CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA761105Orig1s014

Name: Skyrizi (risankizumab-rzaa) injection, 75 mg/0.83 mL

Sponsor: AbbVie, Inc

Approval Date: April 23, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761105Orig1s014

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APPROVAL LETTER

BLA 761105/S-014

SUPPLEMENT APPROVAL

AbbVie Inc.
1 N. Waukegan Road
Dept. PA72/Bldg. AP3-04
North Chicago, IL 60064

Attention: Jiahong Wang, PhD
Director, Global Regulatory Strategy

Dear Dr. Wang:

Please refer to your supplemental biologics license application (sBLA), dated and received March 23, 2021, and your amendments, submitted under section 351(a) of the Public Health Service Act for Skyrizi (risankizumab-rzaa) Injection, 75 mg/0.83 mL and 150 mg/mL.

This Prior Approval supplemental biologics license application provides for use of Skyrizi in the treatment of active psoriatic arthritis (PsA) in adults.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study(ies) requirement for ages 0 to less than 5 years of age because necessary studies are impossible or highly impracticable. This is due to the rarity of the diagnosis of juvenile psoriatic arthritis in this age group.

We are deferring submission of your pediatric study for juvenile psoriatic arthritis for patients 5 to 17 years of age for this application because this product is ready for approval for use in adults and the pediatric study (i.e., PK-based extrapolation from adult PsA study) have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

4206-1 Provide pharmacokinetic (PK) and safety information to support the pediatric assessment of risankizumab for the treatment of juvenile psoriatic arthritis in children 5 to 17 years of age.

Final Report Submission: 03/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Submit the protocol(s) to your IND 118702 with a cross-reference letter to this BLA. Report(s) of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[7]

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[7] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

If you have any questions, call Susan Rhee, Regulatory Project Manager, at 301-796-2402.

Sincerely,

{See appended electronic signature page}

Nikolay P. Nikolov, MD
Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
- Prescribing Information
- Medication Guide
- Instructions for Use

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NIKOLAY P NIKOLOV
01/21/2022 03:22:18 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761105Orig1s014

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SKYRIZI safely and effectively. See full prescribing information for SKYRIZI.

SKYRIZI® (risankizumab-rzaa) injection, for subcutaneous use
Initial U.S. Approval: 2019

RECENT MAJOR CHANGES

Indications and Usage, Psoriatic Arthritis (1.2)	01/2022
Dosage and Administration (2)	04/2021
Dosage and Administration, Psoriatic Arthritis (2.2)	01/2022
Warnings and Precautions, Hypersensitivity Reactions (5.1)	01/2022
Warnings and Precautions, Administration of Vaccines (5.4)	04/2021

INDICATIONS AND USAGE

SKYRIZI is an interleukin-23 antagonist indicated for the treatment of:

- moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. (1.1)
- active psoriatic arthritis in adults. (1.2)

DOSAGE AND ADMINISTRATION

Plaque Psoriasis and Psoriatic Arthritis:
150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter. (2.1, 2.2)

In patients with psoriatic arthritis SKYRIZI can be administered alone or in combination with non-biologic disease-modifying antirheumatic drugs (DMARDs). (2.2)

DOSAGE FORMS AND STRENGTHS

- Injection: 150 mg/mL in each single-dose prefilled pen. (3)
- Injection: 150 mg/mL in each single-dose prefilled syringe. (3)
- Injection: 75 mg/0.83 mL in each single-dose prefilled syringe. (3)

CONTRAINDICATIONS

- SKYRIZI is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Serious hypersensitivity reactions, including anaphylaxis, may occur (5.1)
- Infections: SKYRIZI may increase the risk of infection. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If such an infection develops, do not administer SKYRIZI until the infection resolves. (5.2)
- Tuberculosis (TB): Evaluate for TB prior to initiating treatment with SKYRIZI. (5.3)
- Administration of Vaccines: Avoid use of live vaccines. (5.4)

ADVERSE REACTIONS

Most common adverse reactions (≥ 1%) are upper respiratory infections, headache, fatigue, injection site reactions, and tinea infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Plaque Psoriasis

SKYRIZI® is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

1.2 Psoriatic Arthritis

SKYRIZI is indicated for the treatment of active psoriatic arthritis in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Plaque Psoriasis

The recommended dosage is 150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.

2.2 Psoriatic Arthritis

The recommended dosage is 150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.

SKYRIZI may be administered alone or in combination with non-biologic disease-modifying antirheumatic drugs (DMARDs).

2.3 Procedures Prior to Treatment Initiation

- Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SKYRIZI *[see Warnings and Precautions (5.3)]*.
- Complete all age-appropriate vaccinations as recommended by current immunization guidelines *[see Warnings and Precautions (5.4)]*.

2.4 Preparation Instructions

- Before injecting, remove the carton with SKYRIZI from the refrigerator and without removing the prefilled pen or prefilled syringe(s) from the carton, allow SKYRIZI to reach room temperature out of direct sunlight (30 to 90 minutes for the prefilled pen and 15 to 30 minutes for the prefilled syringe(s)).
- Visually inspect SKYRIZI for particulate matter and discoloration prior to administration.

  SKYRIZI 150 mg/mL is a colorless to yellow and clear to slightly opalescent solution. SKYRIZI 75 mg/0.83 mL is a colorless to slightly yellow and clear to slightly opalescent solution.

The solution may contain a few translucent to white particles. Do not use if the solution contains large particles or is cloudy or discolored.

2.5 Administration Instructions

- SKYRIZI is intended for use under the guidance and supervision of a healthcare professional. Patients may self-inject SKYRIZI after training in subcutaneous injection technique. Provide proper training to patients and/or caregivers on the subcutaneous injection technique of SKYRIZI according to the "Instructions for Use" *[see Instructions for Use]*.
- Administer SKYRIZI subcutaneously. Do not inject into areas where the skin is tender, bruised, erythematous, indurated or affected by psoriasis. Administration of SKYRIZI in the upper, outer arm may only be performed by a healthcare professional or caregiver.
- When using SKYRIZI 150 mg/mL prefilled pen or prefilled syringe, inject one 150 mg single-dose prefilled pen or prefilled syringe.
- When using SKYRIZI 75 mg/0.83 mL prefilled syringes, for a 150 mg dose, two 75 mg prefilled syringes are required. Inject one prefilled syringe after the other in different anatomic locations (such as thighs or abdomen).
- Discard prefilled pen or prefilled syringe(s) after use. Do not reuse.
- If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

3 DOSAGE FORMS AND STRENGTHS

SKYRIZI Pen

Injection: 150 mg/mL as a colorless to yellow and clear to slightly opalescent solution in each single-dose prefilled pen.

SKYRIZI Prefilled Syringe

Injection: 150 mg/mL as a colorless to yellow and clear to slightly opalescent solution in each single-dose prefilled syringe.

Injection: 75 mg/0.83 mL as a colorless to slightly yellow and clear to slightly opalescent solution in each single-dose prefilled syringe.

4 CONTRAINDICATIONS

SKYRIZI is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with use of SKYRIZI. If a serious hypersensitivity reaction occurs, discontinue SKYRIZI and initiate appropriate therapy immediately *[see Adverse Reactions (6.1)]*.

5.2 Infections

SKYRIZI may increase the risk of infections. In clinical studies, infections occurred in 22.1% of the SKYRIZI group compared with 14.7% of the placebo group through 16 weeks of treatment. Upper respiratory tract infections and tinea infections occurred more frequently in the SKYRIZI group than in the placebo group. Subjects with known chronic or acute infections were not enrolled in clinical studies *[see Adverse Reactions (6.1)]*.

The rate of serious infections for the SKYRIZI group and the placebo group was ≤ 0.4%. Treatment with SKYRIZI should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, monitor the patient closely and do not administer SKYRIZI until the infection resolves.

5.3 Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SKYRIZI. Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent TB who were concurrently treated with SKYRIZI and appropriate TB prophylaxis during the studies, none developed active TB during the mean follow-up of 61 weeks on SKYRIZI. Two subjects taking isoniazid for treatment of latent TB discontinued treatment due to liver injury. Of the 31 subjects from the PsO-3 study with latent TB who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 55 weeks on SKYRIZI. Consider anti-TB therapy prior to initiating SKYRIZI in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

5.4 Administration of Vaccines

Avoid use of live vaccines in patients treated with SKYRIZI. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating therapy with SKYRIZI, complete all age-appropriate vaccinations according to current immunization guidelines. No data are available on the response to live or inactive vaccines.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse drug reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Plaque Psoriasis

A total of 2234 subjects were treated with SKYRIZI in clinical development trials in plaque psoriasis. Of these, 1208 subjects with psoriasis were exposed to SKYRIZI for at least one year.

Data from placebo- and active-controlled trials were pooled to evaluate the safety of SKYRIZI for up to 16 weeks. In total, 1306 subjects were evaluated in the SKYRIZI 150 mg group.

Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% and at a higher rate in the SKYRIZI group than the placebo group during the 16-week controlled period of pooled clinical trials.

Table 1. Adverse Drug Reactions Occurring in ≥ 1% of Subjects on SKYRIZI through Week 16

Adverse Drug Reactions	SKYRIZI N = 1306 n (%)	Placebo N = 300 n (%)
Upper respiratory infections[a]	170 (13.0)	29 (9.7)
Headache[b]	46 (3.5)	6 (2.0)
Fatigue[c]	33 (2.5)	3 (1.0)
Injection site reactions[d]	19 (1.5)	3 (1.0)
Tinea infections[e]	15 (1.1)	1 (0.3)

[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis
[b] Includes: headache, tension headache, sinus headache, cervicogenic headache
[c] Includes: fatigue, asthenia
[d] Includes: injection site bruising, erythema, extravasation, hematoma, hemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth
[e] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, tinea infection, onychomycosis

Adverse drug reactions that occurred in < 1% but > 0.1% of subjects in the SKYRIZI group and at a higher rate than in the placebo group through Week 16 were folliculitis and urticaria.

Specific Adverse Drug Reactions

Infections

In the first 16 weeks, infections occurred in 22.1% of the SKYRIZI group (90.8 events per 100 subject-years) compared with 14.7% of the placebo group (56.5 events per 100 subject-years) and did not lead to discontinuation of SKYRIZI. The rates of serious infections for the SKYRIZI group and the placebo group were ≤0.4%. Serious infections in the SKYRIZI group included cellulitis, osteomyelitis, sepsis, and herpes zoster. In Studies PsO-1 and PsO-2, through Week 52, the rate of infections (73.9 events per 100 subject-years) was similar to the rate observed during the first 16 weeks of treatment.

Safety Through Week 52

Through Week 52, no new adverse reactions were identified, and the rates of the adverse reactions were similar to those observed during the first 16 weeks of treatment. During this period, serious infections that led to study discontinuation included pneumonia.

Psoriatic Arthritis

The overall safety profile observed in subjects with psoriatic arthritis treated with SKYRIZI is generally consistent with the safety profile in subjects with plaque psoriasis. Additionally, in the Phase 3 placebo-controlled trials the incidence of hepatic events was higher in the SKYRIZI group (5.4%, 16.7 events per 100 patient years) compared to the placebo group (3.9%, 12.6 events per 100 patient years). Of these, the most common events that were reported more frequently in both the placebo group and the SKYRIZI group were ALT increased (placebo: n=12 (1.7%); SKYRIZI: n=16 (2.3%)), AST increased (placebo: n=9 (1.3%); SKYRIZI: n=13 (1.8%)), and GGT increased (placebo: n=5 (0.7%); SKYRIZI: n=8 (1.1%)). There were no serious hepatic events reported. The incidence of hypersensitivity reactions was higher in the SKYRIZI group (n=16, 2.3%) compared to the placebo group (n=9, 1.3%). In the Phase 3 placebo-controlled trials, hypersensitivity reactions reported at a higher rate in the SKYRIZI group included rash (placebo: n=4 (0.6%); SKYRIZI: n=5 (0.7%), allergic rhinitis (placebo: n=1 (0.1%); SKYRIZI: n=2 (0.3%), and facial swelling (placebo: n=0 (0.0%); SKYRIZI n=1 (0.1%). One case of anaphylaxis was reported in a subject who received SKYRIZI in the Phase 2 clinical trial.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products, including other risankizumab products, may be misleading.

Plaque Psoriasis

By Week 52, approximately 24% (263/1079) of subjects treated with SKYRIZI at the recommended dose developed antibodies to risankizumab-rzaa. Of the subjects who developed antibodies to risankizumab-rzaa, approximately 57% (14% of all subjects treated with SKYRIZI)

had antibodies that were classified as neutralizing. Higher antibody titers in approximately 1% of subjects treated with SKYRIZI were associated with lower risankizumab-rzaa concentrations and reduced clinical response.

Psoriatic Arthritis

By Week 28, approximately 12.1% (79/652) of subjects treated with SKYRIZI at the recommended dose developed antibodies to risankizumab-rzaa. None of the subjects who developed antibodies to risankizumab-rzaa had antibodies that were classified as neutralizing. Antibodies to risankizumab-rzaa were not associated with changes in clinical response for psoriatic arthritis. A higher proportion of subjects with anti-drug antibodies experienced hypersensitivity reactions (6.3% (5/79)) and injection site reactions (2.5% (2/79)) compared to subjects without anti-drug antibodies (3.8% (22/574) with hypersensitivity reactions and 0.7% (4/574) with injection site reactions). None of these hypersensitivity and injection site reactions led to discontinuation of risankizumab-rzaa.

6.3 Postmarketing Experience

The following adverse reactions have been reported during post-approval of SKYRIZI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to SKYRIZI exposure:

- *Skin and subcutaneous tissue disorders*: eczema and rash

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors outcomes in women with plaque psoriasis who become pregnant while treated with SKYRIZI. Patients should be encouraged to enroll by calling 1-877-302-2161.

Risk Summary

Available data with SKYRIZI use in pregnant women are insufficient to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcome. Human IgG is known to cross the placental barrier; therefore, SKYRIZI may be transmitted from the mother to the developing fetus.

In an enhanced pre- and post-natal developmental toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of 5 and 50 mg/kg risankizumab-rzaa once weekly during the period of organogenesis up to parturition. At the 50 mg/kg dose [20 times the maximum recommended human dose (MRHD); 2.5 mg/kg based on administration of a 150 mg dose to a 60 kg individual], increased fetal/infant loss was noted in pregnant monkeys *(see Data)*. No risankizumab-rzaa-related effects on functional or immunological development were observed in infant monkeys from birth through 6 months of age. The clinical significance of these findings for humans is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

An enhanced pre- and post-natal developmental toxicity study was conducted in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered weekly subcutaneous doses of risankizumab-rzaa of 5 or 50 mg/kg from gestation day 20 to parturition, and the cynomolgus monkeys (mother and infants) were monitored for 6 months after delivery. No maternal toxicity was noted in this study. There were no treatment-related effects on growth and development, malformations, developmental immunotoxicology, or neurobehavioral development. 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 no observed adverse effect level (NOAEL) for maternal toxicity was identified as 50 mg/kg (20 times the MRHD, based on mg/kg comparison) and the NOAEL for developmental toxicity was identified as 5 mg/kg (2 times the MRHD, based on mg/kg comparison). In the infants, mean serum concentrations increased in a dose-dependent manner and were approximately 17%-86% of the respective maternal concentrations. Following delivery, most adult female cynomolgus monkeys and all infants from the risankizumab-rzaa-treated groups had measurable serum concentrations of risankizumab-rzaa up to 91 days postpartum. Serum concentrations were below detectable levels at 180 days postpartum.

8.2 Lactation

Risk Summary

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. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SKYRIZI and any potential adverse effects on the breastfed infant from SKYRIZI or from the underlying maternal condition.

8.4 Pediatric Use

The safety and efficacy of SKYRIZI in pediatric patients younger than 18 years of age have not yet been established.

8.5 Geriatric Use

Of the 2234 subjects with plaque psoriasis exposed to SKYRIZI, 243 subjects were 65 years or older and 24 subjects were 75 years or older. No overall differences in risankizumab-rzaa exposure, safety or effectiveness were observed between older and younger subjects who received SKYRIZI. However, the number of subjects aged 65 years and older was not sufficient to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

11 DESCRIPTION

Risankizumab-rzaa, an interleukin-23 (IL-23) antagonist, is a humanized immunoglobulin G1 (IgG1) monoclonal antibody. Risankizumab-rzaa is produced by recombinant DNA technology in Chinese hamster ovary cells and has an approximate molecular weight of 149 kDa.

SKYRIZI 150 mg/mL prefilled syringe and prefilled pen

SKYRIZI (risankizumab-rzaa) injection is a sterile, preservative-free, colorless to yellow, and clear to slightly opalescent solution for subcutaneous use.

Each SKYRIZI 150 mg/mL prefilled pen and prefilled syringe contains acetic acid (0.054 mg), polysorbate 20 (0.2 mg), sodium acetate trihydrate (1.24 mg), trehalose dihydrate (70 mg), and Water for Injection, USP. The pH is 5.7.

SKYRIZI 75 mg/0.83 mL prefilled syringe

SKYRIZI (risankizumab-rzaa) injection is a sterile, preservative-free, colorless to slightly yellow, and clear to slightly opalescent solution for subcutaneous use.

Each SKYRIZI 75 mg/0.83 mL prefilled syringe contains disodium succinate hexahydrate (0.88 mg), polysorbate 20 (0.17 mg), sorbitol (34 mg), succinic acid (0.049 mg), and Water for Injection, USP. The pH is 6.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Risankizumab-rzaa is a humanized 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-rzaa inhibits the release of pro-inflammatory cytokines and chemokines.

12.2 Pharmacodynamics

No formal pharmacodynamics studies have been conducted with risankizumab-rzaa.

12.3 Pharmacokinetics

Risankizumab-rzaa plasma concentrations increased dose-proportionally from 90 to 180 mg and from 18 to 300 mg (0.6 to 1.2 and 0.12 to 2.0 times the approved recommended dosage) following subcutaneous administration in subjects with plaque psoriasis and healthy volunteers, respectively. Steady-state concentrations were achieved by Week 16 following subcutaneous administration of risankizumab-rzaa at Weeks 0, 4, and every 12 weeks thereafter. At the 150 mg

dose, the estimated steady-state peak concentration (C_{max}) and trough concentration (C_{trough}) were approximately 12 mcg/mL and 2 mcg/mL, respectively.

With the same dosing regimen, the pharmacokinetics of risankizumab-rzaa in subjects with psoriatic arthritis was similar to that in subjects with plaque psoriasis.

Absorption

The absolute bioavailability of risankizumab-rzaa was estimated to be 89% following subcutaneous injection. C_{max} was reached by 3-14 days.

Distribution

The estimated steady-state volume of distribution (inter-subject CV%) was 11.2 L (34%) in subjects with plaque psoriasis.

Elimination

The estimated systemic clearance (inter-subject CV%) was 0.31 L/day (24%) and terminal elimination half-life was approximately 28 days in subjects with plaque psoriasis.

Metabolism

The metabolic pathway of risankizumab-rzaa has not been characterized. As a humanized IgG1 monoclonal antibody, risankizumab-rzaa is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG.

Specific Populations

No clinically significant differences in the pharmacokinetics of risankizumab-rzaa were observed based on age (≥18 years). No specific studies have been conducted to determine the effect of renal or hepatic impairment on the pharmacokinetics of risankizumab-rzaa.

Body Weight

Risankizumab-rzaa clearance and volume of distribution increase and plasma concentrations decrease as body weight increases; however, no dose adjustment is recommended based on body weight.

Drug Interaction Studies

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and mutagenicity studies have not been conducted with SKYRIZI.

No effects on male fertility parameters were observed in sexually mature male cynomolgus monkeys subcutaneously treated with 50 mg/kg risankizumab-rzaa (at 20 times the clinical exposure at the MRHD, based on mg/kg comparison) once weekly for 26 weeks.

14 CLINICAL STUDIES

14.1 Plaque Psoriasis

Four multicenter, randomized, double-blind studies [PsO-1 (NCT02684370), PsO-2 (NCT02684357), PsO-3 (NCT02672852), and PsO-4 (NCT02694523)] enrolled 2109 subjects 18 years of age and older with moderate to severe plaque psoriasis who had a body surface area (BSA) involvement of ≥10%, a static Physician's Global Assessment (sPGA) score of ≥3 ("moderate") in the overall assessment (plaque thickness/induration, erythema, and scaling) of psoriasis on a severity scale of 0 to 4, and a Psoriasis Area and Severity Index (PASI) score ≥12.

Overall, subjects had a median baseline PASI score of 17.8 and a median BSA of 20%. Baseline sPGA score was 4 ("severe") in 19% of subjects. A total of 10% of study subjects had a history of diagnosed psoriatic arthritis.

Across all studies, 38% of subjects had received prior phototherapy, 48% had received prior non-biologic systemic therapy, and 42% had received prior biologic therapy for the treatment of psoriasis.

Studies PsO-1 and PsO-2

In studies PsO-1 and PsO-2, 997 subjects were enrolled (including 598 subjects randomized to the SKYRIZI 150 mg group, 200 subjects randomized to the placebo group, and 199 to the biologic active control group). Subjects received treatment at Weeks 0, 4, and every 12 weeks thereafter.

Both studies assessed the responses at Week 16 compared with placebo for the two co-primary endpoints:

- the proportion of subjects who achieved an sPGA score of 0 ("clear") or 1 ("almost clear")
- the proportion of subjects who achieved at least a 90% reduction from baseline PASI (PASI 90)

Secondary endpoints included the proportion of subjects who achieved PASI 100, sPGA 0, and Psoriasis Symptom Scale (PSS) 0 at Week 16.

The results are presented in Table 2.

Table 2. Efficacy Results at Week 16 in Adults with Plaque Psoriasis in PsO-1 and PsO-2

	PsO-1		**PsO-2**	
	SKYRIZI (N=304) n (%)	**Placebo (N=102) n (%)**	**SKYRIZI (N=294) n (%)**	**Placebo (N=98) n (%)**

sPGA 0 or 1 ("clear or almost clear")[a]	267 (88)	8 (8)	246 (84)	5 (5)
PASI 90[a]	229 (75)	5 (5)	220 (75)	2 (2)
sPGA 0 ("clear")	112 (37)	2 (2)	150 (51)	3 (3)
PASI 100	109 (36)	0 (0)	149 (51)	2 (2)
[a] Co-primary endpoints				

Examination of age, gender, race, body weight, baseline PASI score and previous treatment with systemic or biologic agents did not identify differences in response to SKYRIZI among these subgroups at Week 16.

In PsO-1 and PsO-2 at Week 52, subjects receiving SKYRIZI achieved sPGA 0 (58% and 60%, respectively), PASI 90 (82% and 81%, respectively), and PASI 100 (56% and 60%, respectively).

Patient Reported Outcomes

Improvements in signs and symptoms related to pain, redness, itching and burning at Week 16 compared to placebo were observed in both studies as assessed by the PSS. In PsO-1 and PsO-2, about 30% of the subjects who received SKYRIZI achieved PSS 0 ("none") at Week 16 compared to 1% of the subjects who received placebo.

Study PsO-3

Study PsO-3 enrolled 507 subjects (407 randomized to SKYRIZI 150 mg and 100 to placebo). Subjects received treatment at Weeks 0, 4, and every 12 weeks thereafter.

At Week 16, SKYRIZI was superior to placebo on the co-primary endpoints of sPGA 0 or 1 (84% SKYRIZI and 7% placebo) and PASI 90 (73% SKYRIZI and 2% placebo). The respective response rates for SKYRIZI and placebo at Week 16 were: sPGA 0 (46% SKYRIZI and 1% placebo); PASI 100 (47% SKYRIZI and 1% placebo); and PASI 75 (89% SKYRIZI and 8% placebo).

Maintenance and Durability of Response

In PsO-1 and PsO-2, among the subjects who received SKYRIZI and had PASI 100 at Week 16, 80% (206/258) of the subjects who continued on SKYRIZI had PASI 100 at Week 52. For PASI 90 responders at Week 16, 88% (398/450) of the subjects had PASI 90 at Week 52.

In PsO-3, subjects who were originally on SKYRIZI and had sPGA 0 or 1 at Week 28 were re-randomized to continue SKYRIZI every 12 weeks or withdrawal of therapy. At Week 52, 87% (97/111) of the subjects re-randomized to continue treatment with SKYRIZI had sPGA 0 or 1 compared to 61% (138/225) who were re-randomized to withdrawal of SKYRIZI.

14.2 Psoriatic Arthritis

The safety and efficacy of SKYRIZI were assessed in 1407 subjects in 2 randomized, double-blind, placebo-controlled studies (964 in PsA-1 [NCT03675308] and 443 in PsA-2 [NCT03671148]) in subjects 18 years and older with active psoriatic arthritis (PsA).

Subjects in these studies had a diagnosis of PsA for at least 6 months based on the Classification Criteria for Psoriatic Arthritis (CASPAR), a median duration of PsA of 4.9 years at baseline, ≥ 5 tender joints and ≥ 5 swollen joints, and active plaque psoriasis or psoriatic nail disease at baseline. Regarding baseline clinical presentation, 55.9% of subjects had ≥3% BSA with active plaque psoriasis; 63.4% and 27.9% of subjects had enthesitis and dactylitis, respectively. In PsA-1 where psoriatic nail disease was further assessed, 67.3% had psoriatic nail disease.

In PsA-1, all subjects had a previous inadequate response or intolerance to non-biologic DMARD therapy and were biologic naïve. In PsA-2, 53.5% of subjects had a previous inadequate response or intolerance to non-biologic DMARD therapy, and 46.5% of subjects had a previous inadequate response or intolerance to biologic therapy.

In both studies, subjects were randomized to receive SKYRIZI 150 mg or placebo at Weeks 0, 4, and 16. Starting from Week 28, all subjects received SKYRIZI every 12 weeks. Both studies included a long-term extension for up to an additional 204 weeks. Regarding use of concomitant medications, 59.6% of subjects were receiving concomitant methotrexate (MTX), 11.6% were receiving concomitant non-biologic DMARDs other than MTX, and 28.9% were receiving SKYRIZI monotherapy.

For both studies, the primary endpoint was the proportion of subjects who achieved an American College of Rheumatology (ACR) 20 response at Week 24.

Clinical Response

In both studies, treatment with SKYRIZI resulted in significant improvement in measures of disease activity compared with placebo at Week 24. See Tables 3 and 4 for key efficacy results.

In both studies, similar responses were seen regardless of concomitant non-biologic DMARD use, number of prior non-biologic DMARDs, age, gender, race, and BMI. In PsA-2, responses were seen regardless of prior biologic therapy.

Table 3. Efficacy Results in Study PsA-1

Endpoint	**Placebo N=481 Response Rate**	**SKYRIZI N=483 Response Rate**	**Difference from Placebo (95% CI)**
ACR20 Response*			
Week 16	33.4%	56.3%[a]	23.1% (16.8, 29.4)
Week 24	33.5%	57.3%[a]	24.0% (18.0, 30.0)
ACR50 Response*			
Week 16	11.1%	26.4%	15.4% (10.6, 20.2)
Week 24	11.3%	33.4 %	22.2% (17.3, 27.2)
ACR70 Response*			
Week 16	2.7%	11.8%	9.2% (6.1, 12.4)
Week 24	4.7%	15.3%	10.5% (6.9, 14.2)

a. multiplicity-controlled p≤0.001, SKYRIZI vs. placebo comparison.
*A Subject was considered as a non-responder after initiation of rescue medication or concomitant medications for PsA that could meaningfully impact efficacy assessment.

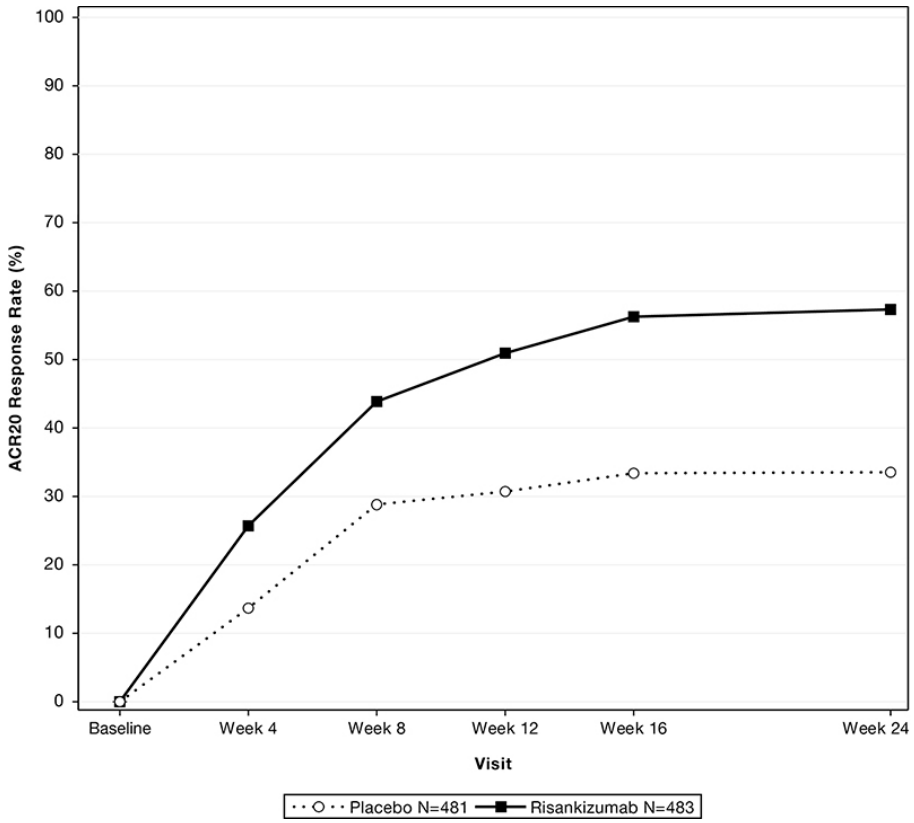
Table 4. Efficacy Results in Study PsA-2

Endpoint	Placebo N=219 Response Rate	SKYRIZI N=224 Response Rate	Difference from Placebo (95% CI)
ACR20 Response*			
Week 16	25.3%	48.3% [a]	22.6% (13.9, 31.2)
Week 24	26.5%	51.3% [a]	24.5% (15.9, 33.0)
ACR50 Response*			
Week 16	6.8%	20.3%	13.5% (7.3, 19.7)
Week 24	9.3%	26.3%	16.6% (9.7, 23.6)
ACR70 Response*			
Week 16	3.4%	11.2%	7.8% (3.0, 12.6)
Week 24	5.9%	12.0%	6.0% (0.8, 11.3)

a. multiplicity-controlled p≤0.001, SKYRIZI vs. placebo comparison.
*A Subject was considered as a non-responder after initiation of rescue medication or concomitant medications for PsA that could meaningfully impact efficacy assessment.

The percent of subjects achieving ACR20 responses in study PsA-1 through Week 24 is shown in Figure 1.

Figure 1. Percent of Subjects Achieving ACR20 Responses in Study PsA-1 through Week 24



The results of the components of the ACR response criteria for both studies are shown in Table 5.

Table 5. Mean Change from Baseline in ACR Components

	PsA-1		PsA-2	
	Placebo (N=481) Mean (SD)	**SKYRIZI (N=483) Mean (SD)**	**Placebo (N=219) Mean (SD)**	**SKYRIZI (N=224) Mean (SD)**
Number of Swollen Joints (0-66)				
Baseline	12.2 (8.0)	12.1 (7.8)	13.6 (9.0)	13.0 (8.7)
Mean change at Week 16	-5.5 (7.0)	-7.7 (7.2)	-5.4 (8.5)	-8.0 (7.4)
Mean change at Week 24	-6.7 (7.2)	-8.7 (7.2)	-6.5 (7.8)	-9.1 (7.6)
Number of Tender Joints (0-68)				
Baseline	20.5 (12.8)	20.8 (14.0)	22.3 (13.8)	22.8 (14.9)
Mean change at Week 16	-6.3 (11.1)	-10.7 (11.4)	-6.0 (13.1)	-11.3 (13.0)
Mean change at Week 24	-7.9 (10.7)	-12.0 (12.3)	-8.3 (11.3)	-13.0 (12.5)
Patient's Assessment of Pain [a]				
Baseline	57.1 (22.6)	57.1 (22.6)	57.0 (23.1)	55.0 (23.5)
Mean change at Week 16	-8.6 (23.7)	-18.4 (26.3)	-5.7 (22.7)	-14.4 (26.4)
Mean change at Week 24	-10.9 (25.4)	-21.4 (26.5)	-8.7 (25.3)	-15.3 (26.5)
Patient's Global Assessment [a]				
Baseline	57.4 (22.1)	57.9 (21.7)	56.2 (23.0)	56.2 (21.8)
Mean change at Week 16	-10.2 (23.9)	-19.4 (25.7)	-4.9 (23.6)	-17.0 (27.1)
Mean change at Week 24	-11.1 (25.1)	-22.6 (26.9)	-8.7 (25.4)	-17.7 (27.7)
Physician Global Assessment [a]				
Baseline	62.4 (17.0)	61.3 (17.6)	60.7 (16.4)	63.0 (17.0)
Mean change at Week 16	-18.3 (22.5)	-31.1 (23.4)	-19.0 (23.3)	-32.7 (24.7)
Mean change at Week 24	-22.2 (22.8)	-34.8 (23.2)	-21.3 (25.2)	-35.5 (25.6)
Health Assessment Questionnaire - Disability Index (HAQ-DI) [b]				
Baseline	1.2 (0.7)	1.2 (0.7)	1.1 (0.6)	1.1 (0.6)
Mean change at Week 16	-0.1 (0.5)	-0.3 (0.5)	-0.1 (0.5)	-0.2 (0.5)
Mean change at Week 24	-0.1 (0.5)	-0.3 (0.5)	-0.1 (0.4)	-0.2 (0.5)
High sensitivity C-reactive protein (hs-CRP) mg/L				
Baseline	11.3 (14.1)	11.9 (15.9)	8.2 (17.1)	7.4 (10.9)
Mean change at Week 16	-0.3 (14.7)	-4.8 (14.2)	-0.1 (6.8)	-2.1 (7.5)
Mean change at Week 24	-0.2 (11.7)	-4.3 (12.8)	-0.5 (14.5)	-1.8 (13.4)

SD= Standard Deviation.

a. Assessment based on Visual Analog Scale (100 mm) with the left end indicating "no pain" (for patient's assessment of pain), "very well" (for patient global assessment), or "no arthritis activity" (for physician global

assessment) and the right end indicating "the worst possible pain" (for patient assessment of pain), "poor" (for patient global assessment), or "extremely active arthritis" (for physician global assessment).

b. Disability Index of the Health Assessment Questionnaire; 0 = no difficulty to 3 = inability to perform, measures the patient's ability to perform the following: dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living.

Treatment with SKYRIZI resulted in improvement in dactylitis and enthesitis in subjects with pre-existing dactylitis or enthesitis.

In patients with coexistent plaque psoriasis receiving SKYRIZI, the skin lesions of psoriasis improved with treatment, relative to placebo, as measured by the Psoriasis Area Severity Index (PASI 90) at Week 24.

Physical Function

In both studies, patients treated with SKYRIZI showed statistically significant improvement from baseline in physical function compared with placebo as assessed by HAQ-DI at Week 24 (Table 5). The mean difference (95% CI) from placebo in HAQ-DI change from baseline at Week 24 was -0.20 (-0.26, -0.14) in study PsA-1 and -0.16 (-0.26, -0.07) in study PsA-2.

In both studies, a greater proportion of subjects achieved a reduction of at least 0.35 in HAQ-DI score from baseline in the SKYRIZI group compared with placebo at Week 24.

Other Health Related Outcomes

In both studies, general health status was assessed by the 36-Item Short Form Health Survey (SF-36 V2). Fatigue was assessed by Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-Fatigue).

In both studies at Week 24, subjects treated with SKYRIZI showed improvements in the SF-36 physical component summary scores compared with subjects who received placebo. There were also numerical improvements in subjects treated with SKYRIZI in physical functioning, role physical, bodily pain, general health, vitality, social functioning, mental health, role emotional domain scores and mental component summary scores in both studies at week 24 compared to placebo. In both studies at Week 24, subjects treated with SKYRIZI showed improvements in FACIT-Fatigue scores compared with subjects who received placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

SKYRIZI (risankizumab-rzaa) injection is supplied in the following strengths:

Strength	Pack Size	NDC
150 mg/mL single-dose pen	Carton of 1	0074-2100-01
150 mg/mL single-dose prefilled syringe	Carton of 1	0074-1050-01
75 mg/0.83 mL single-dose prefilled syringe	Carton of 2	0074-2042-02

SKYRIZI (risankizumab-rzaa) injection 150 mg/mL prefilled syringe and prefilled pen contain a sterile, preservative-free, colorless to yellow, and clear to slightly opalescent solution. Each single-dose prefilled syringe or prefilled pen consists of a 1 mL glass syringe with a fixed 27-gauge ½ inch needle with needle guard.

SKYRIZI (risankizumab-rzaa) injection 75 mg/0.83 mL prefilled syringe contains a sterile, preservative-free, colorless to slightly yellow and clear to slightly opalescent solution. Each single-dose prefilled syringe consists of a 1 mL glass syringe with a fixed 29-gauge ½ inch needle with needle guard.

Storage and Handling

- Store in a refrigerator at 2°C to 8°C (36°F to 46° F).
- Do not freeze.
- Do not shake.
- Keep prefilled pens and prefilled syringes in the original cartons to protect from light.
- Not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Hypersensitivity Reactions

Advise patients to discontinue SKYRIZI and seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

Infections

Inform patients that SKYRIZI may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the healthcare provider and contacting their healthcare provider if they develop any symptoms of an infection *[see Warnings and Precautions (5.2)]*.

Administration of Vaccines

Advise patients that vaccination with live vaccines is not recommended during SKYRIZI treatment and immediately prior to or after SKYRIZI treatment. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Instruct patients to inform the healthcare practitioner that they are taking SKYRIZI prior to a potential vaccination *[see Warnings and Precautions (5.4)]*.

Administration Instruction

Instruct patients or caregivers to perform the first self-injected dose under the supervision and guidance of a qualified healthcare professional for training in preparation and administration of SKYRIZI, including choosing anatomical sites for administration, and proper subcutaneous injection technique *[see Instructions for Use]*.

If using SKYRIZI 75 mg/0.83 mL, instruct patients or caregivers to administer two 75 mg single-dose syringes to achieve the full 150 mg dose of SKYRIZI *[see Instructions for Use]*.

Instruct patients or caregivers in the technique of pen or syringe disposal *[see Instructions for Use]*.

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women with plaque psoriasis exposed to SKYRIZI during pregnancy and patients can call 1-877-302-2161 *[see Use in Specific Populations (8.1)]*.

Manufactured by:
AbbVie Inc.
North Chicago, IL 60064, USA
US License Number 1889

20070928 01/2022

Medication Guide
SKYRIZI® (sky-RIZZ-ee)
(risankizumab-rzaa)
injection, for subcutaneous use

What is the most important information I should know about SKYRIZI?
SKYRIZI may cause serious side effects, including:
Serious allergic reactions. Stop using SKYRIZI and get emergency medical help right away if you get any of the following symptoms of a serious allergic reaction:

- fainting, dizziness, feeling lightheaded (low blood pressure)
- swelling of your face, eyelids, lips, mouth, tongue, or throat
- trouble breathing or throat tightness
- chest tightness
- skin rash, hives
- itching

Infections. SKYRIZI may lower the ability of your immune system to fight infections and may increase your risk of infections. Your healthcare provider should check you for infections and tuberculosis (TB) before starting treatment with SKYRIZI and may treat you for TB before you begin treatment with SKYRIZI if you have a history of TB or have active TB. Your healthcare provider should watch you closely for signs and symptoms of TB during and after treatment with SKYRIZI. Tell your healthcare provider right away if you have an infection or have symptoms of an infection, including:

- fever, sweats, or chills
- cough
- shortness of breath
- blood in your mucus (phlegm)
- muscle aches
- warm, red, or painful skin or sores on your body different from your psoriasis
- weight loss
- diarrhea or stomach pain
- burning when you urinate or urinating more often than normal

See **"What are the possible side effects of SKYRIZI?"** for more information about side effects.

What is SKYRIZI?
SKYRIZI is a prescription medicine used to treat adults:

- with moderate to severe plaque psoriasis who may benefit from taking injections or pills (systemic therapy) or treatment using ultraviolet or UV light (phototherapy).
- with active psoriatic arthritis (PsA).

It is not known if SKYRIZI is safe and effective in children under 18 years of age.

Who should not use SKYRIZI?
Do not use SKYRIZI if you are allergic to risankizumab-rzaa or any of the ingredients in SKYRIZI. See the end of this Medication Guide for a complete list of ingredients in SKYRIZI.

Before using SKYRIZI, tell your healthcare provider about all of your medical conditions, including if you:

- have any of the conditions or symptoms listed in the section **"What is the most important information I should know about SKYRIZI?"**
- have an infection that does not go away or that keeps coming back.
- have TB or have been in close contact with someone with TB.
- have recently received or are scheduled to receive an immunization (vaccine). Medicines that interact with the immune system may increase your risk of getting an infection after receiving live vaccines. You should avoid receiving live vaccines right before, during, or right after treatment with SKYRIZI. Tell your healthcare provider that you are taking SKYRIZI before receiving a vaccine.
- are pregnant or plan to become pregnant. It is not known if SKYRIZI can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if SKYRIZI passes into your breast milk.
- If you become pregnant while taking SKYRIZI, you are encouraged to enroll in the Pregnancy Registry. The purpose of the pregnancy registry is to collect information about the health of you and your baby. Talk to your healthcare provider or call 1-877-302-2161 to enroll in this registry.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use SKYRIZI?
See the detailed "Instructions for Use" that comes with SKYRIZI for information on how to prepare and inject a dose of SKYRIZI, and how to properly throw away (dispose of) a used SKYRIZI prefilled pen or prefilled syringe.

- Use SKYRIZI exactly as your healthcare provider tells you to use it.

- If you miss your SKYRIZI dose, inject a dose as soon as you remember. Then, take your next dose at your regular scheduled time. Call your healthcare provider if you are not sure what to do.
- If you inject more SKYRIZI than prescribed, call your healthcare provider right away.

What are the possible side effects of SKYRIZI?

SKYRIZI may cause serious side effects. See "What is the most important information I should know about SKYRIZI?"

The most common side effects of SKYRIZI include:

- upper respiratory infections
- headache
- feeling tired
- injection site reactions
- fungal skin infections

These are not all of the possible side effects of SKYRIZI. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SKYRIZI?

- Store SKYRIZI in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Do not freeze SKYRIZI.
- Do not shake SKYRIZI.
- Keep SKYRIZI in the original carton to protect it from light.
- SKYRIZI is not made with natural rubber latex.

Keep SKYRIZI and all medicines out of the reach of children.

General information about the safe and effective use of SKYRIZI

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SKYRIZI for a condition for which it was not prescribed. Do not give SKYRIZI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about SKYRIZI that is written for health professionals.

What are the ingredients in SKYRIZI?

Active ingredient: risankizumab-rzaa

SKYRIZI 150 mg/mL inactive ingredients: acetic acid, polysorbate 20, sodium acetate trihydrate, trehalose dihydrate, and Water for Injection, USP.

SKYRIZI 75 mg/0.83 mL inactive ingredients: disodium succinate hexahydrate, polysorbate 20, sorbitol, succinic acid, and Water for Injection, USP.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, U.S.A.
US License Number 1889

For more information, call 1-866-SKYRIZI (1-866-759-7494) or go to www.SKYRIZI.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 01/2022
20070928

INSTRUCTIONS FOR USE
SKYRIZI® (sky-RIZZ-ee) **Pen**
(risankizumab-rzaa)
injection, for subcutaneous use

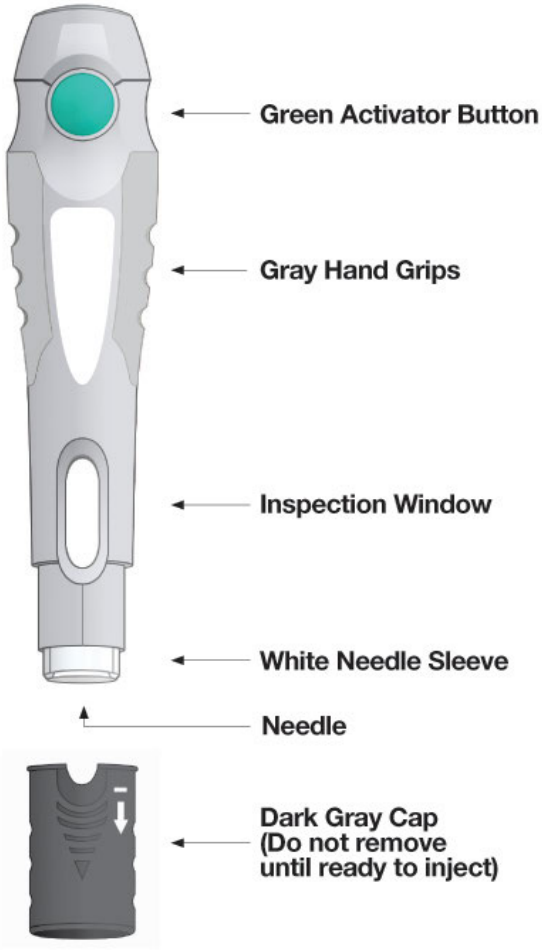
Read Before First Use

Refer to the **Medication Guide** for product information.

Read this Instructions for Use before using SKYRIZI Pen (risankizumab-rzaa) injection.

Before using SKYRIZI, you should receive training from your healthcare provider on how to inject SKYRIZI.

SKYRIZI Single-Dose Pen



Important Information

- Store SKYRIZI in the **refrigerator** at 36°F to 46°F (2°C to 8°C).
- Keep SKYRIZI in the original carton to protect from light until you are ready to use.
- **Before injecting,** take the SKYRIZI carton out of the refrigerator. **Leave** the carton at room temperature and out of direct sunlight for **30 to 90 minutes.**

- The liquid in the inspection window should look clear to yellow and may contain tiny white or clear particles.
- **Do not** use SKYRIZI if the liquid is **cloudy** or contains **flakes** or **large particles**.
- **Do not** use SKYRIZI if the **expiration date (EXP)** has passed.
- **Do not** use SKYRIZI if the liquid has been **frozen,** even if it has been thawed.
- **Do not** shake SKYRIZI.
- **Do not** use if the SKYRIZI Pen has been **dropped or damaged.**
- **Do not** use SKYRIZI if carton perforations are **broken. Return product to pharmacy.**
- **Do not** remove the dark gray cap until right before injection.
- SKYRIZI is not made with natural rubber latex.

Prepare SKYRIZI injection

Take the SKYRIZI carton out of the refrigerator. **Leave** the carton at room temperature and out of direct sunlight for **30 to 90 minutes** before injecting.

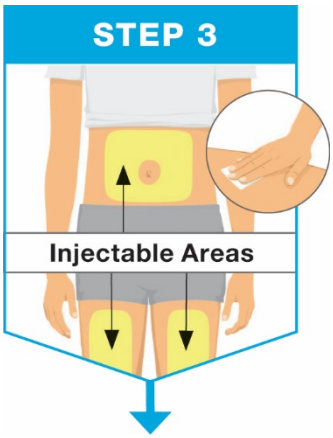
- **Do not** remove the Pen from the carton while allowing SKYRIZI to reach room temperature.
- **Do not** warm SKYRIZI in any other way. For example, **do not** warm it in a microwave or in hot water.
- **Do not** use the Pen if the liquid has been frozen, even if it has been thawed.

Check expiration date **(EXP). Do not** use the Pen if expiration date has passed.

Place the following on a clean, flat surface:

- 1 single-dose SKYRIZI Pen (included)
- 1 alcohol swab (not included)
- 1 cotton ball or gauze pad (not included)
- FDA-cleared sharps disposal container (not included). See "**Used SKYRIZI Prefilled Pen Disposal**" for information on how to throw away (dispose of) used Pens.

Wash and dry your hands.

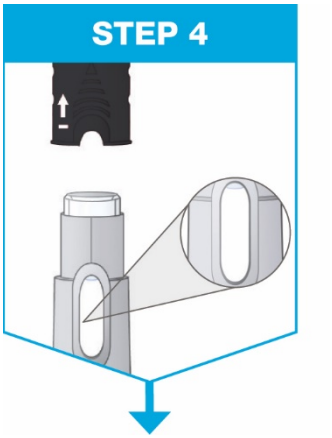


Choose an injection site:

- on the front of your **thighs** or
- your **abdomen** (belly) at least 2 inches from your navel (belly button)

Wipe the injection site in a circular motion with the alcohol swab and let it dry.

- **Do not** touch or blow on the injection site after it is cleaned. Allow the skin to dry before injecting.
- **Do not** inject through clothes.
- **Do not** inject into skin that is sore, bruised, red, hard, scarred, has stretch marks, or areas with psoriasis.



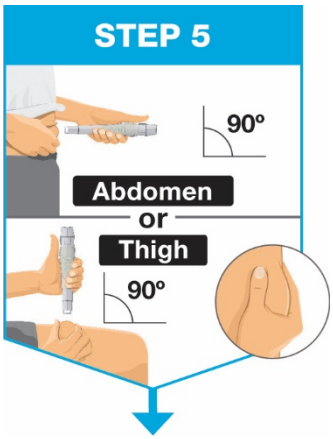
Hold the Pen with the dark gray cap pointing up.

- **Pull** the dark gray cap straight off.
- **Throw** the dark gray cap away.

Check the liquid through the inspection window.

- It is normal to see 1 or more bubbles in the liquid.
- The liquid should look clear to yellow and may contain tiny white or clear particles.
- **Do not** use if the liquid is cloudy or contains flakes or large particles.

Give SKYRIZI injection

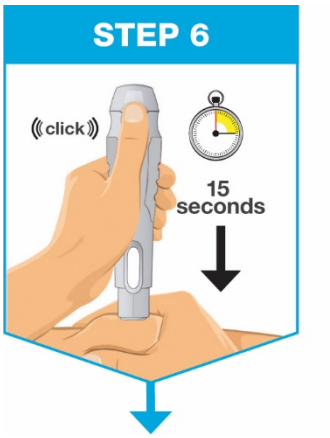


Hold the Pen with your fingers on the gray hand grips.

Turn the Pen so that the white needle sleeve points toward the injection site and you can see the green activator button.

Pinch the skin at your injection site to make a raised area and hold it firmly.

Place the white needle sleeve straight (90-degree angle) against the raised injection site.



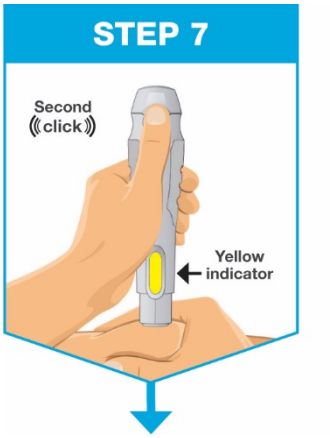
Hold the Pen so that you can see the green activator button and inspection window.

Push and keep pressing the Pen **down** against the raised injection site.

- The Pen will activate only if the white needle sleeve is pressed down against the injection site before pressing the green activator button.

Press the green activator button and hold the Pen for **15** seconds.

- The first loud “click” means the **start** of the injection.



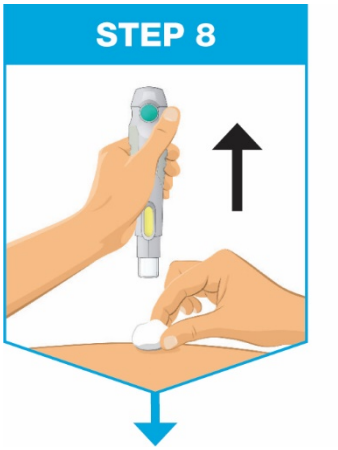
Keep pressing the Pen **down** against the injection site.

The injection is **complete** when:

- the Pen has made a second “click” **or**
- the yellow indicator has filled the inspection window

This takes **up to 15** seconds.

After SKYRIZI injection



When the injection is complete, slowly pull the Pen straight out from the skin.

The white needle sleeve will cover the needle tip and make another “click.”

After completing the injection, place a cotton ball or gauze pad on the skin at the injection site.

- **Do not** rub the injection site.
- Slight bleeding at the injection site is normal.

Throw away (dispose of) the used Pen in a FDA-cleared **sharps disposal container right away after use.**

- **Do not** dispose of used Pens in your household trash unless your community guidelines permit this.
- **Do not** recycle your sharps disposal container.

The dark gray cap, alcohol swab, cotton ball or gauze pad, and packaging may be placed in your household trash.

For more information, see "Used SKYRIZI Prefilled Pen Disposal".

Important Information

- Store SKYRIZI in the **refrigerator** at 36°F to 46°F (2°C to 8°C).
- Keep SKYRIZI in the original carton to protect from light until you are ready to use.
- **Before injecting,** take the SKYRIZI carton out of the refrigerator. **Leave** the carton at room temperature and out of direct sunlight for **30 to 90 minutes.**
- The liquid in the inspection window should look clear to yellow and may contain tiny white or clear particles.
- **Do not** use SKYRIZI if the liquid is **cloudy** or contains **flakes** or **large particles**.
- **Do not** use SKYRIZI if the **expiration date (EXP)** has passed.
- **Do not** use SKYRIZI if the liquid has been **frozen,** even if it has been thawed.
- **Do not** shake SKYRIZI.
- **Do not** use if the SKYRIZI Pen has been **dropped or damaged.**
- **Do not** use SKYRIZI if carton perforations are **broken. Return product to pharmacy.**
- **Do not** remove the dark gray cap until right before injection.
- SKYRIZI is not made with natural rubber latex.

Keep the SKYRIZI Pen and sharps disposal container out of the reach of children.

Call your healthcare provider or **(866) SKYRIZI or (866) 759-7494** if you need help or do not know how to proceed.

Questions About Using the SKYRIZI Pen

Q. What if I need help on how to inject SKYRIZI?
A. Call your healthcare provider **or (866) SKYRIZI or (866) 759-7494** if you need help.

Q. I have removed the dark gray cap and pressed the green activator button. Why isn't my injection starting?
A. The green activator button will not start the injection unless the white needle sleeve is pressed firmly against the injection site.

Q. How do I know when the injection is complete?
A. The injection is complete if the Pen makes a second "click" or the yellow indicator fills the inspection window. This takes up to **15** seconds.

Q. What should I do if there are more than a few drops of liquid on the injection site?
A. Call (866) SKYRIZI or (866) 759-7494 for help.

Q. What should I do with the used Pen after my injection?

A. Dispose of the used Pen in a sharps disposal container right after use. **Do not** dispose of the used Pen in your household trash.
You can sign up to receive sharps containers for SKYRIZI Pen disposal at no additional cost by going to **www.SKYRIZI.com** or calling **(866) SKYRIZI or (866) 759-7494.**

Call (866) SKYRIZI or (866) 759-7494 or go to www.SKYRIZI.com for help with your injection.

To help remember when to inject, mark your calendar with the date you give your SKYRIZI injection.

Keep the SKYRIZI Pen and sharps disposal container out of the reach of children.

Call your healthcare provider or (866) SKYRIZI or (866) 759-7494 if you need help or have questions about the use of SKYRIZI.

Used SKYRIZI Prefilled Pen Disposal

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used Pens.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: www.fda.gov/safesharpsdisposal.

Do not recycle your used sharps disposal container.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, U.S.A.
US License Number 1889

20071035

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

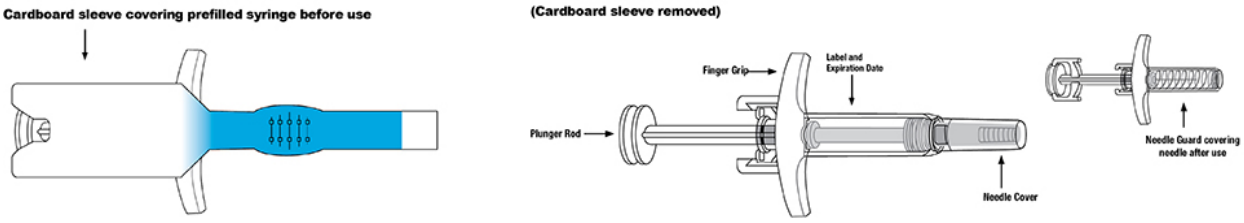
Revised: 01/2022

INSTRUCTIONS FOR USE
SKYRIZI® (sky-RIZZ-ee)
(risankizumab-rzaa)
injection, for subcutaneous use
150 mg/mL prefilled syringe

Read Before First Use

Refer to the **Medication Guide** for product information.

SKYRIZI Single-Dose Prefilled Syringe



Important Information
- Keep SKYRIZI in the original carton to protect from light until time to use.
- The liquid should look clear to yellow and may contain tiny white or clear particles.
- **Do not** use SKYRIZI if the liquid is **cloudy** or contains **flakes** or **large particles**.
- **Do not** use SKYRIZI if the **expiration date (EXP:)** shown on the carton and prefilled syringe has passed.
- **Do not** use SKYRIZI if the liquid has been **frozen** (even if thawed).
- **Do not** shake SKYRIZI.
- **Do not** use SKYRIZI if the prefilled syringe has been **dropped or damaged**.
- **Do not** use SKYRIZI if carton perforations are **broken**. **Return product to the pharmacy**.
- **Do not** remove the needle cover until right before giving the injection.

Keep SKYRIZI and all medicines out of the reach of children.

Please Read Complete Instructions for Use Before Using SKYRIZI Prefilled Syringe

Before Injecting
- **Receive** training on how to inject SKYRIZI before giving injection. Call your healthcare provider or **(866) SKYRIZI or (866) 759-7494** if you need help.
- **Mark your calendar** ahead of time to remember when to take SKYRIZI.
- **Leave** the carton at room temperature and out of direct sunlight for **15 to 30 minutes** to warm.
  - **Do not** remove the syringe from the carton while allowing SKYRIZI to reach room temperature.
  - **Do not** warm SKYRIZI in any other way (for example, **do not** warm it in a microwave or in hot water).

Important Information
- The liquid should look clear to yellow and may contain tiny white or clear particles.
- **Do not** use SKYRIZI if the liquid is **cloudy** or contains **flakes** or **large particles**.

- **Do not** use SKYRIZI if the **expiration date (EXP:)** shown on the carton and prefilled syringe has passed.
- **Do not** use SKYRIZI if the syringe has been **dropped or damaged**.
- **Do not** use SKYRIZI if carton perforations are **broken**. **Return product to the pharmacy**.

Storage Information

- Store SKYRIZI in the refrigerator between 36°F to 46°F (2°C to 8°C).
- **Do not** shake SKYRIZI.
- Keep SKYRIZI in the original carton to protect from light until time to use.
- SKYRIZI is not made with natural rubber latex.
- **Do not** use if the liquid has been frozen (even if thawed).

Keep SKYRIZI and all medicines out of the reach of children.

Call your healthcare provider or **(866) SKYRIZI or (866) 759-7494** if you need help or do not know how to proceed.

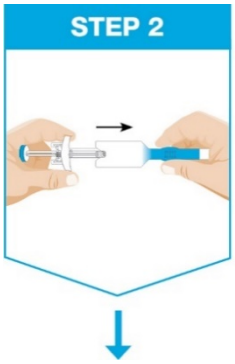
Gather the supplies for the injection.

- **Do not** hold or pull the plunger rod when removing the prefilled syringe from the sleeve.

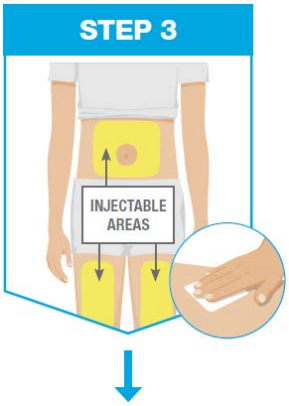
Place the following on a clean, flat surface:

- **1 prefilled syringe (included)**
- **1 alcohol swab** (not included)
- **1 cotton ball** or gauze pad (not included)
- **FDA-cleared sharps disposal container** (not included). See "**Used SKYRIZI Prefilled Syringe Disposal**" for information on how to throw away (dispose of) used prefilled syringes.

Wash and dry your hands.



Remove prefilled syringe from cardboard sleeve by holding the finger grip.



Pick from the 3 injectable areas:

- Front of **left thigh** or **right thigh**
- Your **abdomen** (belly) at least 2 inches from your navel (belly button)

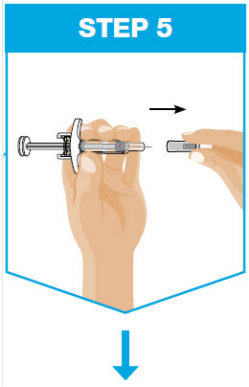
Wipe the injection site in a circular motion with the alcohol swab **before the injection.**

- **Do not** touch or blow on the injection site after it is cleaned. Allow the skin to dry before injecting.
- **Do not** inject through clothes.
- **Do not** inject into skin that is sore, bruised, red, hard, scarred, or has stretch marks, or into areas affected by psoriasis.

Hold the prefilled syringe with covered needle facing down, as shown.

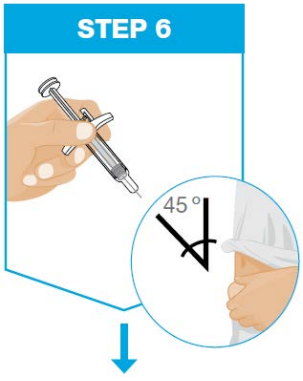
Check the liquid in the prefilled syringe.

- It is normal to see 1 or more bubbles in the window.
- The liquid should look clear to yellow and may contain tiny white or clear particles.
- **Do not** use the prefilled syringe if the liquid is **cloudy** or contains **flakes** or **large particles**.



Remove the needle cover.

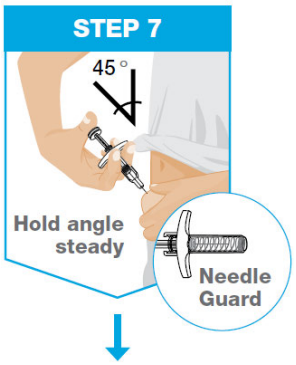
- Hold the prefilled syringe in 1 hand between the finger grip and needle cover.
- With the other hand, gently pull the needle cover straight off.
- **Do not** hold or the pull plunger rod when removing the needle cover.
- You may see a drop of liquid at the end of the needle. This is normal.
- Throw away the needle cover.
- **Do not** touch the needle with your fingers or let the needle touch anything.



Hold the body of the prefilled syringe in 1 hand between the thumb and index fingers.

Pinch the area of cleaned skin with your other hand and hold it firmly.

Insert the needle into the skin at about a **45-degree angle** using a quick, short movement. Hold angle steady.



Slowly push the plunger rod all the way in until all of the liquid is injected, and the prefilled syringe is empty.
Pull the needle out of the skin while keeping the prefilled syringe at the same angle.
Release the plunger rod and allow the prefilled syringe to move up until the entire needle is covered by the needle guard.
The prefilled syringe needle guard will not activate unless all the liquid has been injected.

- **Press** a cotton ball or gauze pad over the injection site and hold for 10 seconds.
- **Do not** rub the injection site. You may have slight bleeding. This is normal.

Put your used prefilled syringe in a **FDA-cleared sharps disposal container right away after use**.

- **Do not** throw away (dispose of) the used prefilled syringe in the household trash.

For more information, see "Used SKYRIZI Prefilled Syringe Disposal" section.

Questions About Using SKYRIZI

Q. **What if I need help on how to inject SKYRIZI?**
A. Call your healthcare provider or **(866) SKYRIZI or (866) 759-7494** if you need help.

Q. **What should I do with the used prefilled syringe after my injection?**
A. Throw away (dispose of) the used prefilled syringe in a sharps disposal container and not your household trash.
You can sign up to receive sharps containers for SKYRIZI syringe disposal at no additional cost by going to **www.SKYRIZI.com** or calling **(866) SKYRIZI or (866) 759-7494**.

Q. **How do I know when the injection is complete?**
A. The injection is complete when the prefilled syringe is empty, the plunger rod is pushed all the way in, and the syringe needle guard is activated.

Used SKYRIZI Prefilled Syringe Disposal

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: www.fda.gov/safesharpsdisposal.

Do not recycle your used sharps disposal container.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, U.S.A.
US License Number 1889

20071033

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 01/2022

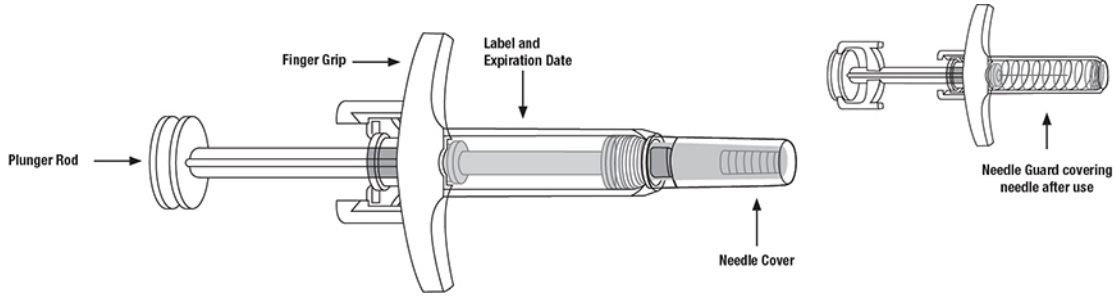
Instructions for Use
SKYRIZI® (sky-RIZZ-ee)
(risankizumab-rzaa)
injection, for subcutaneous use

75 mg/0.83 mL prefilled syringe

Read Before First Use

Refer to the **Medication Guide** for product information.

SKYRIZI Single-Dose Prefilled Syringe



Important Information:

- Keep SKYRIZI in the original carton to protect from light until time to use.
- The liquid should look clear to slightly yellow and may contain tiny white or clear particles.
- **Do not** use SKYRIZI if the liquid is **cloudy** or contains **flakes** or **large particles**.
- **Do not** use SKYRIZI if the **expiration date (EXP:)** shown on the carton and prefilled syringe has passed.
- **Do not** use SKYRIZI if the liquid has been **frozen** (even if thawed).
- **Do not** shake SKYRIZI.
- **Do not** use SKYRIZI if the prefilled syringe has been **dropped or damaged**.
- **Do not** use SKYRIZI if carton perforations are **broken**. **Return product to the pharmacy**.
- **Do not** remove the needle cover until right before giving the injections.

Keep SKYRIZI and all medicines out of the reach of children.

Please Read Complete Instructions For Use Before Using SKYRIZI Prefilled Syringe

Before Injecting:

- **Receive** training on how to inject SKYRIZI before giving injections. Call your healthcare provider or **(866) SKYRIZI or (866) 759-7494** if you need help.
- **Mark your calendar** ahead of time to remember when to take SKYRIZI.
- **Leave** the carton at room temperature and out of direct sunlight for **15 to 30 minutes** to warm.
  - **Do not** remove the prefilled syringes from the carton while allowing SKYRIZI to reach room temperature.
  - **Do not** warm SKYRIZI in any other way (for example, **Do not** warm it in a microwave or in hot water).

Important Information:

- The liquid should look clear to slightly yellow and may contain tiny white or clear particles.
- **Do not** use SKYRIZI if the liquid is **cloudy** or contains **flakes** or **large particles**.
- **Do not** use SKYRIZI if the **expiration date (EXP:)** shown on the carton and prefilled syringe has passed.
- **Do not** use SKYRIZI if the prefilled syringe has been **dropped or damaged**.
- **Do not** use SKYRIZI if carton perforations are **broken**. **Return product to the pharmacy**.

Storage Information:

- Store SKYRIZI in the refrigerator between 36°F to 46°F (2°C to 8°C).
- **Do not** shake SKYRIZI.
- Keep SKYRIZI in the original carton to protect from light until time to use.
- SKYRIZI is not made with natural rubber latex.
- **Do not** use if the liquid has been frozen (even if thawed).

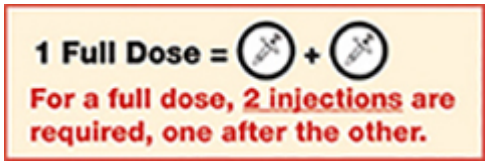
Keep SKYRIZI and all medicines out of the reach of children.

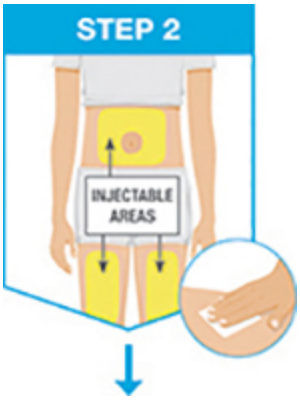
Call your healthcare provider or **(866) SKYRIZI or (866) 759-7494** if you need help or do not know how to proceed.

Gather the supplies for the injections and place the following on a clean, flat surface:

- **2 prefilled syringes** and **2 alcohol swabs (included)**
- **2 cotton balls** or gauze pads (not included)
- **FDA-cleared sharps disposal container** (not included). See "**Used SKYRIZI Prefilled Syringe Disposal**" for information on how to throw away (dispose of) used prefilled syringes.

Wash and dry your hands.
Start with 1 prefilled syringe for the first injection.





Pick from the 3 injectable areas:

- Front of **left thigh** or **right thigh**
- Your **abdomen** (belly) at least 2 inches from your navel (belly button)

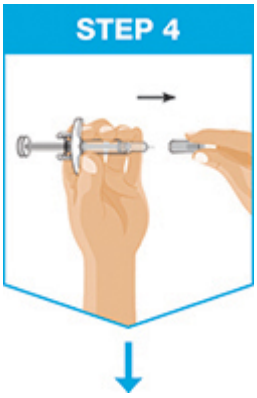
When using 2nd syringe: Pick an injection site **at least 1 inch away** from 1st site. **DO NOT inject into the same site.**

Wipe the injection site in a circular motion with the alcohol swab (before **both injections**)

- **Do not** touch or blow on the injection site after it is cleaned. Allow the skin to dry before injecting.
- **Do not** inject through clothes.
- **Do not** inject into skin that is sore, bruised, red, hard, scarred, or has stretch marks, or into areas affected by psoriasis.

Hold the prefilled syringe with the covered needle facing down, as shown.
Check the liquid in the prefilled syringe.

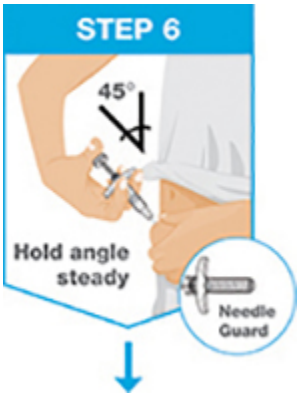
- It is normal to see 1 or more bubbles in the window.
- The liquid should look clear to slightly yellow and may contain tiny white or clear particles.
- **Do not** use the prefilled syringe if liquid is **cloudy** or contains **flakes** or **large particles**.



Remove the needle cover.

- Hold the prefilled syringe in 1 hand between the finger grip and needle cover.
- With the other hand, gently pull the needle cover straight off.
- **Do not** hold or pull the plunger rod when removing the needle cover.
- You may see a drop of liquid at the end of the needle. This is normal.
- Throw away the needle cover.
- **Do not** touch the needle with your fingers or let the needle touch anything.

Hold the body of the prefilled syringe in 1 hand between the thumb and index fingers.
Gently pinch the area of cleaned skin with your other hand and hold it firmly.
Insert the needle into the skin at about a **45-degree angle** using a quick, short movement. Hold angle steady.



Slowly push the plunger rod all the way in until all of the liquid is injected, and the prefilled syringe is empty.
Pull the needle out of the skin while keeping the prefilled syringe at the same angle.
Release the plunger rod and allow the prefilled syringe to move up until the entire needle is covered by the needle guard.
The prefilled syringe needle guard will not activate unless all the liquid has been injected.

- **Press** a cotton ball or gauze pad over the injection site and hold for 10 seconds.
- **Do not** rub the injection site. You may have slight bleeding. This is normal.

Repeat Step 2 through Step 6 with the 2nd prefilled syringe for a **full dose**.

- Use the 2nd prefilled syringe right after using the 1st prefilled syringe.

Put your used prefilled syringes in a FDA-cleared sharps disposal container right away after use.

- **Do not** throw away (dispose of) used prefilled syringes in the household trash.

For more information, see "Used SKYRIZI Prefilled Syringe Disposal" section.

Questions About Using SKYRIZI

Q. **What if I need help on how to inject SKYRIZI?**
A. Call your healthcare provider or **(866) SKYRIZI or (866) 759-7494** if you need help.

Q. **What should I do with both used prefilled syringes after my injections?**
A. Throw away (dispose of) both used prefilled syringes in a sharps disposal container and not your household trash.
You can sign up to receive sharps containers for SKYRIZI syringe disposal at no additional cost by going to **www.SKYRIZI.com** or calling **(866) SKYRIZI or (866) 759-7494**.

Q. **How do I know when the injection is complete?**
A. The injection is complete when the prefilled syringe is empty, the plunger rod is pushed all the way in, and the syringe needle guard is activated.

Used SKYRIZI Prefilled Syringe Disposal

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: www.fda.gov/safesharpsdisposal.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, U.S.A.
US License Number 1889

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 01/2022

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761105Orig1s014

LABELING REVIEW(s)

Division of Rheumatology and Transplant Medicine

REGULATORY PROJECT MANAGER LABELING REVIEW

Application:	BLA 761105/S-014
Name of Drug:	Skyrizi (risankizumab-rzaa) 90 mg/mL and 150 mg/mL
Applicant:	Abbvie
Submission Date:	March 23, 2021
Receipt Date:	March 23, 2021
Reviewer:	Susan Rhee, PharmD, Regulatory Project Manager January 10, 2022
Concurrence:	Christine Ford, MS, RPh, Acting CPMS January 20, 2022

Background and Summary Description:

Skyrizi (risankizumab-rzaa) injection was approved on April 23, 2019 for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for system therapy or phototherapy. AbbVie has submitted this prior approval efficacy supplement for a new indication, treatment of active psoriatic arthritis (PsA) in adults. Subsequently, the 150 mg/mL formulation and product presentation (pre-filled syringe with needle stick prevention) (supplement 9) and autoinjector using the 150 mg/mL formulation (supplement 10) were approved on April 26, 2021.

Review:

A comparison of the Prescribing Information (PI) received on December 22, 2021 was conducted with the last approved PI for supplements 009 and 010 on April 26, 2021. The updates were consistent with the information relevant for the addition of the new indication of PsA; there were no other changes than that provided for in this supplement.

Recommendations:

Comments provided by consult reviews from OPDP, DMEPA, and Patient Labeling Team have been communicated to the Applicant along with comments for the PI from the review team. This supplement should be approved pending labeling agreement.

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/s/

SUSAN RHEE
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	December 23, 2021
To:	Susan Rhee, PharmD Senior Regulatory Project Manager **Division of Rheumatology and Transplant Medicine (DRTM)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adewale Adeleye, Pharm.D., MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	SKYRIZI (risankizumab-rzaa)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761105
Supplement Number:	S-014
Applicant:	AbbVie Inc.

1 INTRODUCTION

On March 23, 2021 AbbVie Inc. submitted for the Agency's review an Efficacy Supplement for Psoriatic Arthritis Indication to the Biologics License Application (BLA) 761105 for SKYRIZI (risankizumab-rzaa) injection, for subcutaneous use. The purpose of this supplemental BLA is to request Agency approval of SKYRIZI (risankizumab-rzaa) Injection for the treatment of active psoriatic arthritis (PsA) in adults.

SKYRIZI (risankizumab-rzaa) injection, for subcutaneous use was approved on April 23, 2019 and is an interleukin-23 antagonist indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

This review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Rheumatology and Transplant Medicine (DRTM) on May 6, 2021 and April 22, 2021, respectively, for DMPP and OPDP to review the Applicant's Medication Guide (MG) and Instructions for Use (IFU) for SKYRIZI (risankizumab-rzaa) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft SKYRIZI (risankizumab-rzaa) injection, for subcutaneous use MG and IFU received on March 23, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 15, 2021.
- Draft SKYRIZI (risankizumab-rzaa) injection, for subcutaneous use Prescribing Information (PI) received on March 23, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 15, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

Following this Page, 36 Pages of Draft Labeling haven been Withheld in Full

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/s/

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12/23/2021 08:09:11 AM

MARCIA B WILLIAMS
12/23/2021 08:18:05 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 23, 2021
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761105/S-014
Product Name, Dosage Form, and Strength:	Skyrizi (Risankizumab-rzaa) Injection, 75 mg / 0.83 mL and 150 mg/mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AbbVie. Inc
FDA Received Date:	March 23, 2021 and May 4, 2021
OSE RCM #:	2021-848
DMEPA 1 Safety Evaluator:	Teresa McMillan, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

AbbVie. Inc submitted a prior approval efficacy supplement for Skyrizi (Risankizumab-rzaa) Injection for the treatment of active psoriatic arthritis (PsA) in adults.

Subsequently, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed Skyrizi Prescribing Information (PI) and Information for Use (IFU) for areas of vulnerability that may lead to medication errors.

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

We previously reviewed the HF validation study data for the approved 75 mg/0.5 mL and 150 mg single-dose prefilled syringe and 150 mg/mL prefilled pen to support adult self-administration in the proposed adult PsA indication under BLA 761105, BLA 761105/S-009 and BLA 761105/S-10 submitted to the Division of Dermatology and Dentistry (DDD)[a b cd] . All recommendations were implemented prior to the approval of BLA 761105 and the listed corresponding supplements.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F-N/A

[a] Patel, M. Human Factor Results and Label –Labeling Review for risankizumab BLA 761105. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 22. RCM No.: 2018-886 and 2018-910.

[b] Patel, M. Human Factor Results and Label –Labeling Review for risankizumab BLA 761105/009. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 26. RCM No.: 2020-1366.

[c] Patel, M. Human Factor Results and Label –Labeling Review for risankizumab BLA 761105/009. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 13. RCM No.: 2020-1366-1.

[d]Oguntimein, M. Human Factor Results and Label –Labeling Review for risankizumab BLA 761105/S-10. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 DEC 28. RCM No.: . 2020-1621.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Prescribing Information and Instructions for Use did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Skyrizi received on May 4, 2021 from AbbVie. Inc.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Skyrizi</th></tr>
<tr><td>Initial Approval Date</td><td>April 23, 2019</td></tr>
<tr><td>Proper Name</td><td>Risankizumab-rzaa</td></tr>
<tr><td>Indication</td><td>treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.
treatment of active psoriatic arthritis (PsA) in adults (proposed)</td></tr>
<tr><td>Route of Administration</td><td>Subcutaneous</td></tr>
<tr><td>Dosage Form</td><td>Injection</td></tr>
<tr><td>Strength</td><td>75 mg / 0.83 mL and 150 mg/mL</td></tr>
<tr><td>Dose and Frequency</td><td>Plaque Psoriasis and Psoriatic Arthritis (PsA) (proposed): 150 mg (one 150 mg injection) administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.</td></tr>
<tr><td>How Supplied</td><td><table><tr><th>Strength</th><th>Pack Size</th><th>NDC</th></tr><tr><td>150 mg/mL single-dose pen</td><td>Carton of 1</td><td>0074-2100-01</td></tr><tr><td>150 mg/mL single-dose prefilled syringe</td><td>Carton of 1</td><td>0074-1050-01</td></tr><tr><td>75 mg/0.83 mL single-dose prefilled syringe</td><td>Carton of 2</td><td>0074-2042-02</td></tr></table></td></tr>
<tr><td>Storage</td><td>Store in a refrigerator at 2° C to 8° C (36° F to 46° F)</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 3, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Skyrizi. Our search identified 4 previous reviews[e f gh] and we considered our previous recommendations to see if they are applicable for this current review.

[e] Patel, M. Human Factor Results and Label –Labeling Review for risankizumab BLA 761105. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 22. RCM No.: 2018-886 and 2018-910.

[f] Patel, M. Human Factor Results and Label –Labeling Review for risankizumab BLA 761105/009. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 26. RCM No.: 2020-1366.

[g] Patel, M. Human Factor Results and Label –Labeling Review for risankizumab BLA 761105/009. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 13. RCM No.: 2020-1366-1.

[h] Oguntimein, M. Human Factor Results and Label –Labeling Review for risankizumab BLA 761105/S-10. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 DEC 28. RCM No.: . 2020-1621.

APPENDIX C. N/A

APPENDIX D. ISMP NEWSLETTERS-N/A

APPENDIX E. N/A

APPENDIX F. N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following Skyrizi labels and labeling submitted by AbbVie. Inc

- Instructions for Use and Prescribing Information (Images not shown) received on May 4, 2021, available from \\CDSESUB1\evsprod\bla761105\0126\m1\us\114-labeling\draft\labeling\neg-lbl-7027.pdf

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

TERESA S MCMILLAN
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761105Orig1s014

MULTIDISCIPLINE REVIEW(s)

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761105/S-014
Priority or Standard	Standard
Submit Date(s)	March 23, 2021
Received Date(s)	March 23, 2021
PDUFA Goal Date	January 21, 2022
Division/Office	Division of Rheumatology and Transplant Medicine
Review Completion Date	See electronic stamp date
Established/Proper Name	Risankizumab-rzaa
(Proposed) Trade Name	Skyrizi
Pharmacologic Class	humanized IgG1 monoclonal antibody
Code name	BI655066
Applicant	AbbVie
Doseage form	Solution
Applicant proposed Dosing Regimen	150 mg subcutaneously at Week 0, Week 4, and every 12 weeks thereafter
Applicant Proposed Indication(s)/Population(s)	Psoriatic Arthritis
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	156370009 – Psoriatic arthritis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of active psoriatic arthritis in adults
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	156370009 – Psoriatic arthritis (disorder)
Recommended Dosing Regimen	150 mg subcutaneously at Week 0, Week 4, and every 12 weeks thereafter

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Susan Rhee
Nonclinical Reviewer	Brett Jones
Nonclinical Team Leader	Eleni Salicru
Office of Clinical Pharmacology Reviewer(s)	Liping (Cindy) Pan, Yangbing Li (Pharmacometrics)
Office of Clinical Pharmacology Team Leader(s)	Jianmeng Chen, Jiang Liu (Pharmacometrics)
Clinical Reviewer	Austin Anderson
Clinical Team Leader	Raj Nair
Statistical Reviewer	Hongling Zhou
Statistical Team Leader	Rebecca Rothwell
Cross-Disciplinary Team Leader	Raj Nair
Division Director/Signatory	Nikolay Nikolov

Additional Reviewers of Application

OPQ	Milos Dokmanovic
OPDP	Adewale Adeleye
OSI	Tina Chang/Karen Bleich (TL)
OSE/DMEPA	Teresa Mcmillan/Idalia Rychlik (TL)
OSE/DPV	Jamie Klucken/Tiffany Kim/Lisa Wolf (TL)
Other – Patient Labeling	Nyedra Booker/Marcia Williams (TL)

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Liping (Cindy) Pan	OTS/OCP/DIIP	Section: 6	**Select one:** _x__ Authored ___ Approved
	Signature: Liping Pan -S Digitally signed by Liping Pan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Liping Pan -S, 0.9.2342.19200300.100.1.1=2002455400 Date: 2022.01.21 09:47:18 -05'00'			
Clinical Pharmacology Team Leader	Jianmeng Chen	OTS/OCP/DIIP	Section: 6	**Select one:** ___ Authored __x_ Approved
	Signature: Jianmeng Chen Digitally signed by Jianmeng Chen DN: cn=Jianmeng Chen, o=FDA/CDER/OTS/OCP, ou, email=JIANMENG.CHEN@FDA.HHS.GOV, c=US Date: 2022.01.21 09:38:18 -05'00'			
Pharmacometrics Reviewer	Yangbing Li	OTS/OCP/DPM	Section: 6, 15.4	**Select one:** _x__ Authored ___ Approved
	Signature: Signed on behalf of Yangbing. Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2022.01.21 10:28:34 -05'00'			
Pharmacometrics Team Leader	Jiang Liu	OTS/OCP/DPM	Section: 6, 15.4	**Select one:** ___ Authored _x__ Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2022.01.21 10:32:38 -05'00'			
Clinical Reviewer	Austin Anderson	OND/DRTM	Sections: 1.1, 1.2, 1.3, 1.4, 2.1, 2.2, 3.1, 3.2, 4.1, 4.2, 4.3, 4.4, 7.1, 7.2, 8.1, 8.4, 8.6, 9, 10, 12, 13, 19.5	**Select one:** _X__ Authored ___ Approved
	Signature: Austin M. Anderson -S Digitally signed by Austin M. Anderson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013947548, cn=Austin M. Anderson -S Date: 2022.01.21 09:43:44 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Raj Nair	OND/DRTM	Sections: 1-13	**Select one:** ___ Authored _X__ Approved
	Signature: Raj G. Nair -S	Digitally signed by Raj G. Nair -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Raj G. Nair -S, 0.9.2342.19200300.100.1.1=2001194491 Date: 2022.01.21 09:12:18 -05'00'		
Division Director (Clinical)/Signatory	Nikolay Nikolov	OND/DRTM	Sections: All	**Select one:** ___ Authored _X__ Approved
	Signature: Nikolay P. Nikolov -S	Digitally signed by Nikolay P. Nikolov -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011314790, cn=Nikolay P. Nikolov -S Date: 2022.01.21 10:48:28 -05'00'		
Statistical Reviewer	Hongling Zhou	OTS/OB/DBIII	Sections: 8.1, 8.2, 8.3, 8.5	**Select one:** _x__ Authored ___ Approved
	Signature: Hongling Zhou -S	Digitally signed by Hongling Zhou -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hongling Zhou -S, 0.9.2342.19200300.100.1.1=1300379379 Date: 2022.01.21 09:55:10 -05'00'		
Statistical Team Leader	Rebecca Rothwell	OTS/OB/DBIII	Sections: 1.2, 1.3, 8.1, 8.2, 8.3, 8.5, 8.6	**Select one:** ___ Authored _x__ Approved
	Signature: Rebecca Rothwell -S	Digitally signed by Rebecca Rothwell -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000455521, cn=Rebecca Rothwell -S Date: 2022.01.21 10:09:51 -05'00'		

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Risankizumab (Skyrizi®) is a humanized immunoglobulin G1 monoclonal antibody directed against the p19 subunit of the interleukin-23 (IL-23) cytokine. Risankizumab blocks the binding of extracellular IL-23 to its cell surface receptor, and inhibits IL-23 mediated intracellular signaling and the release of proinflammatory cytokines and chemokines. IL-23 plays a role in the differentiation and function of T-helper (Th) 17 cells. Th-17 cells have emerged as an important T-cell subpopulation in the pathogenesis of immune mediated disorders such as psoriatic arthritis.

Risankizumab is approved in the United States for treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Risankizumab was originally approved on April 23, 2019 with a dose of 150 mg administered as two 75 mg subcutaneous injections at Week 0, Week 4, and every 12 weeks thereafter. The original dosage form was 75 mg/0.83 mL in a single-dose prefilled syringe. A 150 mg/mL formulation was subsequently approved on April 26, 2021 including a 150 mg/mL prefilled syringe and autoinjector pen.

AbbVie Inc. submitted supplement 14 to Biological Licensing Application (BLA) 761105 for the treatment of active psoriatic arthritis (PsA) in adults. The proposed dose is 150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter. The proposed dosage form was originally 75 mg/0.83 mL in a single-dose prefilled syringe; however, during the review of supplement 14, the Applicant proposed to update the U.S. Prescribing Information upon approval of supplemental BLA (sBLA) applications for two new dosage forms including a 150 mg/mL prefilled syringe (supplement 9) and 150 mg/mL autoinjector (supplement 10). These new dosage forms were approved on April 26, 2021 for the treatment of moderate-to-severe plaque psoriasis. The proposed labeling includes three dosage forms including 150 mg/mL in a single-dose prefilled pen, 150 mg/mL in a single-dose prefilled syringe, and 75 mg/0.83 mL in a single-dose prefilled syringe.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The primary data to support the substantial evidence of effectiveness are derived from two adequate and well-controlled, phase 3 studies, study M16-011 and study M15-998. Both studies were multicenter, randomized, double-blind, placebo-controlled studies with open label extensions in patients with active PsA. Study M16-011 enrolled patients who had an inadequate response to at least 1 csDMARD. Study M15-998 enrolled patients who had an inadequate response to 1 or 2 biologic therapies (no more than 50% of the study population) or at least 1 csDMARD. The primary endpoint for both of the phase 3 studies was American College of

Rheumatology (ACR) 20 response criteria at Week 24, a well-established primary endpoint of clinical response in clinical programs for the proposed indication.

In study M16-011, a greater proportion of patients treated with risankizumab (57.3%) achieved the primary endpoint of ACR20 response at Week 24 compared to patients treated with placebo (33.5%), and this difference (24.0%) was statistically significant with a 95% CI of (18.0%, 30.0%) ($p<0.001$)). The efficacy of risankizumab over placebo was further supported by a significantly greater proportion of patients with ACR20 response at Week 16 in patients treated with risankizumab compared to placebo and statistically significant improvement in a key secondary endpoint, HAQ-DI, at Week 24. Treatment with risankizumab failed to demonstrate improvement in the pre-specified radiographic endpoint, change from baseline in the modified Total Sharp Score.

In study M15-998, a greater proportion of patients treated with risankizumab (51.3%)achieved the primary endpoint of ACR20 response at Week 24 compared to patients treated with placebo (26.5%), and this difference (24.5%) was statistically significant with a 95% CI of (15.9%, 33.0%) ($P<0.001$). The efficacy of risankizumab over placebo was further supported by a significantly greater proportion of patients with ACR20 response at Week 16 in patients treated with risankizumab compared to placebo and statistically significant improvement in HAQ-DI at Week 24. Additionally, for both studies, there was an observed greater proportion of patients with ACR50 and ACR70 response at Week 24 and improvements in enthesitis and dactylitis, as clinically-relevant manifestation of the disease.

In conclusion, studies M16-011 and M15-998 provide substantial evidence of efficacy of the risankizumab 150 mg SC at Weeks 0, 4, and every 12 weeks thereafter dosing regimen for the treatment of adult patients with active psoriatic arthritis.

The Division Signatory agrees with this assessment and conclusions.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Psoriatic arthritis (PsA) is a chronic, progressive, inflammatory arthritis associated with psoriasis that may result in pain, disability, and permanent joint damage. Although multiple therapies are approved for PsA in the United States, there remains an unmet need for additional therapeutic options in this population.

Risankizumab is an interleukin-23 blocker approved in the United States for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The approved dose in psoriasis is risankizumab 150 mg SC at Weeks 0, 4, and every 12 weeks thereafter. In this supplemental BLA, AbbVie submitted the results of two phase 3 studies, M16-011 and M15-998, and two phase 2 studies, M16-002 and M16-244, to provide evidence of the efficacy and safety of risankizumab in the treatment of psoriatic arthritis in adults. Study M16-002 was a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study in patients with active PsA. Study M16-244 was a multicenter, single-arm, open label extension study in patients who completed the week 24 visit of Study M16-002. Studies M16-011 and M15-998 were both multicenter, randomized, double-blind, placebo-controlled studies with open label extension in patients with active PsA. Study M16-011 enrolled patients who had an inadequate response to at least 1 csDMARD. Study M15-998 enrolled patients who had an inadequate response to 1 or 2 biologic therapies (no more than 50% of the study population) or at least 1 csDMARD. The primary endpoint for both of the phase 3 studies was American College of Rheumatology (ACR) 20 response criteria at Week 24, a well-established primary endpoint of clinical response in clinical programs for the proposed indication.

Studies M16-011 and M15-998 provide evidence for the effectiveness of risankizumab compared to placebo to improve signs and symptoms, as measured by American College of Rheumatology (ACR) 20% response criteria. The efficacy of risankizumab over placebo was further supported by a key secondary endpoint of HAQ-DI, demonstrating improvement in physical function.

The safety profile of risankizumab was characterized based on a comprehensive evaluation of the phase 3 psoriatic arthritis placebo-controlled analysis set which includes patients who received risankizumab 150 mg or placebo during the 24-week placebo-controlled period in phase 3 studies M16-011 and M15-998, the phase 3 psoriatic arthritis long-term analysis set which includes patients who received at least one dose of risankizumab 150 mg in phase 3 studies M16-011 and M15-998, and the all risankizumab psoriatic analysis set which includes patients in the phase 2 and phase 3 psoriatic arthritis studies who received at least one dose of risankizumab. In addition, safety data from the 120-day safety update was reviewed and generally consistent with the safety presented in the initial summary of clinical safety.

In general, during the placebo controlled period, the number of patients and percentage of patients (and event rate) with treatment emergent adverse events (TEAEs), serious adverse events (SAEs), severe adverse events, drug-related AEs, and TEAEs leading to discontinuation was similar in the risankizumab and placebo groups. There was 1 death in the placebo-controlled analysis set that was assessed by the investigator and Applicant as having no reasonable possibility of being related to study drug. Overall, the safety profile of risankizumab in the treatment of psoriatic arthritis is generally consistent with the previous experience with risankizumab in psoriasis; however, in the psoriatic arthritis program, there were additional safety signals for hepatic events and hypersensitivity reactions which warrant inclusion in product labeling.

In conclusion, supplement 14 has provided adequate data to inform the benefit-risk assessment of risankizumab for the treatment of adult patients with active psoriatic arthritis. The benefit-risk profile is favorable to support the dosing regimen of risankizumab 150 mg SC at Weeks 0, 4, and every 12 weeks thereafter for the proposed indication. The safety of risankizumab in the psoriatic arthritis program was generally consistent with the known safety of risankizumab in the psoriasis program with the addition of hepatic events and hypersensitivity reactions. Risankizumab offers an acceptable risk for the therapeutic benefits, and provides an additional treatment option in the US for adult patients with psoriatic arthritis. The Division Signatory agrees with this assessment and conclusions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Psoriatic arthritis (PsA) is a chronic, progressive, inflammatory arthritis associated with psoriasis. The clinical manifestations of PsA may include peripheral inflammatory arthritis, axial inflammatory arthritis, and periarticular disease such as enthesitis and dactylitis. • Patients with PsA can develop destructive disease characterized by radiographic progression of structural damage to the peripheral and/or axial joints • PsA is a clinical diagnosis and is typically based on the CASPAR criteria. To fulfill the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥ 3 points from the following five categories: ○ Evidence of current psoriasis, personal history of psoriasis,	PsA is an inflammatory arthritis associated with psoriasis that may result in pain, disability, and permanent joint damage.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	or family history of psoriasis if the patient is not affected ○ Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical exam ○ A negative test result for the presence of rheumatoid factor ○ Dactylitis observed on current physical examination or previously documented by a rheumatologist ○ Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot • The goals of PsA treatment are to improve signs and symptoms, improve physical function, and inhibit long-term structural damage	
Current Treatment Options	• The management of patients with PsA includes the use of non-steroidal anti-inflammatory drugs (NSAIDs), systemic glucocorticoids, intra-articular glucocorticoids, and small molecule and biologic disease modifying antirheumatic drugs (DMARDs) • FDA approved drugs for the treatment of PsA include TNFα-inhibitors; apremilast, an oral small molecule inhibitor of phosphodiesterase 4; Ustekinumab, an IL-12/23 inhibitor; secukinumab, an IL-17A inhibitor; abatacept, a T-cell costimulation modulator; ixekizumab, an IL-17A inhibitor; tofacitinib and upadacitinib, janus kinase (JAK) inhibitors; and guselkumab, an IL-23 inhibitor. Other non-biologic DMARDs may be used off label for treatment of PsA.	Although many patients with PsA may respond to the current treatment options, there are patients who may have contraindications to or continued disease despite these available therapies. Therefore, an unmet need remains for additional therapeutic options for this population.
Benefit	• The Applicant submitted two adequate and well-controlled phase 3 studies, M16-011 and M15-998. Both studies were multicenter, randomized, double-blind, placebo-controlled studies of risankizumab in patients with active PsA. Study M16-011 enrolled patients who had an inadequate response to at least 1 csDMARD. Study M15-998	The Applicant has submitted two adequate and well-controlled studies, M16-011 and M15-998, that demonstrate substantial evidence of efficacy of risankizumab for the treatment of PsA in adults. The studies used

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	enrolled patients who had an inadequate response to 1 or 2 biologic therapies (no more than 50% of the study population) or at least 1 csDMARD. • The primary endpoint in each phase 3 study was the proportion of patients who achieved an ACR20 response at Week 24, which achieved statistical significance in each study. In both studies, a greater proportion of subjects on risankizumab (57.3% and 51.3%) compared to placebo (33.5% and 26.5%) achieved an ACR20 response at Week 24, respectively. • Results for key secondary endpoints assessed at Week 24, such as HAQ-DI, provided additional support for the efficacy of risankizumab. Additionally, though the multiplicity control procedure did not allow for assessing statistical significance in each study, improvements were also observed in SF-36 PCS, FACIT-Fatigue, Leeds Enthesitis Index and Leeds Dactylitis Index. • Treatment with risankizumab failed to demonstrate improvement in the pre-specified radiographic endpoint, change from baseline in the modified Total Sharp Score.	validated and well established primary and secondary endpoints that were designed to capture clinically meaningful changes in disease activity. The submitted studies demonstrate the benefit of risankizumab treatment on the signs and symptoms and physical function in adults with active PsA. There was no evidence of significant change in the radiographic endpoint with treatment with risankizumab.
Risk and Risk Management	• The safety assessment of risankizumab in psoriatic arthritis is based primarily on the safety database from the phase 3 studies M16-011 and M15-998. The safety review focuses on the placebo-controlled data from these studies (24-week data). Additional supportive safety data are provided by the phase 2 studies (M16-002 and M16-244), the 120-day safety update, and data from the psoriasis program. • The proportion of patients with SAEs and AEs leading to discontinuation, and event rate of SAEs and AEs leading to discontinuation were similar in the risankizumab and placebo groups.	The safety data from risankizumab in the PsA studies were generally consistent with the known safety profile of risankizumab in psoriasis; however, there was a new safety signal for hepatic events and hypersensitivity reactions. In the phase 3 placebo-controlled analysis set, the percentage of patients with hepatic TEAEs

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There was 1 death in the placebo controlled analysis set. The death was assessed by the investigator and Applicant as having no reasonable possibility of being related to study drug. There were no additional deaths in the phase 3 PsA long-term analysis set. The exposure adjusted death rate with long-term risankizumab exposure was < 0.1 E/100 PY. • The safety profile was generally consistent with the known safety profile of risankizumab in psoriasis. However, there was a new signal for hepatic events and hypersensitivity reactions in the psoriatic arthritis program.	and rate of hepatic events was higher in the risankizumab group than the placebo group. The majority of hepatic events were mild-moderate in severity and there were no serious hepatic events reported. In the phase 3 placebo-controlled analysis set, the number and percentage of patients with hypersensitivity reactions and event rate of hypersensitivity reactions was higher in the risankizumab group than the placebo group. There were no hypersensitivity reactions that were serious or severe. One patient in the phase 2 dose-ranging study (randomized to receive 150 mg every 4 weeks) experienced an anaphylactic event on Day 1 of treatment.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data		**Section 8.3:** • ACR20 • HAQ-DI • PASI-90 • MDA • mNAPSI • PGA-F • LEI • LDI • mTSS • SF-36 • FACIT-Fatigue
		X	Patient reported outcome (PRO)	**Section 8.3:** • SF-36 • FACIT-Fatigue • HAQ-DI
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		

	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify):	
☐	**Patient experience data was not submitted as part of this application.**		

2 Therapeutic Context

2.1.Analysis of Condition

Psoriatic arthritis (PsA) is a chronic, progressive, inflammatory arthritis associated with psoriasis that may result in permanent joint damage and disability. Prevalence estimates of PsA in the United States range from 0.06-0.25% of the general population[1]. PsA is more common among patients with psoriasis with prevalence estimates that range from 6-41%. In the majority of PsA patients, psoriasis precedes the onset of arthritis with a median time between the diagnosis of skin and joint disease of 7-8 years[2]. PsA affects men and women equally, and the peak age of onset of PsA is 40-50 years[3].

The clinical manifestations of PsA may include peripheral inflammatory arthritis, axial inflammatory arthritis, or both. There are five clinical patterns of PsA including distal arthritis, asymmetric oligoarthritis, symmetric polyarthritis, arthritis mutilans, and spondyloarthritis[4]. PsA most often presents as a polyarthritis or as an oligoarthritis, although some patients present with more than one pattern and many patients change the pattern of involvement over time. Periarticular disease may also occur including tenosynovitis and soft tissue inflammation such as enthesitis and dactylitis.

The Classification Criteria for Psoriatic Arthritis have been used to classify patients as having PsA in clinical trials. These criteria were first proposed in 2006 based on the international Classification of Psoriatic Arthritis study[5]. The study authors concluded that patients with inflammatory articular disease (joint, spine, or entheseal) can be classified as having PsA if a total of at least 3 points is obtained from the following five categories: evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis; typical psoriatic nail dystrophy including onycholysis, pitting, or hyperkeratosis observed on exam; a negative test for Rheumatoid factor by any method except latex but preferably enzyme-linked immunosorbent assay or nephelometry; current dactylitis, defined as swelling of an entire digit, or history of dactylitis recorded by a rheumatologist; radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins excluding osteophyte formation, on plain radiographs of the hand or foot.

[1] Ogdie A, Weiss P. The Epidemiology of Psoriatic Arthritis. *Rheum Dis Clin North Am*. 2015;41(4):545-568.
[2] Tillett W, Charlton R, Nightingale A, et al. Interval between onset of psoriasis and psoriatic arthritis comparing the UK Clinical Practice Research Datalink with a hospital-based cohort. *Rheumatology (Oxford)*. 2017;56(12):2109-2113.
[3] Ocampo D V, Gladman D. Psoriatic arthritis. *F1000Res*. 2019;8:F1000 Faculty Rev-1665. Published 2019 Sep 20.
[4] Wright V, Moll JM. Psoriatic arthritis. *Bull Rheum Dis*. 1971;21(5):627-632.
[5] Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum*. 2006;54(8):2665-2673.

2.2. Analysis of Current Treatment Options

The goals of PsA treatment are to improve signs and symptoms, improve physical function, and prevent radiographic progression. Additional goals include improvement of concomitant enthesitis, dactylitis, axial involvement, and psoriasis.

According to 2018 guidelines from the American College of Rheumatology (ACR) and National Psoriasis Foundation (NPF), treatment of PsA may include symptomatic treatments (e.g., nonsteroidal anti-inflammatory drugs, glucocorticoids, or local glucocorticoid injections) in addition to oral small molecule and biologic disease modifying anti-rheumatic drugs. Oral small molecules include methotrexate, sulfasalazine, cyclosporine, leflunomide, and apremilast. FDA approved drugs for the treatment of PsA include tumor necrosis factor alpha inhibitors (TNFα), an interleukin-17 inhibitor (IL-17), an IL-17A inhibitor, an IL-12/23 inhibitor, an IL-23 inhibitor, a phosphodiesterase 4 (PDE4) inhibitor, a T-cell costimulation modulator, and a janus kinase (JAK) inhibitor as shown in Table 1.

Table 1. Drugs Approved for Treatment of Psoriatic Arthritis (PsA)

Drug	Mechanism of Action	Approval Date	Dose & Administration
Etanercept (Enbrel)	TNFα-Inhibitor	1/15/2002	50 mg SC once weekly with or without methotrexate
Infliximab (Remicade)	TNFα-Inhibitor	5/18/2005	5 mg/kg IV at 0, 2, and 6 weeks then every 8 weeks thereafter
Adalimumab (Humira)	TNFα-Inhibitor	10/3/2005	40 mg SC every other week
Golimumab SC (Simponi)	TNFα-Inhibitor	4/24/2009	50 mg SC once per month
Ustekinumab (Stelara)	IL-12/23 Inhibitor	9/20/2013	45 mg SC at 0 and 4 weeks, then 45 mg every 12 weeks
Certolizumab (Cimzia)	TNFα-Inhibitor	9/27/2013	• 400 mg SC initially and at week 2 and 4, followed by 200 mg every other week • For maintenance dosing 400 mg every 4 weeks can be considered
Apremilast (Otezla)	PDE4 Inhibitor	3/21/2014	30 mg PO BID after completion of a 6-day titration schedule

Drug	Mechanism of Action	Approval Date	Dose & Administration
Secukinumab (Cosentyx)	IL-17 Inhibitor	1/15/2016	• With a loading dose: 150 mg SC at Weeks 0, 1, 2, 3, 4, and every 4 weeks thereafter • Without a loading dose: 150 mg SC every weeks • If a patient continues to have active PsA, consider 300 mg SC every 4 weeks
Abatacept (Orencia)	T-cell Costimulation Blocker	6/1/2017	• 500-1000 mg IV at 0, 2, and 4 weeks, then every 4 weeks • 125 mg SC once weekly
Golimumab IV (Simponi Aria)	TNFα-Inhibitor	10/20/2017	2 mg/kg IV at weeks 0 and 4, then every 8 weeks thereafter
Ixekizumab (Taltz)	IL-17A Inhibitor	12/1/2017	160 mg SC at week 0 followed by 80 mg every 4 weeks
Tofacitinib (Xeljanz)	JAK Inhibitor	12/14/2017	• 5 mg PO twice daily • XR: 11 mg PO once daily
Guselkumab (Tremfya)	IL-23 Inhibitor	7/13/2020	100 mg SC at week 0, 4, and every 8 weeks thereafter
Upadacitinib (Rinvoq)	JAK Inhibitor	12/14/2021	15 mg PO once daily

BID = twice daily; IL = interleukin; IV = intravenous; JAK = janus kinase; kg = kilogram; mg = milligram; PDE4 = phosphodiesterase 4; PsA = psoriatic arthritis; PO = per os (oral administration); SC = subcutaneous; TNFα = Tumor Necrosis Factor alpha; XR = extended release

The 2018 ACR/NPF guidelines provide recommendations for management of patients who are treatment-naïve, patients with active PsA despite treatment with an oral small molecule (OSM), and patients with active PsA despite treatment with biologic therapies[6].

In treatment-naïve patients with active PsA, a TNFα-inhibitor is recommended over an OSM as a first-line option. However, OSMs may be used instead of a TNFα-inhibitor in certain circumstances, such as patients without severe PsA and without severe psoriasis, those who prefer an oral drug instead of parenteral therapy, or those with contraindications to TNFα-inhibitor treatment. An IL-17 inhibitor or IL-12/23 inhibitor may be used instead of a TNFα-inhibitor in patients with severe psoriasis or contraindications to TNFα-inhibitors, and may be used instead of OSMs in patients with severe psoriasis or severe PsA. Methotrexate is recommended over NSAIDs in treatment-naïve patients with active PsA; however, NSAIDs may be used instead of Methotrexate after consideration of possible contraindications and side

[6] Singh J, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis & Rheum*. 2019; 71(1): 5–32.

effect profile in patients without evidence of severe PsA or severe psoriasis and in those at risk for liver toxicity. An IL-17 inhibitor is recommended over an IL-12/23 inhibitor. IL-12/23 inhibitors may be used in patients who have concomitant inflammatory bowel disease or in those who desire less frequent drug administration. All recommendations for treatment-naïve patients with active PsA are conditional based on low to very-low quality evidence.

In patients with active PsA despite OSM therapy, switching to a TNFα-inhibitor, an IL-17 inhibitor, or an IL-12/23 inhibitor is recommended over switching to a different OSM. However, a different OSM may be used in patients who prefer an oral medication or those without evidence of severe PsA or severe psoriasis. A TNFα-inhibitor is recommended over an IL-17 inhibitor, an IL-12/23 inhibitor, abatacept, or tofacitinib. An IL-17 inhibitor is recommended over an IL-12/23 inhibitor, abatacept, or tofacitinib. In patients with severe psoriasis, an IL-12/23 inhibitor or an IL-17 inhibitor may be used instead of a TNFα-inhibitor. Tofacitinib may be used instead of a TNFα-inhibitor in patients preferring oral medication who do not have severe psoriasis.

In patients with active PsA despite TNFα-inhibitor or other biologic therapy, change to an alternative treatment in either the same or different therapeutic class is recommended with consideration given to the severity of disease, presence of comorbid conditions, and patient preference.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Risankizumab was first approved in the United States on April 23, 2019 for treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

3.2. Summary of Presubmission/Submission Regulatory Activity

The FDA had several regulatory interactions with the Applicant regarding the development of risankizumab for the treatment of active PsA in adults. Key discussion points are summarized below:

1. End-of-Phase 2 teleconference on October 3, 2017
    - The FDA did not agree that an appropriate dose of risankizumab was identified to support a phase 3 program in PsA. FDA noted that the flat dose-response curve obtained from the phase 2 dose-ranging study suggested a dose lower than 150 mg may be as effective as the proposed 150 mg dose. In addition, the same study demonstrated that 75 mg single dose treatment might be as effective as multiple-dose treatments at Week 16.

- The FDA did not agree with the Applicant's rationale that the 150 mg dose was selected because lower doses were inadequate for skin responses, and the FDA noted that the dose selection needs to be considered in the context of PsA given that the development program is for PsA and not for psoriasis.
- Given these concerns, the FDA recommended to perform an additional dose-ranging study including 75 mg and lower doses to better characterize the appropriate dose and regimen of risankizumab to be used in the phase 3 program for PsA.

2. Type C Written Response Only meeting on May 6, 2020
    - The FDA agreed with the proposed analysis plan for the Integrated Summary of Efficacy and noted that focus would primarily be on efficacy data from individual studies to support approval of the product.
    - The FDA agreed with the proposed analysis plan for the Integrated Summary of Safety, and recommended to include additional safety data from related approved indications such as psoriasis to better contextualize the safety of risankizumab in psoriatic arthritis.
3. Pre-sBLA teleconference on February 5, 2021
    - The FDA recommended to prespecify a treatment policy estimand and while on treatment estimand for each area of safety interest.
    - The FDA recommended to submit study level SDTM and AdaM datasets for the phase 2 study, M16-002, in addition to the two pivotal phase 3 studies, M15-998 and M16-011.
    - The FDA agreed that there is no need to update the current drug abuse and liability assessment for the sBLA since the current report was approved as part of the initial BLA submission for psoriasis in April 2019, and no abuse prone characteristics were identified.
    - The FDA noted that it was premature to provide any agreement regarding an update to the USPI included in the PsA submission upon approval of the 150 mg/mL autoinjector and prefilled syringe sBLAs since review was ongoing at that time.
    - The FDA did not agree with the proposal to add nail psoriasis endpoints to Section 14 of labeling since it could be misconstrued as an expansion of the treatment indication to mild psoriasis for which the benefit-risk profile of risankizumab has not been determined to be favorable.
    - The FDA recommended to include an updated pediatric study plan with the sBLA since thinking on the default waiver for pediatric PsA studies has evolved.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical study site inspections were not performed for this supplemental BLA submission because no single study site appeared to drive efficacy data or have concerning safety results. Clinical study site inspections were previously conducted at the time of the original BLA submission pertaining to use of risankizumab for treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

4.2. Product Quality

No new CMC information was submitted and was not required for the regulatory decision for this supplement. The relevant information was reviewed in the original BLA. For details, refer to the review dated April 17, 2019.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

AbbVie Inc. submitted supplement 14 to Biological Licensing Application (BLA) 761105 for the treatment of active psoriatic arthritis in adults. The proposed dose is 150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter. The proposed dosage form was originally 75 mg/0.83 mL in a single-dose prefilled syringe; however, the Applicant proposed to update the U.S. Prescribing Information upon approval of supplemental BLA (sBLA) applications for two new dosage forms including a 150 mg/mL prefilled syringe (supplement 9) and 150 mg/mL autoinjector (supplement 10). These new dosage forms were approved on April 26, 2021 for the treatment of moderate-to-severe plaque psoriasis.

DMEPA reviewed the human factors validation study for the approved 75 mg/0.83 mL single-dose prefilled syringe, 150 mg/mL single-dose prefilled syringe, and 150 mg/mL prefilled pen to support adult self-administration in the proposed adult psoriatic arthritis indication under BLA 761105, BLA 761105 (supplement 9), and BLA 761105 (supplement 10) submitted to the Division of Dermatology and Dentistry. DMEPA found the 150 mg/mL prefilled syringe and autoinjector acceptable for use in the psoriatic arthritis population. The Division Signatory agrees with this assessment and conclusions.

5 Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology and toxicology studies were conducted or required to support the regulatory decision for this supplement. The relevant information was previously reviewed in the original BLA.

6 Clinical Pharmacology

6.1. Executive Summary

SKYRIZI® (Risankizumab-rzaa), an interleukin-23 antagonist, was approved under Biologics License Application (BLA) 761,105 in 2019 for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. The recommended dose regimen for subjects with psoriasis is 150 mg administered by subcutaneous (SC) injection at Week 0, Week 4, then every 12 weeks (Q12W) thereafter. Risankizumab was originally approved as a 90 mg/mL formulation in a prefilled syringe (PFS) with a needle stick protection device (NSP) to be self-administered in 2 injections per dose (2 × 75 mg/0.83 mL PFS-NSP) for a total dose of 150 mg risankizumab.

Under the current sBLA (BLA 761,105/s-014), the Applicant is seeking the Agency's approval of a new indication for the treatment of active psoriatic arthritis (PsA) in adults. In support of the proposed indication, the Applicant conducted a phase 2 dose-ranging trial (M16-002), two pivotal phase 3 trials (M15-998 and M16-011), and an open label extension trial (M16-244) in subjects with PsA.

The proposed dose regimen is 150 mg SC at Week 0 and Week 4, then Q12W thereafter. Of note, the proposed dose regimen for the PsA indication is the same as the approved dose regimen for the treatment of psoriasis, and has been evaluated in the two pivotal phase 3 trials in PsA patients (M15-998 and M16-011).

The originally approved forumation (90 mg/mL) and device (FPS) were applied in the phase 2 and 3 PsA studies, where the 150 mg Risankizumab was delivered by 2 SC injections of originally approved product (75 mg/0.83 mL in a PFS). During the review of supplement 14, the Applicant proposed to update the U.S. Prescribing Information upon approval of supplemental BLA (sBLA) applications for two new dosage forms including a 150 mg/mL prefilled syringe (supplement 9) and 150 mg/mL autoinjector (supplement 10). These new dosage forms were approved on April 26, 2021 for the treatment of moderate-to-severe plaque psoriasis. As Study M15-990 (reviewed under sBLA 009 and 010) demonstrated bioequivalence between 1x150 mg/mL PFS vs. 2x75 mg/0.83 mL PFS; and bioequivalence between 1x150 mg/mL AI vs. 2x75 mg/0.83 mL PFS, the safety and efficacy of the two new dosage forms can rely on the findings of safety and effectiveness of risankizumab (2x75 mg/0.83 mL PFS) in adult PsA patients. The current labeling

includes three dosage forms: 150 mg/mL in a single-dose prefilled pen, 150 mg/mL in a single-dose prefilled syringe, and 75 mg/0.83 mL in a single-dose prefilled syringe.

6.1.1 Recommendation

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) and Division of Pharmacometrics (DPM) have reviewed the clinical pharmacology data submitted under BLA761,105/s-014. The submission is recommended for approval from a clinical pharmacology perspective for the treatment of active psoriatic arthritis in adults. The Division Signatory agrees with this recommendation.

6.1.2 Post-Marketing Requirements and Commitments (PMR/PMC)

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The pharmacokinetics (PK), immunogenicity, and exposure-response relationships for efficacy and safety of risankizumab have been characterized in healthy subjects and subjects with psoriasis in the original BLA. In support of the registration of the indication of PsA, the Applicant collected blood samples in two phase 2 studies (M16-002 and M16-244) and two pivotal phase 3 studies (M15-998 and M16-011) to characterize risankizumab clinical pharmacology in subjects with PsA.

The major findings for this Clinical Pharmacology review are as follows:

- In general, the PK parameters in subjects with PsA are similar to those observed in subjects with psoriasis.
- Among 652 evaluable subjects in the phase 3 trials, the incidences of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were 12% (79/652) and 0% (0/652), respectively, by 28 weeks of the treatment. Notably, the incidences of ADA and NAb, and ADA titer values in the PsA phase 3 trials are lower than those observed in the psoriasis phase 3 trials. There is no clear impact of immunogenicity on risankizumab PK.
- The dose-response results in the phase 2 trial, the efficacy results in phase 3 trails, and the integrated E-R analyses overall support that a recommendation of the dosing regimen proposed by the Applicant is acceptable.
- Based on the pharmacodynamic (PD) assessment in 100 PsA subjects randomly selected from Study M15-998 (50 subjects on risankizumab arm; 50 subjects on placebo arm), by Week 24, serum levels of IL-17A, IL-17F, and IL-22 were reduced and serum levels of TNF-alpha were increased from the baseline following treatment with risankizumab-rzaa at 150 mg administered subcutaneously at Week 0, Week 4, and every 12 weeks thereafter. These pharmacodynamic activities are based on exploratory analysis of

limited data. The relationship between these pharmacodynamic activities and the mechanism(s) by which risankizumab-rzaa exerts its clinical effects is unknown.

Of note, the observed PD activity levels in PsA patients were initially described in the proposed labeling, but the Applicant chose to remove the paragraph in the agreed labeling. Overall, there were no changes to Section 12.2 (Pharmacodynamics) of the label in this sBLA submission.

6.2.1.1 Pharmacokinetics of Risankizumab in subjects with PsA

Risankizumab trough concentrations across the phase 2 (M16-002 and M16-244) and phase 3 trials (M15-998 and M16-011) after administration of 150 mg SC at Week 0, Week 4, and thenQ12W thereafter in subjects with PsA are summarized in Table 2. With the clinical dosing regimen of 150 mg SC at Weeks 0, 4, and Q12W thereafter, risankizumab steady-state exposure was approximately achieved by Week 16 with the steady-state trough plasma concentrations (C_{trough}) of approximately 2.7 µg/mL in the phase 2 dose-ranging trial M16-002. At Week 28, the mean steady-state C_{trough} (2.4 µg/mL) in phase 2 trial M16-002 were slightly higher than those (~1.5 µg/mL) in the two phase 3 trials (Table 2).

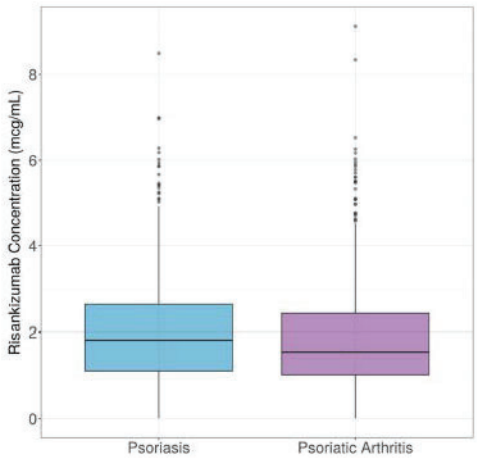
Of note, with the same dosing regimen, the mean steady-state c_{trough} concentrations of risankizumab observed in the PsA phase 3 trials were slightly lower than those in subjects with psoriasis (1.5 µg/mL *vs*. 2 µg/mL) (Figure 1). The observed differences in risankizumab exposures between two patient populations are probably due to body weight which has been found as a statistically significant covariate on risankizumab clearance (CL). Compared to subjects with psoriasis, the overall body weights in subjects with PsA are relatively higher.

Table 2. Risankizumab Trough Concentrations (µg/mL) in Subjects with PsA Across Clinical Trials

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

Cross reference: Study M16-002 CSR; Study M16-244 CSR; Study M15-998 Interim CSR; Study M16-011 Interim CSR

Figure 1. Comparison of Week 28 Predose Observed Risankizumab Concentrations in Subjects with Psoriatic Arthritis and Psoriasis



(Source of data: [redacted] (b) (4), Figure 5)

Based on the cross-study population PK analysis, risankizumab CL, volume of distribution at steady state and $t_{1/2}$ were estimated to be 0.31 L/day, 11.1 L, [redacted] (b) (4), respectively, for a typical 90 kg subject. The inter-individual variability (%CV) for risankizumab clearance and central volume of distribution were 31% and 42%, respectively.

Overall, the PK parameters in subjects with PsA are similar to those observed in subjects with psoriasis (for details, see *Unireview of BLA761,105 in DARRT dated 04/23/2019)*.

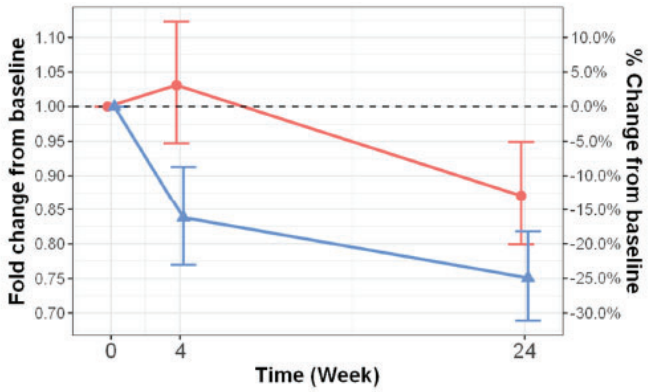
6.2.1.2 Pharmacodynamics of Risankizumab in subjects with PsA

Pharmacodynamic effect of Risankizumab on serum levels of IL-17A, IL-17F, IL-22, IL-6, and TNF-α were assessed in 100 PsA subjects randomly selected from Study 15-998 (50 subjects on Risankizumab arm, 50 subjects on placbo arm).

- *Change from Baseline in Serum Levels of IL-17A*

Observed serum levels of IL-17A were lower from the baseline at Week 4 (-16.2%, p=0.041) and 24 (-24.9%, p=0.0012) in the Risanizumab arm (Figure 2). Compared to the placebo arm, relative levels of IL-17A were numerically lower in the Risankizumab arm at Week 4 (p=0.088) and Week 24 (p=0.22).

Figure 2 Serum Levels of IL-17A at Week 4 and Week 24

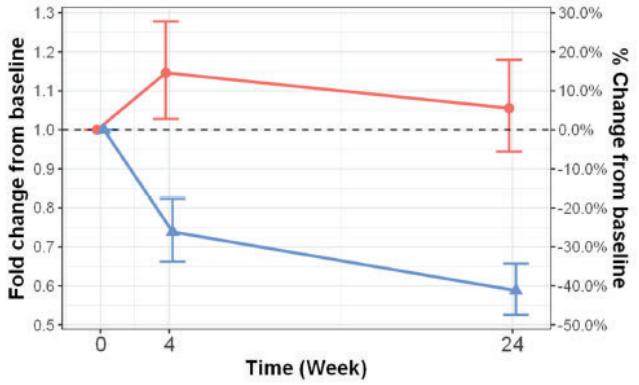


Placebo: ●; Risankizumab 150 mg SC: ▲
Statistical model based mean profile and ± SE as the error bar
(Source of data: R&D/21/0058, Figure 1)

- *Change from Baseline in Serum Levels of IL-17F*

Observed serum levels of IL-17F were lower from the baseline at Week 4 (-26.1%, p=0.0063) and Week 24 (-41.2%, p<0.0001) in the Risanizumab arm (Figure 3). Compared to the placebo arm, relative levels of IL-17F in the Risanizuamb arm were significantly lower at Week 24 (p=0.00033), but not at Week 4 (p=0.0052).

Figure 3 Serum Levels of IL-17F at Week 4 and Week 24

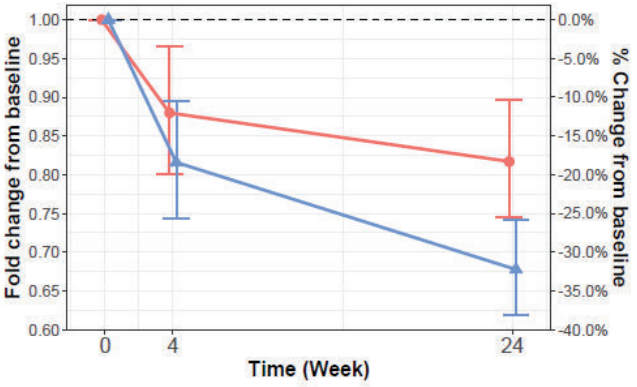


Placebo: ●; Risankizumab 150 mg SC: ▲
Statistical model based mean profile and +/- SE as the error bar
(Source of data: R&D/21/0058, Figure 2)

- *Change from Baseline in Serum Levels of IL-22*

Observed serum levels of IL-22 were lower from the baseline at Week 4 (-18.4%, p=0.031) and Week 24 (-32.2%, p<0.0001) in the Risanizumab arm (Figure 4). Compared to the placebo arm, relative levels of IL-22 in the Risanizuamb treatment arm were numerically lower at Week 4 (p=0.57) and at Week 4 (p=0.15).

Figure 4 Serum Levels of IL-22 at Week 4 and Week 24



Placebo: ●; Risankizumab 150 mg SC: ▲
Statistical model based mean profile and +/- SE as the error bar
(Source of data: R&D/21/0058, Figure 3)

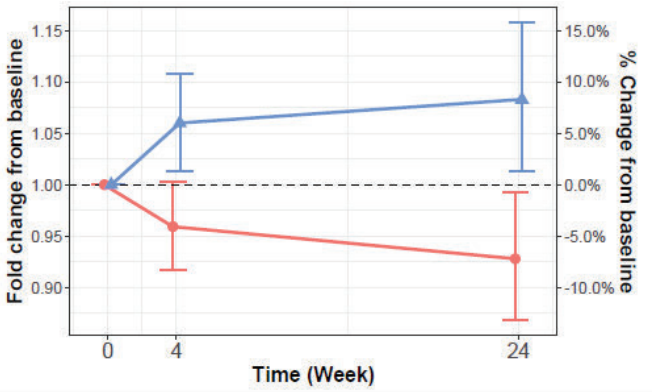
- *Change from Baseline in Serum Levels of IL-6*

Serum levels of IL-6 at Week 4 and 24 in the Risankizumab arm were similar to that in the placebo arm. Serum levels of IL-6 at Week 4 and 24 were not significantly different from baseline.

- *Change from Baseline in Serum Levels of TNF-α*

An increase of serum levels of TNF-α from the baseline was noted at Week 4 (6%, p=0.19)and 24 (8.3%, p=0.24) in the Risankizumab arm. Compared to the placebo arm, relative levels of TNF-α were numerically higher at Week 4 (p=0.12) and Week 24 (p=0.11).

Figure 4 Serum Levels of TNF-α at Week 4 and Week 24



Placebo: ●; Risankizumab 150 mg SC: ▲
Statistical model based mean profile and +/- SE as the error bar
(Source of data: R&D/21/0058, Figure 5)

6.2.1.3 Immunogenicity

Among 652 evaluable subjects in the phase 3 trials, the incidences of ADAand NAb were 12% (79/652) and 0% (0/652), respectively, by 28 weeks of the treatment. Among 33 evaluable subjects in the phase 2 open label extension trial (M16-244), the incidences of ADA and NAb were 30% (10/33) and 3% (1/33), respectively over 76 weeks of assessment duration following 72 weeks of treatment. The median time to ADA development was 12 weeks following start of treatment in the phase 2 trials.

The median ADA titer values at Week 28 ranged from 24 to 26 across the two phase 3 trials. The median (range) time to the first appearance of ADA was 12 (8-24) weeks in the phase 2 study M16-002 where time-course immunogenicity data were collected.

Notably, the incidences of ADA and NAb, and ADA titer values in the PsA phase 3 trials are lower than those observed in the psoriasis phase 3 trials. For details, see *Unireview of BLA761,105 in DARRT dated 04/23/2019.*

- *Effect of immunogenicity on risankizumab exposures*

Based on inter-subject comparison using pooled data across the two phase 3 studies, risankizumab trough serum concentrations (central tendency and distribution) were comparable between subjects who were ADA positive and those who were ADA negative over time (Table 3 and Figure 5). There is no clear impact of immunogenicity on risankizumab PK.

Table 3. Risankizumab Serum Trough Concentrations (µg/mL) by ADA Status from the Phase 3 Studies

	Geometric Mean (Arithmetic Mean, %CV) [N]	
	Week 28	
Treatment Regimen	ADA Positive	ADA Negative
Risankizumab 150 mg SC[a]	1.23 (1.53, 65.4) [81]	1.52 (1.89, 67.5) [550]
Placebo to Risankizumab 150 mg SC[b]	4.88 (5.58, 51.2) [43]	5.31 (5.69, 40.0) [578]

ADA = Anti-drug antibody (anti-risankizumab antibody); %CV = coefficient of variation; SC = subcutaneous

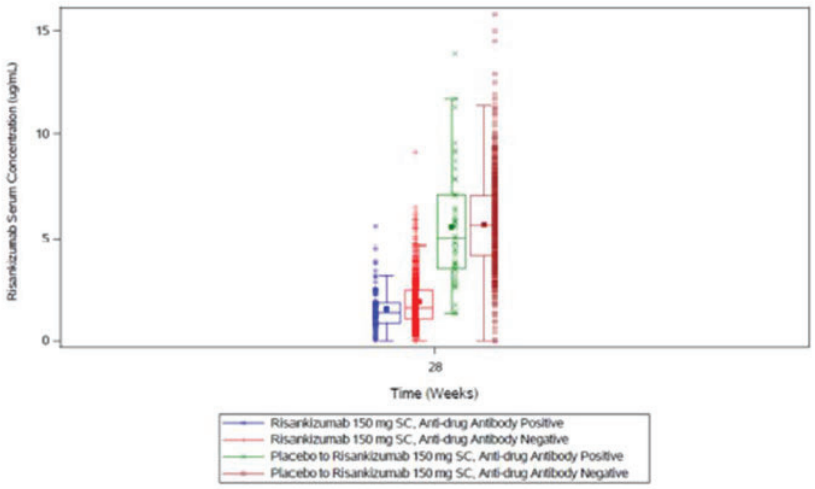
a. Subjects who received risankizumab from Week 0, i.e., 150 mg SC at Weeks 0, 4 and q12w thereafter.

b. Subjects received placebo at Weeks 0, 4 and 16, and switched to risankizumab at Week 24.

Note: Subjects who had both risankizumab serum concentration and ADA assessment at Week 28 are included in this summary.

Cross reference: Table 11.1__1

Figure 5. Comparison of Risankizumab Serum Concentrations by ADA Status in the Phase 3 Studies



Risankizumab 150 mg SC group includes subjects who received risankizumab from Week 0, i.e., 150 mg SC at Week 0, Week 4 and q12w thereafter.

Placebo to risankizumab 150 mg SC group includes subjects received placebo at Weeks 0, 4 and 16, and switched to risankizumab at Week 24.

Note: In the box plots, solid square and horizontal bar within each box represents arithmetic mean and median values, respectively. The other symbols (*, +, x, #) represent risankizumab concentration values from individual subjects.

Cross reference: Integrated Immunogenicity Report (R&D/20/1406) Figure 1

- *Effect of immunogenicity on risankizumab efficacy*

To assess the effect of immunogenicity on risankizumab efficacy, ACR20 responses were compared between ADA+ and ADA- using pooled data across phase 3 studies (Table 4). ACR20 responses at Week 24 were comparable between subjects who were ADA+ and those who were ADA-.

Of note, none of the subjects who developed treatment-emergent ADAs had positive NAb results.

Table 4. Risankizumab ACR20 Responses at Week 24 by ADA Status from the Phase 3 Trials

Efficacy Response (NRI-C)	ACR20 Response at Week 24 (Placebo-Controlled Analysis Set; N=653)	
	ADA positive (N = 79)	ADA negative (N = 574)
ACR20, n (%)	44 (55.7%)	319 (55.6%)

ACR20 = American College of Rheumatology 20% improvement criteria

Table shows number (percentage) of subjects who achieved ACR20 response.

Note: Risankizumab cumulative efficacy data from Phase 3 studies (Studies M15-998 and M16-011) up to data cutoff date (14Dec2020).

Cross reference: Integrated Immunogenicity Report (R&D/20/1406) Table 9

- *Effect of immunogenicity on risankizumab safety*

Among subjects in the risankizumab 150 mg arm (no cross-over from placebo) in the phase 3 PsA long term analysis set, the incidences of hypersensitivity reactions and injection site reactions in subjects with the treatment-emergent ADA+ were slightly higher (6.3% and 2.5%, respectively) than those in subjects with ADA- (3.8% and 0.7%, respectively) (Table 5). See clinical Section 8.4 of this review for detailed information.

Table 5. Comparison of Hypersensitivity Reaction and Injection Site Reaction by Treatment-Emergent ADA Status for the Phase 3 PsA Long Term Analysis Set

	Phase 3 PsA Long Term Analysis Set[a]			
	Risankizumab 150 mg (No Cross-over from Placebo)[b] (N = 653)		Any risankizumab 150 mg[c] (N = 1293)	
	TEADA Positive (N = 79)	TEADA Negative (N = 574)	TEADA Positive (N = 122)	TEADA Negative (N = 1171)
hypersensitivity reaction (per SMQ), n (%)	5 (6.3%)	22 (3.8%)	5 (4.1%)	31 (2.6%)
injection site reaction (per CMQ), n (%)	2 (2.5%)	4 (0.7%)	2 (1.6%)	6 (0.5%)

TEADA = treatment-emergent anti-drug antibody

a. This only includes subjects who had TEADA information: 653/707 subjects for "Risankizumab 150 mg (No Cross-over from Placebo)" and 1293/1365 subjects for "Any risankizumab 150 mg."

b. This includes Phase 3 study subjects starting on risankizumab 150 mg at randomization and does not include subjects who switched from placebo.

c. This includes Phase 3 study subjects who received risankizumab 150 mg who were either: (1) randomized to risankizumab 150 mg in Period 1 and continued on risankizumab 150 mg in Period 2, or (2) randomized to placebo in Period 1 and subsequently received 150 mg risankizumab in Period 2.

Note: Risankizumab exposure through the data-cutoff (14Dec2020) at the time of submission (Studies M15-998 and M16-011).

Cross reference: ISS (R&D/20/1090) Table 2.4__1.2.6.3.4, Table 2.4__1.2.6.3.5

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

The dose-response results in the Phase 2 trial, the efficacy results in Phase 3 trails, and the integrated E-R analyses overall support that a recommendation of the dosing regimen as proposed by the Applicant is acceptable.

6.2.2.2 Therapeutic Individualization

Therapeutic individualization based on intrinsic and extrinsic is not necessary. Population PK analysis identified body weight (BW) as a significant covariate on risankizumab PK: risankizumab concentrations decreased as BW increased. Risankizumab concentrations were approximately 20% lower or 30% higher in PsA subjects with BW>99 kg or <74 kg, respectively, compared to the reference subjects with BW of 74 to 99 kg. However, these differences are not considered clinically meaningful and dose adjustment based on BW is not necessary based on the available efficacy data from the phase 3 trials.

6.2.3. Outstanding Issues

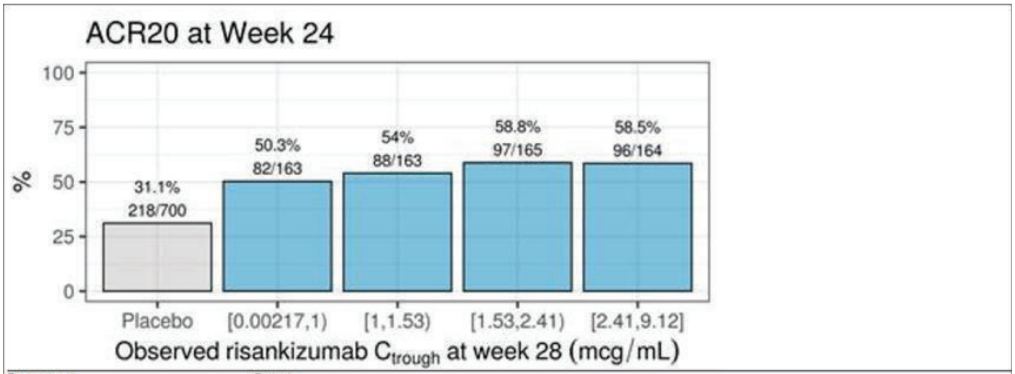
There are no outstanding issues that would preclude the approval of risankizumab for the treatment of active PsA from a Clinical Pharmacology's perspective.

6.3.Question-Based Clinical Pharmacology Review

6.3.1. *Does the clinical pharmacology program provide supportive evidence of effectiveness?*

The efficacy and safety of SKYRIZI for the treatment of active psoriatic arthritis in adults was established in the phase 3 studies (M15-998 and M16-011). In addition, the exposure-response relationship and clinical results from the phase 3 studies provides supportive evidence of effectiveness. In exposure-response efficacy analysis, logistic regression showed that subjects treated with risankizumab showed statistically significant higher response rates compared to placebo for all evaluated efficacy endpoints(Figure 6). Although subjects with relatively lower risankizumab exposures had numerically lower response rates compared to the higher exposures, the systemic exposures showed no statistically significant exposure-response relationships after accounting for the treatment effect (Figure 6). In exposure-response safety analysis, no apparent relationship between risankizumab exposure and any AE, SAE, infection, or serious infection over the first 24 weeks were identified in the phase 3 studies of risankizumab in subjects with active psoriatic arthritis.

Figure 6. Logistic regression analysis on ACR20 at Week 24.



Response Variable	Model	Converged	AIC	Variable	Estimate(SEE)	95% CI	p Value
ACR20	Treatment Effect Model (Slope, Intercept), with stratification factors	YES	1748	Intercept	-0.151 (0.236)	-0.613 - 0.311	p>0.05
				EXPOSURE	0.094 (0.065)	-0.033 - 0.221	p>0.05
				TRT=Placebo	-0.866 (0.165)	-1.189 - -0.543	p<0.01
				nCS-DMARDS=0	-0.428 (0.478)	-1.364 - 0.508	p>0.05
				nBIOT=0	0.610 (0.176)	0.265 - 0.955	p<0.01
				Psoriasis Surface Area <3% BSA	-0.460 (0.117)	-0.689 - -0.230	p<0.01
				Presence of Enthesitis at Baseline = yes	-0.178 (0.132)	-0.436 - 0.081	p>0.05
				Presence of Dactylitis at Baseline = yes	0.082 (0.129)	-0.171 - 0.336	p>0.05

(Source: Population PK and ER report (b) (4) Page 72, Figure 10 and Page 589, Table 13.3_5.)

6.3.2. *Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?*

The recommended dose of SKYRIZI is 150 mg (two 75-mg injections) administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter. SKYRIZI may be administered alone or in combination with nonbiologic disease-modifying antirheumatic drugs (DMARDs).

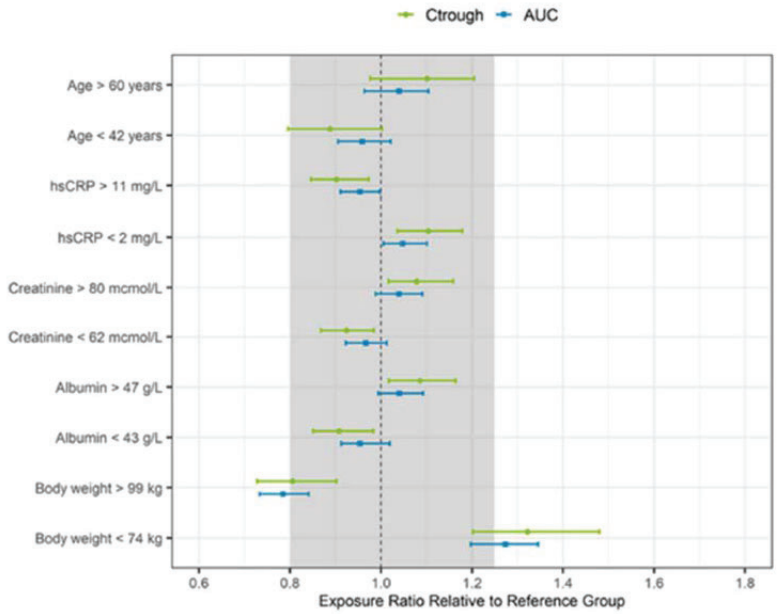
The recommended dose is the same as the approved dose regimen for moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. For active psoriatic arthritis in adults, the recommended dose is supported by the efficacy and safety data obtained from the Phase 3 studies, as well as exposure-response analysis.

6.3.3. *Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?*

No. Overall, risankizumab PK were not significantly impact by age, baseline serum albumin, baseline high-sensitivity C-reactive protein (hsCRP), and baseline serum creatinine in this BLA-s014, except for BW (Figure 7).

Psoriatic arthritic subjects with relatively high BW (>75th percentile; 99 kg) and low BW (<25th percentile; 74 kg) were predicted to have approximately 20% lower and 30% higher exposures, respectively, compared to the reference subjects (74 kg to 99 kg). However, a dose adjustment based on BW is not necessary based on the available efficacy and safety data from the phase 3 trials and E-R modeling analyses. (Figure 21 and Figure 23).

Figure 7. Impact of Statistically Significant Covariates on Risankizumab Steady-State Exposure (C_{max} and AUC) in Subjects with Psoriatic Arthritis



AUC=area under the concentration-time curve between Week 16 and 28 (AUC_{tau}); C_{trough}=concentration after a dosing interval at Week 28, hs-CRP=high-sensitivity C-reactive protein
(*Source of data:* (b) (4) *Figure 9*)

6.3.4. *Which bioanalytical methods were used for the determination of the concentrations of Risankizumab and the immunogenicity assessment?*

- *Determination of risankizumab concentrations*

The samples from the phase 2 PsA Studies M16-002 and M16-244 were analyzed for risankizumab concentrations using ligand binding assays previously validated and submitted for the psoriasis application. For the pivotal phase 3 PsA Studies M15-998 and M16-011, a bridging electrochemiluminescence (ECL) assay was employed for determination of risankizumab concentrations in human serum samples. While this assay is based on the same ligand binding assay principles as the previous risankizumab assay used for the phase 2 studies, it uses serum instead of plasma for sample matrix as well as new critical reagents compared the previous assay.

Selectivity for psoriatic arthritis matrix was demonstrated in partial validation (R&D/17/1135). Cross-validation experiments using spiked quality control samples were conducted and demonstrated full comparability between in-house validated serum ECL (R&D/17/0345) and plasma ECL assays (R&D/17/0342). The plasma ELISA or ECL assays applied in the psoriasis programs were applicable for the quantitation of risankizumab within a nominal range of 5 to 100 ng/mL, with lower limit of quantitation (LLOQ) of 5 ng/mL. In the current sBLA, the serum ECL method is applicable for the quantitation of risankizumab within a nominal range of 4.34 to 1670 ng/mL, with LLOQ of 4.34 ng/mL.

- *Detection of ADAs and 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 applied for determination of ADA and NAb in the current sBLA, respectively.

Briefly, the main difference between the original BLA immunogenicity assays and the developed 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 psoriatic arthritis phase 2 studies (M16-002 and M16-244) were the same assays used in the original psoriasis submission. The new ADA and NAb assays were only applied in the PsA phase 3 studies (M15-998 and M16-011).

Refer to the Product Quality Review for more information regarding the performance and validation of the immunogenicity assays.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 6. Table of Clinical Studies

Study	Study Design & Duration	Dosing Regimen	Patients	Endpoints	Status
M16-002	Phase 2, MC, R, DB, PC proof-of-concept and dose ranging study of RZB in patients with active PsA Duration: 32 weeks	Arm 1: 150 mg SC at Wks 0, 4, 8, 12, 16 Arm 2: 150 mg SC at Wks 0, 4, 16 (PBO at wks 8 and 12) Arm 3: 150 mg SC at Wks 0 and 12 (PBO at Wks 4, 8, 16) Arm 4: 75 mg SC at Wk 0 (PBO at Wks 4, 8, 12, 16) Arm 5: PBO SC at Wks 0, 4, 8, 12, 16	185	Primary: ACR20 response at Wk 16 Secondary: ACR50, ACR70, TJC, SJC, HAQ-DI, SF-36, dactylitis, SPARCC enthesitis index, mNAPSI, PASI90	Complete Full CSR
M16-244	Phase 2, MC, single-arm OLE study to investigate safety of RZB in PsA patients who have completed week 24 visit of study M16-002 Duration: 56 weeks	150 mg SC at Wk 0 and then every 12 Wks thereafter	145	Adverse events, serious adverse events, clinical laboratory values, physical exam, vital signs, 12-lead ECG, local tolerability	Complete Full CSR
M16-011	Phase 3, MC, R, DB, PC study with OLE to evaluate the efficacy and safety of RZB in patients with moderate-severe PsA and IR to at least 1 csDMARD Duration: 228 weeks	Period 1: RZB 150 mg (or PBO) SC at Wks 0, 4, 16 Period 2: RZB to RZB: PBO at Wk 24, then RZB 150 mg SC at Wk 28 and every 12 Wks thereafter PBO to RZB: RZB 150 mg SC at Wks 24, 28, and every 12 Wks thereafter	964	Primary: ACR20 response at Wk 24 Secondary: HAQ-DI, PASI90, ACR20 at Wk 16, MDA, mNAPSI, PGA-F, enthesitis, dactylitis, mTSS, SF-36 PCS, FACIT-F, ACR50, ACR70 Safety: Adverse events, serious adverse events, clinical laboratory	Ongoing Interim Full CSR (up to Wk 24)

Study	Study Design & Duration	Dosing Regimen	Patients	Endpoints	Status
				values, physical exam, vital signs, 12-lead ECG, local tolerability, ADA	
M15-998	Phase 3, MC, R, DB, PC study with OLE to evaluate the efficacy and safety of RZB in patients with moderate-severe PsA and IR to 1 or 2 biologic therapies (no more than 50%) or IR to at least 1 csDMARD Duration: 228 weeks	Period 1: RZB 150 mg (or PBO) SC at Wks 0, 4, 16 Period 2: RZB to RZB: PBO at Wk 24, then RZB 150 mg SC at Wk 28 and every 12 Wks thereafter PBO to RZB: RZB 150 mg SC at Wks 24, 28, and every 12 Wks thereafter	444	Primary: ACR20 response at Wk 24 Secondary: HAQ-DI, PASI90, ACR20 at Wk 16, MDA, SF-36 PCS, FACIT-F, ACR50, ACR70, enthesitis, dactylitis Safety: Adverse events, serious adverse events, clinical laboratory values, physical exam, vital signs, 12-lead ECG, local tolerability, ADA	Ongoing Interim Full CSR (up to Wk 24)

ACR = American College of Rheumatology; ADA = anti-drug antibodies; csDMARD = conventional synthetic Disease Modifying Anti-rheumatic Drug; CSR = complete study report; DB = double blind; ECG = electrocardiogram; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; IR = inadequate response; MC = multicenter; MDA = minimal disease activity; mNAPSI = Modified Nail Psoriasis Severity Index; mTSS = modified Total Sharp Score; OLE = open label extension; PASI = Psoriasis Areas Severity Index; PBO = placebo; PC = placebo controlled; PGA-F = Physician Global Assessment of Fingernail Psoriasis; PsA = psoriatic arthritis; R = randomized; RZB = Risankizumab; SC = subcutaneous; SF-36 = 36-Item Short Form Health Survey; SJC = swollen joint count; SPARCC = Spondyloarthritis Research Consortium of Canada; TJC = tender joint count; Wk = week; Wks = weeks

7.2. Review Strategy

This supplemental BLA consisted of two phase 3 studies, M16-011 and M15-998, and two phase 2 studies, M16-002 and M16-244, to provide the efficacy and safety of risankizumab in the treatment of psoriatic arthritis.

Study M16-002 was a phase 2, multicenter, randomized, double-blind, placebo-controlled, proof-of-concept dose ranging study of risankizumab in patients with active psoriatic arthritis. Patients were randomized at a 2:2:2:1:2 ratio, stratified based on prior tumor necrosis factor inhibitor use and concurrent methotrexate use into 5 treatment arms: risankizumab 150 mg SC every 4 weeks; risankizumab 150 mg SC at Weeks 0, 4, and 16; risankizumab 150 mg SC at Weeks 0 and 12; risankizumab 75 mg SC at Week 0; and placebo. The primary endpoint was the

proportion of patients who achieved an American College of Rheumatology (ACR) 20 response at Week 16. Secondary endpoints, each evaluated at Week 16, included additional assessments of physical function and signs and symptoms of PsA. Safety endpoints included assessments of adverse events, serious adverse events, clinical laboratory values, physical examination, vital signs, 12-lead electrocardiogram, and local tolerability.

Study M16-244 was a phase 2, multicenter, single-arm, open-label extension study to investigate the safety of risankizumab in patients with psoriatic arthritis who completed all doses of study drug and the week 24 visit of study M16-002. Patients received treatment with risankizumab 150 mg SC beginning at Week 0 of study M16-244 and then every 12 weeks thereafter. There was no primary efficacy endpoint. Secondary endpoints included assessments of physical function, radiographic changes, and signs and symptoms of PsA. Safety endpoints included assessments of adverse events, serious adverse events, clinical laboratory values, physical examination, vital signs, 12-lead electrocardiogram, and local tolerability.

Study M16-011 was a multicenter, randomized, double-blind, placebo-controlled study of risankizumab in patients with moderately to severely active PsA who had an inadequate response (defined as lack of efficacy after a minimum 12-week duration of therapy) or intolerance to at least 1 csDMARD. The study design consisted of two study periods including a placebo-controlled period (referred to as period 1) and an open-label extension period (referred to as period 2). During period 1, patients were randomized in a 1:1 ratio to either placebo or risankizumab 150 mg SC at Weeks 0, 4, and 16. During period 2, the patients initially randomized to placebo received treatment with risankizumab 150 mg SC at Weeks 24, 28, and then every 12 weeks thereafter. The patients initially randomized to risankizumab received treatment with placebo at week 24 followed by risankizumab at week 28 and every 12 weeks thereafter. The primary endpoint was the proportion of patients who achieved ACR20 response at Week 24. Secondary endpoints, each evaluated at Week 24 except for evaluation of ACR20 response at Week 16, included additional assessments of physical function, radiographic changes, and signs and symptoms of PsA. Safety endpoints included assessments of adverse events, serious adverse events, clinical laboratory values, physical examination, vital signs, 12-lead electrocardiogram, local tolerability, and antidrug antibodies.

Study M15-998 was a multicenter, randomized, double-blind, placebo-controlled study of risankizumab in patients with moderately to severely active PsA who had an inadequate response to 1 or 2 biologic therapies (up to 50% of patients) or inadequate response to at least 1 csDMARD (remainder of patients). The study design consisted of two study periods including a placebo-controlled period (referred to as period 1) and an open-label extension period (referred to as period 2). During period 1, patients were randomized in a 1:1 ratio to either placebo or risankizumab 150 mg SC at Weeks 0, 4, and 16. During period 2, the patients initially randomized to placebo received treatment with risankizumab 150 mg SC at Weeks 24, 28, and then every 12 weeks thereafter. The patients initially randomized to risankizumab received treatment with placebo at week 24 followed by risankizumab at week 28 and every 12 weeks thereafter. The primary endpoint was the proportion of patients who achieved ACR20 response

at Week 24. Secondary endpoints, each evaluated at Week 24 except for evaluation of ACR20 response at Week 16, included additional assessments of physical function and signs and symptoms of PsA. Safety endpoints included assessments of adverse events, serious adverse events, clinical laboratory values, physical examination, vital signs, 12-lead electrocardiogram, local tolerability, and antidrug antibodies.

The primary evidence of efficacy to support risankizumab dosing in psoriatic arthritis is based on the data collected through Week 24 from studies M16-011 and M15-998 including assessment of the primary endpoint and secondary endpoints. Data from study M16-002 provides supportive evidence that the Week 4 dose included in the loading regimen (risankizumab 150 mg SC at Weeks 0, 4, and 16) does not drive efficacy compared to the maintenance dosing regimen (risankizumab 150 mg SC every 12 weeks).

The safety assessment of risankizumab in psoriatic arthritis is based primarily on the safety database from studies M16-011 and M15-998. The safety review focuses on the placebo-controlled data from these studies (24-week data). Additional supportive safety data are provided by the phase 2 studies (M16-002 and M16-244), the 120-day safety update, and data from the psoriasis program.

The statistical reviewer will present the Applicant's assessment of efficacy and supplement this with their own analyses. The clinical reviewer will present the Applicant's safety data with additional commentary.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. M16-011

Study Design

M16-011 was a phase 3, multicenter, randomized, double-blind, placebo-controlled study of risankizumab in 964 patients with moderately to severely active PsA who had an inadequate response (defined as lack of efficacy after a minimum 12-week duration of therapy) or intolerance to at least 1 csDMARD.

The study consisted of two periods referred to as Period 1 and Period 2. Period 1 was a 24-week randomized, double-blind, placebo-controlled, parallel-group period. Patients were randomized in a 1:1 ratio stratified by the extent of psoriasis (≥ 3% BSA vs < 3% BSA), current use of at least 1 csDMARD (0 vs ≥ 1), presence of dactylitis (yes vs no), and presence of enthesitis (yes vs no) to one of two groups:

- Group 1 (n = 483): Risankizumab 150 mg SC at Weeks 0, 4, and 16
- Group 2 (n = 481): Placebo SC at Weeks 0, 4, and 16

Period 2 was an open-label period starting at Week 24. During Period 2, all patients received treatment with risankizumab. To maintain the blind to the original treatment allocation, treatment at Week 24 was blinded so that patients initially randomized to placebo received risankizumab 150 mg and patients initially randomized to risankizumab received placebo. At Week 28, and for the remaining dosing visits to Week 208, all patients received risankizumab 150 mg every 12 weeks. The total study duration was 228 weeks including a telephone call 140 days (20 weeks) after the last dose of study drug.

The follow-up period consisted of a completion visit 12 weeks after the last study drug dose. An additional follow-up phone call would occur 8 weeks later, 20 weeks after the last study drug dose, to determine the status of any ongoing adverse events or the occurrence of any new adverse events.

Dosage and Administration

Risankizumab 150 mg was provided in 2 pre-filled syringes of 75 mg each for subcutaneous administration at Weeks 0, 4, and 16 during Period 1. Matching liquid placebo (0.9% sodium chloride solution) was provided for subcutaneous administration at Weeks 0, 4, and 16 during Period 1. To maintain the blind, treatment at Week 24 was blinded and patients randomized to placebo received blinded risankizumab 150 mg, and patients randomized to risankizumab received blinded placebo. At Week 28, and for the remaining dosing visits to Week 208, all patients received open-label risankizumab 150 mg every 12 weeks.

Rescue Therapy

At Week 16, patients classified as non-responders (defined as not achieving at least a 20% improvement in either or both tender joint count (TJC) and swollen joint count (SJC) at both Week 12 and Week 16 compared to baseline) were permitted to add or modify rescue therapy and concomitant medications as follows:

- Add or modify doses of NSAIDs, acetaminophen/paracetamol, low potency opiates (tramadol, codeine, or hydrocodone, alone or in combination with acetaminophen); OR
- Receive 1 intra-articular, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroid injection for 1 peripheral joint or 1 enthesis. Injected joints or enthesitis sites were considered not assessable for 90 days from the time of injection for analysis of TJC, SJC, and enthesitis; OR
- Titrate current background csDMARD or add an additional csDMARD, as allowed by eligibility criteria. Use of no more than 2 csDMARDs was permitted, and doses could not exceed the maximums defined in the eligibility criteria. Addition of a biologic therapy was not permitted.

Concomitant Medications

Permitted concomitant medications in this study included non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics (e.g., acetaminophen and low potency opiates), oral corticosteroids up to an equivalent dose of 10 mg/day of prednisone, methotrexate (MTX) up to 25 mg/week, sulfasalazine (SSZ) up to 3000 mg/day, leflunomide (LEF) up to 20 mg/day, hydroxychloroquine up to 400 mg/day, apremilast up to 60 mg/day, bucillamine up to 300 mg/day, iguratimod up to 50 mg/day, and ciclosporin up to 5 mg/kg/day. Patients were allowed to be on 0, 1, or 2 background csDMARDs.

Study Location and Dates

The study was conducted at 186 sites in 38 countries: Argentina, Australia, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, Croatia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Israel, Italy, South Korea, Latvia, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Poland, Portugal, Romania, Russia, Serbia, Singapore, Slovakia, South Africa, Spain, Sweden, Taiwan, Ukraine, United Kingdom, and the US including Puerto Rico.

The study was conducted from March 25, 2019 (first patient first visit) to November 2, 2020 (data cutoff date for the interim clinical study report). The last patient completed their Week 24 visit on October 8, 2020.

Study Eligibility Criteria

- Adult male or female at least 18 years old
- Willing and able to comply with procedures required in the study protocol
- Have a clinical diagnosis of PsA with symptom onset of at least 6 months prior to the screening visit and fulfillment of the Classification Criteria for PsA (CASPAR) at screening
- Have active disease defined as ≥ 5 tender joints (based on 68 joint count) and ≥ 5 swollen joints (based on 66 joints) at both the screening visit and baseline visit
- Have a diagnosis of active plaque psoriasis with at least one psoriatic plaque of ≥ 2 cm diameter or nail changes consistent with psoriasis at the screening visit
- Have either Hs-CRP ≥ 3.0 mg/L or ≥ 1 erosion on radiograph
- Have either an inadequate response to csDMARD, or intolerance to csDMARDs
    - Patient must have demonstrated an inadequate response (defined as lack of efficacy after a minimum 12-week duration of therapy) to previous or current treatment with at least 1 of the following csDMARDs at maximally tolerated dose: methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), apremilast, bucillamine and iguratimod, or ciclosporin A

    - An inadequate response to methotrexate must be at the following dose ranges: ≥ 15 mg/week, or ≥ 10 mg/week in patients who are intolerant of MTX at doses ≥ 12.5 mg/week after complete titration (for patients in countries such as China, Korea, Malaysia, Singapore, Hong Kong, Taiwan, and Japan inadequate response to MTX is defined as ≥ 7.5 mg/week or as required per local authorities)
- Have laboratory values meeting the following criteria within the screening period:
    - Serum aspartate transaminase (AST) < 2 x upper limit of normal (ULN)
    - Serum alanine transaminase (ALT) < 2 x ULN
    - Serum total bilirubin ≤ 2.0 mg/dL except for patients with an isolated elevation of indirect bilirubin relating to Gilbert syndrome
    - Total white blood cell (WBC) count > 3,000/µL
    - Absolute neutrophil count (ANC) > 1,500/µL
    - Platelet count > 100,000/µL
    - Hemoglobin > 8.0 g/dL
- No evidence of hepatitis B, hepatitis C, HIV, or tuberculosis
- No active systemic infection during the last 2 weeks prior to the baseline visit as assessed by the investigator (exception: common cold)
- No active or suspected malignancy or history of malignancy within the last 5 years except for successfully treated non-melanoma skin cancer or localized carcinoma in situ of the cervix
- No history of organ transplantation requiring continued immunosuppression
- No major surgery performed within 12 weeks prior to randomization or planned during the conduct of the trial (e.g., hip replacement, aneurysm removal, stomach ligation)
- No history of clinically significant medical conditions or any other reason, including any physical, psychological, or psychiatric condition that in the opinion of the investigator would compromise the safety or interfere with the patient's participation in this study, would make the patient an unsuitable candidate to receive study drug, or would put the patient at risk by participating in the protocol; or permanently wheelchair-bound or bedridden or very poor functional status which prevents the ability to perform self-care
- No active skin disease other than psoriasis which could interfere with the assessment of psoriasis
- No history of extra-articular manifestations of PsA (e.g., PsO, uveitis, or inflammatory bowel disease) that is not clinically stable for at least 30 days prior to screening
- No prior joint surgery at joints to be assessed within this study in the 8 weeks prior to the baseline visit, or treatment with intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroids in the 8 weeks prior to the baseline visit
- No history of fibromyalgia, any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than PsA (including but not limited to

rheumatoid arthritis, gout, overlap connective tissue disease, scleroderma, polymyositis, dermatomyositis, systemic lupus erythematosus)
    - Prior history of reactive arthritis or axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis is permitted if documentation of change in diagnosis to PsA or additional diagnosis of PsA is made
    - Prior history of fibromyalgia is permitted if documentation of change in diagnosis to PsA or documentation that the diagnosis of fibromyalgia was made incorrectly
- No history of clinically significant drug or alcohol abuse within the last 6 months
- No history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class
- All female patients of childbearing potential must have a negative serum pregnancy test at the screening visit. In addition, a negative urine pregnancy test is required at baseline prior to the first dose of study drug for all female patients of childbearing potential. Patients with a borderline serum pregnancy test at screening must have a negative serum pregnancy test ≥ 3 days later to document continued lack of a positive result
- Female patients must either be of non-childbearing potential or use at least 1 protocol specified method of birth control that is effective from study day 1 through at least 140 days (20 weeks) after the last dose of study drug. Local practices may require 2 methods of birth control.
- Female patients may not be pregnant, breastfeeding, or have plans to become pregnant during the study and for at least 140 days (20 weeks) after the last dose of study drug

Safety Variables

Safety evaluations included adverse event monitoring, physical examinations, vital sign measurements, 12-lead electrocardiogram, and clinical laboratory testing (hematology, chemistry) as a measure of safety and tolerability.

Patient Discontinuation Criteria

A patient was permitted to voluntarily withdraw or be withdrawn from the study or study treatment at any time for reasons including, but not limited to, the following:

- Lack of clinical response defined as not achieving at least a 20% improvement in either or both TJC and SJC, compared to baseline, on 2 consecutive visits. Evaluation for lack of clinical response began at Week 32; therefore, Week 36 was the first possible time point that a patient might be discontinued for lack of clinical response
- Clinically significant abnormal laboratory result(s) or adverse events, which rule out continuation of the study drug as determined by the Investigator or the therapeutic area medical director

- The Investigator believes withdrawal from the study treatment or study is in the best interest of the patient
- The patient requests withdrawal from the study treatment or study
- Eligibility criteria violation(s) are noted after the patient started study drug, if continuation of the study drug would place the patient at risk as determined by the therapeutic area medical director after consultation with the investigator
- Patient needs to initiate prohibited medication(s) or dosages, and continuation of the study drug would place the patient at risk as determined by the therapeutic area medical director
- The patient becomes pregnant while on study drug
- Patient is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study
- Patient is diagnosed with a malignancy (Exception: localized non-melanoma skin cancer or carcinoma in-situ of the cervix, where continuation of the patient is at the discretion of the investigator)
- Patient is significantly non-compliant with study procedures which would put the patient at risk for continued participation in the trial as determined by the Investigator or therapeutic area medical director
- Occurrence of a hepatic test abnormality that is confirmed on a separate sample following a repeated blood draw:
    - ALT or AST > 8x Upper Limit of Normal (ULN)
    - ALT or AST > 5x ULN for more than 2 weeks
    - ALT or AST > 3x ULN and (Total Bilirubin > 2x ULN or INR > 1.5)
    - ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

Study Endpoints

Primary Endpoint:

The primary endpoint was the proportion of patients achieving American College of Rheumatology (ACR) 20 response at Week 24.

Secondary Endpoints:

Ranked secondary endpoints with multiplicity adjustment included:

1. Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24
2. Proportion of patients achieving Psoriasis Areas Severity Index (PASI) 90 response at Week 24 in the subset of patients with a body surface area (BSA) ≥ 3% at baseline

3. Proportion of patients achieving ACR20 at Week 16
4. Proportion of patients achieving Minimal Disease Activity (MDA) at Week 24
5. Change from baseline in modified Nail Psoriasis Severity Index (mNAPSI) at Week 24 in the subset of patients with nail psoriasis at baseline
6. Change from baseline in Fingernail-Physician Global Assessment (PGA-F) at Week 24 in the subset of patients with nail psoriasis at baseline
7. Proportion of patients with resolution of enthesitis (Leeds Enthesitis Index = 0) at Week 24 in patients with enthesitis at baseline
8. Proportion of patients with resolution of dactylitis (Leeds Dactylitis Index = 0) at Week 24 in patients with dactylitis at baseline
9. Change from baseline in modified Total Sharp Score (mTSS) at Week 24
10. Change from baseline in 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) at Week 24
11. Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Questionnaire at Week 24

Other secondary endpoints without multiplicity adjustment included:

- Proportion of patients achieving ACR50 response at Week 24
- Proportion of patients achieving ACR70 response at Week 24

Sample Size Determination

A total of 888 patients were planned to be randomized to risankizumab 150 mg or placebo in a ratio of 1:1 (440 patients per treatment group). This sample size was chosen to provide at least 90% power to detect at least 25% difference in ACR20 response rate at Week 24 (assuming a placebo ACR20 response rate of 35%). The sample size also was chosen to provide approximately 80% power to detect a standardized effect size of 0.20 for mTSS change from baseline for risankizumab versus placebo group at Week 24. All power and sample size determinations were calculated based on a two-sided significance level of 0.05 and accounting for a 10% dropout rate.

Protocol Amendments

The original protocol (Version 1.0) was submitted on July 26, 2018 with 3 subsequent amendments and 4 subsequent administrative changes. The amendments were as follows:

- Protocol Version 2.0 was submitted on February 14, 2019. Changes were made to the collection method of the Physician Global Assessment (PGA) from paper to an ePRO device; eligibility criteria were updated to specify that patients must be functionally able to read and understand a written informed consent form, study-related instructions, and study questionnaires; to specify that the use of Legally Authorized Representatives

is prohibited for this protocol; to clarify that employees of the Applicant and/or study sites and their family members may not be enrolled in the study; and to specify that in addition to being at least 18 years old, patients must also meet the legal age of majority per local law

- Amendment 2.1 was submitted on January 6, 2020 for sites in Russia only. Details were added around patients in Russia only receiving 150 mg (1 x 150 mg PFS) SC open-label risankizumab starting at Week 28 and every 12 weeks thereafter
- Protocol Version 3.0 was submitted on March 13, 2020 and Amendment 3.1 for sites in Russia only was submitted on April 10, 2020. Changes were made to secondary endpoints related to the resolution of enthesitis and dactylitis, and the observed case imputation method was removed
- Protocol Version 4.0 was submitted on September 10, 2020 and Amendment 4.1 for sites in Russia only was submitted on October 2, 2020. Changes included the addition of ACR20 at Week 16 as a ranked secondary endpoint, separation of the Modified Nail Psoriasis Severity Index (mNAPSI) and Physician Global Assessment of Fingernail Psoriasis Score (PGA-F) into 2 individual endpoints, adjustment to the ranking of the mTSS endpoint in the secondary ranked endpoints, correction of the description of endpoint "Change from Baseline in Modified Psoriatic Arthritis Response Criteria (PsARC)" to "Proportion of patients who achieve a Modified Psoriatic Arthritis Response Criteria (PsARC) response", modification to wording on the non-responder imputation (NRI)-C and As Observed (AO) imputation methods as well as the Mixed-Effect Model Repeat Measurement analysis for continuous variables. Additional changes due to the COVID-19 pandemic were as follows:
    - Included information on the re-evaluation of benefit and risk to patients
    - Added instructions to refer to the Operations Manual for necessary changes to activities or procedures
    - Provided instructions in the event of temporary study drug interruption/halt due to COVID-19 and that in the event the patient cannot complete an onsite visit, administration of study drug at the patient's house is to be performed by study staff if feasible and permitted by local regulations
    - Clarified that protocol deviations may include modifications due to COVID-19
    - Replaced NRI with non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C) to incorporate handling of missing data due to COVID-19
    - Noted that AbbVie could modify the study protocol as necessary due to the pandemic
    - Noted that remote monitoring may be employed as needed

Compliance with Good Clinical Practices

The Applicant attests that the study was conducted in compliance with ICH Good Clinical Practice guidelines in addition to applicable local regulatory requirements.

Financial Disclosure

The Applicant reported that 13 investigators had disclosable financial interests for study M16-011. These investigators received significant payments that have a total value in excess of (b) (4) other than payments for conducting the clinical study. The investigators reported were as follows:

- (b) (4)

None of the investigational sites enrolled a significant number of patients that could potentially bias the clinical study results. For the studies included in this sBLA as support for safety, no single investigator or site made a significant contribution to the demonstration of safety.

The Applicant has taken steps to minimize the potential bias of clinical investigators with financial interests and arrangements by using proper study design and operations. The clinical study was blinded to the study site personnel and the participating patients throughout the course of the study. Each active dose of investigational drug product was identical in appearance to its matched placebo. Additionally, each patient was randomly assigned to their treatment arm independently of the investigator and the study site.

Patient Disposition

A total of 964 patients were randomized at 186 sites in 38 countries including the United States. The rate of study discontinuation was low with 97.9% (473/483) of patients in the risankizumab group and 97.1% (467/481) of patients in the placebo group completing Period 1 study participation and entering Period 2 study participation. Among the patients discontinued in Period 1, withdrawal of consent was the most common primary reason reported in both

groups. No patients completed periods 1 and 2 at the time of submission since period 2 was ongoing.

Table 7. Patient Disposition in M16-011 (Full Analysis Set)

Outcome	Placebo (N = 481) N (%)	Risankizumab (N = 483) N (%)	Total (N = 964) N (%)
Completed Period 1	467 (97.1)	473 (97.9)	940 (97.5)
Discontinued in Period 1 (Due to primary reason)	14 (2.9)	10 (2.1)	24 (2.5)
Adverse event	3 (0.6)	2 (0.4)	5 (0.5)
Withdrew consent	6 (1.2)	4 (0.8)	10 (1.0)
Lost to follow-up	3 (0.6)	0	3 (0.3)
Lack of efficacy	1 (0.2)	1 (0.2)	2 (0.2)
COVID-19 infection	0	0	0
COVID-19 logistics	1 (0.2)	2 (0.4)	3 (0.3)
Other	0	1 (0.2)	1 (0.1)
Entered Period 2	467 (97.1)	473 (97.9)	940 (97.5)
Ongoing in Period 2	453 (94.2)	460 (95.2)	913 (94.7)
Discontinued in Period 1 (all reasons)[a]	14 (2.9)	10 (2.1)	24 (2.5)
Adverse event	3 (0.6)	2 (0.4)	5 (0.5)
Withdrew consent	8 (1.7)	4 (0.8)	12 (1.2)
Lost to follow-up	3 (0.6)	0	3 (0.3)
Lack of efficacy	1 (0.2)	1 (0.2)	2 (0.2)
COVID-19 infection	0	0	0
COVID-19 logistics	1 (0.2)	2 (0.4)	3 (0.3)
Other	0	1 (0.2)	1 (0.1)
Completed Period 1 & 2	0	0	0

a. Patients who discontinued the study were counted under each reason given for discontinuation; therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations [Source: Reviewer]

Protocol Violations/Deviations

Protocol deviations were defined in accordance with ICH guidelines and included, but were not limited to inclusion/exclusion criteria violation, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications. Deviations were assessed for their impact on analyses and data integrity or patient safety.

The assigned treatment allocation for 43 patients was potentially viewable in the interactive response technology system to 12 blinded users. However, it was confirmed that only one individual viewed the unblinded treatment allocation information. This individual was a study project manager at a site where a single patient was enrolled at the time of the potential

unblinding event. The Applicant considered this a major protocol deviation and therefore excluded that patient from the Per-Protocol Analysis Set. No personnel responsible for the analysis or interpretation of study results were unblinded. No patient or investigator was unblinded to treatment allocations. To evaluate any potential bias caused by this potential unblinding event for the patients who were not categorized as major deviations, a sensitivity analysis excluding these 42 patients was performed for the primary endpoint and first ranked secondary endpoint. This sensitivity analysis did not reveal any difference in efficacy results compared to the full analysis set.

All non-ICH deviations were reviewed in addition to ICH-defined deviations. Non-ICH deviations were defined in accordance with standard guidelines and included, but were not limited to study procedure issues, concomitant medication issues, interactive response technology data entry stratification, missed visits, missed procedures, out of window visits, and IP administration. In addition to the patients with deviations per the above described ICH categories, 56 patients received a medication not permitted during the study phase.

Due to the COVID-19 pandemic and logistical limitations for patients and sites to follow, 18 patients did not have the Week 24 visit performed, 4 baseline and 56 Week 24 visits had laboratory testing performed at a local laboratory due to laboratory sample stability issues related to shipment to the central laboratory, 2 patients at baseline and 5 patients at Week 24 did not have central laboratory results reported due to sample instability, and 16 patients had only partial rather than total targeted source data verification at the time of database lock though 99.71% of the overall targeted source data verification was completed.

These protocol deviations did not impact patient safety and were not considered to have affected the overall assessment of study results.

Demographic Characteristics

Table 8 presents the baseline demographic characteristics of patients in study M16-011. Demographic characteristics were generally balanced between treatment groups. The study population was largely white (93.9%). Approximately half of the patients were male (50.4%) with an average age of 51 years. Anthropometric variables were comparable between placebo and risankizumab groups.

Table 8. Demographic Characteristics (Full Analysis Set)

Demographic Category	Placebo (N = 481) N (%)	Risankizumab (N = 483) N (%)	Total (N = 964) N (%)
Female	247 (51.4%)	231 (47.8)	478 (49.6)
Male	234 (48.6%)	252 (52.2)	486 (50.4)
Age – mean (SD)	51.2 (12.10)	51.3 (12.21)	51.3 (12.15)
White	451 (93.8)	454 (94.0)	905 (93.9)
Black/African American	2 (0.4)	4 (0.8)	6 (0.6)

Demographic Category	Placebo (N = 481) N (%)	Risankizumab (N = 483) N (%)	Total (N = 964) N (%)
Asian	22 (4.6)	13 (2.7)	35 (3.6)
Hawaiian/Pacific Islander	1 (0.2)	3 (0.6)	4 (0.4)
American Indian/Alaskan	0	1 (0.2)	1 (0.1)
Multiple race	5 (1.0)	8 (1.7)	13 (1.3)
Hispanic or Latino	92 (19.1)	93 (19.3)	185 (19.2)
Not Hispanic or Latino	389 (80.9)	390 (80.7)	779 (80.8)
Weight (kg) – mean (SD)	86.40 (18.993)	88.33 (19.252)	87.37 (19.138)
BMI – mean (SD)	30.3 (6.21)	30.7 (6.43)	30.5 (6.32)

BMI = Body Mass Index; Kg = kilogram; N = number of patients; SD = standard deviation [Source: Reviewer]

Other Baseline Characteristics

Table 9 presents disease characteristics for patients in study M16-011. Baseline disease characteristics were generally similar between the placebo and risankizumab groups including disease duration, disease severity, severity of radiographic changes, presence of dactylitis, presence of enthesitis, presence of spondylitis, and baseline use of concomitant csDMARDs.

Table 9. Baseline Disease Characteristics (Full Analysis Set)

Disease Category	Placebo (N = 481) N (%)	Risankizumab (N = 483) N (%)	Total (N = 964) N (%)
PsA duration – mean (SD)	7.09 (7.711)	7.14 (6.983)	7.12 (7.351)
DAS28 – mean (SD) *N = 479 (P), 482 (R)*	4.92 (0.951)	4.90 (1.005)	4.91 (0.978)
mTSS – mean (SD) *N = 460 (P), 460 (R)*	13.49 (29.025)	13.04 (29.869)	13.27 (29.435)
Dactylitis present	147 (30.6)	148 (30.6)	295 (30.6)
Dactylitis not present	334 (69.4)	335 (69.4)	669 (69.4)
Enthesitis present	290 (60.3)	297 (61.5)	587 (60.9)
Enthesitis not present	191 (39.7)	186 (38.5)	377 (39.1)
Spondylitis present	95 (19.8)	94 (19.5)	189 (19.6)
Spondylitis not present	386 (80.2)	389 (80.5)	775 (80.4)
0 prior csDMARDs	2 (0.4)	2 (0.4)	4 (0.4)
1 prior csDMARD	311 (64.7)	338 (70.0)	649 (67.3)
2 prior csDMARDs	136 (28.3)	105 (21.7)	241 (25.0)
≥ 3 prior csDMARDs	32 (6.7)	38 (7.9)	70 (7.3)
OCS use at baseline	87 (18.1)	101 (20.9)	188 (19.5)
No OCS at baseline	394 (81.9)	382 (79.1)	776 (80.5)
MTX use at baseline	315 (65.5)	314 (65.0)	629 (65.2)
No MTX at baseline	166 (34.5)	169 (35.0)	335 (34.8)
Use of any csDMARD	364 (75.7)	366 (75.8)	730 (75.7)

Disease Category	Placebo (N = 481) N (%)	Risankizumab (N = 483) N (%)	Total (N = 964) N (%)
Use of any MTX	315 (65.5)	314 (65.0)	629 (65.2)
Use of MTX alone	286 (59.5)	294 (60.9)	580 (60.2)
MTX and other csDMARD	29 (6.0)	20 (4.1)	49 (5.1)
csDMARD other than MTX	49 (10.2)	52 (10.8)	101 (10.5)
Any SSZ without MTX	22 (4.6)	20 (4.1)	42 (4.4)
Any LEF without MTX	19 (4.0)	28 (5.8)	47 (4.9)
Any Apremilast w/o MTX	8 (1.7)	4 (0.8)	12 (1.2)
No csDMARD at baseline	117 (24.3)	117 (24.2)	234 (24.3)

CsDMARD = conventional synthetic disease modifying antirheumatic drug; DAS28 = disease activity score (28 joints); LEF = leflunomide; mTSS = modified Total Sharp Score; MTX = methotrexate; OCS = oral corticosteroid; PsA = Psoriatic Arthritis; SD = standard deviation; SSZ = sulfasalazine [Source: Reviewer]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was defined as the number of injections administered during the patient's participation up to week 24 divided by the number of injections planned during this time period. Overall treatment compliance in Period 1 was generally similar between the risankizumab arm (99.72% compliance, SD 3.024) and placebo arm (99.31% compliance, SD 4.761).

The proportion of patients taking concomitant csDMARDs at baseline was comparable between the risankizumab arm (76%) and the placebo arm (76.7%). The most frequently reported concomitant csDMARD was methotrexate (61.6% total). The rest of the csDMARDs were used by < 10% of patients. The proportion of patients taking concomitant corticosteroids was slightly higher in the risankizumab arm (20.6% in the placebo arm vs 22.2% in the risankizumab arm), whereas the proportion of patients taking concomitant NSAIDs was slightly higher in the placebo arm (66.3% in the placebo arm vs 63.8% in the risankizumab arm).

A greater number of patients in the placebo arm required use of rescue medications overall (35 or 7.3% in the placebo arm vs 25 or 5.2% in the risankizumab arm). The proportion of patients who required rescue therapy with analgesics, ani-inflammatory drugs, and immunosuppressants (e.g., leflunomide or methotrexate) was higher in the placebo arm. One patient in the risankizumab arm required use of sulfasalazine, and another patient in the risankizumab required use of hydroxychloroquine in comparison to no patients in the placebo arm.

8.1.2. M15-998

Study Design

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled study of risankizumab in 443 patients with moderately to severely active PsA who had an inadequate

response (defined as lack of efficacy after a minimum 12-week duration of therapy) or intolerance to 1 or 2 biologic therapies (Bio-IR) or inadequate response/intolerance to at least 1 csDMARD (csDMARD-IR).

The study consisted of two periods referred to as Period 1 and Period 2. Period 1 was a 24-week randomized, double-blind, placebo-controlled, parallel-group period. Patients were randomized in a 1:1 ratio stratified by the extent of psoriasis (≥ 3% BSA vs < 3% BSA), current use of at least 1 csDMARD (0 vs ≥ 1), and number of prior biologic therapies (0 vs ≥ 1) to one of two groups:

- Group 1 (n = 224): Risankizumab 150 mg SC at Weeks 0, 4, and 16
- Group 2 (n = 219): Placebo SC at Weeks 0, 4, and 16

Period 2 was an open-label period starting at Week 24. During Period 2, all patients received treatment with risankizumab. To maintain the blind to the original treatment allocation, treatment at Week 24 was blinded so that patients initially randomized to placebo received risankizumab 150 mg and patients initially randomized to risankizumab received placebo. At Week 28, and for the remaining dosing visits to Week 208, all patients received risankizumab 150 mg every 12 weeks. The total study duration was 228 weeks including a telephone call 140 days (20 weeks) after the last dose of study drug.

Dosage and Administration

Risankizumab 150 mg was provided in 2 pre-filled syringes of 75 mg each for subcutaneous administration at Weeks 0, 4, and 16 during Period 1. Matching liquid placebo (0.9% sodium chloride solution) was provided for subcutaneous administration at Weeks 0, 4, and 16 during Period 1. To maintain the blind, treatment at Week 24 was blinded and patients randomized to placebo received blinded risankizumab 150 mg, and patients randomized to risankizumab received blinded placebo. At Week 28, and for the remaining dosing visits to Week 208, all patients received open-label risankizumab 150 mg every 12 weeks.

Rescue Therapy

At Week 16, patients classified as non-responders (defined as not achieving at least a 20% improvement in either or both tender joint count (TJC) and swollen joint count (SJC) at both Week 12 and Week 16 compared to baseline) were permitted to add or modify rescue therapy and concomitant medications as follows:

- Add or modify doses of NSAIDs, acetaminophen/paracetamol, low potency opiates (tramadol, codeine, or hydrocodone, alone or in combination with acetaminophen); OR
- Receive 1 intra-articular, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroid injection for 1 peripheral joint or 1 enthesis. Injected joints or enthesitis sites were considered not assessable for 90 days from the time of injection for analysis of TJC, SJC, and enthesitis; OR

- Titrate current background csDMARD or add an additional csDMARD, as allowed by eligibility criteria. Use of no more than 2 csDMARDs was permitted, and doses could not exceed the maximums defined in the eligibility criteria. Addition of a biologic therapy was not permitted.

Concomitant Medications

Permitted concomitant medications in this study included non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics (e.g., acetaminophen and low potency opiates), oral corticosteroids up to an equivalent dose of 10 mg/day of prednisone, methotrexate (MTX) up to 25 mg/week, sulfasalazine (SSZ) up to 3000 mg/day, leflunomide (LEF) up to 20 mg/day, hydroxychloroquine up to 400 mg/day, apremilast up to 60 mg/day, bucillamine up to 300 mg/day, iguratimod up to 50 mg/day, and ciclosporin up to 5 mg/kg/day. Patients were permitted to be on 0, 1, or 2 background csDMARDs.

Study Location and Dates

This study was conducted at 99 sites in 21 countries: Argentina, Australia, Belgium, Brazil, Canada, Denmark, Estonia, France, Germany, Greece, Hungary, Israel, Italy, New Zealand, Poland, Portugal, South Africa, Spain, Sweden, United Kingdom, and the US including Puerto Rico.

The study was conducted from March 7, 2019 (first patient first visit) to November 2, 2020 (data cutoff date for the interim clinical study report). The last patient completed their Week 24 visit on June 22, 2020.

Study Eligibility Criteria

- Adult male or female at least 18 years old
- Willing and able to comply with procedures required in the study protocol
- Have a clinical diagnosis of PsA with symptom onset of at least 6 months prior to the screening visit and fulfillment of the Classification Criteria for PsA (CASPAR) at screening
- Have active disease defined as ≥ 5 tender joints (based on 68 joint count) and ≥ 5 swollen joints (based on 66 joints) at both the screening visit and baseline visit
- Have a diagnosis of active plaque psoriasis with at least one psoriatic plaque of ≥ 2 cm diameter or nail changes consistent with psoriasis at the screening visit
- Have either an inadequate response or intolerance to biologic therapies
    - Patient must have demonstrated an inadequate response (defined as lack of efficacy after a minimum 12-week duration of therapy) or intolerance to treatment with 1 or 2 biologic therapies intended to treat psoriatic arthritis
- No prior exposure to the following biologic therapies is permitted:

  - anti-IL-23 agents (e.g., Guselkumab, Tildrakizumab, or Risankizumab)
  - anti-IL-12/23 agents (e.g., Ustekinumab)
  - anti-IL-17 agents (e.g., Secukinumab or Ixekizumab)
- Patients must have discontinued all biologic therapy prior to the first dose of study drug
  - 4 weeks prior to the baseline visit for etancerpt
  - 8 weeks for adalimumab, infliximab, certolizumab, and golimumab
  - 8 weeks for abatacept
  - 1 year for rituximab
    - OR 6 months if B-cells have returned to pretreatment levels
- Have either an inadequate response to csDMARD, or intolerance to csDMARDs
  - Patient must have demonstrated an inadequate response (defined as lack of efficacy after a minimum 12-week duration of therapy) to previous or current treatment with at least 1 of the following csDMARDs at maximally tolerated dose: methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), apremilast, bucillamine and iguratimod, or ciclosporin A
  - An inadequate response to methotrexate must be at the following dose ranges: ≥ 15 mg/week, or ≥ 10 mg/week in patients who are intolerant of MTX at doses ≥ 12.5 mg/week after complete titration (for patients in countries such as China, Korea, Malaysia, Singapore, Hong Kong, Taiwan, and Japan inadequate response to MTX is defined as ≥ 7.5 mg/week or as required per local authorities)
  - Patient enrolling in the csDMARD inadequate response population must not have had any prior exposure to biologic immunomodulation agents used to treat psoriatic arthritis
- Have laboratory values meeting the following criteria within the screening period:
  - Serum aspartate transaminase (AST) < 2 x upper limit of normal (ULN)
  - Serum alanine transaminase (ALT) < 2 x ULN
  - Serum total bilirubin ≤ 2.0 mg/dL except for patients with an isolated elevation of indirect bilirubin relating to Gilbert syndrome
  - Total white blood cell (WBC) count > 3,000/µL
  - Absolute neutrophil count (ANC) > 1,500/µL
  - Platelet count > 100,000/µL
  - Hemoglobin > 8.0 g/dL
- No evidence of hepatitis B, hepatitis C, HIV, or tuberculosis
- No active systemic infection during the last 2 weeks prior to the baseline visit (exception: common cold) as assessed by the investigator
- No active or suspected malignancy or history of malignancy within the last 5 years except for successfully treated non-melanoma skin cancer or localized carcinoma in situ of the cervix
- No history of organ transplantation requiring continued immunosuppression

- No major surgery performed within 12 weeks prior to randomization or planned during the conduct of the trial (e.g., hip replacement, aneurysm removal, stomach ligation)
- No history of clinically significant medical conditions or any other reason, including any physical, psychological, or psychiatric condition that in the opinion of the investigator would compromise the safety or interfere with the patient's participation in this study, would make the patient an unsuitable candidate to receive study drug, or would put the patient at risk by participating in the protocol; or permanently wheelchair-bound or bedridden or very poor functional status which prevents the ability to perform self-care
- No active skin disease other than psoriasis which could interfere with the assessment of psoriasis
- No history of extra-articular manifestations of PsA (e.g., PsO, uveitis, or inflammatory bowel disease) that is not clinically stable for at least 30 days prior to screening
- No prior joint surgery at joints to be assessed within this study in the 8 weeks prior to the baseline visit, or treatment with intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroids in the 8 weeks prior to the baseline visit
- No history of fibromyalgia, any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than PsA (including but not limited to rheumatoid arthritis, gout, overlap connective tissue disease, scleroderma, polymyositis, dermatomyositis, systemic lupus erythematosus)
    - Prior history of reactive arthritis or axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis is permitted if documentation of change in diagnosis to PsA or additional diagnosis of PsA is made
    - Prior history of fibromyalgia is permitted if documentation of change in diagnosis to PsA or documentation that the diagnosis of fibromyalgia was made incorrectly
- No history of clinically significant drug or alcohol abuse within the last 6 months
- No history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class
- All female patients of childbearing potential must have a negative serum pregnancy test at the screening visit. In addition, a negative urine pregnancy test is required at baseline prior to the first dose of study drug for all female patients of childbearing potential. Patients with a borderline serum pregnancy test at screening must have a negative serum pregnancy test ≥ 3 days later to document continued lack of a positive result
- Female patients must either be of non-childbearing potential or use at least 1 protocol specified method of birth control that is effective from study day 1 through at least 140 days (20 weeks) after the last dose of study drug. Local practices may require 2 methods of birth control.

- Female patients may not be pregnant, breastfeeding, or have plans to become pregnant during the study and for at least 140 days (20 weeks) after the last dose of study drug

Safety Variables

Safety evaluations included adverse event monitoring, physical examinations, vital sign measurements, 12-lead electrocardiogram, and clinical laboratory testing (hematology, chemistry) as a measure of safety and tolerability.

Patient Discontinuation Criteria

A patient was permitted to voluntarily withdraw or be withdrawn from the study or study treatment at any time for reasons including, but not limited to, the following:

- Lack of clinical response defined as not achieving at least a 20% improvement in either or both TJC and SJC, compared to baseline, on 2 consecutive visits. Evaluation for lack of clinical response began at Week 32; therefore, Week 36 was the first possible time point that a patient might be discontinued for lack of response
- Clinically significant abnormal laboratory result(s) or adverse events, which rule out continuation of the study drug, as determined by the Investigator or the therapeutic area medical director
- The Investigator believes withdrawal from the study treatment or study is in the best interest of the patient
- The patient requests withdrawal from the study treatment or study
- Eligibility criteria violation(s) are noted after the patient started study drug, if continuation of the study drug would place the patient at risk as determined by the therapeutic area medical director, after consultation with the investigator
- Patient needs to initiate prohibited medication(s) or dosages, and continuation of the study drug would place the patient at risk as determined by the therapeutic area medical director
- The patient becomes pregnant while on study drug
- Patient is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study
- Patient is diagnosed with a malignancy (Exception: localized non-melanoma skin cancer or carcinoma in-situ of the cervix, where continuation of the patient is at the discretion of the investigator)
- Patient is significantly non-compliant with study procedures which would put the patient at risk for continued participation in the trial as determined by the Investigator or therapeutic area medical director

- Occurrence of following hepatic test abnormalities that is confirmed on a separate sample following a repeated blood draw:
    - ALT or AST > 8x Upper Limit of Normal (ULN)
    - ALT or AST > 5x ULN for more than 2 weeks
    - ALT or AST > 3x ULN and (Total Bilirubin > 2x ULN or international normalized ratio > 1.5)
    - ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

Study Endpoints

Primary Endpoint:

The primary endpoint is the proportion of patients achieving American College of Rheumatology (ACR) 20 Response (ACR20) at Week 24

Secondary Endpoints:

Ranked secondary endpoints with multiplicity adjustment:

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

Other secondary endpoints without multiplicity adjustment:

- Proportion of patients achieving ACR50 response at Week 24
- Proportion of patients achieving ACR70 response at Week 24
- Proportion of patients with resolution of enthesitis (LEI = 0) at Week 24
    - In patients with enthesitis at baseline
- Proportion of patients with resolution of dactylitis (LDI = 0) at Week 24
    - In patients with dactylitis at baseline

Safety endpoints:

Safety evaluations included adverse event monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (hematology, chemistry) as a measure of safety and tolerability for the entire study duration.

Sample Size Determination

A total of 420 patients were planned to be randomized to risankizumab 150 mg or placebo in a ratio of 1:1 (210 patients per treatment group). A sample size of 210 in each group was chosen to have 90% power to detect a difference in HAQ-DI mean change from baseline of 0.24 (the difference between risankizumab 150 mg mean change from baseline of -0.37 and placebo mean change from baseline of -0.13) assuming that the common standard deviation is 0.72 using a two-group Satterthwaite t-test with a two-sided significance level of 0.05. This sample size also was chosen to ensure that analyses would have at least 90% power to detect a 20% treatment difference in ACR20 at Week 24, with an assumed placebo response rate of 35%, using a two-sided test at a 0.05 significance level and accounting for a 10% dropout rate.

Protocol Amendments

The original protocol (Version 1.0) was submitted on July 26, 2018. Subsequent protocol versions were submitted on 12 November 2018 (Version 2.0), 14 February 2019 (Version 3.0), and 17 March 2020 (Version 4.0). The final protocol (Version 5.0) was submitted on September 10, 2020 and included modifications due to the COVID-19 pandemic and modifications not related to the pandemic.

Changes due to the COVID-19 pandemic were made as follows:

- Included information on the re-evaluation of benefit and risk to patients
- Added instructions to refer to Operations Manual for changes to activities or procedures
- Provided instructions in the event of temporary study drug interruption due to COVID-19 and that in the event the patient cannot complete an onsite visit, administration of study drug at the patient's house is to be performed by study staff if feasible and permitted by local regulations
- Clarified that protocol deviations may include modifications due to COVID-19
- Replaced NRI with NRI-C to incorporate handling of missing data due to COVID-19
- Noted that the Applicant will modify the study protocol as necessary due to the pandemic, and that investigators must notify the Applicant if any urgent safety measures are taken
- Noted that remote monitoring may be employed as needed
- Added reference to the Operations Manual for allowed modification

- Updated the Operations Manual to include details on how to perform specific activities or procedures that may be impacted by changes in global/local regulations due to the pandemic

Changes not due to the COVID-19 pandemic were made as follows:

- Added the ranked secondary endpoint ACR20 at Week 16
- Modified resolution of enthesitis and dactylitis to be unranked additional secondary endpoints without multiplicity adjustment
- Corrected the description of the endpoint "Change from Baseline in Modified Psoriatic Arthritis Response Criteria (PsARC)" to "Proportion of patients who achieve a Modified Psoriatic Arthritis Response Criteria (PsARC) response."
- Modified wording on the NRI-C and AO imputation methods
- Modified wording on MMRM analysis for continuous variables

Compliance with Good Clinical Practices

The Applicant attests that the study was conducted in compliance with ICH Good Clinical Practice guidelines in addition to applicable local regulatory requirements.

Financial Disclosure

The Applicant reported that 12 investigators had disclosable financial interests for study M15-998. These investigators received significant payments that have a total value in excess of (b) (4) other than payments for conducting the clinical study. The investigators were as follows:

- (b) (4)

None of the investigational sites enrolled a significant number of patients that could potentially bias the clinical study results. For the studies included in this sBLA as support for safety, no single investigator or site made a significant contribution to the demonstration of safety.

The Applicant has taken steps to minimize the potential bias of clinical investigators with financial interests and arrangements by using proper study design and operations. The clinical study was blinded to the study site personnel and the participating patients throughout the course of the study. Each active dose of investigational drug product was identical in appearance to its matched placebo. Additionally, each patient was randomly assigned to their treatment arm independently of the investigator and the study site.

Patient Disposition

A total of 444 patients were enrolled in the study at 99 sites including the United States. One patient was randomized but not dosed due to the inability to obtain blood samples despite multiple attempts. The rate of study discontinuation was low overall with 96% of patients in the risankizumab group and 90.9% of patients in the placebo group completing Period 1 study participation and entering Period 2 study participation. No patients completed periods 1 and 2 at the time of submission since period 2 was ongoing.

Table 10. Patient Disposition in M15-998 (Full Analysis Set)

Outcome	Placebo (N = 219) N (%)	Risankizumab (N = 224) N (%)	Total (N = 443) N (%)
Completed Period 1	199 (90.9)	215 (96.0)	414 (93.5)
Discontinued in Period 1 (Due to Primary Reason)	20 (9.1)	9 (4.0)	29 (6.5)
Adverse Event	3 (1.4)	2 (0.9)	5 (1.1)
Withdrew Consent	8 (3.7)	2 (0.9)	10 (2.3)
Lost to Follow-up	1 (0.5)	2 (0.9)	3 (0.7)
Lack of Efficacy	7 (3.2)	2 (0.9)	9 (2.0)
COVID-19 Infection	0	0	0
COVID-19 Logistics	0	1 (0.4)	1 (0.2)
Other	1 (0.5)	0	1 (0.2)
Entered Period 2	199 (90.9)	215 (96.0)	414 (93.5)
Ongoing in Period 2	183 (83.6)	199 (88.8)	382 (86.2)
Discontinued in Period 2 (Due to Primary Reason)	16 (7.3)	16 (7.1)	32 (7.2)
Adverse Event	0	0	0
Withdrew Consent	4 (1.8)	6 (2.7)	10 (2.3)
Lost to Follow-up	3 (1.4)	1 (0.4)	4 (0.9)
< 20% Improvement in TJC/SJC vs Baseline	2 (0.9)	4 (1.8)	6 (1.4)
Lack of Efficacy	2 (0.9)	4 (1.8)	6 (1.4)
COVID-19 Infection	0	0	0
COVID-19 Logistics	2 (0.9)	0	2 (0.5)
Other	3 (1.4)	1 (0.4)	4 (0.9)

Completed Period 1 & 2	0	0	0

N = number of patients; SJC = swollen joint count; TJC = tender joint count [Source: Reviewer]

Protocol Violations/Deviations

Protocol deviations were defined in accordance with ICH guidelines and included, but were not limited to inclusion/exclusion criteria violation, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications. Deviations were assessed for their impact on analyses and data integrity or patient safety.

A total of 79 patients had at least one protocol deviation. 38 (17.3%) patients in the placebo group had at least one protocol deviation, and 41 (18.3%) patients in the risankizumab group had at least one protocol deviation.

6 patients with eligibility criteria deviations had the incorrect eligibility criteria selected in the eCRF. This error was identified after the interim database lock for this CSR, but did not affect the data analysis. The data will be corrected for the data set and reflected correctly in the final CSR for these patients.

All non-ICH deviations were reviewed in addition to ICH-defined deviations. Non-ICH deviations were defined in accordance with standard guidelines and included, but were not limited to study procedure issues, concomitant medication issues, interactive response technology data entry stratification, missed visits, missed procedures, out of window visits, and IP administration. In addition to the patients with deviations per the above described ICH categories, 38 patients received a medication not permitted during the study phase.

Due to the COVID-19 pandemic and restrictions precluding patients/sites from following study procedures, 5 patients did not have the Week 24 visit performed. 11 patients had Week 24 laboratory testing performed at a local laboratory due to a stability issue with shipment to the central laboratory, 3 patients did not have Week 24 central laboratory results reported due to sample instability, and 6 patients had only partial targeted source data verification at the time of database lock though more than 99.9% of the overall targeted source data verification was completed.

All deviations were assessed for their impact on analyses and data integrity or patient safety. These protocol deviations did not impact patient safety and were not considered to have affected the overall assessment of study results.

Demographic Characteristics

Table 11 presents the baseline demographic characteristics of patients in study M15-998. Demographic characteristics were generally balanced between treatment groups. The study population was largely white (96.6%). The majority of patients were female (55.1%), and the

average age of patients was approximately 53 years. Anthropometric variables were comparable between placebo and risankizumab groups.

Table 11. Demographic Characteristics (Full Analysis Set)

Demographic Category	Placebo (N = 219) N (%)	Risankizumab (N = 224) N (%)	Total (N = 443) N (%)
Female	120 (54.8)	124 (55.4)	244 (55.1)
Male	99 (45.2)	100 (44.6)	199 (44.9)
Age – Mean (SD)	52.7 (12.64)	53.1 (12.53)	52.9 (12.57)
White	210 (95.9)	218 (97.3)	428 (96.6)
Black or African American	3 (1.4)	2 (0.9)	5 (1.1)
Asian	3 (1.4)	2 (0.9)	5 (1.1)
Multiple	3 (1.4)	2 (0.9)	5 (1.1)
Hispanic or Latino	43 (19.6)	42 (18.8)	85 (19.2)
Not Hispanic or Latino	176 (80.4)	182 (81.3)	358 (80.8)
Weight (kg) – Mean (SD)	89.21 (21.583)	88.86 (21.475)	89.03 (21.505)
BMI – Mean (SD)	31.2 (6.81)	31.5 (7.98)	31.4 (7.42)

BMI = Body Mass Index; kg = kilograms; N = number of patients; SD = standard deviation [Source: Reviewer]

Other Baseline Characteristics

Table 12 presents disease characteristics for patients in study M15-998. Baseline disease characteristics were generally similar between the placebo and risankizumab groups including disease duration, disease severity, presence of dactylitis, presence of enthesitis, presence of spondylitis, baseline use of concomitant csDMARDs, prior use of biologics, and the number of prior failed biologic therapies.

Table 12. Baseline Disease Characteristics (Full Analysis Set)

Disease Category	Placebo (N = 219) N (%)	Risankizumab (N = 224) N (%)	Total (N = 443) N (%)
PsA duration – mean (SD) Number of years	8.2 (8.29)	8.2 (8.24)	8.2 (8.26)
DAS28 – mean (SD) *N = 219 (P), 224 (R)*	4.86 (1.046)	4.92 (0.984)	4.89 (1.015)
Dactylitis present	57 (26.3)	40 (17.9)	97 (22.0)
Dactylitis not present	160 (73.7)	184 (82.1)	344 (78.0)
Enthesitis present	158 (72.1)	147 (65.6)	305 (68.8)
Enthesitis not present	61 (27.9)	77 (34.4)	138 (31.2)
Spondylitis present	39 (17.8)	48 (21.4)	87 (19.6)
Spondylitis not present	180 (82.2)	176 (78.6)	356 (80.4)
0 prior csDMARDs	11 (5.0)	12 (5.4)	23 (5.2)
1 prior csDMARD	81 (37.0)	88 (39.3)	169 (38.1)
2 prior csDMARDs	60 (27.4)	60 (26.8)	120 (27.1)
≥ 3 prior csDMARDs	67 (30.6)	64 (28.6)	131 (29.6)

Disease Category	Placebo (N = 219) N (%)	Risankizumab (N = 224) N (%)	Total (N = 443) N (%)
0 prior Biologics	118 (53.9)	119 (53.1)	237 (53.5)
≥ 1 prior Biologics	101 (46.1)	105 (46.9)	206 (46.5)
0 prior failed Biologics	132 (60.3)	137 (61.2)	269 (60.7)
1 prior failed Biologic	64 (29.2)	72 (32.1)	136 (30.7)
≥ 2 prior failed Biologics	23 (10.5)	15 (6.7)	38 (8.6)
0 prior TNF antagonists	119 (54.3)	121 (54.0)	240 (54.2)
≥ 1 prior TNF antagonists	100 (45.7)	103 (46.0)	203 (45.8)
OCS use at baseline	22 (10.0)	28 (12.5)	50 (11.3)
No OCS at baseline	197 (90.0)	196 (87.5)	393 (88.7)
MTX use at baseline	99 (45.2)	110 (49.1)	209 (47.2)
No MTX at baseline	120 (54.8)	114 (50.9)	234 (52.8)
Use of any csDMARD	129 (58.9)	141 (62.9)	270 (60.9)
Use of any MTX	99 (45.2)	110 (49.1)	209 (47.2)
Use of MTX alone	89 (40.6)	102 (45.5)	191 (43.1)
MTX and other csDMARD	10 (4.6)	8 (3.6)	18 (4.1)
csDMARD other than MTX	30 (13.7)	31 (13.8)	61 (13.8)
Any SSZ without MTX	9 (4.1)	9 (4.0)	18 (4.1)
Any LEF without MTX	15 (6.8)	12 (5.4)	27 (6.1)
Any Apremilast w/o MTX	5 (2.3)	9 (4.0)	14 (3.2)
No csDMARD at baseline	90 (41.1)	83 (37.1)	173 (39.1)

csDMARD = conventional synthetic disease-modifying anti-rheumatic drug; DAS28 = disease activity score (28 joints); MTX = methotrexate; OCS = oral corticosteroid; PsA = psoriatic arthritis; SD = standard deviation; SSZ = sulfasalazine; TNF = tumor necrosis factor [Source: Reviewer]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was defined as the number of injections administered during the patient's participation up to week 24 divided by the number of injections planned during this time period. Treatment compliance in Period 1 was 99.7% in both the risankizumab and placebo groups.

The proportion of patients taking concomitant csDMARDs at baseline was similar between the risankizumab arm (62.9%) and the placebo arm (58.9%). The most frequently reported concomitant csDMARD was methotrexate (47.2% total). The proportion of patients taking concomitant NSAIDs was slightly higher in the placebo arm (66.2% in the placebo arm vs 62.9% in the risankizumab arm), whereas the proportion of patients taking concomitant corticosteroids was slightly higher in the risankizumab arm (10.0% in the placebo arm vs 12.5% in the risankizumab arm).

A greater number and proportion of patients in the placebo arm required use of rescue medications overall (28 patients or 12.8% in the placebo arm vs 15 patients or 6.7% in the risankizumab arm). A greater number and proportion of patients in the placebo arm required use of rescue therapy with analgesics, anti-inflammatory products, sulfasalazine, and

corticosteroids. The proportion of patients taking rescue therapy with immunosuppressants was 2.7% in both the risankizumab and placebo groups.

8.1.3. M16-002

Study Design

This was a phase 2, multicenter, randomized, parallel-design, dose-ranging, multiple-dose, placebo-controlled, double-blind study of risankizumab in patients with active psoriatic arthritis.

185 patients were randomized in a 2:2:2:1:2 ratio with stratification based on prior TNF inhibitor use and concurrent methotrexate use into 5 treatment arms as follows:

- Arm 1 – Risankizumab 150 mg at week 0, 4, 8, 12, 16
- Arm 2 – Risankizumab 150 mg at week 0, 4, 16
- Arm 3 – Risankizumab 150 mg at week 0, 12
- Arm 4 – Risankizumab 75 mg at week 0
- Arm 5 – Placebo

The overall study treatment duration was 16 weeks with an additional 16 weeks of follow-up. Patients who completed all doses of study drug and the week 24 visit had the option to enroll in a separate open-label extension study. Patients rolling over to the open-label extension study did not complete any remaining follow-up visits in this study.

Dosage and Administration

Risankizumab was provided as a pre-filled syringe for subcutaneous use (75 mg/0.83 mL). Patients in arms 1-3 received risankizumab 150 mg provided in 2 pre-filled syringes. Patients in arm 4 received risankizumab 75 mg provided in 1 pre-filled syringe. Matching liquid placebo (0.9% sodium chloride solution) was provided for subcutaneous administration.

Rescue Therapy

If patients had reduction in both tender joint count and swollen joint count of < 20% relative to baseline at the week 16 assessment, they were able to alter their concomitant psoriatic arthritis treatment or start additional treatment (except biologics) as per investigator discretion and local standard of care after receiving the week 16 study drug dose. After week 24, patients that were not enrolling in the open-label extension study were able to start rescue therapy with local standard of care including biologics regardless of joint count improvement.

Concomitant Medications

Permitted concomitant medications in this study included acetaminophen/NSAIDs (patients must be on a stable dose for at least 2 weeks before randomization, and refrain from intake for at least 24 hours before a visit with disease activity assessment), oral corticosteroids (patients must be on stable dose up to a maximum daily dose of 10 mg prednisone equivalent), and

methotrexate (up to 25 mg/week and patients must be taking folic acid supplementation according to local standard of care). Additionally, stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the patient from participation, were permitted.

Study Location and Dates

The study was conducted at 47 sites in 11 countries: Belgium, Canada, Czech Republic, Finland, France, Germany, Japan, Poland, Spain, Taiwan, and United States. The study was conducted from May 5, 2016 (first patient first visit) to August 24, 2017 (last patient last visit).

Main Eligibility Criteria

Inclusion Criteria

- Males or females with age ≥ 18 years at the time of screening
- Have PsA symptoms for ≥ 6 months prior to screening
- Have PsA on the basis of the Classification Criteria for Psoriatic Arthritis (CASPAR)
- Have ≥ 5 tender joints and ≥ 5 swollen joints at screening and randomization
- Have at least one PsO lesion or a documented personal history of PsO at screening
- If on concurrent PsA treatment, must be on a stable dose as follows:
    - For patients on methotrexate: must have been on treatment for ≥ 3 months with a stable dose and stable route of administration (up to 25 mg/week) for ≥ 4 weeks prior to randomization to week 24. Patients must also be taking folic acid supplementation according to local standard of care to minimize the likelihood of methotrexate toxicity
    - For patients on oral corticosteroids: must be on a stable dose (up to the equivalent of 10 mg of prednisone per day) for ≥ 2 weeks prior to randomization to week 24
    - For patients on acetaminophen or NSAIDs: must be on stable dose for ≥ 2 weeks prior to randomization to week 24
- Have active PsA that has been inadequately controlled by standard doses of NSAIDs administered for ≥ 4 weeks, traditional DMARDs (including sulfasalazine) administered for ≥ 3 months, or TNF inhibitors, or patients are intolerant to these treatments as assessed by the investigator
- Willing to provide signed and dated written informed consent prior to admission to the study in accordance with Good Clinical Practice (GCP) and local legislation
- Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly.

Exclusion Criteria

- Major chronic inflammatory or connective tissue disorder other than PsA
- Presence of fibromyalgia as assessed by the investigator
- Has received any therapeutic agent directly targeted to IL-12/23, IL-23, or IL-17
- Prior use of more than two different TNF inhibitor agents
- Use of the following treatments:
    - TNF inhibitors within 12 weeks prior to randomization
        - Etanercept within 8 weeks prior to randomization
    - Leflunomide without cholestyramine wash-out within 8 weeks prior to randomization
    - Systemic non-biologic medications for PsA or PsO within 4 weeks prior to randomization
    - Photochemotherapy within 4 weeks prior to randomization
    - Intraarticular, intramuscular, or intravenous steroids within 4 weeks
    - Topical PsO medications and phototherapy within 2 weeks prior to randomization
    - Low and high potency opiates within 2 weeks prior to randomization
- Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 (e.g. rituximab), investigational agents (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
- Participation in another trial with an investigational drug or device within 4 weeks (or within 12 weeks if the trial is for PsA) or 5 half-lives (whichever is greater) prior to randomization
- Use of any restricted medication or any drug considered likely to interfere with the safe conduct of the study as assessed by the investigator
- Plan for live vaccine during the study period or within 6 weeks prior to randomization
- History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients
- Active systemic infection during the last 2 weeks prior to randomization (except common cold)
- Chronic or relevant acute infections including HIV, viral hepatitis, and/or active tuberculosis
    - Patients with a positive QuantiFERON TB or PPD test may participate in the study if further work up (according to local practice guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If the presence of latent tuberculosis is established, then tuberculosis treatment may be deferred until completion of the trial according to clinical judgement of the investigator and local country guidelines

- Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix
- Major surgery performed within 12 weeks prior to randomization or planned within 32 weeks after randomization (e.g. hip replacement, aneurysm removal, stomach ligation) as assessed by the investigator
- Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than PsA and PsO, surgical procedure (i.e. organ transplant), medical examination finding (including vital signs and electrocardiogram), or laboratory value at the screening visit outside the reference range that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data
- Total white blood count < 3,000/µL, neutrophils < 1,500/µL, hemoglobin < 8.5 g/dL, or platelets < 100,000/µL at screening
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2x the upper limit of normal, or serum direct bilirubin ≥ 1.5 mg/dL at screening
- Positive rheumatoid factor or anti-cyclic-citrullinated peptide (anti-CCP) antibodies at screening
- Women who are pregnant, nursing, or who plan to become pregnant while in the trial
- Patients with cochlear implants, cardiac pacemakers, metallic foreign bodies in their eye or who have an aneurysm clip in their brain, and/or ferromagnetic surgical implants in the body or claustrophobia (MRI sub-study patients only)
- Patients who are legally institutionalized

Safety Variables of the Study

Safety evaluations included adverse event monitoring, physical examinations, vital sign measurements, clinical laboratory testing, 12-lead electrocardiogram, and assessment of local tolerability at the administration site of the subcutaneous injection.

Patient Discontinuation Criteria

All patients had the right to discontinue the study treatment early and/or withdraw from the study at any time without the need to justify their decision. The investigator had the right to remove patients from the study for non-compliance. In order to minimize missing data in the evaluation of intention-to-treat data analysis, the Applicant planned for patients who discontinue study treatment to complete early EOT visit at the first missed visit and continue follow-up for all regularly scheduled visits for safety and efficacy assessments.

Study medication was discontinued in the following cases:

- The patient withdraws consent for study treatment or study participation
- The patient can no longer be treated with trial medication for medical reasons such as surgery, adverse events, other disease, or pregnancy
- Development of a toxicity or adverse event which warrants risankizumab discontinuation including but not limited to serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs)
- If the patient received a live vaccine during the study
- If prohibited treatment is used during the study for any indication, the patient must discontinue use of the prohibited treatment if he/she wishes to continue the study drug. In case of undue safety risk for the patient, the patient should discontinue study treatment at the discretion of the investigator
- If the patient experiences an intolerable increase of PsA during the course of the trial treatment, then the patient will be discontinued from the trial treatment to receive rescue therapy as deemed appropriate by the investigator

Study Endpoints

Primary endpoint:

- ACR 20 response at week 16

Secondary endpoints:

- ACR 50 response at week 16
- ACR 70 response at week 16
- Change in Tender Joint Count at week 16 as compared to baseline
- Change in Swollen Joint Count at week 16 as compared to baseline
- Change in HAQ-DI at week 16 as compared to baseline
- Change in SF-36 at week 16 as compared to baseline
- Change in Dactylitis count at week 16 as compared to baseline
    - In patients with dactylitis at baseline
- Change in SPARCC Enthesitis Index at week 16 as compared to baseline
    - In patients with enthesitis at baseline
- Change in mNAPSI at week 16 as compared to baseline
    - In patients with nail psoriasis
- PASI 90 response at week 16
    - In patients with ≥ 3% baseline PsO BSA

Sample Size Determination

The sample size was determined on the basis of a one-sided comparison between the average ACR 20 response at week 16 of Arm 1 and Arm 2 versus placebo. With the assumed week 16 ACR 20 response rate of 38% in the combined arms (Arm 1 and Arm 2) and of 15% in the placebo arm, 40 participants each for Arm 1, Arm 2, and placebo would provide 85% power to detect a 23% difference in proportion (combination of Arm 1 and Arm 2 versus placebo) using a one-sided test of 0.05 significance.

Protocol Amendments

1 global amendment was submitted on October 12, 2016 which included the following changes:

- Added description of stratification within the study
- Added albumin/creatinine ratio in urine as a laboratory parameter
- Updated information for source data of ECG
- Revision of PK assessments to describe how summary statistics will be provided
- Added additional types of analyses to be performed on samples
- Updated protocol to clarify that MRI images will be read in random order
- Updated protocol to clarify that PROs have to be done first at a visit
- Updated instructions for joint count
- Updated instructions for mNAPSI

Compliance with Good Clinical Practices

The Applicant attests that the study was conducted in compliance with ICH Good Clinical Practice guidelines in addition to applicable local regulatory requirements.

Financial Disclosure

No financial disclosure was provided for study M16-002 per agreement at the pre-sBLA meeting.

Patient Disposition

A total of 185 patients were randomized from 47 sites in 11 countries including the United States. 12 patients discontinued from the study in the placebo and risankizumab treatment arms through week 16 of the study (1 patient discontinued in the placebo group; 11 patients discontinued in the risankizumab arms). The rate of study discontinuation was low overall with 97.6% and 90.0-94.9% of patients in the placebo arm and risankizumab arms completing the

study period. Adverse events and withdrawal of consent were the most frequently reported reasons for study discontinuation.

Table 13. Patient Disposition in M16-002 (Full Analysis Set)

Outcome	Placebo N = 42 N (%)	Arm 1 N = 42 N (%)	Arm 2 N = 42 N (%)	Arm 3 N = 39 N (%)	Arm 4 N = 20 N (%)	Risan. Total N = 143 N (%)	Overall Total N = 185 N (%)
Total Discontinuation	1 (2.4)	4 (9.5)	3 (7.1)	2 (5.1)	2 (10.0)	11 (7.7)	12 (6.5)
Adverse event (AE)	1 (2.4)	2 (4.8)	0	0	2 (10.0)	4 (2.8)	5 (2.7)
Worsened disease	1 (2.4)	0	0	0	0	0	1 (0.5)
Worsened PEC	0	1 (2.4)	0	0	1 (5.0)	2 (1.4)	2 (1.1)
Other AE	0	1 (2.4)	0	0	1 (5.0)	2 (1.4)	2 (1.1)
Protocol violation	0	0	0	0	0	0	0
Lost to follow-up	0	0	1 (2.4)	0	0	1 (0.7)	1 (0.5)
Patient withdrawal	0	2 (4.8)	2 (4.8)	1 (2.6)	0	5 (3.5)	5 (2.7)
Other	0	0	0	1 (2.6)	0	1 (0.7)	1 (0.5)
Completion	41 (97.6)	38 (90.5)	39 (92.9)	37 (94.9)	18 (90.0)	132 (92.3)	173 (93.5)

AE = adverse event; N = number of patients; PEC = pre-existing condition [Source: Reviewer]. Patients who discontinued the study were counted under each reason given for discontinuation. Therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations. Treatment arms: Arm 1 (Risankizumab 150 mg at week 0, 4, 8, 12, 16), Arm 2 (Risankizumab 150 mg at week 0, 4, 16), Arm 3 (Risankizumab 150 mg at week 0 and 12), and Arm 4 (Risankizumab 75 mg at week 0).

Protocol Violations/Deviations

Protocol deviations were defined in accordance with ICH guidelines and included, but were not limited to inclusion/exclusion criteria violation, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications. Deviations were assessed for their impact on analyses and data integrity or patient safety.

A total of 37 patients had at least one protocol deviations. A total of 7 patients (16.7%) in the placebo arm had at least one protocol deviation, and a total of 30 patients had at least one protocol deviation in the risankizumab arms (17 (16.7%) in Arm 1, 10 (23.8%) in Arm 2, 6 (15.4%) in Arm 3, and 4 (20.0%) in Arm 4). None of the deviations were considered to have affected the study outcome or interpretation of the study results or conclusions.

In addition to the important reportable deviations defined in the protocol, the following issues were identified: 3 patients at 1 study site were not administered an updated version of the informed consent form and withdrew consent before the correct version could be administered; 3 patients did not receive a complete physical exam at the end of the study (all 3 patients continued into the open-label extension Study M16-244 and 2 of the patients had complete physicals at the first visit of that study, which was not considered to have a meaningful impact on patient safety); 6 patients had 9 episodes of taking NSAIDs within 24

hours of visit assessments; 1 patient did not take 2 doses of methotrexate due to an adverse event as allowed by the protocol, but did not take the second dose despite resolution of the adverse event; 1 patient withheld their topical NSAID on multiple days; 2 patients on 3 informed consent forms did not denote whether they consented to the collection of biomarker biobanking samples (these forms were subsequently signed at a later date); 1 patient did not denote consent to DNA biobanking on the main informed consent form, but did agree on the specific DNA biobanking consent form (this sample was destroyed); 1 patient did not sign an informed consent form but did not enroll in the trial.

Demographic Characteristics

Tables 14 and 15 present the baseline demographic characteristics of patients in study M16-002. Demographic characteristics were balanced between the placebo and risankizumab groups. The majority of patients were male (57.1% in the placebo group and 56.6% overall in the risankizumab groups) and white (85.7% in the placebo group and 87.7% overall in the risankizumab groups). The mean age was 49.0 years and 51.5 years in the placebo group and risankizumab groups respectively. Anthropomorphic variables were similar between the groups.

Table 14. Demographic Characteristics - Categorical Variables (Full Analysis Set)

Variable	Placebo N = 42 N (%)	Arm 1 N = 42 N (%)	Arm 2 N = 42 N (%)	Arm 3 N = 39 N (%)	Arm 4 N = 20 N (%)	Total RZB N = 143 N (%)
Female	18 (42.9)	21 (50.0)	14 (33.3)	17 (43.6)	10 (50.0)	62 (43.4)
Male	24 (57.1)	21 (50.0)	28 (66.7)	22 (56.4)	10 (50.0)	81 (56.6)
White	36 (85.7)	35 (85.4)	37 (92.5)	34 (89.5)	15 (78.9)	121 (87.7)
Black	0	0	0	0	0	0
Asian	5 (11.9)	6 (14.6)	3 (7.5)	4 (10.5)	4 (21.1)	17 (12.3)
American Indian Alaska Native	1 (2.4)	0	0	0	0	0
Race Missing	0	1	2	1	1	5
Hispanic	2 (4.8)	0	1 (2.5)	0	0	1 (0.7)
Not Hispanic	40 (95.2)	41 (100)	39 (97.5)	38 (100)	19 (100)	137 (99.3)
Ethnicity Missing	0	1	2	1	1	5
Age < 65	39 (92.9)	34 (81.0)	37 (88.1)	34 (87.2)	16 (80.0)	121 (84.6)
Age ≥ 65	3 (7.1)	8 (19.0)	5 (11.9)	5 (12.8)	4 (20.0)	22 (15.4)
Weight < 100 kg	33 (78.6)	32 (76.2)	35 (83.3)	32 (82.1)	18 (90.0)	117 (81.8)
Weight ≥ 100 kg	9 (21.4)	10 (23.8)	7 (16.7)	7 (17.9)	2 (10.0)	26 (18.2)
BMI < 30	25 (59.5)	26 (61.9)	27 (64.3)	24 (61.5)	10 (50.0)	87 (60.8)
BMI ≥ 30	17 (40.5)	16 (38.1)	15 (35.7)	15 (38.5)	10 (50.0)	56 (39.2)

BMI = body mass index; kg = kilogram; N = number of patients; RZB = Risankizumab. Treatment arms: Arm 1 (Risankizumab 150 mg at week 0, 4, 8, 12, 16), Arm 2 (Risankizumab 150 mg at week 0, 4, 16), Arm 3 (Risankizumab 150 mg at week 0 and 12), and Arm 4 (Risankizumab 75 mg at week 0). [Source: Reviewer]

Table 15. Demographic Characteristics - Continuous Variables (Full Analysis Set)

Variable & Treatment	N	Mean	Standard Deviation	Median
Age (years) - Placebo	42	49.0	11.16	48.5
Age (years) – Arm 1	42	51.8	14.56	51.5
Age (years) – Arm 2	42	50.1	12.33	50.0
Age (years) – Arm 3	39	51.6	11.87	53.0
Age (years) – Arm 4	20	53.8	10.98	52.5
Age (years) – RZB total	143	51.5	12.66	52.0
Weight (kg) - Placebo	42	84.8	20.64	83.3
Weight (kg) – Arm 1	42	86.0	17.49	86.0
Weight (kg) – Arm 2	42	83.3	19.70	81.9
Weight (kg) – Arm 3	39	84.6	12.98	85.0
Weight (kg) – Arm 4	20	83.8	17.38	87.6
Weight (kg) – RZB total	143	84.5	16.94	85.0
BMI – Placebo	42	29.4	6.72	27.9
BMI – Arm 1	42	29.4	5.55	28.0
BMI – Arm 2	42	27.8	5.30	27.3
BMI – Arm 3	39	29.1	3.85	28.9
BMI – Arm 4	20	30.1	5.28	29.2
BMI – RZB total	143	28.9	5.04	28.4

BMI = body mass index; kg = kilogram; N = number of patients; RZB = Risankizumab. Treatment arms: Arm 1 (Risankizumab 150 mg at week 0, 4, 8, 12, 16), Arm 2 (Risankizumab 150 mg at week 0, 4, 16), Arm 3 (Risankizumab 150 mg at week 0 and 12), and Arm 4 (Risankizumab 75 mg at week 0). [Source: Reviewer]

Treatment Compliance and Concomitant Medications

Treatment compliance was defined as the number of visits where injections are received divided by the number of visits where injections are supposed to be received. This numerical value was then multiplied by 100 to produce an overall measurement of treatment compliance percentage. Treatment compliance was high through the week 16 visit (greater than 99%) and similar in the placebo and risankizumab groups.

The proportions of patients taking methotrexate and concomitant systemic corticosteroids were comparable between the placebo and risankizumab groups. The majority of patients took concomitant methotrexate (58.0% in the risankizumab group and 59.5% in the placebo group), while a minority of patients took concomitant steroids (23.8% in the risankizumab and placebo groups).

8.2.Statistical Methodologies

8.2.1. M16-011

The main estimand for the primary endpoint in this study was defined as follows:

a. Treatment: risankizumab 150 mg vs. placebo
b. Population: subjects who were randomized and received at least one dose of study drug
c. Variable: ACR20 response at Week 24
d. Intercurrent events: Intercurrent events include initiation of rescue medications or initiation of concomitant medications for PsA that could meaningfully impact efficacy assessment. Subjects with these events were treated as non-responders.
e. Population Level Summary: difference in response proportions between treatment conditions

The primary analysis for study M16011 was to be conducted after all ongoing subjects completed Week 24. The Full Analysis Set (FAS) included all randomized subjects who received at least one dose of study drug. The FAS was used for all efficacy and baseline analyses, with subjects analyzed according to the treatment group they were randomized to. All tests were to be conducted at the two-sided alpha level of 0.05.

The primary analysis for the primary endpoint used a Cochran-Mantel-Haenszel (CMH) test, adjusting for the stratification factors. Subjects will be considered as non-responders after initiation of rescue medications or initiation of concomitant medications for PsA that could meaningfully impact efficacy assessment; these medications were identified prior to database lock and unblinding.

The statistical analysis plan (SAP) stated that the probability of having missed visits and missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic would be assumed to be unrelated to the unobserved values. Therefore, for the purpose of statistical analysis, the Applicant stated that it is reasonable to assume that these missing data are missing at random (MAR) and the statistical models that require MAR assumption are appropriate. Based on this rationale, missing data due to COVID-19 infection or logistical restriction related to COVID-19 pandemic was handled via multiple imputation (MI). For subjects who have missing data for other reasons, the missing components were to be imputed with last observation carry forward to derive a composite score before imputing missing evaluations as a nonresponder.

For the primary endpoint, a supplementary analysis was performed using a treatment policy strategy for the intcurrent events described above. This analysis used the same CMH method and other estimand attributes but including all observed data, regardless of adherence to study drug or initation of concomitant medications for PsA. Subjects with missing data were imputed

as non-responders. An additional supplementary analysis with this estimand and analysis was performed but using MI to impute missing data.

Furthermore, to assess the robustness of the primary analysis using the missing data handling described, a tipping point analysis was conducted on ACR20 at Week 24. The analysis was conducted on the full analysis set using all observed data, i.e., all observed data regardless of concomitant medications use for PsA, study drug adherence or rescue. Thus, this is a sensitivity analysis for the supplementary analysis that utilized the treatment policy strategy, rather than the primary analysis utilizing the composite strategy. The tipping point analyses are two-dimensional, i.e., assumptions about the missing outcomes on the risankizumab treatment group and the placebo group can vary independently. Missing binary values are first imputed via MI under MAR assumption. Two sets of shift parameters are applied to the imputed values to systematically vary from 0% to 100% in both risankizumab and placebo, respectively. This is accomplished by modifying the predicted probabilities for the responses through shifting the log odds (shift parameters are log odds ratios), then directly sampling the missing response from the Bernoulli distribution with the modified probabilities. For each pair of shift parameters, the same CMH method used for the primary analysis were performed on each of the multiple imputed datasets to obtain the results for each comparison of the risankizumab treatment group versus the placebo group adjusted by stratification factors. The results were aggregated for the final statistical inference using Rubin's method.

The SAP notes that assigned treatment information on several subjects was inadvertently shared with the Study project manager (SPM). The blind was restored immediately upon discovery. There was no unblinding to the subjects or investigators nor to the Applicant personnel engaged in the scientific analysis of the study. However, conservatively, a sensitivity analysis for primary endpoint excluding those unblinded subjects from Full Analysis Set will also be performed.

Additionally, a supplemental analysis was performed on the Per Protocol Analysis Set (consists of a subset of FAS subjects who did not have any major protocol deviations that are determined to have a potential impact on the primary efficacy endpoint up to Week 24 in Period 1 of the study).

A multiple testing procedure was used to provide control of the type 1 error rate at alpha = 0.05 (2-sided) across analyses comparing risankizumab versus placebo with respect to the primary and the ranked secondary endpoints. The testing procedure is provided in Figure 8. Notably, this procedure indicates that the testing of resolution of enthesitis and resolution of dactylitis will use pooled data from the two phase 3 studies.

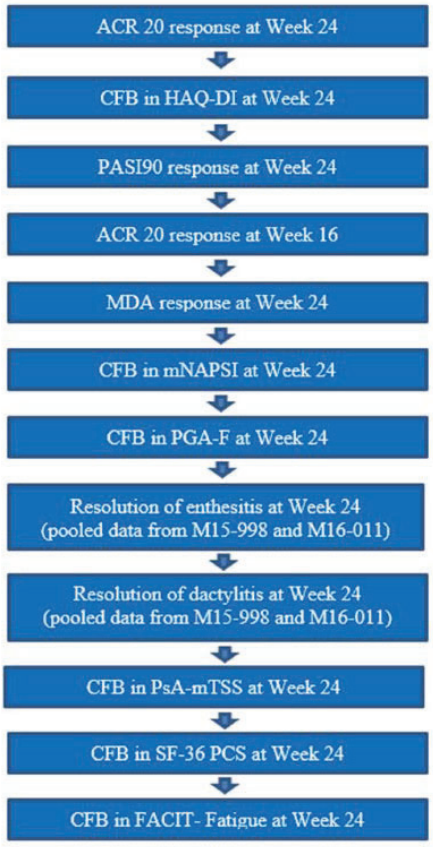


Figure 8 Graphical Testing Procedure for M16-011

Source: M16-011 SAP, p. 51

Abbreviations: ACR20 = American College of Rheumatology 20% Response, CFB=change from baselin, HAQ-DI= Health Assessment Questionnaire-Disability Index, PASI=Psoriasis Areas Severity Index, MDA= Minimal Disease Activity, mNAPSI= modified Nail Psoriasis Severity Index, PGA-F= Fingernail-Physician Global Assessment, mTSS= modified Total Sharp Score (mTSS), 36-Item Short Form Health Survey, PCS=Physical Component Summary (PCS), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Questionnaire

For all binary secondary endpoints, the primary estimand and analysis method were as defined for the primary efficacy endpoint. For secondary endpoints applicable only for a subgroup of the randomized population, the analyses used the following analysis sets: PASI90, subjects with BSA ≥ 3% at baseline; mNAPSI with nail psoriasis at baseline; PGA-F subjects with nail psoriasis at baseline; resolution of enthesitis (LEI = 0), subjects with baseline presence of enthesitis; resolution of dactylitis (LDI = 0), subjects with baseline presence of dactylitis. Comparisons of resolution of enthesitis/dactylitis pooled from M15-998 and M16-011 were made between the risankizumab and placebo group using the CMH adjusting for common stratification factors (extent of psoriasis and current use of csDMARD) and study.

For non-radiographic continuous secondary endpoints, the primary analysis was based on the hypothetical estimand. Specifically this estimand targets the hypothetical scenario where subjects had not started concomitant medications for PsA. Statistical inference was conducted

using a mixed model for repeated measures (MMRM). For the MMRM analysis, data collected after initiation of concomitant medications for PsA that could meaningfully impact efficacy assessment or initiation of rescue therapy was excluded. The mixed model includes the categorical fixed effects of treatment, visit and treatment-by-visit interaction, stratification factors, and the continuous fixed covariate of baseline measurement. An unstructured variance covariance matrix will be used. Parameter estimation is based on the assumption of data being missing at random and using the method of restricted maximum likelihood (REML). Thus, no explicit imputation was performed for missing data for any reason.

Supplemental analyses for the binary secondary endpoints and the non-radioagraphic continuous secondary endpoints followed the primary analysis procedure described but used all observed data, i.e., using the treatment policy strategy for handling rescue medication use and treatment discontinuation. For HAQ-DI at Week 24, additional supplementary analyses were conducted using all observed data and MI based under MAR assumption for missing data. To assess deviations from MAR, the tipping point analyses will also be conducted using MI as additional sensitivity analyses.

For change from baseline in mTSS at Week 24, statistical inference was conducted using an ANCOVA model with treatment and the stratification factors and the corresponding baseline values as the covariates. Linear extrapolation was applied to subjects with missing data or subjects who prematurely discontinued study drug or received rescue medication, where the radiographic data at the time point of interest was imputed with data from prior visits assuming a linear relationship. The SAP indicates that this approach is intended to align with a hypothetical strategy for handling the intercurrent event of premature study durg discontinuation or rescue.

The SAP defined additional analyses for the analysis of mTSS. First, the Applicant conducted a sensitivity analysis using MI rather than linear extrapolation for the handling of missing data and the intercurrent events described in order to incorporate uncertainty that may be missed via single imputation. ANCOVA was performed on each of the multiple imputed datasets and aggregated via Rubin's method. Additionally, a supplementary analysis using a treatment policy strategy for the described interecurrent events was performed. This approach included all observed data regardless of study drug adherence or rescue, handled with the same ANCOVA model. Other analyses used a random coefficient model and a non-paratmetric analysis. Finally, a tipping point analysis was also conducted for radiographic continuous endpoints.

Additional efficacy analyses included an analysis of the proportion of subjects without any readiographic progression at Week 24, were conducted using a CMH test and conducted using two approaches for handling intercurrent events (linear extrapolation imputation and including all observed data). For change from baseline in joint space narrowing score and joint erosion score at Week 24, linear extrapolation analysis and all observed data analysis was performed similarly as described for change from baseline in mTSS.

The primary efficacy endpoint was examine in the following subgroups, with treatment differences and 95% confidence intervals presented: age, sex, BMI, race, geographic region, number of prior csDMARDs, presence of enthsitis at baseline, presence of dactylitis at baseline, CRP at baseline, extent of psoriasis at baseline, duration of PsA, and concomitant csDMARD at baseline.

8.2.2. M15-998

The statistical analyses, including the estimands, for study M15-998 are the same as those described for study M16-011 for the primary endpoint and the binary and non-radiographic continuous secondary endpoints.

A multiple testing procedure was used to provide control of the type 1 error rate at alpha = 0.05 (2-sided) across analyses comparing risankizumab versus placebo with respect to the primary and the ranked secondary endpoints. The testing procedure is provided in Figure 9.

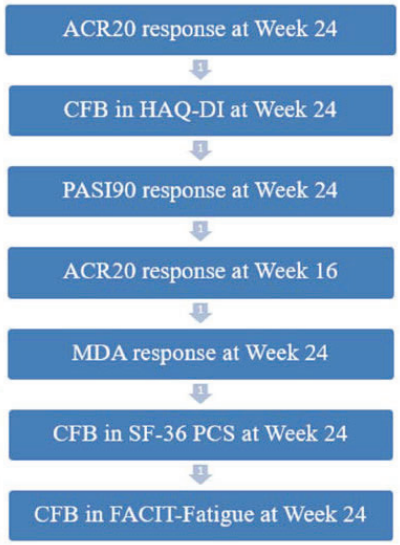


Figure 9 Graphical Testing Procedure for M15-998
Source: M15-998 SAP, p. 48
Abbreviations: ACR20 = American College of Rheumatology 20% Response, CFB=change from baselin, HAQ-DI= Health Assessment Questionnaire-Disability Index, PASI=Psoriasis Areas Severity Index, MDA= Minimal Disease Activity, 36-Item Short Form Health Survey, PCS=Physical Component Summary (PCS), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Questionnaire

8.2.3. M16-002

In this phase 2 dose-ranging study, the treatment effect was to be evaluated based on a two-sided significance level of 0.1 (when rounded to three decimal places). The efficacy analysis was to be conducted in the FAS which was defined as all randomized subjects who have received at least one dose of study medication.

The primary endpoint to assess the efficacy of risankizumab was ACR20 response at Week 16. The difference in proportion of participants that achieved ACR 20 between the combined groups of risankizumab (Arm 1 and Arm 2) and the placebo arm (Arm 5) was estimated and tested using the stratified Cochran-Mantel-Haenszel risk difference estimate, stratified based on prior TNFi use and concurrent MTX use. Pairwise comparisons of the risankizumab dose groups versus the placebo, as well as comparison of the combined groups of risankizumab (Arm 2 and Arm 3) versus the placebo, were conducted using the same stratified Cochran-Mantel-Haenszel methods. There would be no adjustments for multiplicity in these analyses. The sensitivity analyses for the primary endpoint ACR20 at Week 16 was conducted in the same manner as the primary analysis for point estimate and treatment comparisons but using as observed cases without any imputation.

Binary secondary endpoints including ACR50/70 and PASI90 were analyzed in a similar fashion as the primary endpoint. For continuous secondary endpoints such as HAQ-DI at Week 16, between-treatment differences in the change in HAQ-DI at Week 16 (from baseline) were to be evaluated using a MMRM with treatment regimen, clinical visit and stratification factors such as prior TNF and MTX use as fixed factors, and baseline HAQ-DI score as a fixed continuous covariate. An unstructured covariance structure was used to model the within-patient measurements. Parameter estimation of the MMRM was based on the residual maximum likelihood method (REML).

8.3.Efficacy Results for M16-011 and M15-998

Data Quality and Integrity
Data were submitted by the Applicant to the CDER electronic data room in SAS transport format. Protocols, correspondence, data listings, program code, and study reports were accessed through EDR \\CDSESUB1\evsprod\bla761105\0108 During the review process, an information request was made to facilitate review of this application.

In general, the data and source documentation requested were considered adequate for review of this application. The statistical reviewer found that there were small discrepancies between the dataset and the study report. An information request was sent to the Applicant for clarification. The Applicant responded that the dataset adresp.xpt included imputed values using LOCF for subjects with missing evaluations due to COVID-19 which were not used for analysis. The primary analysis used the imputed values for these subjects based on multiple imputation for the missing response due to COVID-19. There are no other issues about data and analysis quality identified.

Based on the information provided in this submission, the study appeared to be conducted properly and was consistent with the history of regulatory interactions and protocol revisions/amendments.

8.3.1. M16-011 and M15-998

Efficacy Results – Primary Endpoint

In both Study M16-011 and Study M15-998, there was a significantly greater proportion of subjects in the risankizumab group achieving an ACR20 response compared with subjects in the placebo group using the Applicant's main estimand (Table 16). Under this estimand (referred to as the composite estimand in this section), the intercurrent events of initiation of rescue medications or initiation of concomitant medications for PsA that could meaningfully impact efficacy assessment were handled using a composite strategy and these subjects were considered non-responders in the analysis. In Study M16-011, 57.3% in the risankizumab arm achieved an ACR20 response compared with 33.5% subjects in the placebo arm (22.2%). In Study M15-998, 51.3% in risakizumab arm achieved an ACR20 response compared with subjects in the placebo arm (26.5%).

Table 16 Primary Analysis: ACR20 Response at Week 24 Based on Composite Strategy

Treatment	Responder 95% CI*	Response Rate difference Compared to Placebo (95%CI) / P-value**
M16-011		
Risankizumab N=483	277 (57.3%) (52.9%, 61.8%)	24.0% (18.0%, 30.0%) P<0.001
Placebo N=481	161 (33.5%) (29.3%, 37.8%)	
M15-998		
Risakizumab N=224	115 (51.3%) (44.8%, 57.9%)	24.5% (15.9%, 33.0%) P<0.001
Placebo N=219	58 (26.5%) (20.7%, 32.4%)	

*Difference in proportions with 95% CI based on normal approximation.
** confidence interval based on Wald statistics; The p-values are based on the CMH test stratified by stratification factors of current use of csDMARD, presence of dactylitis, presence of enthesitis, and extent of psoriasis at baseline.
[Source: Statistical Reviewer, Table 14.2 1.1 of the Clinical Study Report R&D/20/1462 Risankizumab/Protocol M16-011, Clinical Study Report R&D/20/1461 Risankizumab/Protocol M15-998]

The number of non-responders are listed by different categories in Table 17. The majority of non-responders were due to failure to meet the ACR20 response criteria.

Table 17 Number of Non-responders for ACR20 at Week 24

Reason	Risakizumab	Placebo
Study M16-011		
Total	206	320
Did not meet ACR20	163 (79.1%)	256 (80%)
Rescue medication	25 (12.1%)	35 (10.9%)
Concomitant medication	1(0.5%)	5 (1.6%)
Missing due to COVID-19	2 (1.0%)	6 (1.9%)
Missing due to other reasons	15 (7.3%)	18 (5.6%)
Study M15-998		
Total	109	161
Did not meet ACR20	83 (76.1%)	110 (68.3%)
Rescue medication	15 (13.8%)	28 (17.4%)
Concomitant medication	2 (1.8%)	5 (3.1%)
Missing due to COVID-19	1 (0.9%)	2 (1.2%)
Missing due to other reasons	8 (7.3%)	16 (9.9%)

[Source: Statistical Reviewer]

Based on the data imputation rule in the SAP, if the composite score was missing due to non-COVID reason, the missing components were imputed using LOCF to recalculate the composite score before imputing missing evaluations as a non-responder. In genearl, we have concerns regarding the use of LOCF to impute missing data. As discussed in the 2010 National Research Council report The Prevention and Treatment of Missing Data in Clinical Trials, LOCF is generally not based on reasonable scientific assumptions and is also statistically inappropriate because it does not take into account the uncertainty in the imputation process. Therefore, an information request was sent to ask the Applicant to provide a list of subjects whose ACR composite score was recalculated using LOCF and to provide the results of an analysis that instead include these subjects as non-responders. The Applicant conducted a post-hoc analysis for the primary endpoint of ACR20 at Week 24 that imputed these subjects as requested. Results from the post-hoc analysis are shown in Table 18. Compared to the pre-specified primary analysis results in Table 16, the estimated treatment difference between risakizumab and placebo is similar and the conclusion is consistent.

Table 18 ACR20 Response at Week 24 Imputing Subjects with LOCF as Non-Responders

Treatment	Responder 95% CI	Response Rate difference Compared to Placebo (95% CI)	P-Value
M16-011			
Risankizumab (N=483)	270 (55.9%)	23.7% (17.8%, 29.7%)	<0.001
Placebo (N=481)	155 (32.3%)		
M15-998			

Risakizumab (N=224)	112 (50.0%)	24.1 (15.6%, 32.6%)	<0.001
Placebo (N=219)	56 (25.6%)		

Source: Abbvie Response to 17 November 2021 FDA Information Request Table 1

Results based on a estimand using a treatment policy strategy, where observed ACR20 responses were used for patients who took rescue medication at Week 16 and patients who took concomitant medications for psoriatic arthritis that could potentially impact efficacy at Week 24 , are shown in Table 19. Only patients who had missing evaluations were imputed as non-responders for this estimand. The results were consistent with the primary analysis for both Study M16-011 and Study M15-998, with each risankizumab group showing significant efficacy over placebo.

Table 19 ACR20 Response at Week 24 Based on the Treatment Policy Strategy

Treatment	Responder 95% CI*	Response Rate difference Compared to Placebo (95% CI) / P-value**
M16-011		
Risankizumab N=483	267 (55.3%) (50.8%, 59.7%)	22.4% (16.3%, 28.5%) P<0.001
Placebo N=481	158 (32.8%) (28.7%, 37.1%)	
M15-998		
Risakizumab N=224	111 (49.6%) (43.0%, 56.1%)	21.7% (12.9%, 30.5%) P<0.001
Placebo N=219	61 (27.9%) (21.9%, 33.8%)	

*calculated based on normal approximation to the binomial distribution.
** Difference in proportions with 95% CI based on Wald statistics
[Source: Statistical Reviewer]

The Applicant also performed two-dimensional tipping point analyses based on the treatment policy estimand to assess the robustness of these results to the assumption of MAR. The tipping point analysis was performed by multiple imputations using logistic regression, allowing the imputed ACR response rate to systematically vary from 0% to 100% in both risankizumab and placebo respectively. The results of the tipping point analysis for ACR20 response at Week 24 showed that results of the primary efficacy analysis are robust to missing data assumptions.

Change from Baseline in ACR Components at Week 24

Table 20 and Table 21 show that the results of the analyses of the mean change from baseline in each component of ACR, the primary endpoint, in both studies. These results show that all 7 ACR components were in favor of risakizumab compared to placebo in both phase 3 studies.

Table 20 Mean Change from Baseline in ACR Components (Study M16-011)

	Treatment Group		Mean difference of change compared to Placebo
	Risakizumab (N=483)	Placebo (N=481)	
Number of Swollen Joints			
Baseline	12.1 (7.8)	12.2 (8.0)	
Change at Week 16	-7.7 (7.2)	-5.5 (7.0)	-2.2 (-3.1, -1.3)
Change at Week 24	-8.7 (7.2)	-6.7 (7.2)	-2.0 (-3.0, -1.0)
Number of Tender Joints			
Baseline	20.8 (14.0)	20.5 (12.8)	
Change at Week 16	-10.7 (11.4)	-6.3 (11.1)	-4.4 (-5.8, -2.9)
Change at Week 24	-12.0 (12.3)	-7.9 (10.7)	-4.1 (-5.6, -2.5)
Patient's Assessment of Pain			
Baseline	57.1 (22.6)	57.1 (22.6)	
Change at Week 16	-18.4 (26.3)	-8.6 (23.7)	-9.1 (-12.3, -5.9)
Change at Week 24	-21.4 (26.5)	-10.9 (25.4)	-10.5 (-14.0, -7.0)
Patient's Global Assessment			
Baseline	57.9 (21.7)	57.4 (22.1)	
Change at Week 16	-19.4 (25.7)	-10.2 (23.9)	-9.0 (-12.2, -5.8)
Change at Week 24	-22.6 (26.9)	-11.1 (25.1)	-11.5 (-15.0, -8.0)
Physician Global Assessment			
Baseline	61.3 (17.6)	62.4 (17.0)	
Change at Week 16	-31.1 (23.4)	-18.3 (22.5)	-12.8 (-15.8, -9.8)
Change at Week 24	-34.8 (23.2)	-22.2 (22.8)	-12.6 (-15.8, -9.4)
Health Assessment Questionnaire - Disability Index (HAQ-DI)			
Baseline	1.2 (0.7)	1.2 (0.7)	
Change at Week 16	-0.3 (0.5)	-0.1 (0.5)	-0.15 (-0.22, -0.09)
Change at Week 24	-0.3 (0.5)	-0.1 (0.5)	-0.19 (-0.27, -0.13)
High sensitivity C-reactive protein (hs-CRP) mg/L			
Baseline	11.9 (15.9)	11.3 (14.1)	
Change at Week 16	-4.8 (14.2)	-0.3 (14.7)	-4.5 (-6.4, -2.6)
Change at Week 24	-4.3 (12.8)	-0.2 (11.7)	-4.1 (-5.8, -2.4)

Source: Statistical Reviewer

Table 21 Mean Change from Baseline in ACR Components (Study M15-998)

	Treatment Group		Mean difference of change compared to Placebo
	Risakizumab (N=224)	Placebo (N=219)	
Number of Swollen Joints			
Baseline	13.0 (8.7)	13.6 (9.0)	
Change at Week 16	-8.0 (7.4)	-5.4 (8.5)	-2.6 (-4.1, -1.0)
Change at Week 24	-9.1 (7.6)	-6.5 (7.8)	-2.6 (-4.2, -1.0)
Number of Tender Joints			
Baseline	22.8 (14.9)	22.3 (13.8)	
Change at Week 16	-11.3 (13.0)	-6.0 (13.1)	-5.3 (-7.8, -2.8)
Change at Week 24	-13.0 (12.5)	-8.3 (11.3)	-4.7 (-7.2, -2.2)
Patient's Assessment of Pain			
Baseline	55.0 (23.5)	57.0 (23.1)	
Change at Week 16	-14.4 (26.4)	-5.7 (22.7)	-8.7 (-13.5, -3.9)
Change at Week 24	-15.3 (26.5)	-8.7 (25.3)	-6.6 (-12.0, -1.2)
Patient's Global Assessment			
Baseline	56.2 (21.8)	56.2 (23.0)	
Change at Week 16	-17.0 (27.1)	-4.9 (23.6)	-12.1 (-17.0, -7.1)
Change at Week 24	-17.7 (27.7)	-8.7 (25.4)	-9.0 (-14.5, -3.5)
Physician Global Assessment			
Baseline	63.0 (17.0)	60.7 (16.4)	
Change at Week 16	-32.7 (24.7)	-19.0 (23.3)	-13.6 (-18.4, -8.8)
Change at Week 24	-35.5 (25.6)	-21.3 (25.2)	-14.3 (-19.7, -8.9)
Health Assessment Questionnaire - Disability Index (HAQ-DI)			
Baseline	1.1 (0.6)	1.1 (0.6)	
Change at Week 16	-0.2 (0.5)	-0.1 (0.5)	-0.07 (-0.16, 0.02)
Change at Week 24	-0.2 (0.5)	-0.1 (0.4)	-0.16 (-0.26, -0.06)
High sensitivity C-reactive protein (hs-CRP) mg/L			
Baseline	7.4 (10.9)	8.2 (17.1)	
Change at Week 16	-2.1 (7.5)	-0.1 (6.8)	-2.0 (-3.5, -0.6)
Change at Week 24	-1.8 (13.4)	-0.5 (14.5)	-1.2 (-4.2, 1.8)

Source: Statistical Reviewer

Efficacy Results - Ranked Secondary Endpoints

A multiple testing procedure was used to provide control of the type 1 error rate at alpha = 0.05 (2-sided) across analyses comparing risankizumab versus placebo with respect to the primary and the ranked secondary endpoints. Specifically, the testing utilized a fix sequence of

hypothesis testing for the primary endpoint followed by the ranked secondary endpoints in the order as specified in Figure 8 for Study m16-011 and Figure 9 for Study M15-998.

HAQ-DI at Week 24

Change from Baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 24 was the first ranked secondary endpoints with multiplicity adjustment. Table 22 lists analysis results for HAQ-DI at Week 24 for Study M16-011. There was a statistically significantly greater decrease from baseline in HAQ-DI at Week 24 for subjects in the risakizumab arm compared with subjects in the placebo arm based on the MMRM. The supplemental analysis results based on the simple t test and ANCOVA model, each using all observed data and comparing the mean difference of change from baseline of the two groups, showed similar results.

Table 22 Change from baseline in HAQ-DI at Week 24 (Study M16-011)

Treatment Group	N	Mean (SD)	Mean difference of change compared to Placebo (95% CI)	p-value
MMRM				
Placebo	479	-0.11 (-0.16, -0.06)	-0.20 (-0.26, -0.14)*	<0.001
Risakizumab	482	-0.31 (-0.36, -0.27)		
Observed mean difference between the groups based on Student's t test				
Placebo	456	-0.11 (-0.16, -0.07)	-0.19 (-0.26, -0.13)	<0.001
Risakizumab	460	-0.31 (-0.36, -0.26)		
ANCOVA				
Placebo	456	-0.12 (-0.17, -0.07)	-0.20 (-0.26, -0.14)**	<0.001
Risakizumab	460	-0.31 (-0.36, -0.26)		

*based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factors as fixed factors and the baseline measurement as covariates.
** based on ANCOVA model including treatment and the stratification factors and baseline value as covariates.
Source: [Statistical Reviewer and Table 14.2 3.1.1 of the Clinical Study Report R&D/20/1462 Risankizumab/Protocol M16-011]

Table 23 Change from baseline in HAQ-DI at Week 24 (Study M15-998)

Treatment Group	N	Mean (SD)	Mean difference of change compared to Placebo (95% CI)	p-value
MMRM				
Placebo	219	-0.05 (-0.12, 0.02)	-0.16 (-0.26, -0.07)*	<0.001
Risakizumab	224	-0.22 (-0.28, -0.15)		

Observed mean difference between the groups based on Student's t test				
Placebo	195	-0.10 (-0.17, -0.03)	-0.12 (-0.22, -0.03)	0.0135
Risakizumab	213	-0.22 (-0.29, -0.15)		
ANCOVA				
Placebo	195	-0.09 (-0.16, -0.02)	-0.13 (-0.22, -0.03)**	0.009
Risakizumab	213	-0.21 (-0.28, -0.15)		

*based on MMRM analysis wih unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factors as fixed factors and the baseline measurement as covariates.
** based on ANCOVA model including treatment and the stratification factors and baseline value as covariates.
Source: [Statistical Reviewer and Table 14.2 3.1.1 of the Clinical Study Report R&D/20/1461 Risankizumab/Protocol M15-998]

Table 24 shows proportion of subjects who achieved improvement in physical function as assessed by ≥0.35 decrease in HAQ-DI score by treatment group. In Study M16-011, 46.6% subjects in risakizumab group had ≥0.35 improvement in HAQ-DI score compared with 27.5% subjects in placebo group. The difference of the proportion of subjects with this improvement was 19.1% with a 95% CI of (13.0%, 25.3%). In Study M15-998, 38.0% subjects in risakizumab group had ≥0.35 improvement in HAQ-DI score compared with 27.7% subjects in placebo group, with a difference of 10.3% and 95% CI of (1.3%, 19.4%). The Applicant proposed to add a statement in the label that in both studies, a greater proportion of subjects achieved a reduction of at least 0.35 in HAQ-DI score from baseline in the SKYRIZI group compared with placebo at Week 24. Similar statements have been included in other PsA labelings to further describe the key secondary endpoint of HAQ-DI.

Table 24 Proportion of subjects who achieved improvement ≥0.35 in HAQ-DI score at Week 24 from baseline by Treatment Group

	Response rate	Response rate difference compared to placebo (95% CI)
Study M16-011		
Placebo (n=458)	126 (27.5%)	19.1% (13.0%, 25.3%)
Risakizumab (n=461)	215 (46.6%)	
Study M15-998		
Placebo (n=195)	54 (27.7%)	10.3% (1.3%, 19.4%)
Risakizumab (213)	81 (38.0%)	

Source: Statistical Reviewer

PASI90 Response at Week 24

The proportion of subjects achieving Psoriasis Area Severity Index (PASI) 90 response at Week 24 (in the subset of subjects with a body surface area (BSA) ≥ 3% at baseline) was defined as the

2nd ranked secondary endpoint in both Study M16-011 and Study M15-998. Among the subjects with BSA ≥ 3% at baseline, subjects in the risankizumab arm showed improvements in PASI90 response. The difference of percentage of subjects who achieved PASI 90 response at Week 24 between the two treatment groups was a statistically significant.

Table 25 Analysis of Psoriasis Area Severity Index (PASI) 90 Response at Week 24 (For Subjects with BSA >= 3% at Baseline)

	Response rate	Response rate difference compared to placebo (95% CI)	P-value
Study M16-011			
Placebo (n=272)	27 (9.9%)	42.8% (35.9%, 49.7%)	<0.001
Risakizumab (n=273)	144 (52.7%)		
Study M15-998			
Placebo (n=119)	13 (10.9%)	45.2% (34.8%, 55.6%)	<0.001
Risakizumab (123)	69 (56.1%)		

Source: Statistical Reviewer

These results were interpreted in consultation with the Division of Dermatology and Dentistry review team. Typically, inclusion criteria for trials to support the indication of moderate-to-severe psoriasis, for which risankizumab is already approved, include a minimum BSA percentage of 10%, a minimal PASI score of 12, and PGA score of at least 3 on a 5 point scale. However, as summarized above, the inclusions criteria in Study M16-011 and Study M15-998 did not specifically select for this patient population. Respectively, the results from the PASI90 responses were interpreted in that context. The review teams acknowledged that the protocols did not propose specific eligibility criteria based on psoriasis disease severity, limiting the evaluation of psoriasis by PASI90 in the PsA clinical trials did not necessarily provide additional clinically meaningful evidence on the efficacy of risankizumab in the treatment of moderate-to-severe psoriasis lesions in patients with active PsA based on the trial design. However, the PASI90 data were statistically robust and were considered relevant to the population of PsA patient with concomitant psoriatic skin involvement to support qualitative statements, consistent with current labeling practices of products approved for the same indication.

ACR20 Response at Week 16

The proportion of subjects with ACR20 response at Week 16 was the 3rd ranked secondary endpoint in both Studies M16-011 and M15-998. Note that subjects classified as non-responders had the option to add/modify rescue/concomitant meds/therapy beginning from Week 16. Therefore, this analysis differs from the primary analysis because it is not impacted by these specific intercurrent events. As shown in Table 26, there was a statistically significantly greater percentage of subjects achieved ACR20 response in the risankizumab arm compared with subjects in the placebo arm at Week 16 in both studies.

Table 26 ACR20 Response at Week 16

	Response rate	Response rate difference compared to placebo (95% CI)	P-value
Study M16-011			
Placebo (n=481)	153 (31.8%)	22.6% (16.6%, 28.7%)	<0.001
Risakizumab (n=483)	263 (54.5%)		
Study M15-998			
Placebo (n=219)	50 (22.8%)	25.4% (16.8%, 34.0%)	<0.001
Risakizumab (n=224)	104 (48.2%)		

Source: Statistical Reviewer

MDA Response at Week 24

Minimal Disease Activity (MDA) response at Week 24 was 4th ranked secondary endpoint in both Studies M16-011 and M15-998. Table 27 showed at Week 24, a statistically significantly higher percentage of subjects achieved MDA in the risankizumab arm compared with subjects in the placebo arm in both studies.

Table 27 Analysis of Minimal Disease Activity (MDA) Response at Week 24

	Response rate	Response rate difference compared to placebo (95% CI)	P-value
Study M16-011			
Placebo (n=481)	48 (10.0%)	14.5% (9.8%, 19.1%)	<0.001
Risakizumab (n=483)	118 (24.4%)		
Study M15-998			
Placebo (n=219)	28 (12.8%)	12.7% (5.4%, 19.9%)	<0.001
Risakizumab (n=224)	57 (25.5%)		

Change from Baseline in modified Nail Psoriasis Severity Index (mNAPSI) at Week 24 and Change from Baseline in Physician Global Assessment of Fingernail Psoriasis (PGA-F) at Week 24 (FAS) were 5th and 6th ranked secondary endpoints and also achieved statistical significance. However, the clinical meaningfulness of this assessment in the proposed PsA population is not clear based on the lack of enrollment criteria addressing nail manifestations of psoriasis.

Dactylitis and Enthesitis

In October of 2020, the Applicant proposed to remove resolution of enthesitis and resolution of dactylitis from the ranked secondary endpoint analyses of Study M15-998 and pool the enthesitis and dactylitis data from the two trials (Study M15-998 and Study M16-011) under the multiplicity control of Study M16-011 as a pre-specified analysis in the Study M16-011 SAP. Enthesitis and dactylitis have historically been included in labeling with descriptive statements, despite a lack of multiplicity control, and a similar approach was used in the guselkumab development program for PsA. Therefore, while the review team accepted the Applicant's

proposal to pool the enthesitis and dactylitis data from the two trials (Study M15-998 and Study M16-011) under the multiplicity control of Study M16-011 as a prespecified analysis in the Study M16-011, the review team noted how the results on resolution of enthesitis and dactylitis will appear in labeling will be a review issue and that we will also take into consideration the results from the individual studies to ensure that a consistent trend in improvement would be observed in both studies. Additional discussion is provided in Section 8.5.

Subjects with dactylitis at baseline were pooled from M16-011 and M15-998 for the analysis of dactylitis resolution. A total of 295 subjects were from M16-011 and a total of 97 subjects were from M15-998. Table 28 shows the analysis results based on the non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19, described in Section 8.2. The proportion of subjects with dactylitis resolution was greater in risakizumab group (68.1%) compared with the placebo group (51.0%) (diff: 16.9%, 95% CI: (7.5%, 26.4%)), meeting the significance threshold as specified by the Applicant's testing scheme. Efficacy from each study separately was assessed to ensure consistent trends in improvement were observed. There was a higher proportion of subjects with dactylitis resolution in risakizumab compared to placebo group in both studies. The difference between the treatment groups showed nominal statistical significance in each individual study.

Table 28 Resolution of Dactylitis at Week 24 based on Composite Estimand

Treatment Group (N)	Responder	Non-responder	Compared to placebo (95% CI)/ p-value
Pooled analysis			
Placebo (204)	104 (51.0%)	100 (49.0%)	16.9% (7.5%, 26.4%)
Risakizumab (188)	128 (68.1%)	60 (31.9%)	P<0.001
Study M16-011			
Placebo (147)	80 (54.4%)	67 (45.6%)	12.5% (1.4%, 23.5%)
Risakizumab (148)	99 (66.9%)	49 (33.1%)	P=0.0286
Study M15-998			
Placebo (57)	24 (42.1%)	33 (57.9%)	30.4% (9.4%, 51.4%)
Risakizumab (40)	29 (72.5%)	11 (27.5%)	P<0.001

N=Number of subjects with dactylitis at baseline
Source: Statistical Reviewer

Table 29 shows the analysis results based on the estimand using a treatment policy strategy (including all observed data but imputing missing outcomes as non-responder). Though the difference between the treatment groups is smaller, the results are consistent with the main analysis for both the pooled data and for each individual study. The difference between the treatment groups showed nominal statistical significance in each individual study.

Table 29 Resolution of Dactylitis at Week 24 based on Treatment Policy Estimand

Treatment Group (N)	Responder	Non-responder	Compared to placebo (95% CI)/ p-value
Pooled analysis			
Placebo (204)	116 (56.9%)	88 (43.1%)	13.9% (4.5%, 23.3%) P=0.0043
Risakizumab (188)	133 (70.7%)	55 (29.3%)	
Study M16-011			
Placebo (147)	85 (57.8%)	62 (42.2%)	
Risakizumab (148)	103 (69.6%)	45 (30.4%)	11.8% (0.9%, 22.7%) P=0.0358
Study M15-998			
Placebo (57)	31 (54.4%)	26 (45.6%)	
Risakizumab (40)	30 (75.0%)	10 (25.0%)	20.6% (2.0%, 39.3%) P=0.0396

N=Number of subjects with dactylitis at baseline
Source: Statistical Reviewer

Subjects with enthesitis at baseline were pooled from M16-011 and M15-998 for the analysis of enthethitis resolution. A total of 587 subjects were from M16-011 and a total of 305 subjects were from M15-998. In pooled analysis, the proportion of subjects with enthethitis resolution was greater in risakizumab group (48.4%) compared with the placebo group (34.8%) as shown in Table 30, based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 (diff: 13.6%, 95% CI: (7.0%, 20.2%)). There was a higher proportion of subjects with enthethitis resolution in risakizumab compared to placebo group in both studies. The difference between the treatment groups showed nominal statistical significance in each individual study.

Table 30 Resolution of Enthesitis at Week 24 based on Composite Estimand

Treatment Group (N)	Responder	Non-responder	Compared to placebo (95% CI)/ p-value
Pooled analysis			
Placebo (448)	156 (34.8%)	292 (65.2%)	
Risakizumab (444)	215 (48.4%)	229 (51.6%)	13.6% (7.0%, 20.2%) P<0.001
Study M16-011			
Placebo (290)	108 (37.2%)	182 (62.8%)	
Risakizumab (297)	152 (51.2%)	145 (48.8%)	13.9% (5.6%, 22.2%) p=0.001
Study M15-998			
Placebo (158)	48 (30.4%)	110 (69.6%)	
Risakizumab (147)	63 (42.9%)	84 (57.1%)	12.5% (1.7%, 23.2%) P=0.0239

N=Number of subjects with dactylitis at baseline

Source: Statistical Reviewer

Table 31 shows the analysis results based on the observed data imputing missing outcome as non-responder. Though the difference between the treatment groups is smaller, the results are consistent with the main analysis for the pooled data and for Study M16-011. For study M15-998, while there was a higher proportion of subjects with dactylitis resolution on risakizumab group compared to placebo, the difference did not show nominal statistical significance at α=0.05 level.

Table 31 Resolution of Enthesitis at Week 24 baased on Treatment Policy Estimand

Treatment Group (N)	Responder	Non-responder	Compared to placebo (95% CI)/ p-value
Pooled analysis			
Placebo (448)	174 (38.8%)	274 (61.2%)	
Risakizumab (444)	222 (50.0%)	222 (50.0%)	11.2% (4.7%, 17.6%) P<0.001
Study M16-011			
Placebo (290)	116 (40.0%)	174 (60.0%)	
Risakizumab (297)	158 (53.2%)	139 (46.8%)	13.2% (5.2%, 21.2%) p=0.0014
Study M15-998			
Placebo (158)	58 (36.7%)	100 (63.3%)	
Risakizumab (147)	64 (43.5%)	83 (56.5%)	6.8% (-4.2%, 17.8%) P=0.2238

N=Number of subjects with dactylitis at baseline
Source: Statistical Reviewer

SF-36 PCS at Week 24

Change from baseline in 36-Item Short Form Health Survey Physical Component Score (SF-36 PCS) at Week 24 was the 10th ranked secondary endpoint for Study M16-011 and was 5th ranked secondary endpoint for Study M15-998. In Study M16-011, the 9th ranked secondary endpoint Change from Baseline in modified Total Sharp Score (mTSS) at Week 24 failed to reach pre-specified statistical significance level (α=0.05) compared to placebo. Therefore, statistical testing could not be conducted for the remaining endpoints in the hierarchy, change from baseline in SF-36 PCS score and change from baseline the FACIT-Fatigue at Week 24. The analysis results for SF-36 for Study M16-011 is presented in Table 33. Though significance testing did not continue based on the testing procedure, the confidence interval does exclude the null value.

In Study M15-998, the MMRM analysis showed that subjects in the risankizumab arm experienced improvements in their perceptions of physical function as shown by a statistically significant difference between the risankizumab and placebo arms in the change from Baseline

in 36-Item Short Form Health Survey Physical Component Score (SF-36 PCS) at Week 24. The supplemental analysis results based on the simple t test and ANCOVA model, each using all observed data and comparing the mean difference of change from baseline of the two groups, showed similar results.

Table 32 Analysis of Change from Baseline in SF-36 PCS at Week 24 (Study M15-998)

Treatment Group	N	Mean (95% CI)	Mean difference of change compared to Placebo (95% CI)	P-value
MMRM				
Placebo	219	2.0 (0.9, 3.1)	3.9 (2.4, 5.3)*	<0.001
Risakizumab	224	5.9 (4.9, 6.9)		
Observed mean difference between the groups based on Student's t test				
Placebo	196	2.5 (1.4, 3.6)	3.5 (2.1, 5.0)	<0.001
Risakizumab	213	6.1 (5.0, 7.1)		
ANCOVA				
Placebo	196	2.2 (1.2, 3.3)	3.5 (2.1, 4.9)**	<0.001
Risakizumab	213	5.7 (4.7, 6.7)		

*based on MMRM analysis wih unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factors as fixed factors and the baseline measurement as covariates.
** based on ANCOVA model including treatment and the stratification factors and baseline value as covariates.
Source: Source: [Statistical Reviewer and Table 14.2 3.5 of the Clinical Study Report R&D/20/1461 Risankizumab/Protocol M15-998]

Table 33 Analysis of Change from Baseline in SF-36 PCS at Week 24 (Study M16-011)

Treatment Group	N	Mean (95% CI)	Mean difference of change compared to Placebo (95% CI)
MMRM			
Placebo	477	3.2 (2.5, 3.9)	3.3 (2.4, 4.2)*
Risakizumab	482	6.5 (5.8, 7.2)	
Observed mean difference between the groups based on Student's t test			
Placebo	456	3.0 (2.4, 3.6)	
Risakizumab	460	6.6 (5.9, 7.3)	
ANCOVA			
Placebo	456	3.0 (2.3, 3.7)	3.6 (2.7, 4.5)**
Risakizumab	460	6.6 (5.9, 7.3)	

*based on MMRM analysis wih unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factors as fixed factors and the baseline measurement as covariates.

** based on ANCOVA model including treatment and the stratification factors and baseline value as covariates.
Source: [Statistical Reviewer and Table 14.2 3.10 of the Clinical Study Report R&D/20/1462 Risankizumab/Protocol M16-011]

FACIT-Fatigure at Week 24

Change from Baseline in FACIT-Fatigue score at Week 24 was 11th ranked secondary endpoint for Study M16-011 and was 6th ranked secondary endpoint for Study M15-998. In Study M16-011, statistical testing was not conducted for this endpoint because the 9th ranked secondary endpoint mTSS failed to reach pre-specified statistical significance level of 0.05. The analysis results with nominal significance for FACIT-Fatigue for Study M16-011 is presented in Table 35.

In Study M15-998, the MMRM analysis showed that subjects in the risankizumab arm experienced improvements in their perceptions of fatigue as shown by a statistically significant difference between the risankizumab and placebo arms in the change from Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue at Week 24. The supplemental analysis results based on the simple t test and ANCOVA model, each using all observed data and comparing the mean difference of change from baseline of the two groups, showed similar results.

Table 34 Analysis of Change from Baseline in FACIT - Fatigue at Week 24 (Study M15-998)

Treatment Group	N	Mean (95% CI)	Mean difference of change compared to Placebo (95% CI)	P-value
MMRM				
Placebo	219	2.6 (1.4, 3.9)	2.2 (0.6, 3.9)*	0.0174
Risakizumab	224	4.9 (3.7, 6.0)		
Observed mean difference between the groups based on Student's t test				
Placebo	196	3.0 (1.6, 4.3)	2.2 (0.4, 3.9)	0.009
Risakizumab	213	5.1 (0.6, 8.7)		
ANCOVA				
Placebo	196	2.6 (1.4, 3.8)	2.1 (0.5, 3.7)**	0.011
Risakizumab	213	4.7 (3.6, 5.9)		

*based on MMRM analysis wih unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factors as fixed factors and the baseline measurement as covariates.
** based on ANCOVA model including treatment and the stratification factors and baseline value as covariates.
Source: [Statistical Reviewer and Table 14.2 3.6 of the Clinical Study Report R&D/20/1461 Risankizumab/Protocol M15-998]

Table 35 Analysis of Change from Baseline in FACIT - Fatigue at Week 24 (Study M16-011)

Treatment Group	N	Mean (95% CI)	Mean difference of change compared to Placebo (95% CI)
MMRM			
Placebo	477	3.9 (3.1, 4.7)	
Risakizumab	482	6.5 (5.6, 7.3)	2.6 (1.5, 3.7)*
Observed mean difference between the groups based on Student's t test			
Placebo	456	3.4 (2.6, 4.3)	
Risakizumab	460	6.2 (5.3, 7.0)	2.8 (1.6, 4.0)
ANCOVA			
Placebo	456	3.6 (2.7, 4.4)	
Risakizumab	460	6.4 (5.5, 7.2)	2.8 (1.7, 3.9)**

*based on MMRM analysis wih unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factors as fixed factors and the baseline measurement as covariates.
** based on ANCOVA model including treatment and the stratification factors and baseline value as covariates.
Source: [Statistical Reviewer and Table 14.2 3.11 of the Clinical Study Report R&D/20/1462 Risankizumab/Protocol M16-011]

Efficacy Results - Other Secondary Efficacy Endpoints

The analysis results for ACR50 and ACR70 are also included in the proposed label. Both endpoints were not included in the multiplicity controlled testing hierarchy, however, they are considered clinically important endpoints to further describe the ACR response.

ACR50

Table 36 shows the proportion of subjects achieving ACR50 response at Week 24 by treatment group based on the same approach for ACR20 with regard to missing data and intercurrent events. There is a greater proportion of subjects achieving ACR50 response in the risakizumab group compared to the placebo group.

Table 36 ACR50 Response at Week 24 based on Composite Estimand

	Response rate	Response rate difference compared to placebo (95% CI)
Study M16-011		
Placebo (n=481)	54 (11.3%)	
Risakizumab (n=483)	162 (33.4%)	22.3% (17.2%, 27.4%)
Study M15-998		
Placebo (n=219)	20 (9.1%)	
Risakizumab (n=224)	59 (26.3%)	17.2% (10.3%, 24.1%)

Source: [Statistical Reviewer and Table 14.2 3.12 of the Clinical Study Report R&D/20/1462 Risankizumab/Protocol M16-011 and Table 14.2 3.7 of the Clinical Study Report R&D/20/1461 Risankizumab/Protocol M15-998]

Table 37 shows the analysis results for ACR50 response at Week 24 based on including all observed data and imputing subjects with missing outcomes as non-responders. Though the difference between the treatment groups is smaller, the results are consistent with the main analysis. The difference of ACR50 response between the treatment groups based on the treatment policy strategy also showed consistent results for both studies.

Table 37 ACR50 Response at Week 24 Based on the Treatment Policy Estimand

	Response rate	Response rate difference compared to placebo (95% CI)
Study M16-011		
Placebo (n=481)	52 (10.8%)	20.5% (15.5%, 25.4%)
Risakizumab (n=483)	151 (31.3%)	
Study M15-998		
Placebo (n=219)	24 (11.0%)	14.5% (7.4%, 21.5%)
Risakizumab (n=224)	57 (25.5%)	

Source: Statistical Reviewer

ACR70

Table 38 shows proportion of subjects achieving ACR70 response at Week 24 by treatment group based on the same approach for ACR20 with regard to missing data and intercurrent events. There is a greater proportion of subjects achieving ACR70 response in the risakizumab group compared to the placebo group for both study M16-011 and study M15-998.

Table 38 ACR70 Response at Week 24 Based on the Composite Estimand

	Response rate	Response rate difference compared to placebo (95% CI)
Study M16-011		
Placebo (n=481)	23 (4.8%)	10.5% (6.8%, 14.3%)
Risakizumab (n=483)	74(15.3%)	
Study M15-998		
Placebo (n=219)	13 (5.9%)	6.1% (0.8%, 11.4%)
Risakizumab (n=224)	27 (12.1%)	

Source: [Statistical Reviewer and Table 14.2 3.13 of the Clinical Study Report R&D/20/1462 Risankizumab/Protocol M16-011 and Table 14.2 3.8 of the Clinical Study Report R&D/20/1461 Risankizumab/Protocol M15-998]

Table 39 shows the analysis results for ACR70 based on including all observed data and imputing subjects with missing outcomes as non-responder. For Study M16-011, though the difference between the treatment groups is smaller, the results are consistent with the main analysis. For study M15-998, while there was still a higher proportion of subjects who achieved ACR70 response on risakizumab group compared to placebo, the confidence interval for the difference did not exclude the null value.

Table 39 ACR70 Response at Week 24 Based on the Treatment Policy Estimand

	Response rate	Response rate difference compared to placebo (95% CI)
Study M16-011		
Placebo (n=481)	21 (4.4%)	9.9% (6.3%, 13.5%)
Risakizumab (n=483)	69 (14.3%)	
Study M15-998		
Placebo (n=219)	14 (6.4%)	5.2% (-0.1%, 10.5%)
Risakizumab (n=224)	26 (11.6%)	

Source: Statistical Reviewer

As for the primary analysis of ACR20, LOCF approach was used for both ACR50 and ACR70 to recalculate the composite score before imputing a subject as a non-responder, if the composite score was missing due to non-COVID reason. We have similar concerns regarding the use of LOCF to impute missing 24-Week data for these endpoints. An additional information request was sent to ask the Applicant to provide the analysis results for ACR50 and ACR70 that instead include the subjects with LOCF imputation as non-responder. The Applicant conducted a post-hoc analysis for the ACR50 and ACR70 at Week 24 that imputed these subjects as requested. Results from the post-hoc analysis are shown in Table 40. Compared to the pre-specified primary analysis results in Table 36 and Table 38, the estimated treatment difference between risakizumab and placebo is slightly smaller, but the conclusion is consistent.

Table 40 ACR50 and ACR70 Responses at Week 24 Imputing Subjects with LOCF as Non-Responder

Treatment	Responder 95% CI	Response Rate difference Compared to Placebo
M16-011		
ACR50		
Risankizumab (N=483)	154 (31.8%)	21.0% (16.1%, 25.9%)
Placebo (N=481)	52 (10.8%)	
ACR70		
Risakizumab ((N=483)	72 (14.9%)	10.1% (6.5%, 13.8%)
Placebo (n=481)	23 (4.7%)	
M15-998		
ACR50		
Risakizumab (N=224)	59 (26.3%)	16.6% (9.7%, 23.6%)
Placebo (N=219)	20 (9.3%)	
ACR70		
Risakizumab (n=224)	27 (12.0%)	6.0% (0.8%, 11.3%)
Placebo (n=219)	13 (5.9%)	

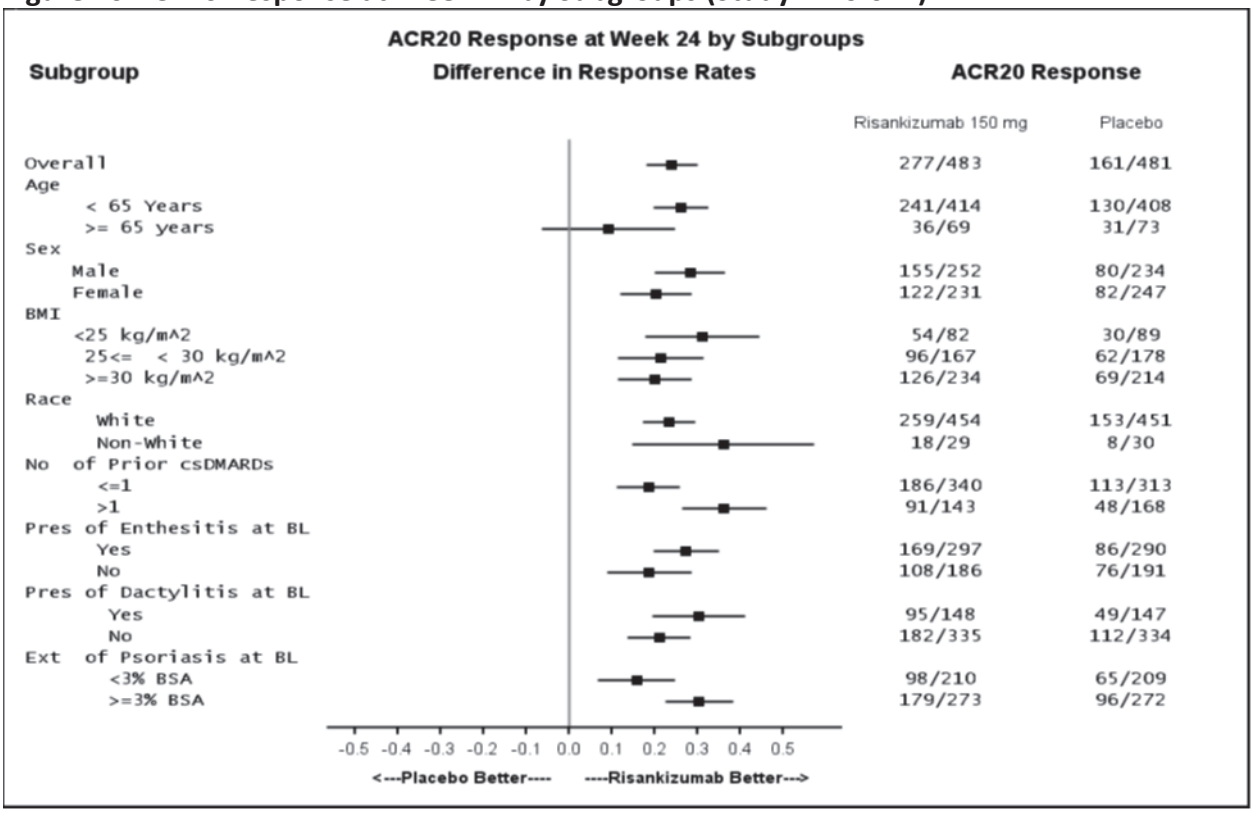
Source: Applicant's Response to FDA's December 15, 2021 Information Request Table 1

Additional Analyses Conducted on the Individual Trial

Subgroup analyses for demographics and key clinical characteristics were evaluated using the primary efficacy endpoint, ACR20. In addition to the common demographic factors such as gender, race, age and geographic region, subgroup analyses by stratification factors [current use of csDMARD (0 vs >= 1), presence of dactylitis (yes vs no), presence of enthesitis (yes vs no) and extent of psoriasis (>= 3% BSA or < 3% BSA) at baseline] were also included in the forest plots below for comparison. Note that the subgroup analyses results presented in this section are considered descriptive and no definitive conclusions can be drawn based on observed treatment differences between the subgroups.

Figure 9 shows summary and comparison of ACR20 response between risakizumab group and placebo at Week 24 for Study M16-011 by age, gender, BMI, race, and the stratification factors of current use of csDMARD (0 vs >= 1), presence of dactylitis (yes vs no), presence of enthesitis (yes vs no) and extent of psoriasis (>= 3% BSA or < 3% BSA) at baseline. The majority of the 95% CI of the difference of ACR20 response between the test and control groups in each subgroup considered in Figure 9 excluded 0. Only the CI of the difference of ACR20 for older than 65 years age group did not exclude 0 but still had numerically higher response rate in risakizumab group than in the placebo group. This subgroup had a small number of patients, and therefore, there is a lack of precision surrounding this estimate.

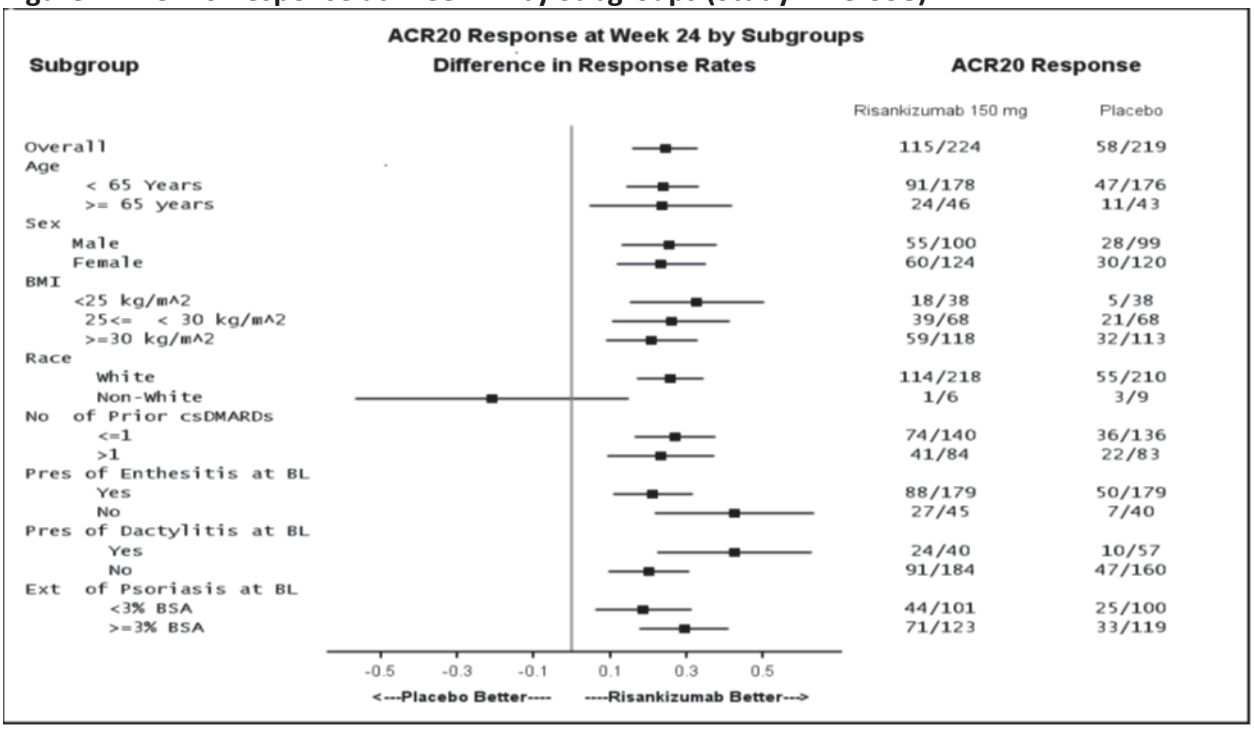
Figure 10 ACR20 Response at Week 24 by Subgroups (Study M16-011)



Source: Statistical Reviewer

Figure 10 shows summary and comparison of ACR20 response between risakizumab group and placebo at Week 24 for Study M15-998 by age, gender, BMI, race, and the stratification factors of current use of csDMARD (0 vs >= 1), presence of dactylitis (yes vs no), presence of enthesitis (yes vs no) and extent of psoriasis (>= 3% BSA or < 3% BSA) at baseline. With the exception of non-white subgroup, the 95% CI of the difference of ACR20 response between the risakizumab and placebo groups in each subgroup considered in **Figure 11** excluded 0. Only the non-White subgroup patients had numerically higher response rate in placebo group than in the Risakizumab group; however the number of observations is very small with wide confidence interval, limiting definitive conclusions.

Figure 11 ACR20 Response at Week 24 by Subgroups (Study M15-998)



Source: Statistical Reviewer

8.3.2. M16-002

The purpose of the request for the datasets for this phase 2 dose ranging study was to use the efficacy from the study to consider whether the loading dose in the phase 3 studies (same as Arm 2 in M16-002 - risankizumab 150 mg at week 0, 4, and 16) was required to show an effect at Week 16, compared to a dosign regimen that does not include a loading dose (Arm 3 - risankizumab 150 mg at week 0 and 12). For this purpose, the primary endpoint analysis is summarized below.

Efficacy Results – Primary endpoint

The primary endpoint was achieved in all risankizumab treatment arms. Patients in each of the risankizumab treatment arms experienced improvement in the signs and symptoms of psoriatic arthritis, as demonstrated by statistically significant differences in the proportion of patients who achieved ACR20 response at Week 16 in comparison to the placebo arm. The results for treatment arm 2 (risankizumab 150 mg administered at weeks 0, 4, and 16) and arm 3 (risankizumab 150 mg administered at weeks 0 and 12) are particularly notable because they demonstrate that efficacy of risankizumab can be achieved without an additional loading dose at week 4. This provides support for the chronic dosing regimen (every 12 weeks) proposed by the Applicant.

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Table 41 ACR20 Response Rate at Week 16 (Study M16-002)

Treatment Group	Responder	Response rate compared to placebo (90% CI*)	P-value*
Placebo (n=42)	15 (35.7%)		
Arms 1+2 (n=84)	50 (59.5%)	24.0% (9.3%, 38.7%)	0.007
Arm 1 (n=42)	24 (57.1)	21.8% (4.6%, 39.1%)	0.038
Arm 2 (n=42)	26 (61.9%)	26.4% (9.8%, 43.0%)	0.009
Arm 3 (n=39)	23 (59.0%)	23.1% (5.7%, 40.4%)	0.029
Arm 4 (n=20)	13 (65.0%)	28.5% (7.7%, 49.4%)	0.024

[Source:Statistical reviewer and Table 14.2_1.1 of Clinical Study Report R&D/17/0134 Risankizumab/Protocol M16-002 (1311.5)]
*Multiplicity control was not applied for this phase 2 study

8.4.Review of Safety

8.4.1 Safety Review Approach

The safety assessment of risankizumab in psoriatic arthritis is primarily based on safety data from the two phase 3 studies, studies M16-011 and M15-998. A summary of the key design features for these studies is presented in the Table of Clinical Studies (Section 7.1). Studies M16-011 and M15-998 enrolled patients with psoriatic arthritis who had comparable baseline demographics and disease characteristics to those of the targeted population in the United States. Each of the studies provided controlled comparisons between risankizumab 150 mg SC at week 0, 4, and every 12 weeks thereafter and placebo. Patients initially treated with placebo received treatment with risankizumab 150 mg SC at week 24. At week 28, and for the remaining dosing visits to week 208, all patients received risankizumab 150 mg SC every 12 weeks. The safety population included all randomized patients who received at least one dose of the study drug.

The safety profile of risankizumab was characterized based on a comprehensive evaluation of the phase 3 psoriatic arthritis placebo-controlled analysis set which includes patients who received risankizumab 150 mg or placebo during the 24-week placebo-controlled period in phase 3 studies M16-011 and M15-998, the phase 3 psoriatic arthritis long-term analysis set which includes patients who received at least one dose of risankizumab 150 mg in phase 3 studies M16-011 and M15-998, and the all risankizumab psoriatic analysis set which includes patients in the phase 2 and phase 3 psoriatic arthritis studies who received at least one dose of risankizumab. In addition, safety data from the 120-day safety update was reviewed and generally consistent with the safety presented in the initial summary of clinical safety.

8.4.2 Review of the Safety Database

Overall Exposure

The phase 3 psoriatic arthritis placebo-controlled analysis set includes data from 707 patients who received at least 1 dose of risankizumab for a median duration of 168.0 days. As shown in Table 41, the phase 3 psoriatic arthritis long-term analysis set includes data from 1,365 patients who received at least 1 dose of risankizumab for a mean duration of 420.4 days in the risankizumab group without cross over from placebo and 342.5 days in the any risankizumab group. Of these patients, 597 (43.7% in the Any Risankizumab group) had exposure to risankizumab for at least 12 months.

Table 42. Exposure to Study Drug by Duration Intervals through the Safety Update Report on March 1, 2021 (Phase 3 PsA Long-term Analysis Set)

Duration of Exposure	RZB 150 mg (No cross-over) N = 707 N (%)	Any RZB 150 mg N = 1365 N (%)
≥ 1 dose	707 (100)	1365 (100)
< 90 days (3 months)	5 (0.7)	10 (0.7)
≥ 90 days (3 months)	702 (99.3)	1355 (99.3)
≥ 180 days (6 months)	687 (97.2)	1197 (87.7)
≥ 360 days (12 months)	498 (70.4)	597 (43.7)
≥ 540 days (18 months)	89 (12.6)	90 (6.6)
≥ 720 days (24 months)	0	0
Mean duration (days)	420.4	342.5

N = number of patients; PsA = psoriatic arthritis; RZB = Risankizumab [Source: Reviewer; Adapted from 120-day SUR pg. 25]

The all risankizumab psoriatic arthritis analysis set includes data from 1,542 patients who received at least 1 dose of risankizumab for a median duration of 279.0 days. Of these patients, 464 (30.1%) had exposure to risankizumab for at least 12 months.

Adequacy of the safety database:

The psoriatic arthritis safety database is comprised of data from 707 patients exposed to risankizumab in the 24 week placebo-controlled period of the phase 3 studies, data from 1,365 patients exposed to at least one dose of risankizumab in the phase 3 studies, and data from 1,542 patients exposed to at least one dose of risankizumab in the phase 2 and phase 3 studies. Additional supportive safety data for risankizumab are provided by study M16-002 and the available data from risankizumab in psoriasis. The types of safety assessments conducted were consistent with reasonable monitoring for the known adverse events of risankizumab and for this patient population. Overall, the studies provide adequate data for drug exposure in the targeted patient population to support the safety assessment of risankizumab in patients with

psoriatic arthritis in the context of the established safety profile in the approved indication of plaque psoriasis.

8.4.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No concerns arose regarding data integrity and submission quality as related to the safety assessment.

Categorization of Adverse Events

In study M16-002, adverse events and serious adverse events were defined using standard definitions. An assessment of severity grade was made according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by OMERACT. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

In studies M16-011 and M15-998, adverse events and serious adverse events were defined using standard definitions. When criteria were available, events were graded according to the 5 criteria described in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. If no grading criteria were available for the reported event, an assessment of severity grade was made using mild, moderate, and severe categories. Adverse events were coded using MedDRA.

In study M16-002, hepatic injury was considered an adverse event of special interest (AESI). Hepatic injury was defined by the following alterations of hepatic laboratory parameters: an elevation of AST and/or ALT ≥ 3 fold upper limit of normal (ULN) combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood sample draw, and/or marked peak aminotransferase (AST and/or ALT) elevation ≥ 10 fold ULN.

In studies M16-011 and M15-998, the predefined areas of safety interest were major adverse cardiac events (MACE), infections, malignancies, hepatic events, injection site events, and hypersensitivity reactions.

Routine Clinical Tests

Clinical laboratory evaluations for studies M16-011 and M15-998 included:

- Hematology: hematocrit, hemoglobin, red blood cell count, white blood cell count, neutrophils, bands, lymphocytes, monocytes, basophils, eosinophils, platelet count, international normalized ratio
- Chemistry: blood urea nitrogen, creatinine, total bilirubin, direct and indirect bilirubin, alanine transaminase, aspartate transaminase, gamma glutamyl transferase, alkaline

phosphatase, sodium, potassium, calcium, cholesterol, total protein, glucose, LDL, HDL, triglycerides, albumin, chloride, bicarbonate, estimated glomerular filtration rate

- Urinalysis: specific gravity, ketones, pH, protein, blood, glucose, urobilinogen, bilirubin, leukocyte esterase, nitrite, microscopic (reflex)
- Anaphylaxis testing: tryptase, histamine, serum risankizumab concentrations, ADA/nAb
- Local labs: tuberculosis screen (PPD skin test), urine hCG for females
- Other tests: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis B virus DNA, hepatitis C antibody, hepatitis C virus RNA, HIV-1 and HIV-2 antibody, serum hCG for females, rheumatoid factor, anti-CCP antibodies, HsCRP, FSH, tuberculosis screen (QuantiFERON-TB Gold Test)

Clinical laboratory evaluations for study M16-002 included:

- Hematology: hematocrit, hemoglobin, red blood cell, reticulocyte count, white blood cell count, platelet count, neutrophils, eosinophils, basophils, monocytes, lymphocytes, bands, polymorphonuclear neutrophils, partial thromboplastin time, prothrombin time, international normalized ratio, fibrinogen
- Chemistry: glycosylated Hbc, aspartate transaminase, alanine transaminase, alkaline phosphatase, gamma glutamyl transferase, creatine kinase (CK), CK-MB if CK is elevated, lactic dehydrogenase, amylase, lipase, calcium, sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, uric acid, creatinine, estimated glomerular filtrate rate, bilirubin total, bilirubin direct, bilirubin indirect, troponin in case of elevated CK, total protein, albumin, HsCRP, total cholesterol, triglycerides, LDL, HDL
- Urinalysis: nitrite, protein, glucose, ketone, urobilinogen, bilirubin, red blood cells, white blood cells, pH, creatinine, sediment bacteria, casts, squamous epithelial cells, sediment crystals, sediment red blood cells, sediment white blood cells
- Other tests: urine hCG for females, serum hCG for females if urine test is positive, TSH, free T3 and free T4 in case of an abnormal TSH result, rheumatoid factor, anti-CCP antibodies, HLA-B27, hepatitis B surface antigen, hepatitis C antibodies, HIV-1 and HIV-2 antibody, QuantiFERON-TB, PPD skin test

8.4.4 Safety Results

An overview of the treatment-emergent adverse events (TEAEs) and exposure adjusted event rate (EAER per 100 patient years) in the phase 3 PsA placebo-controlled analysis set and phase 3 PsA long-term analysis set is presented in Table 42.

Table 43. Treatment-Emergent Adverse Events EAER per 100 PY (Phase 3 PsA PBO-Controlled Analysis Set) and Comparison with Long-term Risankizumab Treatment (Phase 3 PsA Long-term Analysis Set)

	Phase 3 PsA PBO-Controlled Analysis Set					Phase 3 PsA Long-term Analysis Set
Event	**Placebo N = 700, PY = 325.1**		**Risankizumab N = 707, PY = 328.5**		**Comparison**	**Any RZB N = 1365 PY = 1047.9**
	N (%)	**Events (E/100 PY)**	**N (%)**	**Events (E/100 PY)**	**(%) Difference RZB - PBO (95% CI)**	**Events (E/100 PY)**
Any TEAE	307 (43.9)	688 (211.6)	322 (45.5)	689 (209.7)	1.6 (-3.5, 6.8)	1759 (167.9)
COVID-19 related TEAE	2 (0.3)	2 (0.6)	2 (0.3)	2 (0.6)	0.0 (-0.6, 0.6)	39 (3.7)
Study drug related TEAE	88 (12.6)	178 (54.8)	91 (12.9)	166 (50.5)	0.3 (-3.2, 3.7)	367 (35.0)
Serious TEAE	31 (4.4)	38 (11.7)	21 (3.0)	29 (8.8)	-1.5 (-3.4, 0.5)	79 (7.5)
Severe TEAE	17 (2.4)	21 (6.5)	16 (2.3)	23 (7.0)	-0.2 (-1.8, 1.4)	47 (4.5)
TEAE → D/C	10 (1.4)	11 (3.4)	6 (0.8)	9 (2.7)	-0.6 (-1.7, 0.5)	18 (1.7)
TEAE → Death	0	0	1 (0.1)	1 (0.3)	0.1 (-0.1, 0.4)	1 (< 0.1)
All Deaths	0	0	1 (0.1)	1 (0.3)	0.1 (-0.1, 0.4)	1 (< 0.1)
COVID-19 related deaths	0	0	0	0	0	0
Deaths ≤ 140 days after last dose of drug	0	0	1 (0.1)	1 (0.3)	0.1 (-0.1, 0.4)	1 (< 0.1)
Deaths > 140 days after last dose of drug	0	0	0	0	0	0

D/C = discontinuation; EAER = exposure adjusted event rate; N = number of patients; PBO = placebo; PsA = psoriatic arthritis; PY = patient years; RZB = Risankizumab; TEAE = treatment emergent adverse event [Source: Reviewer; Adapted from Summary of Clinical Safety pg. 35-36]

Deaths

There was 1 death in the placebo controlled analysis set. The death occurred ≤ 140 days after the last dose of study drug. The patient was 81 years old and hospitalized for pneumonia on post-treatment day 62 (enrolled in Study M16-011). The patient later developed urosepsis on post-treatment day 96 resulting in death. The event of urosepsis was assessed by the investigator and Applicant as having no reasonable possibility of being related to study drug. There were no additional deaths in the phase 3 PsA long-term analysis set and no non-treatment emergent deaths. The exposure adjusted death rate with long-term risankizumab exposure was < 0.1 E/100 PY.

No additional deaths were reported through March 1, 2021 in the 120-day safety update.

Serious Adverse Events

The number and proportion of patients with serious TEAEs was higher in the placebo group (31 patients or 4.4% in the placebo group vs 21 patients or 3.0% in the risankizumab group). The rate of serious TEAEs was higher in the placebo group (11.7 E/100 PY in the placebo group vs 8.8 E/100 PY in the risankizumab group), and the rate of serious TEAEs was stable with long-term risankizumab exposure (8.8 E/100 PY in the placebo-controlled analysis set vs 7.5 E/100 PY in the long-term analysis set).

A total of 67 patients in the all risankizumab analysis set experienced serious TEAEs. Infections and infestations were the most common serious TEAEs and occurred in 26 patients (1.7%). All other serious TEAEs occurred in less than 1% of patients.

In the 120-day safety update, the rate of serious AEs in the long-term analysis set was stable at 7.9 E/100 PY as compared to 7.5 E/100 PY in the original submission.

Dropouts and/or Discontinuations Due to Adverse Effects

Few patients discontinued the study drug due to TEAEs. The number and proportion of patients who discontinued the study drug due to TEAEs was slightly higher in the placebo group (10 patients or 1.4% in the placebo group vs 6 patients or 0.8% in the risankizumab group). The rate of discontinuation was low and stable with long-term risankizumab exposure (2.7 E/100 PY in the placebo-controlled analysis set vs 1.7 E/100 PY in the long-term analysis set).

In the 120-day safety update, 16 patients (2.3%) treated with risankizumab without cross-over from placebo experienced TEAEs leading to study drug discontinuation (2.3 E/100 PY). 22 patients (1.6%) treated with any risankizumab experienced TEAEs leading to study drug discontinuation (2.0 E/100 PY).

Significant Adverse Events

In studies M16-011 and M15-998, the predefined areas of safety interest were major adverse cardiac events (MACE), infections, malignancies, hepatic events, injection site events, and hypersensitivity reactions.

The number of patients, percentage of patients, and overall event rate of treatment-emergent areas of safety interest were generally similar in the placebo and risankizumab groups as shown in Tables 43 and 44. However, numerical imbalances in hypersensitivity and hepatic events were seen and investigated further.

Table 44. Number and Percentage of Patients with Treatment-Emergent Areas of Safety Interest (Phase 3 PsA Placebo-Controlled Analysis Set)

Area of Safety Interest	Placebo (N = 700) N (%)	Risankizumab (N = 707) N (%)	Comparison (%) Difference (95% CI)
Adjudicated MACE	0	1 (0.1)	0.1 (-0.1, 0.4)
Extended MACE	1 (0.1)	1 (0.1)	0.0 (-0.4, 0.4)
Serious infections	11 (1.6)	7 (1.0)	-0.6 (-1.8, 0.6)
Active tuberculosis	0	0	0
Opportunistic infection excluding tuberculosis and herpes zoster	0	0	0
Herpes zoster	2 (0.3)	2 (0.3)	0.0 (-0.6, 0.6)
Any malignant tumors	3 (0.4)	1 (0.1)	-0.3 (-0.8, 0.3)
Non-melanoma skin cancer	1 (0.1)	1 (0.1)	0.0 (-0.4, 0.4)
Malignant tumors excluding NMSC	2 (0.3)	0	-0.3 (-0.7, 0.1)
Hypersensitivity	9 (1.3)	16 (2.3)	1.0 (-0.4, 2.3)
Serious hypersensitivity	0	0	0
Adjudicated anaphylaxis	0	0	0
Hepatic events	27 (3.9)	38 (5.4)	1.5 (-0.7, 3.7)

CI = confidence interval; Extended MACE = extended major cardiac event (defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, and coronary revascularization procedures; MACE = major adverse cardiac event (defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke); N = number of patients; NMSC = non-melanoma skin cancer [Source: Reviewer; Adapted from Summary of Clinical Safety pg 52-53]

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

Table 45. Exposure-Adjusted Event Rate (per 100 PY) of Treatment-Emergent Areas of Safety Interest in the Phase 3 PsA Placebo-Controlled Analysis Set and Comparison to the Long-term Analysis Set

	PBO-Controlled Analysis Set			Long-term Analysis Set
Area of Safety Interest	Placebo (N = 700) PYs = 325.1 Events (E/100 PYs)	Risankizumab (N = 707) PYs = 328.5 Events (E/100 PYs)	Comparison Rate Difference (95% CI)	Any RZB N = 1365 PY = 1047.9 Events (E/100 PYs)
Adjudicated MACE	0	1 (0.3)	0.3 (-0.3, 0.9)	3 (0.3)
Extended MACE	1 (0.3)	1 (0.3)	0.0 (-0.8, 0.8)	3 (0.3)
Serious infections	13 (4.0)	9 (2.7)	-1.3 (-4.1, 1.6)	27 (2.6)
Active tuberculosis	0	0	0	0

	PBO-Controlled Analysis Set			Long-term Analysis Set
Area of Safety Interest	**Placebo (N = 700) PYs = 325.1 Events (E/100 PYs)**	**Risankizumab (N = 707) PYs = 328.5 Events (E/100 PYs)**	**Comparison Rate Difference (95% CI)**	**Any RZB N = 1365 PY = 1047.9 Events (E/100 PYs)**
Opportunistic infection excluding tuberculosis and herpes zoster	0	0	0	1 (< 0.1)
Herpes zoster	2 (0.6)	2 (0.6)	0.0 (-1.2, 1.2)	4 (0.4)
Any malignant tumors	5 (1.5)	1 (0.3)	-1.2 (-2.7, 0.2)	8 (0.8)
Non-melanoma skin cancer	3 (0.9)	1 (0.3)	-0.6 (-1.8, 0.6)	6 (0.6)
Malignant tumors excluding NMSC	2 (0.6)	0	-0.6 (-1.5, 0.2)	2 (0.2)
Hypersensitivity	10 (3.1)	18 (5.5)	2.4 (-0.8, 5.6)	44 (4.2)
Serious hypersensitivity	0	0	0	0
Adjudicated anaphylaxis	0	0	0	0
Hepatic events	41 (12.6)	55 (16.7)	4.2 (-1.7, 10.0)	129 (12.3)

CI = confidence interval; E = events; Extended MACE = extended major cardiac event (defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, and coronary revascularization procedures; MACE = major adverse cardiac event (defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke); N = number of patients; NMSC = non-melanoma skin cancer; PY(s)= patient year(s); RZB = Risankizumab [Source: Reviewer; Adapted from Summary of Clinical Safety pg 52-53]

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

MACE

MACE was defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Extended MACE was defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina and coronary revascularization procedures.

In the placebo-controlled analysis set, 1 patient experienced a MACE (non-fatal stroke) in the risankizumab group. The patient was 70 years old with a history of hypertension. The event was considered unrelated to the study drug by both the investigator and Applicant. 1 patient in the placebo group experienced an extended MACE of hospitalization for unstable angina.

In the long-term analysis set, 2 MACE of non-fatal myocardial infarction were reported with long-term risankizumab exposure. One of the patients had a history of smoking and dyslipidemia. The other patient had a history of smoking, coronary artery disease with previous

myocardial infraction and coronary stent, hyperlipidemia, and hypertension. Both cases were considered unrelated to study drug by both the investigator and Applicant. There were no additional cases of extended MACE.

The MACE rate (0.3 E/100 PY) was stable with long-term risankizumab exposure and within the range anticipated for the patient population (0.46 E/100 PY[7]). Overall, the data did not suggest an increased risk of MACE with risankizumab treatment in patients with psoriatic arthritis.

In the 120-day safety update, the rate of any adjudicated MACE was stable at 0.2 E/100 PY.

Infections

In the placebo-controlled analysis set (treatment duration of 24 weeks), 19.0% of patients in the risankizumab experienced infection adverse events compared to 19.3% of patients in the placebo group. The most common infections in the risankizumab group were upper respiratory tract infections (4.1%), nasopharynigitis (3.5%), and gastroenteritis (1.0%).

In the long-term analysis set, the overall rates of infection were stable with long-term risankizumab exposure. The most common infections in the any risankizumab group were nasopharyngitis (65 events), upper respiratory tract infections (61 events), COVID-19 (32 events), urinary tract infection (17 events), and gastroenteritis (15 events). The majority of events were nonserious and mild to moderate in severity.

The number and rate of serious infections was lower in the risankizumab group (9 events with a rate of 2.7 E/100 PYs) compared to the placebo group (13 events with a rate of 4.0 E/100 PYs). The rate of serious infections was stable with long-term risankizumab exposure. Cellulitis was the most common serious infection (0.3%) for patients treated with risankizumab in the placebo-controlled analysis set. Pneumonia (0.4%) and COVID-19 (0.4%) were the most common serious infections for patients in the long-term analysis set.

There were no opportunistic infections for either treatment group in the placebo-controlled analysis set. One event (< 0.1 E/100 PY) of opportunistic infection was reported with long-term risankizumab exposure. The patient was an 84 year old woman with history of chronic use of inhaled steroids for seasonal allergies. The patient developed an oral fungal infection.

There were no cases of active tuberculosis infection reported in the psoriatic arthritis development program across the analysis sets. The number and rate of herpes zoster infections was the same in both the placebo and risankizumab groups (2 events with a rate of 0.6 E/100 PY), and the rate was stable with long-term exposure (0.4 E/100 PY).

[7] Li L, Hagberg KW, Peng M, Shah K, Paris M, Jick S. Rates of Cardiovascular Disease and Major Adverse Cardiovascular Events in Patients With Psoriatic Arthritis Compared to Patients Without Psoriatic Arthritis. J Clin Rheumatol. 2015 Dec;21(8):405-10.

In the 120-day safety update, the rate of serious infection was stable at 2.6 E/100 PY as compared to 2.6 E/100 PY in the Phase 3 PsA Long-term Analysis Set. Three additional patients developed herpes zoster (reported in 7 patients total; rate of 0.5 E/100 PY) compared to the original submission (reported in 4 patients total; rate of 0.4 E/100 PY). One additional patient developed an opportunistic infection reported as oropharyngeal candidiasis, and the rate of opportunistic infection was low at 0.2 E/100 PY (2 patients) as compared to < 0.1 E/100 PY (1 patient) in the original submission. No cases of active tuberculosis were reported.

Non-Melanoma Skin Cancer (NMSC)

In the placebo-controlled analysis set, 1 patient in the risankizumab reported basal cell carcinoma and 1 patient in the placebo group reported Bowen's disease.

The rate of non-melanoma skin cancer with long-term risankizumab exposure was 0.6 E/100 PY. The rate is similar to the epidemiologic reference rate of non-melanoma skin cancer in the psoriatic arthritis population (0.61 E/100 PY[8]), and the rate is comparable to that observed in the psoriasis development program (0.7 E/100 PY).

In the 120-day safety update, 1 additional patient developed NMSC. The overall rate of NMSC was stable at 0.5 E/100 PY as compared to 0.6 E/100 PY in the original submission.

Malignancies excluding NMSC

In the placebo-controlled analysis set, no malignancies excluding NMSC were reported in patients in the risankizumab group. Two malignancies were reported in the placebo group (breast cancer and non-small cell lung cancer).

A total of 2 malignancies were reported with long-term exposure (acral lentiginous melanoma reported 78 days after first risankizumab exposure, and papillary thyroid cancer reported 177 days after first risankizumab exposure). The time-to-onset of both events was considered by the Applicant to be biologically implausible for a causal role of risankizumab.

The rate of malignancies excluding NMSC with long-term risankizumab exposure was 0.2 E/100 PY. The rate is lower than the epidemiologic reference rate of malignancies (excluding NMSC) in the psoriatic arthritis population (0.48 E/100 PY[8]), and the rate is lower than the rate observed in the psoriasis development program (0.6 E/100 PY).

In the 120-day safety update, 2 additional patients developed malignancy. The overall rate of malignancy was stable at 0.3 E/100 PY as compared to 0.2 E/100 PY in the original submission.

[8] Vaengebjerg S, Skov L, Egeberg A, Loft ND. Prevalence, Incidence, and Risk of Cancer in Patients With Psoriasis and Psoriatic Arthritis: A Systematic Review and Meta-analysis. JAMA Dermatol. 2020 Apr 1;156(4):421-429.

Hypersensitivity Reactions

In the placebo-controlled analysis set, the number and percentage of patients in the risankizumab group with hypersensitivity reactions (16 patients, 2.3%) was higher than the placebo group (9 patients, 1.3%). No patients had serious hypersensitivity reactions or adjudicated anaphylactic reactions.

The Applicant notes that some of the preferred terms in the hypersensitivity reaction SMQ include events that are known adverse reactions, such as injection site reaction. Additionally, some preferred terms such as contact dermatitis and allergic rhinitis suggest alternative etiologies. The Applicant notes that if these events were excluded from the analysis, then the percentage of patients with hypersensitivity reactions in the risankizumab group would be 1.8% compared to 1.0% of patients in the placebo group.

The rate of hypersensitivity reactions was stable with long-term risankizumab exposure (4.2 E/100 PY) compared to the placebo-controlled analysis set (5.5 E/100 PY), but higher than the rate seen in patients treated with placebo (3.1 E/100 PY). The hypersensitivity reactions were generally mild. The most common hypersensitivity reaction was rash (1.4 E/100 PY in patients who received risankizumab without cross-over from placebo, 1.2 E/100 PY in patients who received any risankizumab). There were no serious hypersensitivity reactions or adjudicated anaphylactic reactions with long-term risankizumab exposure.

Among the patients who had antidrug antibody (ADA) tests available in the long-term analysis set, the incidence of hypersensitivity reactions was numerically higher in ADA positive patients (6.3%) compared to ADA negative patients (3.8%).

In the all risankizumab analysis set, 1 patient enrolled in the phase 2 dose-ranging study M16-002 had a serious hypersensitivity reaction (anaphylactic reaction). This biologic naïve patient without any past history of atopy experienced symptoms of dizziness and weakness followed by nausea, anxiety, and macular rash on the thorax and neck. The patient was randomized to receive 150 mg every 4 weeks, but the anaphylactic event occurred on Day 1 of treatment. The event was considered by the investigator to have a reasonable possibility of relationship to study drug.

The results with long-term risankizumab treatment in the psoriatic arthritis clinical studies were lower than the rate of hypersensitivity reactions in the psoriasis program (5.2 E/100 PY). No cases were adjudicated as an anaphylactic reaction in the psoriasis program.

In the 120-day safety update, 7 additional patients developed hypersensitivity reactions. The overall rate of hypersensitivity reactions was stable at 3.9 E/100 PY as compared to 4.2 E/100 PY in the original submission. No cases of serious hypersensitivity or anaphylaxis were reported.

Hepatic events

In the placebo-controlled analysis set, the percentage of patients with investigator reported hepatic TEAEs was higher in the risankizumab group (5.4%) compared to the placebo group (3.9%). The rate of hepatic events for patients in the risankizumab group was 16.7 E/100 PY compared to 12.6 E/100 PY for patients in the placebo group. The most common hepatic TEAEs were ALT increase, AST increase, and GGT increase in both groups. There were no serious hepatic events reported. There were no confirmed events meeting biochemical Hy's law.

In the long-term analysis set, the rate of hepatic events was 12.3 E/100 PY. The most common hepatic TEAEs with rates ≥ 1 E/100 PY were ALT increase, AST increase, GGT increase, hepatic steatosis, hepatic enzyme increase, and transaminase increase. There were no serious hepatic events reported. There were no confirmed events meeting biochemical Hy's law.

There was a single case associated with biochemical Hy's law which was confounded by a confirmed positive Hepatitis E IgM serology and excessive alcohol use. Therefore, the case was not deemed to be attributable to risankizumab.

The Drug-Induced Liver Injury (DILI) team within the Division of Hepatology and Nutrition was consulted regarding the increased incidence of hepatic events observed in the phase 3 trials of risankizumab in patients with psoriatic arthritis. The DILI review team agreed that more transaminase elevations were seen in the risankizumab arms compared to placebo, and noted that there were imbalances in peak transaminases over 3x ULN (ALT: 2.9% in placebo versus 3.3% in risankizumab) and 5x ULN (ALT: 0.8% in placebo versus 1.7% in risankizumab) in one phase 3 study (M16-011, n = 964) but not the other (M15-998, n = 440). In M16-011, risankizumab interaction with, or in addition to, other medications known to cause DILI may have contributed. Five cases of liver injury were attributable to isoniazid over risankizumab. The number of patients on isoniazid was equal between arms, but none in the placebo arm had liver injury. The risankizumab label for psoriasis patients also mentions two patients with liver injury due to isoniazid. Study M15-998 may not have been powered to see an isoniazid and risankizumab interaction. The DILI team determined that labeling for hepatotoxicity should be informative of the liver enzyme elevations seen in the clinical trials, and mention of isoniazid liver injury when given concomitantly with risankizumab may be considered.

In the psoriasis program, the most common hepatic TEAEs in the initial filing were related to liver enzyme elevations. In the updated analysis set for the psoriasis program, there were 7 additional serious hepatic events which had clear alternative etiologies. There were 5 patients with lab values meeting criteria for biochemical Hy's law, and these patients had alternative etiologies so the lab abnormalities were not attributed to risankizumab.

- Patient 9400486 experienced a serious adverse event of liver injury associated with Grade 3 lab elevations of ALT, AST, and total bilirubin along with alkaline phosphatase (> 6 x ULN) and GGT (> 25 x ULN) elevations reported four months after the last dose of risankizumab. The case is confounded by use of medications with known hepatotoxic

potential (atorvastatin and amiodarone; started approximately 2 months prior to liver injury) and history of alcohol use.

- Patient (b) (6) experienced Grade 4 lab elevations of ALT and AST in addition to Grade 3 elevation of total bilirubin meeting criteria for potential Hy's law 1 month after the last dose of risankizumab. A diagnosis of fulminant autoimmune hepatitis and steatohepatitis was made on liver biopsy. The patient also had a history of hypothyroidism.

- Patient (b) (6) experienced Grade 1-2 elevations of ALT and Grade 1 elevation of AST in addition elevation of total bilirubin (2.08 x ULN); however, the lab elevations were not concurrent. The case is confounded by elevation of liver enzymes at baseline.

- Patient (b) (6) had normal aminotransferase levels through two treatment periods of risankizumab totaling 381 days on treatment (separated by a placebo period). On the last day of treatment, day 575, the patient experienced elevations of ALT, AST, and total bilirubin.

- Patient (b) (6) experienced Grade 3 elevations in ALT, AST, and bilirubin meeting criteria for potential Hy's law on treatment day 743. The patient was diagnosed with bile duct cancer which is considered the most likely cause of elevated LFTs and unrelated to risankizumab by the investigator.

In the 120-day safety update, 14 additional patients developed hepatic events. The rate of hepatic events was lower at 10.9 E/100 PY as compared to 12.3 E/100 PY in the original submission. Consistent with the original submission, there were no laboratory values in the safety update report meeting criteria for biochemical Hy's law with risankizumab treatment.

Treatment Emergent Adverse Events

The number and proportion of patients with a TEAE was similar in the placebo and risankizumab groups in the phase 3 PsA PBO-controlled analysis set (307 patients or 43.9% in the placebo group vs 322 patients or 45.5% in the risankizumab group). The number and proportion of patients with severe TEAEs was similar in both groups (17 patients or 2.4% in the placebo group vs 16 patients or 2.3% in the risankizumab group).

The rate of TEAEs with stable with long-term risankizumab exposure with no increase in the rate of TEAEs, TEAEs related to study drug, serious TEAEs, severe TEAEs, or TEAEs leading to discontinuation of the study drug. There was an increase in the rate of COVID-19 related events, which the Applicant attributes to the timing of the pandemic in relation to study conduct.

The most frequently reported adverse events were in the infections and infestations system organ class (19.3% in the placebo group vs 19.0% in the risankizumab group) and the

musculoskeletal and connective tissue disorders system organ class (8.7% in the placebo group vs 9.6% in the risankizumab group). The most frequently reported adverse events by preferred term within the infections and infestations system organ class were nasopharyngitis, upper respiratory tract infection, and gastroenteritis. These preferred terms were similar in the placebo and risankizumab groups. The most frequently reported adverse events by preferred term within the musculoskeletal and connective tissue disorders system organ class were arthralgia and psoriatic arthropathy. These preferred terms were similar in the placebo and risankizumab groups. Of note, there were numerical increases in the report of GGT increase, ALT increase, and AST increase when comparing Risankizumab to placebo.

There were no TEAEs by preferred term that occurred in ≥ 5% of patients in any treatment group. TEAEs that occurred in ≥ 1% of patients by preferred term in the risankizumab group are shown in Table 45.

Table 46. TEAEs Reported in ≥ 1% of Patients in the Risankizumab Group by Decreasing Frequency (Phase 3 PBO-Controlled Analysis Set)

MedDRA Preferred Term	Placebo (N = 700) N (%) [SSA %]	Risankizumab (N = 707) N (%) [SSA %]
Upper respiratory tract infection	32 (4.6) [4.6]	29 (4.1) [4.1]
Nasopharynigitis	23 (3.3) [3.3]	25 (3.5) [3.5]
Hypertension	15 (2.1) [2.1]	19 (2.7) [2.7]
ALT increased	12 (1.7) [1.7]	16 (2.3) [2.3]
Arthralgia	15 (2.1) [2.1]	15 (2.1) [2.1]
Headache	16 (2.3) [2.3]	15 (2.1) [2.1]
Psoriatic arthropathy	17 (2.4) [2.4]	15 (2.1) [2.1]
AST increased	9 (1.3) [1.3]	13 (1.8) [1.8]
Nausea	9 (1.3) [1.3]	9 (1.3) [1.3]
Abdominal pain upper	1 (0.1) [0.1]	8 (1.1) [1.1]
GGT increased	5 (0.7) [0.7]	8 (1.1) [1.1]
Diabetes mellitus	7 (1.0) [1.0]	7 (1.0) [1.0]
Diarrhea	11 (1.6) [1.6]	7 (1.0) [1.0]
Dizziness	4 (0.6) [0.6]	7 (1.0) [1.0]
Gastroenteritis	7 (1.0) [1.0]	7 (1.0) [1.0]

[Source: Reviewer; Adapted from the Summary of Clinical Safety pg. 38]

Laboratory Findings

Hematology

- Hemoglobin

Grade 3 hemoglobin was defined as values from 65.0 to < 80 g/L. Grade 4 hemoglobin was defined as values < 65.0 g/L.

In the placebo-controlled analysis set, a total of 4 patients (0.6%) in the placebo group reported hemoglobin values of Grade 3 (3 patients) or Grade 4 (1 patient). No patients in the risankizumab group reported hemoglobin values of Grade 3 or Grade 4.

In the long-term analysis set, no patients in the risankizumab group without cross-over from placebo reported hemoglobin values of Grade 3 or Grade 4. In the any risankizumab group, 1 patient (< 0.1%) reported hemoglobin of Grade 3 and 1 patient (< 0.1%) reported hemoglobin of Grade 4.

- Platelets

Grade 3 platelets were defined as values from 25.0 to < 50.0 x 10^9/L. Grade 4 platelets were defined as values < 25.0 x 10^9/L.

In the placebo-controlled analysis set, 1 patient (0.1%) in the placebo group reported platelet of Grade 3 and no patients reported platelets of Grade 4. No patients in the risankizumab group reported platelets of Grade 3 or Grade 4.

In the long-term analysis set, no patients in the risankizumab group without cross-over from placebo and no patients in the any risankizumab group reported platelets of Grade 3 or Grade 4.

- Leukocytes

Grade 3 leukocytes were defined as values from 1.0 to < 2.0 x 10^9/L. Grade 4 leukocytes were defined as values < 1.0 x 10^9/L.

In the placebo-controlled analysis set, 2 patients (0.3%) in the placebo group reported leukocytes of Grade 3 and no patients reported leukocytes of Grade 4. No patients in the risankizumab group reported leukocytes of Grade 3 or 4.

In the long-term analysis set, no patients in the risankizumab group without cross-over from placebo and no patients in the any risankizumab group reported leukocytes of Grade 3 or Grade 4.

- Neutrophils

Grade 3 neutrophils were defined as values from 0.5 to < 1.0 x 10^9/L. Grade 4 neutrophils were defined as values < 0.5 x 10^9/L.

In the placebo-controlled analysis set, 2 patients (0.3%) in the placebo group reported neutrophils of Grade 3 and no patients reported neutrophils of Grade 4. In the risankizumab group, 3 patients (0.4%) reported neutrophils of Grade 3 and no patients reported neutrophils

of Grade 4.

In the long-term analysis set, 3 patients (0.4%) in the risankizumab group without cross-over from placebo and 3 patients (0.2%) in the any risankizumab group reported neutrophils of Grade 3. No patients in either group reported neutrophils of Grade 4.

- Lymphocytes

Grade 3 lymphocytes were defined as values from 0.2 to < 0.5 x 10^9/L. Grade 4 lymphocytes were defined as values < 0.2 x 10^9/L.

In the placebo-controlled analysis set, 4 patients (0.6%) in the placebo group reported lymphocytes of Grade 3 and no patients reported lymphocytes of Grade 4. In the risankizumab group, 2 patients (0.3%) reported lymphocytes of Grade 3 and no patients reported lymphocytes of Grade 4.

In the long-term analysis set, 2 patients (0.3%) in the risankizumab group without cross-over from placebo and 2 patients (0.1%) in the any risankizumab group reported lymphocytes of Grade 3. No patients in either group reported lymphocytes of Grade 4.

Chemistry

- Creatinine

Grade 3 creatinine was defined as values from 3.0 x ULN to ≤ 6.0 x ULN or 3.0 x baseline. Grade 4 creatinine was defined as values > 6.0 x ULN. In the placebo-controlled analysis set, 3 patients (0.4%) in the placebo group reported creatinine of Grade 3 and no patients reported creatinine of Grade 4. No patients in the risankizumab group reported creatinine of Grade 3 or Grade 4.

In the long-term analysis set, no patients in the risankizumab group without cross-over from placebo reported creatinine of Grade 3 or Grade 4. In the any risankizumab group, 2 patients (0.1%) reported creatinine of Grade 3 and no patients reported creatinine of Grade 4.

- Calcium

Grade 3 hypocalcemia was defined as values from 1.5 to ≤ 1.75 mmol/L. Grade 4 hypocalcemia was defined as values < 1.5 mmol/L. Grade 3 hypercalcemia was defined as values from 3.1 to ≤ 3.4 mmol/L. Grade 4 hypercalcemia was defined as values > 3.4 mmol/L.

In the placebo-controlled analysis set, no patients in the placebo or risankizumab groups reported Grade 3 or Grade 4 hypocalcemia, and no patients reported Grade 3 or Grade 4 hypercalcemia.

In the long-term analysis set, no patients in the risankizumab group without cross-over from placebo or the any risankizumab group reported Grade 3 or Grade 4 hypocalcemia. No patients reported Grade 3 or Grade 4 hypercalcemia.

- Sodium

Grade 3 hyponatremia was defined as values from 120 to ≤ 130 mmol/L. Grade 4 hyponatremia was defined as values < 120 mmol/L. Grade 3 hypernatremia was defined as values from 155 to ≤ 160. Grade 4 hypernatremia was defined as values > 160 mmol/L.

In the placebo-controlled analysis set, 2 patients (0.3%) in the placebo group and 2 patients (0.3%) in the risankizumab group reported hyponatremia of Grade 3. No patients in either group reported hyponatremia of Grade 4. No patients in either group reported hypernatremia of Grade 3 or Grade 4.

In the long-term analysis set, 2 patients (0.3%) in the risankizumab group without cross-over from placebo and 2 patients (0.1%) in the any risankizumab group reported hyponatremia of Grade 3 and no patients reported hyponatremia of Grade 4. No patients in either group reported hypernatremia of Grade 3 or Grade 4.

- Potassium

Grade 3 hypokalemia was defined as values from 2.5 to ≤ 3.0 mmol/L. Grade 4 hypokalemia was defined as values < 2.5 mmol/L. Grade 3 hyperkalemia was defined as values from 6.0 to ≤ 7.0 mmol/L. Grade 4 hyperkalemia was defined as values > 7.0 mmol/L.

In the placebo-controlled analysis set, no patients in either group reported hypokalemia of Grade 3 or Grade 4. In the placebo group, no patients reported hyperkalemia of Grade 3 and 1 patient (0.1%) reported hyperkalemia of Grade 4. In the risankizumab group, 2 patients (0.3%) reported hyperkalemia of Grade 3 and no patients reported hyperkalemia of Grade 4.

In the long-term analysis set, 1 patient (0.1%) in the risankizumab group without cross-over from placebo and 1 patient (< 0.1%) in the any risankizumab group reported hypokalemia of Grade 3. No patients reported hypokalemia of Grade 4. 3 patients (0.4%) in the risankizumab group without cross-over from placebo and 5 patients (0.4%) in the any risankizumab group reported Grade 3 hyperkalemia. No patients in either group reported Grade 4 hyperkalemia.

- Glucose

Grade 3 hypoglycemia was defined as values from 1.7 to ≤ 2.2 mmol/L. Grade 4 hypoglycemia was defined as values from < 1.7 mmol/L. Grade 3 hyperglycemia was defined as values from 13.9 to ≤ 27.8 mmol/L. Grade 4 hyperglycemia was defined as values > 27.8 mmol/L.

In the placebo-controlled analysis set, no patients in either group reported hypoglycemia of Grade 3 or Grade 4. 10 patients (1.4%) reported hyperglycemia of Grade 3 and no patients reported hyperglycemia of Grade 4. In the risankizumab group, 19 patients (2.7%) reported hyperglycemia of Grade 3 and 1 patients (0.1%) reported hyperglycemia of Grade 4.

In the long-term analysis set, no patients in the risankizumab group without cross-over from placebo reported hypoglycemia of Grade 3 or Grade 4. No patients in the any risankizumab group reported hypoglycemia of Grade 3 and 1 patient (< 0.1%) reported hypoglycemia of Grade 4. 32 patients (4.5%) in the risankizumab group without cross-over from placebo and 36 patients (2.6%) in the any risankizumab group reported Grade 3 hyperglycemia. 1 patient (0.1%) in the risankizumab group without cross-over from placebo and 1 patient (< 0.1%) in the any risankizumab group reported Grade 4 hyperglycemia.

- Albumin

Grade 3 albumin was defined as values < 20 g/L.

In the placebo-controlled analysis set, 1 patient (0.1%) in the placebo group reported albumin of Grade 3. No patients in the risankizumab group reported albumin of Grade 3.

In the long-term analysis set, no patients in the risankizumab group without cross-over from placebo and no patients in the any risankizumab group reported albumin of Grade 3.

Liver Function Tests

Table 46 shows potentially clinically significant liver test values from patients in the placebo-controlled analysis set. The number and percentage of patients with potentially clinically significant elevations of ALT, AST, and alkaline phosphate was higher in the risankizumab group. No patients in either group had ALT or AST elevations ≥ 20 x ULN. No patients in either group had elevation of total bilirubin ≥ 2 x ULN. No patients in either group had ALT or AST elevations ≥ 3 x ULN with concomitant elevation of total bilirubin ≥ 1.5 x ULN.

Table 47. Summary of Potentially Clinically Significant Liver Test Values (Phase 3 PsA PBO-Controlled Analysis Set)

Criteria	Placebo (N = 700) n/N_OBS (%)	Risankizumab (N = 707) n/N_OBS (%)	Comparison (95% CI)
ALT ≥ 3 x ULN	17/693 (2.5)	19/704 (2.7)	0.3 (-1.4, 1.9)
ALT ≥ 5 x ULN	4/693 (0.6)	8/704 (1.1)	0.6 (-0.4, 1.5)
ALT ≥ 10 x ULN	0	3/704 (0.4)	0.4 (-0.1, 0.9)
ALT ≥ 20 x ULN	0	0	0
AST ≥ 3 x ULN	7/693 (1.0)	12/704 (1.7)	0.7 (-0.5, 1.9)
AST ≥ 5 x ULN	2/693 (0.3)	6/704 (0.9)	0.6 (-0.2, 1.4)
AST ≥ 10 x ULN	0	3/704 (0.4)	0.4 (-0.1, 0.9)

Criteria	Placebo (N = 700) n/N_OBS (%)	Risankizumab (N = 707) n/N_OBS (%)	Comparison (95% CI)
AST ≥ 20 x ULN	0	0	0
Alk Phos ≥ 1.5 x ULN	11/693 (1.6)	16/704 (2.3)	0.7 (-0.8, 2.1)
TBL ≥ 2 x ULN	0	0	0
ALT and/or AST ≥ 3 x ULN And TBL ≥ 1.5 x ULN	0	0	0
ALT and/or AST ≥ 3 x ULN And TBL ≥ 2 x ULN	0	0	0

Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; n = number of patients; N_OBS = number of patients with at least one post-baseline value for the respective parameter; TBL = total bilirubin; ULN = upper limit of normal [Source: Reviewer; Adapted from Summary of Clinical Safety pg. 91]

Table 47 shows results for increases of ALT and AST based on whether patients used methotrexate at baseline. The number and percentage of patients not on methotrexate at baseline with elevations of ALT and AST ≥ Grade 3 were higher in the risankizumab group (7 patients with elevation of ALT ≥ Grade 3 in the risankizumab group vs no patients in the placebo group; 4 patients with elevation of AST ≥ Grade 3 in the risankizumab group vs no patients in the placebo group). Elevations of ALT and AST were otherwise comparable between the risankizumab and placebo groups.

Table 48. Frequency of Patients with Transaminase Increases Post-Baseline by Methotrexate in the Phase 3 PsA Placebo-Controlled Period

	Placebo		Risankizumab	
CTCAE Elevation	MTX at Baseline N = 414 n/N_OBS (%)	No MTX N = 286 n/N_OBS (%)	MTX at Baseline N = 424 n/N_OBS (%)	No MTX N = 283 n/N_OBS (%)
ALT Grade 1 (> 1 to ≤ 3 x ULN)	89/413 (21.5)	40/280 (14.3)	91/422 (21.6)	39/282 (13.8)
ALT Grade 2 (> 3 to ≤ 5 x ULN)	9/413 (2.2)	3/280 (1.1)	6/422 (1.4)	3/282 (1.1)
≥ ALT Grade 3 (> 5 x ULN)	4/413 (1.0)	0	1/422 (0.2)	7/282 (2.5)
AST Grade 1 (> 1 to ≤ 3 x ULN)	56/413 (13.6)	28/280 (10.0)	67/422 (15.9)	34/282 (12.1)
AST Grade 2 (> 3 to ≤ 5 x ULN)	4/413 (1.0)	1/280 (0.4)	0	6/282 (2.1)
≥ AST Grade 3 (> 5 x ULN)	2/413 (0.5)	0	2/422 (0.5)	4/282 (1.4)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria of Adverse Events; MTX = methotrexate; n = number of patients; N_OBS = number of patients with at least one post-baseline value for the respective parameter; ULN = upper limit of normal [Source: Reviewer; Adapted from Summary of Clinical Safety pg. 93]

Table 48 shows potentially clinically important liver test elevations for patients in the long-term analysis set. 1 patient in the all risankizumab PsA analysis set had liver test elevations that met biochemical Hy's law on Day 183 of the study. The Applicant notes that this case did not meet

the criteria for biochemical Hy's law since the patient was confirmed to be Hepatitis E IgM positive and the liver biopsy revealed histological aspects suggestive of alcohol induced steatohepatitis.

Table 49. Summary of Potentially Clinically Important Liver Function Test Values (Phase 3 PsA Long-term Analysis Set and All Risankizumab Analysis Set)

Criteria	Risankizumab No Cross-over from Placebo N = 707 n/N_OBS (%)	Any Risankizumab N = 1365 n/N_OBS (%)	All Risankizumab N = 1542 n/N_OBS (%)
ALT ≥ 3 x ULN	27/704 (3.8)	37/1360 (2.7)	46/1537 (3.0)
ALT ≥ 5 x ULN	11/704 (1.6)	11/1360 (0.8)	14/1537 (0.9)
ALT ≥ 10 x ULN	4/704 (0.6)	4/1360 (0.3)	4/1537 (0.3)
ALT ≥ 20 x ULN	0	0	0
AST ≥ 3 x ULN	15/704 (2.1)	19/1360 (1.4)	27/1537 (1.8)
AST ≥ 5 x ULN	7/704 (1.0)	8/1360 (0.6)	11/1537 (0.7)
AST ≥ 10 x ULN	3/704 (0.4)	3/1360 (0.2)	3/1537 (0.2)
AST ≥ 20 x ULN	0	0	0
Alk Phos ≥ 1.5 x ULN	17/704 (2.4)	29/1360 (2.1)	30/1537 (2.0)
TBL ≥ 2 x ULN	0	0	1/1537 (< 0.1)
ALT and/or AST ≥ 3 x ULN And TBL ≥ 1.5 x ULN	0	0	1/1537 (< 0.1)
ALT and/or AST ≥ 3 x ULN And TBL ≥ 2 x ULN	0	0	1/1537 (< 0.1)

Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; n = number of patients; N_OBS = number of patients with at least one post-baseline value for the respective parameter; TBL = total bilirubin; ULN = upper limit of normal [Source: Reviewer; Adapted from Summary of Clinical Safety pg. 94]

Table 49 shows results for increases of ALT and AST based on whether patients in the Phase 3 PsA long-term analysis set used methotrexate at baseline. The percentage of patients with Grade 1 and Grade 2 elevations of ALT was higher in patients on methotrexate at baseline; however, the percentage of patients with ≥ Grade 3 elevations of ALT was higher in patients not on methotrexate at baseline. The percentage of patients with Grade 1 elevations of AST was higher in the patients on methotrexate at baseline; however, the percentage of patients with Grade 2 or ≥ Grade 3 elevations of AST was higher in patients not on methotrexate at baseline.

Table 50. Frequency of Patients with Transaminase Increases Post-Baseline by Methotrexate in the Phase 3 PsA Long-term Analysis Set (Any Risankizumab through 1 year)

CTCAE Elevation	MTX at Baseline (N = 824) n/N_OBS (%)	No MTX at Baseline (N = 541) n/N_OBS (%)
ALT Grade 1 (> 1 to ≤ 3 x ULN)	180/821 (21.9)	89/539 (16.5)
ALT Grade 2 (> 3 to ≤ 5 x ULN)	16/821 (1.9)	4/539 (0.7)
≥ ALT Grade 3 (> 5 x ULN)	4/821 (0.5)	7/539 (1.3)
AST Grade 1 (> 1 to ≤ 3 x ULN)	148/821 (18.0)	75/539 (13.9)

AST Grade 2 (> 3 to ≤ 5 x ULN)	4/821 (0.5)	7/539 (1.3)
≥ AST Grade 3 (> 5 x ULN)	4/821 (0.5)	4/539 (0.7)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria of Adverse Events; MTX = methotrexate; n = number of patients; N_OBS = number of patients with at least one post-baseline value for the respective parameter; ULN = upper limit of normal [Source: Reviewer; Adapted from Summary of Clinical Safety pg. 96]

Vital Signs

In the phase 3 PsA placebo-controlled analysis set, mean changes in vital sign parameters during risankizumab administration were comparable to changes observed in the placebo group, and not considered to be clinically meaningful. The proportion of patients treated with risankizumab who experienced potentially clinically important vital sign abnormalities was low (< 4%) and consistent with the comparator treatment group.

In the phase 3 PsA long-term analysis set, the proportion of patients who experienced potentially clinically important vital sign abnormalities was low (< 4%).

Electrocardiograms (ECGs)

In both phase 3 studies, electrocardiograms were performed at screening only.

Immunogenicity

Pre-existing anti-drug antibodies were detected at baseline in 1.3% (5/376) of patients who received at least one dose of risankizumab in study M15-998, and 2.4% (21/863) of patients who received at least one dose of risankizumab in study M16-011.

In study M15-998, the incidence of treatment emergent anti-drug antibodies over 28 weeks was 13.1% (27/206) in patients who received risankizumab at weeks 0, 4, and q12 weeks thereafter. The incidence of treatment emergent anti-drug antibodies over 28 weeks was 7.5% (14/186) in patients who received placebo at weeks 0, 4, and 16, and switched to risankizumab at week 24. No patients developed neutralizing antibodies.

In study M16-011, the incidence of treatment emergent anti-drug antibodies over 28 weeks was 11.7% (52/446) in patients who received risankizumab at weeks 0, 4, and q12 weeks thereafter. The incidence of treatment emergent anti-drug antibodies over 28 weeks was 6.5% (29/446) in patients who received placebo at weeks 0, 4, and 16, and switched to risankizumab at week 24. No patients developed neutralizing antibodies.

Across the phase 3 studies, the median ADA titers at week 28 ranged from 24.2 to 25.9.

Based on long term data with limited sample size from the phase 2 studies with 76 weeks of assessment duration, the incidence of treatment emergent anti-drug antibodies was 30.3% (10/33) in patients who received risankizumab 150 mg SC at weeks 0, 4, and 16 in study M16-002, and continued to receive open-label risankizumab 150 mg SC q12 weeks thereafter. The

incidence of treatment emergent neutralizing antibodies was 3.0% (1/33). The median time to the first appearance of anti-drug antibodies was 12 (range of 8-24) weeks in the phase 2 study M16-002 in which time-course immunogenicity data was collected.

Across all analysis sets, the rates of hypersensitivity reactions and injection site reactions were low but numerically higher in the treatment emergent anti-drug antibody positive patients. All reactions were mild or moderate in severity, and none led to treatment discontinuation.

8.4.5 Analysis of Submission-Specific Safety Issues

The potential risks and areas of safety interest were identified based on the the known biologic activity related to the IL-23 pathway, the safety profile of risankizumab in the psoriasis program, and the safety profile of other biologic DMARDs. The predefined areas of safety interest were major adverse cardiac events (MACE), infections, malignancies, hepatic events, injection site events, and hypersensitivity reactions. These areas of safety interest are discussed in section 8.4.4.

Hepatic Events & Hypersensitivity Reactions (Response to IR)

An Information Request (IR) was sent to the Applicant on July 27, 2021 to obtain additional data on hepatic events and hypersensitivity reactions. The Applicant noted the following in their response to the IR:

In the placebo-controlled analysis set of the phase 3 psoriatic arthritis program, higher event rates were observed in the risankizumab group compared with placebo for most of the evaluation criteria. The percentage of patients with a medical history of hepatic steatosis at study entry was higher in the risankizumab group (4.5%) compared with the placebo group (3.3%). In addition, there was a higher percentage of patients with BMI ≥ 30 kg/m^2 in the risankizumab group compared to the placebo group (49.8% vs 46.7%).

The Applicant noted the hepatic event rate difference between the psoriasis and psoriatic arthritis populations. Based on the risankizumab clinical trial data, the percentage of patients in the psoriatic arthritis population who were receiving methotrexate at baseline was higher compared with patients in the 3 pivotal studies of the psoriasis program (60% vs < 1%).

The EAER for any hypersensitivity event was 3.1 E/100 PY in the placebo group and 5.5 E/100 PY in the risankizumab group. A total of 25 patients reported 28 hypersensitivity events. Seven of these events were assessed as moderate in severity (2 events in 2 placebo patients, and 4 events in 3 risankizumab patients). The rest of events were assessed as mild in severity. There were no severe hypersensitivity events, no serious hypersensitivity events, and no anaphylactic reactions in either treatment group.

8.4.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.4.7 Safety Analyses by Demographic Subgroups

The Applicant conducted safety analyses for each of the following subgroups: age, sex, BMI, and race. The Applicant also examined the impact of geographic region and duration of psoriatic arthritis diagnosis.

Age

In the Phase 3 PsA Placebo-Controlled Analysis Set, the percentages of patients with treatment-emergent adverse events, severe treatment-emergent adverse events, serious adverse events, and adverse events leading to discontinuation were numerically higher in patients ≥ 75 years of age compared to younger patients in both the risankizumab and placebo groups. In the Phase 3 PsA Long-term Analysis Set, the rates of these categories of events and the areas of safety interest were generally numerically lower in the youngest age category (< 65 years) and higher in the oldest age group (≥ 75 years). Interpretation of data regarding the impact of age upon safety is limited due to the small number of patients ≥ 75 years of age.

Sex

In the Phase 3 PsA Placebo-Controlled Analysis Set and the Phase 3 PsA Long-term Analysis Set, the percentages of patients with treatment-emergent adverse events, severe treatment-emergent adverse events, and serious adverse events were generally higher in females than males in both the risankizumab and placebo groups. While these events were numerically higher, they were similar to placebo and based on the available data, risankizumab presents a favorable safety profile in female patients.

BMI

In the Phase 3 PsA Placebo-Controlled Analysis Set and the Phase 3 PsA Long-term Analysis Set, no clear pattern was observed with respect to BMI for treatment-emergent adverse event categories including serious adverse events, severe treatment-emergent adverse events, and treatment-emergent adverse events leading to discontinuation.

Race

The majority of patients (94.8%) in the study population were white, limiting the subgroup analyses by race. In the Phase 3 PsA Placebo-Controlled Analysis Set, the percentage of patients with any treatment-emergent adverse event was higher in non-white patients than white patients in both risankizumab and placebo groups. However, the interpretation of this finding is

limited by the small number of non-white patients (n = 35 in the risankizumab group, n = 39 in the placebo group) compared to the number of white patients (n = 672 in the risankizumab group, n = 661 in the placebo group).

In the Phase 3 PsA Long-term Analysis Set, the rates of serious adverse events, severe treatment-emergent adverse events, and adverse events leading to discontinuation were generally consistent between white and non-white patients across the any risankizumab group.

Geographic Region

In the Phase 3 PsA Placebo-Controlled Analysis Set and the Phase 3 PsA Long-term Analysis Set, no clear pattern was observed with respect to geographic region for treatment-emergent adverse event cateogires including serious adverse events, severe treatment-emergent adverse events, and treatment-emergent adverse events leading to discontinuation.

Duration of Psoriatic Arthritis Diagnosis

In the Phase 3 PsA Placebo-Controlled Analysis Set and the Phase 3 PsA Long-term Analysis Set, no clear pattern was observed with respect to the duration of psoriatic arthritis diagnosis for any category of treatment-emergent adverse events including overall treatment-emergent adverse events, serious adverse events, severe treatment-emergent adverse events, and treatment-emergent adverse events leading to discontinuation.

8.4.8 Specific Safety Studies/Clinical Trials

As noted in section 8.4.1, the safety assessment of risankizumab in psoriatic arthritis is primarily based on safety data from the two phase 3 studies, studies M16-011 and M15-998. These studies enrolled patients with psoriatic arthritis who had comparable baseline demographics and disease characteristics to those of the targeted population in the United States. Each of the studies provided controlled comparisons between risankizumab 150 mg SC at week 0, 4, and every 12 weeks thereafter and placebo. Patients initially treated with placebo received treatment with risankizumab 150 mg SC at week 24. At week 28, and for the remaining dosing visits to week 208, all patients received risankizumab 150 mg SC every 12 weeks. The safety population included all randomized patients who received at least one dose of the study drug.

The safety profile of risankizumab was characterized based on a comprehensive evaluation of the phase 3 psoriatic arthritis placebo-controlled analysis set which includes patients who received risankizumab 150 mg or placebo during the 24-week placebo-controlled period in phase 3 studies M16-011 and M15-998, the phase 3 psoriatic arthritis long-term analysis set which includes patients who received at least one dose of risankizumab 150 mg in phase 3 studies M16-011 and M15-998, and the all risankizumab psoriatic analysis set which includes patients in the phase 2 and phase 3 psoriatic arthritis studies who received at least one dose of risankizumab.

8.4.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No data on human carcinogenicity or tumor development are included.

Human Reproduction and Pregnancy

There is a limited amount of data regarding the use of risankizumab in pregnant women. Human IgG is known to cross the placental barrier especially in the third trimester; therefore, risankizumab may be transmitted from the mother to the developing fetus later in pregnancy.

Animal studies do not indicate harmful effects with risankizumab on pregnancy. A pre-natal and post-natal developmental toxicity study was conducted in cynomolgus monkeys. In this study, no drug-related fetal or infant malformations, deaths, or effects on growth development of infants of up to 6 months of age were observed.

In the risankizumab psoriatic arthritis clinical development program, female patients of childbearing potential were required to use a highly effective method of birth control (that results in a low failure rate of less than 1% per year). Lactating or pregnant females were not eligible to participate in the studies. If a pregnancy occurred during the study, the patient was to have been discontinued. Pregnancy in a study patient was not considered an adverse event.

Male patients and their female partners were not required in the protocols to use contraception. Risankizumab is not genotoxic and the amounts detected in seminal fluid transferred to the conceptus are negligible. Therefore, male-mediated seminal transfer of a large molecule drug like risankizumab should not present a health risk to the female partner, and the drug is not bioavailable to the developing conceptus.

No material exposure pregnancies occurred in the psoriatic arthritis development program. One paternal exposure pregnancy occurred in the psoriatic arthritis development program in study M16-011. The pregnancy is ongoing.

According to the 120-day safety update report, there were no additional pregnancies reported in the Phase 3 PsA Long-term Analysis Set since the data cutoff for the CSS of the initial psoriatic arthritis submission.

Pediatrics and Assessment of Effects on Growth

At this time, risankizumab is not indicated for any pediatric populations. See section 10 for details regarding the plan for pediatric assessment.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No case of risankizumab overdose has been reported and no dose-limiting toxicity was observed during clinical studies. There were no reports of drug abuse, dependence, or other information relevant for drug abuse in clinical studies. There were no reports of withdrawal or rebound effects in any of the studies in the risankizumab psoriatic arthritis program.

8.4.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Risankizumab 150 mg (75 mg/0.83 mL x 2 SC injections) administered by SC injection at week 0, week 4, and q12 weeks thereafter was first approved for the treatment of moderate to severe plaque psoriasis in adults on 26 March 2019 in Japan. Through 25 September 2020, risankizumab has been approved in 67 countries with estimated cumulative postmarketing patient exposure of 47,997 patient years since first approval.

The safety of risankizumab 150 mg was evaluated through review of postmarketing reports (spontaneous, solicited, literature) received from 26 March 2019 through 25 September 2020. Search of the Applicant's global safety database retrieved 17,103 cases. Overall, 92.5% (15,820/17,103) of the reports were considered non-serious. The most frequently reported MedDRA SOC (35% of all cases) was general disorders and administration site conditions, in which the preferred terms of fatigue, drug ineffective, and therapeutic response shortened were most frequently reported.

The most commonly reported adverse events included psoriasis (7.8%), fatigue (3.9%), drug ineffective (3.9%), pruritis (3.3%), and headache (3.2%). These events are either labeled for risankizumab or commonly seen in the general population or patients with psoriasis.

The most commonly reported serious adverse event was death (0.17%). Of the 57 reports of death, 49 reports contained limited information to establish a causal association and 8 reports were attributable to the patient's significant comorbidities and natural causes. Overall, serious adverse events were reported in less than 0.2% of the retrieved reports.

There were postmarketing reported cases of anaphylaxis and angioedema; however, the reports were not sufficient to determine any unequivocal cases of angioedema or anaphylaxis. Hypersensitivity reactions will be added to the labeling for risankizumab.

Expectations on Safety in the Postmarket Setting

Based on the safety analyses in the PsA population, new safety issues pertaining to hepatic events and hypersensitivity reactions have been identified.

8.4.11 Integrated Assessment of Safety

There was 1 death in the placebo controlled analysis set. The death occurred ≤ 140 days after the last dose of study drug. The patient was 81 years old and hospitalized for pneumonia on post-treatment day 62 (enrolled in Study M16-011). The patient later developed urosepsis on post-treatment day 96 resulting in death. The event of urosepsis was assessed by the investigator and Applicant as having no reasonable possibility of being related to study drug. There were no additional deaths in the phase 3 PsA long-term analysis set and no non-treatment emergent deaths. The exposure adjusted death rate with long-term risankizumab exposure was < 0.1 E/100 PY.

The number and proportion of patients with serious TEAEs was higher in the placebo group (31 patients or 4.4% in the placebo group vs 21 patients or 3.0% in the risankizumab group). The rate of serious TEAEs was higher in the placebo group (11.7 E/100 PY in the placebo group vs 8.8 E/100 PY in the risankizumab group), and the rate of serious TEAEs was stable with long-term risankizumab exposure (8.8 E/100 PY in the placebo-controlled analysis set vs 7.5 E/100 PY in the long-term analysis set). Infections and infestations were the most common serious TEAEs and occurred in 26 patients (1.7%). All other serious TEAEs occurred in less than 1% of patients.

The number and proportion of patients who discontinued the study drug due to TEAEs was slightly higher in the placebo group (10 patients or 1.4% in the placebo group vs 6 patients or 0.8% in the risankizumab group). The rate of discontinuation was low and stable with long-term risankizumab exposure (2.7 E/100 PY in the placebo-controlled analysis set vs 1.7 E/100 PY in the long-term analysis set).

In studies M16-011 and M15-998, the predefined areas of safety interest were major adverse cardiac events (MACE), infections, malignancies, hepatic events, injection site events, and hypersensitivity reactions. The event rate for these areas of safety interest was generally balanced between treatment groups except for hepatic events and hypersensitivity reactions.

In the placebo-controlled analysis set, the percentage of patients with investigator reported hepatic TEAEs was higher in the risankizumab group (5.4%) compared to the placebo group (3.9%). The rate of hepatic events for patients in the risankizumab group was 16.7 E/100 PY compared to 12.6 E/100 PY for patients in the placebo group. The most common hepatic TEAEs were ALT increase, AST increase, and GGT increase in both groups. There were no serious hepatic events reported. There were no confirmed events meeting biochemical Hy's law.

In the long-term analysis set, the rate of hepatic events was 12.3 E/100 PY. The most common hepatic TEAEs with rates ≥ 1 E/100 PY were ALT increase, AST increase, GGT increase, hepatic steatosis, hepatic enzyme increase, and transaminase increase. There were no serious hepatic events reported. There were no confirmed events meeting biochemical Hy's law.

In the all risankizumab analysis set, there was a single case associated with biochemical Hy's law which was confounded by a confirmed positive Hepatitis E IgM serology and excessive alcohol use. Therefore, the case was not deemed to be a Hy's law case.

The EAER for any hypersensitivity event was 3.1 E/100 PY in the placebo group and 5.5 E/100 PY in the risankizumab group. A total of 25 patients reported 28 hypersensitivity events. Seven of these events were assessed as moderate in severity (2 events in 2 placebo patients, and 4 events in 3 risankizumab patients). The rest of events were assessed as mild in severity. There were no severe hypersensitivity events, no serious hypersensitivity events, and no anaphylactic reactions in either treatment group.

The labeled warning and precautions for risankizumab from the psoriasis program include infections and tuberculosis. In the psoriatic arthritis program, the percentage of patients with infection adverse events was lower in the risankizumab group (19.0%) compared to the placebo group (19.3%). The most common infections in the risankizumab group were upper respiratory tract infections (4.1%), nasopharynigitis (3.5%), and gastroenteritis (1.0%). The number and rate of serious infections was lower in the risankizumab group (9 events with a rate of 2.7 E/100 PYs) compared to the placebo group (13 events with a rate of 4.0 E/100 PYs). The rate of serious infections was stable with long-term risankizumab exposure. Cellulitis was the most common serious infection (0.3%) for patients treated with risankizumab in the placebo-controlled analysis set. Pneumonia (0.4%) and COVID-19 (0.4%) were the most common serious infections for patients in the long-term analysis set.

8.5 Statistical Issues

For the review of this application, the main statistical issues noted were the impact of LOCF imputation on the primary analysis and the pooling of data across studies to support the enthesitis and dactylitis endpoints.

Based on the missing data handling rule specified in the SAP for composite binary endpoints, including the primary endpoint ACR20 as well as the secondary endpoints ACR50 and ACR70, if the composite score was missing due to non-COVID reason, the missing components were imputed using last observation carry forward (LOCF) to recalculate the composite score before imputing missing evaluations as a non-responder. In general, we have concerns regarding the use of LOCF to impute missing data. As discussed in the 2010 National Research Council report The Prevention and Treatment of Missing Data in Clinical Trials, LOCF is generally not based on reasonable scientific assumptions and is also statistically inappropriate because it does not take into account the uncertainty in the imputation process. The Applicant was asked to provide a list of subjects whose ACR composite score was recalculated using LOCF and to provide the analysis results for ACR20, ACR50 and ACR70 endpoints that instead include these subjects as non-responders and the time point from which the outcome was carried forward. The number of patients in both studies where this approach was applied was small (7 (1.4%) risankizumab-treated subjects and 6 (1.2%) placebo-treated subjects

in Study M16-011, and 3 (1.3%) risankizumab-treated subjects and 2 (0.9%) placebo-treated subjects in Study M15-998). And for majority of these patients, the outcome was carried from Week 16, the most recent visit. The Applicant also conducted post-hoc analyses for endpoints of ACR20 as well as ACR50 and ACR70 at Week 24 that imputed these subjects as non-responder. Compared to the pre-specified primary analysis results, the estimated treatment difference between risakizumab and placebo is slightly smaller, but similar and the conclusion is consistent. The tipping point analyses performed by the Applicant further confirmed that the findings on the primary efficacy endpoint were robust to departures in missing data assumptions.

Dactylitis (the proportion of subjects with dactylitis resolution) and enthesitis (the proportion of subjects with enthesitis resolution) endpoints were originally among the ranked secondary endpoints in both Study M16-011 and Study M15-998. In Oct 2020, the Applicant proposed to remove resolution of enthesitis and resolution of dactylitis from the ranked secondary endpoint analyses of Study M15-998 and pool the enthesitis and dactylitis data from the two trials (Study M15-998 and Study M16-011) under the multiplicity control of Study M16-011 as a pre-specified analysis in the Study M16-011 SAP. Considering the regulatory precedent with labeling practices for PsA, the review team allowed for the Applicant's proposal to pool the enthesitis and dactylitis data from the two trials (Study M15-998 and Study M16-011) under the multiplicity control of Study M16-011 and as a prespecified analysis in the Study M16-011. However, the team's comments noted that how the results on resolution of enthesitis and dactylitis will appear in labeling will be a review issue and that we will also take into consideration the results from the individual studies to ensure that a consistent trend in improvement would be observed in both studies. During the review of this BLA, the statistical review team further raised concerns that the operating characteristics of this approach to pooling data and including this test in the hierarchy of one study are not clear and it may not be the case that this type 1 error is adequately controlled. Therefore, the statistical review team recommended that language regarding statistical significance be removed from labeling.

Using the pooled data, both the enthesitis and dactylitis endpoints met the significance level of 0.05 as pre-specified by the Applicant. In addition, for each individual study, the difference of dactylitis resolution rates between the treatment groups showed nominal statistical significance in each individual study based on the primary efficacy analysis approach to intercurrent events and missing data, as well as the analysis including all observed data but imputing missing outcomes as non-responder. For the proportion of subjects with enthesitis resolution, the difference between the treatment groups showed nominal statistical significance in each individual study based on the primary efficacy analysis approach to missing data. However, the analysis results based on the inclusion of all observed data and imputing missing outcome as non-responder showed nominal statistical significance only for Study M16-011. For study M15-998, while there was a higher proportion of subjects with dactylitis resolution on risakizumab group compared to placebo, the difference did not show nominal statistical significance at α=0.05. Overall, the supplemental analyses for each individual study provides some additional support for the evaluation of enthesitis and dactylitis.

There was also a concern about the inclusion of ACR50 and ACR70 in the label since both endpoints were not included in the multiplicity controlled testing hierarchy. Because these endpoints were considered clinically important for patients and prescribers to provide additional information about ACR response, these endpoints were included in labeling. However, the sponsor was asked to remove reference to nominal p-values with respect to these two endpoints.

8.6 Conclusions and Recommendations

The primary data to support this application are derived from two phase 3 studies, study M16-011 and study M15-998. Both studies were multicenter, randomized, double-blind, placebo-controlled studies with open label extension in patients with active PsA. Study M16-011 enrolled patients who had an inadequate response to at least 1 csDMARD. Study M15-998 enrolled patients who had an inadequate response to 1 or 2 biologic therapies (no more than 50% of the study population) or at least 1 csDMARD. The primary endpoint for both of the phase 3 studies was American College of Rheumatology (ACR) 20 response criteria at Week 24.

Studies M16-011 and M15-998 provide evidence for the effectiveness of risankizumab compared to placebo to improve signs and symptoms, as measured by American College of Rheumatology (ACR) 20% response criteria. The efficacy of risankizumab over placebo was further supported by key secondary endpoints such as HAQ-DI.

In general, during the placebo controlled period, the number of patients and percentage of patients (and event rate) with treatment emergent adverse events (TEAEs), serious adverse events (SAEs), severe adverse events, drug-related AEs, and TEAEs leading to discontinuation was similar in the risankizumab and placebo groups. There was 1 death in the placebo-controlled analysis set that was assessed by the investigator and Applicant as having no reasonable possibility of being related to study drug. Overall, the safety profile of risankizumab in the treatment of psoriatic arthritis is generally consistent with the previous experience with risankizumab in psoriasis; however, in the psoriatic arthritis program, there were additional safety signals for hepatic events and hypersensitivity reactions that warrant inclusion in product labeling.

In conclusion, studies M16-011 and M15-998 provide substantial evidence of efficacy of the risankizumab 150 mg SC at Weeks 0, 4, and every 12 weeks thereafter dosing regimen for the treatment of adult patients with active psoriatic arthritis.

9 Advisory Committee Meeting and Other External Consultations

An advistory committee meeting was not held for this supplemental BLA. No issues were identified warranting advisory committee input.

10 Pediatrics

A proposed initial pediatric study plan (iPSP), outlining a proposal for a request for full waiver from the requirements of pediatric studies in psoriatic arthritis, was agreed upon in March 2018.

Following the pediatric juvenile idiopathic arthritis workshop in October 2019[9] and internal policy discussions, the FDA notified the Applicant of the Division's reconsideration of the approach to PREA for psoriatic arthritis. Based on the evolving understanding of the high degree of similarity of the disease between adults and pediatric patients with psoriatic arthritis and the considerations of pharmacokinetic (PK)-matching and extrapolation of efficacy from adults to pediatric patients, the Division considers that pediatric assessment is possible. The Division noted that efficacy established in adequate and well-controlled studies in adults with psoriatic arthritis could be extrapolated to pediatric patients with psoriatic arthritis based on matching of the PK exposures between the two populations. This extrapolation of efficacy could be based on appropriate scientific justification and evidence provided by the Applicant, which could be product-specific, to support the expectation that exposures at effective doses in adults will provide similar or better responses in the pediatric population. Safety in pediatric patients cannot be extrapolated from the studies in adults, and would need to be supplemented by a reasonable safety database in pediatric patients with psoriatic arthritis, or with appropriate justification, a relevant pediatric patient population (e.g., pediatric psoriasis).

The Applicant's updated pediatric study plan, based on the above considerations, was submitted on March 23, 2021. AbbVie requested a partial waiver for risankizumab for the treatment of juvenile PsA in patients aged 0 to < 5 years as PsA is extremely rare in this age group. For juvenile PsA patients aged 5 to < 18 years, the Applicant proposed a deferred assessment to extrapolate efficacy data from the adult PsA population, leverage safety data from adult PsA and pediatric PsO, and determine an appropriate dosing regimen in juvenile PsA through PK modeling and simulationg using data from adult PsO, adult PsA, and pediatric PsO.

[9] https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/accelerating-drug-development-polyarticular-juvenile-idiopathic-arthritis-pjia-10022019-10022019

Confirmation of an age-appropriate dosing regimn of risankizumab will occur after approval of the therapeutic dose in adults with PsA, and after availability of risankizumab PK data from the pediatric PsO study M19-977 that was part of the post-marketing commitment for BLA approval of risankizumab in moderate to severe plaque PsO (BLA 761105).

The Applicant proposes to establish the safety and efficacy of risankizumab for the treatment of juvenile PsA through a PK exposure matching and extrapolation approach which is acceptable. The proposed pediatric study plan was discussed at PeRC on January 11, 2022. The PeRC agreed with the proposed partial waiver and deferral.

This approach warrants a post-marketing requirement under PREA:

- Provide pharmacokinetic (PK) and safety information to support the pediatric assessment of risankizumab for the treatment of juevenile psoriatic arthritis in children 5 to 17 years of age.

  Final Report Submission: 03/2026

11 Labeling Recommendations

11.1 Prescription Drug Labeling

The following table presents a high-level summary of the labeling proposal and subsequent interactions between the Applicant and the FDA.

Table 51. Prescription Drug Labeling

Section	Labeling Discussions
Highlights of prescribing information – 1.2 Indications and Usage	FDA agreed with the proposed new indication: treatment of active psoriatic arthritis in adults
Highlights of prescribing information – 2.2 Dosage and Administration	FDA agreed with the proposed dosage of 150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter
Highlights of prescribing information – Contraindications & Section 4	FDA added that SKYRIZI is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab or any of the exicipients
Highlights of prescribing information – Warnings and precautions & Section 5.1	FDA added a warning and precaution for hypersentivity reactions and a statement that serious hypersensitivity reactions, including anaphylaxis, may occur
Clinical Trials Experience, Section 6.1	FDA added new safety findings including hepatic adverse reactions and hypersensitivity reactions to the previously known safety profile of SKYRIZI
Immunogenicity, Section 6.2	FDA modified the statement provided by the Applicant and added language to reflect the impact of anti-drug antibodies on safety (i.e., hypersensitivity reactions and injection site reactions)
Postmarketing Experience, Section 6.3	FDA added postmarketing experience to describe the hypersensitivity reactions and immune system disorders that have been reported
Pharmacodynamics, Section 12.2	(b) (4)

Section	Labeling Discussions
	(b) (4) [redacted]
Psoriatic Arthritis, Section 14.2	
	Based on feedback from the collaborating review team from the Division of Dermatology and Dental, FDA agreed with the inclusion of a statement on improvement in psoriatic skin lesions in patients with PsA.
	(b) (4) [redacted]
Patient Counseling Information, Section 17	FDA added counseling information for hypersensitivity reactions
Medication Guide	FDA added information on serious allergic reactions

12 Risk Evaluation and Mitigation Strategies (REMS)

No new risk management plans are submitted as part of this supplement.

13 Postmarketing Requirements and Commitment

In accordance with the Pediatric Research Equity Act (PREA), the Applicant will provide PK and safety information to support the pediatric assessment of risankizumab for the treatment of

juvenile psoriatic arthritis in children 5 to 17 years of age.

The Applicant has confirmed agreement with the following timelines:

- Study/Trial Completion: N/A
- Final Report Submission: March 2026

14 Division Director (Clinical)/Signatory Comments

This Division Signatory agrees with the team's review, assessment, conclusions and recommendations.

The action on this supplemental BLA for risankizumab 150 mg SC at Weeks 0, 4, and every 12 weeks thereafter for the treatment of adult patients with active psoriatic arthritis is Approval. Labeling has been agreed upon with the Applicant.

A post-marketing requirement under PREA will be issued:

- Provide pharmacokinetic (PK) and safety information to support the pediatric assessment of risankizumab for the treatment of juevenile psoriatic arthritis in children 5 to 17 years of age.

  Final Report Submission: 03/2026

No other post-marketing requirements or commitments are warranted.

15 Appendices

15.1 References

[Insert text here]

15.2 Financial Disclosure

Details regarding the financial disclosures provided by the Applicant for the pivotal studies M16-011 and M15-998 are included below. See Section 8.1.1 and Section 8.1.2 for details regarding the adequacy of the financial disclosures.

Covered Clinical Studies (Name and/or Number): M16-011 and M15-998

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: **M16-011 (1,102) and M15-998 (631); Total 1,733**		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): **none**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): (b) (4)		
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: **none** Significant payments of other sorts (b) (4) Proprietary interest in the product tested held by investigator: **none** Significant equity interest held by investigator in Sponsor of covered study: **none**		
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) **none**		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3 Nonclinical Pharmacology/Toxicology

[Insert carci data as needed. Limit to 2 pages]

15.4 OCP Appendices (Technical documents supporting OCP recommendations)

15.4.1 *Population PK Analysis*

19.4.1.1 Population PK Summary

General Information		
Objectives of PPK Analysis		• Evaluate the population pharmacokinetics of risankizumab in subjects with active psoriatic arthritis. • Identify source of variability on drug exposure
Study Included (Table 52)		• Phase 1: M16-513 • Phase 2: M16-002, M16-244 • Phase 3: M15-998, M16-011
Dose(s) Included		Single dose: • SC: 18 mg, 90 mg, 300 mg • IV: 200 mg, 600 mg, 1200 mg. Multiple doses: • 75 mg SC Week 0; • 150 mg SC Weeks 0 and 12; • 150 mg SC Weeks 0, 4, and 16; • 150 mg SC Weeks 0, 4, 8, 12, and 16. 150 mg SC Weeks 0, 4, 16 and q12w thereafter
Population Included		• Healthy volunteer: 67 in Study M16-513 • ITT (Psoriatic Arthritis): 1459 in Studies M16-002, M16-244, M15-998 and M16-011
Population Characteristics (Table 53)	General	• Age (years): 52 (range: 20 – 85; 204, 13.3% subj >=65 yr; 32, 2% subj >=75 yr) • Body Weight (kg): 85 (range: 28.6 -186) • Sex: 791 (52%) male, 735 (48%) female. • Race: White: 1380 (90%) Black or African American: 8 (1%) Asian: 112 (7%) Other: 21 (1%)

		Missing: 5 (0%)
No. of Patients, PK Samples, and BLQ		BLQ: 11 (0.3%) was excluded from analysis 3631 observations from 1527 subjects were involved in population PK analysis.
Sampling Schedule	Rich Sampling	67 in HV
	In ITT Population	No rich sampling in ITT
Covariates Evaluated	Static	• For CL: – Demographics: Age, sex, and race – Baseline lab values: Alanine transaminase, aspartate transaminase, total bilirubin, creatinine clearance – Disease characteristics: Extent of disease at baseline (Disease Activity Score in 28 joints [DAS28], HAQ-DI, PASI Score at baseline), duration of psoriatic arthritis, with or without axial spondylitis at baseline – Number of prior biologic therapies (0 versus ≥ 1), number of prior conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) (≤ 1 versus > 1), psoriatic arthritis (versus healthy) – Concomitant use of methotrexate – Immunogenicity: Treatment-emergent ADAs and nAbs • For V2: – Demographics: Age, sex, race, and psoriatic arthritis
	Time-varying	For CL: Treatment-emergent ADAs and nAbs

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM (Version 7.4.4) compiled with the GNU Fortran compiler (Version 7.5.5)	Acceptable
Model Structure	Two-compartment model with first-order absorption for SC administration, and first-order elimination.	Acceptable
Model Parameter Estimates		Acceptable

	Table 54	
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	The inter-individual variability (%CV) for risankizumab CL, V2, and Ka were 31.4%, 43.2%, and 42.2%, respectively. The computed η-shrinkages for CL, V2, and Ka were 16.0%, 46.7% and 79.2%, respectively.	The high η-shrinkages for V2 and Ka indicates less informative at individual level.
BLQ for Parameter Accuracy	BLQ samples were excluded from population PK analysis	Acceptable due to low number of BLQ samples
GOF, VPC, Bootstrap	GOF: Figure 12 VPC: Figure 13 Bootstrap: Table 55	Acceptable, no significant bias was observed
Significant Covariates and Clinical Relevance	Forest plot: Figure 14 Bodyweight was statistically correlated with risankizumab CL Subjects with relatively high body weight (> 75th percentile; 99 kg) and low body weight (< 25th percentile; 74 kg) were predicted to have approximately 20% lower and 30% higher exposures.	Acceptable, Additional analysis for bodyweight effect on efficacy and safety was added in FDA comments
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	The pharmacokinetics of risankizumab-rzaa in subjects with psoriatic arthritis was similar to that in subjects with plaque psoriasis.	Acceptable based on the comparison of population PK analysis in subjects with psoriatic and plaque psoriasis.

Table 52. Summary of studies and data included in population PK and E-R analyses for efficacy and safety.

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

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

Source: Population PK and ER report R&D/20/1395, Page 21-22, Table 1

Table 53. Demographic characteristics of subjects included for population PK analysis.

Characteristic		Study M16-513 (N = 67)	Study M16-002/ M16-244 (N = 177)	Study M15-998 (N = 443)	Study M16-011 (N = 964)	Phase 3 Studies (N = 1282)	Phase 2 + 3 Studies (N = 1459)	All Studies (N = 1592)
Sex	Male, N (%)	67 (100%)	101 (57%)	176 (45%)	447 (50%)	623 (49%)	724 (50%)	791 (52%)
	Female, N (%)	--	76 (43%)	215 (55%)	444 (50%)	659 (51%)	735 (50%)	735 (48%)
Body Weight (kg)	Mean (SD)	65.8 (10.1)	84.5 (17.4)	89.5 (22.0)	87.2 (18.7)	87.9 (19.8)	87.5 (19.6)	86.6 (19.7)
	Median	64.2	85.0	87.3	85.6	86.0	86.0	85.0
	Min – Max	50.6 – 94.4	48.1 – 139	28.6 – 168	40.5 – 186	28.6 – 186	28.6 – 186	28.6 – 186
Age (years)	Mean (SD)	28.5 (6.47)	51.3 (12.5)	53.2 (12.6)	51.2 (12.1)	51.8 (12.3)	51.7 (12.3)	50.7 (13.0)
	Median	27	51	53	52	52	52	52
	Min – Max	21 – 45	21 – 79	23 – 84	20 – 85	20 – 85	20 – 85	20 – 85
Race	White, N (%)	12 (18%)	149 (84%)	379 (97%)	840 (94%)	1219 (95%)	1368 (94%)	1380 (90%)
	Black, N (%)	--	--	4 (1%)	4 (0%)	8 (1%)	8 (1%)	8 (1%)
	Asian, N (%)	55 (82%)	22 (12%)	4 (1%)	31 (3%)	35 (3%)	57 (4%)	112 (7%)
	Other, N (%)	--	1 (1%)	4 (1%)	16 (2%)	20 (2%)	21 (1%)	21 (1%)
	Missing, N (%)	--	5 (3%)	--	--	--	5 (0%)	5 (0%)
Country	US/Canada, N (%)	--	49 (28%)	152 (39%)	93 (10%)	245 (19%)	294 (20%)	294 (19%)
	Europe, N (%)	--	108 (61%)	125 (32%)	542 (61%)	667 (52%)	775 (53%)	775 (51%)
	Asia, N (%)	67 (100%)	20 (11%)	13 (3%)	27 (3%)	40 (3%)	60 (4%)	127 (8%)
	Rest of the World, N (%)	--	--	101 (26%)	229 (26%)	330 (26%)	330 (23%)	330 (22%)
Body Height (cm)	Mean (SD)	173 (7.22)	170 (10.1)	169 (10.4)	169 (10.1)	169 (10.2)	169 (10.2)	169 (10.1)
	Median	173	169	168	169	168	169	169
	Min – Max	161 – 194	147 – 196	125 – 196	137 – 210	125 – 210	125 – 210	125 – 210
Lean Body Weight (kg)	Mean (SD)	53.3 (6.19)	55.8 (11.8)	55.3 (12.3)	55.5 (11.8)	55.4 (11.9)	55.4 (11.9)	55.3 (11.7)
	Median	52.4	54.6	54.0	54.8	54.6	54.6	54.5
	Min – Max	43.3 – 71.3	32.9 – 84.9	21.6 – 89.6	28.1 – 97.2	21.6 – 97.2	21.6 – 97.2	21.6 – 97.2
Body Mass Index (kg/m^2)	Mean (SD)	21.9 (2.38)	29.1 (5.32)	31.5 (7.56)	30.5 (6.24)	30.8 (6.69)	30.6 (6.56)	30.2 (6.67)
	Median	21.4	28.4	30.4	29.5	29.8	29.6	29.2
	Min – Max	18.5 – 29.1	18.3 – 52.0	10.4 – 87.2	15.5 – 64.4	10.4 – 87.2	10.4 – 87.2	10.4 – 87.2
Body Surface Area (m^2)	Mean (SD)	1.78 (0.16)	1.96 (0.23)	1.99 (0.25)	1.97 (0.23)	1.98 (0.24)	1.97 (0.24)	1.97 (0.24)
	Median	1.77	1.95	1.98	1.97	1.97	1.97	1.96
	Min – Max	1.52 – 2.24	1.45 – 2.61	1.08 – 2.75	1.27 – 2.87	1.08 – 2.87	1.08 – 2.87	1.08 – 2.87
Baseline Serum Creatinine (µmol/L)	Mean (SD)	80.6 (10.4)	73.3 (20.1)	72.3 (16.5)	72.1 (17.2)	72.2 (17.0)	72.3 (17.4)	72.7 (17.2)
	Median	80.5	70.7	70.7	71.0	70.7	70.7	70.9
	Min – Max	55.7 – 105	37.0 – 230	36.0 – 150	35.0 – 177	35.0 – 177	35.0 – 230	35.0 – 230
Creatinine Clearance (mL/min)	Mean (SD)	113 (16.7)	124 (40.6)	127 (46.4)	127 (38.6)	127 (41.1)	126 (41.0)	126 (40.4)
	Median	112	123	120	122	121	121	121
	Min – Max	76.0 – 153	38.5 – 269	34.1 – 320	37.7 – 348	34.1 – 348	34.1 – 348	34.1 – 348

Characteristic		Study M16-513 (N = 67)	Study M16-002/ M16-244 (N = 177)	Study M15-998 (N = 443)	Study M16-011 (N = 964)	Phase 3 Studies (N = 1282)	Phase 2 + 3 Studies (N = 1459)	All Studies (N = 1592)
Total Bilirubin (µmol/L)	Mean (SD)	14.6 (4.66)	8.26 (4.24)	7.57 (3.96)	7.73 (4.18)	7.68 (4.12)	7.75 (4.13)	8.05 (4.39)
	Median	13.7	7.00	6.84	7.00	7.00	7.00	7.00
	Min – Max	6.84 – 25.7	3.00 – 29.0	3.00 – 32.0	3.00 – 48.0	3.00 – 48.0	3.00 – 48.0	3.00 – 48.0
Aspartate Aminotransferase (U/L)	Mean (SD)	21.0 (5.31)	24.1 (9.70)	22.0 (11.1)	22.1 (10.8)	22.1 (10.9)	22.3 (10.8)	22.3 (10.6)
	Median	20.0	21.0	20.0	20.0	20.0	20.0	20.0
	Min – Max	12.0 – 37.0	8.00 – 62.0	10.0 – 158	7.00 – 158	7.00 – 158	7.00 – 158	7.00 – 158
Alanine Aminotransaminase (U/L)	Mean (SD)	20.8 (11.4)	29.1 (17.3)	24.0 (13.5)	25.6 (17.3)	25.1 (16.3)	25.6 (16.4)	25.4 (16.3)
	Median	17.0	25.0	21.0	21.0	21.0	21.0	21.0
	Min – Max	7.00 – 59.0	9.00 – 128	5.00 – 86.0	7.00 – 179	5.00 – 179	5.00 – 179	5.00 – 179
Baseline C-Reactive Protein (mg/L)	Mean (SD)	0.58 (0.90)	9.77 (18.5)	6.98 (9.83)	11.2 (14.3)	9.92 (13.2)	9.90 (14.0)	9.50 (13.8)
	Median	0.30	4.30	3.20	6.66	5.67	5.56	5.21
	Min – Max	0.10 – 6.10	0.20 – 183	0.20 – 91.6	0.20 – 121	0.20 – 121	0.20 – 183	0.10 – 183
Baseline Serum Albumin (g/L)	Mean (SD)	46.4 (2.18)	44.1 (3.01)	45.0 (2.99)	45.1 (2.98)	45.1 (2.98)	45.0 (3.00)	45.0 (2.98)
	Median	46.0	44.0	45.0	45.0	45.0	45.0	45.0
	Min – Max	42.0 – 51.0	35.0 – 54.0	32.0 – 55.0	34.0 – 55.0	32.0 – 55.0	32.0 – 55.0	32.0 – 55.0
Baseline PASI Score	N	N/A	84	391	890	1281	1365	1432
	Mean (SD)		7.88 (8.37)	4.92 (6.60)	6.61 (8.69)	6.09 (8.15)	6.20 (8.17)	5.91 (8.08)
	Median		5.55	2.80	3.50	3.30	3.40	3.10
	Min – Max		0.00 – 41.0	0.00 – 60.4	0.00 – 72.0	0.00 – 72.0	0.00 – 72.0	0.00 – 72.0
Baseline HAQ-DI Score	N	N/A	175	391	888	1279	1454	1521
	Mean (SD)		1.07 (0.68)	1.12 (0.62)	1.15 (0.66)	1.14 (0.65)	1.13 (0.65)	1.08 (0.68)
	Median		1.13	1.13	1.13	1.13	1.13	1.13
	Min – Max		0.00 – 2.50	0.00 – 2.88	0.00 – 2.88	0.00 – 2.88	0.00 – 2.88	0.00 – 2.88
Baseline DAS28 Score	N	N/A	177	391	888	1279	1456	1523
	Mean (SD)		4.72 (1.07)	4.88 (1.02)	4.92 (0.96)	4.91 (0.98)	4.88 (0.99)	4.67 (1.39)
	Median		4.60	4.90	4.89	4.89	4.86	4.80
	Min – Max		1.69 – 7.49	1.60 – 7.67	1.49 – 7.56	1.49 – 7.67	1.49 – 7.67	0.00 – 7.67
Psoriatic Arthritis Disease Duration at Baseline (years)	Mean (SD)	N/A	6.61 (7.25)	8.29 (8.36)	7.04 (7.24)	7.42 (7.62)	7.33 (7.58)	7.00 (7.56)
	Median		3.91	5.65	4.56	4.85	4.77	4.41
	Min – Max		0.05 – 36.8	0.57 – 59.8	0.32 – 49.8	0.32 – 59.8	0.05 – 59.8	0.00 – 59.8
Number of Prior Biologic Therapies	0, N (%)	67 (100%)	134 (76%)	219 (56%)	886 (99%)	1105 (86%)	1239 (85%)	1306 (86%)
	≥ 1, N (%)	--	43 (24%)	172 (44%)	5 (1%)	177 (14%)	220 (15%)	220 (14%)
Number of Prior csDMARDs	≤ 1, N (%)	67 (100%)	157 (89%)	168 (43%)	418 (47%)	586 (46%)	743 (51%)	810 (53%)
	> 1, N (%)	--	20 (11%)	223 (57%)	473 (53%)	696 (54%)	716 (49%)	716 (47%)
Methotrexate Use	No, N (%)	67 (100%)	78 (44%)	205 (52%)	313 (35%)	518 (40%)	596 (41%)	663 (43%)
	Yes, N (%)	--	99 (56%)	186 (48%)	578 (65%)	764 (60%)	863 (59%)	863 (57%)
Axial Spondylitis at Baseline	No, N (%)	67 (100%)	154 (87%)	317 (81%)	720 (81%)	1037 (81%)	1191 (82%)	1258 (82%)
	Yes, N (%)	--	23 (13%)	74 (19%)	171 (19%)	245 (19%)	268 (18%)	268 (18%)
Treatment-Emergent ADAs	Negative, N (%)	63 (94%)	142 (80%)	350 (90%)	812 (91%)	1162 (91%)	1304 (89%)	1367 (90%)
	Positive, N (%)	4 (6%)	35 (20%)	41 (10%)	79 (9%)	120 (9%)	155 (11%)	159 (10%)
Treatment-Emergent nAbs	Negative, N (%)	67 (100%)	176 (99%)	391 (100%)	891 (100%)	1282 (100%)	1458 (100%)	1525 (100%)
	Positive, N (%)	--	1 (1%)	--	--	--	1 (0%)	1 (0%)

Source: Population PK and ER report R&D/20/1395, Page 48-52, Table 2.

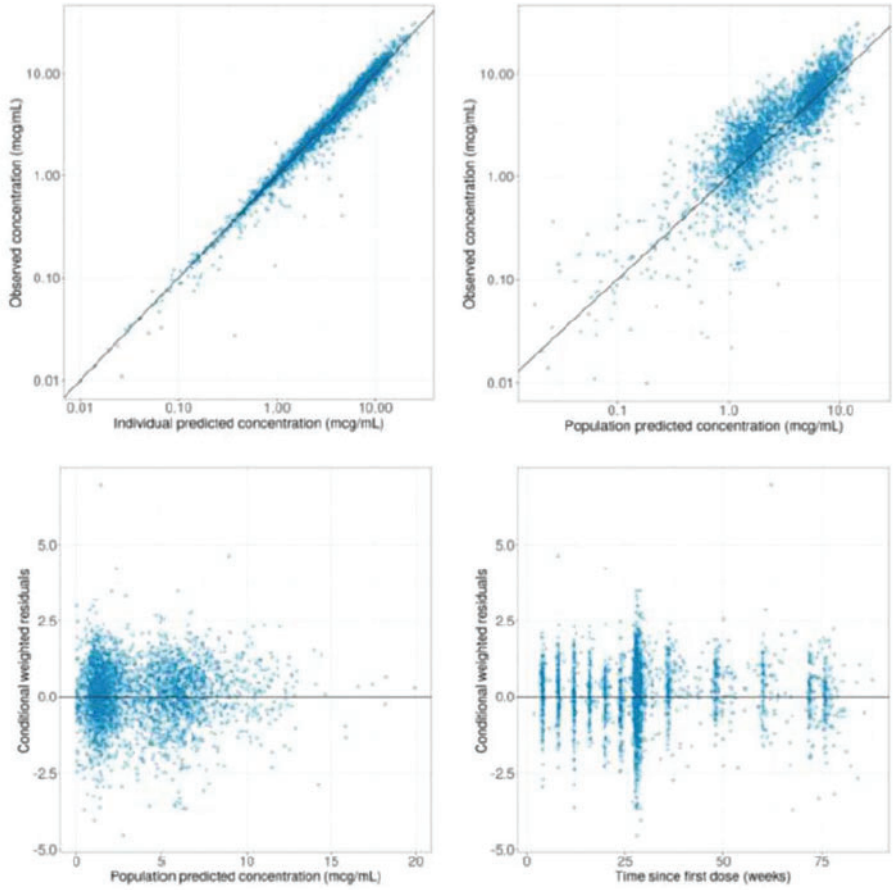
Table 54. Parameter estimates for final risankizumab population PK model

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

RSE = relative standard error

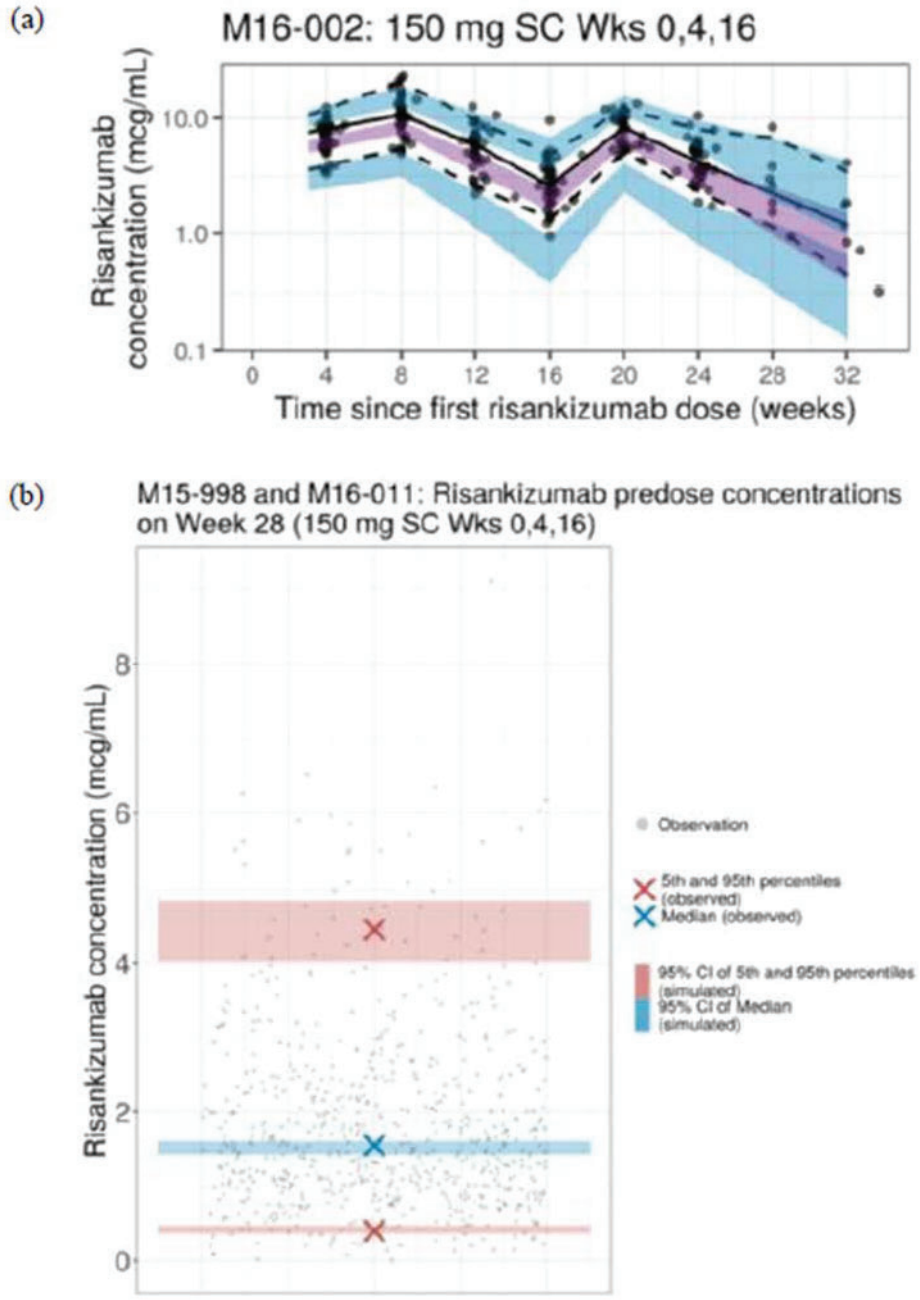
Source: Population PK and ER report R&D/20/1395, Page 62, Table 5.

Figure 12. Goodness-of-fit plots for final population PK model.



Source: Population PK and ER report R&D/20/1395, Page 64, Figure 7.

Figure 13. VPC for dosing interval between weeks 4 and 28 with final population PK model.



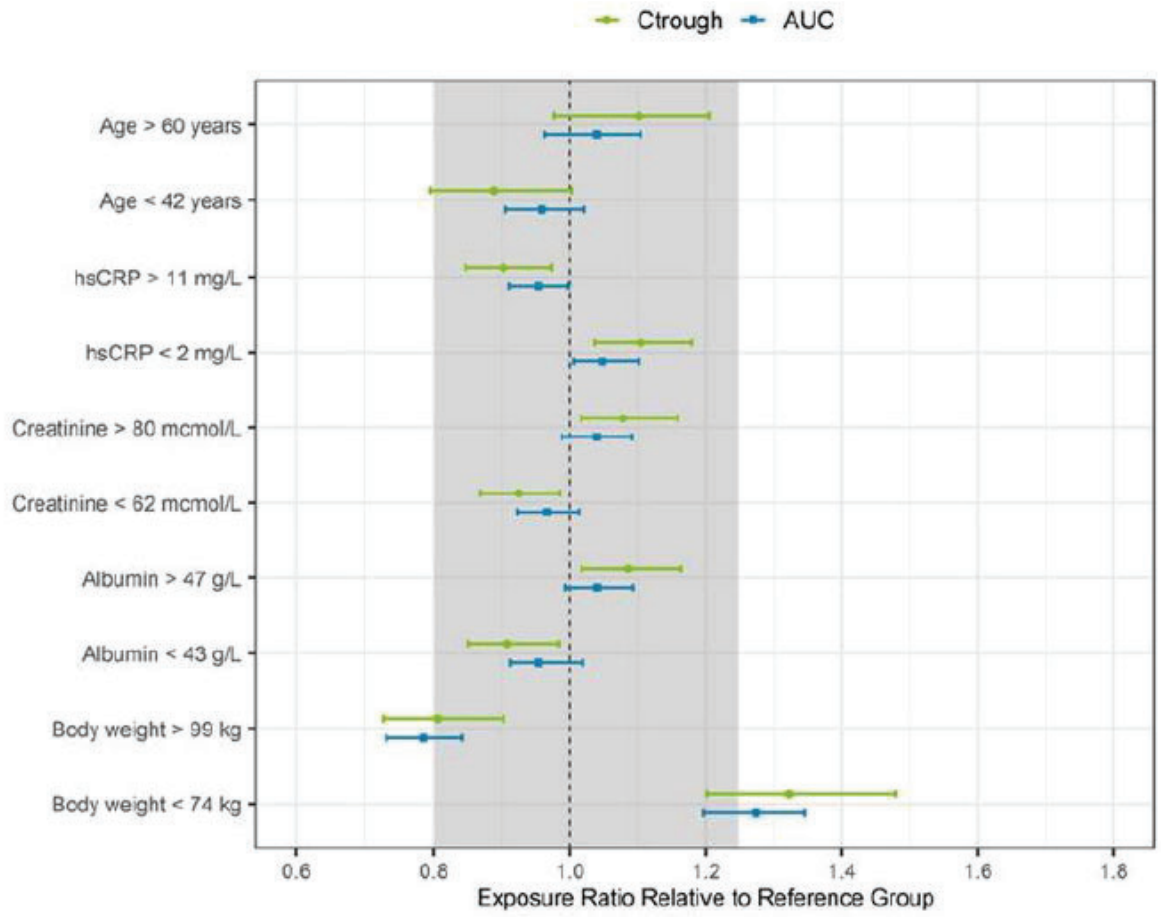
Source: Population PK and ER report R&D/20/1395, Page 66, Figure 8.

Table 55. Bootstrap result for final population PK model.

PARAMETER	REFERS TO THE FINAL MODEL PARAMETER	MODEL RESULT	BOOTSTRAP RESULT N = 999 MEAN	MEDIAN	95% CONFIDENCE INTERVAL
CL (L/day)	THETA1	0.248	0.249	0.248	0.229 - 0.271
V2 (L)	THETA2	4.710	4.723	4.700	4.240 - 5.340
Q (L/day)	THETA3	0.839	0.843	0.842	0.701 - 0.993
V3 (L)	THETA4	4.260	4.257	4.270	3.950 - 4.550
Ka (1/day)	THETA5	0.218	0.218	0.217	0.189 - 0.255
F	THETA6	0.835	0.837	0.836	0.770 - 0.910
Body Weight on CL	THETA7	0.869	0.868	0.866	0.769 - 0.969
Body Weight on V2	THETA8	1.460	1.465	1.470	1.280 - 1.660
Baseline Serum Albumin on CL	THETA9	-0.703	-0.702	-0.699	-0.961 - -0.458
Baseline Serum Creatinine on CL	THETA10	-0.201	-0.199	-0.198	-0.270 - -0.128
Baseline C-Reactive Protein on CL	THETA11	0.047	0.047	0.047	0.032 - 0.062
Age on CL	THETA12	-0.138	-0.139	-0.138	-0.194 - -0.084
Variance of Proportional Residual Error	EPS1	0.038	0.038	0.038	0.032 - 0.046
Variance of IIV on CL	ETA1_1	0.094	0.094	0.094	0.077 - 0.112
Variance of IIV on V2	ETA2_2	0.171	0.170	0.169	0.116 - 0.231
Variance of IIV on Ka	ETA3_3	0.164	0.172	0.170	0.029 - 0.314

Source: Population PK and ER report R&D/20/1395, Page 578, Table 13.2__7.3.

Figure 14. Forest plot for statistically significant covariates in the population PK on risankizumab exposures.



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

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

Source: Population PK and ER report R&D/20/1395, Page 68, Figure 9.

19.4.1.2 The FDA's Comments

The population PK model of risankizumab in subjects with psoriatic arthritis developed by the Applicant were verified by the reviewer. The models appear to be reasonable because of the good agreement between observations and predictions. The PK of risankizumab in subjects with psoriatic arthritis was similar to subjects with plaque psoriasis. Bodyweight was identified as statistically covariates for risankizumab CL. Subjects with higher bodyweight tend to have lower risankizumab exposures (C_{trough} and AUC in Figure 14). While the efficacy endpoints (ACR20/50/70, PASI 90/100 and MDA) evaluated in the treatment groups showed similar responses in different bodyweight groups. And the incidence of safety events (any AE,

SAE, infections, serious infections) were also similar across the exposure range of risankizumab or bodyweight, and comparable to subjects treated with placebo. The bodyweight effect on risankizumab exposure may not be clinically relevant. (Figure 21 and Figure 23).

15.4.2 *Exposure-Response Analysis for Efficacy*

15.4.2.1 E-R Efficacy Summary Table

General Information (E-R analysis)	
Goal of ER analysis	Evaluate the relationships between risankizumab systemic exposures and efficacy in subjects with active psoriatic arthritis
Study Included	Phase 2: M16-002 Phase 3: M15-998 and M16-011
Endpoint	Primary: ACR20 at Week 16/24 Other: ACR50 at Week 16/24 ACR70 at Week 16/24 PASI 90 (for subjects with ≥ 3% body surface area [BSA] psoriasis at baseline) at Week 16/24 PASI 100 (for subjects with ≥ 3% BSA psoriasis at baseline) at Week 16/24 Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 16/24 Minimal Disease Activity (MDA) at Week 16/24 Endpoints at Week 24 were studied in Phase 3 studies

		Endpoints at Week 16 were studied in Phase 2 and Phase 3 studies
No. of Patients		Placebo: 742 Treatment: 850
Population Characteristics (Table XX)	General	In treatment group: Age (year): 52 (range: 20 -85) Weight (kg): 86.7 (range: 28.6 – 186) Gender: 433 (50.9%) Male Race: 793 (93.3%) White; 32 (3.8%) Asian; (0.7%) Black; 20 (2.2%) Other or missing
	Pediatrics (if any)	No pediatrics were involved in the analysis
Dose(s) Included		150 mg SC Weeks 0, 4, 16 and every 12 weeks thereafter 150mg sc Weeks 0 4 and 16 150mg sc Weeks 0 and 12 75mg sc Weeks 0 Placebo
Exposure Metrics Explored (range)		Observed C_{trough}: 0.00217-9012 mcg/mL

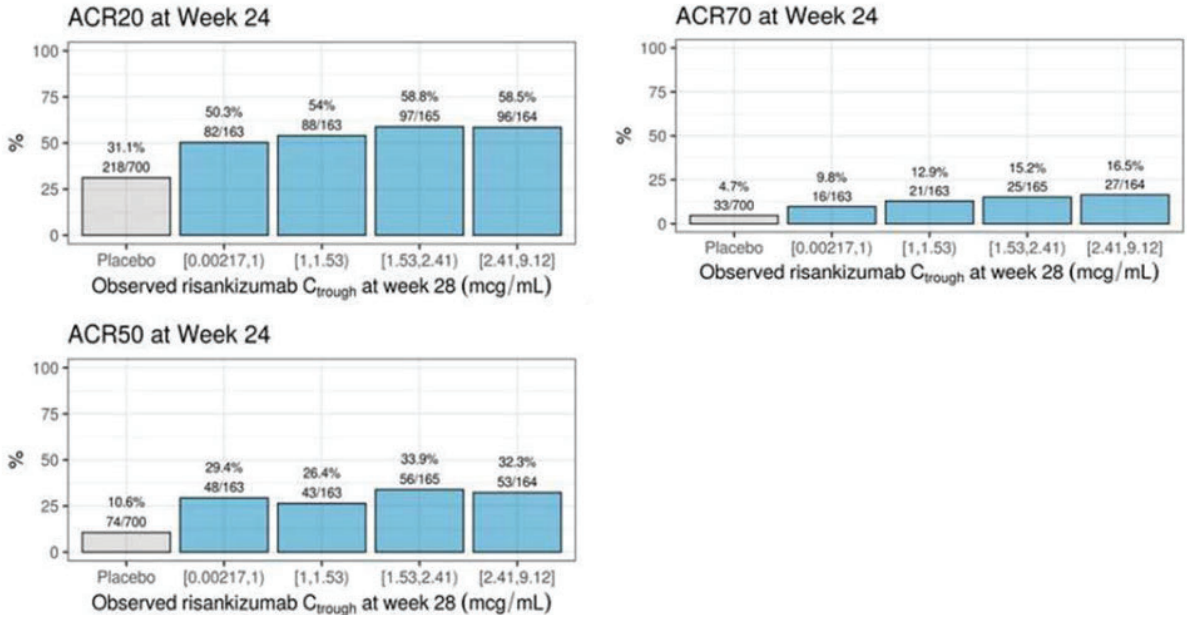
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	Logistic Regression	Acceptable
Model Parameter Estimates	Table 56	Acceptable
Covariates and Clinical Relevance	Stratification factors were included in the logistic regression	

Visualization of E-R relationships	Logistic regression analyses showed that subjects treated with risankizumab had statistically significant higher response rates compared to placebo group. Systemic exposures showed no statistically significant E-R relationship after accounting for the treatment effect. (Figure 15 - Figure 18)	Acceptable

General Information (Pharmacodynamics study)		
Goal of ER analysis		Determine and compare the change from baseline in the levels of IL-17A, IL-17F, IL-22, IL-6, and TNF-alpha at Week 4 and Week 24 in risankizumab- and placebo-treated psoriatic arthritis (PsA) subjects.
Study Included		M15-998
Endpoint		Change from baseline in the levels of IL-17A, IL-17F, IL-22, IL-6, and TNF-alpha at Week 4 and Week 24
No. of Patients		Placebo: 50 Treatment: 50
Population Characteristics	General	Table 57
	Pediatrics (if any)	No pediatrics were involved in the analysis
Dose(s) Included		150 mg SC Weeks 0, 4, 16 and every 12 weeks thereafter
Final Model Parameters	**Summary**	**Acceptability**

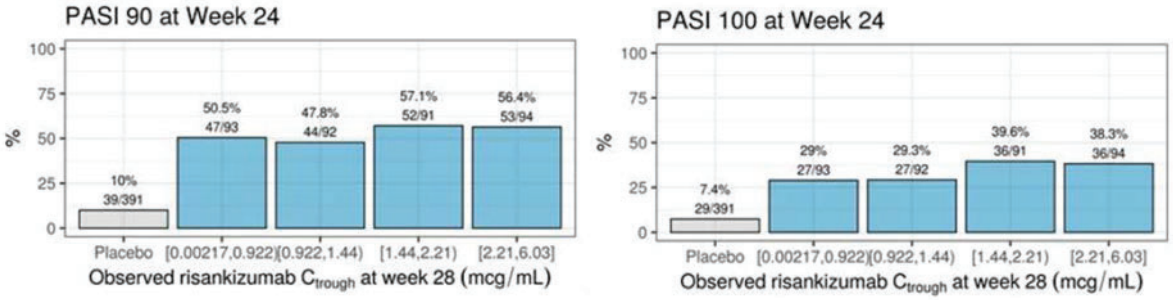
		[FDA's comments]
Visualization	Pharmacodynamics study showed that treatment with risankizumab 150 mg SC at Week 0, Week 4 and q12w thereafter resulted in statistically significant decrease in the levels of IL-17A, IL-17F and IL-22 compared to baseline. No clear change of IL-6 and TNF-alpha levels were observed. Compared to PBO, risankizumab treatment resulted in significantly decrease in IL-17A, IL-17F and IL-22 levels. (Figure 20)	Acceptable

Figure 15. E-R analyses for ACR20/50/70 responses (NRI) from phase 3 studies M15-998 and M16-011 at Week 24.



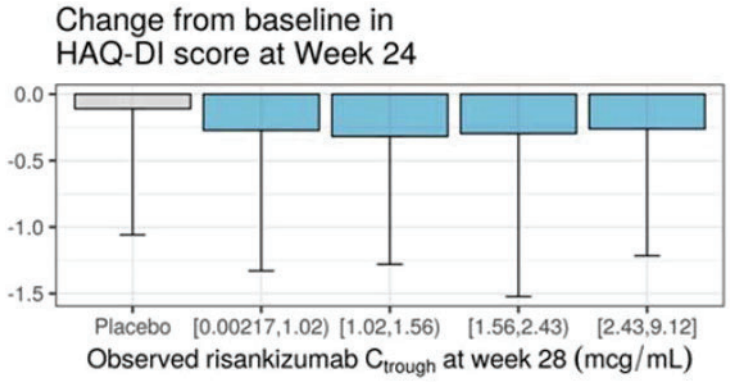
Source: Population PK and ER report R&D/20/1395, Page 72, Figure 10.

Figure 16. E-R analyses for PASI 90/100 responses from phase 3 studies M15-998 and M16-011 at Week 24



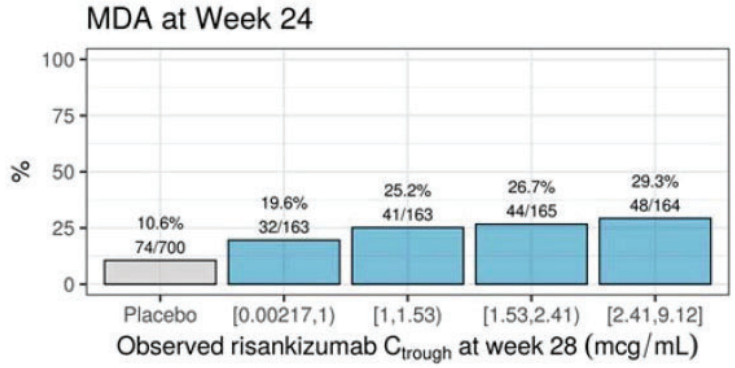
Source: Population PK and ER report R&D/20/1395, Page 74, Figure 11.

Figure 17. E-R analysis for HAQ-DI score change from baseline from phase 3 studies M15-998 and M16-011 at Week 24



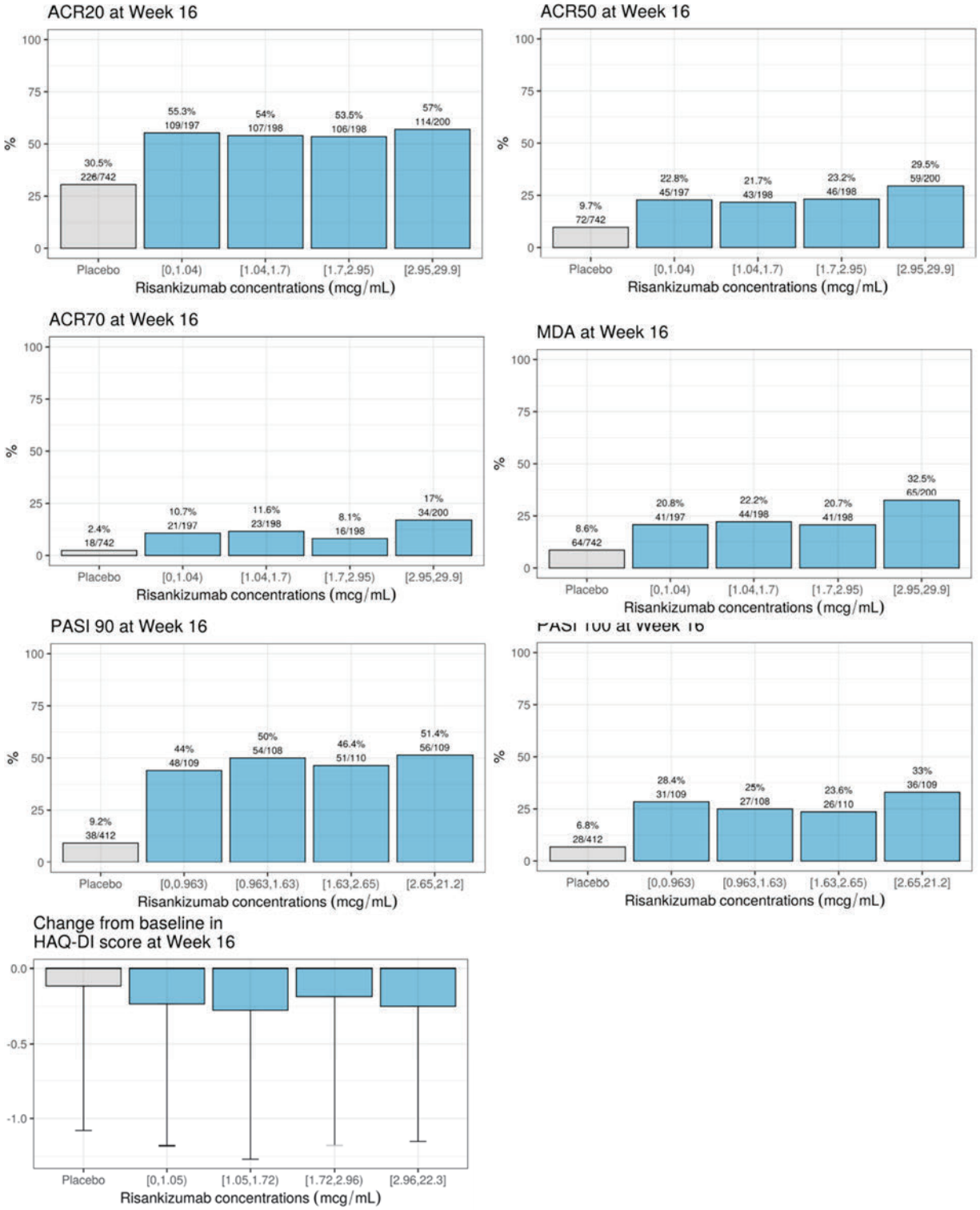
Source: Population PK and ER report R&D/20/1395, Page 75, Figure 12.

Figure 18. E-R analysis for MDA response from phase 3 studies M15-998 and M16-011 at Week 24



Source: Population PK and ER report R&D/20/1395, Page 76, Figure 13.

Figure 19. Exposure-response analysis for efficacy endpoints at Week 16.



Source: Population PK and ER report R&D/20/1395, Page 582-588, Figure 13.3.

Table 56. Logistic regression model parameters for all efficacy endpoints at Week 24.

Response Variable	Model	Converged	AIC	Variable	Estimate(SEE)	95% CI	p Value
ACR20	Treatment Effect Model (Slope, Intercept), with stratification factors	YES	1748	Intercept	-0.151 (0.236)	-0.613 - 0.311	p>0.05
				EXPOSURE	0.094 (0.065)	-0.033 - 0.221	p>0.05
				TRT=Placebo	-0.866 (0.165)	-1.189 - -0.543	p<0.01
				nCS-DMARDS=0	-0.428 (0.478)	-1.364 - 0.508	p>0.05
				nBIOT=0	0.610 (0.176)	0.265 - 0.955	p<0.01
				Psoriasis Surface Area <3% BSA	-0.460 (0.117)	-0.689 - -0.230	p<0.01
				Presence of Enthesitis at Baseline = yes	-0.178 (0.132)	-0.436 - 0.081	p>0.05
				Presence of Dactylitis at Baseline = yes	0.082 (0.129)	-0.171 - 0.336	p>0.05
ACR50	Treatment Effect Model (Slope, Intercept), with stratification factors	YES	1262	Intercept	-1.336 (0.300)	-1.923 - -0.748	p<0.01
				EXPOSURE	0.071 (0.069)	-0.066 - 0.207	p>0.05
				TRT=Placebo	-1.214 (0.199)	-1.604 - -0.825	p<0.01
				nCS-DMARDS=0	0.340 (0.553)	-0.743 - 1.423	p>0.05
				nBIOT=0	0.713 (0.243)	0.237 - 1.190	p<0.01
				Psoriasis Surface Area <3% BSA	-0.603 (0.149)	-0.895 - -0.311	p<0.01
				Presence of Enthesitis at Baseline = yes	-0.094 (0.161)	-0.409 - 0.222	p>0.05
				Presence of Dactylitis at Baseline = yes	0.252 (0.156)	-0.053 - 0.558	p>0.05
ACR70	Treatment Effect Model (Slope, Intercept), with stratification factors	YES	783	Intercept	-2.625 (0.434)	-3.474 - -1.775	p<0.01
				EXPOSURE	0.153 (0.088)	-0.021 - 0.326	p>0.05
				TRT=Placebo	-0.886 (0.276)	-1.427 - -0.346	p<0.01
				nCS-DMARDS=0	0.273 (0.793)	-1.281 - 1.827	p>0.05
				nBIOT=0	0.718 (0.358)	0.016 - 1.420	p<0.05
				Psoriasis Surface Area <3% BSA	-0.516 (0.207)	-0.921 - -0.111	p<0.05
				Presence of Enthesitis at Baseline = yes	-0.122 (0.219)	-0.551 - 0.306	p>0.05
				Presence of Dactylitis at Baseline = yes	0.452 (0.205)	0.049 - 0.854	p<0.05

Response Variable	Model	Converged	AIC	Variable	Estimate(SEE)	95% CI	p Value
MDA	Treatment Effect Model (Slope, Intercept), with stratification factors	YES	1208	Intercept	-1.047 (0.287)	-1.609 - -0.484	p<0.01
				EXPOSURE	0.128 (0.070)	-0.009 - 0.265	p>0.05
				TRT=Placebo	-0.815 (0.204)	-1.215 - -0.414	p<0.01
				nCS-DMARDS=0	-0.835 (0.763)	-2.332 - 0.661	p>0.05
				nBIOT=0	0.232 (0.228)	-0.215 - 0.678	p>0.05
				Psoriasis Surface Area <3% BSA	-0.150 (0.150)	-0.443 - 0.144	p>0.05
				Presence of Enthesitis at Baseline = yes	-0.519 (0.158)	-0.829 - -0.208	p<0.01
				Presence of Dactylitis at Baseline = yes	-0.130 (0.170)	-0.463 - 0.202	p>0.05
PASI 90	Treatment Effect Model (Slope, Intercept), with stratification factors	YES	776	Intercept	-0.045 (0.332)	-0.696 - 0.606	p>0.05
				EXPOSURE	0.145 (0.093)	-0.038 - 0.329	p>0.05
				TRT=Placebo	-2.069 (0.254)	-2.568 - -1.570	p<0.01
				nCS-DMARDS=0	0.282 (0.585)	-0.864 - 1.428	p>0.05
				nBIOT=0	-0.042 (0.264)	-0.559 - 0.475	p>0.05
				Presence of Enthesitis at Baseline = yes	-0.088 (0.199)	-0.479 - 0.302	p>0.05
				Presence of Dactylitis at Baseline = yes	0.023 (0.197)	-0.363 - 0.409	p>0.05
PASI 100	Treatment Effect Model (Slope, Intercept), with stratification factors	YES	691	Intercept	-1.068 (0.362)	-1.778 - -0.359	p<0.01
				EXPOSURE	0.175 (0.094)	-0.009 - 0.360	p>0.05
				TRT=Placebo	-1.560 (0.279)	-2.107 - -1.013	p<0.01
				nCS-DMARDS=0	-0.342 (0.693)	-1.701 - 1.017	p>0.05
				nBIOT=0	0.057 (0.289)	-0.509 - 0.623	p>0.05
				Presence of Enthesitis at Baseline = yes	0.062 (0.216)	-0.362 - 0.486	p>0.05
				Presence of Dactylitis at Baseline = yes	0.051 (0.211)	-0.363 - 0.464	p>0.05

Source: Population PK and ER report R&D/20/1395, Page 589-591, Table 13.3_5.

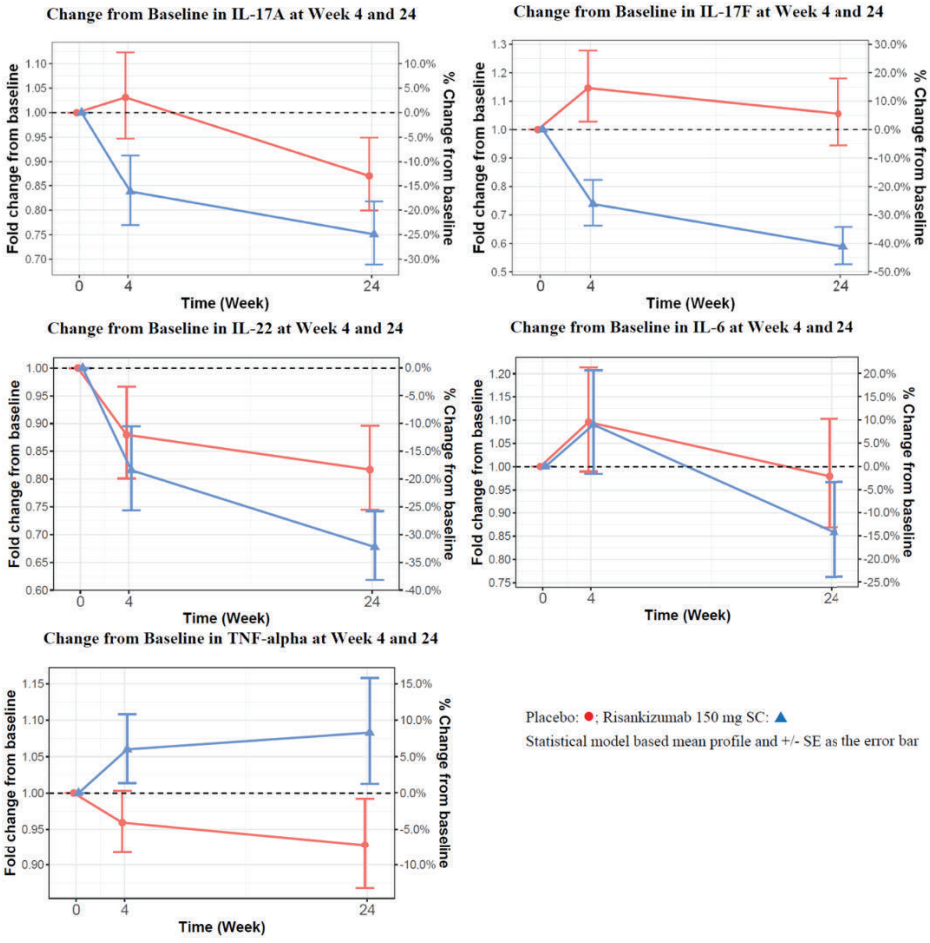
Table 57. Biomarker subjects sub-population baseline characteristics

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

PBO (placebo); RZB (risankizumab)

Source: Pharmacodynamics Report, R&D/21/0058, Page 6, Table 1.

Figure 20. Change from baseline in biomarkers at Week 4 and Week 24.



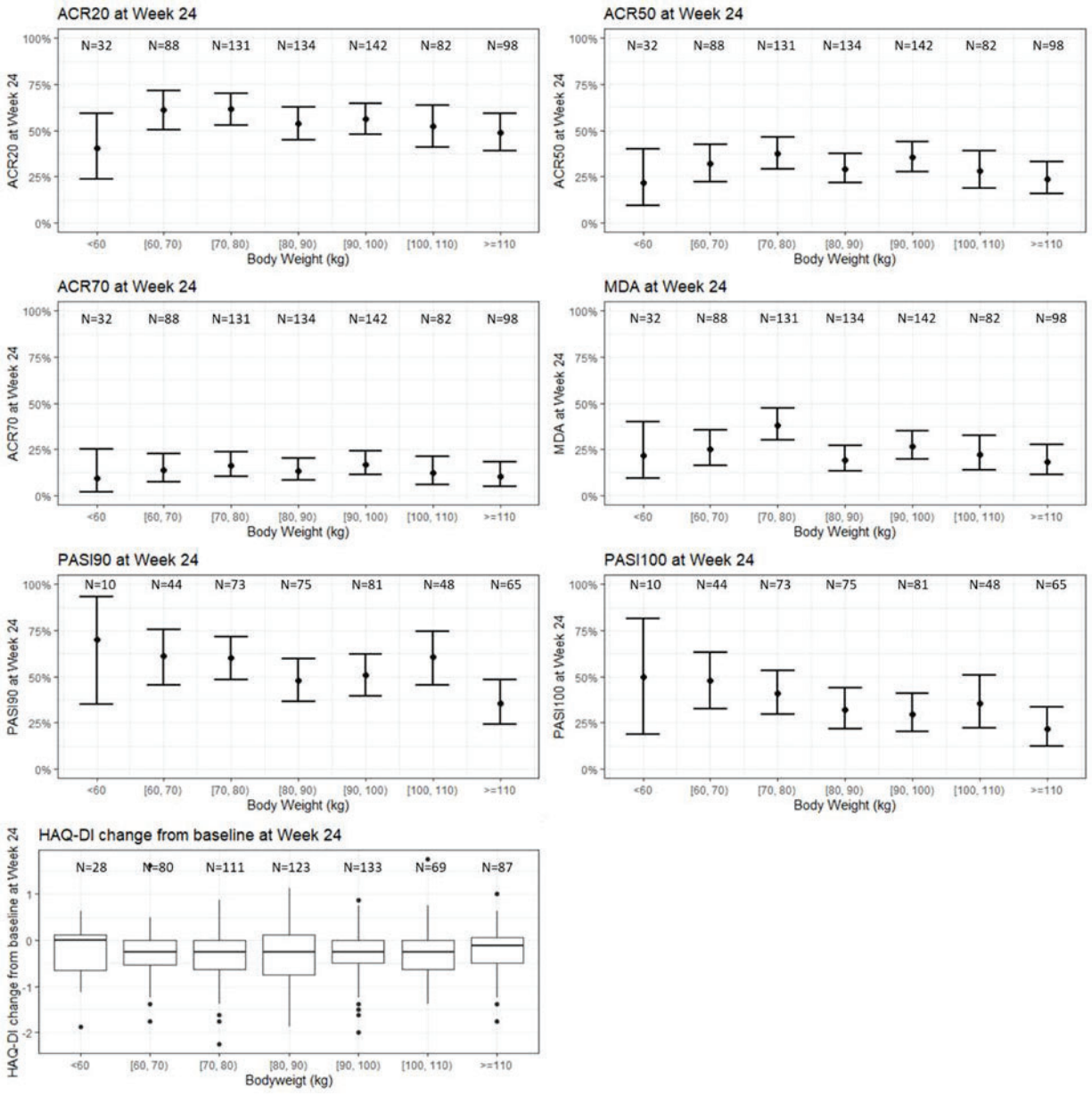
Source: Pharmacodynamics Report, R&D/21/0058, Page 7-12, Figure 1-5.

19.4.2.2 The FDA's Assessment

The results of E-R efficacy analysis by the Applicant were verified by reviewer. Efficacy endpoints (ACR20, ACR50, ACR70, MDA in all subjects and PASI 90, PASI 100 in subject with psoriasis surface area >3% BSA) at Week 24 were analyzed by logistic regression. Subjects treated with risankizumab showed statistically significant higher response rates compared to placebo for all evaluated efficacy endpoints in the analysis. While E-R quartile analyses showed that subjects with relatively lower risankizumab exposures had numerically lower response rates compared to the higher exposures for ACR20/50/70, PASI 100, and MDA. The relationship is not statistically significant after accounting for the treatment effect. Bodyweight was identified as a significant covariate on CL in the population PK analysis, while no apparent difference on efficacy

endpoints were observed between the different bodyweight groups in Phase 3 Studies (M15-998 and M16-011) treatment arms. (Figure 21)

Figure 21. Reponses at Week at 24 in phase 3 studies M15-998 and M16-011 treatment arms in different bodyweight groups.



Source: Reviewer's analysis.

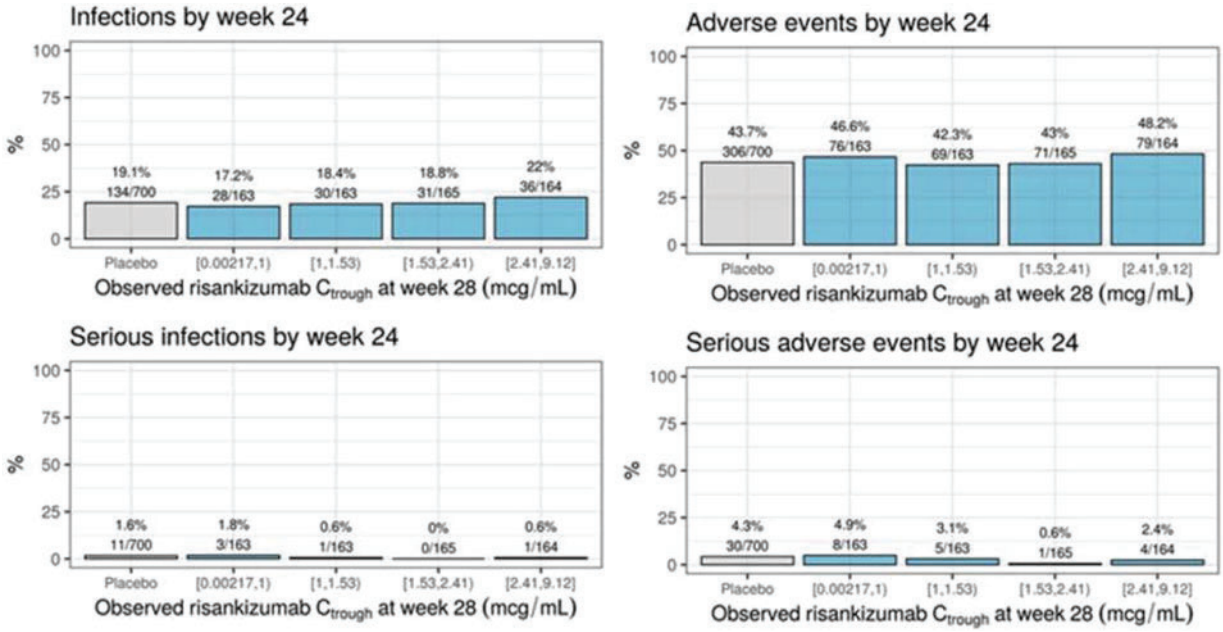
15.4.3 *Exposure-Response Analysis for Safety*

15.4.3.1 ER Safety Summary Table

General Information			
Goal of ER analysis		Evaluate the relationships between risankizumab systemic exposures and safety parameters in subjects with active psoriatic arthritis	
Study Included		Phase 3: M15-998 and M16-011	
Population Included		ITT	
Endpoint		Infections, serious infections, adverse events, and serious adverse events by Week 24	
No. of Patients		Placebo: 700 Treatment: 655	
Population Characteristics (Table XX)	General	Age median: 52 yr (range: 20 - 85) Weight median: 86 kg (range: 28.6 - 186) Gender: 659 (48.6%) male Race: 1285 (94.8%) White, 10 (0.74%) Black, 38 (2.8%) Asian, 22 (1.6%) Other.	
	Organ impairment	Renal (CrCL): 1121 (82.7%) Normal, 199 (14.7%) Mild Impairment, 35 (2.6%) Moderate Impairment	
	Pediatrics (if any)	No pediatrics involved in the analysis	
	Geriatrics (if any)	192 (13.6%) subj >=65 yr 30 (2.1%) subj >=75 yr	
Dose(s) Included		150 mg SC Weeks 0, 4, 16 and every 12 weeks thereafter	
Exposure Metrics Explored (range)		In treatment group: Observed C_{trough} at Week 28: 0.00217 – 9.12	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**

Model Structure	Graphical analyses	Acceptable
Visualization of E-R relationships	No apparent relationship between risankizumab exposure and any AE, SAE, infection, or serious infection over the first 24 weeks in the Phase 3 studies were observed (**Figure 23**).	Acceptable

Figure 22. E-R analysis for selected safety events in phase 3 studies M15-998 and M16-011 over Weeks 0 to 24.

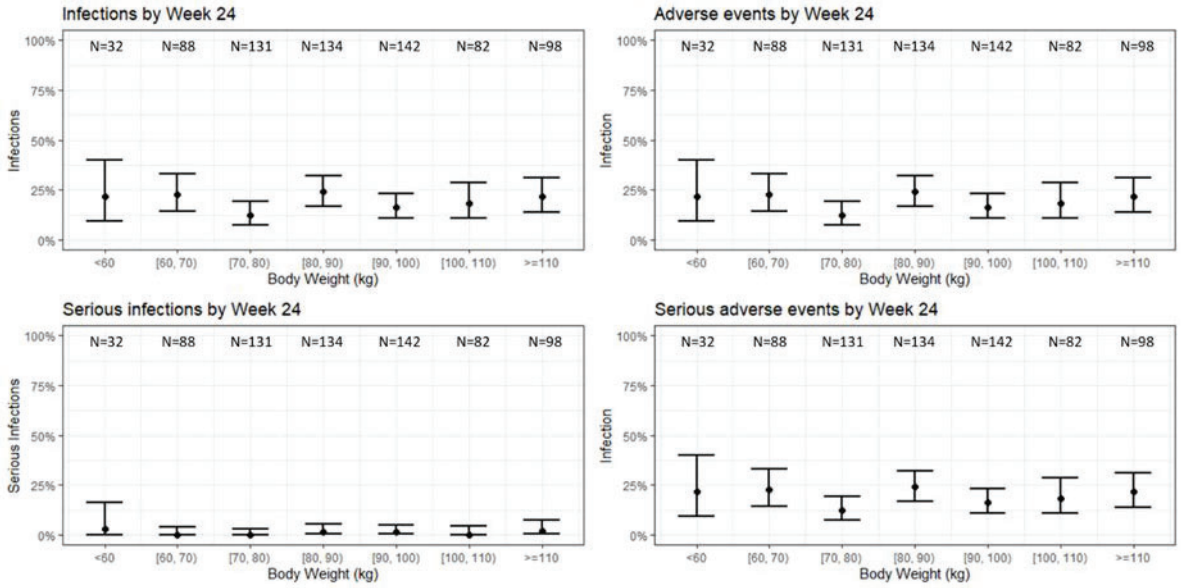


Source: Population PK and ER report R&D/20/1395, Page 78, Figure 14.

15.4.3.2 The FDA's Assessment:

The E-R analysis for any AE, SAE, infection, or serious infection over the first 24 weeks with risankizumab exposures in the Phase 3 studies were checked by the reviewer. The incidence rates of these selected safety endpoints in risankizumab treatment group didn't increase with observed C_{trough} at Week 28 and were similar as the incidence rates in placebo group. The incidence rates were also similar between the different bodyweight groups in Phase 3 Studies (M15-998 and M16-011) treatment arms. (Figure 23)

Figure 23. Safety events in phase 3 studies M15-998 and M16-011 treatment arms in different bodyweight groups.



Source: Reviewer's analysis.

Overall benefit-risk evaluation based on E-R analyses:

E-R analysis for efficacy showed that subjects with treatment had statistically significant higher response rates compared to placebo. Risankizumab systemic exposures showed no evident exposure-response relationships after accounting the treatment effecter. E-R safety analysis showed no apparent relationship between risankizumab exposure and any AE, SAE, infection, or serious infection over the first 24 weeks in the Phase 3 studies of risankizumab in subjects with active psoriatic arthritis. The incidence rates were also similar to placebo groups. Overall, the proposed dosing for risankizumab is acceptable.

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RAJ NAIR
01/21/2022 11:01:39 AM

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01/21/2022 11:09:15 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761105Orig1s014

STATISTICAL REVIEW(s)

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	BLA 761105
Supplement #:	014
Related IND #:	118702
Product Name:	Skyrizi (risankizumab-rzza) injection
Indication(s):	Psoriatic Arthritis
Applicant:	AbbVie
Dates:	Receipt Date: March 23, 2021 PDUFA Date: January 23, 2022
Review Priority:	Standard
Biometrics Division:	III
Statistical Reviewer:	Hongling Zhou, Ph.D.
Concurring Reviewers:	David Petullo, M.S.
Medical Division:	Division of Pulmonary, Allergy and Rheumatology Products
Clinical Team:	Clinical Reviewer: Austin Anderson, MD Clinical Team Leader: Raj Nair, MD
Project Manager:	Susan Rhee

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

The applicant submitted a supplemental Biologics License Application (sBLA) for the approval of SKYRIZI® (risankizumab-rzaa) Injection for the treatment of active psoriatic arthritis (PsA) in adults. The data to support this efficacy supplement will primarily be based on two phase 3 studies. Study M16-011 is titled "A Phase 3, Randomized, Double-Blind, Study Comparing Risankizumab to Placebo in Subjects with Active Psoriatic Arthritis (PsA) Who Have a History of Inadequate Response to or Intolerance to at Least One Disease Modifying Anti-Rheumatic Drug (DMARD) Therapy (KEEPsAKE 1)." And Study M15-998 is titled "A Phase 3, Randomized, Double-Blind Study Comparing Risankizumab to Placebo in Subjects with Active Psoriatic Arthritis Including Those Who Have a History of Inadequate Response or Intolerance to Biologic Therapy(ies) (KEEPsAKE 2)." The data for a phase 2 study (M16-002) was included in the sBLA submission per the Division's request to address whether the loading dose at Week 4 drives the efficacy compared to chronic dosing every 12 weeks. The studies are summarized in Table 1 below.

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment Arms	Number of subjects	Primary Endpoint/ Analysis	Preliminary Findings
M16-011	MC, R, DB, PG, PC Subjects with moderately to severely active psoriatic arthritis who have had an inadequate response (lack of efficacy after a minimum 12-wk duration of therapy) or intolerance to at least 1 csDMARD (csDMARD-IR).	Risankizumab 150 mg Placebo	483 481	The proportion of subjects achieving ACR20** response at Week 24. The comparisons between the Risankizumab and placebo groups for the primary efficacy endpoint was performed using the Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors.	Subjects in the risankizumab arm experienced improvement in signs and symptoms of psoriatic arthritis, as demonstrated by a statistically significant difference between the risankizumab and placebo arms in the percentage of subjects who achieved ACR20 response at Week 24. The first 8 ranked secondary endpoints were also achieved
M15-998	MC, R, DB, PG, PC Subjects with moderately to severely active psoriatic arthritis who have had an inadequate response (lack of efficacy after a minimum 12-wk duration of therapy) or intolerance to at least 1 csDMARD	Risankizumab 150 mg Placebo	224 219	The proportion of subjects achieving ACR20** response at Week 24. The comparisons between the Risankizumab and placebo groups for the primary efficacy endpoint was performed using the Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors.	Subjects in the risankizumab arm experienced improvement in signs and symptoms of psoriatic arthritis, as demonstrated by a statistically significant difference between the risankizumab and placebo arms in the percentage of subjects who achieved ACR20 response at Week 24. All ranked

	(csDMARD-IR).				secondary efficacy endpoints were also achieved.
M16-002	MC, R, DB, PG, PC, DR Subjects with active psoriatic arthritis	Arm 1: risankizumab 150 mg every 4 weeks Arm 2: risankizumab 150 mg Weeks 0, 4, and 16 Arm 3: risankizumab 150 mg Weeks 0 and 12 Arm 4: risankizumab 75 mg Week 0 Arm 5: placebo	42 42 39 20 42	the proportion of patients who achieve ACR20** at Week 16 The difference of ACR20 response rates at Week 16 were estimated and tested using the stratified Cochran-Mantel-Haenszel risk difference estimate.	Efficacy in treating the arthritic manifestations of psoriatic arthritis was demonstrated by achievement of the primary endpoint of ACR 20 response at Week 16. Statistically significant differences were also observed in the proportion of subjects who achieved ACR 70 responses at Week 16.

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, DR: dose ranging
** ACR20 = American College of Rheumatology 20 Response is defined as at least 20% improvement in SJC* compared to baseline AND At least 20% improvement in TJC* compared to baseline AND At least 20% improvement in at least 3 out of the following 5 variables: Patient's assessment of pain on VAS, Patient's global assessment of the disease on VAS, Investigator's global assessment of the disease on VAS, Patient's assessment of disability on HAQ, and Acute phase reactant (serum CRP).

2. Assessment of Protocols and Study Reports

Table 3: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	**Yes**
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	**No interim analyses were planned for the studies.**
Appropriate details and/or references for novel statistical	**NA**

methodology (if present) are included (e.g., codes for simulations).	
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Missing data handling included NRI-C*, MMRM, AO, AO with imputation, MI, linear extrapolation for radiographic data, and tipping point analysis. The appropriateness of these methodology will be a review issue and subsequent IRs may be needed.

*NRI-C = non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19, MMRM=Mixed-Effect Model Repeat Measurement (MMRM) model

3. Electronic Data Assessment

Table 4: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\BLA761105\0108\m5\datasets
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	SDTM and ADaM
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	adresp.xpt
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 5: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc..	X			

Content Parameter	Yes	No	NA	Comments
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.).	X			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups.	X			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			
Application appears to be free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements.	X			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?
Yes.

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

None.

5.2. Information Requests/Review Issues

Potential Review Issues (Internal)

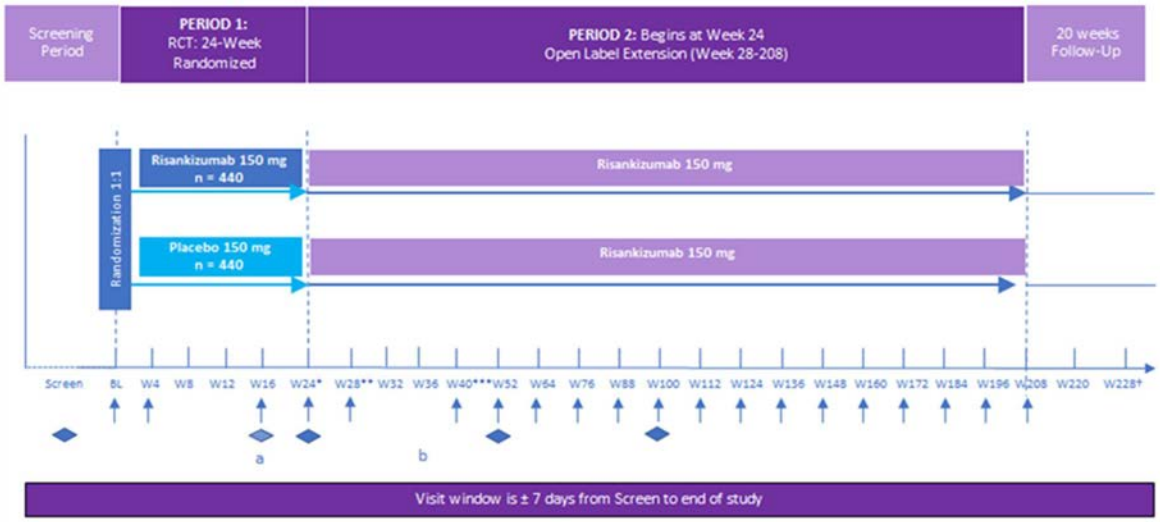
1. Since subjects classified as non-responders at Week 16 had the option to add or modify rescue concomitant medications/therapy, analyses and interpretation for efficacy endpoints after Week 16 will be a review issue.
2. The impact of missing data on the analysis results were assessed using different ways to handle missing data: NRI-C, MMRM, AO, AO with imputation, MI, linear extrapolation for radiographic data, and tipping analysis. The appropriateness of these methodology will be a review issue.

Appendix I Summary of Study M16-011

The primary objective of the study was to compare the efficacy of risankizumab 150 mg versus placebo for the treatment of signs and symptoms of psoriatic arthritis in the study population during the double-blind Period 1. The secondary objectives in Period 1 were to compare the efficacy of risankizumab 150 mg vs. placebo for the inhibition of progression of structural damage as assessed by radiographs in the study population, and to compare the safety and tolerability of risankizumab 150 mg vs. placebo in the study population.

This is a Phase 3, global, multicenter study that evaluated subjects with moderately to severely active psoriatic arthritis who have had an inadequate response (lack of efficacy after a minimum 12-wk duration of therapy) or intolerance to at least 1 csDMARD (conventional synthetic disease modifying anti-rheumatic drugs) (csDMARD-IR). The study consists of a Screening Period (approximately 35 days), Period 1, Period 2, and a 20-week Follow-up Period (See the study schematic in Figure 1). Period 1 was a 24-week randomized, double blind, placebo-controlled, parallel-group period. Period 2 was the long-term treatment period and started at Week 24. To maintain the blind to the original treatment allocation, treatment at the Week 24 Visit was to be blinded: subjects randomized to placebo receive a blinded dose of risankizumab 150 mg, and subjects randomized to risankizumab receive a blinded dose of placebo. At Week 28 and for the remaining dosing visits (to Week 208), all subjects are to receive open-label risankizumab 150 mg q12w. Subjects are to remain blinded to the original randomization allocation for the duration of the study. The total study duration is 228 weeks including a telephone call 140 days (20 weeks) after last dose of study drug. See dosing schedule outlined in Figure 1.

Figure 1 Study M16-011 Design Schematic



BL = Baseline; RCT = randomized clinical trial; W = Week
* At Week 24, subjects randomized to placebo in Period 1 were to receive a blinded dose of risankizumab. Subjects randomized to risankizumab treatment in Period 1 were to receive a blinded dose of placebo.
** At Week 28, subjects randomized to placebo in Period 1 were to receive a 2nd dose of risankizumab. Subjects randomized to risankizumab in Period 1 were to receive risankizumab (scheduled dose).
*** From Week 40 to Week 208 Visits, doses were to occur q12w.

† Follow up phone call. Dosing.
Bilateral radiographs of hands and feet.

a. At Week 16, subjects classified as non-responders (defined as not achieving at least a 20% improvement in either or both tender joint count [TJC] and swollen joint count [SJC] at both Week 12 and Week 16) compared to Baseline had the option to add or modify rescue concomitant medications/therapy. Rescue therapy qualification was to occur only at Week 16 Visit.
b. Starting at Week 36, subjects classified as non-responders are to be discontinued from study drug.

Source: M16-011 Clinical Study Report-Interim Figure 1

A total of 964 subjects were randomized in a ratio of 1:1 to risankizumab 150 mg (483) or placebo (481). This sample size provides at least 90% power to detect at least 25% difference in American College of Rheumatology 20% improvement criteria (ACR20) response rate (assuming a placebo ACR20 response rate of 35.7%). With the given sample size, there is approximately 80% power to detect a standardized effect size of 0.20 in change from Baseline in modified Total Sharp Score (mTSS) for risankizumab vs. placebo arm at Week 24 using the van der Heijde-Sharp score modified for psoriatic arthritis (distal interphalangeal joints of hands added).

The primary endpoint was defined as the proportion of subjects achieving American College of Rheumatology (ACR)20 Response (ACR20) at Week 24. ACR20 Response is defined as at least 20% improvement in SJC* compared to baseline AND At least 20% improvement in TJC* compared to baseline AND At least 20% improvement in at least 3 out of the following 5 variables: Patient's assessment of pain on VAS, Patient's global assessment of the disease on VAS, Investigator's global assessment of the disease on VAS, Patient's assessment of disability on HAQ, and Acute phase reactant (serum CRP). The comparisons between the Risankizumab and placebo groups for the primary efficacy endpoint was performed using the Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors. The study achieved the primary endpoint as shown in sponsor’s analysis results (Table A1). Subjects in the risankizumab arm experienced improvement in signs and symptoms of psoriatic arthritis, as demonstrated by a statistically significant difference between the risankizumab and placebo arms in the percentage of subjects who achieved ACR20 response at Week 24.

Table A1 ACR20 Response at Week 24 for Study M16-011 (NRI-C, FAS)

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

ACR20 = American College of Rheumatology 20% improvement criteria; CI = confidence interval; COVID-19 = coronavirus disease-2019; Diff = difference; FAS = Full Analysis Set; NRI-C = non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19

Source: M16-011 Clinical Study Report – Interim Table 8

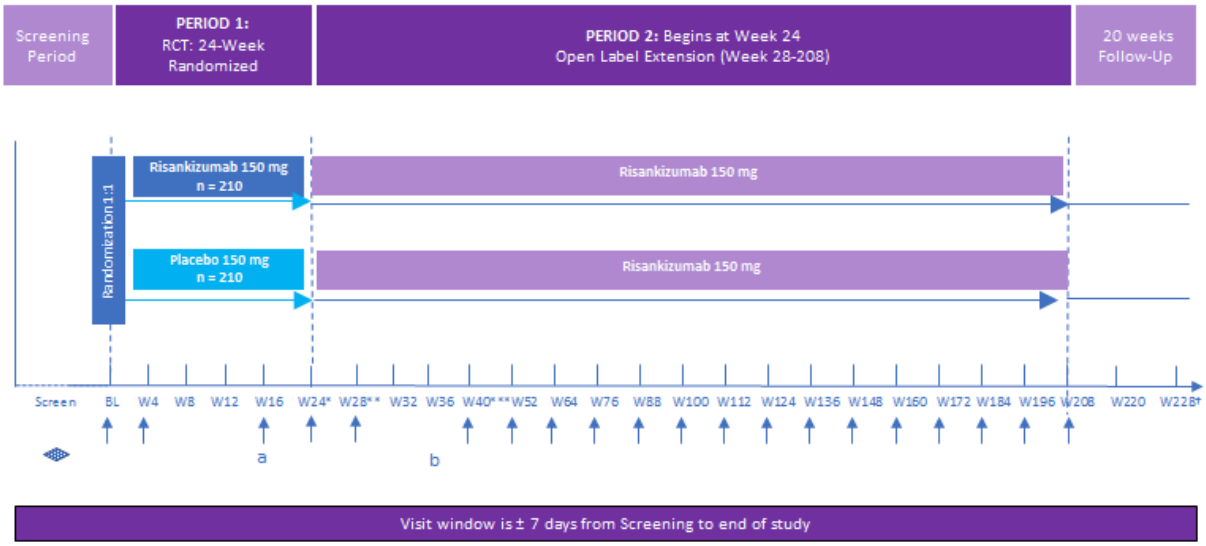
The first 8 ranked secondary endpoints were also achieved. These 8 ranked secondary endpoints are Change from Baseline in HAQ-DI at Week 24, HAQ-DI at Week 24, PASI 90 response at Week 24 (for subjects with BSA ≥ 3% at Baseline), ACR20 response at Week 16, MDA response at Week 24, Change from Baseline in modified Nail Psoriasis Severity Index (mNAPSI) at Week 24, Change from Baseline in Physician Global Assessment of Fingernail Psoriasis (PGA-F) at Week 24, Resolution of enthesitis defined as Leeds Enthesitis Index (LEI) at Week 24, and resolution of dactylitis (LDI = 0) at Week 24 in subjects with dactylitis at Baseline. The analysis for 7th and 8th ranked secondary endpoints used pooled data from Study M16-001 and Study M15-998.

Appendix II Summary of Study M15-998

This is a Phase 3, global, multicenter study that evaluated subjects with moderately to severely active psoriatic arthritis. The subject population consists of no more than 50% with a demonstrated inadequate response (lack of efficacy after a minimum 12-week duration of therapy) or intolerance to 1 or 2 biologic therapies (Bio-IR). The remaining study population consists of subjects who had an inadequate response (lack of efficacy after a minimum 12-week duration of therapy) or intolerance to at least 1 csDMARD (csDMARD-IR).

The study consists of a Screening Period (approximately 35 days), Period 1, Period 2, and a 20-week Follow-up Period (See study schematic in Figure 2). Period 1 is a 24-week randomized, double-blind, placebo-controlled, parallel-group period. Period 2 is the long-term period and starts at Week 24. To maintain the blind to the original treatment allocation, treatment at the Week 24 Visit is blinded: subjects randomized to placebo receive a blinded dose of Risankizumab 150 mg, and subjects randomized to risankizumab receive a blinded dose of placebo. At Week 28 and for the remaining dosing visits (to Week 208), all subjects receive open-label risankizumab 150 mg q12w. See dosing schedule outlined in Figure 2. Subjects remain blinded to the original randomization allocation for the duration of the study. The total study duration is 228 weeks including a telephone call 140 days (20 weeks) after last dose of study drug.

Figure 2 Study M15-998 Design Schematic



Source:

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

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

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

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

† Follow up phone call.

Dosing.

Bilateral radiographs of hands and feet.

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

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

Source: M15-998 Clinical Study Report – Interim Figure 1

A total of 443 subjects were randomized in a ratio of 1:1 to risankizumab 150 mg (224) or placebo (219). A sample size of 210 in each group provides at least 90% power to detect a difference in HAQ-DI mean change from Baseline of 0.24 (the difference between risankizumab 150 mg mean change from Baseline of –0.37 and placebo mean change from Baseline of –0.13) assuming that the common standard deviation is 0.72 using a two-group Satterthwaite t-test with a two-sided significance level of 0.05. This sample size also ensures that analyses had at least a 90% power to detect a 20% treatment difference in ACR20 response at Week 24, with assumed placebo response rate of 35%, using a two-sided test at a 0.05 significance level and accounting for a 10% dropout rate.

The primary endpoint was defined as the proportion of subjects achieving American College of Rheumatology (ACR)20 Response (ACR20) at Week 24.The comparisons between the Risankizumab and placebo groups for the primary efficacy endpoint was performed using the Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors.achieved. The sponsor's reported results (Table A2) show that subjects in the risankizumab arm experienced improvement in signs and symptoms of psoriatic arthritis, as demonstrated by a statistically significant difference between the risankizumab and placebo arms in the percentage of subjects who achieved ACR20 response at Week 24.

Table A2 ACR20 Response at Week 24 for Study M15-998 (NRI-C, FAS)

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

ACR20 = American College of Rheumatology 20% improvement criteria; CI = confidence interval; FAS = Full Analysis Set; NRI-C = Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19

a. 95% CI for response rate is calculated based on normal approximation to the binomial distribution.

b. Rate difference, 95% CI and nominal p-value are determined using Cochran-Mantel-Haenszel test adjusting for the stratification factors of current use of csDMARD (0 vs ≥ 1), number of prior biologic therapies (0 vs ≥ 1), and extent of psoriasis (≥ 3% BSA or < 3% BSA) at baseline.

Source: M15-998 Clinical Study Report – Interim Table 8

All 6 ranked secondary efficacy endpoints were achieved. The ranked secondary endpoints are change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24, proportion of subjects achieving Psoriasis Area Severity Index (PASI) 90 response at Week 24 (in the subset of subjects with a body surface area (BSA) ≥ 3% at Baseline), proportion of subjects achieving ACR20 at Week 16, proportion of subjects achieving Minimal Disease Activity (MDA) at Week 24, change from baseline in 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) at Week 24, and change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue) Questionnaire at Week 24.

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/s/

HONGLING ZHOU
06/08/2021 08:49:53 PM

DAVID M PETULLO
06/09/2021 11:44:16 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761105Orig1s014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Immunology and Inflammation

ELECTRONIC CORRESPONDENCE

DATE: January 14, 2022

To: Jiahong Wang Director, Global Regulatory Strategy	**From:** Susan Rhee, PharmD Regulatory Management Officer
Company: AbbVie	Division of Rheumatology and Transplant Medicine
email: jiahong.wang@abbvie.com	**email:** susan.rhee@fda.hhs.gov
Phone number: 847-937-3167	**Phone number:** 301-796-2402

Subject: BLA 761105/S-014 Skyrizi information request

Total no. of pages including cover:

Comments: Please confirm receipt.

Document to be mailed: ☐ **YES** ☑ **NO**

BLA 761105/S-014
Skyrizi (risankizumab-rzaa)
AbbVie

We request further information and clarification of figures for subject (b) (6) (Study M16-002). Provide narrative information on the presentation, course, and outcome regarding the CTCAE Grade 3 elevation in alanine aminotransferase (ALT). The narrative should follow the format in item 1 below with tabular information on any evaluation testing that was done. Provide tabular laboratory results as outlined in item 2 below. Please clarify your line graph figures for liver enzymes and bilirubin over time. The figure provided for this subject (Sequence number 0108, 5.3.5.1, Study M16002 Narratives-CSS, pages 43-45) does not coincide with the data in the narrative nor with Figure 14.3_12 (Sequence number 0108, 5.3.5.1, Study M16002-Report-PboCtrl Dose Ranging Trt 16wk PTFU 16wk, page 1534).

1. Narratives: Patient narratives should follow a chronologic order of events giving both dates and study days. They should be written or edited by physicians or other medical personnel skilled in differential diagnosis and history writing. The narratives should include the following information:
    a. Age, sex, race/ethnicity
    b. Indication for investigational product (IP)
    c. Dose and exposure by dates and study day of IP including any interruptions
    d. Medical history including medical illnesses, body mass index, alcohol intake history, concomitant medications, and herbal dietary supplements with start and stop dates
    e. Treatment emergent, liver or DILI related symptoms and course (i.e., jaundice, pruritus, rash, abdominal pain, nausea, vomiting, fatigue, altered mental status, fever, liver transplant, death)
    f. Details on clinical events that can cause liver injury including surgeries, shock, heart failure, and sepsis
    g. Details on hospitalizations and treatments (e.g., antibiotics, endoscopies, surgeries, corticosteroids) given for the liver injury
    h. All follow-up data available including laboratory values and clinical course
    i. Site investigator opinion on cause of liver injury
    j. Hepatology Assessment Committee's (or equivalent independent review committee's) opinion on cause of liver injury, if available
    k. Evaluation testing for other causes of liver injury. Send in tabular form embedded in or with the narrative (See Table 1). This list is not exhaustive nor implies that each item is absolutely necessary (e.g., liver histology), particularly if a firm non-DILI diagnosis is obvious.

Table 1: Line-item accounting of evaluation testing done and results.

Test	**Test done after injury onset**	**Date, study day done and result**
Hepatitis A IgM antibody	{Yes**//**No}	
Hepatitis B surface antigen	{Yes**//**No}	
Hepatitis B anti-HB core IgM antibody	{Yes**//**No}	
Hepatitis C antibody	{Yes**//**No}	
Hepatitis C RNA	{Yes**//**No}	
Hepatitis E IgM antibody	{Yes**//**No}	
ANA (anti-nuclear antibody)	{Yes**//**No}	
ASMA (anti-smooth muscle antibody)	{Yes**//**No}	
Immunoglobulin G (IgG) level	{Yes**//**No}	
CMV (cytomegalovirus) antibody IgM	{Yes**//**No}	
EBV (Epstein Barr Virus) heterophile antibody	{Yes**//**No}	
EBV capsid antibody IgM	{Yes**//**No}	
EBV early antigen IgG	{Yes**//**No}	
Abdominal or liver ultrasound	{Yes**//**No}	
Abdominal computerized tomography scan	{Yes**//**No}	
Abdominal magnetic resonance imaging	{Yes**//**No}	
MRCP or MRC (magnetic resonance cholangiopancreatography or MR cholangiography)	{Yes**//**No}	
Cholangiogram (ERCP* or percutaneous)	{Yes**//**No}	
Liver histology	{Yes**//**No}	

*endoscopic retrograde cholangiopancreatography

2. Liver Related Laboratory Data

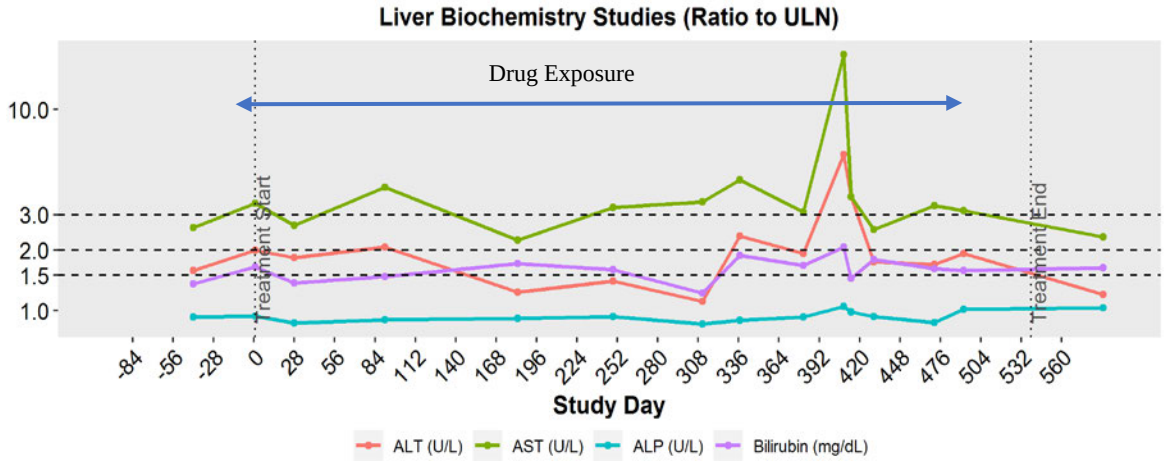
   a. Tabular: Provide ALT, AST, ALP, GGT total bilirubin (TB), direct bilirubin (DB), CPK, LDH and INR values over time (See Table 2 for format). Please send in a separate Microsoft Excel or equivalent spreadsheet file.

   Table 2: Laboratory tests pertinent to liver injury course and evaluation by visit date and study day.

Visit Date	Study Day	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	TB (mg/dL)	DB (mg/dL)	CPK (U/L)	LDH (U/L)

   b. Graphic: Provide an ALT, AST, ALP, total bilirubin line graph as multiples of ULN over time with IP exposure including IP interruptions. (See Figure 1). The line graph provided for this case is formated correctly, but the data contradict the narrative. Please clarify.

   Figure 1: Liver biochemistries by mulitiples of ULN by study day and IP exposure.



Abbreviations:
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
CPK: creatinine phosphokinase
DB: direct bilirubin
DILI: drug-induced liver injury
GGT: gamma-glutamyl transferase
IP: investigational product
LDH: lactate dehydrogenase
TB: total bilirubin
ULN: upper limit of normal

Submit your response to the BLA supplement by **Tuesday January 18, 2022**. If you have any questions, please contact me at susan.rhee@fda.hhs.gov or at 301-796-2402.

Drafted by: 1.14.22 R Nair/A Anderson
Initialed by: 1.14.22 C Ford
Finalized by: 1.14.22 S Rhee

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/s/

SUSAN RHEE
01/14/2022 03:12:56 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Immunology and Inflammation

ELECTRONIC CORRESPONDENCE

DATE: January 10, 2022

To: Jiahong Wang Director, Global Regulatory Strategy	**From:** Susan Rhee, PharmD Regulatory Management Officer
Company: AbbVie	Division of Rheumatology and Transplant Medicine
email: jiahong.wang@abbvie.com	**email:** susan.rhee@fda.hhs.gov
Phone number: 847-937-3167	**Phone number:** 301-796-2402

Subject: BLA 761105/S-014 Skyrizi PREA PMR information request

Total no. of pages including cover: 2

Comments: Please confirm receipt.

Document to be mailed: ☐ **YES** ☑ **NO**

BLA 761105/S-014
Skyrizi (risankizumab-rzaa)
AbbVie

Your supplemental BLA 761105/014 is under review and we request your agreement to conduct the following study by the milestone date provided below.

Postmarketing Requirements (PMR)

Provide pharmacokinetic (PK) and safety information to support the pediatric assessment of risankizumab for the treatment of juvenile psoriatic arthritis in children 5 to 17 years of age.

Final Report Submission: 03/2026

Submit your agreement and/or revisions to the PMR by January 13, 2022, to the BLA supplement. If you have any questions, please contact me at susan.rhee@fda.hhs.gov or at 301-796-2402.

Drafted by: 1.07.22 A Austin, R Nair, SRhee, O Belen
Initialed by: 1.10.22 C Ford
Finalized by: 1.10.22 S Rhee

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/s/

SUSAN RHEE
01/10/2022 05:59:28 PM

BLA 761105 – Supplement 14
Submission Date: March 23, 2021
Drug Name: risankizumab
Brand Name: Skyrizi
Indication: treatment of active psoriatic arthritis in adults
Sponsor: AbbVie
Clinical Reviewer: Austin Anderson, D.O.
Clinical Team Leader: Raj Nair, M.D.
Clinical Office: Office of Immunology and Inflammation
OND Division: Division of Rheumatology and Transplant Medicine
Review Type: standard review

The primary clinical review is complete and has been added to the multidisciplinary review and evaluation document. My review is based on the information currently in the administrative record. If I must review information that is subsequently added to the administrative record, I will update my part of the multidisciplinary review and evaluation document accordingly.

Pending the statistics review, and provided agreement can be reached with the Applicant on labeling, I recommend approval of risankizumab for the treatment of adult patients with active psoriatic arthritis from a clinical perspective. The dose of risankizumab is 150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.

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/s/

AUSTIN M ANDERSON
12/15/2021 08:49:32 AM

RAJ NAIR
12/15/2021 03:05:08 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Immunology and Inflammation

ELECTRONIC CORRESPONDENCE

DATE: December 15, 2021

To: Jiahong Wang Director, Global Regulatory Strategy	**From:** Susan Rhee, PharmD Regulatory Management Officer
Company: AbbVie	Division of Rheumatology and Transplant Medicine
email: jiahong.wang@abbvie.com	**email:** susan.rhee@fda.hhs.gov
Phone number: 847-937-3167	**Phone number:** 301-796-2402

Subject: BLA 761105/S-014 Skyrizi labeling and Statistical information request

Total no. of pages including cover:

Comments: Please confirm receipt.

Document to be mailed: **YES** X **NO**

BLA 761105/S-014
Skyrizi (risankizumab-rzaa)
AbbVie

Your submission to BLA 761104, supplement 14 dated March 23, 2021 is under review. Attached are our revisions to your proposed Prescribing Information and Medication Guide dated May 4, 2021. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the label.

Submit a clean copy and a tracked-change version of the label incorporating our recommended changes to the BLA supplement by **December 22, 2021**.

We also have the following requests for information:

Statistics:

As specified in the SAP, the LOCF approach was also used for ACR50 and ACR70. The analysis results for these two binary endpoints are also included in the proposed label. Also provide the analysis results for ACR50 and ACR70 that instead include the subjects with LOCF imputation as non-responder.

In addition, for the subjects whose ACR composite score was recalculated using LOCF at Week 24, provide the visit time when the observed values were carried forward.

Submit your response to the above Statistical information request to the BLA supplement by **December 20, 2021**.

If you have any questions, please contact me at susan.rhee@fda.hhs.gov or at 301-796-2402.

Drafted by: 12.10.21 SRhee, H Zhou
Initialed by: 12.14.21 S Barnes
Finalized by: 12.15.21 S Rhee

Following this Page, 35 Pages of Draft Labeling haven been Withheld in Full

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/s/

SUSAN RHEE
12/15/2021 08:32:20 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Immunology and Inflammation

ELECTRONIC CORRESPONDENCE

DATE: November 17, 2021

To: Jiahong Wang Director, Global Regulatory Strategy	**From:** Susan Rhee, PharmD Regulatory Management Officer
Company: AbbVie	Division of Rheumatology and Transplant Medicine
email: jiahong.wang@abbvie.com	**email:** susan.rhee@fda.hhs.gov
Phone number: 847-937-3167	**Phone number:** 301-796-2402

Subject: BLA 761105/S-014 Skyrizi information request

Total no. of pages including cover:

Comments: Please confirm receipt.

Document to be mailed: **YES** X **NO**

BLA 761105/S-014
Skyrizi (risankizumab-rzaa)
AbbVie

Your submission to BLA 761104, supplement 14 dated March 23, 2021 is under review. We have the following requests for information:

Statistics:

1. According to the data imputation rule in the SAP, if the composite score was missing due to non-COVID reason, the missing components were imputed using LOCF to recalculate the composite score before imputing missing evaluations as a non-responder.

   Please provide a list of subjects whose ACR composite score was recalculated using LOCF. Also, provide the analysis results that instead include these subjects as non-responder.

2. In the Study report 16-011, there were 2 subjects in risankizumab arm and 6 subjects in placebo arm with missing ACR20 response due to COVID-19, whereas 3 subjects in risankizumab arm had missing ACR20 response due to COVID in the dataset adresp.xpt. Similarly for Study 15-998, there were 1 subject in risankizumab arm and 2 subjects in placebo arm in the study report with missing ACR20 response due to COVID-19, whereas 3 subjects in placebo arm who had missing ACR20 response due to COVID in the dataset.

   Please provide the list of subjects who had missing data due to COVID as well as the list of subjects with missing data due to reasons other than COVID, and clarify the discrepancies between the dataset and the Study Report.

Submit your response to the BLA supplement by **December 6, 2021**. If you have any questions, please contact me at susan.rhee@fda.hhs.gov or at 301-796-2402.

Drafted by: SRhee
11.17.21 – H Zhou
Initialed by: SBarnes 11.17.21
Finalized by: JStevens for S Rhee 11.18.21

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/s/

JAVONNA STEVENS
11/18/2021 08:47:03 AM
for Susan Rhee, PharmD

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Immunology and Inflammation

ELECTRONIC CORRESPONDENCE

DATE: July 27, 2021

To: Jiahong Wang Director, Global Regulatory Strategy	**From:** Susan Rhee, PharmD Regulatory Management Officer
Company: AbbVie	Division of Rheumatology and Transplant Medicine
email: jiahong.wang@abbvie.com	**email:** susan.rhee@fda.hhs.gov
Phone number: 847-937-3167	**Phone number:** 301-796-2402

Subject: BLA 761105/S-014 Skyrizi information request

Total no. of pages including cover:

Comments: Please confirm receipt.

Document to be mailed: **YES** X **NO**

BLA 761105/S-014
Skyrizi (risankizumab-rzaa)
AbbVie

Your submission to BLA 761104, supplement 14 dated March 23, 2021 is under review. We have the following requests for information:

Hepatic Events

We note that no safety concerns regarding hepatic events were identified with risankizumab treatment in the psoriasis program at the time of initial filing. However, we would like additional information on the hepatic events observed in the psoriasis program given the results observed in the psoriatic arthritis program.

Please provide data from the psoriasis program in the following tables:

Table 1. Overview of the Number and Percentage of Subjects with Treatment-Emergent Hepatic Events (Phase 3 Psoriasis Placebo-Controlled subset of Primary Safety Pool)

Area of Safety Interest	**Placebo (N = ***) N (%) [SSA%]**	**Risankizumab (N = ***) N (%) [SSA%]**	**% Difference RZB - Placebo (95% CI)**
Hepatic events			

CI = confidence interval; N = number of subjects; RZB = risankizumab; SSA = study size adjusted; % = percentage of subjects

Table 2. Overview of Treatment-Emergent Hepatic Events in Exposure-Adjusted Event Rate per 100 PY (Phase 3 Psoriasis Placebo-Controlled subset of Primary Safety Pool)

Area of Safety Interest	**Placebo (N = ***) PY = *** Events (E/100 PY) [SSA E/100 PY]**	**Risankizumab (N = ***) PY = *** Events (E/100 PY) [SSA E/100 PY)**	**Rate Difference RZB – Placebo (95% CI)**
Hepatic events			

CI = confidence interval; E = events; N = number of subjects; PY = patient years; RZB = risankizumab; SSA = study size adjusted

Table 3. Summary of Potentially Clinically Significant Liver Test Values through Week 16 (Phase 3 Psoriasis Placebo-Controlled subset from the Primary Safety Pool)

Criteria	**Placebo (N = ***) n/N_OBS (%)**	**Risankizumab (N = ***) n/N_OBS (%)**	**% Difference RZB - PBO (95% CI)**
ALT ≥ 3 x ULN			
ALT ≥ 5 x ULN			
ALT ≥ 10 x ULN			
ALT ≥ 20 x ULN			
AST ≥ 3 x ULN			

AST ≥ 5 x ULN			
AST ≥ 10 x ULN			
AST ≥ 20 x ULN			
Alk Phos ≥ 1.5 x ULN			
TBL ≥ 2 x ULN			
ALT and/or AST ≥ 3 x ULN And TBL ≥ 1.5 x ULN			
ALT and/or AST ≥ 3 x ULN And TBL ≥ 2 x ULN			

Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; n = number of subjects; N_OBS = number of subjects with at least one post-baseline value for the respective parameter; PBO = placebo; RZB = risankizumab; TBL = total bilirubin; ULN = upper limit of normal; % = percentage of subjects

Table 4. Exposure-Adjusted Event Rate of Treatment-Emergent Potentially Clinically Significant Liver Test Values (Phase 3 Psoriasis Placebo-Controlled subset from the Primary Safety Pool)

Criteria	**Placebo (N = ***) (PY = ***)**	**Risankizumab (N = ***) (PY = ***)**	**Comparison (95% CI)**
	Events (E/100 PY) [SSA E/100 PY]	**Events (E/100 PY) [SSA E/100 PY]**	**Rate Difference RZB - Placebo [95% CI]**
ALT ≥ 3 x ULN			
ALT ≥ 5 x ULN			
ALT ≥ 10 x ULN			
ALT ≥ 20 x ULN			
AST ≥ 3 x ULN			
AST ≥ 5 x ULN			
AST ≥ 10 x ULN			
AST ≥ 20 x ULN			
Alk Phos ≥ 1.5 x ULN			
TBL ≥ 2 x ULN			
ALT and/or AST ≥ 3 x ULN And TBL ≥ 1.5 x ULN			
ALT and/or AST ≥ 3 x ULN And TBL ≥ 2 x ULN			

Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; E = events; n = number of subjects; N_OBS = number of subjects with at least one post-baseline value for the respective parameter; PY = patient years; TBL = total bilirubin; ULN = upper limit of normal; RZB = risankizumab; SSA = study size adjusted event rate

Please provide data from the psoriatic arthritis program in the following table:

Table 5. Exposure-Adjusted Event Rate of Treatment-Emergent Potentially Clinically Significant Liver Test Values (Phase 3 Psoriatic Arthritis Placebo-Controlled Analysis Set)

Criteria	Placebo (N = ***) (PY = ***)	Risankizumab (N = ***) (PY = ***)	Comparison (95% CI)
	Events (E/100 PY) [SSA E/100 PY]	Events (E/100 PY) [SSA E/100 PY]	Rate Difference RZB - Placebo [95% CI]
ALT ≥ 3 x ULN			
ALT ≥ 5 x ULN			
ALT ≥ 10 x ULN			
ALT ≥ 20 x ULN			
AST ≥ 3 x ULN			
AST ≥ 5 x ULN			
AST ≥ 10 x ULN			
AST ≥ 20 x ULN			
Alk Phos ≥ 1.5 x ULN			
TBL ≥ 2 x ULN			
ALT and/or AST ≥ 3 x ULN And TBL ≥ 1.5 x ULN			
ALT and/or AST ≥ 3 x ULN And TBL ≥ 2 x ULN			

Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; E = events; n = number of subjects; N_OBS = number of subjects with at least one post-baseline value for the respective parameter; PY = patient years; TBL = total bilirubin; ULN = upper limit of normal; RZB = risankizumab; SSA = study size adjusted event rate

Hypersensitivity Events

We note that hypersensitivity reactions were generally mild, and that the most common reaction was rash. However, we would like additional information on the specific types of events observed in subjects treated with risankizumab vs placebo in the psoriatic arthritis program.

Provide a list of the 18 hypersensitivity events that occurred in the risankizumab group, and a list of the 10 hypersensitivity events that occurred in the placebo group. Additionally, please provide the severity grade for each of the events.

Submit your response to the BLA supplement by **August 16, 2021**. If you have any questions, please contact me at susan.rhee@fda.hhs.gov or at 301-796-2402.

Drafted by: SRhee
7.26.21 – R Nair/A Anderson
Initialed by: 7.26.21 – S Barnes
Finalized by: 7.27.21 – S Rhee

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/s/

SUSAN RHEE
07/27/2021 09:31:28 AM

BLA 761105/S-014

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

AbbVie Inc.
1 N. Waukegan Road
Dept. PA72/Bldg. AP3-04
North Chicago, IL 60064

Attention: Jiahong Wang, PhD
Director, Global Regulatory Strategy

Dear Dr. Wang:

Please refer to your supplemental biologics license application (sBLA) dated March 23, 2021, received March 23, 2021, under section 351(a) of the Public Health Service Act for Skyrizi (risankizumab-rzaa) solution for injection, 90 mg/mL and 150 mg/mL.

We also refer to your amendment dated May 4, 2021.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 23, 2022.

We are reviewing your application according to the processes described in the draft guidance for industry *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications*.[1] Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 23, 2021. This date conforms to the 21st Century Review timeline for your application.

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

During our filing review of your application, we identified the following potential review issues:

CLINICAL:

1. We note that you have proposed to include claims for nail psoriasis endpoints, mNAPSI and PGA-F, in the labeling for risankizumab. This will be a review issue as this may be misconstrued as an expansion of the indication for risankizumab to mild psoriasis for which the benefit-risk profile has not been determined to be favorable.

2. We note that you have proposed to include the Minimal Disease Activity (MDA) response endpoint in the labeling for risankizumab. The MDA response endpoint may represent overlapping and ancillary benefits with respect to the core outcome measures used to support the new indication (i.e., American College of Rheumatology (ACR) response). Redundant efficacy information and claims may not be considered appropriate for inclusion in labeling, even if those claims are supported by adequate instruments, an adequate statistical analysis approach, and adequate multiplicity control. The inclusion of MDA response in the product labeling will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and PLLR Requirements for Prescribing Information[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

[2] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[3] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential

- Regulations and related guidance documents

- A sample tool illustrating the format for Highlights and Contents

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances, and

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed Prescribing Information (PI), Medication Guide, and Instructions for Use. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[4] Do not submit launch materials until you have received our proposed revisions to the Prescribing Information (PI), Medication Guide, and Instructions for Use, and you believe the labeling is close to the final version.

[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

For more information regarding OPDP submissions, please see FDA.gov.[5] If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies (for patients less than five years of age) for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We also acknowledge receipt of your request for a partial deferral of pediatric studies (for patients five to less than 18 years old) for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call me at 301-796-2402.

Sincerely,

{See appended electronic signature page}

Nikolay P. Nikolov, MD
Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

[5] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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/s/

NIKOLAY P NIKOLOV
05/21/2021 02:38:41 PM