism was "insidious." The Applicant attributed this event to multiple underlying risk factors including CD, obesity (BMI 30.1 kg/m2), and family history of DVT. *Reviewer comments: Given the presence of multiple underlying risk factors for VTE, the underlying cause of this event is likely multifactorial.*

Subject ID	Trial	Adverse Event	Study Intervention	Case Details
(b) (6)	M16-000 (Substudy 1)	Cerebral Infarction	Treatment during event: Placebo Previous treatment: Risankizumab 1200 mg IV during IP1 and IP2 This event occurred 420 days after first dose of study intervention and 250 days from first dose of placebo. Study intervention was continued.	Refer to Table 103 for full details.
Long Term Extension Trial (M16-000 Substudy 3)				
(b) (6)	M16-000 (Substudy 3)	Transient Ischemic Attack	Treatment during event: Risankizumab 180 mg SC Previous treatment: Enrolled in Trial M15-993: Risankizumab 200 mg IV every 4 weeks x 3 doses Risankizumab 600 mg IV every 4 weeks x 3 doses This event occurred 1709 days after first dose of study intervention. Study intervention was continued.	Refer to Table 103 for full details.

Source: Reviewer Generated
Abbreviations: AE, adverse event; BMI, body mass index; CD, Crohn's disease; CT, computed tomography; IV, intravenous; SAE, serious adverse event; SC, subcutaneous

Potential Risk of VTE Associated With IL-23 Inhibitor Exposure

(b) (4)

A review of the drug labels for currently FDA-approved IL-23 inhibitors and literature review were completed to assess whether this risk of VTE may represent a class effect. At the time of this review, increased risk of clotting or risk of VTE are not included in the Warnings & Precautions or Adverse Reactions sections of the drug label for the following FDA-approved IL-23 inhibitors: risankizumab, guselkumab, and tildrakizumab. Additionally, a literature review did not reveal concern for increased clotting risk associated with IL-23 inhibitor exposure.

Discussion

Further review of the primary induction and maintenance safety databases were completed to determine whether risankizumab exposure may be associated with an increased risk of VTE in the patients with CD. A minority of enrolled subjects reported VTE during the trial duration. In the primary induction safety database, 3 of 577 (.005%) subjects treated with risankizumab 1200 mg IV, 0 of 620 (0%) subjects treated with risankizumab 600 mg IV, and 1 of 432 (0.002%) placebo subjects developed VTE. In addition, in the primary maintenance safety database, 3 of 184 (0.02%) placebo subjects developed VTE. There were no VTE events in the maintenance treatment arms (360 mg SC or 180 mg SC).

Importantly, there are several risk factors that may be associated with an increased risk of VTE. Known risk factors include obesity, smoking status, sedentary lifestyle, diabetes, and metabolic syndrome. In addition, many commonly used medications (e.g., oral contraceptives) may increase risk of clotting and/or VTE. Importantly, inflammatory bowel disease (IBD) may predispose to a hypercoagulable state. In fact, several consensus guidelines recommend anticoagulation for IBD patients who require hospitalization (Kornbluth et al. 2010; Van Assche et al. 2010; Van Assche et al. 2013). Additionally, corticosteroid exposure, which is commonly used for IBD treatment, may be associated with increased clotting risk. Therefore, it is oftentimes difficult to assess underlying cause of VTE that may occur in IBD patients. This was demonstrated in the case review completed for this review, as all affected subjects had underlying comorbid conditions or concomitant medications that may increase risk of VTE.

Finally, a review of the drug labels for currently FDA-approved IL-23 inhibitors (risankizumab, guselkumab, and tildrakizumab) and a literature search did not provide sufficient information to determine whether IL-23 inhibitor may be associated with an increased risk of VTE.

Conclusions

At the time of this review, there are insufficient data available to determine whether risankizumab exposure may be associated with an increased risk of VTE in CD patients.

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Not applicable.

19. Other Drug Development Considerations: Additional Information and Assessment

19.1. Patient Reported Outcome (PRO) Measures Proposed in Labeling

The Applicant proposed the following language in the annotated label for Skyrizi (risankizumab-rzaa):

(b) (4)	Module 2.7.3, Summary of Clinical Efficacy, 2.7.3.3.2.3.1, Table 16. Module 5.3.5.4, FACIT-Fatigue COA dossier

19.2. FACIT-F

The Functional Assessment of Chronic Illness Therapy–Fatigue score (FACIT-F) is a legacy 13-item PRO measure assessing symptoms and impacts of fatigue. Responses to FACIT-F items are scored from 0 (“Not at all”) to 4 (“Very Much”), and item scores are calculated by subtracting the item response score from 4, such that lower scores reflect greater fatigue (items 7 and 8 are reverse scored, i.e., item scores are calculated as 0+response score). The FACIT-F total score is calculated as the sum of item scores multiplied by 13, then divided by the number of items answered. The potential FACIT-F total scores range from 0 to 52, with higher scores reflecting less fatigue. A FACIT-F total score ≥40 is considered normal in the general healthy population (Cella et al. 2002; Montan et al. 2018; Villoria et al. 2017). Improvement in fatigue based on the FACIT-F total score has been included in FDA-approved labeling for medical products indicated to treat rheumatoid arthritis (RA), psoriatic arthritis, plaque psoriasis, iron deficiency anemia, and paroxysmal nocturnal hemoglobinuria.

Based on qualitative input from patients with moderate-severely active CD (n=30), fatigue is an important and relevant symptom that is part of their CD experience. Over 90% of participants interpreted the FACIT-F instructions, recall period, and response options as intended. Over 70% of participants interpreted the item stems as intended with the lowest proportion of correct

interpretation for items 1 “I feel fatigued” (n=22/30, 73%), 3 “I feel listless (“washed out”)” (n=21/30, 70%), and 6 “I have trouble finishing things because I am tired” (n=25/30, 83.3%).

Quantitative assessment of FACIT-F Item and Total Scores was conducted using data from the phase 3 induction studies (Study M16-006 and M15-991) and the phase 3 maintenance study (Study M16-000 Substudy 1). There was little FACIT-F missing data in all three studies indicating high adherence to this assessment. Extreme floor effects (i.e., >40% of participants endorsing the lowest response option) at baseline were not observed for any items in Study M15-991; however, they were observed in Study M16-006 for Items 10 “I am too tired to eat” and 11 “I need help doing my usual activities.” Extreme floor effects were observed at maintenance baseline in Study M16-000 for Item 2 “I feel weak all over,” Item 3 “I feel listless ('washed out'),” Item 5 “I have trouble starting things because I am tired,” Item 6 “I have trouble finishing things because I am tired,” Item 12 “I am frustrated by being too tired to do the things I want to do,” and Item 13 “I have to limit my social activity because I am tired.” Nonetheless, the FACIT-F Total Score seemed adequate to describe the baseline severity of fatigue in patients with moderate-severely active CD and sensitive to change in the context of use. Other quantitative assessments of reliability, validity, and ability to detect change for the FACIT-F total score demonstrated adequate results.

The Applicant proposed a range of 7 to 10 points as representation of clinically meaningful within-patient change from baseline to week 12 in the FACIT-F total score, derived by triangulating the results of anchor-based and distribution-based methods in the phase 3 induction studies. Interpretation of meaningful change based on the 7-category Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) is supported by the results of cognitive interviews for the PGI scales with 36 participants with moderate-severely active CD. The COA review determined the threshold proposed by the Applicant for interpretation of FACIT-F total scores is supported by the meaningful change analysis. However, the PGIS and PGIC anchor scales ask subjects to rate overall CD symptoms and do not directly address change in fatigue. Therefore, improvement on the anchor scales likely reflect improvement in more proximal CD symptoms. Thus, improvement in FACIT-F scores that is interpreted based on these anchor scales is likely an imprecise estimate of meaningful change in fatigue.

The evidence submitted by the Applicant demonstrates that the FACIT-F is fit-for-purpose in the proposed context of use for the risankizumab-rzaa development program. A statistically significant improvement in fatigue assessed by the FACIT-F comparing the risankizumab treatment arms to placebo was observed in the induction studies, but not in the maintenance study. Larger improvement in FACIT-F total scores was observed in the induction studies. Descriptively, there was still an improvement in the mean FACIT-F total score at Week 52 of the maintenance study compared to maintenance baseline. However, this improvement was not statistically tested due to multiple hypothesis testing procedure, and it was also not nominally significant The mean FACIT-F score at week 52 of the maintenance study was 38.2 (standard deviation 11.4, median 41.0, range 2.0 to 52.0).

19.3. Other PRO Data to Support Application

The Applicant assessed overall patient experience with SC self-injection with the SIAQ in the RLHS. The SIAQ is a 21-item PRO measure developed as a generic questionnaire based on

qualitative input from 6 patients with RA and 6 patients with CD and was quantitatively assessed in a population of RA subjects. It produces a transformed score ranging from 0 to 10 where higher scores reflect a better injection experience.

The Applicant did not propose labeling claims for the SIAQ. However, based on literature, the SIAQ appears appropriate to assess injection experience.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

Site inspections were conducted at four clinical sites, Sites# 120610 (Dr. Jonathan Chapman), 134989 (Dr. George Aaron DuVall), 87887 (Dr. Paul A. Hellstern Jr.), and 33899 (Dr. Shahriar Sedghi), and the Applicant, AbbVie, Inc. to assess the quality and integrity of the data submitted in this marketing application. Minor discrepancies in the CDAI subcomponents of patient-reported stool frequency, abdominal pain, and well-being scores were noted at one of the 4 clinical investigator sites (Site# 120610, Dr. Jonathan Chapman). These minor discrepancies between source records and Applicant data line listings had no impact on the primary or secondary efficacy endpoint assessments because they either resulted in no change in the total CDAI score for the visit or the discrepancy occurred at a timepoint that was not used in the primary or secondary efficacy endpoints. No discrepancies or issues were noted in the central reviewer's endoscopy subscores by segment and the SES-CD documenting endoscopic response. Refer to the Clinical Inspection Summary finalized in DARRTS on February 11, 2022, for full details.

During the Applicant inspection, data reliability concerns were identified related to data collection of CDAI subcomponent and total CDAI scores, related to inadequate protocol training, inadequate monitoring, and issues related to eCRF design and validation. Errors in the CDAI subcomponent and total CDAI score occurred in at least 104 subjects at 74 sites in Study M15-991 and in at least 207 subjects at 123 sites in Study M16-006. In general, most errors were attributed to transcriptional errors (e.g., Days 1 to 7 entered as Days 7 to 1) and due to incorrect entry of hematocrit values (e.g., incorrect entry as a decimal value versus percentage) and/or CDAI scores that should be excluded (i.e., CDAI scores from day(s) of endoscopy, bowel prep prior to endoscopy, or immediately after endoscopy). OSI review of the listing of CDAI score errors noted that the changes made to the Week 12 total CDAI score after the interim database lock in December 2020 resulted in a change in the patient's coprimary efficacy outcome (e.g., change from nonresponder to responder) in at least six subjects, and changes made to the Baseline total CDAI scores impacted subject eligibility in at least six subjects. The Applicant corrected and updated the CDAI data and included the primary analysis conducted on the final version of the corrected database in this submission, and FDA statistical team confirmed the conclusions.

Notwithstanding the data collection issues noted during the inspections, the data otherwise generated by the 4 clinical investigator sites inspected appear acceptable in support of the proposed indication.

In addition, the Office of Study Integrity and Surveillance (OSIS) conducted a remote regulatory assessment (RRA) of two clinical sites involved in the clinical portion of Study M19-128. An onsite inspection was not possible due to the ongoing COVID-19 global pandemic. At the sites reviewed, ORA investigators observed some objectionable conditions, including incomplete source documentation of two AEs by the principal investigator, incomplete documentation of unreported AEs and concomitant medications, and enrollment of subjects not eligible for trial enrollment. Refer to memo uploaded by Melkamu Getie Kebtie on March 8, 2022, under BLA 761105 for full details. After review, the review team concluded the data discrepancies did not impact the primary safety or efficacy analyses as majority of discrepancies did not result in change in overall clinical status (e.g., CDAI clinical response or remission). Therefore, the data generated are suitable to evaluate the proposed indication.

21. Labeling Summary of Considerations and Key Additional Information

Table 107. Summary of Prescribing Information

Full Prescribing Information Sections[a]	High-Level Summary of the Major Issues with the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI[b]
1 INDICATIONS AND USAGE	The Applicant's proposed indication for the treatment of patients with moderately to severely active Crohn's disease (CD) aged 16 years and older was narrowed to include only adults with CD. There were insufficient numbers of pediatric patients exposed to the to-be-marketed (TBM) dosing regimen in phase 3 trials to support approval in pediatric patients with CD (see Section 7.7.3).
2 DOSAGE AND ADMINISTRATION 2.1 Procedures Prior to Treatment Initiation	The recommended dosing regimen is 600 mg intravenously (IV) at Weeks 0, 4 and 8, followed by risankizumab 360 mg subcutaneously (SC) at Week 12 and every 8 weeks thereafter, which is consistent with the Applicant's proposal. Safety review of subjects with CD enrolled in phase 3 trials highlighted concern of hepatotoxicity associated with risankizumab exposure (see Section 7.7.1). Monitoring of liver enzymes and bilirubin is recommended baseline, prior to treatment initiation, and during induction up to at least 12 weeks.
3 DOSAGE FORMS AND STRENGTHS	A new vial presentation (600 mg/10 mL) was added for IV administration of the induction dose by a healthcare provider (see Section 6.1.1). In addition, to deliver the maintenance dosage, a new presentation of on-body injector with prefilled cartridge (360 mg/2.4 mL) was also added (see Sections 6.1.2 and 7.7.4). The IV induction dose is administered by a healthcare provider, but the patient can administer the subcutaneous maintenance dose after training in SC injection technique.
5 WARNINGS AND PRECAUTIONS 5.4 Hepatotoxicity in Treatment of Crohn's Disease	One subject enrolled in trial M16-006 developed concern for drug-induced liver injury (DILI) with a temporal association to risankizumab administration (see Section 7.7.1). The adverse reaction (AR) was added to the Warnings & Precautions section as a new subsection specific to CD and not the other approved indications because risk of hepatotoxicity has implications for prescribing decisions and patient management in subjects with CD at the recommended dosing regimen, which is higher than the dosing regimen for the other indications. Monitoring of liver enzymes and bilirubin is recommended at baseline, during induction, and up to 12 weeks after treatment initiation.

Full Prescribing Information Sections[a]	High-Level Summary of the Major Issues with the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI[b]
6 ADVERSE REACTIONS	6.1 Clinical Trials Experience Common ARs are described for induction separately from maintenance given the difference in doses and duration of treatment. The table of ARs for induction is based on pooled data from two phase 3 induction studies and one phase 2 study using 600 mg IV at Weeks 0, 4 and 8 versus placebo. The table of ARs reported with maintenance treatment is from a single placebo-controlled maintenance study. Rates of infection and serious infection during maintenance are higher in the treatment versus placebo arms and are included in labeling. A subsection describing change in baseline low-density lipoprotein (LDL-C) and total cholesterol levels observed during induction and maintenance treatment is included. 6.2 Immunogenicity The number of subjects enrolled in clinical trials that developed antidrug antibodies (ADA) was included, but the number of subjects was too small to make a meaningful comparison to ADA negative subjects and no conclusion regarding the two groups is made in labeling.
8 USE IN SPECIFIC POPULATIONS	8.1 Pregnancy Pregnancy Exposure Registry At the time of this review, there are insufficient data to support whether risankizumab exposure during pregnancy may be associated with risk to maternal, fetal, and/or infant health. Therefore, at the time of approval for the CD indication, a PMR requiring a prospective, registry-based, observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to risankizumab containing products regardless of indication during pregnancy will be issued (see Section 22). A statement to inform patients and prescribers about this pregnancy registry was included in labeling. Clinical Considerations Information regarding risk of adverse pregnancy outcomes and embryo/fetal risk associated with risankizumab exposure in patients with CD was added. 8.4 Pediatric Use The data available were insufficient to support approval in pediatric patients with CD (see Section 7.7.3). A statement that safety and effectiveness in pediatric patients with CD have not been established is included. 8.5 Geriatric Use There were insufficient data to assess differences in safety/effectiveness in geriatric versus younger subjects with CD (see Sections 16.3.1.2 and 16.3.2.2). The recommended dosage for treatment of patients with CD aged 65 years and older is the same as in younger adults.

Full Prescribing Information Sections[a]	High-Level Summary of the Major Issues with the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI[b]
12 CLINICAL PHARMACOLOGY	12.2 Pharmacodynamics (b) (4) in labeling was removed as these biochemical factors are not validated as biomarkers to monitor disease progression. In addition, (b) (4) on its own is not well established as a marker of disease improvement (as many factors can impact (b) (4)). 12.3 Pharmacokinetics Specific Populations Pharmacokinetics (PK) data comparing geriatric (patients aged 65 years and older) and younger adult subjects is included. Drug Interaction Studies A statement to specify that drug-drug interactions in patients with CD was not established is included.
14 CLINICAL STUDIES 14.3 Crohn's Disease	Induction Studies: Given baseline differences in enrolled subjects, all efficacy analysis results are provided separately for each induction study (CD-1 and CD-2) in the prescribing information (PI). Results from the two induction studies are presented in separate tables. Endpoint results for the subgroups of with/without prior biologic failure (i.e., inadequate response, loss of response, or intolerance to one or more biologics) are included descriptively in the table. Endpoints in the tables were revised to include the coprimary and key secondary endpoints. Results from the 12-week open-label extended induction period are not included because the study design did not allow for interpretation of results. A general description of timing of onset of clinical response and clinical remission during induction therapy was included in the text. Information regarding improvement in abdominal pain and stooling frequency from baseline was included descriptively in the text, as improvement in these symptoms is clinically relevant for patients with CD. Maintenance Study: Only subjects who met criteria for clinical response defined by CDAI score (a decrease of 100 points or more from baseline) at baseline were included in labeling to reflect the Division's currently recommended definition of clinical response. Endpoints in the table were updated to include the clinically relevant endpoints that demonstrated statistical significance. Endpoint results for the subgroups of with/without prior biologic failure are included descriptively in the table. Secondary endpoints of "(b) (4)" and "(b) (4) and (b) (4)" were removed as these endpoints could not be tested based on the prespecified multiplicity-controlled testing hierarchy.

Full Prescribing Information Sections[a]	High-Level Summary of the Major Issues with the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI[b]
	The terminology of "(b) (4) is not included because there is currently no standard and widely accepted definition for this term. Patient-level data regarding the proportion of subjects who met criteria for (b) (4) (b) (4) were removed as these were not included as prespecified endpoints, and there are no data to support a treatment difference between treatment and placebo arms Induction and Maintenance: "(b) (4)" was removed from labeling as the SES-CD score, which is used in the coprimary endpoints and other secondary endpoints, provides a comprehensive assessment of endoscopic improvement. (b) (4) results were not included as clinical relevance of these results were unclear in labeling as a difference between treatment and placebo subjects was only observed in the induction trials and not sustained through maintenance treatment. (b) (4) were not included in labeling as rate of hospitalizations may be affected by factors unrelated to underlying CD, and this secondary endpoint did not reach statistical significance between risankizumab treatment arms and placebo in the maintenance trial.

[a] Some sections may not be included because those sections may not have major issues (or changes).
[b] The finalized PI is the PI that will be approved or is close to being approved
Abbreviations: ADA, antidrug antibodies; AR, adverse reaction; CD, Crohn's disease; CDAI, Crohn's disease activity index; CRP, c-reactive protein; DILI, drug-induced liver injury; FACIT-F, functional assessment of chronic illness therapy - fatigue; IV, intravenously; LDL-C, low-density lipoprotein cholesterol; PI, prescribing information; PK, pharmacokinetics; PMR, postmarketing requirement; SC, subcutaneously; SES-CD, Simple endoscopic score-Crohn's disease; TBM, To-be-marketed

22. Postmarketing Requirements and Commitments

The following postmarketing requirements (PMRs) and postmarketing commitments (PMCs) will be issued at the time of approval of risankizumab for the moderately to severely active CD indication.

22.1. Postmarketing Requirements Under 505(o)3

4294-1 Conduct an observational study to assess the incidence of severe acute liver injury in adults with moderately to severely active Crohn's disease who are exposed to risankizumab, relative to other therapies used to treat Crohn's disease. Compare rates (per person-time) or risks (proportion of patients with a minimum amount of follow-up). Describe and justify the choice of appropriate comparator population(s). Specify concise case definition for severe liver injury and validation of algorithm(s) to identify severe liver injury in the proposed data source. For the risankizumab-exposed and

comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Ensure that the data source allows for average follow-up for at least 1 year. Specify a minimum sample size and justify the precision of the estimate achievable with the proposed study.

Draft Protocol Submission: *12/2022*
Final Protocol Submission: *06/2023*
Study Completion: *06/2033*
Interim /Other:[12] *06/2028*
Final Report Submission: *12/2033*

4294-2 A prospective, registry-based, observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to risankizumab-containing products regardless of indication during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, preterm births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, neonatal deaths, and infections, will be assessed through at least the first year of life.

Draft Protocol Submission: *12/2022*
Final Protocol Submission: *06/2023*
Study Completion: *06/2033*
Final Report Submission: *06/2034*

4294-3 Conduct an additional pregnancy study that uses a different design from the prospective pregnancy registry established to fulfil postmarketing requirement study 2 (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm births in women exposed to risankizumab-containing products regardless of indication during pregnancy compared to an unexposed control population.

Draft Protocol Submission: *12/2022*
Final Protocol Submission: *12/2023*
Study Completion: *06/2032*
Final Report Submission: *06/2033*

[12] Interim or "other" milestones may include interim report submission or subject accrual milestones. Justification for these milestones should be described in Section D.3.

4294-4 Perform a lactation study (milk only) in lactating women who have received Skyrizi (risankizumab) to assess concentrations of Skyrizi (risankizumab) in breast milk using a validated assay and to assess the effects on the breastfed infant.

Draft Protocol Submission: 06/2023
Final Protocol Submission: 12/2023
Study Completion: 06/2025
Final Report Submission: 06/2026

22.2. Postmarketing Commitments

The Applicant has received orphan designation for the indication of pediatric CD and are exempt from required pediatric studies under Pediatric Research Equity Act (PREA). In anticipation of a need for data to support the use of Skyrizi (risankizumab) in the treatment of pediatric patients with CD, the following PMC was proposed.

4294-5 Conduct a one-year, randomized, trial to evaluate the safety, efficacy, and pharmacokinetics of Skyrizi (risankizumab) in pediatric patients 2 to 17 years of age with moderately to severely active Crohn's disease.

Draft Protocol Submission: 10/2022
Final Protocol Submission: 03/2023
Trial Completion: 03/2029
Final Report Submission: 12/2029

4294-6 Conduct a LTE study to evaluate the long-term safety of Skyrizi (risankizumab) in pediatric patients 2 to 17 years of age with moderately to severely active Crohn's disease who participated in postmarketing commitment study 5. This study can be conducted as part of postmarketing commitment study 5.

Draft Protocol Submission: 12/2022
Final Protocol Submission: 03/2023
Trial Completion: 03/2033
Final Report Submission: 09/2033

Although the drug interaction information included in labeling for the plaque psoriasis indication may not be directly applicable for the proposed CD indication because of the differences in two populations, such as inflammatory burden and the proposed higher dosage for CD than the approved dosage for plaque psoriasis and psoriatic arthritis. Therefore, the following PMC is proposed.

4294-7 Conduct a clinical trial to assess whether Skyrizi (risankizumab-rzaa) alters the metabolism or pharmacokinetics of cytochrome P450 (CYP) substrates in patients with

Crohn's disease treated with risankizumab-rzaa (e.g., using a cocktail of relevant CYP probe drugs).

Study Completion: *08/2022*
Final Report Submission: *03/2023*

There was no verification testing performed on the functionality of the audible cue to signal the initiation of injection to mitigate the potential device related delivery issues (i.e., leakage, incomplete dosing, etc.). The following PMC was proposed:

4295-1 Conduct verification testing or establish acceptance criteria related to the audible feedback (click, timing, correlation with dose delivery, click decibels) function of the device. Provide verification study results including verifiable design input requirements or testing requirements for the audible feedback used to indicate the activation button has been fully pressed.

Final Report Submission: *12/2022*

22.3. Enhanced Pharmacovigilance

In addition to the above studies, the Applicant has agreed to provide expedited reports of liver injury (for any indication). The Applicant developed a detailed questionnaire for follow-up for these reports (Figure 30). Additionally, the Applicant will include interim and cumulative summaries of liver injury in periodic safety reports, by indication.

22.3.1. Preferred Terms for Expedited Reporting of Liver Injury

The Applicant proposed to report on serious cases from clinical trials that meet the following preferred term (PT) search criteria for potential drug-induced liver injury (DILI) cases:

- Acute hepatic failure
- Cholestatic liver injury
- Drug-induced liver injury
- Hepatic encephalopathy
- Hepatic failure
- Hepatic necrosis
- Hepatitis fulminant
- Hepatocellular injury
- Hepatotoxicity
- Liver injury
- Mixed liver injury

22.3.2. Skyrizi Liver Injury Questionnaire

Figure 30. Skyrizi Liver Injury Questionnaire

Follow-up Questionnaire for Hepatic Adverse Events Reported with Risankizumab

Patient Information:
Name:
Street Address:
City: State: Zip code:

Reference Numbers:
AER#:
Affiliate#:
Other Reference#:

Patient Information:

Initials:	Patient ID:	Sex: Male ☐ Female ☐	Date of Birth:	Age at time of event:	Age group^:

^ Age group codes: Neonate (Day 0 to Day 27), Infant (28 days to 23 months), Child (2 years to 11 years), Adolescent (12 years to 17 years), Adult (18 years to 64 years), Elderly (65 years and over)

Adverse Event	Event Onset date (d/m/y)	Event end date (d/m/y)	Event Criteria+	Was this caused by suspect product? ++	Outcome **

+ Event Criteria codes: Serious (Death, Hospitalization, Prolonged Hospitalization, Congenital anomaly, Life-threatening, Medically Important, Persistent or Significant Disability) or Non-serious
++ Causality Code: Reasonable Possibility, No Reasonable Possibility, Non-Assessable
**Outcome codes: Death, Recovered, Not recovered, Recovering, Worsened, Unknown, or Recovered with Sequela (provide Sequela if available)

Please provide detailed event information including symptoms the patient experienced leading up to the events:

Please provide what treatment or interventions the patient underwent for the events:

Were there any prodromal or associated signs or symptoms, including fever, malaise, rash, eosinophilia, dark urine, jaundice, etc? Specify:

Did the event result in a liver transplant or placement on a waiting list? Yes ☐ No ☐ If yes, provide date:

Patient Medical History:

Liver disease Yes ☐ No ☐	History of Guillain-Barre syndrome Yes ☐ No ☐	History of signs of hepatic decompensation (i.e., ascites, esophageal varices, hepatic encephalopathy) Yes ☐ No ☐	
Hepatitis Yes ☐ No ☐ Specify: A ☐ B ☐ C ☐ other:	Connective Tissue Disease Yes ☐ No ☐ Specify:	Transplant Yes ☐ No ☐ Organ: Date:	Cardiac disorders-specifically right heart failure or hypotension Yes☐ No ☐
Fatty liver disease Yes☐ No ☐ Specify: Grade:	Biliary Tract disease Yes ☐ No ☐ Specify:	Autoimmune Liver disease Yes ☐ No ☐ Specify:	Recent non-hepatitis Viral Illness Yes ☐ No ☐
Alcoholic hepatitis Yes ☐ No ☐	Hepatocellular cancer Yes ☐ No ☐	HIV Yes ☐ No ☐	Cirrhosis Yes ☐ No ☐ Specify baseline cirrhosis status and Child-Pugh score:
Blood transfusion Yes ☐ No ☐	Hepatitis Vaccination history:	Tattoo History:	
Recent Travel history:	Pertinent family liver disease:	Recent Acetaminophen Yes ☐ No ☐ If YES, provide details in Suspect Product table below	

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Follow-up Questionnaire for Hepatic Adverse Events Reported with Risankizumab

Suspect Product:

Name	Dose	Form	Frequency	Route	Start Date (d/m/y)	End Date (d/m/y)	Indication	If stopped, did event abate? If so, provide date

Please provide product Lot number for time of event: **Expiration date:**

If unable to provide Lot number, provide rationale: discarded ☐ not accessible to physician ☐ not on patient's file ☐ did not receive in original package ☐ not legible on package ☐

If Abbvie product was discontinued, was it restarted? Yes ☐ No ☐	**Date:**	**Did the event recur? Yes ☐ No ☐ Unknown ☐**

Concomitant (medication at time of event) **(C), Past (P), Treatment (T) medication information** (Please include herbal, recreational, over the counter and supplements):

Name	C, P or T	Form	Dose	Frequency	Route	Start date (d/m/y)	End Date (d/m/y)	Indication

Please provide Laboratory and Diagnostic Test results (or attach lab/diagnostic reports)

Laboratory test	Date (prior to Abbvie Product)	Results (units of measure)	Date (Peak during treatment)	Results (units of measure)	Date (when improved or resolved	Results (unit of measure)	Reference range (units of measure)
Albumin							
Alkaline Phosphatase							
ALT							
AST							
Ammonia							
Direct Bilirubin							
Indirect Bilirubin							
Total Bilirubin							
GGT							
LDH							
CPK							
PT/INR							
ANA							
CMV IgM and IgG							

Diagnostic test	Date	Results (key findings) (If desired attach results)
Liver biopsy (with histology)		
Ultrasound		
CT Scan		
ERCP		
MRI		
HIV Ab		

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Risankizumab AESI Hepatic Letter Ver 1- 08 Apr 2021 2

Follow-up Questionnaire for Hepatic Adverse Events Reported with Risankizumab

EBV panel (VCA IgM, VCA IgG, EBNA)										
ASMA										
Anti-mitochondrial Ab Test										
IgG										
Anti-LKM-1, 2, or 3										
ANCA										
Double-stranded DNA										
Anti-SLA/LP										
Complete Blood Count with Differential										
Acetaminophen levels										
Hepatitis A,B,C, E serologies										

Height: cm ☐ in ☐	Weight: kg ☐ lbs ☐	Race/Ethnicity:
Tobacco use: Yes ☐ No ☐ (amount/start/stop dates):		Alcohol use: Yes ☐ No ☐ (amount/type/start and stop dates):
Allergies: Yes ☐ No ☐ (type and manifestation):		Illicit drug use: Yes ☐ No ☐ (amount/type/start and stop dates):
IV Drug Use: Yes ☐ No ☐ (amount/type/start and stop dates):		Obesity: Yes ☐ No ☐; Specify BMI:

If the patient died, Date of Death:	Autopsy: Yes ☐ No ☐ Unknown ☐	Autopsy Date:
Autopsy results:	Cause of Death:	

Does reporter agree to have HCP/MD contacted? Yes ☐ No ☐ Not Applicable ☐

Physician/HCP Name and Specialty:		
Street Address:		
City:	State:	Zip:
Phone Number:		

Person completing form:

Name:		
Street Address:		
City:	State:	Zip:
Phone Number:		

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Source: BLA 761262/761105-S016 Applicant's Information Request submission dated May 25, 2022,

23. Financial Disclosure

Table 108. Covered Clinical Studies: M16-006, M15-991, M16-000, M19-128[1]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4921		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 64		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

[1] A remote regulatory assessment (RRA) completed by OSIS for two clinical sites involved in Study M19-128 revealed that several subinvestigators had not filed financial disclosure forms. Further information was requested from the Applicant. In response, the Applicant clarified that the subinvestigators identified were considered AbbVie employees, and, therefore, not required (February 2013) to file financial disclosure forms. Subsequently, the Applicant submitted an updated list of investigators which clearly outlined which investigators or subinvestigators involved in Study M19-128 were considered AbbVie employees.

24. References

Literature

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25. Review Team

Table 109. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Jay Fajiculay
Nonclinical Reviewer	Dinesh Gautam
Nonclinical Team Leader	Sushanta Chakder
Office of Clinical Pharmacology Reviewer(s)	Liping Pan (DIIP), Hongshang Li (DPM)
Office of Clinical Pharmacology Team Leader(s)	Insook Kim (DIIP), Lian Ma (DPM)
Clinical Reviewer	Suruchi Batra
Clinical Team Leader	Suna Seo
Analytics and Informatics Staff **Associate Director for Analytics and Informatics**	Ki Chung Matilde Kam
Statistical Reviewer	Ben Wong
Statistical Team Leader	Paul Imbriano
Cross-Disciplinary Team Leader	Suna Seo
Associate Director for Labeling	Joette Meyer
Division Director (pharm/tox)	
Division Director (OCP)	
Division Director (OB)	Laura Lee Johnson
Division Director (clinical/designated signatory authority)	Jessica Lee

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 110. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	**BLA 761262**: Andrea George (Reviewer); Riley Myers (Team Leader); Anita Brown (Regulatory Business Project Manager); Vicky Boarders-Hemphill, Zhong Li, Maxwell Van Tassell, Wendy Tan, Lindsey Brown **BLA 761105/S-016**: Milos Dokmanovic (Reviewer); Riley Myers (Team Leader); Anita Brown (Regulatory Business Project Manager); Vicky Borders-Hemphill, Wendy Tan, Zhong Li, Maxwell Van Tassell
OPDP	Kyle Snyder (Reviewer)
OSI	Cheryl Grandinetti (Reviewer); Phillip Kronstein (Team Leader)
OMPI/DMPP	Maria Nguyen (Reviewer); Marcia Williams (Team Leader)
OSE/DEPI	Joel Weissfeld (Reviewer)
OSE/DMEPA	Sarah Vee (Reviewer); Idalia Rychlik (Team Leader)
OSE/DRM	Theresa Ng (Reviewer); Laura Zendel (Team Leader)
OSE/DPV	Jamie Klucken (Reviewer); Lisa Wolf (Team Leader)
OSE/DMEPAI	Matthew Barlow (Reviewer); Oluwamurewa Oguntimein (Team Leader); Jason Flint (Associate Director)
OND/DPMH	Carrie Ceresa (Reviewer); Miriam Dinatale (Team Leader)
OND/CDS	Anne Bunner (Reviewer); Deangelo McKinley (Team Leader)
OND/DCOA	Susan Pretko (Reviewer); David Reasner (Director)
OCP	Bindi Nikhar (Reviewer)
CDRH	Kyran Gibson (Reviewer); Alan Stevens (Team Leader)
Medical Editor	Hyo Sook Song (Reviewer); Elizabeth Hayes (Reviewer)

Abbreviations: CDRH, Center for Devices and Radiological Health; CDS, Clinical Data Science; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPV, Division of Pharmacovigilance; DRM, Division of Risk Management; OCP, Office of Combination Products; OND, Office of New Drugs; OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Table 111. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Signatory Authority	**Signature:** Jessica J. Lee -S Digitally signed by Jessica J. Lee -S Date: 2022.06.13 12:13:59 -04'00'		
Clinical	Jessica Lee	OND/OII/DG	All sections ☐ Authored ☐ Contributed ☒ Approved – all

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Suna Seo	OND/OII/DG	Sections 1, 2, 7.7.4, 8.4, 9.1, 11 ☒ Authored ☒ Contributed 3.1, 4, 6.2, 6.3, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7.1, 7.7.2, 7.7.3, 8.3, 10 ☒ Approved – all
Cross-Disciplinary Team Lead	**Signature:** Suna Seo -S Digitally signed by Suna Seo -S Date: 2022.06.13 12:06:27 -04'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Cross-Disciplinary	Joette Meyer	OND/OII/DG	Section 21 ☐ Authored ☐ Contributed ☒ Approved
Associate Director for Labeling	**Signature:** Joette M. Meyer -S Digitally signed by Joette M. Meyer -S Date: 2022.06.10 08:55:59 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Suruchi Batra	OND/OII/DG	Sections 3, 4, 6.2, 6.3, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7.1, 7.7.2, 7.7.3, 8.3, 10, 15, 17 ☒ Authored ☒ Contributed Sections 2, 7.7.4,8.4, ☐ Approved
Reviewer	**Signature:** Suruchi K. Batra -S Digitally signed by Suruchi K. Batra -S Date: 2022.06.13 12:00:53 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Jay Fajiculay	OND/ORO/ DRO-II	Section 12 ☒ Authored ☐ Contributed ☐ Approved
Project Manager	**Signature:** Jay R. Fajiculay -S Digitally signed by Jay R. Fajiculay -S Date: 2022.06.09 14:51:55 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Insook Kim	OCP/DIIP	Sections 5, 6.1, 6.3, 8.1, 8.2, 14 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Insook Kim -S Digitally signed by Insook Kim -S Date: 2022.06.10 14:18:48 -04'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Clinical Pharmacology	Liping Pan	OCP/DIIP	Sections 5, 6.1, 6.3, 8.1, 8.2, 14 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Liping Pan -S Digitally signed by Liping Pan -S Date: 2022 06 10 08:20:20 04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Lian Ma	OCP/DPM	Sections 6.1, 6.3, 14.4 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Lian Ma -S Digitally signed by Lian Ma -S Date: 2022.06.13 10:53:54 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Clinical Pharmacology/Pharmacometrics	Hongshan Li	OCP/DPM	Sections 5, 6.1, 14.4 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Hongshan Li -S Digitally signed by Hongshan Li -S Date: 2022.06.13 11:09:26 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Sushanta Chakder	OND/DPTII	Sections 5.1, 7.1, 8.4 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Sushanta K. Chakder -S Digitally signed by Sushanta K. Chakder -S Date: 2022.06.10 09:55:17 -04'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Pharmacology/Toxicology	Dinesh Gautam	OND/DPTII	Sections 5.1, 7.1 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Dinesh C. Gautam -S Digitally signed by Dinesh C. Gautam -S Date: 2022.06.10 09:44:21 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Riley Myers	OPQ/OBP/DBRRI	Section 9 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Riley Myers -S Digitally signed by Riley Myers -S Date: 2022.06.10 15:01:45 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Andrea George	OPQ/OBP/DBRRI	Section 9 ☐ Authored ☐ Contributed ☒ Approved
Reviewer	**Signature:** Andrea L. George -S Digitally signed by Andrea L. George -S Date: 2022.06.09 18:24:51 -04'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Product Quality	Milos Dokmanovic	OPQ/OBP/DBRRI	Section 9 ☐ Authored ☐ Contributed ☒ Approved
Reviewer	**Signature:** Milos Dokmanovic -S Digitally signed by Milos Dokmanovic -S Date: 2022.06.13 11:35:02 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Biometrics	Paul Imbriano	OB/DBIII	Sections 6.2, 6.3.1, 6.3.2, 7.6.3, 16 ☒ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Paul M. Imbriano -S Digitally signed by Paul M. Imbriano -S Date: 2022.06.09 20:45:02 -04'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Biometrics	Hong Wen B. Wong	OB/DBVII	Sections 6.2, 6.3.1, 6.3.2, 16 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Hong Wen B. Wong -S Digitally signed by Hong Wen B. Wong -S Date: 2022.06.09 21:40:33 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Cross-Disciplinary	David Reasner	OND/ODES/DCOA	Section 19 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** David Reasner -S Digitally signed by David Reasner -S Date: 2022.06.09 17:27:20 -04'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Cross-Disciplinary	Susan Pretko	OND/ODES/DCOA	Section 19 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Susan M. Pretko -S Digitally signed by Susan M. Pretko -S Date: 2022.06.09 16:47:04 -04'00'		

Continued: Table 93. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Laura Higginbotham	OND/OCHEN/DDLO	Section 7.7.2 ☐ Authored ☐ Contributed ☒ Approved
Consult	**Signature:** Laura B. Higginbotham -S Digitally signed by Laura B. Higginbotham -S Date: 2022.06.09 15:36:17 -04'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Clinical	Eileen Craig	OND/OCHEN/DDLO	Section 7.7.2 ☒ Authored ☐ Contributed ☐ Approved
Consult	**Signature:** Eileen M. Craig -S Digitally signed by Eileen M. Craig -S Date: 2022.06.09 15:26:00 -04'00'		

Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

SUNA C SEO
06/16/2022 03:22:07 PM