CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761262Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761262 and 761105 (s-016)
PDUFA Goal Date	June 16, 2022
OSE RCM #	2021-1863
Reviewer Name(s)	Theresa Ng, PharmD, BCPS
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD , BCPS
Review Completion Date	June 15, 2022
Subject	Evaluation of Need for a REMS
Established Name	Risankizumab-rzaa
Trade Name	Skyrizi
Name of Applicant	AbbVie, Inc
Therapeutic Class	Interleukin-23 (IL-23) inhibitor
Formulation(s)	For intravenous (IV) infusion: 600 mg/10 mL (60 mg/mL) in single-dose vial For subcutaneous (SC) injection: 360 mg/2.4 mL (150mg/ml) in single-dose prefilled cartridge in an on-body delivery system (OBDS)
Dosing Regimen	Induction therapy with 600 mg administered by IV at Week 0, Week 4, and Week 8; followed by maintenance therapy with 360 mg administered by SC at Week 12, and every 8 weeks thereafter

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Skyrizi (rizankizumab-rzaa) is necessary to ensure the benefits outweigh its risks. Skyrizi was previously approved in adults under a Biologics Licensing Application (BLA) 761105 on April 23, 2019 for the treatment of plaque psoriasis (PsO) and on January 21, 2022 for plaque arthritis (prior approval supplement [PAS] 14). Both approved indications have the same dosing regimen of 150 mg injected subcutaneously (SC) at Week 0, Week 4, and every 12 weeks thereafter. AbbVie, Inc (AbbVie) submitted two separate applications for rizankizumab which are being reviewed concurrently: a Non-NME original BLA 761262 and a supplemental BLA (sBLA) 761105 (S-16) for the proposed indication as a treatment for moderately to severely active Crohn's Disease (CD) in patients 16 years and older. BLA 761262 is proposed for the intravenous (IV) induction regimen of 600 mg IV at Week 0, 4, and 8, and BLA 761105/ S-16 is proposed for the SC maintenance regimen of 360 mg at Week 12, and every 8 weeks thereafter via an on-body delivery system (OBDS). The risks associated with Skyrizi for CD are similar to those associated with the previously approved indications of PsO and PsA except for two new safety concerns, dyslipidemia and the risk of hepatotoxicity observed with the induction dosing regimen. The Applicant did not submit a REMS with this application but proposed additional risk management activities involving additional pharmacovigilance studies to evaluate the safety risks including (b) (4) , and use in pregnancy.

The Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of Skyrizi outweigh its risks. Most of the risks associated with Skyrizi for CD are similar to those known for currently approved indications and are included in the approved labeling, except for two new safety concerns of dyslipidemia and hepatotoxicity. Dyslipidemia will be included as an Adverse Reaction in labeling to inform prescribers of this adverse event as the clinical reviewer concluded that the magnitude of changes in lipid parameters seen in the CD clinical development program were considered not clinically significant. The risk of hepatotoxicity is thought to be due to the higher dose exposure for induction in CD compared to the approved dose for psoriasis. The Agency's hepatologist and clinical reviewer agreed that limiting exposure to three doses of 600 mg IV over 8 weeks with liver test monitoring would lower the risk to an acceptable level. The hepatotoxicity risk will be added in labeling under Warnings and Precautions with instructions for liver test monitoring and as an Adverse Reaction to inform prescribers of this risk. In addition, the Applicant will be required to conduct postmarketing studies to detect significant drug induced liver injuries. Gastroenterologists are the likely prescribers for Skyrizi for CD. They are expected to be familiar with the risk of hepatotoxicity and monitoring needs as several of the biologics (e.g., infliximab and natalizumab) used in the treatment of CD are labeled with this risk.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the Biological Licensing Application (BLA) Skyrizi (rizankizumab-rzaa) is necessary to ensure the benefits outweigh its risks. AbbVie, Inc (AbbVie) submitted a Biologic Licensing Application (BLA) 761262 and an efficacy

supplement to BLA 761105 (S-16) for Skyrizi with the proposed indication as a treatment for moderately to severely active Crohn's disease (CD) in patients 16 years and older. Skyrizi (BLA 761105) was approved for adults with plaque psoriasis (PsO) in April 2019 and psoriatic arthritis (PsA) in January 2022. This application is under review in the Division of Gastroenterology (DG). Other than known risks associated with IL-23 antagonists such as hypersensitivity reactions, increased risk of infections, reactivation of latent infections (i.e., tuberculosis), and increased risk of infection with live vaccines, two new risks of dyslipidemia and hepatotoxicity were identified in the Skyrizi CD development program. The Applicant did not submit a REMS with this application but proposed risk management activities consisting of enhanced pharmacovigilance, a postmarketing epidemiologic study, and voluntary pregnancy registry to evaluate the safety risks including (b) (4) (b) (4) infections, (b) (4), and use in pregnancy.

2 Background

2.1 PRODUCT INFORMATION

Skyrizi (Risankizumab-rzaa), an interleukin 23 (IL-23) antagonist, is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. Risankizumab (RZB) inhibits the release of pro-inflammatory cytokines and chemokines. AbbVie submitted two 351(a) applications for RZB: a Non-NME original BLA 761262 and an efficacy supplement BLA (sBLA) 761105 (S-16) for the proposed indication as a treatment for moderately to severely active CD in patients 16 years and older.[a] BLA 761262 is for the proposed intravenous (IV) induction regimen of 600 mg IV to be infused every 4 weeks at Week 0, 4, and 8 and BLA 761105/ S-16 is for the proposed subcutaneous (SC) maintenance regimen of 360 mg SC (i.e., 360 mg single-dose prefilled cartridge (PFC)) to be administered starting at Week 12, and every 8 weeks thereafter via an on-body delivery system (OBDS). The OBDS is further discussed in section 6 below. The induction dose should be administered by IV infusion over a period of at least one hour by a healthcare professional in a healthcare setting such as an infusion clinic or inpatient setting, whereas the SC maintenance regimen may be self-administered into the thigh or abdomen by patients in their home after receiving training and demonstrating appropriate use of the OBDS with the prefilled cartridge.

Skyrizi was previously approved in 2019 in the United States (US) under BLA 761105 and by the European Medicines Agency (EMA) for the treatment of moderate to severe plaque psoriasis (PsO) in adult patients who are candidates for systemic therapy or phototherapy with a dosing regimen of 150 mg SC at Week 0, Week 4, and every 12 weeks thereafter. Skyrizi also recently received approval in the US under BLA 761105/S-14 on January 21, 2022 for the treatment of active psoriatic arthritis (PsA) in adults with the same dosing regimen as in the PsO indication. Several approved Skyrizi formulations are available for PsO and PsA indications consisting of single-dose prefilled pens (at 150 mg/ml and 75mg/0.83ml), and single-dose prefilled syringes (at 150mg/ml) for SC injection. For the proposed indication of CD, the Applicant is proposing a singled-dose vial of 600 mg/10ml (60mg/ml) for the

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

induction treatment as an IV infusion, and a single-dose prefilled cartridge of 360mg/2.4ml (150mg/ml) to be used with the on-body delivery system (OBDS) for the maintenance regimen.

Other IL-23 antagonists currently available in the US include Tremfya (guselkumab), BLA 761061, approved in 2017 for PsO and PsA, and Ilumya (tildrakizumab-ASMN), BLA 761067, approved in 2018 for PsO. Stelara (ustekinumab) is an IL-12/IL-23 antagonist, approved for PsO and PsA under BLA 125261, and CD under BLA 761044.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA761262 and BLA 761105 (S-16) relevant to this review:

- 4/23/2019: BLA 761105 for Skyrizi (Risankizumab-rzaa) injection approved for the treatment of moderate-to-severe plaque psoriasis (PsO) in adults who are candidates for systemic therapy or phototherapy
- 3/23/2021: AbbVie submitted a Prior Approval Supplement (PAS) for Skyrizi, BLA 761105, Supplement-14 (S-14), for the proposed indication of PsA
- 9/16/2021: AbbVie submitted BLA 761262 and BLA 761105/S-016 for the treatment of moderately to severely active Crohn's disease in patients 16 years and older
- 11/15/2021: BLA 761105/S-16 granted priority review via the Filing Communication letter
- 12/28/20211: The Agency sent an Information Request (IR) for additional information on the use of the OBDS in its intended environment
- 1/10/2022: AbbVie submitted an amendment for BLA 761105/S-16 in response to the Agency's December 28, 2021 Information Request (IR)
- 1/21/2022: Skyrizi (BLA 761105/S-14) approved for PsA. No new safety issues were identified.
- 2/24/2022: Major amendment granted for BLA 761262 and BLA 761105 (S-16) in response to the January 10, 2022 IR which provided additional information on the use of the OBDS. The goal date was extended to June 16, 2022
- 5/16/2022: The Agency sent labeling and PMR/PMC Discussion Comments to the Applicant.[1]
- 5/20/2022: The Agency conducted a teleconference with AbbVie to discuss the inclusion of both the 180 mg and 360 mg SC maintenance dose in labeling.[2]
- 5/25/2022: AbbVie submitted an amendment in response to the Agency's May 16, 2022 labeling comments. In addition, AbbVie submitted an efficacy supplement to BLA 761105/S-18 which includes the Chemistry Manufacturing and Controls (CMC) data to support the 180 mg/1.2 ml PFC and OBDS combination product presentation, updated PFC and OBDS stability data, updates to the USPI label, carton, and container labeling for the 180 mg presentation, along with a cross-reference to supporting dosing, safety, and efficacy information.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Crohn's disease (CD) is a chronic inflammatory bowel disease that may affect any part of the gastrointestinal tract from the mouth to the anus. The pattern of inflammation is often cyclical, and individuals experience periods of symptomatic relapse and remission. The disease can affect persons of any age, and its onset is most common in the second and third decades. Female individuals are affected slightly more than males. The CD incidence is highest in North America and Europe, with estimates of 23.8 and 15.4 per 100,000 person-years in North America and Europe, respectively.[3] The clinical presentation includes abdominal pain and diarrhea which may be complicated by intestinal fistulization or obstruction.[b] Total hospitalization costs for CD increased annually by 3% from 2003 to 2008, and the mean hospitalization cost was $11,345 in 2014.[4]

3.2 Description of Current Treatment Options

The goal of CD therapy is to induce and then maintain remission. Several groups of drugs are approved to treat CD. Patients with mild disease are typically treated with 5-aminosalicylic acid (5-ASA), antibiotics, and nutritional therapies. Corticosteroids and immunomodulators such as methotrexate or 6-mercaptopurine (6-MP) may be given if the patient does not respond or presents with more extensive disease. Patients with moderately to severely active CD are candidates for treatment with biologic therapies such as tumor necrosis factor (TNF) antagonists (adalimumab, infliximab, certolizumab pegol), anti-integrin agents, (natalizumab and vedolizumab), and interleukin antagonist (ustekinumab).

Several factors may limit the use of conventional therapies such as corticosteroids and immunomodulators for CD. Systemic corticosteroids are ineffective as maintenance therapy and immunomodulators have a slow onset of action, have limited efficacy, and are associated with adverse events (AEs), such as allergic reactions, pancreatitis, myelosuppression, nausea, infections, hepatotoxicity, and malignancy. Biologics provide new options for patients failing conventional therapy and lead to improved treatment beyond symptom control. Despite the benefits of available biologic therapies, many patients do not respond to initial treatment (primary non-response) or lose treatment response over time (secondary loss of response).[5c] For approved anti-TNFs, approximately 40% of patients will experience primary non-response, and secondary loss of response occurs in approximately 50% of patients at 1 year. Approximately 61% of patients on vedolizumab will experience primary non-response at 6 weeks, and 48% will have loss of response between 6 months and 1 year. For patients receiving ustekinumab, approximately 55% will experience primary non-response at Week 8, and loss of response is about 41% at 1 year. Associated risks of biologics and factors that exclude candidates for biologics (e.g., patients with prior demyelinating disorders, patients with congestive heart failure,

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

patients at increased risk of serious infections or patients with history of malignancies) may limit their use.

Of note, the TNF alfa antagonists (Humira BLA 125057 , Cimzia BLA 125160, and Remicade BLA 103772) for CD were approved with a REMS consisting of a MG and a Communication Plan (CP) to mitigate the risk of serious infections, including serious fungal infections such as histoplasmosis; the MG remains as part of the approved labeling and the CP REMS have since been eliminated (Humira on July 2011, Cimzia on July 2011, and Remicade in August 2011) as the goals of communicating the risk were met.[6] Similarly, Stelara, an IL-12/IL-23 antagonist, was approved with a Medication Guide (MG) and CP REMS in 2009 to mitigate the risk of serious infections, malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS) by alerting and warning healthcare providers about these risks. The MG was removed from the REMS and maintained as part of the approved labeling in 2012 and the CP REMS was eliminated in 2017 as the Stelara REMS goal of educating prescribers on the risks were satisfied and no further safety issues were identified necessitating continuation of the REMS. All of the IL-23 antagonists, including Skyrizi, have warnings related to hypersensitivity reactions, infections, use in patients with tuberculosis, and need for appropriate vaccination prior to initiating therapy in their prescribing information (PI). While multiple treatment options are available for moderate-to-severe CD, there remains a need for additional treatments, particularly in those who do not respond or those who experienced lost treatment effect, and those who are not able to tolerate available therapies. See appendix for summary of FDA approved biologic therapies for CD.

4 Benefit Assessment

The efficacy and safety of RZB for CD was evaluated in three global phase 3 studies consisting of two induction studies, Study M15-991 (NCT03104413) and Study M16-006 (NCT03105128) and a maintenance study, Study M16-000 Sub-study 1 (NCT03105102). The Applicant also provided a pharmacokinetic bridging study, Study M19-128 (NCT05274100) to establish bioequivalence of the proposed to-be-marketed (TBM) induction IV (600 mg/vial, 60 mg/mL) and maintenance SC (360 mg/2.4 mL OBDS, 150 mg/mL) products to the products used in the phase 3 studies (induction IV product: 300 mg/vial, 90 mg/mL; maintenance SC product: 4 injections x 90 mg/mL in a prefilled syringe (PFS), 90 mg/mL) as they were quantitatively and qualitatively different.

For the induction studies, both M15-991 and M16-000 were multicenter, randomized, double-blind, 12-week, placebo-controlled studies evaluating RZB induction treatment (RZB 600 mg IV or 1200 mg IV or placebo) at Weeks 0, 4, and 8 in subjects 16 years to 80 years of age with moderately to severely active CD[d]. For the maintenance study, Study M16-000 Sub-study 1 was a 52-week randomized withdrawal, double-blind, placebo-controlled maintenance study (RZB 180 mg or 360 mg or had RZB treatment

[d] Moderately to severely active CD is defined as a CDAI of 220 to 450, a daily average SF of ≥ 4 and/or average daily APS ≥ 2, and a Simple Endoscopic Score (SES) – CD (excluding the narrowing component) of ≥ 6, or ≥ 4 for isolated ileal disease, confirmed by central review.

withdrawn [referred to as placebo] SC every 8 weeks). Sub-study 1 enrolled subjects who were clinical responders in Studies M15-991 and M16-006. The co-primary endpoints for all three pivotal studies were clinical remission defined as a Crohn's Disease Activity Index (CDAI) less than 150 and endoscopic response (i.e., greater than 50% decrease in simple endoscopic score for Crohn's disease [SES-CD] from baseline) at Week 12 for the induction studies and at Week 52 for the maintenance study. Evaluation of secondary endpoints would be conducted based on a prespecified ranked testing sequence and include assessments over various timepoints of measures associated with improvement in signs and symptoms of CD (i.e., SF/APS clinical remission, CDAI clinical response[e] and remission), quality of life (QoL) such as FACIT-Fatigue scores, and healing of the gastrointestinal mucosa (i.e., endoscopic remission, ulcer-free endoscopy). Data from the Intent-to-Treat population (i.e., those who received at least one dose of the study drug during the 12-week induction period or those who received one dose of study drug from the Sub-study 1) were analyzed for efficacy.

Induction studies: Study M15-991 and Study M16-006

Study M15-991 included subjects who had inadequate response or intolerance to one or more approved biologic agents (BIO-IR) for CD (infliximab, adalimumab, certolizumab, natalizumab, vedolizumab, and/or ustekinumab) while Study M16-006 enrolled subjects who were BIO-IR and non-BIO-IR (i.e., those who were intolerant to conventional therapy such as corticosteroids, aminosalicylates, and immunomodulators, but not biologic therapy). Additionally, both studies included a second treatment period (Induction Period 2) to evaluate continued treatment with RZB in subjects who did not achieve clinical response[f] at Week 12 after the initial 12-week induction treatment. These subjects received either reinduction with RZB 1200 mg IV or initiation of RZ 180 mg or 360 mg SC maintenance treatment.

Subjects in Study M15-991 and Study M16-006 were randomized 1:1:1 and 2:2:1, respectively. Study M15-991 consisted of 569 subjects (191 subjects in the RZB 600 mg IV arm, 191 subjects in the RZB 1200 mg IV arm, and 187 subjects in the placebo arm). Study M16-006 consisted of 850 subjects (336 subjects in the RZB 600 mg IV arm, 339 subjects in the RZB 1200 mg IV arm, and 175 subjects in the placebo arm).

The two induction studies achieved statistical significance for the two primary co-endpoints of clinical remission and endoscopic response for both doses of RZB with similar results across both studies. See below for a summary of results from the induction studies for the co-primary endpoints of clinical remission (Table 1) and endoscopic response (Table 2) .

[e] CDAI clinical response as a reduction of CDAI $\geq$ 100 points in baseline, or CR-100

[f] Clinical response per the Applicant as based on SF and APS (≥ 30% decrease in SF and/or ≥ 30% decrease in APS and both not worse than baseline)

Table 1. CDAI Remission Results at Week 12 , Studies M15-991 and M16-006

	Study M15-991			Study M16-006		
Parameter	**Placebo (N=187)**	**RZB 600mg (N=191)**	**RZB 1200mg (N=191)**	**Placebo (N=175)**	**RZB 600mg (N=336)**	**RZB 1200mg (N=339)**
CDAI remission, n (%)	37 (19.8)	80 (42.0)	77 (40.3)	43 (24.6)	152 (45.2)	141 (41.6)
Missing due to COVID-19	2	1	0	2	2	1
Treatment difference, % [CI[1]]		22.1 [13.1, 31.0]	20.5 [11.6, 29.5]		20.7 [12.4, 29.0]	16.7 [8.5, 24.9]
p-value		<0.001	<0.001		<0.001	<0.001

Source: Draft Integrated Review for BLA 761262 and BLA 761105/ S-16, accessed May 12, 2022

Table 2. Endoscopic Response at Week 12, Studies M15-991 and M16-006

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

Source: Draft Integrated Review for BLA 761262 and BLA 761105/ S-16, accessed May 12, 2022

Clinical statistical significance ($p < 0.001$) was demonstrated by RZB in both treatment arms over placebo for both studies in the majority of key secondary endpoints except for no draining fistular at Week 12 (not statistically significant for both RZB doses in both studies), resolution of extraintestinal manifestations (EIMs) at Week 12 (not statistically significant for RZB 1200 mg dose in Study M16-006), and enhanced SF/APS clinical response at Week 4 (not statistically significant for RZB 1200 mg dose in Study M15-991).

Maintenance study: M16-000

Four hundred forty subjects were randomized 1:1:1 (155 subjects in the RZB 180 mg arm, 142 subjects in the RZB 360 mg arm, and 143 subjects in the withdrawal [placebo SC] arm) and evaluated for efficacy. The demographic ratios in M16-000 were similar to those in the induction studies, with a similar ratio of males to females and the majority of subjects were White. Baseline characteristics were representative of the population of moderate to severe CD.

The co-primary endpoints of clinical remission and endoscopic response met statistical significance for both RZB 180 and 360 mg SC arms compared to placebo. See Table 3 for a summary of results for the maintenance study.

Table 3. M16-600 Sub-Study 1 Maintenance Study Results at Week 52

		CDAI Clinical Remission		Endoscopic Response	
Treatment	**Sample Size**	**Remission rate (%) and 95% CI**	**Difference in rate versus placebo, 95% CI, and p-values1**	**Response rate (%) and 95% CI**	**Difference in rate versus placebo, 95% CI, and p-values1**
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	56.8 (47.7, 65.8)	14.2 (2.6, 25.7) (p = 0.016)	48.5 (39.4, 57.6)	30.6 (20.6, 40.7) (p < 0.001)

Source: Draft Integrated Review for BLA 761262 and BLA 761105/ S-16, accessed May 12, 2022

All secondary endpoints failed to show a statistically significant difference between treatment and placebo arm with the exception of RZB 360 mg SC for the first key secondary endpoint of SF/APS clinical remission. However, several key secondary endpoints such as ulcer-free endoscopy and deep remission, endoscopic remission were numerically higher in both RZB maintenance doses than placebo. Due to the multiplicity hierarchy strategy, no further statistical testing on the rest of the secondary endpoints were conducted. The clinical reviewer concluded that both maintenance doses were comparable. Though not statistically significant, the 360 mg dose was favored over the 180 mg dose in 6 other endpoints (ulcer-free endoscopy, endoscopic remission, FACIT-Fatigue, SF, abdominal pain remission, and CDAI clinical remission and endoscopic remission) while the 180 mg dose was favored over 360 mg dose in 5 endpoints (maintenance of CDAI clinical remission, corticosteroid-free remission, CDAI clinical response, CDAI clinical remission and endoscopic response, and CD-related hospitalization). Efficacy results were similar to those seen in the induction studies for clinical responses rates of subjects with Bio-IR versus non-Bio-IR status; the RZB groups consistently showed higher CDAI clinical remission and endoscopic response rates compared to placebo across the RZB subgroups. Both maintenance doses were comparable.

Overall, the clinical reviewer concludes that RZB demonstrated statistically significant results for the two primary endpoints of clinical remission and endoscopic response for both induction and maintenance therapies.[g] Several secondary endpoints favor RZB compared to placebo. In addition, response rates for clinical remission and endoscopic remission favor those who are non-BIO-IR, and for RZB treatment groups compared to placebo.

[g] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5 Risk Assessment & Safe-Use Conditions

The safety population for RZB for CD consists of subjects in the induction and maintenance trials. The induction safety database consists of 1197 subjects who received RZB induction therapy from the two pivotal Phase 3 induction studies, M15-991 and M16-006, with additional support from a Phase 2 study, M15-993 (NCT02031276). Study M15-993 is a randomized double-blinded placebo-controlled study assessing 200mg IV and 600 mg IV induction therapy (n = 41) versus placebo (n = 39). The maintenance safety database consists of 297 Sub-study 1 subjects in Study M16-000. The overall safety database includes 620 subjects exposed to the proposed TBM induction dose (RZB 600 mg IV) and 142 subjects exposed to the TBM maintenance dose (360 mg SC). Total exposure for the TBM dose is 141 person years and 130 in-person years for induction and maintenance, respectively.

In the induction studies, a greater proportion of subjects treated with RZB reported mild treatment-emergent adverse events (TEAEs), whereas a greater proportion of placebo subjects reported severe AEs (SAEs), SAEs with fatal outcome, and AEs leading to study drug discontinuation compared to subjects treated with RZB. The proportion of patients who reported at least one SAE was 41 of 620 subjects (6.6%) in the RZB 600 mg IV arm, 23 of 577 (4%) subjects in the RZB 1200 mg IV arm, and 67 of 432 (15.5%) subjects in the placebo arm. The most frequent SAEs reported by system organ class (SOC) preferred term was gastrointestinal disorder with the highest events of CD. Similarly, the most frequent AE leading to treatment discontinuation was CD and was more frequent in the placebo group, likely due to poorly controlled underlying CD. Treatment emergent adverse events (TEAEs) greater than 2% of patients and higher than placebo in the induction studies include upper respiratory infections, rash, headache which are already include in the approved labeling for RZB.

In the maintenance study, the proportion of subjects that reported SAEs was similar across treatment and placebo groups: 17 of 155 (11%) subjects in the RZB 180 mg SC arm, 18 of 142 (12.7%) subjects in the RZB 360 mg SC arm, and 15 of 143 (10.5%) subjects in the placebo arm. The clinical reviewer determined that the SAEs yielded no meaningful differences between RZB treatment groups versus placebo and the proportion of SAEs were similar across RZB treatment groups. Ten subjects discontinued study drug due to AEs (RZB 180 mg SC: 3 AEs (1.9%), RZB 360 mg SC: 4 AEs (2.8%), and placebo group: 3 AEs (2.1%)) with GI disorder the most commonly reported event. The clinical reviewer concluded these events were likely due to long-term sequelae of underlying CD, rather than ongoing inflammation secondary to poorly controlled underlying CD. TEAEs greater than 3% of patients and higher than placebo include upper respiratory tract infection, arthralgia, abdominal pain, and injection site reactions.

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 patient populations were generally similar. No clinically meaningful trends were identified in the types of AEs reported in the two groups.

Infection

Infection is a known risk and is included as a Warnings and Precautions of approved IL-23 antagonists, including RZB. Infections and serious infections during the 12-week induction studies occurred in 20%

and 1%, respectively, of the RZB 600 mg group compared with 25% and 4%, respectively, of the placebo group. In the maintenance study (through Week 52), the rate of infections and serious infections for RZB 360 mg occurred in 34% and 65% compared with 40% and 2% of the placebo group after induction.

Hypersensitivity

Hypersensitivity reactions are a known risk for IL-23 antagonists and are included as a warning and precaution in the current labeling of several of the IL-23 antagonists for PsO. Hypersensitivity including anaphylaxis (b) (4) was added to the Warnings and Precautions section of labeling for RZB with the recently approved supplement for the PsA indication (BLA 761105/S-14) but was not originally included in the proposed labeling for RZB for CD. No significant differences in hypersensitivity reactions between treatment arms and placebo were identified in the RZB CD program. Hypersensitivity/injection site reaction incidence was low: 8.5% in the RZB treatment arms vs 3.5% in the placebo arm for RZB. Less than 5% of subjects developed antibodies to RZB and none of the antibodies to RZB were associated with changes in clinical response or safety for CD. The Division of Pharmacovigilance (DPV-1) conducted a postmarket analysis of all adverse events associated with RZB using the FDA Adverse Event Reporting System (FAERS) database and the medical literature and found an association between RZB and anaphylaxis.[7] Accordingly, the clinical reviewer recommended to add hypersensitivity including anaphylaxis (b) (4) to the Warnings and Precautions section to align with the currently approved labeling.

Deaths

A total of 3 deaths occurred in the safety population: 1 in the RZB treatment group who received the 1200 mg induction dose (Study M15-991) and 2 in the placebo arm (Study M16-006); no deaths occurred in subjects < 18 years old, and no deaths occurred in the maintenance study safety population. The clinical reviewer concluded the death that occurred in the subject receiving RZB 1200 mg was unrelated to the study drug and likely due to complications from underlying squamous cell lung cancer.

Overall, the clinical reviewer concluded that the safety profile of RZB for CD is consistent with the approved indications for RZB except for two new risks identified in the clinical program for CD. These new risks include dyslipidemia and hepatotoxicity and are further described below.

5.1 DYSLIPIDEMIA

Dyslipidemia was noted by the clinical reviewer in both the induction and maintenance studies with small numerical increases in the lipid parameters of total cholesterol, low density lipoprotein cholesterol (LDL-C), triglyceride (TG) and decreases in high density lipoprotein cholesterol (HDL-C), which did not vary notably from baseline compared with placebo. LDL-C increased 6.6 mg/dl from baseline at Week 12 with the RZB 600 mg IV induction dose and LDL-C increased by 2.8 mg/dl from baseline at Week 52 with the RZB 360 mg SC maintenance dose. There were no MACE events reported in the induction study and 5 MACE events in the maintenance study; 3 were in study Sub-study 1 (1 subject treated with RZB 180 mg SC, 1 subject treated with RZB 360 mg SC, and 1 subject in the placebo treatment group) and 2 in Sub-study 2, however, the clinical reviewer concluded these cases were unrelated to study drug as all of the subjects associated with these cases had underlying comorbid conditions and/or concomitant medications that increased the risk of dyslipidemia. Overall, the clinical reviewer noted that the

magnitude of dyslipidemia did not appear to be clinically meaningful and unlikely to significantly impact overall cardiovascular disease risk. As dyslipidemia is not a known class-related risk for IL-23 antagonists, this risk will be included in section 6.1 (Adverse reaction) in labeling.

5.2 HEPATOTOXICITY

Hepatotoxicity is a new safety risk identified in the RZB CD clinical development program. Hepatic adverse reactions and elevations in aminotransferases up to 3-fold the upper limit of normal (ULN) were reported in patients in both the induction and maintenance studies. The most common event was transient elevation in liver enzymes, which spontaneously resolved over time and study drug was continued. Thirty-seven subjects exposed to RZB were evaluated for potential drug induced liver injury (DILI) across the three pivotal studies; 32 were determined as unlikely, the remaining 5 were considered probable with one that met Hy's law criteria.[h] All 5 of the probable cases were in Study M16-006. No cases were identified in the placebo subjects and no cases were identified in studies M16-991 or M16-000. The case that met the Hy's law criteria consisted of a 30-year old Asian man with normal baseline liver enzymes and no history of alcohol who presented with rash after two doses of RZB 600 mg. This subject's alanine aminotransferase (ALT) was > 1000 but presented with mild scleral icterus. The subject was treated with methylprednisolone and quickly recovered. Four of the Temple's corollary cases were concerning for transient elevations of liver enzymes that may be associated with RZB exposure.

The review team was concerned that RZB therapy may be associated with transient elevation in liver enzymes and potential for hepatotoxicity if used in individuals with pre-existing liver disease and/or individuals receiving concomitant medications that carry risk of hepatotoxicity. Of note, more severe clinical manifestations of hepatoxicity (DILI) were seen with the higher induction doses, while transient elevation in liver enzymes (that self-resolved despite continuation of RZB maintenance therapy) was observed with maintenance therapy. DG consulted the Division of Hepatology and Nutrition (DHN) for their input. The DHN reviewer concurred that the case that met Hy's law criteria as probable RZB associated DILI.[8] The DHN reviewer could not determine if there is a dose dependent relationship between the 600 mg and 1200 mg arms in the clinical studies but believes the liver injury is likely due to a dose threshold that was reached for the CD indication and not of significant risk for the lower doses used in the approved indications. The DHN reviewer suggested limiting RZB induction to 600 mg IV for 3 doses over 8 weeks with liver test monitoring to mitigate the risk to an acceptable level. The reviewer also recommended risk mitigation through labeling via the Warnings and Precautions (Section 5) and potentially in other sections (labeling negotiations are ongoing at the time of this review), enhanced pharmacovigilance, and postmarket studies to detect significant DILI should RZB receive approval for CD. The labeling should include information on liver enzyme monitoring (at baseline and monthly before each 600 mg dose and one month after last induction dose). The clinical reviewer agreed with the DHN reviewer.

[h] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

6 Expected Postmarket Use

6.1 Healthcare Setting

The likely prescribers for RZB are gastroenterologists who manage patients with Crohn's disease. The likely prescribers for RZB would be familiar with the risk for hepatotoxicity as several biologics (e.g., infliximab and natalizumab) approved for moderate to severe CD have a similar risk described in labeling.

The IV induction regimen for RZB for CD is intended to be administered by a healthcare professional in a healthcare setting such as an infusion clinic or in a healthcare provider setting, whereas the SC maintenance regimen may be self-administered by patients in their home after receiving training and demonstrating appropriate self-administration with the OBDS.

6.2 On-Body Delivery System (OBDS)

The Applicant proposed an on-body delivery system (OBDS) for the SC administration of the TBM maintenance dose of RZB for CD. (b) (4)

The Applicant did not evaluate the proposed OBDS in the phase 3 maintenance trial (M16-000, Sub-study 1), instead, the maintenance dose was administered via four SC injections of RZB 90 mg/ml PFS. The Applicant performed a pharmacokinetic (PK) study, Study M19-128, in 393 healthy subjects to bridge the bioequivalence (BE) of the drug substances. In addition, the Applicant conducted a human factor (HF) study on the safety and usability of the OBDS in parallel to the BE study but did not evaluate the TBM user interface (e.g., packaging, labeling, devices).[9] In the BE study, 10% of subjects reported device-related complaints and dosing failures. The BE study identified 14 total device failures due to use errors, fluid path obstruction, and manufacturing.[10] Additionally, there was a high rate of injection site reactions (ISRs) due to pain, itching, erythema, pruritus, swelling, induration, edema, discomfort, bruising, and irritation reported in subjects receiving the proposed SC maintenance doses using the OBDS compared to the PFS; the ISRs were of mild severity and self-limiting with resolution within 72 hours and mainly related to device adhesive and injection volume. During the review of the HF study, there were theoretical concerns brought up by the review team that the auditory alarms may be misinterpreted as the alarms for when the on-body injector is not working and when the injection is "completed" were similar. Patients may misinterpret this and remove the device prematurely causing leakage of drug. As a result of the identified deficiencies, the Applicant submitted revisions to the information for use (IFU) to mitigate the risks associated with the identified manufacturing and use error issues. In addition, the Applicant submitted interim data from a Real Life Handling Study (RLHS), M116-000 Sub-study 4, to further support the safety and efficacy of the OBDS for the SC maintenance dose of RZB for CD. Interim data from the RLHS did not report ISR events in patients with CD. DG consulted the Division of Pharmacovigilance (DPV -1) to perform a search in FAERS for cases of selected device issues, specifically for device leakage and audio alarm errors with the Repatha OBDS.[11] The FAERS search (reports received through February 15, 2022) results were reassuring as there were very few reported cases of device error from leakage during injection (59 cases out of 1,254 reports or 5%; of those 6 cases (< 1%) were attributed to user error); no cases were identified related to audio alarm

misinterpretation. Based on the interim RLHS and FAERS report, the clinical reviewer concluded that the OBDS for the administration of the maintenance dose of RZB is acceptable and labeling is sufficient to mitigate potential user errors.

7 Risk Management Activities Proposed by the Applicant

In addition to proposed labeling and routine reporting/pharmacovigilance, the Applicant proposes additional pharmacovigilance studies to evaluate the safety risks associated with RZB including (b) (4) and use in pregnancy.

8 Discussion of Need for a REMS

CD is a chronic progressive disease of the GI tract and patients often undergo cycles of relapse and remission. Patients may experience severe and debilitating symptoms that could result in surgical intervention. Available treatment options, specifically biologics have improved the outcomes in patients with moderate to severe CD, however, 40% to 60% of patients on biologics may not respond or lose treatment effect within a year. In addition, some patients may not be candidates for biologics due to health-related conditions. While multiple treatment options are available for moderate-to-severe CD, there remains a large unmet need for additional treatments.

The clinical reviewer recommends approval of RZB for moderately to severely active CD in adults on the basis of the efficacy and safety information currently available. The clinical reviewer concluded that Studies M16-006, M15-991, and M16-000 demonstrated clinically meaningful and statistically significant benefit of RZB compared to placebo for both achieving clinical remission and endoscopic response in subjects with moderately to severely active CD. Both induction doses (600 mg IV and 1200 mg IV) and maintenance doses (180 mg SC and 360 mg SC) demonstrated statistical significance at week 12 after 3 IV induction doses, and up to Week 52 on SC maintenance doses, respectively. Key secondary endpoints of endoscopic remission and clinical relapse further support the efficacy of RZB for CD. Given the currently available efficacy and safety data, the clinical reviewer concluded that the induction dose be limited to 600mg IV. However, for the maintenance dose, based on comparable efficacy and safety data, the clinical reviewer concluded that both the 180 mg and 360 mg SC maintenance doses are acceptable for approval. The clinical reviewer acknowledges ongoing CMC validation review for the 180 mg PFC and 180 mg/1.2 ml OBDS presentation, as only the 360 mg PFC and 360 mg/2.4 ml OBDS presentation were originally proposed as the TBM dose. At the time of this review, the review division intends to approve the 360 mg PFC and OBDS presentation for the maintenance dose in this review cycle and update the labeling post-approval when the review of the CMC data for the 180 mg PFC and OBDS presentation is completed and acceptable.

Although the Applicant proposes RZB for the treatment of moderately to severely active CD in patients 16 years and older, there were very few subjects aged 16 to less than 18 enrolled in the clinical trials and the pediatric patients enrolled in the CD clinical trials were of Tanner stage 5 pubertal development, which is closer to the adult prepubertal development. For this application cycle, the clinical reviewer

does not recommend approval of RZB for CD in the 16 to less than 18 year age group due to inadequate safety data and recommends issuing a postmarketing commitment (PMC) to assess long-term safety and efficacy of RZB in adolescent pediatric subjects with moderately to severely active CD age 12 to less than 18 years. The approved indication for RZB will be for moderately to severely active CD in adults.

The clinical reviewer agreed that BE was established in the PK bridging study between the products used in the phase 3 studies and the RZB TBM products. Though there were deficiencies in the safety data for the proposed TBM OBDS device, the clinical reviewer determined the TBM OBDS device acceptable based on supportive data from the interim RLHS submitted during the review cycle and the results from the FAERS report on the Repatha OBDS, which is functionally the same OBDS proposed for the maintenance dose of RZB for CD. The FAERS report found a very low incidence of device failures due to leakage or auditory malfunctions. Mitigation of possible errors associated with use of the OBDS will be done via labeling, which will include an IFU.

The safety profile of RZB for CD for both induction and maintenance doses was similar and consistent with known risks for IL-23 antagonists. Many of the risks such as hypersensitivity reactions, infections, use in patients with tuberculosis, and need for appropriate vaccination prior to initiating therapy are already listed in currently approved labeling for RZB as well as in other approved IL-23 antagonists. Two new safety risks identified with the RZB CD clinical development program include the risk of dyslipidemia and the risk of hepatotoxicity associated with the IV induction dosing regimen. Elevations in lipid parameters (i.e., total cholesterol and LDL-C) were seen in both induction and maintenance studies, however, the clinical reviewer concluded the magnitude of dyslipidemia did not appear to be clinically meaningful and unlikely to significantly impact overall cardiovascular disease risk. The clinical reviewer recommended to include dyslipidemia in labeling under Section 6.1 (Adverse Reactions) to inform prescribers of this new risk, not seen in previously approved RZB indications. Transient elevations in liver enzymes were observed in both induction and maintenance studies with the majority spontaneously resolving over time and study drug was continued. However, there was one case in Study M16-000 (induction study) that met Hy's law criteria for DILI. The DHN reviewer proposes the DILI case may be associated with the higher IV dosing for induction treatment in CD and recommends limiting the induction dosing to 600mg and informing prescribers on this risk via labeling along with requiring further postmarketing studies. The clinical reviewer agreed with the recommendations from DHN. The risk of hepatotoxicity will be included in labeling in Warnings and Precautions (Section 5.4) and Adverse Reactions (Section 6). In addition, the Applicant will be required to conduct enhanced pharmacovigilance and a postmarketing requirement (PMR) study to detect significant DILI.

This DRM reviewer agrees with the DG clinical reviewer that labeling is sufficient and a REMS is not necessary to mitigate the risks of dyslipidemia and hepatotoxicity with RZB for CD.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits of Skyrizi outweigh the risks. Many of the AEs associated with RZB in the CD development program are known risks in the IL-23 drug class and already included in current labeling for RZB. The two new safety concerns associated with RZB

for CD can be communicated in labeling. The risk of dyslipidemia will be included in section 6.1, Adverse Reactions. The risk of hepatotoxicity will be added in labeling in Warnings and Precautions (Section 5.4) and in Adverse Reactions (Section 6) along with enhanced pharmacovigilance and a PMR to monitor for DILI. Healthcare providers, mainly gastroenterologists, treating patients with moderate to severe CD are expected to be familiar with the risk and need for monitoring for hepatotoxicity as several approved biologics (e.g., infliximab and natalizumab) have this risk in labeling. At the time of this review, labeling negotiations are ongoing along with validation of the RZB 180 mg PFC and OBDS presentation.

Should DG have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 Appendices

Appendix 1: US Approved Biologic Therapies for Moderate-Severe Crohn's Disease

Biologics / Biosimilars	Warning and Precautions	Box Warning	REMS
Tumor necrosis factor (TNF) α antagonists			
Humira (adalimumab) Approved in 2002 Biosimilars: • (b) (4) • adalimumab-bwwd • adalimumab-afzb	Serious infections, Hepatitis B Reactivation, Increased risk of Infection when used with anakinra and abatacept Malignancies Hypersensitivity and Autoimmunity Immunizations - no live or attenuated vaccines Neurologic and Hematologic Reactions Heart Failure	Serious Infections Malignancies	*No
Cimzia (certolizumab pegol) Approved 2008	Serious Infections, Hepatitis B Reactivation, Increased risk of serious infections when use with biological DMARDs Malignancies Heart Failure Hypersensitivity Reactions and Autoimmunity Neurologic and Hematologic Reactions Immunizations – no live or attenuated vaccines Immunosuppression	Serious Infections Malignancies	*No
Remicade (infliximab) Approved 1998 Biosimilars: • infliximab-abda • infliximab dyyb • infliximab-qbtx	Serious Infections and Invasive Fungal infections, Hepatitis B Reactivation Increased Risk of Infections When Use with Anakinra, Abatacept, and Biological DMARDs Malignancies Immunizations - no live or attenuated vaccines Hepatotoxicity Heart Failure, Cardiovascular and Cerebrovascular Reactions Neurologic and Hematologic Reactions Autoimmunity and Hypersensitivity	Serious Infections Malignancies	*No
Anti-integrin Agents			

Tysabri (natalizumab) Approved in 2004	Progressive Multifocal Leukoencephalopathy (PML) Herpes Encephalitis and Meningitis Hepatotoxicity Hypersensitivity, Immunosuppression Laboratory Test Abnormalities Thrombocytopenia Immunosuppression/ Infections	PML	PML (ETASU)
Entyvio (vedolizumab) Approved in 2014	Infusion-Related Reactions and Hypersensitivity Reactions Infections PML Liver Injury	None	No
Interleukin (IL) 12/23 inhibitor			
Stelara (ustekinumab) Approved in 2009	Infections, Theoretical Risk for Particular Infections, Tuberculosis, Noninfectious Pneumonia Malignancies Hypersensitivity reactions Posterior Reversible Encephalopathy Syndrome (PRES) Immunization - no live or (b) (4) vaccines	None	No
* Approved with a REMS that has since been released. Sources: DailyMed, Drugs @FDA, and REMS@FDA			

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