

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761105Orig1s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Office Director**

**Cross Discipline Team Leader Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

NDA/BLA Multi-disciplinary Review and Evaluation – BLA 761105  
(Skyrizi, Risankizumab)

**NDA/BLA Multi-disciplinary Review and Evaluation**

|                                                                |                                                                                                                               |
|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| <b>Application Type</b>                                        | BLA                                                                                                                           |
| <b>Application Number(s)</b>                                   | 761105                                                                                                                        |
| <b>Priority or Standard</b>                                    | Standard                                                                                                                      |
| <b>Submit Date(s)</b>                                          | 4/23/2018                                                                                                                     |
| <b>Received Date(s)</b>                                        | 4/23/2018                                                                                                                     |
| <b>PDUFA Goal Date</b>                                         | 4/23/2019                                                                                                                     |
| <b>Division/Office</b>                                         | ODE 3/DDDP                                                                                                                    |
| <b>Review Completion Date</b>                                  | April 17, 2019                                                                                                                |
| <b>Established Name</b>                                        | Risankizumab                                                                                                                  |
| <b>(Proposed) Trade Name</b>                                   | Skyrizi                                                                                                                       |
| <b>Pharmacologic Class</b>                                     | An interleukin-23 antagonist                                                                                                  |
| <b>Code name</b>                                               |                                                                                                                               |
| <b>Applicant</b>                                               | AbbVie, Inc.                                                                                                                  |
| <b>Formulation(s)</b>                                          | Solution for injection                                                                                                        |
| <b>Dosing Regimen</b>                                          | 150 mg administered by subcutaneous injection at Weeks 0, 4, and every twelve weeks thereafter                                |
| <b>Applicant Proposed Indication(s)/Population(s)</b>          | For the treatment of moderate to severe plaque psoriasis in adults                                                            |
| <b>Recommendation on Regulatory Action</b>                     | Approval                                                                                                                      |
| <b>Recommended Indication(s)/Population(s) (if applicable)</b> | For the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. |

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**Reviewers Team and Signature Approval Section**

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| DISCIPLINE                              | REVIEWER                                                                                                                                                                                                                                     | OFFICE/DIVISION | SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED | AUTHORED/ ACKNOWLEDGED/ APPROVED                                                                                                                 |
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| <b>Signatory</b>     | Kendall A. Marcus, MD                                                                                                                                                                                                                                          | ODE 3/DDDP      |                                           | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input type="checkbox"/> Acknowledged<br><input checked="" type="checkbox"/> Approved |
|                      | Signature: <b>Kendall A. Marcus -S</b> <small>Digitally signed by Kendall A. Marcus -S<br/>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300160022, cn=Kendall A. Marcus -S<br/>Date: 2019.04.23 08:21:56 -04'00'</small> |                 |                                           |                                                                                                                                                  |
|                      |                                                                                                                                                                                                                                                                |                 |                                           |                                                                                                                                                  |
|                      |                                                                                                                                                                                                                                                                |                 |                                           |                                                                                                                                                  |

### Additional Reviewers of Application

|            |                                                                                                                                                                                                                                           |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>OPQ</b> | Milos Dokmanovic (OBP Product Quilaty Reviewer)<br>Rachel Novak (OBP Application Technical Lead)<br>Diane Racassi (DMA Microbiology Reviewer)<br>Max Van Tassell (DMA Microbiology Reviewer)<br>Maria Candauchacon (DMA Microbiology QAL) |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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|                     |                                                                                                                                                    |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
|                     | Michael Shanks (DIA Facilities Reviewer)<br>Qui (Peter) Zhihao (DIA QAL)<br>Melinda Bauerlien (OPRP RBPM)<br>Vicky Borders-Hemphill (OBP Labeling) |
| <b>Microbiology</b> |                                                                                                                                                    |
| <b>OPDP</b>         |                                                                                                                                                    |
| <b>OSI</b>          |                                                                                                                                                    |
| <b>OSE/DEPI</b>     |                                                                                                                                                    |
| <b>OSE/DMEPA</b>    |                                                                                                                                                    |
| <b>OSE/DRISK</b>    |                                                                                                                                                    |
| <b>Other</b>        |                                                                                                                                                    |

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

## Glossary

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|           |                                                                         |
|-----------|-------------------------------------------------------------------------|
| AC        | advisory committee                                                      |
| ADME      | absorption, distribution, metabolism, excretion                         |
| AE        | adverse event                                                           |
| 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 Harmonization                               |
| 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                                                 |

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|      |                                         |
|------|-----------------------------------------|
| PK   | pharmacokinetics                        |
| PMC  | postmarketing commitment                |
| PMR  | postmarketing requirement               |
| PP   | per protocol                            |
| PPI  | patient package insert                  |
| 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

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### 1.1. Product Introduction

Skyrizi (risankizumab) injection for subcutaneous use is a humanized IgG1 monoclonal antibody that specifically binds to the p19 protein subunit of the IL-23 cytokine and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine, composed of 2 subunits (IL-23p19 and IL-12/23p40), that is involved in inflammatory and immune responses.

The proposed indication is "the treatment of moderate to severe plaque psoriasis in adults." However, enrollment criteria for the clinical trials included "adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy". The risankizumab pharmaceutical formulation is a solution for injection at a concentration of 90 mg/mL presented in a pre-filled syringe (PFS) for subcutaneous (SC) injection. Each syringe contains 75 mg risankizumab. The proposed dosing regimen for patients with psoriasis is 150 mg (two 75 mg injections) administered by SC injection at Week 0, Week 4, and every 12 weeks (q12w) thereafter.

The Agency concluded that the proposed proprietary name, Skyrizi, was acceptable from both a promotional and safety perspective [Proprietary Name Review by Carlos Mena-Grillasca, Division of Medication Error Prevention and Analysis (DMEPA) dated 7/6/2018].

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant submitted data from two adequate and well-controlled [trials M15-995 (1311.28), M16-008 (1311.3)], which provided evidence of the effectiveness of risankizumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The trials assessed the changes from Baseline to Week 16 compared to placebo in the two co-primary endpoints:

- the proportion of subjects who achieved at least a 90% reduction in the PASI composite score (PASI 90)
- the proportion of subjects who achieved a static Physician's Global Assessment (sPGA) score of score of 0 ("clear") or 1 ("almost clear").

Risankizumab was statistically superior to placebo (p-values < 0.001) on the co-primary endpoints. The applicant has demonstrated that risankizumab is effective for its intended use in the target population, and has met the evidentiary standard required by 21 CFR 314.126(a)(b) to support approval.

### 1.3. Benefit-Risk Assessment

#### Benefit-Risk Summary and Assessment

Psoriasis is a chronic, inflammatory disease that primarily affects the skin and is characterized by erythematous, scaly plaques and substantial impairment of quality of life

Skyrizi (risankizumab) injection, for subcutaneous use is proposed for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Skyrizi (risankizumab) injection for subcutaneous use is a humanized IgG1 monoclonal antibody that specifically binds to the p19 protein subunit of the IL-23 cytokine and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine, composed of 2 subunits (IL-23p19 and IL-12/23p40), that is involved in inflammatory and immune responses. Risankizumab is available as 75 mg PFS to be administered as a 150 mg dose (two injections).

For the treatment of moderate to severe plaque psoriasis, current therapeutic options include phototherapy and photochemotherapy with methoxsalen, systemic small molecule drugs (acitretin, apremilast, cyclosporine, methotrexate), and biologic products (adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, and tildrakizumab). Although the efficacy varies, no product produces a response in all patients or provides a permanent cure. Phototherapy and photochemotherapy may be impractical due to office-based administration requirements. All the systemic products may have one or more serious adverse reactions, including malignancy, serious infections, teratogenicity, depression, nephrotoxicity, hepatotoxicity, and bone marrow suppression. Because of these limitations, there is a recognizable need for additional therapeutic options despite the number of available therapies.

Substantial efficacy was demonstrated in two pivotal Phase 3 trials (M15-995 [1311.28], M16-008 [1311.3]). In these trials, 997 adult subjects with moderate to severe plaque psoriasis who were eligible for systemic therapy or phototherapy were treated with risankizumab 150 mg (N=598), placebo (N=200) or EU-sourced ustekinumab (N=199). Subjects had a Static Physician's Global Assessment (sPGA) score of  $\geq 3$  ("moderate") on a 5-point scale of overall disease severity, a Psoriasis Area and Severity Index (PASI) score  $\geq 12$ , and a minimum affected body surface area (BSA) involvement of  $\geq 10\%$ . In both trials, subjects were randomized in a 3:1:1 ratio to risankizumab 150 mg, ustekinumab (EU-sourced) [45 mg for  $<100\text{kg}$  and 90 mg for  $>100\text{kg}$  weight] or placebo. Subjects received subcutaneous injections at Weeks 0 and 4, then every 12 (Q12) weeks.

The co-primary endpoints were assessed at Week 16: i) the proportion of subjects who achieved an sPGA score of 0 ("clear") or 1 ("almost clear"), and ii) the proportion of subjects who achieved at least a 90% reduction in the PASI composite score (PASI 90). In Trials M15-995 [1311.28], M16-008 [1311.3], risankizumab was superior to placebo on both sPGA (Trial 1311.28: 84% vs 5% and Trial 1311.3: 88% vs 8%; p-values  $< 0.001$ ) and PASI 90 (Trial 1311.28: 75% vs 2% and Trial 1311.3: 75% vs 5%; p-values  $< 0.001$ ) at Week 12.

Secondary endpoints for both trials included the proportion of subjects at Week 16 who achieved an sPGA of 0, PASI 100 and patient reported

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outcomes [Psoriasis Symptom Scale (PSS) and Dermatology Life Quality Index (DLQI)]. In both trials, risankizumab was statistically superior to placebo (with p-values<0.001) in the overall population for all the secondary efficacy endpoints. Evidence submitted by the applicant sufficiently demonstrates that the PSS is fit-for-purpose for labeling. It is recommended that the PSS is included in labeling. The DLQI does not appear to be fit-for-purpose for labeling in the context of this drug development program due to lack of item relevancy. Labeling for DLQI results are not recommended.

In the clinical trials, the applicant used EU-approved ustekinumab and did not provide an adequate scientific bridge between the U.S. licensed Stelara and EU-sourced ustekinumab. (b) (4)

To evaluate maintenance and durability of response, subjects in Trials 1311.28 and 1311.3 were followed to Week 52. For subjects receiving risankizumab in Trials 1311.28 and 1311.3 who were PASI 100 responders at Week 16, 80% of subjects who continued on risankizumab had a PASI 100 response at Week 52. For PASI 90 responders at Week 16, 88% of subjects had a PASI 90 response at Week 52. In Trial 1311.4, subjects were rerandomized at Week 28 to continue risankizumab every 12 weeks or to withdrawal therapy. For subjects who were clear or almost clear (sPGA 0/1) at Week 28, 87% re-randomized to continued treatment with risankizumab had an sPGA response of 0 or 1 at Week 52 compared to 61% who were re-randomized to withdrawal.

The primary safety database, which consisted of data from the pooled Phase 2/3 Trials[1311.2, M15-995 (1311.28), M16-008 (1311.3), M16-010 (1311.30) and M15-992 (1311.4)] is adequate to characterize the safety profile of risankizumab 150 mg for subcutaneous injection in the treatment of psoriasis. The size of the overall safety database was considered adequate and consistent with ICH E1 and includes 2,234 subjects exposed to at least 1 dose of risankizumab and a total of 1,091 subjects receiving at least 1 dose of risankizumab 150 mg for ≥ 1 year.

Treatment with risankizumab did not appear to increase the risk of mortality as compared to placebo through 16 weeks of randomized, blinded treatment. A limited number of serious adverse events (SAEs) in the risankizumab group led to discontinuation of study drug. An association between the product and malignancy was not observed. . An increased incidence of treatment-related adverse reactions in the categories of suicidal ideation and behavior (SIB) and major adverse cardiovascular events (MACE) was not observed, given the limited clinical experience to date. Serious cases of hypersensitivity and injection site reactions did not occur. Some serious non-MACE cardiovascular and hepatic events occurred. Most of the events were confounded with concomitant medication or comorbid conditions. Compared to placebo, subjects treated with risankizumab experienced more infections, more serious infections and a higher rate of fungal infections. There were no reports of active TB. Subjects with active TB were excluded and those with latent TB were required to start treatment prophylaxis prior to starting on risankizumab. Language pertaining to infections and pre-treatment for tuberculosis is recommended for product labeling. The available data are insufficient to inform risankizumab-associated risk in pregnant women and children.

Prescription and patient labeling, as well as pharmacovigilance are adequate to manage the risk of risankizumab in the postmarketing setting; a Risk Evaluation and Mitigation Strategy (REMS) is not needed. Postmarketing requirements under 505(o) will include: studies to evaluate maternal, fetal, and infant outcomes of women exposed to risankizumab during pregnancy, and a safety study to assess for malignancy and other serious adverse reactions (e.g., serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease,

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neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events). Required pediatric assessments, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) will include: a safety, efficacy and PK study in pediatric subjects 6 years to < 18 years of age with moderate to severe plaque psoriasis.

The available safety and efficacy data support the approval of risankizumab 150 mg for subcutaneous injection for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Although there are a number of FDA-approved products with an acceptable benefit-risk profile for this indication, none of these treatments provides a permanent cure or universal response and all of these products are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options.

| Dimension                               | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><u>Analysis of Condition</u></p>     | <ul style="list-style-type: none"> <li>Psoriasis is a common, chronic, inflammatory multi-system disorder which primarily affects the skin and joints and is associated with substantial impairment of quality of life. The prevalence of psoriasis in the U.S. is approximately 2-3 %, of which an estimated 20% have moderate to severe disease. One third of patients have concomitant arthritis. Comorbidities that have been reported to be potentially associated with psoriasis include depression/suicide, autoimmune disease, cardiovascular disease, and metabolic syndrome.</li> </ul>                                                                                                                                                                                                                                                                                          | <p>Moderate to severe plaque psoriasis is a serious disease because of its chronicity, impact on quality of life, and potential for associated co-morbidities.</p>                                                                                                                                                                                                                                                                                                                                                          |
| <p><u>Current Treatment Options</u></p> | <ul style="list-style-type: none"> <li>FDA approved drugs for the treatment of moderate to severe psoriasis include anti-metabolites (methotrexate), tumor necrosis factor (TNF) inhibitors (etanercept, adalimumab and infliximab), IL-12/23 blockers (ustekinumab), IL-17A blockers (secukinumab and ixekizumab), an IL-17A receptor antagonist (brodalumab), IL-23 blockers (guselkumab and tildrakizumab), a T cell inhibitor (cyclosporine), retinoids (acitretin) and phosphodiesterase 4 inhibitors (apremilast). Other treatment options include phototherapy with either PUVA (UVA light combined with methoxsalen) or UVB light (narrow or broadband).</li> <li>All approved therapeutic options may be associated with the risk of serious adverse reactions or administration challenges. The use of phototherapy and photochemotherapy are limited by the need for</li> </ul> | <p>There are several FDA-approved products with an acceptable benefit-risk profile for the treatment of moderate-to-severe plaque psoriasis in adults. None of these treatments provides a permanent cure or universal response and all these products are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options.</p> |

| Dimension             | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                       | <p>office administration and additional photoprotection. Teratogenicity and hyperlipidemia are labeled risks with acitretin. Depression and weight loss are safety concerns with apremilast. The primary risks of cyclosporine use are nephrotoxicity and hypertension. Methotrexate has teratogenic, hepatotoxic, and nephrotoxic effects and may cause bone marrow toxicity and pulmonary fibrosis. Other systemic products may cause immunosuppression, serious infections and malignancy. All biologic products may be associated with loss of effect and serious hypersensitivity reactions. See the Summary of Treatment Armamentarium for Moderate to Severe Psoriasis for the specific labeled safety issues for each product.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <p><b>Benefit</b></p> | <ul style="list-style-type: none"> <li>Substantial efficacy was demonstrated in two pivotal Phase 3 trials (M15-995 [1311.28], M16-008 [1311.3]). In these trials, 997 adult subjects with moderate to severe plaque psoriasis who were eligible for systemic therapy or phototherapy were treated with risankizumab 150 mg (N=598), placebo (N=200) or EU-sourced ustekinumab (N=199). Subjects had a Static Physician’s Global Assessment (sPGA) score of ≥3 (“moderate”) on a 5-point scale of overall disease severity, a Psoriasis Area and Severity Index (PASI) score ≥12, and a minimum affected body surface area (BSA) involvement of ≥10%. In both trials, subjects were randomized in a 3:1:1 ratio to risankizumab 150 mg, ustekinumab (EU-sourced) [45 mg for &lt;100kg and 90 mg for &gt;100kg weight] or placebo. Subjects received subcutaneous injections at Weeks 0 and 4, then every 12 (Q12) weeks.</li> <li>The co-primary endpoints were assessed at Week 16: i) the proportion of subjects who achieved an sPGA score of 0 (“clear”) or 1 (“almost clear”), and ii) the proportion of subjects who achieved at least a 90% reduction in the PASI composite score (PASI 90). In Trials M15-995 [1311.28], M16-008 [1311.3], risankizumab was superior to placebo on both sPGA (Trial 1311.28: 84% vs 5% and Trial 1311.3: 88% vs 8%; p-values&lt; 0.001) and PASI 90 (Trial</li> </ul> | <p>The data submitted by the applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled. The results are persuasive.</p> <p>Achievement of clear or almost-clear skin is an intrinsically meaningful outcome for a cutaneous disease such as psoriasis. The data suggest that a patient with moderate-to-severe plaque psoriasis treated with 150 mg risankizumab at Week 0, 4 and every 12 weeks is likely to achieve clear or almost clear skin by Week 16, and to maintain this effect with continued treatment to Week 52.</p> |

| Dimension          | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                    | <p>1311.28: 75% vs 2% and Trial 1311.3: 75% vs 5%; p-values &lt; 0.001) at Week 12.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p><u>Risk</u></p> | <ul style="list-style-type: none"> <li>• The primary safety database, which consisted of data from the pooled Phase 2/3 Trials [1311.2, M15-995 (1311.28), M16-008 (1311.3), M16-010 (1311.30) and M15-992 (1311.4)] is adequate to characterize the safety profile of risankizumab 150 mg for subcutaneous injection in the treatment of psoriasis. The size of the overall safety database was considered adequate and consistent with ICH E1 and includes 2,234 subjects exposed to at least 1 dose of risankizumab and a total of 1,091 subjects receiving at least 1 dose of risankizumab 150 mg for ≥ 1 year.</li> <li>• An increased risk of mortality was not observed with risankizumab as compared to placebo through 16 weeks of blinded, randomized treatment.</li> <li>• A limited number of serious adverse events (SAEs) in the risankizumab group led to discontinuation of study drug.</li> <li>• An association between the product and increased risk for malignancy was not observed.</li> <li>• Treatment with risankizumab does not appear to be associated with an increased incidence of treatment-related adverse suicidal ideation and behavior (SIB) given the limited clinical experience to date</li> <li>• Treatment with risankizumab does not appear to be associated with an increased incidence of treatment-related major adverse cardiovascular events (MACE).</li> <li>• Serious cases of hypersensitivity and injection site reactions did not occur.</li> <li>• Some serious non-MACE cardiovascular and hepatic events occurred. Most of the events were confounded with concomitant</li> </ul> | <p>The safety profile of risankizumab has been adequately characterized. Based on the available information, the safety profile appears to be similar to the premarket safety database for guselkumab and tildrakizumab, which are approved human monoclonal IgG1 antibodies that target the p19 subunit of IL-23.</p> <p>It is not expected that that postmarketing exposure will identify risks for malignancy or specific organ toxicities of a magnitude that would alter the benefit-risk conclusion.</p> |

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| Dimension                     | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                  |
|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                               | <p>medication or comorbid conditions.</p> <ul style="list-style-type: none"> <li>• Compared to placebo, subjects treated with risankizumab experienced more infections, more serious infections and a higher rate of fungal infections. There were no reports of active TB.</li> <li>• The available data are insufficient to inform risankizumab-associated risk in pregnant women and children.</li> <li>• There is limited safety data beyond one year for the use of risankizumab 150 mg subcutaneous injection.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                          |
| <p><b>Risk Management</b></p> | <ul style="list-style-type: none"> <li>• The following PMRs will be required:               <ol style="list-style-type: none"> <li>1. Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to risankizumab during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including neonatal deaths, infections in the first 6 months of life, and effects on postnatal growth and development, will be assessed through at least the first year of life.</li> <li>2. Conduct (b) (4) retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths, and infant infections in women exposed to risankizumab during pregnancy compared to an unexposed control population.</li> <li>3. Conduct an observational study to assess the long-term safety of risankizumab compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or</li> </ol> </li> </ul> | <p>Prescription labeling, patient labeling and routine pharmacovigilance, in conjunction with the post marketing requirements, are adequate to manage the risks of the product.</p> <p>A REMS is not recommended for this application.</p> <p>A REMS was not recommended for the most recent approvals in this IL 23 category for systemic treatments for psoriasis.</p> |

| Dimension | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Conclusions and Reasons |
|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
|           | <p>phototherapy in the course of actual clinical care. The study's primary outcome is long-term malignancy. Secondary outcomes include, but are not limited to, serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events. Describe and justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to risankizumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a pre-specified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the risankizumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial 4-year period and follow for a minimum of 8 years from the time of enrollment.</p> <p>4. Conduct a Pharmacokinetics (PK), Safety and Efficacy Study in pediatric subjects 6 years to &lt;18 years of age with moderate-to-severe plaque psoriasis (with a duration of exposure to risankizumab of at least one year).</p> <ul style="list-style-type: none"> <li>• Labeling: Prescription labeling adequately addresses the risks identified during product development. Labeling can also adequately convey the lack of pediatric data and data for exposure during pregnancy.</li> <li>• A REMS is not recommended. Precedent biologic products with comparable safety profiles have a similar approach to post-marketing risk management.</li> </ul> |                         |

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#### **1.4 Patient Experience Data**

Patient experience data pertaining and submitted with this application are outlined in Table 1.

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**Table 1: Patient Experience Data Relevant to this Application**

|                          |                                                                                                                                                             |                                        |
|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| x                        | The patient experience data that was submitted as part of the application include:                                                                          | Section where discussed, if applicable |
|                          | <input checked="" type="checkbox"/> Clinical outcome assessment (COA) data, such as                                                                         |                                        |
|                          | <input checked="" type="checkbox"/> Patient reported outcome (PRO)                                                                                          | 7.2.6                                  |
|                          | <input type="checkbox"/> Observer reported outcome (ObsRO)                                                                                                  |                                        |
|                          | <input checked="" type="checkbox"/> Clinician reported outcome (ClinRO)                                                                                     | 7                                      |
|                          | <input type="checkbox"/> Performance outcome (PerfO)                                                                                                        |                                        |
|                          | <input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) |                                        |
|                          | <input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports                                                      |                                        |
|                          | <input type="checkbox"/> Observational survey studies designed to capture patient experience data                                                           |                                        |
|                          | <input type="checkbox"/> Natural history studies                                                                                                            |                                        |
|                          | <input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)                                                    |                                        |
|                          | <input type="checkbox"/> Other: (Please specify)                                                                                                            |                                        |
| <input type="checkbox"/> | Patient experience data that were not submitted in the application, but were considered in this review:                                                     |                                        |
|                          | <input type="checkbox"/> Input informed from participation in meetings with patient stakeholders                                                            |                                        |
|                          | <input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports                                                      |                                        |
|                          | <input type="checkbox"/> Observational survey studies designed to capture patient experience data                                                           |                                        |
|                          | <input type="checkbox"/> Other: (Please specify)                                                                                                            |                                        |
| <input type="checkbox"/> | Patient experience data was not submitted as part of this application.                                                                                      |                                        |

## 2 Therapeutic Context

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### 2.1. Analysis of Condition

Psoriasis is a common, chronic, immune-mediated, inflammatory skin disorder with a strong hereditary component. The pathogenesis of psoriasis is complex and the etiology is not completely understood. Inflammatory cytokines appear to play a role in the pathogenesis and a number of cytokines have been targeted and have demonstrated therapeutic benefit.

The prevalence of psoriasis in the US is approximately 2-4%, of which an estimated 20% have moderate to- severe disease. Psoriasis can first appear at any age, but more commonly appears in adulthood. Two peaks in age of onset have been reported: one at 20–30 years of age and a second peak at 50–60 years.

The most common form of the disease is chronic plaque psoriasis (*psoriasis vulgaris*). The characteristic lesion is a sharply demarcated scaly, erythematous plaque with scale, and the plaques may be localized or widespread in distribution and symmetrically distributed. These plaques are the result of increased keratinocyte proliferation and commonly involve the extensor surfaces of the extremities, but may present anywhere from the scalp to the soles of the feet. The natural history of psoriasis is chronic with intermittent remissions. A diagnosis of psoriasis can typically be made by history and physical examination, though skin biopsy can provide confirmation if needed.

The extent of body surface area affected may vary from limited to extensive, and the extent of involvement is one consideration in the approach to patient management. Disease of limited extent may be effectively managed with topical treatment. Moderate to severe psoriasis is often treated with phototherapy or systemic therapy.

Associations between psoriasis and other comorbid diseases are under investigation; it is postulated that psoriasis is part of a multisystem inflammatory disorder. The pathogenesis of comorbid disease in patients with psoriasis remains unknown.

Due to the variability in effectiveness and tolerability, access to treatment and uncertainty regarding long-term effects of available treatments, the development of additional safe and effective therapies for the treatment of psoriasis continues to be an important goal.

### 2.2. Analysis of Current Treatment Options

**Table 2: Summary of Treatment Armamentarium for Moderate to Severe Psoriasis**

| Product (s)<br>Name/year<br>approved     | Relevant<br>Indication                                                                                                                                                                                                                                            | Dosage<br>& Admin                                                                                                                                                                                                                                                                            | Efficacy<br>Information                                                                                                                                                                                                       | Important Safety<br>and Tolerability<br>Issues                                                                                                                                                                                                                                                                                                                                                                 | Other<br>Comments                                                                                                                                                                         |
|------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>FDA Approved Treatments</b>           |                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                           |
| <b>Antimetabolite/ Immunosuppressant</b> |                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                           |
| Methotrexate<br>1972                     | Severe, recalcitrant, disabling, psoriasis not adequately responsive to other forms of therapy; <i>but only when diagnosis established, by biopsy and/or dermatologic consultation.</i> Must rule out undiagnosed concomitant disease affecting immune responses. | Starting Dose Schedules<br>1. Weekly single oral, intramuscular (IM) or intravenous (IV) dose schedule: 10 to 25 mg per week until adequate response is achieved.<br>2. Divided oral dose schedule: 2.5 mg at 12-hour intervals for three doses. 30 mg/wk should not ordinarily be exceeded. | No efficacy information for psoriasis in the label.                                                                                                                                                                           | Boxed Warning (BW)- potentially fatal toxic reactions including bone marrow suppression, aplastic anemia, and gastrointestinal toxicity with concomitant NSAID <sup>1</sup> Tx; hepatotoxicity, pulmonary toxicity, kidney toxicity, opportunistic infections, malignant lymphoma, tumor lysis syndrome, severe skin toxicity, fetal death and anomalies “should not be used in pregnant women with psoriasis” | Major AE derm dosing: ↑Liver enzymes stomatitis, diarrhea, nausea and vomiting, lymphoproliferative disorders;<br><br>Recommend Periodic liver biopsy if tx long-term<br><br>Pregnancy: X |
| <b>Tumor Necrosis Factor Inhibitors</b>  |                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                           |
| Infliximab (Remicade)<br>2006            | Chronic severe (extensive or disabling) plaque psoriasis, candidates for phototherapy or systemic therapy and when other systemic therapies are medically less appropriate.                                                                                       | 5 mg/kg IV at 0, 2 and 6 weeks, then every 8 weeks                                                                                                                                                                                                                                           | From the label: 3 R,DB,PC <sup>2</sup> trials PASI75 at week 10<br>1-Inflix <sup>3</sup> (5mg/kg)- 80% vs 3% placebo<br>2- Inflix (5mg/kg)- 75% vs 2% placebo<br>3- Inflix (5mg/kg)- 88% vs Inflix (3mg/kg) 72% vs 6% placebo | BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), malignancies including Hepatosplenic T-cell lymphomas (adolescents and young adults)<br>Warnings: Hep B reactivation, heart failure, hepatotoxicity, cytopenias, hypersensitivity events, malignancy                                                                                                                 | Pregnancy: B                                                                                                                                                                              |

<sup>1</sup> Non-steroidal anti-inflammatory drug

<sup>2</sup> R=randomized, DB=double-blind, PC= placebo-controlled

<sup>3</sup> Inflix=infliximab

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| Product (s)<br>Name/year<br>approved | Relevant<br>Indication                                                                                                                           | Dosage<br>& Admin                                                                                                                                                                                                    | Efficacy<br>Information                                                                                                                                                        | Important Safety<br>and Tolerability<br>Issues                                                                                                                                                                                                                                  | Other<br>Comments |
|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Adalimumab<br>(Humira)<br>2008       | Moderate to severe chronic plaque psoriasis, candidates for phototherapy or systemic therapy                                                     | 80 mg via subcutaneous injection (SC) initial dose, followed by 40 mg SC every other week starting one week after initial dose                                                                                       | From the label: 2 R, DB, PC <sup>5</sup> trials<br>PASI75 at week 16<br>1-Ada <sup>4</sup> -71% vs 7% placebo<br>2- Ada-78% vs 19% placebo                                     | BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), malignancy including hepatosplenic T-cell lymphoma<br>Warnings: hypersensitivity reactions, Hep B reactivation, demyelinating disease, cytopenias, heart failure, Lupus-like syndrome | Pregnancy: B      |
| Etanercept<br>(Enbrel)<br>2004; 2016 | Chronic moderate to severe psoriasis, candidates for photo- therapy or systemic therapy; 11/2016- approved for patients 4 years of age and older | 50 mg SC twice weekly for 3 months, followed by 50 mg once weekly; <63 kg (138 lb)- 0.8 mg/kg SC weekly                                                                                                              | From the label: 2 R, DB, PC5 trials<br>PASI75 at 3 months<br>1-Etan <sup>5</sup> -47% vs 4% placebo<br>2-Etan-46% vs 3% placebo                                                | BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), lymphomas, other malignancies<br>Warnings: demyelinating disease, worsen CHF, pancytopenia, malignancy, Hep B reactivation                                                            | Pregnancy: B      |
| <b>IL-12 and IL-23 blocker</b>       |                                                                                                                                                  |                                                                                                                                                                                                                      |                                                                                                                                                                                |                                                                                                                                                                                                                                                                                 |                   |
| Ustekinumab<br>(Stelara)<br>2009     | Moderate to severe psoriasis, candidates for phototherapy or systemic therapy                                                                    | For patients weighing <100 kg :45 mg SC initially and 4 weeks later, followed by 45 mg SC every 12 weeks<br>For patients weighing >100 kg: 90 mg SC initially and 4 weeks later, followed by 90 mg SC every 12 weeks | From the label: 2 R, DB, PC trials<br>PASI75 at week 12<br>1-uste <sup>6</sup> (90mg)-66% vs uste(45mg)-67% vs 3% placebo<br>2-uste (90mg)-76% vs uste(45mg)-67% vs 4% placebo | Warnings and Precautions (W&Ps): Infections (serious bacterial, fungal and viral), theoretical risk for serious infections, malignancy, reversible posterior leukoencephalopathy syndrome, pretreatment eval for TB.                                                            | Pregnancy: B      |
| <b>IL- 17A blocker</b>               |                                                                                                                                                  |                                                                                                                                                                                                                      |                                                                                                                                                                                |                                                                                                                                                                                                                                                                                 |                   |
| Secukinumab<br>(Cosentyx)<br>2015    | Moderate to severe psoriasis, candidates for phototherapy or systemic therapy                                                                    | 300 mg SC at Weeks 0, 1, 2, 3 and 4 followed by 300 mg SC every 4 weeks. For some patients, a dose of 150 mg may be                                                                                                  | From the label: 4 R, DB, PC trials<br>PASI75 at week 12<br>1-sec <sup>7</sup> (300mg)-82% vs sec (150mg)-71% vs 4% placebo<br>2-sec (300mg)-76%                                | W&Ps: Infections (serious bacterial, fungal and viral), theoretical risk for serious infections, Crohn's disease, hypersensitivity                                                                                                                                              | Pregnancy: B      |

<sup>4</sup> Ada=adalimumab

<sup>5</sup> Etan= etanercept

<sup>6</sup> Uste=ustekinumab

<sup>7</sup> Sec= secukinumab

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| Product (s)<br>Name/year<br>approved | Relevant<br>Indication                                                                                                                                                                                                         | Dosage<br>& Admin                                                                                                                         | Efficacy<br>Information                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Important Safety<br>and Tolerability<br>Issues                                                                                                                                                                                                             | Other<br>Comments                                                                                                                            |
|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
|                                      |                                                                                                                                                                                                                                | acceptable                                                                                                                                | vs sec (150mg)-67%<br>vs 5% placebo<br>3-sec (300mg)-75%<br>vs sec (150mg)-69%<br>vs 0% placebo<br>4-sec (300mg)-87%<br>vs sec (150mg)-70%<br>vs 3% placebo                                                                                                                                                                                                                                                                                                                                                | reactions, pretreatment<br>eval for TB.                                                                                                                                                                                                                    |                                                                                                                                              |
| Ixekizumab<br>(Taltz)<br>2016        | Moderate-to-<br>severe plaque<br>psoriasis in<br>adults who are<br>candidates for<br>systemic therapy<br>or phototherapy                                                                                                       | 160 mg (two 80 mg<br>injections) SC at<br>Week 0, followed by<br>80 mg at Weeks 2,<br>4, 6, 8, 10, and 12,<br>then 80 mg every 4<br>weeks | From the label: 3 R,<br>DB, PC trials<br>PASI75 at Week 12<br>1: Ixe <sup>8</sup> (80 mg q2wk)<br>89% vs 4% placebo<br>2: Ixe (80 mg q2wk)<br>90% vs 2% placebo<br>3: Ixe (160 mg x 1,<br>then 80 mg q2wk)<br>87% vs 7% placebo                                                                                                                                                                                                                                                                            | W&Ps:<br>Infections (Upper<br>respiratory tract, oral<br>candidiasis,<br>conjunctivitis and tinea<br>infections; Inflammatory<br>Bowel Disease (Crohn's<br>disease and ulcerative<br>colitis); hypersensitivity<br>reactions; pretreatment<br>eval for TB. |                                                                                                                                              |
| <b>IL- 17 Receptor A antagonist</b>  |                                                                                                                                                                                                                                |                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                            |                                                                                                                                              |
| Brodalumab<br>(Siliq)<br>2017        | Moderate to<br>severe plaque<br>psoriasis in adult<br>patients who are<br>candidates for<br>systemic therapy<br>or phototherapy<br>and have failed<br>to respond or<br>have lost<br>response to other<br>systemic<br>therapies | 210 mg by<br>subcutaneous<br>injection at Weeks<br>0, 1, and 2 followed<br>by 210 mg every 2<br>weeks                                     | From the Label: 3 R,<br>DB, PC trials<br>PASI 75 and sPGA<br>of 0 ("clear") or 1<br>("almost clear") at<br>Week 12<br>1: Bro <sup>9</sup> (210 mg<br>q2wk) PASI 75 83%<br>vs 3% placebo;<br>sPGA 0 or 1 Bro<br>76% vs 1% placebo<br>2: Bro (210 mg<br>q2wk) PASI 75 86%<br>vs 8% placebo;<br>sPGA 0 or 1 Bro<br>79% vs 4% placebo;<br>PASI 100 Bro 44%<br>vs Uste 22%<br>3: Bro (210 mg<br>q2wk) PASI 75 85%<br>vs 6% placebo;<br>sPGA 0 or 1 Bro<br>80% vs 4% placebo;<br>PASI 100 Bro 37%<br>vs Uste 19% | Box warning for Suicidal<br>Ideation and Behavior<br><br>W&Ps:<br>Suicidal ideation and<br>behavior; Infections<br>(serious infections and<br>fungal infections);<br>Crohn's disease;<br>pretreatment eval for<br>TB; avoid live vaccines.                 | REMS requires<br>prescribers<br>and<br>pharmacies to<br>be certified;<br>patients must<br>sign a Patient-<br>Prescriber<br>agreement<br>form |
| <b>IL-23 blocker</b>                 |                                                                                                                                                                                                                                |                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                            |                                                                                                                                              |
| Guselkumab<br>(Tremfya)<br>2017      | Moderate-to-<br>severe plaque<br>psoriasis in<br>adults who are<br>candidates for<br>systemic therapy                                                                                                                          | 100 mg by<br>subcutaneous<br>injection at<br>Week 0, Week 4,<br>and every 8 weeks<br>thereafter                                           | From the Label: 3 R,<br>DB, PC, AC <sup>10</sup> trials;<br>1 & 2: PASI 90 and<br>sPGA of 0<br>("cleared") or 1<br>("minimal") at Week                                                                                                                                                                                                                                                                                                                                                                     | W&Ps:<br>Infections (upper<br>respiratory tract<br>infections,<br>gastroenteritis, tinea<br>infections, and herpes                                                                                                                                         |                                                                                                                                              |

<sup>8</sup> Ixe= Ixekizumab

<sup>9</sup> Bro= Brodalumab

<sup>10</sup> AC= Active comparator

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| Product (s)<br>Name/year<br>approved       | Relevant<br>Indication                                                                                | Dosage<br>& Admin                                                                              | Efficacy<br>Information                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Important Safety<br>and Tolerability<br>Issues                                                                         | Other<br>Comments |
|--------------------------------------------|-------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|-------------------|
|                                            | or phototherapy                                                                                       |                                                                                                | 16<br>1: Gus <sup>11</sup> (100 mg wk 0 & 4 then q8wk)<br>PASI 90 73% vs 3% placebo; IGA 0 or 1 85% vs 7% placebo<br>2: Gus (100 mg wk 0 & 4 then q8wk) PASI 90 70% vs 2% placebo; IGA 0 or 1 84% vs 8% placebo<br>3: Subjects began tx with Uste; at wk16 subjects with IGA ≥2 R to Gus or continued Uste; endpoint at wk 28 IGA 0 or 1 with ≥2 grade improvement; Gus 31% vs 14% Uste                                                                                                                                                                                  | simplex infections); pretreatment eval for TB; avoid live vaccines.                                                    |                   |
| Tildrakizumab (Ilumya) 2018                | Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy | 100 mg administered by subcutaneous injection at Weeks 0, 4, and every twelve weeks thereafter | 3 R, DB, PC, AC <sup>12</sup> trials; The co-primary endpoints were assessed at Week 12: i) the proportion of subjects who achieved an PGA score of 0 (“cleared”) or 1 (“minimal”), and ii) the proportion of subjects who achieved at least a PASI 75. Tildrakizumab was superior to placebo on both PGA (Trial P010: 58% vs 7% and Trial P011: 55% vs 4%) and PASI 75 (Trial P010: 64% vs 6% and Trial P011: 61% vs 6%) at Week 12. Applicant did not establish an adequate scientific bridge between U.S.-licensed Enbrel and EU-approved etanercept for labeling AC. | W&Ps: Hypersensitvity, Infections (upper respiratory tract infections); pretreatment eval for TB; avoid live vaccines. |                   |
| <b>T-Cell Inhibitor/ Immunosuppressant</b> |                                                                                                       |                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                        |                   |

<sup>11</sup> Gus= Guselkumab

<sup>12</sup> AC= Active comparator

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(Skyrizi, Risankizumab)

| Product (s)<br>Name/year<br>approved        | Relevant<br>Indication                                                                                                           | Dosage<br>& Admin                                                                                                                                                   | Efficacy<br>Information                                                                                                                                                                                                 | Important Safety<br>and Tolerability<br>Issues                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Other<br>Comments                                                                                                                                                                                                               |
|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cyclosporine<br>1997                        | Adult, nonimmuno-compromised patients with severe recalcitrant disabling psoriasis who have failed at least one systemic therapy | Starting dose: 2.5 mg/kg/day, taken twice daily, dosage ↑ by 0.5 mg/kg/day at 2-week intervals, to a maximum of 4.0 mg/kg/day.                                      | From the label: PASI75 - 51% at 8 weeks, 79% at 16 weeks                                                                                                                                                                | BW-Should only be used by MDs experienced in management of systemic immunosuppressive Rx, ↑ susceptibility to infections and development of neoplasia including lymphoma, also hypertension, nephrotoxicity which ↑ with ↑ doses. In psoriasis patients with history of PUVA, UVB, coal tar or radiation Rx- ↑ risk of skin malignancies<br>Warnings: Hepatotoxicity, hyperkalemia, thrombotic microangiopathy, progressive multifocal leukoencephalopathy (PML), malignancies, serious infection, neurotoxicity | Pregnancy Category C                                                                                                                                                                                                            |
| <b>Retinoid</b>                             |                                                                                                                                  |                                                                                                                                                                     |                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                 |
| Acitretin (Soriatane)<br>1996               | Severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments         | Starting dose: 25 to 50 mg orally (PO) per day, Maintenance doses of 25 to 50 mg per day may be given dependent upon an individual patient's response to initial Rx | From the label: 2 DB, PC trials- Mean change in PGA at 8 weeks A-Acitretin(50mg)-2 vs -0.29 on placebo B- Acitretin (50mg)- 1.57 vs Acitretin (25 mg)-1.06 vs -0.06 on placebo (no multiplicity adjustment for trial B) | BW-pregnancy must be prevented during Rx and for 3 years following due to teratogenicity, no ethanol ingestion by females of childbearing potential (FOCBP) due to metabolism to etretinate and ↑ 1/2life, REMS (Do Your P.A.R.T.) participation required for FOCBP-see Drugs @ FDA for details. Patients cannot donate blood for 3 years post Rx, See label for data on pregnancies in partners of male patients on acitretin                                                                                   | W&P: hepatotoxicity, skeletal abnormalities, lipids↑, Cardiovascular risk ↑, Ophthalmologic effects, Pancreatitis, capillary leak syndrome, pseudotumor cerebri, exfoliative dermatitis, depression<br><br>Pregnancy category X |
| <b>Phosphodiesterase 4 (PDE4) inhibitor</b> |                                                                                                                                  |                                                                                                                                                                     |                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                 |
| Apremilast (Otezla)                         | Moderate to severe psoriasis,                                                                                                    | To reduce risk of gastrointestinal                                                                                                                                  | From the label: 2 R, DB, PC trials                                                                                                                                                                                      | W&P: depression, weight decrease, drug                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Diarrhea, nausea, URI,                                                                                                                                                                                                          |

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| Product (s)<br>Name/year<br>approved   | Relevant<br>Indication                                                             | Dosage<br>& Admin                                                           | Efficacy<br>Information                                                                                | Important Safety<br>and Tolerability<br>Issues                                                                                                                                           | Other<br>Comments                                                                                                                                          |
|----------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2014                                   | candidates for phototherapy or systemic therapy                                    | symptoms, titrate to recommended dose of 30 mg PO twice daily               | PASI75 at 16 weeks<br>1- aprem <sup>13</sup> 33% vs 5% in placebo<br>2- aprem 28.8% vs 5.8% in placebo | interactions with strong P450 enzyme inducers (rifampin, phenobarbital, carbamazepine, phenytoin)                                                                                        | headache<br><br>Pregnancy Category C                                                                                                                       |
| <b>Phototherapy</b>                    |                                                                                    |                                                                             |                                                                                                        |                                                                                                                                                                                          |                                                                                                                                                            |
| PUVA-8-MOP (methoxsalen) + UVA therapy | Severe, recalcitrant, disabling psoriasis not responsive to other forms of therapy | 20 -70 mg PO (based on weight) taken 2-4 hours before exposure to UVA light | No efficacy information for psoriasis in the label.                                                    | BW: Should only be used by MDs who have special competence in psoriasis management<br>Warnings: serious skin burning, ocular damage, aging of the skin, skin cancer (including melanoma) | Nausea, erythema, pruritus, must avoid all exposure to sunlight (even through windows) to eyes and skin for 24 hours after ingestion; Pregnancy category C |

<sup>13</sup> aprem=apremilast

### 3 Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

Because risankizumab is an original BLA and is not currently marketed in the United States, this section is not applicable.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

The applicant developed risankizumab injection under IND 113306. On February 28, 2012, the applicant opened the IND. During their development program, the applicant interacted with the Agency at the following milestones/meetings: Pre-IND 01/18/2012; Guidance 04/05/2017, 03/29/2017, 11/16/2016 and 11/17/2015; Written Responses 06/14/2017, 11/04/2016 and 10/29/2015; End-of-Phase 2 (EOP2) 06/24/2015; Pre-BLA 12/12/2017.

At the End-of-Phase 2 (EOP2) meeting the Agency made the following recommendations (how these were addressed by the applicant is in italics):

- The 150 mg dose with dosing at Week 0, Week 4 and every 12 weeks thereafter for Phase 3 appears reasonable based on the provided information (*dose used in Phase 3 studies*)
- We recommend that you continue to evaluate the impact of body-weight on the efficacy and safety measures in the Phase 3 trials and submit these evaluations in the BLA submission to assist in reviewing the appropriateness of dosing for different body-weight ranges (*elected to examine a single dosage level and regimen in the phase 3 program, pre-specified subgroup analyses were performed to evaluate the impact of body-weight*)
- The proposed coprimary endpoint of PASI 90 and sPGA of clear/almost clear with 2- grade improvement with an adequate sPGA scale is acceptable. However, we cannot comment on acceptability of the proposed coprimary endpoint sPGA of clear/almost clear, as the briefing document did not contain a description (*scale was submitted with the protocol for review*)
- The design of the trials to evaluate safety is not adequate (*protocol was modified prior to submission*)
- We agree that a TQT study is not required. However, periodic EKG monitoring during the Phase 3 trials should be performed (*ECG monitoring was performed during the Phase 3 program*)
- One of your pivotal Phase 3 trials should include provisions for subjects to self-administer the drug product (*Study M16-010 [1311.30] was modified to require self-administration of study drug*)
- It may be reasonable to use EU-approved ustekinumab as an active control in a superiority clinical trial [REDACTED] (b) (4) [REDACTED] if you can establish an adequate scientific bridge to justify the relevance of data obtained with EU-approved ustekinumab (*has not provided*)

*bridging information, states that the performance of ustekinumab in terms of safety and effectiveness are expected to be the same whether a patient receives ustekinumab from the EU or US marketplace,* (b) (4)

- The regulatory utility of the proposed trial is limited. Humira was approved after 16 weeks of therapy (i.e., an initial dose of 80 mg at Week 0 followed by a dose of 40 mg every other week starting Week 1 through Week 15) using the endpoints of PASI 75 and “clear” or “almost clear” on PGA. In your proposed trial, subjects should receive the approved dose regimen of Humira, and the comparison between your product and Humira should be done at Week 16 using the endpoints of PASI 75 and “clear” or “almost clear” on PGA. In addition, “incomplete response” should be defined as those who did not achieve “clear” or “almost clear” on PGA and PASI 75 at Week 16 (*For Trial 1311.30, the sponsor revised their primary timepoint from Week 12 to Week 16, and proposed co-primary endpoints of sPGA 0 or 1 at Week 16 along with PASI 90 at Week 16 with PASI 75 at Week 16 as a secondary endpoint*)
- The safety database that you propose of 1800 subjects exposed to BI 655066 at 150 mg dosing and of at least 1000 subjects being exposed at this dose for a year seems reasonable (*achieved the proposed exposure*)

The applicant submitted three Phase 3 protocols (1311.3, 1311.28, and 1311.4) for review (not under a special protocol assessment) along with questions seeking specific advice on the protocols. The sPGA scale and safety monitoring was found to be acceptable. The intended study population ( moderate to severe chronic plaque psoriasis BSA of  $\geq 10\%$ , PASI  $\geq 12$ , and IGA score of moderate) was found to be acceptable. Comments on the statistical hierarchy were provided. *For Studies M15-995 (1311.28) and M16-008 (1311.3), the statistical testing hierarchy was re-ordered to prioritize comparisons with placebo.*

The applicant submitted three Phase 3 protocols new clinical protocol 1311.30 with modifications. The Agency provided the following comment (in advice letter March 9, 2016): To support a superiority claim against an active comparator, replication of study findings from two adequate and well-controlled trials is recommended. (b) (4)

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

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### 4.1. Office of Scientific Investigations (OSI)

The clinical sites chosen for inspection were primarily based on numbers of enrolled subjects, treatment effect, and prior inspectional history. The clinical sites of Drs. Toth, Hong, and Tying and the study sponsors, AbbVie, Inc. and Boehringer Ingelheim Pharmaceuticals, Inc. (BI) were inspected in support of this BLA to verify data from study Protocols M15-992 (1311.4), M15-995 (1311.28), and M16-008 (1311.3). The European Medicines Agency (EMA) has received the same marketing authorization application (MAA), and FDA and EMA conducted joint inspections of the study sponsors, AbbVie, Inc. and BI, as part of the FDA-EMA GCP Initiative.

During the sponsor inspection, the following data integrity concerns involving the Psoriasis Area and Severity Index (PASI) and Static Physician Global Assessment (sPGA) scores were identified:

- Inappropriate use of a medical scribe that resulted in no clearly attributable signature of a qualified assessor that was necessary for verifying the accuracy of the assessment data entered by the medical scribe
- Incorrect data attribution
- Alteration of the audit trail information

These observations identified above affected a small percentage of study subjects as follows:

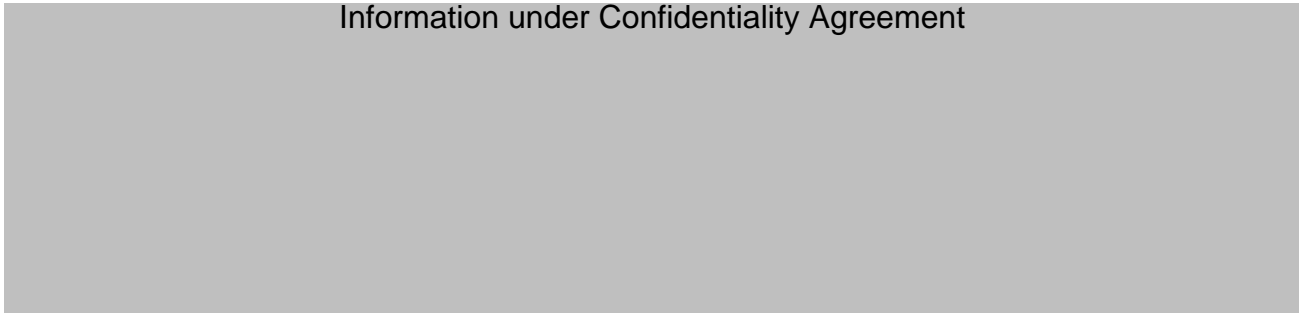
- 54/1504 (3.6%) subjects across all three trials for Visits 2 and 6 PASI scores
- 26/1504 (1.7%) subjects across all three trials for Visits 2 and 6 sPGA scores

Refer to Section 7.2.1.8.2 for sensitivity analysis.

Also noted were 718 cases of incorrect date and time stamps of PASI, sPGA, and Psoriasis Symptoms Scale (PSS) data that occurred when the batteries of the mobile devices used to capture this data were critically low. When date and time stamps could not be corrected, the Sponsor and the Contract Research Organization (CRO) who supplied the devices and data management services deleted the data. The date and time corrections did not impact the reliability of the data because we have confidence in the algorithm used to determine the actual dates and times the data were entered by the qualified assessors and study subjects.

Notwithstanding these observations that affected the reliability of the primary efficacy endpoint data for a small percentage of the study population across all three protocols, the studies appear to have been conducted adequately. The study data, including the primary efficacy endpoint data for the rest of the study population, appear acceptable in support of the respective indication.

The final compliance classification of the inspections of Drs. Toth and Hong was No Action Indicated (NAI). The final classification of the inspection of Dr. Tying was Voluntary Action Indicated (VAI). The final classification of the inspection of the current sponsor, AbbVie, was NAI, and the final classification of the initial sponsor, BI, was VAI.



Information under Confidentiality Agreement

## 4.2. Product Quality

Novel excipients: No  
Any impurity of concern: No

The overall control strategy for risankizumab manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls, process monitoring tests, release, and stability testing ensures process consistency, and drug substance (DS), and drug product (DP) that have appropriate quality and are free of adventitious agents.

## II. Summary of Quality Assessments:

### **A. CQA Identification, Risk and Lifecycle Knowledge Management**

Table 1: The attributes discussed in Table 1 are applicable to the risankizumab DS and DP.

| <b><u>CQA (type)</u></b> | <b><u>Risk</u></b> | <b><u>Origin</u></b>                                                | <b><u>Control Strategy</u></b> | <b><u>Other</u></b> |
|--------------------------|--------------------|---------------------------------------------------------------------|--------------------------------|---------------------|
| IL-23 binding (potency)  | Potency            | Intrinsic to the molecule.<br>Potency can be impacted by<br>(b) (4) | (b) (4)                        | (b) (4)             |
| Identity                 | Safety             | Intrinsic to the                                                    | (b) (4)                        |                     |

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|                                      |                            |                                                                                                                                         |         |  |
|--------------------------------------|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|---------|--|
|                                      | and Efficacy               | molecule.                                                                                                                               | (b) (4) |  |
| High molecular weight species (HMWS) | Potency and immunogenicity | <p>Manufacturing process and exposure to light stress.</p> <p>The level of HMW at about (b) (4)% and does increase over shelf-life.</p> |         |  |
| Low molecular weight species (LMWS)  | Potency                    | <p>Manufacturing process (b) (4)</p> <p>The level of LMWS is around (b) (4)% and does not increase over shelf-life.</p>                 |         |  |
| (b) (4)                              | Potency                    | <p>Exposure to light and chemical stress.</p> <p>(b) (4)</p>                                                                            |         |  |
| (b) (4)                              | Pharmacokinetics           | <p>Exposure to light stress.</p> <p>(b) (4)</p>                                                                                         |         |  |
|                                      |                            |                                                                                                                                         |         |  |

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|                                                                  |                              |                                           |         |         |
|------------------------------------------------------------------|------------------------------|-------------------------------------------|---------|---------|
|                                                                  |                              | (b) (4)                                   |         |         |
| Asp deamidation in the CDR and FcRn binding regions              | Potency and Pharmacokinetics | Manufacturing process ( (b) (4) ).        | (b) (4) |         |
| Appearance of Solution (visible particulates, color and clarity) | Safety and Efficacy          | Formulation, contamination or degradation |         |         |
| Protein Content                                                  | Efficacy                     | Manufacturing process                     |         |         |
| pH                                                               | Safety and Efficacy          | Formulation process                       |         |         |
| Osmolality                                                       | Safety and Efficacy          | Formulation                               |         |         |
| (b) (4)                                                          | Safety                       | Formulation                               |         | (b) (4) |

**B. Drug Substance [risankizumab-rzaa] Quality Summary**

**CQA Identification, Risk, and Lifecycle Knowledge Management**

The DS is (b) (4) at 90 mg/ml (b) (4). (b) (4) Table 2 below is a summary of critical quality attributes and their control strategies that are relevant to the DS.

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

| <u>CQA (type)</u>                         | <u>Risk</u>               | <u>Origin</u>                                                                                   | <u>Control Strategy</u> | <u>Other</u> |
|-------------------------------------------|---------------------------|-------------------------------------------------------------------------------------------------|-------------------------|--------------|
| Residual HCP                              | Immunogenicity            | Production cell line<br><br>HCP levels in DS are consistent at (b) (4) U/mg (or (b) (4) ng/mg). | (b) (4)                 |              |
| Residual DNA                              | Safety                    | Production cell line                                                                            | (b) (4)                 | (b) (4)      |
| (b) (4)<br><br>(Process-related impurity) | Safety and Immunogenicity | Process related impurity (b) (4)                                                                | (b) (4)                 |              |

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|                                            |                                                                                                          |                                                              |         |
|--------------------------------------------|----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|---------|
| (b) (4)<br><br>(Process-related impurity)  | Safety                                                                                                   | (b) (4)                                                      | (b) (4) |
| Cell Culture Derived Impurities<br>(b) (4) | Safety                                                                                                   | Process related impurities                                   |         |
| Viruses<br>(Contaminant)                   | Safety                                                                                                   | Contamination during manufacture, most likely during (b) (4) |         |
| Mycoplasma<br>(Contaminant)                | Safety                                                                                                   | Mycoplasma would most likely be introduced during (b) (4)    |         |
| Endotoxin                                  | Safety and Purity                                                                                        | Raw materials contamination during manufacturing             |         |
| Bioburden                                  | Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination | Raw materials and manufacturing process                      |         |

**Description:** Risankizumab is a humanized monoclonal immunoglobulin G1 (IgG1 isotype) consisting of two identical heavy chains (HC) and two identical light chains (LC) covalently linked through inter- and intra-chain disulfide bonds. Each HC and LC are composed of 449 and 214 amino acids, respectively. Each HC contains a leucine to alanine substitution at amino acid residues 237 and 238 within the Fc domain to minimize the potential for effector function and deletion of lysine at the C terminus to reduce potential for charge heterogeneity. A single N-linked glycosylation site is in the CH2 domain of each HC at asparagine residue 297.

The extinction coefficient was calculated and confirmed experimentally to be  $1.52 \text{ mL} \times \text{mg}^{-1} \times \text{cm}^{-1}$  at 280 nm.

**Mechanism of Action (MoA):** Risankizumab selectively binds to IL-23 p19 and inhibits binding of IL-23 to its receptor. This in turn, inhibits IL-23 inflammatory responses that contribute to the pathogenesis of plaque psoriasis. The generation and characterization of risankizumab was undertaken to include selectivity for the p19 over the p40 subunit, to overcome the high-affinity binding between IL-23 to IL-23R and favorable biophysical properties.

**Potency Assay:** Biological activity of risankizumab is evaluated using a chicken lymphoma cell DT-40 line, which constitutively expresses the human IL-23R complex (IL-23R and IL-12R $\beta$ 1 subunits) and STAT5B. The DT-40 bioassay assay is a luciferase reporter-gene assay which measures the activation of the human IL-23R/STATB pathway. Upon IL-23 binding to the IL-23R, STAT5B is phosphorylated and activates transcription of STAT5B responsive elements and subsequently activates the firefly luciferase. The luciferase activity is then quantified. In the presence of risankizumab, IL-23 cannot bind the IL-23R, leading to the inhibition of luciferase activity. To measure risankizumab potency, DT-40 cells are co-incubated with increasing amounts of risankizumab and a 4-parameter (4-PL) unconstrained logistic analysis is used to calculate the dose response curve. Potency is reported as a percentage relative to the reference standard.

**Reference Materials:**

(b) (4)

(b) (4)

[Redacted] (b) (4)

**Critical starting materials or intermediates:**

[Redacted] (b) (4)

**Manufacturing process summary:**

[Redacted] (b) (4)

[Redacted] (b) (4)

**Container closure:**

[Redacted] (b) (4)

**Dating period and storage conditions:** The dating period for the DS is (b) (4) months when stored at (b) (4) °C.

**C. Drug Product [risankizumab-rzaa] Quality Summary:**

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

| <u>CQA (type)</u>           | <u>Risk</u>                                                                                                       | <u>Origin</u>                                                                          | <u>Control Strategy</u> | <u>Other</u>                           |
|-----------------------------|-------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------|----------------------------------------|
| Sterility (contaminant)     | Safety (Infection), Purity and Efficacy (degradation or modification of products by contaminating microorganisms) | Contamination may be introduced throughout the manufacturing process                   | (b) (4)                 |                                        |
| Endotoxin (contaminant)     | Safety, purity, and immunogenicity                                                                                | Raw materials; contamination may be introduced throughout the DP manufacturing process |                         | Provides over a 10-fold safety factor. |
| Container closure integrity | Safety                                                                                                            | Container closure breaches during storage. May be impacted by storage conditions.      |                         |                                        |
| Extractable volume DP       | Accurate dosing                                                                                                   | Fill volume was identified as CPP that is                                              |                         |                                        |

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|                                                                          |                           |                                                                             |         |                                                                                                          |
|--------------------------------------------------------------------------|---------------------------|-----------------------------------------------------------------------------|---------|----------------------------------------------------------------------------------------------------------|
|                                                                          |                           | controlled within pre-established limits to ensure accurate dosing. (b) (4) | (b) (4) |                                                                                                          |
| Leachables<br>(process-related impurities)                               | Safety                    | Manufacturing equipment and CCS                                             |         | A PMC was conveyed to perform leachable studies on the DP in the final CCS over the proposed shelf life. |
| (b) (4)                                                                  | Safety                    | Manufacturing process and CCS                                               |         |                                                                                                          |
| (b) (4)                                                                  | Safety and Immunogenicity | Manufacturing process and CCS                                               |         |                                                                                                          |
|                                                                          |                           |                                                                             |         |                                                                                                          |
| Subvisible Particulate Matter<br>(Product or Process Related Impurities) | Safety and Immunogenicity | Manufacturing process and CCS.                                              |         |                                                                                                          |
| Visible Particles                                                        | Safety and Immunogenicity | Through the DP manufacturing                                                |         |                                                                                                          |

|                                |                 |                                                                       |         |
|--------------------------------|-----------------|-----------------------------------------------------------------------|---------|
|                                |                 | process via extended hold times and contact with materials<br>(b) (4) | (b) (4) |
| Break-out force, gliding force | Accurate dosing |                                                                       |         |

**Potency and Strength:** Risankizumab (75 mg) pre-filled syringe is supplied at 90 mg/mL in a 1 ml (b) (4) syringe with a nominal fill volume at 0.83 ml. Potency is defined as the percent activity relative to the current reference standard. The potency assay is the same as described for the DS.

**Summary of Product Design:** Risankizumab 75 mg/0.83 ml pre-filled syringe is presented as a sterile, preservative-free, non-pyrogenic liquid formulation in glass syringes for subcutaneous injection at a concentration of 90 mg/ml. The drug product formulation consists of (b) (4) mM succinate ((b) (4) mM succinic acid/(b) (4) mM disodium succinate hexahydrate), (b) (4) mM sorbitol, and (b) (4) g/L polysorbate 20 (PS20) at pH (b) (4). The extractable volume is 0.83 ml.

**List of Excipients:** (b) (4) mM succinate ((b) (4) mM succinic acid/(b) (4) mM disodium succinate hexahydrate), (b) (4) mM sorbitol, and (b) (4) g/L polysorbate 20 (PS20) at pH (b) (4).

**Reference Materials:** The same reference material is used for DS and DP.

**Manufacturing process summary:** (b) (4)

(b) (4)



**Container closure:** The primary container closure system for risankizumab DP consists of a 1 ml glass syringe utilizing USP/Ph.Eur/JP Type (b) (4) glass, and each syringe includes a staked-in place (integrated) 0.5 inch long, 29 gauge, thin wall stainless steel needle for subcutaneous injection, a (b) (4) rubber stopper and a rigid needle shield (RNS) composed of (b) (4). Appropriate compatibility studies were performed for the container closure system.

The secondary container closure system consists of a (b) (4) film blister and a box, which is sufficient for protection from light.

**Dating period and storage conditions:** The dating period for risankizumab DP is 24 months when stored at 2-8°C.

**List of co-package components, if applicable:** None

**Facilities:** Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) proposed for Risankizumab DP manufacture. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility perspective.

**D. OPQ Recommendation:** The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761105 for Skyrizi (risankizumab-rzaa) manufactured by AbbVie, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Skyrizi (risankizumab-rzaa) is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

**Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:**

1. To perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS), and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

**4.3. Clinical Microbiology**

**4.4. Devices and Companion Diagnostic Issues**

During the pivotal Phase 3 trials, risnakizumab was supplied and administered via a single-dose, prefilled syringe (PFS) assembled with a needle stick protection device (NSP). This is the device with which risnakizumab is to be marketed. The device was reviewed by Matthew Ondeck; Center for Devices and Radiological Health, Office of Device Evaluation (CDRH/ODE). CDRH/ODE recommends approval for the BLA for this combination product.

## **5 Nonclinical Pharmacology/Toxicology**

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**5.1. Executive Summary**

Risankizumab is a humanized recombinant IgG1 monoclonal antibody that selectively binds to the p19 subunit of human interleukin 23 (IL-23p19) and blocks the interaction of IL-23 with the IL-23 receptor. The Fc portion of risankizumab has two replacement mutations (Leu234Ala and Leu235Ala) to reduce Fc $\gamma$  receptor and complement binding.

Risankizumab displayed a high affinity binding to its target human IL-23 p19 in vitro, with no detectable binding to human IL-12 or rat IL-23 at the concentration of 1  $\mu$ M. Binding of risankizumab to Cynomolgus monkey IL-23 was also high, with a dissociation constant (Kd) of less than 1 pM. Risankizumab bound to mouse IL-23 with a Kd of 15 nM. Risankizumab inhibited IL-23-dependent phosphorylation of signal transducer and activator of transcription 3 (STAT3) in the human cell line DB with an IC<sub>50</sub> value of 24 pM. Additionally, risankizumab inhibited the induction of IL-17 by

human IL-23 in mouse splenocytes, but does not inhibit the induction of interferon gamma (IFN $\gamma$ ) by human IL-12 in phytohaemagglutinin (PHA) blasts. In an in vivo mouse ear thickening model, risankizumab inhibited human IL-23-induced ear thickening as well as the induction of IL-17 and IL-22 in the ear tissue. The Cynomolgus monkey was identified as the pharmacologically relevant species and used in toxicology studies.

Intravenous treatment with doses up to 50 mg/kg/week risankizumab for 4 weeks did not cause treatment-related effects on neurological or cardiovascular functions in Cynomolgus monkeys. There were no treatment-related effects on respiratory rate or body temperature in Cynomolgus monkeys subcutaneously treated with doses up to 50 mg/kg/week risankizumab for 6 months.

In a 6-month repeat-dose study with a 2-month recovery period, four groups of up to 6 male (4.1 to 6.4 years old) and up to 6 female (2.5 to 3.8 years old) Cynomolgus monkeys were treated subcutaneously with 0 (vehicle, (b) (4) succinic acid, (b) (4) disodium succinate hexahydrate, (b) (4) sorbitol, (b) (4) Polysorbate 20, pH (b) (4)), 5, 20, or 50 mg/kg risankizumab once weekly. There were no treatment-related effects on mortalities, clinical signs, neurobehavioral assessments, ophthalmology, body weights, body temperature, ECG, blood pressure, responses to KLH immunization (IgM and IgG antibody responses), clinical pathology including peripheral blood lymphocyte phenotyping, and macroscopic findings. Hematology analysis showed a slight dose-dependent change in reticulocytes that did not reverse. Findings of potentially treatment-related adverse changes in male reproductive organs/tissues were observed in risankizumab-treated males. However, upon further analysis it was determined that the male monkeys used in this study were not sexually mature. A follow-up study using sexually mature male monkeys was performed to evaluate possible treatment-related effects on male reproductive organs/tissues.

Following subcutaneous administration of risankizumab at 50 mg/kg/week for 26 weeks in 10 sexually mature male Cynomolgus monkeys, there were no treatment-related effects on mortality, clinical signs, body weights, food consumption, hematology, clinical chemistry, testicular volume, male reproductive hormones (serum testosterone, LH, and FSH), semen analysis (sperm count, motility, and morphology; ejaculate volume), gross pathology, organ weights, and histopathological findings including progression of the spermatogenic cycle, cell associations, and cell proportions in the various stages of spermatogenesis. The  $C_{max}$  and  $AUC_{0-168h}$  of risankizumab at the end of the dosing period were 950  $\mu\text{g/mL}$  and 122,000  $\mu\text{g}\cdot\text{h/mL}$ , respectively. The dose tested in this 26-week study, 50 mg/kg, is 20 times (based on mg/kg comparison) the maximum recommended human dose (MRHD) in patients (approximately 2.5 mg/kg based on administration of a 150 mg dose to a 60 kg individual)

In an enhanced pre- and post-natal toxicity study, three groups of 21 or 22 pregnant female Cynomolgus monkeys received subcutaneously 0 (vehicle, (b) (4) succinate, (b) (4) sorbitol, (b) (4) Polysorbate 20, pH (b) (4)), 5, or 50 mg/kg risankizumab once weekly from Gestation Day 20-22 (GD 20-22) until parturition for up

to 22 doses and post-natal development was evaluated in infants for 6 months after birth. There were no treatment-related effects on maternal mortality, clinical signs, body weights, food consumption, and gestation length. There were no treatment-related effects on fetal clinical signs, body weights, hematology, clinical chemistry, growth and development (including external, visceral, skeletal, and neurobehavioral evaluations), developmental immunotoxicology parameters (T-cell dependent antibody response and lymphocyte immunophenotyping), necropsy, organ weights, and histopathologic findings. However, as compared to the control group, a dose-dependent increase in fetal/infant loss was noted in the risankizumab-treated groups. The percent fetal/infant loss was 19%, 32%, and 43% in the vehicle control, 5 mg/kg, and 50 mg/kg groups, respectively. The increased fetal/infant loss in the 50 mg/kg/week group was considered to be related to risankizumab treatment (refer to Section 5.5.4.1 for detailed information concerning the criteria used for the determination of this treatment related effect). The  $AUC_{0-168h}$  in pregnant monkeys treated at 5 or 50 mg/kg/week was 15,700 or 123,000  $\mu\text{g}\cdot\text{h}/\text{mL}$  on GD 132-134, respectively. All infants from mothers in the risankizumab-treated groups had measurable and dose-dependent serum concentrations of risankizumab up to 91 days postpartum, while none of the infants had measurable concentrations of risankizumab by 180 days postpartum. In the infants, mean serum concentrations were approximately 17-86% of the respective maternal concentrations. The 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).

No genetic toxicology or carcinogenicity studies were conducted with risankizumab. The applicant provided a carcinogenic risk assessment, mainly using information from published literature. Overall the risk for malignancy associated with long-term inhibition of IL-23 following administration of risankizumab to humans is considered to be low. No local irritation (erythema or edema) was noted at the injection site in rabbits injected intramuscularly or subcutaneously with risankizumab. Risankizumab did not cause effects on hemocompatibility with human blood in vitro.

This BLA is approvable from a Pharmacology/Toxicology perspective. There is no recommended nonclinical PMC/PMR for this BLA.

## 5.2. Referenced NDAs, BLAs, DMFs

All the pivotal nonclinical studies have been reviewed under INDs 113306 and (b) (4). Summary pharmacology/toxicology information is provided in this review. The code names used for Skyrizi (risankizumab) injection are BI 655066, 655066-01, ABBV-066, and PR-1691244.

## 5.3. Pharmacology

### Primary pharmacology

### **5.3.1. Binding assessment of BI 655066 to human and cyno IL-23** (RD161521/BD0015)

The binding affinity of BI 655066 to human IL-23 and cynomolgus monkey IL-23 was measured via ProteOn XPR36, a label free and micro-fluidics based technology. It showed that the binding affinity of BI 655066 to cynomolgus monkey IL-23 was high, with a dissociation constant (Kd) of less than 1 pM. However, the binding affinity of BI 655066 to human IL-23 varies from double digit pM to less than 1 pM.

### **5.3.2. Binding Assessment of BI 655066 to mouse and rat IL-23 and human IL-12** (RD170961)

The affinity of BI 655066 binding to mouse IL-23, rat IL-23, and human IL-12 was tested in vitro. BI 655066 at a concentration of 1 µM did not bind to rat IL-23 or human IL-12. BI 655066 bound to mouse IL-23 with a Kd of 15 nM.

### **5.3.5. Inhibition of IL-17 production in IL-23-stimulated mouse splenocytes by BI 655066** (RD161518/BD0011)

The ability of BI 655066 to inhibit the production of mouse IL-17 stimulated by IL-23 was evaluated in vitro. No inhibition of IL-17 by BI 655066 (up to 33 nM) was observed when the cells were treated with rat or mouse IL-23. BI 655066 did inhibit IL-17 production in freshly prepared mouse splenocytes stimulated by human and cynomolgus monkey IL-23. The average IC<sub>50</sub> was 6.7 ± 1.0 pM (mean ± SEM) against recombinant human IL-23 with a linker, 7.3 ± 2.8 pM against recombinant human IL-23 without a linker, 2.1 ± 0.8 pM against human endogenous IL-23, and 16.3 ± 4.5 pM against recombinant cynomolgus IL-23.

### **5.3.6. Inhibition of IL-23 induced STAT3 phosphorylation in the DB cell line by BI 655066** (RD161519/BD-0013)

The ability of BI 655066 to inhibit IL-23-induced STAT3 phosphorylation was evaluated in a human B cell line (DB cells). BI 655066 was found to inhibit phosphorylation of STAT3 induced by human IL-23 in DB cells, with IC<sub>50</sub> values ranging between 13 - 36 pM.

### **5.3.7. Demonstration of lack of cross-reactivity of BI 655066 with human IL-12** (RD161522/BD0016)

Human peripheral blood mononuclear cells (PBMCs) from 10 different donors were stimulated with Lectin from Phaseolus vulgaris (PHA) for 3 days. After incubation of these PBMCs with recombinant human IL-12 and test antibodies at 37 °C for 48 hr, IFN-γ in culture supernatants was quantitated. The control antibodies against IL-12 p40 and p70 demonstrated an ability to inhibit IFN-γ production induced by 0.1 or 1 ng/mL IL-12. However, no inhibition of IFN-γ production induced by 0.1 or 1 ng/mL IL-12 was seen when PHA-stimulated human PBMCs were treated with of 5 µg/mL (33 nM) or 10

µg/mL (66 nM) BI 655066, indicating a lack of functional cross reactivity of BI 655066 with recombinant human IL-12.

### **5.3.8. In vivo activity of anti-human p19 antibody BI 655066 in IL-23 induced skin inflammation model (RD161523/IM2580)**

Recombinant human IL-23 injected daily for 4 consecutive days resulted in a significant increase in ear thickness which is accompanied by increases in IL-17 and IL-22 in the ear tissue of mice. Treating mice prior to the initial IL-23 challenge with a single dose of BI 655066 at 1 mg/kg resulted in significantly reduced ear thickness as well as both IL-17 and IL-22 levels in the ear tissue, compared to the vehicle-treated controls challenged by IL-23. In addition, BI 655066 appeared to be more potent than Stelara (a clinically available antibody targeting the p40 subunit of both IL-23 and IL-12) at inhibiting IL-23 induced cytokine production in this mouse model.

### Safety Pharmacology

Intravenous treatment with doses up to 50 mg/kg/week risankizumab for 4 weeks did not cause treatment-related effects on neurological or cardiovascular functions in Cynomolgus monkeys. There were no treatment-related effects on respiratory rate or body temperature in Cynomolgus monkeys subcutaneously treated with doses up to 50 mg/kg/week risankizumab for 6 months.

## **5.4. ADME/PK**

### **5.4.1. Pharmacokinetics and immunogenicity of BI 655066 in Cynomolgus monkeys receiving a single intravenous or subcutaneous dose of BI 655066 (RD161476)**

Two groups of 3 female monkeys received a single intravenous dose of 1.0 mg/kg or subcutaneous dose of 1.5 mg/kg risankizumab. Blood samples for pharmacokinetic analysis were collected at pre-dosing and at 0.167 (IV only), 0.5, 2, 8, 24, 48, 72, 96, 120, 168, 240, 336, 504, 672, 840, and 1008 hr post-dosing. Following intravenous treatment, the serum concentration-time profiles of risankizumab was characterized by a short distribution phase of approximately 1 - 2 days followed by a longer terminal phase. The terminal half-life ( $t_{1/2}$ ) averaged 173 hr. Clearance (CL) of risankizumab averaged 0.243 mL/h/kg and steady-state volume of distribution ( $V_{ss}$ ) averaged 40.7 mL/kg. Following subcutaneous treatment, maximum serum concentrations of risankizumab occurred at 48 - 72 hr and the terminal half-life averaged 184 hr. The bioavailability of BI 655066 following subcutaneous dosing was 71.8%.

### **5.4.2. BI 655066: A 26-Week subcutaneous toxicity and toxicokinetics study in Cynomolgus monkeys with an 8-week recovery period (RD161444/12R003)**

No risankizumab was detected in samples from the control group animals. The systemic exposure of risankizumab ( $C_{\max}$  and  $AUC_{0-168h}$ ) increased in an approximately dose-proportional manner on Day 1 and in Week 26 and no more than 2.2-fold upon repeated dosing at 50 mg/kg/week for 26 weeks. The  $AUC_{0-168h}$  of risankizumab in the 5, 20, and 50 mg/kg/week groups were 5,695, 21,350, and 55,150  $\mu\text{g}\cdot\text{h}/\text{mL}$  on Day 1 and 12,250, 37,350, and 86,250  $\mu\text{g}\cdot\text{h}/\text{mL}$  in Week 26, respectively.

#### **5.4.3. A 26-week reproductive toxicity study with BI 655066 in male Cynomolgus Monkeys, with an 8-Week Recovery Period (RD161448)**

Plasma levels of risankizumab were measured in the samples collected pre-dosing and at 24, 48, 72, 96, and 168 hr post-dosing on Days 1 and 176, and pre-dosing on Days 29 and 92. Plasma concentrations of risankizumab were below LLOQ (30 ng/mL) in all samples from the control group and pre-dosing samples on Day 1. The systemic exposure of risankizumab ( $C_{\max}$  and  $AUC_{0-168h}$ ) increased less than threefold upon repeated dosing at 50 mg/kg/week for 26 weeks. The  $C_{\max}$  and  $AUC_{0-168h}$  were 380  $\mu\text{g}/\text{mL}$  and 50,300  $\mu\text{g}\cdot\text{h}/\text{mL}$  on Day 1 and 950  $\mu\text{g}/\text{mL}$  and 122,000  $\mu\text{g}\cdot\text{h}/\text{mL}$  on Day 176, respectively.

#### **5.4.4. Enhanced pre-postnatal toxicity of BI 655066 administered by subcutaneous injection in pregnant Cynomolgus monkeys with 6-month postnatal evaluation (RD170191)**

Blood samples were collected from pregnant monkeys pre-dosing and at 24, 48, 72, 96, and 168 hr post-dosing on GD 20 and GD 132, pre-dosing on GDs 34, 48, 76, 104, and 146, and PPD 14, 28, 91, and 180. Plasma concentrations of risankizumab were below LLOQ (30 ng/mL) in all samples from the control group. The systemic exposure of risankizumab ( $C_{\max}$  and  $AUC_{0-168h}$ ) increased in a dose-proportional manner. A moderate (approximately 2- to 3-fold) accumulation of risankizumab ( $C_{\max}$  and  $AUC_{0-168h}$ ) was observed upon repeated dosing. The  $AUC_{0-168h}$  in pregnant monkeys treated at 5 or 50 mg/kg/week was 4,690 or 49,400  $\mu\text{g}\cdot\text{h}/\text{mL}$  on GD 20-22 and 15,700 or 123,000  $\mu\text{g}\cdot\text{h}/\text{mL}$  on GD 132-134, respectively. Following delivery, most adult female monkeys in the risankizumab-treated groups had measurable serum concentrations of risankizumab up to 91 days postpartum, but (with the exception of one adult female at 50 mg/kg/week) serum concentrations in adult females were below detectable levels at 180 days postpartum.

Plasma levels of risankizumab were also measured in the samples collected from infants on BDs 14, 28, 91, and 180. All infants from mothers in the risankizumab-treated groups had measurable and dose-dependent serum concentrations of risankizumab up to 91 days after birth, while none of the infants had measurable concentrations of risankizumab by 180 days after birth. The serum concentrations of risankizumab in infants and mothers decreased postpartum without risankizumab treatment. The mean infant serum exposure in the 5 mg/kg/week group was 25%, 31%, and 68% of the mean maternal serum exposure on BD 14, BD 28, and BD 91, respectively. The mean infant serum exposure in the 50 mg/kg/week group was 17%,

36%, and 86% of the mean maternal serum exposure on BD 14, BD 28, and BD 91, respectively.

## 5.5. Toxicology

### 5.5.1. General Toxicology

#### 5.5.1.1. BI 655066: A 26-Week subcutaneous toxicity and toxicokinetics study in Cynomolgus monkeys with an 8-week recovery period (RD161444/12R003)

In this 6-month repeat-dose study with a 2-month recovery period, four groups of up to 6 male (4.1 to 6.4 years old) and up to 6 female (2.5 to 3.8 years old) Cynomolgus monkeys were dosed subcutaneously with 0 (vehicle, (b) (4) succinate, (b) (4) sorbitol, (b) (4) Polysorbate 20, pH (b) (4)), 5, 20, or 50 mg/kg risankizumab (BI 655066) once weekly. There were no treatment-related effects on mortalities, clinical signs, neurobehavioral assessments, ophthalmology, body weights, body temperature, ECG, blood pressure, responses to KLH immunization (IgM and IgG antibody responses), clinical pathology including peripheral blood lymphocyte phenotyping, and macroscopic findings. Hematology analysis showed a slight dose-dependent change in reticulocytes that did not reverse. Males developed a decrease in the weight of the prostate (LD -24%, MD -18%, HD -25%, normalized to brain), which did not reverse after the recovery period (HD -37%, normalized to brain). There was also a decrease in the weight of the epididymis (-27%) and testes (-35%) weight at the HD, with reversal after the recovery period. The change in testicular weight was associated with bilateral, multifocal hypospermatogenesis, which developed in a dose dependent manner [one low-dose male (Grade 1), one mid-dose male (Grade 2) and two high-dose males (Grade 2)], based on both incidence and severity. The testicular finding was reversible. The NOAEL of risankizumab was determined to be 5 mg/kg in males (AUC 12,300 µg·h/mL) and 50 mg/kg in females (AUC 77,200 µg·h/mL).

A Pathology Working Group (PWG) composed of veterinary pathologists experienced in the evaluation of the male cynomolgus monkey reproductive system was convened to review the testicular findings from this 26-week toxicology study. The PWG considered the hypospermatogenesis unrelated to treatment with risankizumab, but rather reflected normal testicular development in young Cynomolgus monkeys. Because of the testicular findings in this 26-week toxicity study in monkeys, a follow-up study using sexually mature male monkeys was performed.

#### 5.5.1.2. A 26-week reproductive toxicity study with BI 655066 in male Cynomolgus Monkeys, with an 8-Week Recovery Period (RD161448/14R097)

Two groups of 10 sexually mature male Cynomolgus monkeys (5.3 to 6.9 years of age with 5.3 to 7.6 kg body weight) were treated with vehicle (b) (4) succinic acid, (b) (4) disodium succinate hexahydrate, (b) (4) sorbitol, (b) (4) Polysorbate 20, pH (b) (4)) or 50 mg/kg risankizumab (BI 655066) subcutaneously once

weekly for 26 consecutive weeks (26 doses total). At the end of the dosing phase (Day 184), 7 males/group were euthanized and necropsied; 3 males/group were euthanized and necropsied after an 8-week recovery period (Day 239). Following subcutaneous administration of risankizumab at 50 mg/kg/week for 26 weeks, there were no treatment-related effects on mortality, clinical signs, body weights, food consumption, hematology, clinical chemistry, testicular volume, male reproductive hormones (serum testosterone, LH, and FSH), semen analysis (sperm count, motility, and morphology; ejaculate volume), gross pathology, organ weights, and histopathological findings including progression of the spermatogenic cycle, cell associations, and cell proportions in the various stages of spermatogenesis. The  $C_{max}$  and  $AUC_{0-168h}$  at the end of the dosing period were 950  $\mu\text{g/mL}$  and 122,000  $\mu\text{g}\cdot\text{h/mL}$ , respectively.

### **5.5.1.3. BI 655066: A 4-week intravenous and subcutaneous toxicity and toxicokinetic study in Cynomolgus monkeys with an 8-week recovery period (RD161429/11R060)**

Five groups of up to 5 male and up to 5 female Cynomolgus monkeys received intravenous doses of 0 [vehicle, (b) (4) Succinate (pH (b) (4)), (b) (4), and (b) (4) ], 5, 20, or 50 mg/kg risankizumab (BI 655066) OR subcutaneous doses of 20 mg/kg risankizumab once weekly for 4 weeks. There were no treatment-related effects on mortality, clinical signs, body weights, ophthalmoscopy, ECG, neurological examinations, clinical pathology, gross pathology, organ weights, and histopathological examinations. The  $AUC_{0-168h}$  for the males and females that received 50 mg/kg/week intravenously was 85,100 and 98,900  $\mu\text{g}\cdot\text{h/mL}$ , respectively. The  $AUC_{0-168h}$  for the males and females that received 20 mg/kg/week subcutaneously was 25,800 and 27,500  $\mu\text{g}\cdot\text{h/mL}$ , respectively.

### **5.5.2. Genetic Toxicology**

Genetic toxicology studies were not needed to support the development and approval of risankizumab, per the ICH S6(R1) guidance.

### **5.5.3. Carcinogenicity**

Conventional rodent carcinogenicity studies were not conducted for the evaluation of the carcinogenic potential of risankizumab, as rodents are not a pharmacologically relevant species. A carcinogenicity study with long-term antagonism of IL23p19 in rodents will not be informative because rodents are not a pharmacologically relevant species. Concurrence has been received from the Executive Carcinogenicity Assessment Committee of CDER that a 2-year rodent carcinogenicity study is not needed. The applicant provided a weight-of-evidence analysis of available information to address the carcinogenic potential of risankizumab. In general, immunosuppressive drugs tend to be associated with increased cancer risk. However, no tumors or histopathological evidence of pre-neoplastic changes were

observed in organs or tissues examined following subcutaneous administration of risankizumab to monkeys at dose levels up to 50 mg/kg once weekly for 26 weeks followed by a 8-week post-dosing observation period. The immune function tests in the monkey toxicity studies showed that risankizumab did not cause immunosuppression [(as assessed by T-dependent antibody response (TDAR)] or deplete T-cells. Animal data from available literature suggests that a risk for malignancy may be reduced in the case of IL-23 inhibition but also reduced in the case of exogenous administration of IL-23. Overall the risk for malignancy associated with long-term inhibition of IL-23 following administration of risankizumab to humans is considered to be low. Therefore, no additional nonclinical studies are recommended to evaluate the carcinogenic potential of risankizumab. Adequate labeling based on animal data from the sponsor and from literature as well as post-marketing patient monitoring of malignancy will be sufficient at this time.

#### 5.5.4. Reproductive and Developmental Toxicology

##### 5.5.4.1. Enhanced pre-postnatal toxicity of BI 655066 administered by subcutaneous injection in pregnant Cynomolgus monkeys with 6-month postnatal evaluation (RD170191)

Three groups of 21 or 22 pregnant female Cynomolgus monkeys subcutaneously received 0 (vehicle, (b) (4) succinate, (b) (4) sorbitol, (b) (4) Polysorbate 20, pH (b) (4) 5, or 50 mg/kg risankizumab (BI 655066) once weekly from Gestation Day 20-22 (GD 20-22) until parturition for up to 22 doses and post-natal development was evaluated in infants for 6 months after birth. The infants were euthanized on Birth Day (BD) 180±2. There were no treatment-related effects on maternal mortality, clinical signs, body weights, food consumption, and gestation length. There were no treatment-related effects on fetal clinical signs, body weights, hematology, clinical chemistry, growth and development (including external, visceral, skeletal, and neurobehavioral evaluations), developmental immunotoxicology (T-cell dependent antibody response and lymphocyte immunophenotyping), necropsy, organ weights, and histopathologic findings. However, as compared to the vehicle control group, a dose-dependent increase in fetal/infant losses were noted in the risankizumab-treated groups (see the following table). The fetal/infant loss (percentage) in the control group in this study was below the Testing Facility historical range (20.0%-42.9%). The fetal/infant loss in the 5 mg/kg/week group (31.8%) was comparable to the historical average (28.8%) of the Testing Facility. Although the combined fetal/infant loss (percentage) in the 50 mg/kg/week group (42.9%) was at the high end of the performing laboratory's background incidence rate for monkeys, it was over two times the increase compared to the control group (19.0%). Therefore, the increased fetal/infant loss in the 50 mg/kg/week group was considered to be related to risankizumab treatment. The AUC<sub>0-168h</sub> in pregnant monkeys treated at 5 or 50 mg/kg/week was 15,700 or 123,000 µg·h/mL on GD 132-134, respectively. All infants from mothers in the risankizumab-treated groups had measurable and dose-dependent serum concentrations of risankizumab up to 91 days after birth, while none

of the infants had measurable concentrations of risankizumab by 180 days after birth (see Section 5.4.4. above)

Pregnancy and Postpartum Outcomes

| Group No.<br>(dose level)                                                                      | No. of<br>Pregnant<br>Females | Mean<br>Gestation<br>Length <sup>a</sup><br>(Days) | Total Fetal<br>Losses as %<br>(Losses per<br>Trimester) <sup>b</sup> | No. of<br>Infants<br>Born<br>(M/F) | No. of<br>Infant<br>Losses as<br>% <sup>d</sup> | Combined<br>(fetal and<br>infant) Losses<br>as % <sup>e</sup> |
|------------------------------------------------------------------------------------------------|-------------------------------|----------------------------------------------------|----------------------------------------------------------------------|------------------------------------|-------------------------------------------------|---------------------------------------------------------------|
| 1<br>(0 mg/kg/week)                                                                            | 21                            | 160 ± 8                                            | 14.3 (3/21)<br>(3/0/0)                                               | 5/13                               | 5.6<br>(1/18)                                   | 19.0<br>(4/21)                                                |
| 2<br>(5 mg/kg/week)                                                                            | 22                            | 164 ± 6                                            | 22.7 (5/22)<br>(3/0/2)                                               | 11/6                               | 11.8<br>(2/17)                                  | 31.8<br>(7/22)                                                |
| 3<br>(50 mg/kg/week)                                                                           | 21                            | 155 ± 10                                           | 28.6 (6/21) <sup>c</sup><br>(3/0/3)                                  | 9/6                                | 20.0<br>(3/15)                                  | 42.9<br>(9/21)                                                |
| <b>Historical Control Data<br/>(n=19 ePPND studies,<br/>2008-2016)<br/>(%, mean and range)</b> |                               | 159 ± 7                                            | 22.0 (68/309)<br>6.7-38.9%                                           | --                                 | 10.2<br>(27/264)<br>0.0-20.0%                   | 28.8 (89/309)<br>20.0-42.9%                                   |

M = male; F = female

<sup>a</sup> Values calculated excluding abortions (GD100-139) and stillbirths (≥ GD140).

<sup>b</sup> First, 2nd, and 3rd trimesters are GD20-50, GD51-100, and > GD100, respectively, and the fetal losses per trimester are shown in parentheses.

<sup>c</sup> Abortion of twins for Adult Female No. 3505 was counted as a single pregnancy abortion.

<sup>d</sup> All infant losses were related to maternal neglect, except for one at 50 mg/kg/week. The infant loss rates were similar to historical control values (mean 4.9%, range 0.0-20.0%) when instances of maternal neglect were excluded.

<sup>e</sup> If infant losses related to maternal-induced trauma and/or neglect are excluded (1, 2, and 2 infants in Groups 1, 2, and 3, respectively; see Section 8.5), the combined fetal/infant loss rates were 15.0% (3/20), 25.0% (5/20), and 36.8% (7/19) in the control, 5 mg/kg/week and 50 mg/kg/week groups, respectively. The historical control average is 24.9% (range 6.7 - 40.0%).

### 5.5.5. Other Toxicology Studies

**5.5.5.1. BI 655066: A tissue irritancy study following a single intramuscular and subcutaneous injection in the rabbit (RD161512/12R050)**

**5.5.5.2. A tissue cross-reactivity study of BI 655066 in normal human tissues (RD161427/11R044)**

**5.5.5.3. Determination of hemocompatibility in human whole blood (RD161513/11R142)**

A local tolerance study was conducted in rabbits. Two groups of 4 male rabbits received single intramuscular and subcutaneous injections of 1 mL of vehicle (b) (4) (b) (4) disodium succinate hexahydrate, (b) (4) succinic acid, (b) (4) sorbitol, (b) (4) polysorbate 20, pH (b) (4) or 90 mg/mL risankizumab (BI 655066) in the vehicle. There were no treatment-related effects on clinical signs, body weights, local irritation (erythema, edema), gross necropsy, and histopathologic findings on injection sites.

The cross-reactivity of risankizumab (BI 655066) was evaluated with cryosections of a panel of normal human tissues. Risankizumab staining was observed

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only on extracellular granular material in the placenta, which was expected as there is IL-23 expression in several placental tissue elements and IL-23 p19 is a secreted protein. Additionally, no effects of risankizumab on hemocompatibility were noted with human blood in vitro.

## 6 Clinical Pharmacology

### 6.1. Executive Summary

Risankizumab (also known as ABBV-066 and BI655066) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that selectively binds to the p19 subunit of human interleukin (IL)-23.

- **Proposed indication:** For the treatment of moderate to severe plaque psoriasis in adults.
- **Proposed dosing regimen:** 150 mg (two 75 mg injections) administered by subcutaneous (SC) injection at Weeks 0, 4, and every 12 weeks (Q12W) thereafter.
- **Proposed dosage form and presentation:** A single-dose pre-filled syringe (PFS) with 75 mg of risankizumab in 0.83 mL of solution (90 mg/mL).

The Applicant evaluated the 150 mg risankizumab dosing regimen in four Phase 3 trials. Risankizumab was administered by SC injection at Weeks 0, 4, and Q12W thereafter. The Applicant conducted a Phase 2 dose-ranging trial to support the dose selection for Phase 3 trials. The Applicant also submitted the results of 3 Phase 1 trials in healthy subjects and subjects with psoriasis to support clinical pharmacology information of risankizumab.

The key review findings with specific recommendations and comments are summarized in **Table 3**.

**Table 3 Summary of Clinical Pharmacology Review**

| Review Issues                                                 | Recommendations and Comments                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pivotal or supportive evidence of effectiveness               | <ul style="list-style-type: none"><li>• The efficacy of risankizumab for the treatment of moderate to severe psoriasis is established in four Phase 3 trials (M16-008 [1311.3], M15-992 [1311.4], M15-995 [1311.28], and M16-010 [1311.30]).</li><li>• Dose-response and exposure-response (E-R) analysis for efficacy based on data from the Phase 2 dose-ranging trial (1311.2) and the four Phase 3 trials provide supportive evidence for effectiveness.</li></ul> |
| General dosing instructions                                   | <ul style="list-style-type: none"><li>• The efficacy data from Phase 3 trials overall support that the proposed dosing regimen (150 mg risankizumab administered by SC injection at Weeks 0, 4, and Q12W thereafter) is acceptable.</li></ul>                                                                                                                                                                                                                          |
| Dosing in patient subgroups (intrinsic and extrinsic factors) | <ul style="list-style-type: none"><li>• No dose individualization is recommended based on intrinsic or extrinsic factors</li></ul>                                                                                                                                                                                                                                                                                                                                     |

|                                                                   |                                                                                                                                                                                                                                                                                                                                                                             |
|-------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Drug interactions                                                 | <ul style="list-style-type: none"> <li>Risankizumab has no clinically meaningful effect on the PK of drugs metabolized by cytochrome P450 (CYP)1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A.</li> </ul>                                                                                                                                                                           |
| Immunogenicity                                                    | <ul style="list-style-type: none"> <li>Subjects who developed anti-drug antibodies (ADA) with titer values <math>\geq 128</math> were associated with reduced risankizumab concentrations and reduced efficacy.</li> <li>Subjects who developed ADA appeared to be more likely to experience injection-site reaction compared to subjects who were ADA negative.</li> </ul> |
| Bridge between the to-be-marketed and clinical trial formulations | <ul style="list-style-type: none"> <li>The to-be-marketed formulation was used in Phase 3 trials; therefore, there is no need to bridge the to-be-marketed formulation to the clinical trial formulation</li> </ul>                                                                                                                                                         |

### 6.1.1. Recommendation

From a Clinical Pharmacology standpoint, this BLA is acceptable to support the approval of SKYRIZI (risankizumab) for the treatment of moderate to severe plaque psoriasis in adults, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling.

### 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

#### 6.2.1.1 Mechanism of action and pharmacodynamics

Risankizumab is a humanized IgG1 mAb that selectively binds to the p19 subunit of human IL-23. Risankizumab inhibits IL-23 dependent cell signaling and release of pro-inflammatory cytokines. The pharmacodynamic (PD) effect of risankizumab in humans has not been characterized.

#### 6.2.1.2 Pharmacokinetics of risankizumab

Risankizumab exhibited linear PK with dose-proportional increase in exposure following a SC injection of doses ranging from 18 mg to 300 mg. The peak plasma concentration ( $C_{max}$ ) was reached by 3-14 days. The absolute bioavailability of risankizumab was estimated to be 89% following SC injection.

Based on population PK analysis, risankizumab CL, volume of distribution at steady state and  $t_{1/2}$  were estimated to be 0.31 L/day, 11.2 L, and 28 days, respectively, for a typical 90 kg subject. The inter-individual variability (%CV) for risankizumab clearance and volume of distribution were 24% and 34%, respectively. At the recommended dosing regimen, 150 mg SC at Weeks 0, 4, and Q12W thereafter, steady-state plasma concentrations were achieved by Week 16. The estimated steady-state  $C_{max}$  and trough concentrations ( $C_{trough}$ ) were approximately 12 mcg/mL and 2 mcg/mL, respectively.

### **6.2.1.3 Drug interactions**

The pharmacokinetic (PK) results of the clinical drug interaction study (M16-007[1311.36]) suggest that risankizumab has no clinically meaningful effect on the PK of drugs metabolized by cytochrome P450 (CYP)1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A. See section 6.3.2.4.

### **6.2.1.4 Immunogenicity**

Among 1288 evaluable subjects in the Phase 3 studies, approximately 19% of subjects treated with risankizumab developed ADA by Week 16. Of the subjects who developed ADA, approximately 42% (8% of all subjects) had neutralizing antibodies (NAb). The ADA and NAb incidences were 24% and 14% (57% of the subjects who developed ADA), respectively, among 1079 evaluable subjects by Week 52. Higher ADA titer appears to have an impact on the PK of risankizumab. A total of 16 subjects (1.5% of ADA evaluable subjects) had ADA titer values  $\geq 128$  and these subjects were associated with reduced risankizumab concentrations and reduced efficacy.

## **6.2.2. General Dosing and Therapeutic Individualization**

### **6.2.2.1 General Dosing**

The dose-response results in the Phase 2 study, the efficacy results in Phase 3 studies, and the integrated exposure-response (E-R) analyses results overall support the acceptability of the proposed dosing regimen, 150 mg at Weeks 0, 4, and Q12W thereafter.

### **6.2.2.2 Therapeutic Individualization**

Therapeutic individualization based on intrinsic or extrinsic factors is not necessary. Population PK analysis identified body weight (BW) as a significant covariate on risankizumab PK. Risankizumab concentrations were lower in subjects with higher BW. However, dose adjustment based on BW is not necessary based on the available efficacy data from the Phase 3 trials. See Section 6.3.2.3.

## **6.2.3 Outstanding Issues**

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

### 6.3. Comprehensive Clinical Pharmacology Review

#### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

General clinical pharmacology, pharmacokinetics and immunogenicity of risankizumab are summarized in **Table 4**.

**Table 4 Summary of Clinical Pharmacology and Immunogenicity of Risankizumab**

| <b>Pharmacology</b>           |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mechanism of Action           | Risankizumab is a humanized IgG1 mAb that selectively binds to the p19 subunit of human IL-23 and inhibits its interaction with IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved inflammatory and immune responses. Risankizumab inhibits IL-23 dependent cell signaling and the release of proinflammatory cytokines.                                                                                                  |
| Pharmacodynamics              | The pharmacodynamic (PD) effect of risankizumab in subjects with psoriasis has not been characterized.                                                                                                                                                                                                                                                                                                                                          |
| <b>General Information</b>    |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Bioanalysis                   | Risankizumab concentrations in human plasma were quantified using a validated enzyme-linked immunosorbent (ELISA) assay with the sensitivity of 5 ng/mL.                                                                                                                                                                                                                                                                                        |
| PK model                      | A two-compartment model with a first-order absorption for SC administration and first-order elimination adequately described the PK of risankizumab                                                                                                                                                                                                                                                                                             |
| Healthy vs. Patients          | Risankizumab PK parameters were similar in healthy subjects and subjects with moderate to severe psoriasis.                                                                                                                                                                                                                                                                                                                                     |
| Drug Exposure at Steady State | Steady-state plasma concentrations of risankizumab were achieved approximately by Week 16 following SC administration of 150 mg risankizumab at Weeks 0, 4, and Q12W thereafter. Geometric mean trough concentrations ( $C_{trough}$ ) in phase 3 trials at Weeks 16, 28, 40, and 52 were 1.84 mcg/mL, 1.60 mcg/mL, 1.57 mcg/mL, and 1.52 mcg/mL, respectively. The inter-individual variability (%CV) for $C_{trough}$ ranged from 60% to 75%. |
| Dose Proportionality          | Risankizumab showed dose proportional PK at the dose ranges of 18 – 300 mg and 200 - 1200 mg following single SC and IV administration, respectively.                                                                                                                                                                                                                                                                                           |
| Body weight                   | Risankizumab concentrations were lower in subjects with higher body weight. Population PK analysis also identified body weight as a significant covariate affecting risankizumab concentrations.                                                                                                                                                                                                                                                |

| <b>ADME</b>           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Absorption            | Following a single SC dose of 1 mg/kg to subjects with psoriasis, risankizumab reached geometric mean (%CV) $C_{max}$ of 5.7 mcg/mL (19%) by approximately 5 days. Following SC administration of 150 mg risankizumab at Weeks 0, 4, and Q12W thereafter, the $C_{max}$ was estimated to be achieved after the second risankizumab dose (Week 4) with mean $\pm$ SD of $15.4 \pm 4.0$ mcg/mL. The steady-state risankizumab $C_{max}$ was estimated to be $11.9 \pm 3.1$ mcg/mL. The absolute SC bioavailability of risankizumab was estimated to be 89%. |
| Distribution          | The geometric mean (%CV) volume of distribution at steady state was 11.2 L (34%) in subjects with psoriasis.                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Elimination           | The geometric mean (%CV) systemic clearance was 0.31 L/day (24%) and half-life was approximately 28 days in subjects with psoriasis.                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <i>Metabolism</i>     | The metabolic pathway of risankizumab has not been characterized. As a humanized IgG1 mAb, risankizumab is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG.                                                                                                                                                                                                                                                                                                                      |
| <i>Excretion</i>      | The renal excretion of risankizumab has not been investigated. As a humanized IgG1 mAb with a molecular weight of approximately 148 kDa, intact risankizumab is unlikely to be filtered by kidney or excreted in urine.                                                                                                                                                                                                                                                                                                                                   |
| <b>Immunogenicity</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Bioanalysis           | <ul style="list-style-type: none"> <li>• Anti-drug antibodies (ADA) were determined using a validated electrochemiluminescent (ECL) assay with an acid dissociation step.</li> <li>• Neutralizing antibodies (NAb) were determined using a validated cell-based assay.</li> </ul>                                                                                                                                                                                                                                                                         |
| Incidence             | Among 1288 evaluable subjects in the Phase 3 studies, approximately 19% of subjects treated with risankizumab developed ADA by Week 16. Of the subjects who developed ADA, approximately 42% (8% of all subjects) had neutralizing antibodies (NAb). The ADA and NAb incidences were 24% and 14% (57% of the subjects who developed ADA), respectively, among 1079 evaluable subjects by Week 52.                                                                                                                                                         |

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Clinical Impact | <ul style="list-style-type: none"><li>• PK: Antibodies to risankizumab did not appear to affect risankizumab concentrations when ADA titer values were &lt;128. The mean risankizumab concentrations in subjects who had ADA titer values <math>\geq</math>128 were approximately 30% lower compared with the concentrations in ADA negative subjects.</li><li>• Efficacy: The development of ADA with antibody titer values <math>\geq</math>128 was associated with reduced efficacy.</li><li>• Safety: Subjects who developed antibodies to risankizumab were more likely to experience injection-site reactions compared to subjects who were ADA negative.</li></ul> |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

ADME=Absorption, Distribution, Metabolism and Excretion.

### 6.3.2. Clinical Pharmacology Questions

#### 6.3.2.1 *Does the clinical pharmacology information provide supportive evidence of effectiveness?*

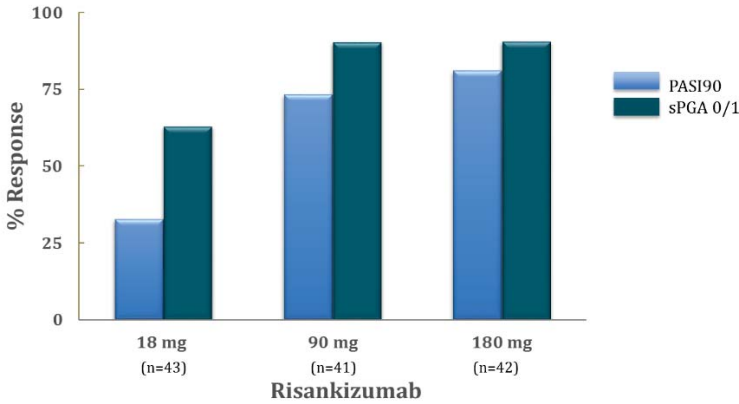
Yes. The overall data from Phase 2 and Phase 3 trials provide evidence that risankizumab is effective for the treatment of adult patients with moderate to severe psoriasis. The dose- and exposure-response relationships for efficacy provide supportive evidence of effectiveness. See Section 7 of this multi-discipline review for details of the study design and efficacy/safety results of the Phase 3 trials.

#### Dose-response relationship for efficacy in Phase 2 trial

The Phase 2 efficacy results demonstrated a clear dose-response relationship for PASI 90 and sPGA 0/1 (**Figure 1**). The PASI 90 response rates were 32.6%, 73.2% and 81.0% at the 18 mg, 90 mg, and 180 mg risankizumab dose groups, respectively. The sPGA 0/1 response rates were 62.8%, 90.2% and 90.5% at the 18 mg, 90 mg, and 180 mg risankizumab dose groups, respectively. Note that PASI 90 was the primary efficacy endpoint for the evaluation of dose-response relationship for efficacy in the Phase 2 trial.

#### **Figure 1 Dose-response for PASI 90 and sPGA 0/1 at Week 12 in Phase 2 Study (1311.2)**

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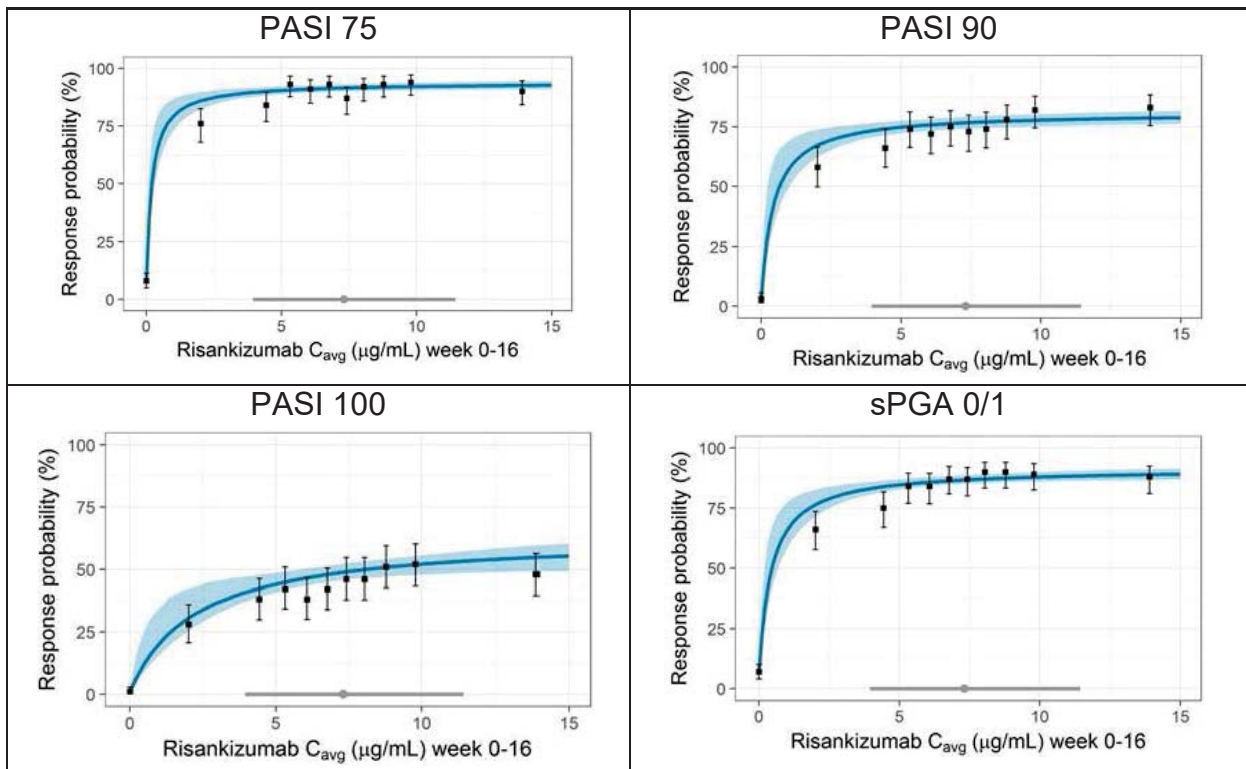


Subjects in the 18 mg dose group received single SC dose of risankizumab at Week 0. Subjects in the 90 mg and 180 mg dose groups received multiple doses of SC risankizumab at Weeks 0, 4, 16. Source of data: CSR 1311.2.

Exposure-response relationship for efficacy in pooled Phase 2/3 trials

The Applicant used an  $E_{max}$  non-linear regression model with average plasma concentrations of risankizumab ( $C_{avg}$ ) from Week 0 to Week 16 to describe exposure-response relationships for PASI75, PASI90, PASI100 and sPGA0/1 at Week 16 based on data from pooled Phase 2 and Phase 3 trials. The results demonstrated exposure-response relationships for the four efficacy variables.

**Figure 2 Exposure-Response for PASI 75, PASI 90, PASI 100 and sPGA0/1 at Weeks 16 in Phase 2 and Phase 3 Trials**



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Black solid symbols with error bars: observed PASI 75, PASI 90, PASI 100 or sPGA0/1 response rates and corresponding 95% exact binomial confidence intervals within each  $C_{avg}$  decile. Blue solid line and shaded area: Model-predicted probability of response and 95% confidence interval. Grey solid symbol and line: Median  $C_{avg}$  and 5<sup>th</sup> and 95<sup>th</sup> percentiles with 150 mg SC dose at Weeks 0, 4, and Q12W thereafter. Number of subjects: N=1732 (Source of data: Exposure Response Report R&D/17/0883, Figure 8)

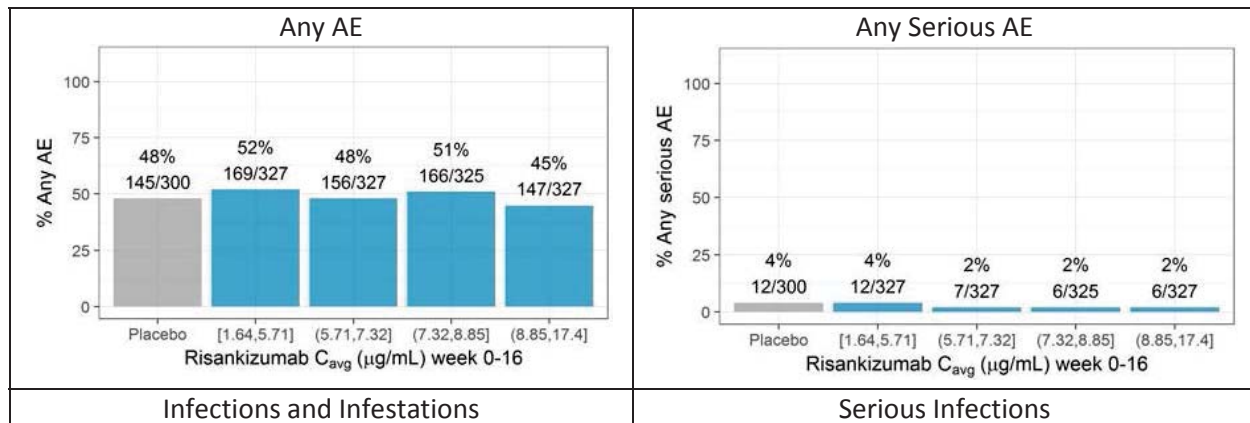
**6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

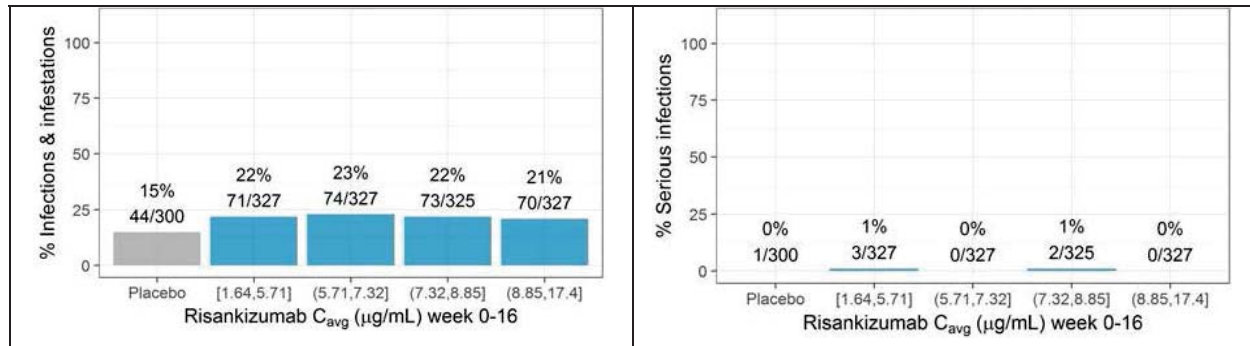
Yes. The efficacy and safety data from Phase 3 trials overall support evidence that the proposed risankizumab 150 mg dosing regimen, administered by SC injection at Weeks 0, 4, and Q12W thereafter, is appropriate for the general patient population.

The risankizumab 150 mg dosing regimen demonstrated consistent clinical response rates ranging from 72% to 75% for PASI 90 and from 84% to 88% for sPGA 0/1 at Week 16 across the four Phase 3 trials. See section 7 of this multidisciplinary review for details of the efficacy data. Exposure-response analysis indicates that the proposed 150 mg dosage regimen has achieved the plateau of efficacy and that higher doses would not result in a meaningful increase in clinical response rate (See section 6.3.2.1).

No apparent exposure-response relationship for safety was observed by Week 16 in Phase 3 trials of risankizumab in subjects with moderate to severe psoriasis. The incidences of any adverse event (AE), any serious adverse event (SAE), infections and infestation, and any serious infection were similar across the risankizumab  $C_{avg}$  quartiles from Week 0 to Week 16. (**Figure 3**).

**Figure 3 Exposure-Response for Safety by Risankizumab  $C_{avg}$  Quartiles Over Week 0-16**





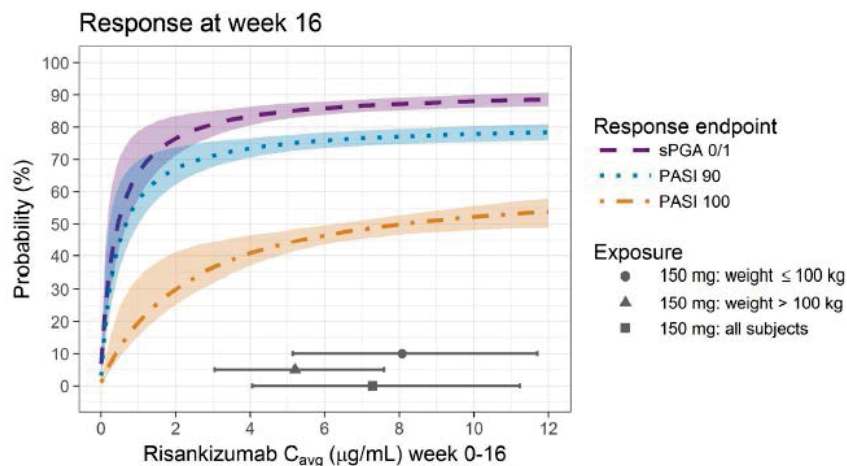
(Source of data: Exposure Response Report R&D/17/0883, Figure 11)

### 6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic factors?

No, an alternative dosing regimen or management strategy is not necessary for subpopulations based on intrinsic factors. Population PK analysis identified body weight (BW) as a significant covariate on risankizumab PK; however, a dose adjustment based on BW is not necessary based on the available efficacy data from the Phase 3 trials and exposure-response analyses.

According to the review team’s E-R analysis results, model-predicted response rates for PASI 75, PASI 90 and PASI 100 at Week 16 are 3 - 7% lower in subjects with body weight >100 kg than in subjects with body weight ≤100 kg at the proposed dosing regimen (**Table 5**). The Applicant’s model-based E-R simulations indicate that the proposed risankizumab dosing regimen has achieved a plateau of efficacy with regard to PASI 90 and sPGA 0/1, regardless of body weight ≤100 kg or >100 kg (**Figure 4**).

**Figure 4 Exposure-Response for Efficacy by Subject Body Weight**



Dashed lines and shaded area: model predicted probability of response, median (dashed lines) and 95% confidence interval (shaded area). Grey solid symbols and lines: median C<sub>avg</sub> and 5<sup>th</sup> and 95<sup>th</sup> percentiles

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with 150 mg SC dose at Weeks 0, 4, and Q12W thereafter across all subjects (solid square), subjects ≤100 kg (solid circle) and subjects >100 kg (solid triangle). (*Source of data: R&D/17/0883, Figure 10*)

**Table 5 Model Predicted Response Rates in Different Body Weight Subgroups**

| BW      | Number of Subjects | C <sub>avg 16-wk</sub> (mcg/mL) | Mean (90% CI) Response Rate |                   |                   |
|---------|--------------------|---------------------------------|-----------------------------|-------------------|-------------------|
|         |                    |                                 | PASI75                      | PASI 90           | PASI 100          |
| ≤100 kg | 931                | 8.071                           | 0.91 (0.89, 0.92)           | 0.76 (0.74, 0.79) | 0.46 (0.43, 0.48) |
| >100 kg | 375                | 5.189                           | 0.88 (0.85, 0.9)            | 0.69 (0.66, 0.72) | 0.40 (0.36, 0.43) |

C<sub>avg 16-wk</sub> = average plasma concentration at Week 16, CI=confidence interval  
(*Source of data: Reviewer's independent analysis*)

**6.3.2.4 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?**

No, risankizumab has no clinically meaningful effect on the PK of drugs metabolized by cytochrome P450 (CYP)1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A.

The Applicant conducted a clinical drug interaction study (M16-007 [1311.36]) to evaluate the potential effect of risankizumab, 150 mg administered SC Q4W x 4, on the activities of CYP1A2 (caffeine), CYP2C9 (warfarin), CYP2C19 (omeprazole), CYP2D6 (metoprolol) and CYP3A (midazolam) using a cocktail approach in subjects with moderate to severe psoriasis. A single oral dose of this cocktail containing these five CYP probe substrates was administered on Day 1 (before risankizumab treatment) and Day 98 (after risankizumab treatment). The PK results showed that the 90% confidence intervals (CI) for the ratios of the probe substrates C<sub>max</sub> and AUC<sub>inf</sub> before and after risankizumab treatment were within the no-effect boundaries of 0.8 to 1.25, except for the lower 90% confidence bound of omeprazole C<sub>max</sub> ratio of 0.73. See Section 13.5.2.3 of this multi-discipline review for detailed information.

## 7 Statistical and Clinical Evaluation

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### 7.1. Sources of Clinical Data and Review Strategy

#### 7.1.1. Table of Clinical Studies

The risankizumab clinical development program included eight clinical trials in support of the proposed indication:

- Three Phase 1 trials in healthy subjects and subjects with psoriasis
  - Study 1311.1: a single IV and SC dose PK trial in subjects with psoriasis
  - Study M16-513 (1311.16): a single IV and SC dose PK trial to evaluate intrinsic factors in healthy Caucasian, Japanese, and Chinese subjects
  - Study M16-007 (1311.36): a drug interaction trial to assess the effect of risankizumab on the PK of CYP probe substrates in subjects with psoriasis
- One Phase 2 dose-ranging trial in subjects with psoriasis
  - Study 1311.2
- Four Phase 3 pivotal trials in subjects with psoriasis
  - Study M16-008 (1311.3)
  - Study M15-995 (1311.28)
  - Study M16-010 (1311.30)
  - Study M15-992 (1311.4); interim results provided as study ongoing
- Two ongoing, long term safety, open-label trials in subjects with psoriasis
  - Study M15-997
  - Study M16-009 (1311.13)

**Table 6: . Listing of Clinical Trials Relevant to this BLA**

| Trial Identity                                           | Trial Design                                                                                | Regimen/ schedule/ route                                                                                                                                                                                              | Study Endpoints                                                                                                                                                                            | Treatment Duration                           | No. of subjects enrolled         | Study Population                                                                                                                                                                                                         | No. of Centers and Countries                                                                                                     |
|----------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| <b>Controlled Studies to Support Efficacy and Safety</b> |                                                                                             |                                                                                                                                                                                                                       |                                                                                                                                                                                            |                                              |                                  |                                                                                                                                                                                                                          |                                                                                                                                  |
| M15-995<br>(1311.28)                                     | Phase 3, randomized, PBO and active comparator controlled, DB, double dummy, parallel study | <u>RZB</u> : 150 mg SC at Wks 0, 4, and q12w<br><br><u>UST</u> : 45 mg SC ( $\leq$ 100 kg BW) or 90 mg SC ( $>$ 100 kg BW) at Wks 0, 4, and q12w<br><br><u>PBO</u> : SC Wk 0, 4, then switch to RZB at Wk 16 and q12w | <u>Co-primary efficacy</u><br>proportion of subjects who achieved PASI 90 response at Week 16 and the proportion of subjects with a PGA score of 0 (“cleared”) or 1 (“minimal”) at Week 16 | 40 weeks; followed through at least 52 weeks | RZB: 294<br>UST: 99<br>PBO: 98   | Adults $\geq$ 18 years; Moderate to severe chronic plaque PsO $\geq$ 6 months; With or without PsA; BSA involvement $\geq$ 10%; PASI $\geq$ 12; sPGA $\geq$ 3; Candidate for systemic or phototherapy; Candidate for UST | 64 sites across 10 countries: Austria, Belgium, Canada, France, Germany, Mexico, Poland, Portugal, Spain, and the United States  |
| M16-008<br>(1311.3)                                      | Phase 3, randomized, PBO and active comparator controlled, DB, double dummy, parallel study | <u>RZB</u> : 150 mg SC at Wks 0, 4, and q12w<br><br><u>UST</u> : 45 mg SC ( $\leq$ 100 kg BW) or 90 mg SC ( $>$ 100 kg BW) at Wks 0, 4, and q12w<br><br><u>PBO</u> : SC Wk 0, 4, then switch to RZB at Wk 16 and q12w | <u>Co-primary efficacy</u><br>proportion of subjects who achieved PASI 90 response at Week 16 and the proportion of subjects with a PGA score of 0 (“cleared”) or 1 (“minimal”) at Week 16 | 40 weeks; followed through at least 52 weeks | RZB: 304<br>UST: 100<br>PBO: 102 | Adults $\geq$ 18 years; Moderate to severe chronic plaque PsO $\geq$ 6 months; With or without PsA; BSA involvement $\geq$ 10%; PASI $\geq$ 12;                                                                          | 79 sites across 8 countries: Australia, Canada, Czech Republic, France, Germany, Japan, Republic of Korea, and the United States |

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| Trial Identity       | Trial Design                                                              | Regimen/ schedule/ route                                                                                                                                                                                                                                                       | Study Endpoints                                                                                                                                                                          | Treatment Duration                       | No. of subjects enrolled | Study Population                                                                                                                                                                                                          | No. of Centers and Countries                                                                                                                   |
|----------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
|                      |                                                                           |                                                                                                                                                                                                                                                                                |                                                                                                                                                                                          |                                          |                          | sPGA ≥ 3;<br>Candidate for systemic or phototherapy;<br>Candidate for UST                                                                                                                                                 |                                                                                                                                                |
| M16-010<br>(1311.30) | Phase 3, randomized, parallel, active controlled, DB, double dummy, study | <u>RZB</u> : 150 mg SC at Wks 0, 4, and q12w<br><br><u>Adalimumab</u> : SC, 80 mg at Wk 0; 40 mg every other week from Wk 1 to Wk 15;<br><br>At Wk 16, subjects continued on adalimumab, switched to RZB, or were re-randomized to RZB or adalimumab, depending on PASI score. | <u>Co-primary efficacy</u><br>proportion of subjects who achieved PASI 90 response at Week 16 and the proportion of subjects with a PGA score of 0 (“cleared”) or 1 (“minimal at Week 16 | 44 weeks and a 4-week follow-up period   | RZB: 301<br>ADA: 304     | Adults ≥ 18 years;<br>Moderate to severe chronic plaque PsO ≥ 6 months;<br>With or without PsA; BSA involvement ≥ 10%;<br>PASI ≥ 12;<br>sPGA ≥ 3;<br>Candidate for systemic or photo therapy;<br>Candidate for adalimumab | 66 sites in 11 countries:<br>Canada, Czech Republic, Finland, France, Germany, Mexico, Poland, Portugal, Sweden, Taiwan, and the United States |
| M15-992<br>(1311.4)  | Phase 3, randomized, DB, PBO-controlled study                             | <u>RZB</u> : 150 mg SC at Wk 0, 4, and 16. At Wk 28, subjects with sPGA 0 or 1 re-randomized to RZB or PBO; Beginning at Wk 32, subjects with sPGA ≥ 3 received OL RZB                                                                                                         | <u>Co-primary efficacy</u><br>proportion of subjects who achieved PASI 90 response at Week 16 and the proportion of subjects with a PGA score of 0                                       | 88 weeks and a 16-week follow-up period. | RZB: 407<br>PBO:100      | ≥ 18 years;<br>Moderate to severe chronic plaque PsO ≥ 6 months;<br>With or without PsA; BSA involvement                                                                                                                  | Study is <u>ongoing</u> at 60 sites in 9 countries:<br>Australia, Belgium, Canada, Czech Republic, France,                                     |

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| Trial Identity | Trial Design                                                                       | Regimen/ schedule/ route                                                                                                                                                 | Study Endpoints                                                                                                                                                                                                                                                                                                                                                                                      | Treatment Duration                   | No. of subjects enrolled                                                   | Study Population                                                                             | No. of Centers and Countries                                                          |
|----------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
|                |                                                                                    | <p><u>PBO</u>: SC at Wk 0, 4; switch to blinded RZB at Wk 16; At Wk 28, subjects with sPGA 0 or 1 received blinded RZB q12w; subjects with sPGA ≥ 2 received OL q12w</p> | <p>(“cleared”) or 1 (“minimal at Week 16. In addition, the maintenance of response following drug withdrawal compared with continued risankizumab treatment in subjects who responded to treatment at Week 28 was assessed after Week 28 through Week 104. Response after re-treatment was evaluated in subjects who experienced relapse after withdrawal and were re-treated with risankizumab.</p> |                                      |                                                                            | <p>≥ 10%; PASI ≥ 12; sPGA ≥ 3; Candidate for systemic or phototherapy</p>                    | <p>Germany, Japan, Korea, and the United States</p>                                   |
| 1311.2         | Phase 2, randomized, parallel, active comparator controlled, DB within dose groups | <p><u>RZB</u>: SC<br/> <b>Group 1</b>: 18 mg at Wk 0<br/> <b>Group 2</b>: 90 mg at Wks 0, 4, and 16<br/> <b>Group 3</b>: 180 mg at Wks 0, 4, and 16</p>                  | The proportion of subjects who achieved PASI 90 response at Week 12                                                                                                                                                                                                                                                                                                                                  | 24 weeks, with 24 weeks of follow up | <p>RZB: 126<br/> 18 mg: 43<br/> 90 mg: 41<br/> 180 mg: 42<br/> UST: 40</p> | <p>Adults 18 to 75 years; Moderate to severe plaque PsO ≥ 6 months; With or without PsA;</p> | <p>32 sites in 7 countries: Canada, Finland, France, Germany, Norway, Sweden, and</p> |

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| <b>Trial Identity</b>            | <b>Trial Design</b>                                                                                                                                                | <b>Regimen/ schedule/ route</b>                                                                  | <b>Study Endpoints</b>        | <b>Treatment Duration</b> | <b>No. of subjects enrolled</b> | <b>Study Population</b>                                                                                                                       | <b>No. of Centers and Countries</b> |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------|---------------------------|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
|                                  | of RZB, single blind between groups, dose ranging study                                                                                                            | <u>UST</u> : SC 45 mg (body weight ≤ 100 kg) or 90 mg (body weight > 100 kg) at Wks 0, 4, and 16 |                               |                           |                                 | BMI ≥ 18.5 and < 40 kg/m <sup>2</sup> ; BSA involvement ≥ 10%; PASI ≥ 12; sPGA ≥ 3; Candidate for systemic or phototherapy; Candidate for UST | the United States                   |
| <b>Studies to Support Safety</b> |                                                                                                                                                                    |                                                                                                  |                               |                           |                                 |                                                                                                                                               |                                     |
| M15-997                          | Phase 3, single-arm OLE for subjects who completed Studies M16-008 (1311.3), M15-992 (1311.4), M15-995 (1311.28), M16-010 (1311.30), M16-004 (1311.38), or M16-178 | RZB 150 mg SC q12w                                                                               | Long-term safety and efficacy | 156 weeks                 | 1392 at data cut-off            | Subjects with moderate to severe chronic plaque PsO who completed lead-in studies                                                             | Ongoing                             |
| M16-009 (1311.13)                | Phase 2, OLE for subjects from Study 1311.2                                                                                                                        | RZB 90 mg SC starting dose for 12 weeks; followed by 90 or 180 mg q12w                           | Long-term safety and efficacy | 4 years                   | 110 at data cut-off             | Adults with moderate to severe chronic plaque PsO who                                                                                         | Ongoing                             |

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| Trial Identity | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration | No. of subjects enrolled | Study Population                                                           | No. of Centers and Countries |
|----------------|--------------|--------------------------|-----------------|--------------------|--------------------------|----------------------------------------------------------------------------|------------------------------|
|                |              |                          |                 |                    |                          | completed Study 1311.2 or had decrease in response to < PASI 50 from Wk 24 |                              |

sPGA 0 or 1 = clear or almost clear; ADA = adalimumab; BMI = body mass index; BSA = body surface area; OL = open-label; OLE = open-label extension; PASI = Psoriasis Area and Severity Index; PBO = placebo; PsA = psoriatic arthritis; PsO = psoriasis; q8w = every 8 weeks; q12w = every 12 weeks; RZB = risankizumab; SC = subcutaneous; sPGA = static Physician Global Assessment; TNF = tumor necrosis factor; UST = ustekinumab; Wk = Week

### 7.1.2. Review Strategy

The sources of data used for the evaluation of the efficacy and safety of risankizumab for the proposed indication included final study reports submitted by the applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)]. This application was submitted in eCTD format and entirely electronic. The electronic submission including protocols, statistical analysis plans (SAPs), clinical study reports, SAS transport datasets in Study Data Tabulation Modal (SDTM), and Analysis Data Model (ADaM) format were in the following network path:

Original submission: \\cdsesub1\evsprod\bla761105\0001\m5\datasets

#### 7.1.2.1 Data and Analysis Quality

In general, the quality of the data submitted by the applicant to support the efficacy and safety of risankizumab for the proposed indication appeared adequate.

## 7.2. Review of Relevant Individual Trials Used to Support Efficacy

### 7.2.1. Pivotal Phase 3 Trials (M15-995 [1311.28], M16-008 [1311.3])

#### 7.2.1.1 Study Design and Endpoints

The applicant conducted two pivotal Phase 3 trials (M15-995 [1311.28], M16-008 [1311.3]) to support the application.

For both trials, the key inclusion criteria that defined the study population were identical and are as follows:

- Male or female 18 years of age or older
- Diagnosis of plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug
- Stable moderate to severe chronic plaque-type psoriasis with or without psoriatic arthritis at both screening and baseline (randomization):
  - Static Physician Global Assessment (sPGA) score of at least 3 (moderate), see Appendix 13.4 for details on the sPGA scale
  - Psoriasis Area and Severity Index (PASI)  $\geq 12$ , see Appendix 13.4 for details on the calculation of PASI
  - Body Surface Area (BSA)  $\geq 10\%$

Subjects with non-plaque forms of psoriasis (including guttate, erythrodermic, or pustular), or with current drug-induced psoriasis (including an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium), or with active ongoing inflammatory diseases other than psoriasis and psoriatic arthritis that might confound trial evaluations according to investigator's judgement were excluded. Subjects who

were previously exposed to risankizumab (BI 655066) or ustekinumab (Stelara®) were also excluded.

Figure 5 presents the study designs for Trials 1311.28 and 1311.3. Both were multicenter, randomized, double-blind, placebo and active-controlled (EU-sourced ustekinumab), parallel-group, Phase 3 trials evaluating the safety and efficacy of risankizumab for the treatment of moderate-to-severe plaque psoriasis. In both trials, the randomization was stratified by baseline body weight ( $\leq 100$  kg vs.  $>100$  kg), and prior exposure to TNF antagonists (0 vs.  $\geq 1$ ).

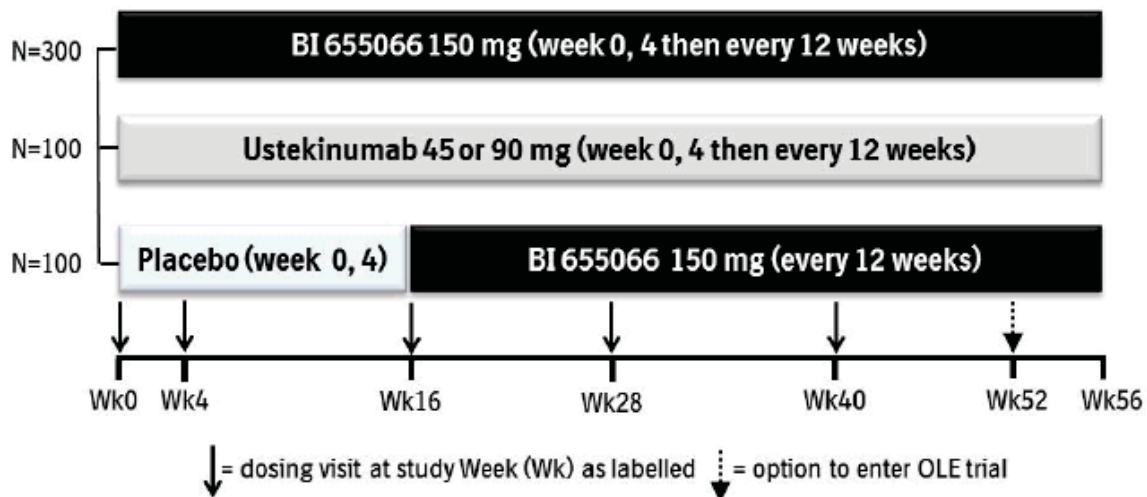
Both trials consisted of the following periods: a screening period, a randomized treatment period (Week 0 through Week 40), and a follow-up period (Week 41 through Week 56).

For the 40-week Randomized Treatment Period in each trial, the protocol specified randomizing approximately 500 subjects to one of the following treatment arms in a 3:1:1 ratio:

- Risankizumab 150 mg subcutaneously (SC) at Weeks 0 and 4, then every 12 (Q12) weeks (300 subjects)
- Ustekinumab (Stelara) [45 mg for  $<100$ kg and 90 mg for  $>100$ kg weight] SC at Weeks 0 and 4, then Q12 weeks (100 subjects)
- Placebo SC at Weeks 0 and 4, then at Week 16 switch to risankizumab 150 mg SC Q12 weeks (100 subjects)

Subjects were evaluated at the following study visits: screening, baseline (Day 1), Weeks 4, 8, 12, 16, 22, 28, 34, 40 (end of treatment), 46, 52, and 56 (follow-up visits 1, 2, and 3, respectively).

**Figure 5. Trial Design (1311.28 and 1311.3)**



Source: sponsor's protocol

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For both trials, the protocol-specified the following co-primary endpoints comparing risankizumab to placebo:

- Proportion of subjects who achieve  $\geq 90\%$  reduction from baseline PASI (PASI 90) at Week 16
- Proportion of subject who achieve an sPGA score of clear or almost clear (0 or 1) at Week 16

The protocol-specified co-primary and secondary endpoints are in Table 7. According to the applicant, the list of secondary endpoints was modified in their final SAPs (dated September 13, 2017 for both Trials 1311.28 and 1311.3) before unblinding of the data (dated September 29, 2017 and September 14 for Trials 1311.28 and 1311.3, respectively). The new secondary endpoints added in the final SAPs include sPGA of 0 at Week 16, PASI 100 at 16, and sPGA 0 at Week 52. It should be noted that the secondary endpoints were tested in a hierarchical order to control the Type I error rate ( $\alpha=0.05$ ) and were included in the prespecified multiplicity testing strategy.

**Table 7 Testing Hierarchy of Endpoints for Trials 1311.28 and 1311.3**

| Rank | Amended Protocol<br>(dated 10/12/2016)                                   | SAP<br>dated 9/12/2017;<br>Database unblinding (9/17/2017)   | Comments                       |
|------|--------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------|
| 1    | sPGA 0 or 1 at Week 16 (vs. placebo)<br>PASI 90 at Week 16 (vs. placebo) | Same                                                         | Co-1 <sup>o</sup><br>endpoints |
| 2    | PASI 90 at Week 16 (vs. ustekinumab)                                     | sPGA of 0 at Week 16 (vs. placebo)                           | New                            |
| 3    | sPGA 0 or 1 at Week 16 (vs.<br>ustekinumab)                              | PASI 100 at Week 16 (vs. placebo)                            | New                            |
| 4    | PASI 75 at Week 12 (vs. ustekinumab)                                     | DLQI 0 or 1 at Week 16 (vs. placebo)                         |                                |
| 5    | sPGA 0 or 1 at Week 12 (vs.<br>ustekinumab)                              | PSS of 0 at Week 16 (vs. placebo)                            |                                |
| 6    | PASI 100 at Week 16 (vs.<br>ustekinumab)                                 | PASI 90 at Week 16 (vs. ustekinumab)                         |                                |
| 7    | PASI 90 at Week 52 (vs. ustekinumab)                                     | sPGA 0 or 1 at Week 16 (vs.<br>ustekinumab)                  |                                |
| 8    | PASI 100 at Week 52 (vs.<br>ustekinumab)                                 | PASI 100 at Week 16 (vs. ustekinumab)                        |                                |
| 9    | Mean change from baseline in PSS at<br>Week 16 (vs. placebo)             | sPGA of 0 at Week 16 (vs. ustekinumab)                       | New                            |
| 10   | DLQI 0 or 1 at Week 16 (vs. placebo)                                     | PASI 90 at Week 52 (vs. ustekinumab)                         |                                |
| 11   | PSS of 0 at Week 16 (vs. placebo)                                        | PASI 100 at Week 52 (vs. ustekinumab)                        |                                |
| 12   | DLQI 0 or 1 at Week 16 (vs.<br>ustekinumab)                              | sPGA of 0 at Week 52 (vs. ustekinumab)                       | New                            |
| 13   |                                                                          | PASI 75 at Week 12 (vs. ustekinumab)                         |                                |
| 14   |                                                                          | sPGA 0 or 1 at Week 12 (vs.<br>ustekinumab)                  |                                |
| 15   |                                                                          | DLQI of 0 or 1 at Week 16 (vs.<br>ustekinumab)               |                                |
| 16   |                                                                          | Mean change from baseline in PSS at<br>Week 16 (vs. placebo) |                                |

Source: Reviewer table; DLQI – Dermatology Life Quality Index; PSS – Psoriasis Symptom Scale

### **Psoriasis Symptom Scale (PSS)**

The PSS is a four-item patient reported outcome (PRO) instrument that assesses the severity of psoriasis symptoms in patients with moderate to severe psoriasis. The symptoms included are pain, redness, itching, and burning from psoriasis. Current symptom severity is assessed as a daily diary, using a 5-point Likert-type scale ranging from 0 (none) to 4 (very severe). According to the protocol, the PSS was developed based on published evidence supporting the development of two similar, proprietary PRO instruments, the Psoriasis Symptom Inventory (PSI) and the Psoriasis Symptom Diary (PSD).

#### **7.2.1.2 Statistical Methodologies**

The primary analysis population was the Intent to Treat (ITT) population defined as all randomized subjects. The SAPs specified conducting supportive analyses using the Per Protocol Set (PPS) defined as the following:

- Subjects who received at least 75% of planned study drug injections (including dummy placebo injections).
- Subjects who had either a PASI or sPGA assessment post-baseline
- Subjects who had stable moderate to severe chronic plaque psoriasis at baseline (BSA $\geq$ 10%, PASI $\geq$ 12, sPGA $\geq$ 3)
- Subjects who had at least one post-baseline assessment for the corresponding endpoint.

For the analysis of the co-primary endpoints and the binary secondary endpoints, the protocols specified using the Cochran Mantel Haenszel (CMH) test stratified by weight ( $\leq$ 100 kg vs.  $>$ 100 kg) and prior exposure to TNF antagonists (0 vs  $\geq$ 1). For the analysis of the continuous endpoint (i.e., the mean change from baseline in PSS at Week 16), the protocol specified the van Elteren test.

The protocols specified testing the endpoints in a hierarchical order as in Table 7 to control the Type I error rate (two-sided,  $\alpha=0.05$ ), and only if the two co-primary endpoints are statistically significant, the secondary endpoints would be tested.

For handling of missing data for the binary endpoints, the protocols specified using No Response Imputation (NRI) approach and consider the missing data as failures. The protocols specified that only if visits before and after the missing are available and are both successes, then the missing data will be considered as a success, otherwise, NRI will be used. Furthermore, the protocols specified that subjects that take prohibited medications to treat psoriasis will be considered as discontinuing the trial, and will be considered as failures for the binary endpoints. For sensitivity analyses for handling missing data of the binary endpoints, the protocols specified using last observation

carried forward (LOCF), logistic regression, and multiple imputation (MI). For the continuous PSS endpoint, the protocols specified using LOCF as the primary imputation method, and the mixed model for repeated measures (MMRM) as a sensitivity analysis method.

### 7.2.1.3 Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial 1311.28 randomized a total of 491 subjects from 65 centers. Trial 1311.3 randomized a total of 506 subjects from 79 centers. Table 8 presents the disposition of subjects during the initial treatment period (16 weeks) of Trials 1311.28 and 1311.3. The discontinuation rates were low in each trial (<5%), and note that with such low rates of missing data along with the large treatment effect, the impact of the imputation method on efficacy is minimal.

**Table 8 Treatment Period Disposition for Trials 1311.28 and 1311.3**

|                                            | Trial 1311.28 (M15-995) |        |        | Trial 1311.3 (M16-008) |        |        |
|--------------------------------------------|-------------------------|--------|--------|------------------------|--------|--------|
|                                            | RZB                     | PBO    | UST    | RZB                    | PBO    | UST    |
| <b>Randomized</b>                          | 294                     | 98     | 99     | 304                    | 102    | 100    |
| <b>Discontinued</b>                        | 2 (<1%)                 | 4 (4%) | 3 (3%) | 5 (2%)                 | 4 (4%) | 1 (1%) |
| <i>Adverse Event, Worsening of Disease</i> | 0                       | 0      | 1      | 0                      | 2      | 0      |
| <i>Adverse Event, Other</i>                | 0                       | 0      | 0      | 1                      | 1      | 0      |
| <i>Withdrawal by Subject</i>               | 0                       | 3      | 0      | 3                      | 0      | 0      |
| <i>Lost to Follow Up</i>                   | 2                       | 0      | 2      | 0                      | 1      | 1      |
| <i>Other</i>                               | 0                       | 1      | 0      | 1                      | 0      | 0      |

Source: Applicant's table 14.1\_\_3; RZB = risankizumab 150 mg, PBO = placebo, UST = ustekinumab.

For both trials, the baseline demographics and baseline disease characteristics are presented in Table 9 and Table 10, respectively. The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial and were similar between the trials. Approximately 70% of the subjects were male, 78% of the subjects were White, 88% of subjects were 18-64 years of age, 72% of the subjects were ≤100 kg, 78% of the subjects had no history of prior TNF use, and 82% of the subjects had sPGA score of moderate (3) at baseline. Note that Trial 1311.3 enrolled more Asians than that of Trial 1311.28.

**Table 9. Baseline Demographics for Trials 1311.28 and 1311.3**

|  | Trial 1311.28 (M15-995) |     |     | Trial 1311.3 (M16-008) |     |     |
|--|-------------------------|-----|-----|------------------------|-----|-----|
|  | RZB                     | PBO | UST | RZB                    | PBO | UST |

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|                                         |           |          |          |           |          |          |
|-----------------------------------------|-----------|----------|----------|-----------|----------|----------|
| <b>Randomized</b>                       | 294       | 98       | 99       | 304       | 102      | 100      |
| <b>Gender</b>                           |           |          |          |           |          |          |
| <i>Female</i>                           | 91 (31%)  | 31 (32%) | 33 (33%) | 92 (30%)  | 23 (23%) | 30 (30%) |
| <i>Male</i>                             | 203 (69%) | 67 (68%) | 66 (67%) | 212 (70%) | 79 (77%) | 70 (70%) |
| <b>Age</b>                              |           |          |          |           |          |          |
| <i>Mean</i>                             | 46.2      | 46.3     | 48.6     | 48.3      | 49.3     | 46.5     |
| <i>SD</i>                               | 13.68     | 13.26    | 14.81    | 13.39     | 13.63    | 13.42    |
| <i>Range</i>                            | 19-76     | 19-75    | 20-75    | 21-84     | 24-85    | 19-76    |
| <i>Median</i>                           | 47        | 46       | 51       | 48        | 49       | 46.5     |
|                                         |           |          |          |           |          |          |
| <65                                     | 266 (90%) | 86 (88%) | 82 (83%) | 268 (88%) | 86 (84%) | 88 (88%) |
| ≥65                                     | 28 (10%)  | 12 (12%) | 17 (17%) | 36 (12%)  | 16 (16%) | 12 (12%) |
| <b>Race</b>                             |           |          |          |           |          |          |
| <i>Asian</i>                            | 25 (9%)   | 7 (7%)   | 4 (4%)   | 86 (29%)  | 28 (27%) | 22 (22%) |
| <i>Black</i>                            | 10 (3%)   | 2 (2%)   | 2 (2%)   | 10 (3%)   | 1 (<1%)  | 1 (1%)   |
| <i>White</i>                            | 255 (87%) | 87 (89%) | 91 (92%) | 200 (66%) | 71 (70%) | 74 (74%) |
| <i>American Indian</i>                  | 2 (1%)    | 1 (1%)   | 0        | 7 (2%)    | 2 (2%)   | 2 (2%)   |
| <i>Native Hawaiian/Pacific Islander</i> | 0         | 1 (1%)   | 1 (1%)   | 1 (<1%)   | 0        | 1 (1%)   |
| <i>Multirace/Other</i>                  | 2 (<1%)   | 0        | 1(1%)    | 0         | 0        | 0        |
| <b>Prior TNF</b>                        |           |          |          |           |          |          |
| Yes                                     | 67 (23%)  | 26 (27%) | 24 (24%) | 67 (22%)  | 22 (22%) | 19 (19%) |
| No                                      | 227 (77%) | 72 (73%) | 75 (76%) | 237 (78%) | 80 (78%) | 81 (81%) |
| <b>Weight</b>                           |           |          |          |           |          |          |
| ≤100 kg                                 | 203 (69%) | 67 (68%) | 69 (70%) | 226 (74%) | 76 (75%) | 74 (74%) |
| >100 kg                                 | 91 (31%)  | 31 (32%) | 30 (30%) | 78 (26%)  | 26 (25%) | 26 (26%) |

Source: Applicant's table 14.1 \_\_3; RZB = risankizumab 150 mg, PBO = placebo, UST = ustekinumab.

**Table 10. Baseline Disease Severity for Trials 1311.28 and 1311.3**

|                   | Trial 1311.28 (M15-995) |          |          | Trial 1311.3 (M16-008) |          |          |
|-------------------|-------------------------|----------|----------|------------------------|----------|----------|
|                   | RZB                     | PBO      | UST      | RZB                    | PBO      | UST      |
| <b>Randomized</b> | 294                     | 98       | 99       | 304                    | 102      | 100      |
| <b>sPGA</b>       |                         |          |          |                        |          |          |
| <i>Moderate</i>   | 228 (78%)               | 77 (79%) | 81 (82%) | 256 (84%)              | 86 (84%) | 85 (85%) |
| <i>Severe</i>     | 66 (22%)                | 21 (21%) | 18 (18%) | 48 (16%)               | 16 (16%) | 15 (15%) |
| <b>PASI</b>       |                         |          |          |                        |          |          |
| <i>mean</i>       | 20.54                   | 18.86    | 18.21    | 20.63                  | 20.50    | 20.08    |
| <i>SD</i>         | 7.83                    | 7.31     | 5.86     | 7.68                   | 6.68     | 6.84     |
| <i>Median</i>     | 18.5                    | 16.4     | 16.4     | 18.1                   | 18.9     | 18.1     |
| <i>Range</i>      | 12-60.3                 | 12-45.6  | 12-40.1  | 12-54.7                | 12-48.7  | 12-44.5  |
| <b>BSA</b>        |                         |          |          |                        |          |          |
| <i>Mean</i>       | 26.2                    | 23.9     | 20.9     | 26.2                   | 27.9     | 25.2     |
| <i>SD</i>         | 15.9                    | 15.7     | 12.1     | 15.4                   | 17.2     | 14.7     |
| <i>median</i>     | 21                      | 18       | 15       | 22                     | 21.5     | 20       |
| <i>range</i>      | 10-95                   | 10-88    | 10-75    | 10-88                  | 10-85    | 10-85    |
| <b>PSS</b>        |                         |          |          |                        |          |          |
| <i>Mean</i>       | 8.27                    | 8.71     | 8.60     | 7.99                   | 7.55     | 8.33     |
| <i>SD</i>         | 3.89                    | 3.46     | 3.47     | 3.64                   | 3.37     | 3.91     |

|               |      |      |      |      |      |      |
|---------------|------|------|------|------|------|------|
| <i>Median</i> | 8    | 8    | 9    | 8    | 8    | 8    |
| <i>Range</i>  | 0-16 | 2-16 | 1-16 | 0-16 | 0-16 | 0-16 |

Source: Applicant's tables 14-1.

#### 7.2.1.4 Results for the Co-Primary Efficacy Endpoints

Table 11 presents the results for the co-primary efficacy endpoints at Week 16 for Trials 1311.28 and 1311.3. Risankizumab was statistically superior to placebo (p-values<0.001) for both co-primary efficacy endpoints in both trials.

**Table 11. Proportion of subjects who achieved sPGA 0 or 1 at Week 16, and PASI 90 at Week 16 in Trials 1311.28 and 1311.3 (Co-primary Endpoints; Non-responder imputation, ITT)**

|                    | Trial 1311.28<br>(M15-995) |        |          | Trial 1311.3<br>(M16-008) |        |          |
|--------------------|----------------------------|--------|----------|---------------------------|--------|----------|
|                    | RZB                        | PBO    | UST      | RZB                       | PBO    | UST      |
| <b>Randomized</b>  | 294                        | 98     | 99       | 304                       | 102    | 100      |
| <b>sPGA 0 or 1</b> | 246 (84%)                  | 5 (5%) | 61 (62%) | 267 (88%)                 | 8 (8%) | 63 (63%) |
| <b>PASI 90</b>     | 220 (75%)                  | 2 (2%) | 47 (47%) | 229 (75%)                 | 5 (5%) | 42 (42%) |

Source: reviewer table; RZB = risankizumab, PBO = placebo; UST = ustekinumab. Analysis based on Cochran-Mantel-Haenszel (CMH) test stratified by weight ( $\leq 100$  kg vs.  $>100$  kg) and prior exposure to TNF antagonists (0 vs.  $\geq 1$ ).

#### 7.2.1.5 Results for the Secondary Efficacy Endpoints

Trials 1311.28 and 1311.3 included ustekinumab as an active comparator. Note that the applicant used EU-approved ustekinumab and did not provide an adequate scientific bridge between the U.S. licensed Stelara and EU-approved ustekinumab (from hereon denoted as ustekinumab).

Table 12 presents the results for the ranked secondary efficacy endpoints for Trials 1311.28 and 1311.3. In both trials, risankizumab was statistically superior to its comparator (placebo or ustekinumab with p-values<0.001) in the overall population for all the secondary efficacy endpoints presented in Table 7.

**Table 12. Results of the Ranked Secondary efficacy endpoints; Non-responder imputation, ITT)**

|                              | Trial 1311.28<br>(M15-995) |                                |         | Trial 1311.3<br>(M16-008) |                                  |         |
|------------------------------|----------------------------|--------------------------------|---------|---------------------------|----------------------------------|---------|
|                              | RZB<br>(N=294)             | PBO (N=98)<br>or<br>UST (N=99) | p-value | RZB<br>(N=304)            | PBO (N=102)<br>or<br>UST (N=100) | p-value |
| <b>Week 16 (vs. Placebo)</b> |                            |                                |         |                           |                                  |         |
| <b>sPGA of 0</b>             | 150<br>(51%)               | 3 (3%)                         | <0.001  | 112 (37%)                 | 2 (2%)                           | <0.001  |
| <b>PASI 100</b>              | 149                        | 2 (2%)                         | <0.001  | 109 (36%)                 | 0 (0%)                           | <0.001  |

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|                                                  |                 |                 |        |                 |                |        |
|--------------------------------------------------|-----------------|-----------------|--------|-----------------|----------------|--------|
|                                                  | (51%)           |                 |        |                 |                |        |
| <b>DLQI 0/1</b>                                  | 196<br>(67%)    | 4 (4%)          | <0.001 | 200 (66%)       | 8 (8%)         | <0.001 |
| <b>PSS of 0</b>                                  | 92 (31%)        | 0 (0%)          | <0.001 | 89 (29%)        | 2 (2%)         | <0.001 |
| <b>Week 16 (vs. Ustekinumab)</b>                 |                 |                 |        |                 |                |        |
| <b>PASI 90</b>                                   | 220<br>(75%)    | 47 (48%)        | <0.001 | 229 (75%)       | 42 (42%)       | <0.001 |
| <b>sPGA 0/1</b>                                  | 246<br>(84%)    | 61 (62%)        | <0.001 | 268 (88%)       | 63 (63%)       | <0.001 |
| <b>PASI 100</b>                                  | 149<br>(51%)    | 24 (24%)        | <0.001 | 109 (36%)       | 12 (12%)       | <0.001 |
| <b>sPGA 0</b>                                    | 150<br>(51%)    | 25 (25%)        | <0.001 | 112 (37%)       | 14 (14%)       | <0.001 |
| <b>Week 52 (vs. Ustekinumab)</b>                 |                 |                 |        |                 |                |        |
| <b>PASI 90</b>                                   | 237<br>(81%)    | 50 (51%)        | <0.001 | 249 (82%)       | 44 (44%)       | <0.001 |
| <b>PASI 100</b>                                  | 175<br>(60%)    | 30 (30%)        | <0.001 | 171 (56%)       | 21 (21%)       | <0.001 |
| <b>sPGA 0</b>                                    | 175<br>(60%)    | 30 (30%)        | <0.001 | 175 (58%)       | 21 (21%)       | <0.001 |
| <b>Week 12 (vs. Ustekinumab)</b>                 |                 |                 |        |                 |                |        |
| <b>PASI 75</b>                                   | 261<br>(89%)    | 69 (70%)        | <0.001 | 265 (87%)       | 70 (70%)       | <0.001 |
| <b>sPGA 0/1</b>                                  | 242<br>(82%)    | 64 (65%)        | <0.001 | 250 (82%)       | 65 (65%)       | <0.001 |
| <b>Week 16 (vs. Ustekinumab)</b>                 |                 |                 |        |                 |                |        |
| <b>DLQI 0/1</b>                                  | 196<br>(67%)    | 46 (47%)        | <0.001 | 200 (66%)       | 43 (43%)       | <0.001 |
| <b>Week 16 (vs. Placebo)</b>                     |                 |                 |        |                 |                |        |
| <b>Change<sup>(1)</sup><br/>in PSS<br/>Score</b> | -6.40<br>(0.22) | -0.03<br>(0.33) | <0.001 | -5.61<br>(0.23) | 0.16<br>(0.35) | <0.001 |

Source: Applicant's Table ; RZB = risankizumab, PBO = placebo; UST = ustekinumab. DLQI – Dermatology Life Quality Index; PSS – Psoriasis Symptom Scale; Analysis based on Cochran-Mantel-Haenszel (CMH) test stratified by weight ( $\leq 100$  kg vs.  $>100$  kg) and prior exposure to TNF antagonists (0 vs.  $\geq 1$ ). (1) LS Mean Change (SE) from baseline

### 7.2.1.6 Patient Reported Outcomes (PROs)

The protocols specified three secondary efficacy endpoints based on patient reported outcomes (PROs). One of these endpoints was based on the Dermatology Life Quality Index (DLQI). In an advice letter dated February 19, 2016, the Agency stated that the clinical relevance of DLQI endpoint would require COA input.

The other two PRO endpoints were based on the Psoriasis Symptom Scale (PSS):

- PSS of 0 at Week 16 (risankizumab vs. placebo)
- Change in PSS score from baseline to Week 16 (risankizumab vs. ustekinumab).

At a Type C Guidance Meeting dated April 5, 2017, the Agency stated that “we do not have sufficient information to determine whether the PSS is a well-defined and reliable

instrument that may be used to support labeling claims”. The Agency requested that the sponsor “provide evidence of the assessment’s content validity and other measurement properties, including reliability, validity, and ability to detect change, as well as the assessment’s conceptual framework and scoring in a PRO evidence dossier for FDA review and comment”. Furthermore, the Agency commented on the limited utility of interpreting the results of a van Elteren non-parametric test, as a mere change in PSS might not reflect a clinically meaningful change.

On July 16, 2018, the clinical team requested a Clinical Outcome Assessment (COA) Consult regarding the proposed PSS. The COA reviewer (Julia Ju, PharmD, PhD) concluded in the COA review (January 23, 2019) that “the evidence submitted by the applicant sufficiently demonstrates that PSS is fit-for-purpose for the context of this drug development program to assess the signs and symptoms of psoriasis”.

For the DLQI, the Study Endpoints and Label Development (SEALD) reviews (October 13, 2004; May 20, 2005) concluded that the DLQI is not fit-for-purpose for labeling in the context of this drug development program due to lack of item relevancy. The DLQI contains questions that measure broad concepts related to general skin conditions (e.g., going shopping, making your home messy) which may lack clinical relevance and be insensitive to treatment effect among [dermatological condition under investigation] patients. Further, there are issues surrounding content validity, specifically the use of multi-barreled questions in the assessment.

Table 12 includes the results for the DLQI endpoints as well as the mean change from baseline in PSS score to Week 16. In both trials, risankizumab was statistically superior to ustekinumab for the DLQI endpoint ( $p$ -values $<0.001$ ), and against placebo for the PSS endpoints ( $p$ -values $<0.001$ ).

*CDTL comment:*

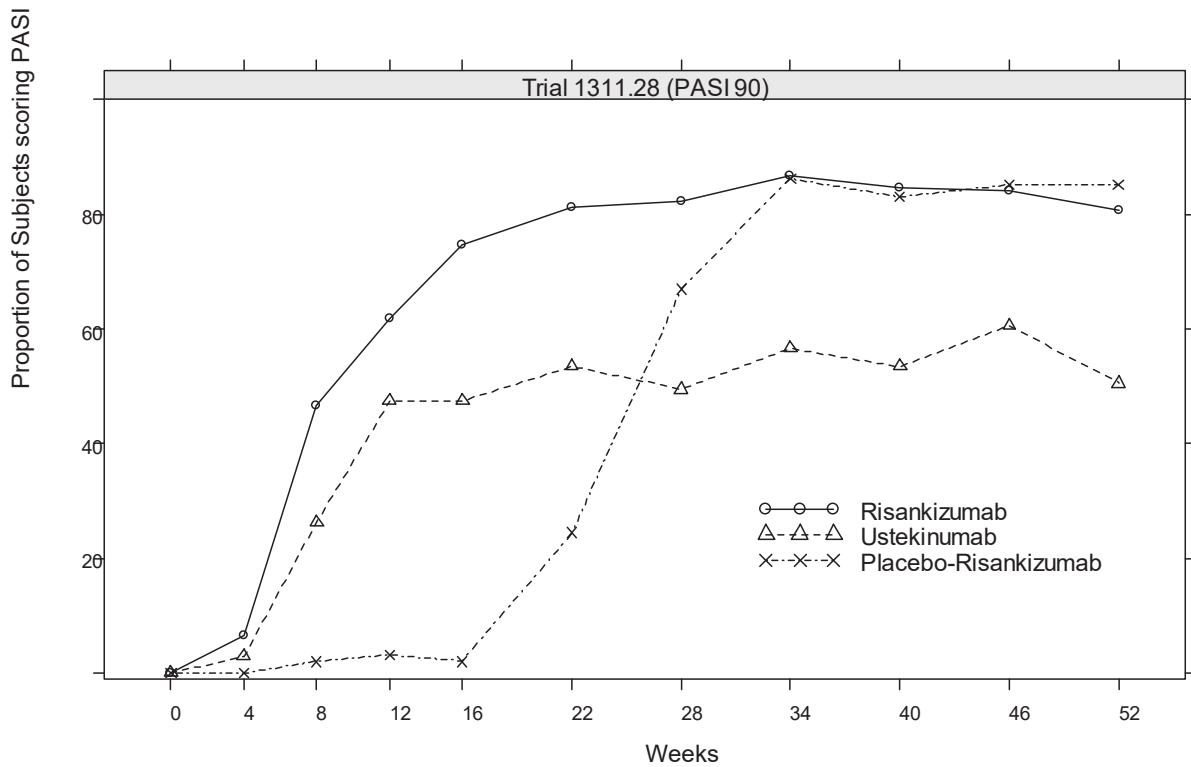
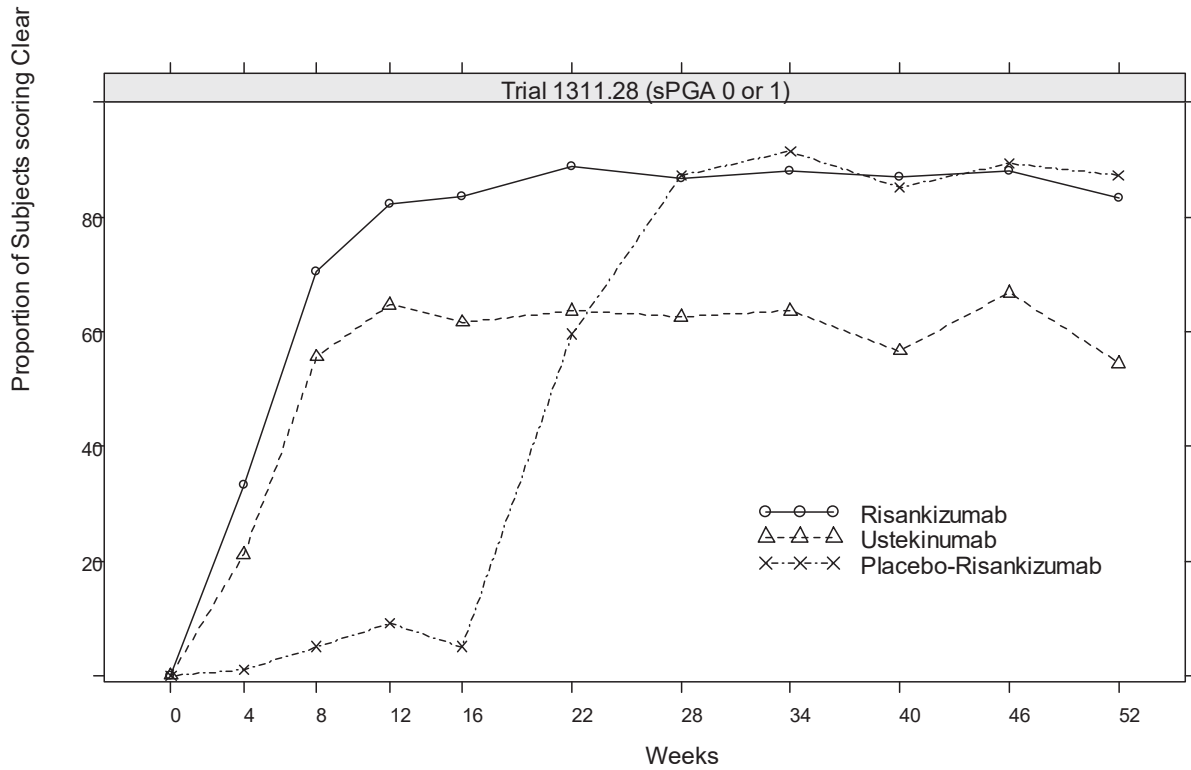
*COA found the PSS but not the DLQI fit for purpose as they relate to inclusion in labeling. PSS information is included in labeling.*

### 7.2.1.7 Efficacy Over Time

Figure 6 **Figure 6** presents the results for sPGA 0 or 1 and PASI 90 through Week 52 for Trial Trials 1311.28. **Figure 7** presents the results for sPGA 0 or 1 and PASI 90 through Week 52 for Trial 1311.3. Note that subjects that received placebo in the initial Treatment Period were switched over to risankizumab at Week 16.

**Figure 6. Results for sPGA score of 0 or 1 and PASI 90 Through Week 52 for Trial 1311.28**

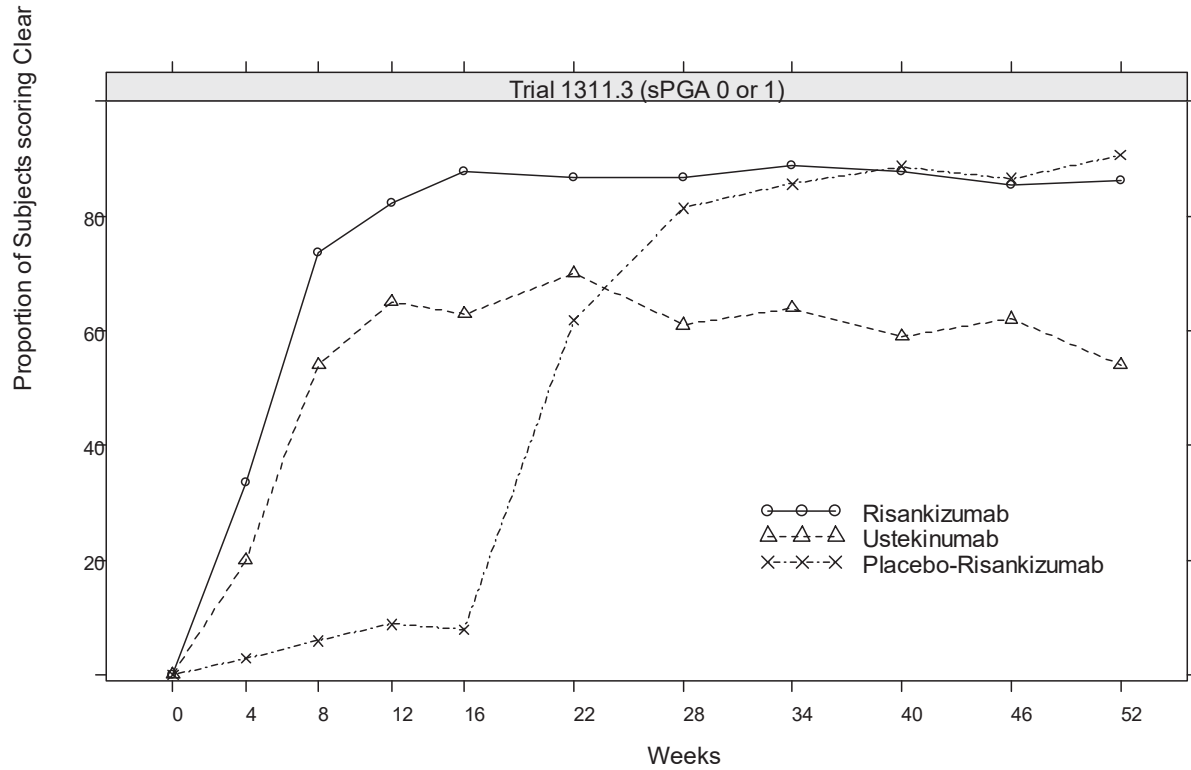
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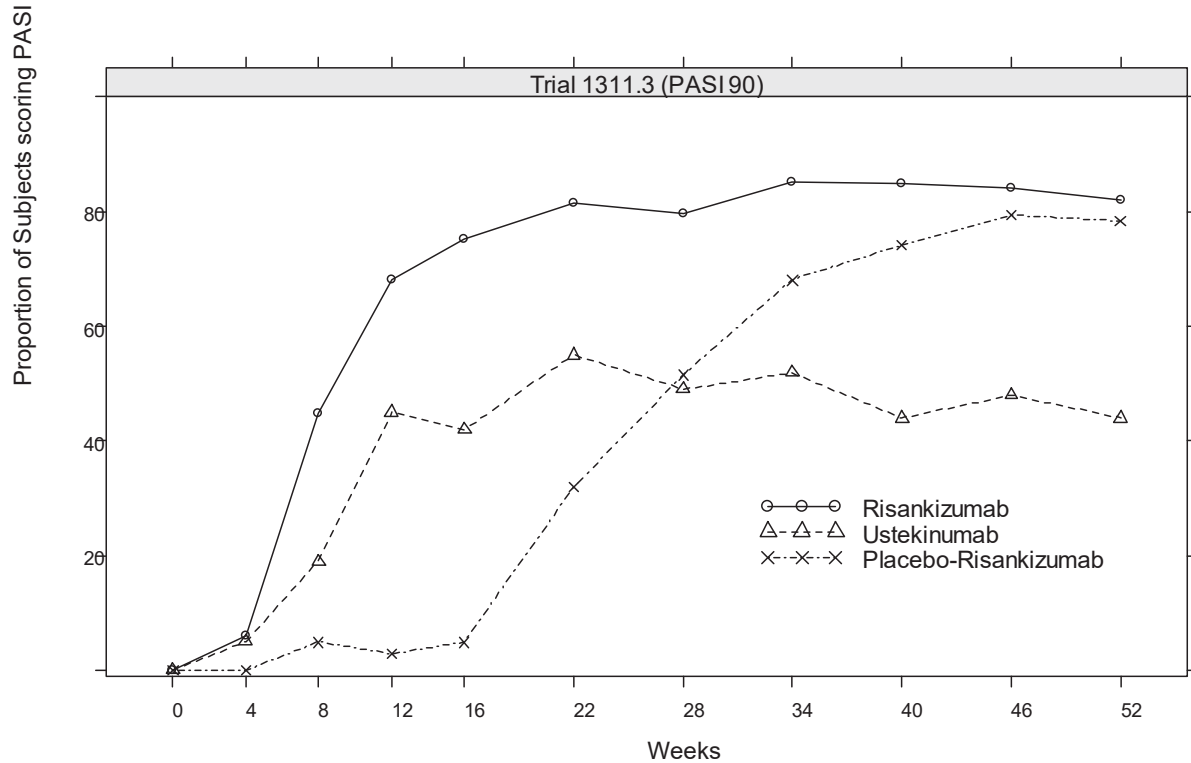
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Source: reviewer figures; Intent-to-Treat (ITT) analysis set; Missing data was imputed using non-responder imputation (NRI).  
Subjects that received placebo in the initial treatment period were switched over to risankizumab at Week 16.

**Figure 7. Results for sPGA score of 0 or 1 and PASI 90 Through Week 52 for Trial 1311.3**



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Source: reviewer figures; Intent-to-Treat (ITT) analysis set; Missing data was imputed using non-responder imputation (NRI). Subjects that received placebo in the initial treatment period were switched over to risankizumab at Week 16.

### 7.2.1.8 Findings in Special/Subgroup Populations

#### 7.2.1.8.1 Sex, Age, Race, Prior TNF use, Weight, Baseline Disease Severity

Table 13 presents the results for the co-primary efficacy endpoint of sPGA score of 0 or 1 at Week 16 by sex, age (<65, ≥65 years), race (Asian, Black, White, American Indian, Native Hawaiian/Pacific Islander, Other), Prior TNF (Yes, No), weight (≤100 kg vs. >100 kg), and baseline sPGA severity for Trial 1311.28 and 1311.3.

**Table 13. sPGA score of 0 or 1 at Week 16 by Sex, Age, Race, Prior TNF, Weight, and Baseline Disease Severity for Trials 1311.28 and 1311.3**

|                   | Trial 1311.28 (M15-995) |              |                | Trial 1311.3 (M16-008) |              |                |
|-------------------|-------------------------|--------------|----------------|------------------------|--------------|----------------|
|                   | RZB                     | PBO          | UST            | RZB                    | PBO          | UST            |
| <b>Randomized</b> | 294                     | 98           | 99             | 304                    | 102          | 100            |
| <b>Gender</b>     |                         |              |                |                        |              |                |
| <i>Female</i>     | 75/91<br>(82%)          | 1/31<br>(3%) | 23/33<br>(70%) | 81/92<br>(88%)         | 2/23<br>(9%) | 20/30<br>(67%) |
| <i>Male</i>       | 171/203<br>(84%)        | 4/67<br>(6%) | 38/66<br>(58%) | 186/212<br>(88%)       | 6/79<br>(8%) | 43/70<br>(61%) |
| <b>Age</b>        |                         |              |                |                        |              |                |

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|                                      |                  |              |                |                  |               |                |
|--------------------------------------|------------------|--------------|----------------|------------------|---------------|----------------|
| <65                                  | 221/266<br>(83%) | 4/86<br>(5%) | 53/82<br>(65%) | 237/268<br>(88%) | 6/86<br>(7%)  | 53/88<br>(60%) |
| ≥65                                  | 25/28<br>(89%)   | 1/12<br>(8%) | 8/17<br>(47%)  | 30/36<br>(83%)   | 2/16<br>(13%) | 10/12<br>(83%) |
| <b>Race</b>                          |                  |              |                |                  |               |                |
| Asian                                | 19/25<br>(76%)   | 0/7<br>(0%)  | 0/4<br>(0%)    | 79/86<br>(92%)   | 2/28<br>(7%)  | 17/22<br>(77%) |
| Black                                | 8/10<br>(80%)    | 1/2<br>(50%) | 2/2<br>(100%)  | 7/10<br>(70%)    | 0/1<br>(0%)   | 1/1<br>(100%)  |
| White                                | 215/255<br>(84%) | 4/87<br>(5%) | 58/91<br>(64%) | 174/200<br>(87%) | 5/71<br>(7%)  | 44/74<br>(59%) |
| American Indian                      | 2/2<br>(100%)    | 0/1<br>(0%)  | 0              | 6/7<br>(86%)     | 1/2<br>(50%)  | 0/2<br>(0%)    |
| Native Hawaiian/<br>Pacific Islander | 0                | 0/1<br>(0%)  | 1/1<br>(100%)  | 1/1<br>(100%)    | 0             | 1/1<br>(100%)  |
| Multirace/<br>Other                  | 2/2<br>(100%)    | 0            | 0/1<br>(0%)    | 0                | 0             | 0              |
| <b>Prior TNF</b>                     |                  |              |                |                  |               |                |
| Yes                                  | 56/67<br>(84%)   | 2/26<br>(8%) | 14/24<br>(58%) | 56/67<br>(84%)   | 1/22<br>(5%)  | 8/19<br>(42%)  |
| No                                   | 190/227<br>(84%) | 3/72<br>(4%) | 47/75<br>(63%) | 211/237<br>(89%) | 7/80<br>(9%)  | 55/81<br>(68%) |
| <b>Weight</b>                        |                  |              |                |                  |               |                |
| ≤100 kg                              | 170/203<br>(84%) | 4/67<br>(6%) | 46/69<br>(67%) | 202/226<br>(89%) | 7/76<br>(9%)  | 45/74<br>(61%) |
| >100 kg                              | 76/91<br>(84%)   | 1/31<br>(3%) | 15/30<br>(50%) | 65/78<br>(83%)   | 1/26<br>(4%)  | 18/26<br>(69%) |
| <b>sPGA</b>                          |                  |              |                |                  |               |                |
| Moderate                             | 193/228<br>(84%) | 3/77<br>(4%) | 52/81<br>(52%) | 226/256<br>(88%) | 8/86<br>(9%)  | 52/85<br>(61%) |
| Severe                               | 53/66<br>(80%)   | 2/21<br>(9%) | 9/18<br>(50%)  | 41/48<br>(85%)   | 0/16<br>(0%)  | 11/15<br>(73%) |

Source: Applicant's table 14.1\_\_3; RZB = risankizumab 150 mg, PBO = placebo, UST = ustekinumab.

### 7.2.1.8.2 Center

Trial 1311.28 was conducted in 65 centers. Note that Trial 1311.28 excluded Dr. Woodson's site. According to the applicant, Dr. Woodson's site was closed due to "non-compliance with protocol requirements". This was communicated to the Agency on April 5, 2017, and the Agency agreed that sensitivity analyses for co-primary endpoints including this site should be performed. It should be noted that Dr. Woodson's site enrolled a total of 11 subjects, and given the relative large treatment effect, the inclusion or exclusion for such site did not impact the conclusion of the efficacy. Table 14 presents the sPGA 0 or 1 results by centers that enrolled at least 10 subjects. Table 15 presents the PASI 90 responses at Week 16 by centers that enrolled at least 10 subjects.

**Table 14. sPGA 0 or 1 at Week 16 by Center<sup>(1)</sup> for Trial 1311.28**

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|                      | Rizankizumab<br>N=294 | Placebo<br>N=98 | Ustekinumab<br>N=99 | Total |
|----------------------|-----------------------|-----------------|---------------------|-------|
| sPGA 0 or 1<br>(ITT) | 246 (84%)             | 5 (5%)          | 61 (62%)            | 491   |
| SiteID               |                       |                 |                     |       |
| 10105                | 18/23 (78%)           | 0/8 (0%)        | 1/5 (20%)           | 36    |
| 10045                | 18/23 (78%)           | 0/5 (0%)        | 4/5 (80%)           | 33    |
| 20021                | 17/19 (89%)           | 0/6 (0%)        | 6/7 (86%)           | 32    |
| 20015                | 15/18 (83%)           | 0/6 (0%)        | 3/5 (60%)           | 29    |
| 20005                | 12/15 (80%)           | 0/6 (0%)        | 1/1 (100%)          | 22    |
| 10053                | 9/11 (82%)            | 1/5 (20%)       | 2/3 (67%)           | 19    |
| 20008                | 7/8 (88%)             | 0/3 (0%)        | 3/5 (60%)           | 16    |
| 33003                | 5/9 (56%)             | 0               | 5/5 (100%)          | 14    |
| 34004                | 10/10 (100%)          | 1/2 (50%)       | 1/1 (100%)          | 13    |
| 52002                | 8/8 (100%)            | 0/2 (0%)        | 2/2 (100%)          | 12    |
| 20018                | 6/7 (86%)             | 0/2 (0%)        | 1/3 (33%)           | 12    |
| 20030                | 7/9 (78%)             | 0/2 (0%)        | 1/1 (100%)          | 12    |
| 10052                | 4/5 (80%)             | 0/2 (0%)        | 3/4 (75%)           | 11    |
| 10062<br>(Woodson)   | 5/7 (71%)             | 1/2 (50%)       | 1/2 (50%)           | 11    |
| 10009                | 7/8 (88%)             | 0/1 (0%)        | 1/1 (100%)          | 10    |

Source: Reviewer table; (1) only those centers that enrolled at least 10 subjects are included in the table.

**Table 15. PASI 90 at Week 16 by Center<sup>(1)</sup> for Trial 1311.28**

|                    | Rizankizumab<br>N=294 | Placebo<br>N=98 | Ustekinumab<br>N=99 | Total |
|--------------------|-----------------------|-----------------|---------------------|-------|
| PASI 90            | 220 (75%)             | 2 (2%)          | 47 (47%)            | 491   |
| SiteID             |                       |                 |                     |       |
| 10105              | 14/23 (61%)           | 0/8 (0%)        | 1/5 (20%)           | 36    |
| 10045              | 19/23 (83%)           | 0/5 (0%)        | 4/5 (80%)           | 33    |
| 20021              | 16/19 (84%)           | 0/6 (0%)        | 5/7 (71%)           | 32    |
| 20015              | 15/18 (83%)           | 0/6 (0%)        | 2/5 (40%)           | 29    |
| 20005              | 9/15 (60%)            | 0/6 (0%)        | 0/1 (0%)            | 22    |
| 10053              | 9/11 (82%)            | 0/5 (0%)        | 1/3 (33%)           | 19    |
| 20008              | 5/8 (63%)             | 0/3 (0%)        | 2/5 (40%)           | 16    |
| 33003              | 6/9 (67%)             | 0               | 4/5 (80%)           | 14    |
| 34004              | 10/10 (100%)          | 0/2 (0%)        | 1/1 (100%)          | 13    |
| 52002              | 7/8 (88%)             | 0/2 (0%)        | 0/2 (0%)            | 12    |
| 20018              | 6/7 (86%)             | 0/2 (0%)        | 1/3 (33%)           | 12    |
| 20030              | 7/9 (78%)             | 0/2 (0%)        | 0/1 (0%)            | 12    |
| 10052              | 4/5 (80%)             | 0/2 (0%)        | 2/4 (50%)           | 11    |
| 10062<br>(Woodson) | 5/7 (71%)             | 1/2 (50%)       | 1/2 (50%)           | 11    |
| 10009              | 4/8 (50%)             | 0/1 (0%)        | 1/1 (100%)          | 10    |

Source: Reviewer table; (1) only those centers that enrolled at least 10 subjects are included in the table.

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Trial 1311.3 was conducted in 79 centers. Table 16 presents the sPGA 0 or 1 results by centers that enrolled at least 10 subjects. Table 17 presents the PASI 90 results by centers that enrolled at least 10 subjects.

**Table 16. sPGA 0 or 1 at Week 16 by Center<sup>(1)</sup> for Trial 1311.3**

|                      | Rizankizumab<br>N=304 | Placebo<br>N=102 | Ustekinumab<br>N=100 | Total |
|----------------------|-----------------------|------------------|----------------------|-------|
| sPGA 0 or 1<br>(ITT) | 267 (88%)             | 8 (8%)           | 63 (63%)             | 506   |
| SiteID               |                       |                  |                      |       |
| 10018                | 9/9 (100%)            | 0/5 (0%)         | 5/7 (71%)            | 21    |
| 10021                | 10/14 (71%)           | 0/2 (0%)         | 2/5 (40%)            | 21    |
| 20009                | 10/10 (100%)          | 0/6 (0%)         | 2/4 (50%)            | 20    |
| 10038                | 8/11 (73%)            | 0/4 (0%)         | 0/4 (0%)             | 19    |
| 10096                | 10/11 (91%)           | 1/5 (20%)        | 2/3 (67%)            | 19    |
| 10086                | 6/7 (86%)             | 0/4 (0%)         | 4/5 (80%)            | 16    |
| 20020                | 7/7 (100%)            | 0/5 (0%)         | 2/2 (100%)           | 14    |
| 10044                | 7/9 (78%)             | 0/3 (0%)         | 1/1 (100%)           | 13    |
| 10072                | 6/7 (86%)             | 2/3 (67%)        | 2/3 (67%)            | 13    |
| 20029                | 7/10 (70%)            | 0/1 (0%)         | 2/2 (100%)           | 13    |
| 20011                | 6/8 (75%)             | 0/3 (0%)         | 1/1 (100%)           | 12    |
| 20004                | 7/8 (88%)             | 0/2 (0%)         | 1/1 (100%)           | 11    |
| 61001                | 8/9 (89%)             | 0                | 1/2 (50%)            | 11    |
| 61002                | 6/7 (86%)             | 0                | 2/3 (67%)            | 10    |
| 82007                | 6/7 (86%)             | 0/2 (0%)         | 1/1 (100%)           | 10    |

Source: Reviewer table; (1) only those centers that enrolled at least 10 subjects are included in the table.

**Table 17. PASI 90 at Week 16 by Center<sup>(1)</sup> for Trial 1311.3**

|         | Rizankizumab<br>N=304 | Placebo<br>N=102 | Ustekinumab<br>N=100 | Total |
|---------|-----------------------|------------------|----------------------|-------|
| PASI 90 | 229 (75%)             | 5 (5%)           | 42 (42%)             | 506   |
| SiteID  |                       |                  |                      |       |
| 10018   | 9/9 (100%)            | 0/5 (0%)         | 5/7 (71%)            | 21    |
| 10021   | 11/14 (79%)           | 0/2 (0%)         | 2/5 (40%)            | 21    |
| 20009   | 8/10 (80%)            | 0/6 (0%)         | 2/4 (50%)            | 20    |
| 10038   | 5/11 (45%)            | 1/4 (25%)        | 1/4 (25%)            | 19    |
| 10096   | 7/11 (64%)            | 0/5 (0%)         | 0/3 (0%)             | 19    |
| 10086   | 4/7 (57%)             | 0/4 (0%)         | 2/5 (40%)            | 16    |
| 20020   | 6/7 (86%)             | 0/5 (0%)         | 2/2 (100%)           | 14    |
| 10044   | 7/9 (78%)             | 0/3 (0%)         | 1/1 (100%)           | 13    |
| 10072   | 5/7 (71%)             | 2/3 (67%)        | 1/3 (33%)            | 13    |
| 20029   | 5/10 (50%)            | 0/1 (0%)         | 1/2 (50%)            | 13    |
| 20011   | 6/8 (75%)             | 0/3 (0%)         | 1/1 (100%)           | 12    |

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|       |           |          |           |    |
|-------|-----------|----------|-----------|----|
| 20004 | 6/8 (75%) | 0/2 (0%) | 0/1 (0%)  | 11 |
| 61001 | 8/9 (89%) | 0        | 0/2 (0%)  | 11 |
| 61002 | 5/7 (71%) | 0        | 1/3 (33%) | 10 |
| 82007 | 3/7 (43%) | 0/2 (0%) | 0/1 (0%)  | 10 |

Source: Reviewer table; (1) only those centers that enrolled at least 10 subjects are included in the table.

Based on the inspection by the Office of Scientific Inspections (OSI), approximately 0.4%, 3.1%, and 1.8% in Trials M15-995 (1311.28), M16-008 (1311.3), and M15-992 (1311.4), respectively, did not have a clearly attributable signature of a certified assessor to verify the accuracy of the baseline and/or Week 16 sPGA data. Similarly, for the PASI score, approximately 1.6%, 4.3%, and 5.3% in Trials 1311.28, 1311.3, and 1311.4, respectively, did not have a clearly attributable signature. However, given the large treatment effect (approximately 80% in all 3 trials) along with a relatively small proportion of subjects without the attributable signature, results from a sensitivity analysis of excluding these subjects would not impact the overall conclusion.

## 7.2.2. Other Phase 3 Trials (M16-010 [1311.30] and M15-992 [1311.4])

### 7.2.2.1 Study Design and Endpoints

**Trial 1311.30** was an active-controlled, double-blind, double-dummy, randomized, parallel design to test superiority of BI 655066 vs. adalimumab with treatment duration of 44 weeks.

Using the Interactive Response Technology (IRT), 605 subjects from 66 centers were randomized to the following treatment arms in a 1:1 ratio:

- Risankizumab (301 subjects)
- Adalimumab (304 subjects)

In this trial, subjects initially randomized to BI 655066 remained on BI 655066. Then subjects randomized to adalimumab were rerandomized to the following treatment depending on their PASI score at Week 16:

- subjects with < PASI 50 at Week 16 switched to the BI 655066
- subjects with ≥ PASI 90 at Week 16 stayed on adalimumab
- subjects with ≥ PASI 50 and < PASI 90 at Week 16 were re-randomized 1:1 to receive either BI 655066 or adalimumab.

The Agency previously stated (June 24, 2015, April 5, 2017) that “As treatment success for Humira was based on PASI 75 and PGA 0 or 1 endpoints, your re-randomization based on PASI 50 and PASI 90 (i.e., PASI50 but <PASI 90) may be arbitrary taking into account that your sub-population for PASI 50 but <PASI 90 could be further partitioned to those who achieve PASI 75 and those who do not. Therefore, we reiterate our previous comments (6/24/2015) that you define success criteria on PASI 75 as well as PGA 0 or 1 at Week 16.”

Furthermore, in an Advice Letter dated 3/9/2016, the Agency stated that “In general, to support a superiority claim against an active comparator, replication of study findings from two adequate and well-controlled trials is recommended”.

To maintain double-blind, the sponsor used a double-dummy design as summarized below.

- **BI 655066 150 mg SC**
  - BI 655066 - 2 syringes of active drug (2x75 mg) at randomization, Weeks 4, 16, and 28,
  - Placebo adalimumab – 2 syringes at randomization and 1 syringe Q2W from Weeks 1 to Week 41
  
- **Adalimumab**
  - Adalimumab – 2 syringes of adalimumab at randomization (2x40 mg) followed by 1 syringe adalimumab (40 mg) Q2W from Weeks 1 to 41
  - Placebo BI 655066 – 2 syringes of placebo BI 655066 at randomization, Weeks 4, 16, 20, 28, and 32.

At Week 16, subjects that switched to the **BI 655066** received the following:

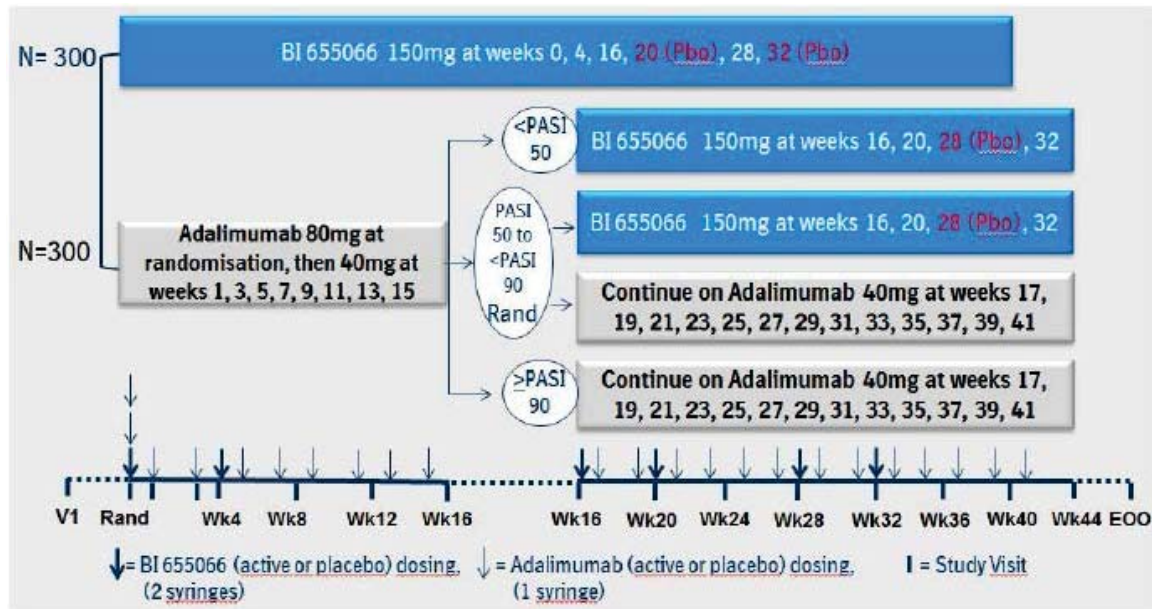
- BI 655066 – 2 syringes at randomization, Week 4 followed by 2 injections (2x75 mg) at Weeks 16, 20, and 32
- Placebo Adalimumab Q2W from Weeks 17 to 41.

At Week 16, subjects that continued on **adalimumab** received the following:

- Adalimumab - 1 syringe of adalimumab (40 mg) Q2W from Weeks 17 to 41
- Placebo BI 655066 – 2 syringes at Week 28.

Study visits occurred on screening (Day -28), baseline (Day 1), Weeks 1, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 (end of treatment), and follow-up.

### **Figure 8. Study Design for Trial 1311.30**



Source: applicant's protocol

For Trial 1311.30, the protocol-specified co-primary endpoints were the following:

- Proportion of subjects achieving sPGA 0 or 1 at Week 16
- Proportion of subjects achieving PASI 90 at Week 16.

The protocol specified testing the following secondary efficacy endpoints in the following:

- Proportion of subjects achieving PASI 75 at Week 16
- Proportion of subjects achieving PASI 100 at Week 16.

Then for the re-randomized subjects at Week 16, the protocol-specified testing the superiority of BI 655066 to placebo for the following endpoint.

- Proportion of subjects achieving PASI 90 at Week 44 (for those who were re-randomized at Week 16).

For **Trial 1311.4**, a total of 507 subjects from 60 centers were enrolled and randomized to one of the following treatment arms in a 4:1 ratio:

- BI 655066 150 mg SC at Weeks 0, 4 and 16 (407 subjects)
- Placebo SC at Weeks 0 and 4, then BI 655066 150 mg SC at Week 16 (100 subjects)

As with the pivotal trials (1311.28 and 1311.3), randomization was stratified by weight ( $\leq 100$  kg vs.  $> 100$  kg), and prior exposure to TNF antagonists (0 vs.  $\geq 1$ ).

There were two parts included in this trial: Part A and Part B.

- Part A: "induction and response period from initial randomization through Week 28"
- Part B: "withdrawal and re-treatment period from Weeks 28-88".

The protocol included a figure depicting the trial design as in Figure 9.

At Week 28,

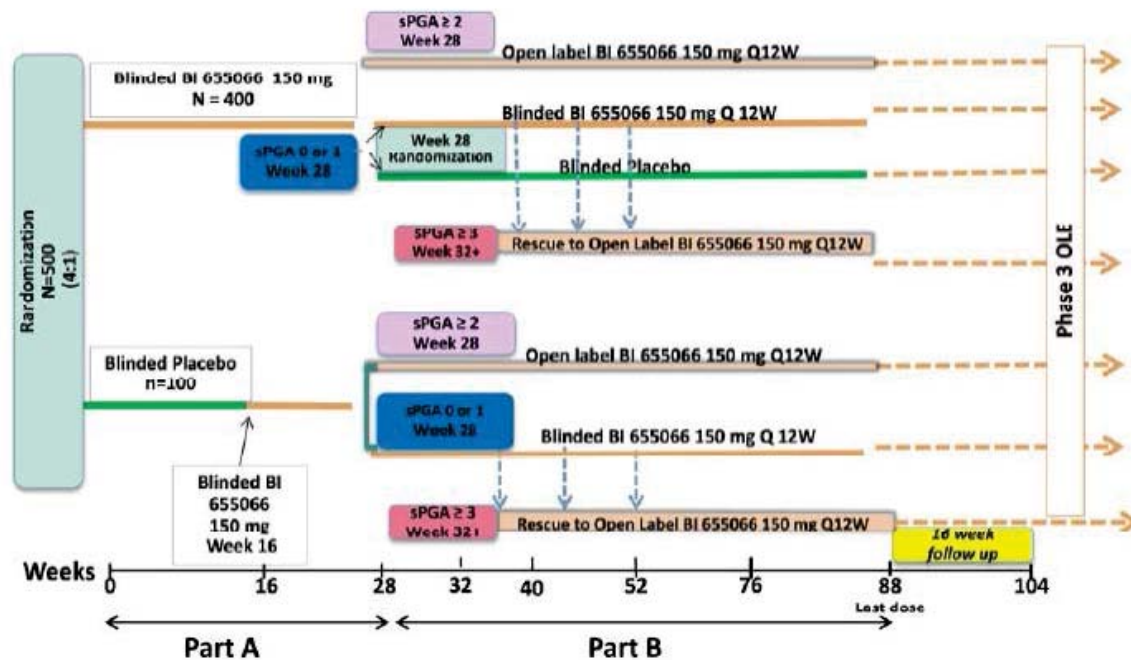
- “Non-responders” (i.e., sPGA $\geq$ 2) received BI 655066 open-label until Week 88 regardless of the original treatment arm in Part A.
- “Responders” (i.e., sPGA 0 or 1) continued to receive the blinded drug, according to the following criteria:
  - Subjects originally randomized to the active were re-randomized to either BI 655066 or placebo in a 1:2 ratio.
  - Subjects originally randomized to placebo continued to receive blinded BI 655066 treatment to maintain blinding.

Once a Week 28 responder subject reached sPGA  $\geq$  3, they switched over to open-label BI 655066.

Subjects were evaluated at the following study visits: screening (Day -28), baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 58, 64, 70, 76, 88 (end of treatment), 94, 104 (follow-ups).

The trial design is shown below.

**Figure 9. Study Design for Trial 1311.4**



Source: applicant's protocol

The protocol specified testing superiority of BI 655066 to placebo in the following secondary efficacy endpoints in the following order:

- Proportion of subjects achieving PASI 75 at Week 16
- Proportion of subjects achieving PASI 100 at Week 16
- Proportion of subjects achieving sPGA of 0 at Week 16

- Proportion of subjects achieving DLQI 0 or 1 at Week 16

For the re-randomized subjects at Week 28, the sponsor included an endpoint of comparing BI 655066 vs. placebo sPGA 0 or 1 at Week 52.

### 7.2.2.2 Statistical Methodologies

The primary analysis population was the Intent to Treat (ITT) population defined as all randomized subjects. The SAPs specified conducting supportive analyses using the Per Protocol Set (PPS) defined as the following:

- Subjects who received at least 75% of planned study drug injections (including dummy placebo injections).
- Subjects who had either a PASI or sPGA assessment post-baseline
- Subjects who had stable moderate to severe chronic plaque psoriasis at baseline (BSA $\geq$ 10%, PASI $\geq$ 12, sPGA $\geq$ 3)
- Subjects who had at least one post-baseline assessment for the corresponding endpoint.

For the analysis of the co-primary endpoints and the binary secondary endpoints, the protocols specified using the Cochran Mantel Haenszel (CMH) test stratified by weight ( $\leq$ 100 kg vs.  $>$ 100 kg) and priori exposure to TNF antagonists (0 vs  $\geq$ 1).

The protocols specified testing the endpoints in a hierarchical order to control the Type I error rate (two-sided,  $\alpha=0.05$ ), and only if the two co-primary endpoints are statistically significant, the secondary endpoints would be tested.

For handling of missing data, the protocols specified using the same methods as in the pivotal trials.

### 7.2.2.3 Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial 1311.30 randomized a total of 615 subjects from 66 centers. Trial 1311.4 randomized a total of 507 subjects from 60 centers. Table 18 presents the disposition of subjects during the initial treatment period (16 weeks) of Trials 1311.30 and 1311.4. The discontinuation rates were low in each trial ( $<$ 5%), and note that with such low rates of missing data along with the large treatment effect, the impact of the imputation method on efficacy is minimal.

**Table 18. Initial Treatment Period Disposition for Trials 1311.30 and 1311.4**

|              | Trial 1311.30 (M16-010) |         | Trial 1311.4 (M15-992) |        |
|--------------|-------------------------|---------|------------------------|--------|
|              | RZB                     | ADA     | RZB                    | PBO    |
| Randomized   | 301                     | 304     | 407                    | 100    |
| Discontinued | 7 (2%)                  | 13 (4%) | 4 (1%)                 | 3 (3%) |

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|                                     |   |   |   |   |
|-------------------------------------|---|---|---|---|
| Adverse Event, Worsening of Disease | 1 | 2 | 0 | 1 |
| Adverse Event, Other                | 2 | 5 | 1 | 0 |
| Protocol Violation                  | 0 | 1 | 0 | 0 |
| Withdrawal by Subject               | 1 | 3 | 1 | 1 |
| Lost to Follow Up                   | 2 | 1 | 2 | 1 |
| Other                               | 1 | 1 | 0 | 0 |

Source: Applicant's table 14.1\_\_3.1; RZB = risankizumab 150 mg, ADA = adalimumab; Treatment Period A

The baseline demographics and baseline disease characteristics are presented in Table 19 and Table 20, respectively. In both trials, the demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial and were similar across the trials.

**Table 19. Initial Treatment Period Disposition for Trials 1311.30 and 1311.4**

|                                         | Trial 1311.30<br>(M16-010) |           | Trial 1311.4<br>(M15-992) |          |
|-----------------------------------------|----------------------------|-----------|---------------------------|----------|
|                                         | RZB                        | ADA       | RZB                       | PBO      |
| <b>Randomized</b>                       | 301                        | 304       | 407                       | 100      |
| <b>Gender</b>                           |                            |           |                           |          |
| <i>Female</i>                           | 91 (30%)                   | 92 (30%)  | 124 (30%)                 | 27 (27%) |
| <i>Male</i>                             | 210 (70%)                  | 212 (70%) | 283 (70%)                 | 73 (73%) |
| <b>Age</b>                              |                            |           |                           |          |
| <i>Mean</i>                             | 45.3                       | 47.0      | 49.6                      | 47.9     |
| <i>SD</i>                               | 13.79                      | 13.09     | 13.17                     | 13.78    |
| <i>Range</i>                            | 18-75                      | 18-81     | 19-74                     | 21-79    |
| <i>Median</i>                           | 46                         | 47        | 49                        | 51       |
|                                         |                            |           |                           |          |
| <65                                     | 277 (92%)                  | 276 (91%) | 354 (87%)                 | 89 (89%) |
| ≥65                                     | 24 (8%)                    | 28 (9%)   | 53 (13%)                  | 11 (11%) |
| <b>Race</b>                             |                            |           |                           |          |
| <i>Asian</i>                            | 41 (14%)                   | 35 (12%)  | 64 (16%)                  | 15 (15%) |
| <i>Black</i>                            | 11 (4%)                    | 6 (2%)    | 18 (4%)                   | 2 (2%)   |
| <i>White</i>                            | 245 (81%)                  | 263 (87%) | 329 (79%)                 | 82 (82%) |
| <i>American Indian</i>                  | 2 (<1%)                    | 0         | 0                         | 0        |
| <i>Native Hawaiian/Pacific Islander</i> | 0                          | 0         | 3 (<1%)                   | 1 (1%)   |
| <i>Multirace/Other</i>                  | 2 (<1%)                    | 0         | 2 (<1%)                   | 0        |
| <b>Prior TNF</b>                        |                            |           |                           |          |
| Yes                                     | 44 (15%)                   | 45 (15%)  | 150 (37%)                 | 35 (35%) |
| No                                      | 257 (85%)                  | 259 (85%) | 257 (63%)                 | 65 (65%) |

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Source: Applicant's table 14.1\_\_3.1; RZB = risankizumab 150 mg, ADA = adalimumab

**Table 20. Baseline Disease Severity for Trials 1311.30 and 1311.4**

|                   | Trial 1311.30 (M16-010) |           | Trial 1311.4 (M15-992) |          |
|-------------------|-------------------------|-----------|------------------------|----------|
|                   | RZB                     | ADA       | RZB                    | PBO      |
| <b>Randomized</b> | 301                     | 304       | 407                    | 100      |
| <b>sPGA</b>       |                         |           |                        |          |
| <i>Moderate</i>   | 243 (81%)               | 246 (81%) | 323 (79%)              | 77 (77%) |
| <i>Severe</i>     | 58 (19%)                | 58 (19%)  | 84 (21%)               | 23 (23%) |
|                   |                         |           |                        |          |
| <b>PASI</b>       |                         |           |                        |          |
| <i>mean</i>       | 19.95                   | 19.72     | 19.91                  | 21.17    |
| <i>SD</i>         | 7.46                    | 7.51      | 7.94                   | 8.68     |
| <i>Median</i>     | 17.8                    | 17.5      | 17.2                   | 18.9     |
| <i>Range</i>      | 12-50.4                 | 12-47.4   | 12-63.4                | 12-54.2  |
|                   |                         |           |                        |          |
| <b>BSA</b>        |                         |           |                        |          |
| <i>Mean</i>       | 26.5                    | 25.5      | 25.6                   | 28.3     |
| <i>SD</i>         | 16.48                   | 16.77     | 17.02                  | 19.07    |
| <i>median</i>     | 21                      | 20        | 19                     | 23       |
| <i>range</i>      | 10-85                   | 10-85     | 10-90                  | 10-90    |

Source: Applicant's tables 14.1.

#### 7.2.2.4 Results for the Co-Primary Efficacy Endpoints

Table 21 presents the results for the co-primary efficacy endpoints at Week 16 for Trials 1311.30 and 1311.4. Risankizumab was statistically superior to adalimumab in Trial 1311.30 (p-values<0.001) for both co-primary efficacy endpoints, and risankizumab was statistically superior to placebo in Trial 1311.4 (p-values <0.001) for both co-primary efficacy endpoints.

**Table 21 Proportion of subjects with sPGA 0 or 1 at Week 16, and PASI 90 at Week 16 in Trials 1311.30 and 1311.4 (Co-primary Endpoints; Non-responder imputation, ITT)**

|                    | Trial 1311.30 (M16-010) |           | Trial 1311.4 (M15-992) |        |
|--------------------|-------------------------|-----------|------------------------|--------|
|                    | RZB                     | ADA       | RZB                    | PBO    |
| <b>Randomized</b>  | 301                     | 304       | 407                    | 100    |
| <b>sPGA 0 or 1</b> | 252 (84%)               | 183 (60%) | 340 (84%)              | 7 (7%) |
| <b>PASI 90</b>     | 218 (72%)               | 144 (47%) | 298 (73%)              | 2 (2%) |

Source: reviewer table; RZB = risankizumab, ADA = adalimumab, PBO = placebo. Analysis based on Cochran-Mantel-Haenszel (CMH) test stratified by weight (≤ 100 kg vs. >100 kg) and prior exposure to TNF antagonists (0 vs. ≥1).

#### 7.2.2.5 Results for the Secondary Efficacy Endpoints

Table 22 presents the results for the ranked secondary efficacy endpoints for Trials 1311.30, and risankizumab was statistically superior to adalimumab in the overall population for all the secondary efficacy endpoints. The analysis for the third secondary

endpoint of the proportion of subjects achieving PASI 100 was done for the subjects who received adalimumab in the initial treatment period with at least PASI 50 but < PASI 90 at Week 16 (i.e., “inadequate responders”). A total of 109 subjects with “inadequate response” were re-randomized at Week 16, subjects either switched over to risankizumab or stayed on adalimumab. For the PASI 100 at Week 44, risankizumab was statistically superior to those that continued to receive adalimumab for the PASI 100 at Week 44.

**Table 22. Results of the Ranked Secondary efficacy endpoints for Trial 1311.30; Non-responder imputation, ITT)**

|                                                                               | <b>Trial 1311.30<br/>(M16-010)</b> |                        |                |
|-------------------------------------------------------------------------------|------------------------------------|------------------------|----------------|
|                                                                               | <b>RZB<br/>(N=301)</b>             | <b>ADA<br/>(N=304)</b> | <b>p-value</b> |
| <b>Week 16</b>                                                                |                                    |                        |                |
| <b>PASI 75</b>                                                                | 274 (91%)                          | 218 (72%)              | <0.001         |
| <b>PASI 100</b>                                                               | 120 (40%)                          | 70 (23%)               | <0.001         |
| <b>Week 44 (PASI 50 to &lt;PASI 90 ADA subjects re-randomized at Week 16)</b> |                                    |                        |                |
|                                                                               | <b>ADA/RZB</b>                     | <b>ADA/ADA</b>         |                |
| <b>Re-randomized</b>                                                          | 53                                 | 56                     |                |
| <b>PASI 100</b>                                                               | 21 (40%)                           | 4 (7%)                 | <0.001         |

Source: reviewer table; RZB = risankizumab, ADA = adalimumab. Analysis based on Cochran-Mantel-Haenszel (CMH) test stratified by weight ( $\leq 100$  kg vs.  $>100$  kg) and prior exposure to TNF antagonists (0 vs.  $\geq 1$ ).

Table 23 presents the results for the ranked secondary efficacy endpoints for Trial 1311.4, and risankizumab was statistically superior to placebo in the overall population for all the secondary efficacy endpoints. There was a protocol-specified endpoint of sPGA 0 or 1 at Week 52 among those subjects that were sPGA responders (i.e., sPGA 0 or 1 response at Week 28) that were re-randomized in a 1:2 ratio to risankizumab or placebo. The proportion of subjects with sPGA 0 or 1 at Week 52 were 87% and 61% for the subjects that received risankizumab or placebo, respectively. The sponsor’s protocol called for testing this endpoint independently with a Type I error rate of 0.05, and the Agency commented (Sponsor Teleconference, April 5, 2017) that “having established efficacy at Week 16 based on formal statistical testing, further formal testing against the placebo for subjects who achieved success might not be meaningful as the goal for the maintenance period is to get estimate for subjects who maintained their response, and not to make formal testing against placebo as efficacy is already established against placebo for subjects with the disease at baseline”. The Agency stated that “we anticipate inclusion in labeling of descriptive study results related to withdrawal/retreatment”.

**Table 23. Results of the Ranked Secondary efficacy endpoints for Trial 1311.4; Non-responder imputation, ITT)**

|                                                 | <b>Trial 1311.4<br/>(M15-992)</b> |                            |                |
|-------------------------------------------------|-----------------------------------|----------------------------|----------------|
|                                                 | <b>RZB<br/>(N=407)</b>            | <b>PBO<br/>(N=100)</b>     | <b>p-value</b> |
| <b>Week 16</b>                                  |                                   |                            |                |
| <b>PASI 75</b>                                  | 361 (89%)                         | 8 (8%)                     | <0.001         |
| <b>PASI 100</b>                                 | 192 (47%)                         | 1 (1%)                     | <0.001         |
| <b>sPGA 0</b>                                   | 189 (46%)                         | 1 (1%)                     | <0.001         |
| <b>DLQI 0/1</b>                                 | 266 (65%)                         | 3 (3%)                     | <0.001         |
| <b>sPGA responders re-randomized at Week 28</b> |                                   |                            |                |
|                                                 | <b>RZB/RZB<br/>(N=111)</b>        | <b>RZB/PBO<br/>(N=225)</b> | <b>p-value</b> |
| <b>sPGA 0 or 1 at Week 52</b>                   | 97 (87%)                          | 138 (61%)                  | <0.001         |

Source: reviewer table; RZB = risankizumab, PBO = placebo. Analysis based on Cochran-Mantel-Haenszel (CMH) test stratified by weight ( $\leq 100$  kg vs.  $>100$  kg) and prior exposure to TNF antagonists (0 vs.  $\geq 1$ ).

### 7.2.2.6 Patient Reported Outcomes (PROs)

The protocol for Trial 1311.4 specified one secondary efficacy endpoint based on patient reported outcomes (PROs), the Dermatology Life Quality Index (DLQI). Table 23 includes the results for the DLQI endpoint, and shows that risankizumab was statistically superior to placebo ( $p$ -values $<0.001$ ) for this endpoint. Refer to Section 7.2.1.6 related to the utility for labeling of the DLQI endpoint.

*CDTL Comment:*

See discussion under 7.2.1.6 for discussion related to the utility for labeling for the DLQI.

### 7.2.2.7 Efficacy Over Time

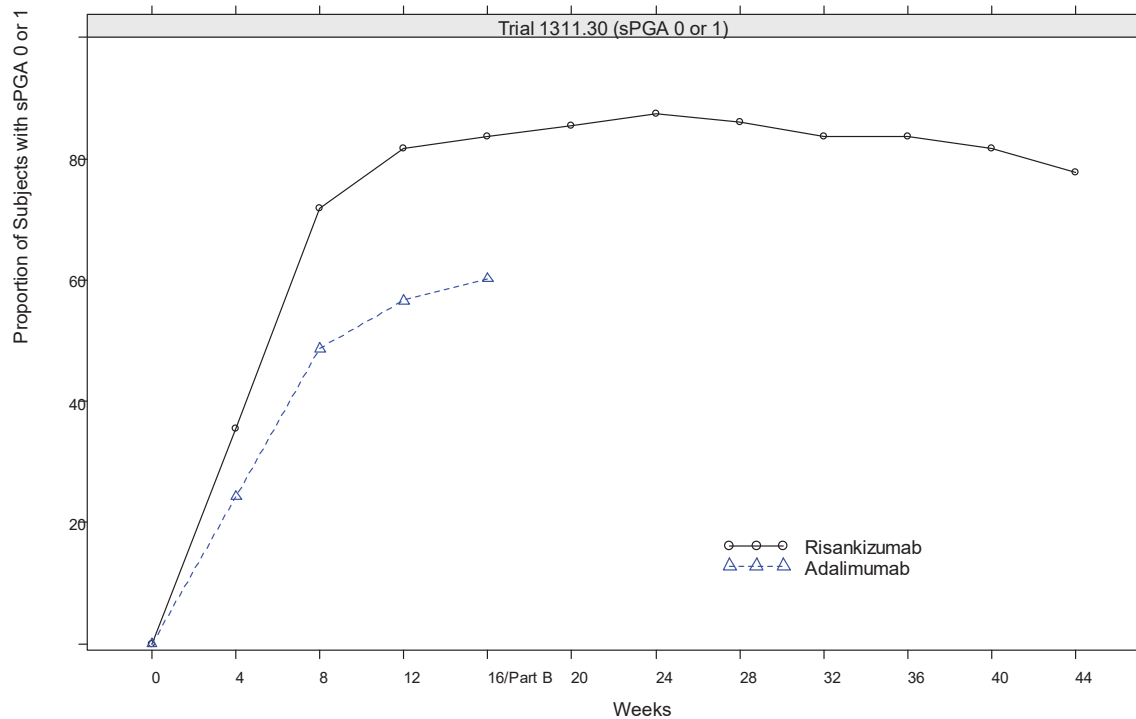
Figure 10 presents the results for sPGA 0 or 1 and PASI 90 through Week 44 for Trial 1311.30. For Trial 1311.30, subjects that receive risankizumab in the initial treatment period continued to receive risankizumab through Week 44 (294 subjects). Then subjects that received adalimumab were re-randomized depending on their PASI score at Week 16:

- subjects with  $<$  PASI 50 at Week 16 switched to risankizumab (38 subjects)
- subjects with  $\geq$  PASI 90 at Week 16 stayed on adalimumab (144 subjects)
- subjects with  $\geq$  PASI 50 and  $<$  PASI 90 at Week 16 were re-randomized 1:1 to receive either risankizumab (53 subjects) or adalimumab (56 subjects).

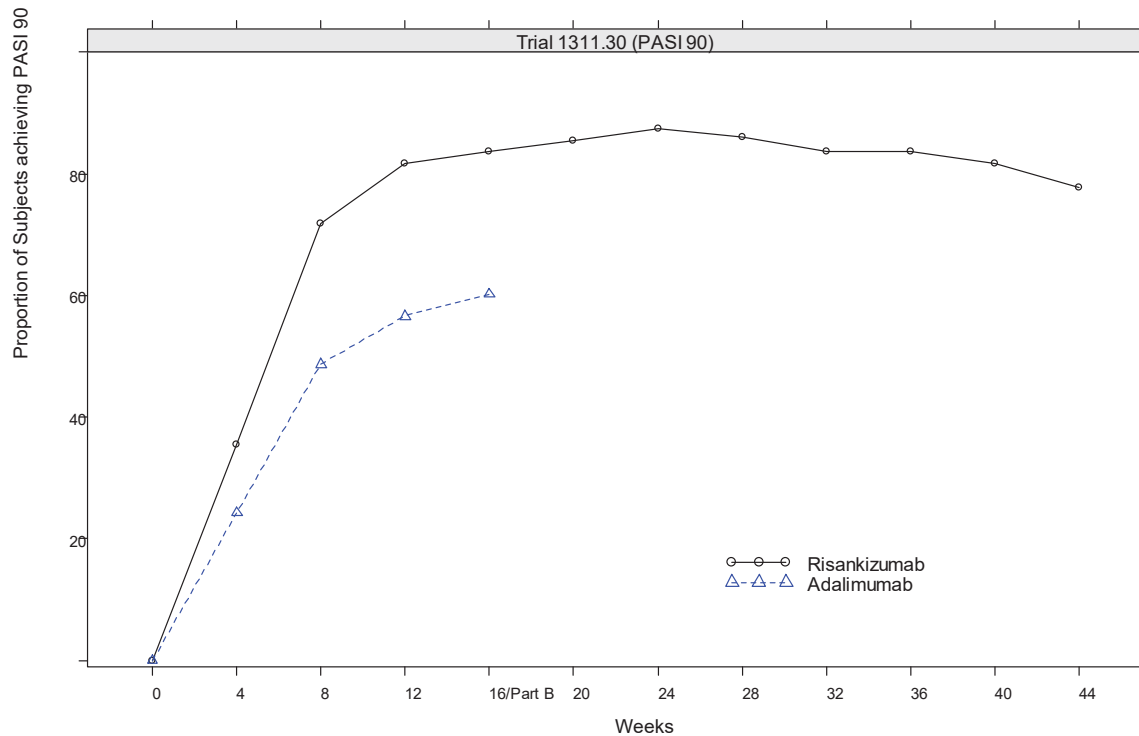
NDA/BLA Multi-disciplinary Review and Evaluation – BLA 761105  
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Due to the re-randomization based on PASI score for those that received adalimumab in the initial treatment period, the sPGA 0 or 1 results are plotted only up to Week 16 for those that that received adalimumab in the initial treatment period.

**Figure 10 Results for sPGA score of 0 or 1 and PASI 90 through Week 44 for Trial 1311.30**



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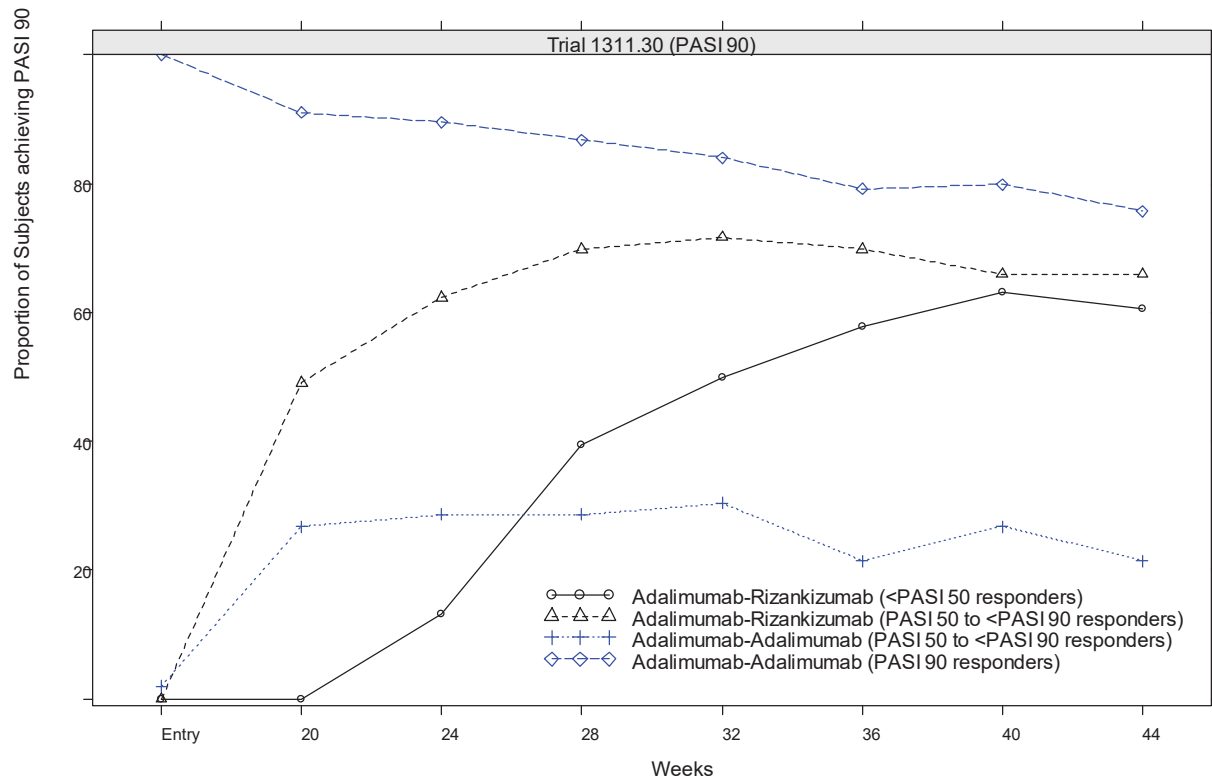
Source: reviewer figures; Intent-to-Treat (ITT) analysis set; Missing data was imputed using non-responder imputation (NRI). Subjects that received risankizumab in the initial treatment period (Week 0 to 16) continued to receive risankizumab through Week 44.

Figure 11 presents the results for PASI 90 from re-randomization at Week 16 through Week 44 for Trial 1311.30. The figure includes results from the following treatment groups:

- Subjects that received adalimumab in the initial treatment period and were PASI 90 responders continued to receive adalimumab
- Subjects that were <PASI 50 at Week 16 received risankizumab.
- Subjects that received adalimumab in the initial treatment period that were >PASI 50 but <PASI 90 were re-randomized in a 1:1 ratio to either risankizumab or adalimumab.

**Figure 11. Results for PASI 90 from Re-randomization (Week 16) to Week 44 for Trial 1311.30**

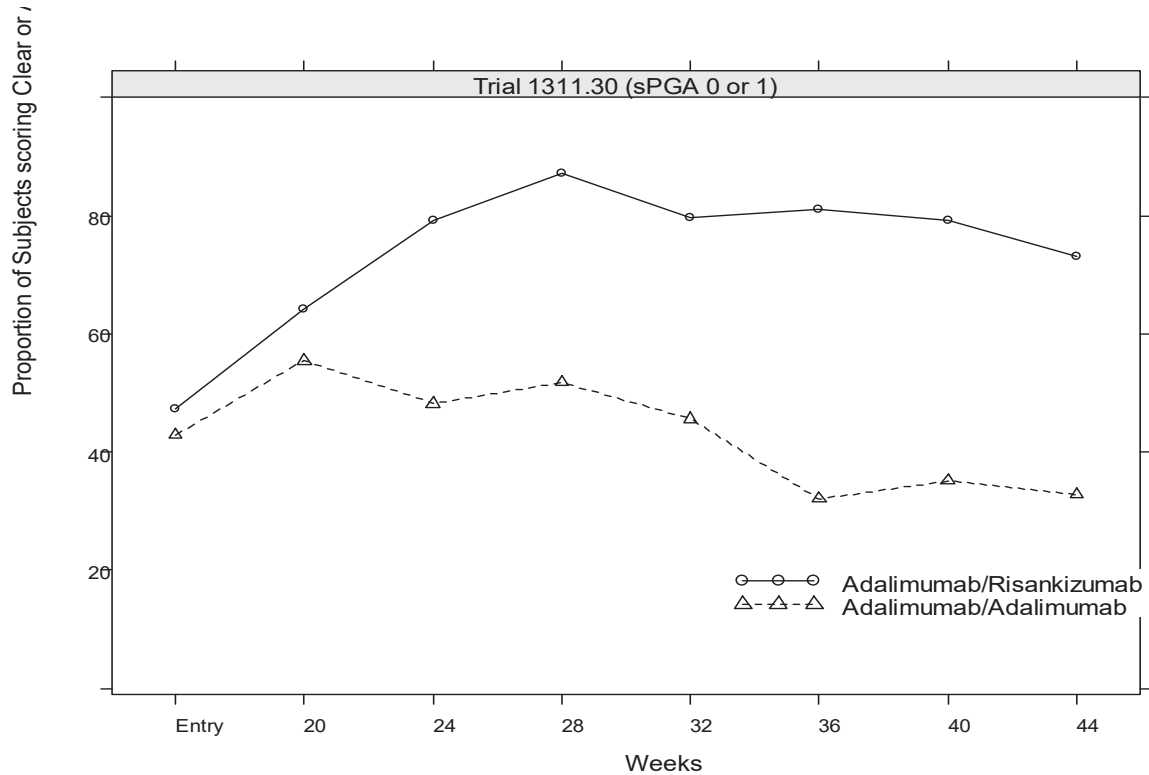
NDA/BLA Multi-disciplinary Review and Evaluation – BLA 761105  
(Skyrizi, Risankizumab)



Source: reviewer figures; Intent-to-Treat (ITT) analysis set; Missing data was imputed using non-responder imputation (NRI).

Note that while the Agency commented that re-randomization be considered based on the sPGA score as well, the protocol-specified criterion for re-randomization criterion was for adalimumab subjects who were at least PASI 50 but did not achieve PASI 90. As the Agency considers sPGA to be the main primary endpoint, presents the results for sPGA 0 or 1 through Week 44 for Trial 1311.30 for the subjects that were re-randomized for descriptive purposes.

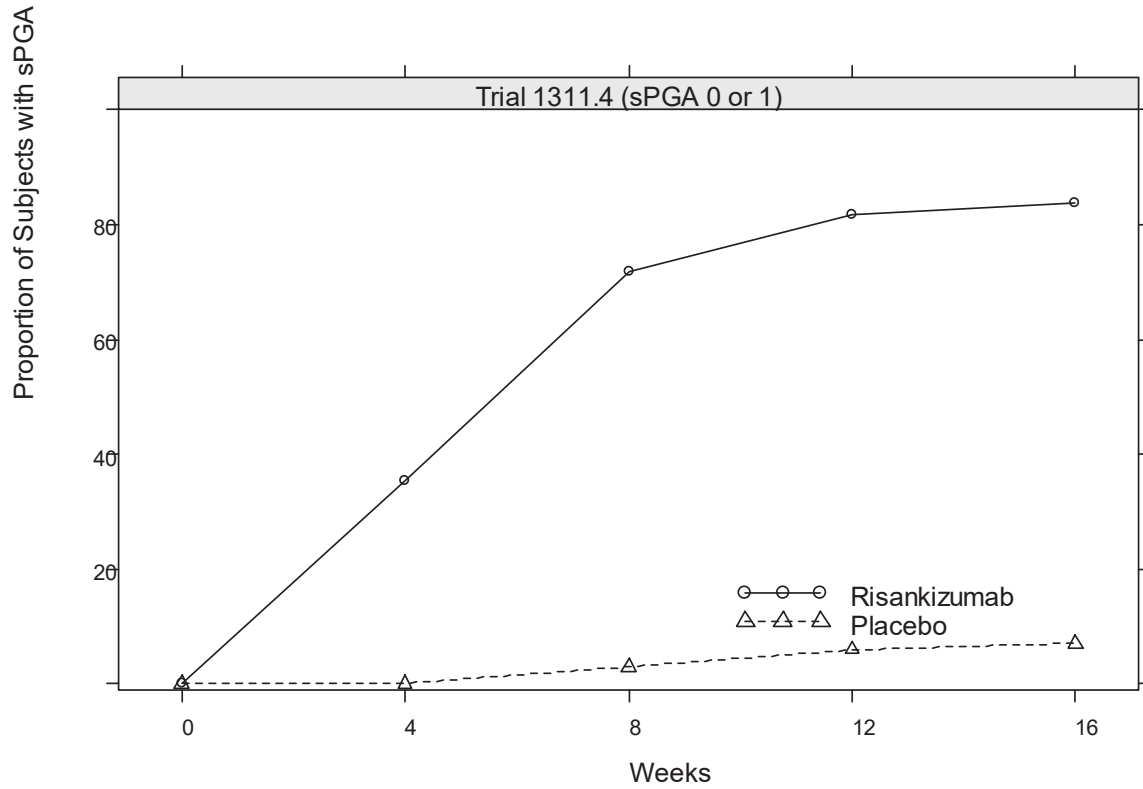
**Figure 12. Results for sPGA score of 0 or 1 from Re-randomization (Week 16) to Week 44 for Trial 1311.30**



Source: reviewer figure. Figure legend shows treatment assignment for Weeks 0-16 as well as Weeks 16-44.

Figure 13 presents the results for sPGA 0 or 1 and PASI 90 through Week 16 for Trial 1311.4. The study design and analysis of the initial 16-week treatment period is identical to that of the pivotal trials (1311.28, 1311.3).

**Figure 13. Results for sPGA score of 0 or 1 and PASI 90 Through Week 16 for Trial 1311.4**



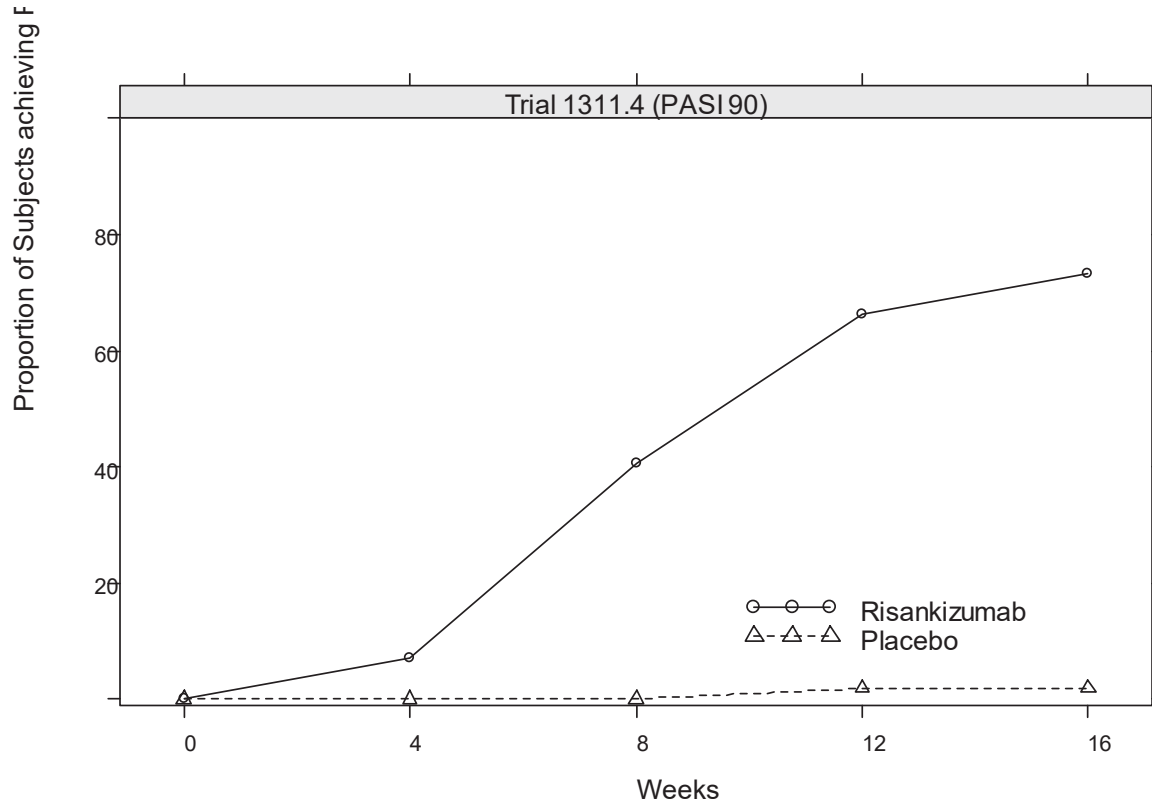
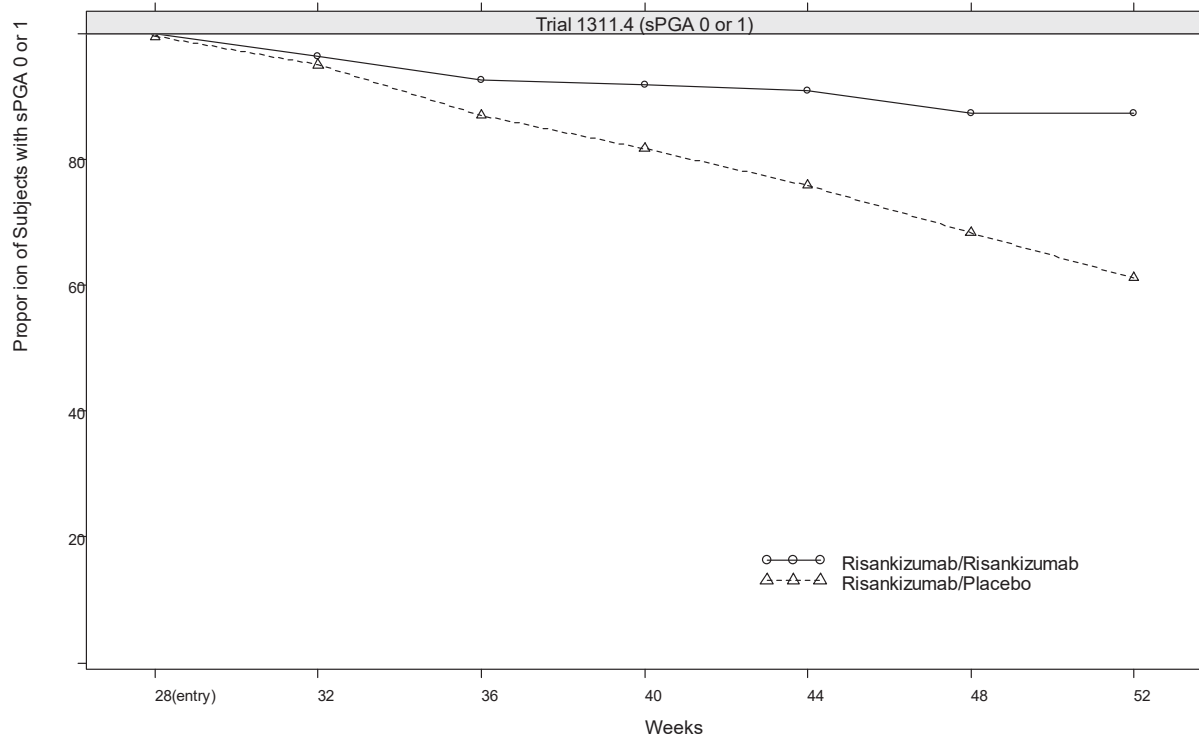


Figure 14 presents the sPGA 0 or 1 results for those sPGA 0 or 1 subjects that were re-randomized at Week 28 in Trial 1311.4. The randomized withdrawal results of sPGA 0 or 1 through Week 52 are plotted.

**Figure 14 Results for sPGA score of 0 or 1 for Subjects that were Re-randomized at Week 28 Through Week 52 for Trial 1311.4**

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Source: reviewer figures; Intent-to-Treat (ITT) analysis set; Missing data was imputed using non-responder imputation (NRI).

### 7.3. Review of Safety

#### 7.3.1. Safety Review Approach

The primary review of safety of risankizumab for the treatment of moderate to severe plaque psoriasis focused on the evaluation of pooled data from Phase 2 Trial 1311.2 and Phase 3 Trials M15-995 (1311.28), M16-008 (1311.3), M16-010 (1311.30) and M15-992 (1311.4).

The Phase 2 Trial 1311.2 was a multicenter, randomized, dose-ranging, active-control, double-blind (within dose groups of risankizumab) evaluation of risankizumab 90 mg or 180 mg subcutaneous (SC) at Weeks 0, 4, and q12w thereafter or 18 mg at Week 0 in adults with stable moderate to severe chronic plaque psoriasis psoriasis  $\geq$  6 months (with or without psoriatic arthritis); body surface area (BSA) involvement  $\geq$  10%; Psoriasis Area and Severity Index (PASI) score  $\geq$  12; Static Physician Global Assessment (sPGA)  $\geq$  3; and candidates for systemic therapy or phototherapy.

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The 4 pivotal studies were multicenter, randomized, double-blind, placebo and/or active comparator-controlled evaluations of the proposed dose and dosing regimen (risankizumab 150 mg subcutaneous (SC) at Weeks 0, 4, and q12w thereafter) in adults with stable moderate to severe chronic plaque psoriasis  $\geq$  6 months (with or without psoriatic arthritis); body surface area (BSA) involvement  $\geq$  10%; Psoriasis Area and Severity Index (PASI) score  $\geq$  12; Static Physician Global Assessment (sPGA)  $\geq$  3; and candidates for systemic therapy or phototherapy. These studies include:

Study M15-995 (1311.28) (UltIMMa-2): Multicenter, randomized, double-blind, placebo- and active-controlled studies that compared the efficacy and safety of risankizumab treatment with placebo and ustekinumab treatment

Study M16-008 (1311.3) (UltIMMa-1): Multicenter, randomized, double-blind, placebo- and active-controlled studies that compared the efficacy and safety of risankizumab treatment with placebo and ustekinumab treatment

Study M15-992 (1311.4) (IMMhance): A multicenter, randomized, doubleblind study that compared the efficacy and safety of risankizumab treatment with placebo, evaluated the effects of continuous risankizumab compared with withdrawal in risankizumab responders, and evaluated re-treatment of subjects who experienced relapse

Study M16-010 (1311.30) (IMMvent): A multicenter, randomized, doubleblind study that compared the efficacy and safety of risankizumab with adalimumab and evaluated switching from adalimumab to risankizumab for adalimumab non-responders and those with inadequate response to adalimumab

The Long-Term Safety Extension Additional trials to inform safety include the following:

- A long-term, open-label extension (OLE) study (Study M15-997) that is planned for 154 weeks and is currently ongoing. Subjects from lead-in Phase 3 studies are dosed subcutaneously at 150 mg of risankizumab every 12 weeks.
- A long-term OLE (Study 1311.13) that is planned for 4 years and is currently ongoing. Subjects from the lead-in Phase 2 study are dosed subcutaneously at 90 mg or 180 mg of risankizumab every 12 weeks.

To assess the safety of risankizumab across clinical studies, subject data were integrated into three integrated analysis sets:

- Primary Safety Pool provides data regarding the short-term (16 week) safety
- Ustekinumab (EU sourced) Controlled provides data regarding the long-term (52 week) safety
- All Risankizumab-Psoriasis provides additional open-label long-term safety

**Table 24: Integrated Safety Analysis Sets**

| Analysis Sets                              | Studies Included                                                                                                                                                                                                        | Study Population and Treatment Period                                                                                                   | Treatment Groups                                                                                                                       | Rationale                                                                                                  |
|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| Primary Safety Pool<br>(N = 2232)          | <a href="#">1311.2</a><br><a href="#">M16-008</a> (1311.3)<br><a href="#">M15-992</a> (1311.4)<br><a href="#">M15-995</a> (1311.28)<br><a href="#">M16-010</a> (1311.30)                                                | Subjects randomized to multiple dose treatment – risankizumab 150 mg in Phase 3/risankizumab 90 mg or 180 mg in Phase 2 through Week 16 | RZB 150 – 180 mg<br>(N = 1348)<br>RZB 150 mg<br>(N = 1306)<br>RZB 90 mg<br>(N = 41)<br>UST (N = 239)<br>ADA (N = 304)<br>PBO (N = 300) | Safety of subjects with psoriasis during the 16-week double-blind phase of the Phase 2 and Phase 3 studies |
| Ustekinumab-Controlled<br>(N = 797)        | M16-008 (1311.3)<br>M15-995 (1311.28)                                                                                                                                                                                   | Subjects randomized to risankizumab 150 mg or ustekinumab followed through the end of exposure during the study                         | RZB 150 mg<br>(N = 598)<br>UST (N = 199)                                                                                               | Safety of risankizumab compared with ustekinumab at 52 weeks in subjects with psoriasis                    |
| All Risankizumab – Psoriasis<br>(N = 2234) | <a href="#">1311.1</a><br><a href="#">1311.2</a><br>M16-008 (1311.3)<br>M15-992 (1311.4)<br>M15-995 (1311.28)<br>M16-010 (1311.30)<br><a href="#">M15-997</a><br>M16-009 (1311.13)<br><a href="#">M16-007</a> (1311.36) | Subjects that received a dose of risankizumab followed through to the end of exposure                                                   | All RZB <sup>a</sup><br>(N = 2234)<br>RZB 150 mg <sup>b</sup><br>(N = 1590)                                                            | Long-term safety of risankizumab treatment in subjects with psoriasis                                      |

ADA = adalimumab; PBO = placebo; RZB = risankizumab; UST = ustekinumab

- In this analysis set, "All RZB" includes all subjects who received RZB, regardless of dose or timing. Note that "RZB 150 mg" is a subset of this grouping.
- In this analysis set, "RZB 150 mg" includes subjects that either (1) randomized to RZB 150 mg in Part A/A1 (Period 1) and continued on 150 mg RZB or (2) Randomized to PBO and subsequently received 150 mg RZB.

Source: Applicant's CSR Table 1

The applicant provided 6 additional analysis sets including a Placebo-Controlled Analysis Set which were supportive of the main sets. The data cutoff date for the integrated analyses is 01 September 2017 for all safety analysis sets.

The applicant did not establish an adequate scientific bridge between U.S. licensed Stelara and EU approved ustekinumab (b) (4)

Discussion regarding the comparative efficacy and safety of the proposed product with the ustekinumab is minimized in this review.

The review team analyzed the following types of pooled data: exposure, demographics and baseline characteristics, prior therapies for psoriasis, treatment emergent adverse events (TEAEs), serious AEs (SAEs), and AEs leading to discontinuation. The applicant identified some adverse events of special interest which included severe infections, malignancies, non-melanoma skin cancer, melanoma skin cancer, adjudicated cardiovascular (CV) events (including major adverse cardiovascular events [MACE]), hepatic events, suicide ideation and behavior, injection site reactions and drug related hypersensitivity reactions. Also, the review team evaluated the impact of anti-drug antibodies on the adverse event profile. Refer to Section 6.1 and the Clinical Pharmacology Appendix.

### **7.3.2. Review of the Safety Database**

#### **Overall Exposure**

In the Phase 2 and Phase 3 risankizumab clinical studies in subjects with plaque psoriasis, 2,234 subjects (2,166.6 patient-years [PY]) were exposed to at least 1 dose of risankizumab (18, 90, 150, or 180 mg), with 1,208 (54.1%) subjects exposed to risankizumab for  $\geq 1$  year, 96 (4.3%) subjects exposed  $\geq 2$  years, and 30 (1.3%) subjects exposed  $\geq 3$  years. Of the total 2,234 subjects, 1,590 subjects received  $\geq 1$  dose of risankizumab 150 mg with a total of 1,688.0 PY of exposure. A total of 1,091 subjects received at least 1 dose of risankizumab 150 mg for  $\geq 1$  year. Ninety-six subjects had  $\geq 2$  years of risankizumab exposure at any dosage level. Thirty subjects had  $\geq 3$  years of risankizumab exposure at any dosage level.

The size of the overall safety database was considered adequate and consistent with ICH E1.

#### **Relevant characteristics of the safety population:**

Demographic characteristics of the subject population in the risankizumab development program are presented in greater detail in Section 7.2.1.3 of this review. The risankizumab psoriasis clinical study population was predominantly male, white, and tumor necrosis factor (TNF) naïve; the average subject was mid-forties in age and weighed approximately 90 kg. Across analysis sets, approximately 10% of subjects were between 65 and 74 years of age and approximately 1% were 75 years of age or older.

The population appears to be representative of the US target population based on age and race. Prevalence of psoriasis is considered to be balanced between the sexes. However, several studies have indicated sex differences in the severity of disease, with women having less severe psoriasis.

Demographic information that was collected was generally balanced across the treatment arms, including history of psoriatic arthritis and cardiovascular disease,

cardiovascular risk factors and prior therapy.

### **Adequacy of the safety database:**

The total exposure to risankizumab, 150 mg SC at Week 0 and 4, then every 12 weeks thereafter for 52 weeks, provides adequate data for the evaluation of safety. The demographics of the study population are sufficiently representative of the target population. Therefore, the safety database presented by the applicant is sufficient to characterize the safety profile of risankizumab for the treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic therapy.

### **7.3.3. Adequacy of Applicant's Clinical Safety Assessments**

#### **Issues Regarding Data Integrity and Submission Quality**

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of risankizumab. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the applicant.

#### **Categorization of Adverse Events**

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20. Each AE was coded to a system organ class (SOC) and preferred term (PT). The coding of adverse events in the BLA submission appeared adequate and allowed for accurate estimation of AE risks.

Treatment-emergent AEs (TEAEs) were defined by the applicant as events with onset after the first dose of study drug and no more than 105 days (i.e., 5 times the half-life of risankizumab) after the last dose of study drug. If an incomplete onset date was collected for an AE, the AE was assumed to be treatment-emergent unless there was evidence that confirmed that the AE was not treatment-emergent (e.g., the AE end date was prior to the date of the first dose of study drug). Exposure-adjusted TEAE rates were calculated as events/100 PY. For this calculation, 1 year was considered to be 365.25 days.

The definition of AE, TEAE, and SAE are acceptable. The classification system used by investigators to describe the severity of AE as well as the causal relationship between AE and study product are also acceptable. The applicant's identification and presentation of AE of special interest was appropriate.

#### **Routine Clinical Tests**

Safety analyses included reporting of AEs, laboratory (screening for tuberculosis, screening for pregnancy, hematology, clinical chemistry, and urinalysis), physical examination (including vital signs and 12-lead electrocardiogram), and local tolerability. The severity of the laboratory test values was assessed using CTCAE version 4.0. The applicant conducted evaluations of mean changes over time and individual subject

changes in hematology and clinical chemistry values, as well as potentially clinically significant abnormalities in hematology and clinical chemistry.

Safety monitoring and the applicant's evaluation of routine clinical tests are appropriate.

#### 7.3.4. Safety Results

##### Deaths

In the overall development plan, deaths occurred in 5 subjects treated with risankizumab and 2 subjects treated with adalimumab. There were no deaths in the clinical studies conducted in other (non-psoriasis) indications. Of the 5 deaths in risankizumab-treated subjects, 4 occurred within 105 days after the last dose of risankizumab. Of the 5 deaths, 2 were adjudicated as cardiac deaths (acute myocardial infarction and sudden cardiac death), 2 were due to unknown cause, and 1 was a cancer death. Of the 2 deaths in adalimumab-treated subjects 1 was cancer (gallbladder) and 1 was sepsis (post-operative). Summaries of deaths in risankizumab-treated subjects are as follows:

1. Subject (b) (6) in Trial M16-010 is a 47-year-old, white male with a history of pre-existing MI, PCI with stent placement (approximately a year prior), obesity, diabetes type II, hypertension, chronic heart failure (NYHA II), dyslipidemia, cardiac hypertrophy, atrial fibrillation, treated with risankizumab 150 mg for psoriasis/ psoriatic arthritis. On Day 73 (9 days after last dose) the subject died at home due to an acute myocardial infarction. Autopsy confirmed that the cause of death was acute myocardial infarction.

The subject had multiple risk factors for AMI which are likely to be contributory to the cause of death.. The contribution of study drug cannot be determined.

2. Subject (b) (6) in Trial M15-995 is a 57-year-old, white male with a history of angina pectoris, diabetes mellitus, hyperlipidemia, hypertension, obesity, coronary artery disease, COPD, left bundle branch block, sleep apnea, and hypertension treated with risankizumab 150 mg for chronic plaque psoriasis. On Day 189 (161 days after last dose) the subject died of an unknown cause. No details were provided regarding his death. The subject experienced significant cardiovascular AEs earlier in the course of treatment. On Day 46, the subject experienced angina and was hospitalized for worsening of coronary artery disease (CAD) and moderate congestive heart failure. A cardiac catheterization revealed small vessel disease and percutaneous transluminal coronary angioplasty was performed, resolving the subject's chest pain.

The subject had multiple risk factors for sudden death which are likely to be contributory to the cause of death. The contribution of study drug cannot be determined.

3. Subject (b) (6) in Trial M15-995 is a 32-year-old, white male with a history of depression, fibromyalgia, chronic pain, tobacco use (3 packs per day), alcohol use, hypertension and obesity treated with risankizumab 150 mg for psoriasis/ psoriatic arthritis. Concomitant medications include oxycodone, amitriptyline, cyclobenzaprine HCl, and lorazepam. On Day 385 (101 days after last dose) the subject experienced a seizure, became unresponsive and pulseless, and was unable to be resuscitated. It was later determined that cause of death was due to a drug overdose (cocaine and oxycodone).

It is not reported if the overdose was intentional or unintentional. The subject had multiple risk factors that could increase his chances for potential drug abuse. The contribution of study drug cannot be determined.

4. Subject (b) (6) in Trial M15-992 is a 60-year-old, white male with a history of hypertension, morbid obesity, diabetes, sleep apnea and hypercholesterolemia and possible MI treated with risankizumab 150 mg for chronic plaque psoriasis. On Day 263 (66 days after last dose) the subject died of an unknown cause. No details were provided regarding his death. The subject experienced significant cardiovascular AEs earlier in the course of treatment. On Day 147 the subject experienced a non-ST segment elevation and was hospitalized with congestive heart failure MI. Cardiac catheterization revealed triple vessel disease and a coronary arterial stent was inserted. On Day 166 the subject experienced unstable angina which was treated medically. Study drug was continued until Day 197.

The subject had multiple risk factors for sudden death which are more likely to be contributory to the cause of death than the study drug.

5. Subject (b) (6) in Trial M15-992 is a 70-year-old, white male with a history of obesity, diabetes, atrial fibrillation, cardiomyopathy, left bundle branch block, hypothyroidism and mitral valve regurgitation treated with risankizumab 150 mg for psoriasis/ psoriatic arthritis. On Day 317 (Post-Treatment Day 33), the subject was hospitalized with abdominal pain, melanic stool, hematuria and dehydration. The subject was diagnosed with multiple hepatic lesions, pulmonary nodules, ascites and plural effusion. Biopsy determined adenocarcinoma and the subject was discharged on palliative care. On Day 224 (55 days after last dose) the subject died of metastatic intestinal adenocarcinoma.

The subject was on study drug for 10 months prior to diagnosis of metastatic intestinal adenocarcinoma. The contribution of study drug cannot be determined.

With the 120 Day safety update, 5 new deaths were reported, all of which occurred in psoriasis studies in subjects treated with risankizumab. Summaries of deaths are as follows:

1. Subject (b) (6) in Trial M15-992 is a 37-year-old, white male with a history of asthma and epilepsy treated with risankizumab 150 mg for chronic plaque psoriasis. On Day 496 (45 days after last dose) the subject experienced an epileptic seizure and died despite attempts of cardiopulmonary resuscitation. Autopsy reported a sudden grand mal seizure as the cause of death. Toxicology of the coronal matter showed tetrahydrocannabinol. Toxicology screening analysis also detected cannabinoids, caffeine, and nicotine.

The subject had an underlying disease that was likely the major contributing factor leading to his death.

2. Subject (b) (6) in Trial M15-992 is a 74-year-old, white male with a history of hypertension, hyperlipidemia, atrial fibrillation, chronic kidney disease, and coronary artery disease status post grafting treated with risankizumab 150 mg for psoriasis/ psoriatic arthritis. On Day 583 (127 days after last dose) the subject died of an unknown cause. No details were provided regarding his death. The subject experienced a significant cardiovascular AE earlier in the course of treatment. On Day 491 (45 days after last treatment) the subject experienced an acute left hemispheric ischemic stroke after laparoscopic cholecystectomy for chronic cholecystitis and cholelithiasis. Carotid Doppler showed complete left internal carotid artery occlusion and right internal carotid artery with more than 50% occlusion. The subject was eventually transferred to a nursing facility for rehabilitation.

The subject had multiple risk factors for sudden death which are more likely to be contributory to the cause of death than the study drug.

3. Subject (b) (6) in Trial M15-997 is a 57-year-old, white male with a history of hypertension, obesity, tobacco use (0.1 pack per day) and alcohol use (2-4 drinks per day) treated with risankizumab 150 mg for chronic plaque psoriasis. On Day 98 the subject sought medical attention for abdominal pain and vomiting. On Day 99, ultrasound of the upper abdomen revealed acute cholecystolithiasis with small pericholecystic collection at the fundus level (rule out probable rupture) and scarce free liquid in Morrison pouch. Evaluation by general surgery was recommended. The subject died in his home on Day 99. The main cause of death on the death certificate was stated as pancreatitis. An autopsy was not performed.

The acute medical issue was likely to be contributory to the cause of death. The contribution of study drug cannot be determined.

4. Subject [REDACTED]<sup>(b) (6)</sup> in Trial M15-997 is a 41-year-old, white male with a history of asthma, hypertension, obesity, diabetes, and tobacco use (1 pack per day) treated with risankizumab 150 mg for chronic plaque psoriasis. The subject had been randomized to adalimumab in prior feeder study. On Day 207 (40 days after last dose) the subject was found unresponsive after complaining of shoulder pain. Cardiopulmonary resuscitation was started, and emergency medical services were called. Resuscitation was unsuccessful and death was pronounced at the hospital.

The subject had multiple risk factors for sudden cardiac death which are likely contributory to the cause of death. The contribution of study drug cannot be determined.

5. Subject [REDACTED]<sup>(b) (6)</sup> in Trial M15-997 is a 64-year-old, white male with a history of asthma, congestive heart failure (CHF), hypertension, coronary artery disease, atrial fibrillation, and former tobacco use (stopped in 2017, 30 pack year) treated with risankizumab 150 mg for chronic plaque psoriasis. On Day 663 (88 days after last dose) the subject died of an unknown cause. No details were provided regarding his death. The subject experienced significant AEs earlier in the course of treatment. On Day 575, alanine aminotransferase and bilirubin elevations reached criteria for Hy's Law. On Day 608 the subject experienced a worsening of CHF and was hospitalized.

The Investigator considered the event of worsening congestive heart failure as having a reasonable possibility of being related to study drug. The contribution of study drug cannot be determined.

### **Serious Adverse Events**

The majority of Serious adverse events (SAEs) observed were consistent with those anticipated for a population of patients with moderate to severe psoriasis treated with an immunosuppressant biologic. Overall, infections and cardiac disorders were the most common SAEs reported. These AEs along with other AEs of interest are discussed further in the sections below.

Over the initial 16 weeks, 31 (2.4%) subjects in the risankizumab group had SAEs compared to 12 (4.0%) subjects in the placebo group, 12 (5.0%) subjects in the ustekinumab group and 9 (3.0%) subjects in the adalimumab group. Serious AEs reported in more than 1 risankizumab-treated subject were cellulitis and squamous cell carcinoma of skin (2 subjects each).

SAEs in the risankizumab group leading to discontinuation of study drug were congestive cardiac failure, drug-induced liver injury, liver injury, invasive lobular breast carcinoma, and esophageal carcinoma. The SAEs assessed by the investigators as

possibly related to study drug were drug-induced liver injury, liver injury, cellulitis, herpes zoster, osteomyelitis, and asthma.

After 52 weeks of exposure, 42 (7.0%) subjects in the risankizumab group had SAEs compared to 18 (9.0%) subjects in the ustekinumab group. SAEs reported by more than 1 risankizumab-treated subject were coronary artery disease/ angina and cardiac failure congestive/ left ventricular failure (3 subjects each; 0.5%), and cellulitis, pneumonia, sepsis, basal cell carcinoma, enteritis/gastroenteritis and abortion spontaneous (2 subjects each; 0.3%). In this analysis set, 8 (1.3%) subjects in the risankizumab group had SAEs in the cardiac disorder SOC compared to 1 (0.5%) subject in the ustekinumab group.

Overall, in the All Risankizumab – Psoriasis Analysis Set, 139 (6.2%) (9.8 E/100 PY) subjects had at least 1 SAE. The most frequently reported SAEs ( $\geq 3$  risankizumab subjects) were basal cell carcinoma, sepsis, cellulitis, pneumonia, coronary artery disease, transient ischemic attack, squamous cell carcinoma of skin, cardiac failure congestive, and myocardial infarction. Infections and infestations was the SOC with the highest number of subjects with SAEs.

In the safety update, 8.3% (9.3 E/100 PY) of subjects had at least 1 SAE. New SAEs reported by  $\geq 3$  subjects in this SUR (cumulative of initial submission and SUR) were acute myocardial infarction (MI), breast cancer, cholecystitis acute, cholelithiasis, depression, erysipelas, fall, ischaemic stroke, osteoarthritis, prostate cancer, and syncope. Infections and infestations continued to be the system order class (SOC) with the highest number of subjects with SAEs.

### **Dropouts and/or Discontinuations Due to Adverse Effects**

In the Primary Safety Pool, at 16 weeks, the proportion of subjects in the risankizumab 150 mg treatment group (0.7%; 9 subjects) who experienced TEAEs leading to discontinuation of study drug was higher than discontinuations in the placebo group (3.0%; 9 subjects). No TEAEs leading to discontinuation of study drug were reported in more than 1 risankizumab-treated subject. In risankizumab-treated subjects, the AEs leading to discontinuation of study drug that were also SAEs were cardiac failure congestive, drug-induced liver injury, liver injury, invasive lobular breast carcinoma, and esophageal carcinoma. These AEs are discussed further in section 7.3.5 Analysis of Submission-Specific Safety Issues.

At 52 weeks, the AEs leading to the discontinuation of risankizumab treatment in 5 subjects (0.8%) included cardiac failure congestive, edema peripheral, drug-induced liver injury, pneumonia, and vasculitis.

In the All Risankizumab – Psoriasis Analysis Set, 35 subjects (1.6%) discontinued due to an adverse event. The Infections and infestations, Investigations (the most frequent

AE was abnormal liver function tests), and Neoplasms benign, malignant and unspecified (the most frequent AE was breast cancer) SOCs had the most subjects with AEs leading to discontinuation of study drug with 7 (0.3%) subjects in each. The AEs leading to discontinuation of study drug in more than 1 subject were pneumonia, ALT increased, and psoriasis (2 subjects each).

Few subjects discontinued by either the 16-week (9 [0.7%] subjects) or 52-week timepoint (5 [0.8%] subjects). Malignancy, infections, hepatic and cardiac events are discussed further in section 7.3.5 Analysis of Submission-Specific Safety Issues.

### **Significant Adverse Events**

Refer to Section 7.3.5 “Analysis of Submission-specific Safety Issues”.

### **Treatment Emergent Adverse Events and Adverse Reactions**

Treatment-emergent AEs (TEAEs) are defined as events with onset after the first dose of study drug (including same as day as study drug start day) and no more than 105 days (i.e., 5 times the half-life of risankizumab) after the last dose of study drug. AEs with an onset during protocol-designed treatment gaps (i.e., placebo period) that occurred more than 105 days from the last dose of the previous risankizumab treatment and before the first dose of retreatment for this study were excluded from TEAE summaries.

Adverse events were summarized as both subject incidence rates and exposure-adjusted event rates per 100 PYs. The former provided the basis of assessment for the 16 week Primary Safety Pool while the latter provided for a more adequate assessment of the long term safety data given the varied duration of exposure across different treatment groups. The exposure adjusted rates also enabled comparison of data across the short-term and long-term analysis sets.

In the first 16 weeks of treatment, 638 (48.9%) subjects in the risankizumab 150 mg group experienced at least 1 AE, which was comparable with placebo in which 145 subjects (48.3%) experienced an AE. The following events occurred in at least 2% of subjects in the 150 mg risankizumab group: upper respiratory tract infections, viral upper respiratory tract infections, headache, arthralgia, and fatigue; of these, arthralgia occurred at a numerically higher rate in the placebo group compared to the risankizumab group.

Upper respiratory infections (URI) are common illnesses and comprise the two most frequent preferred terms upper respiratory tract infection and viral upper respiratory tract infection. These terms may be pooled for labeling. Other common infections (urinary tract infection and gastroenteritis) are reported as common AEs. Infections are discussed in section 7.3.5 and product labeling for infections is recommended. Common adverse events reported in the primary safety pool are shown in the Table 25.

**Table 25: Most Frequent Adverse Events Reported in ≥ 1% of Subjects, by Frequency of PT in 16 Weeks (Primary Safety Pool)**

| System Organ Class<br>Preferred Term    | Placebo<br>(N = 300)<br>n (%) | Ustekinumab<br>(N = 239)<br>n (%) | Adalimumab<br>(N = 304)<br>n (%) | Risankizumab               |                               |                                     | Total<br>(N = 1389)<br>n (%) |
|-----------------------------------------|-------------------------------|-----------------------------------|----------------------------------|----------------------------|-------------------------------|-------------------------------------|------------------------------|
|                                         |                               |                                   |                                  | 90 mg<br>(N = 41)<br>n (%) | 150 mg<br>(N = 1306)<br>n (%) | 150 – 180 mg<br>(N = 1348)<br>n (%) |                              |
| Any adverse event                       | 145 (48.3)                    | 125 (52.3)                        | 173 (56.9)                       | 23 (56.1)                  | 638 (48.9)                    | 658 (48.8)                          | 681 (49.0)                   |
| Viral upper respiratory tract infection | 13 (4.3)                      | 13 (5.4)                          | 24 (7.9)                         | 7 (17.1)                   | 77 (5.9)                      | 83 (6.2)                            | 90 (6.5)                     |
| Upper respiratory tract infection       | 9 (3.0)                       | 10 (4.2)                          | 12 (3.9)                         | 1 (2.4)                    | 55 (4.2)                      | 55 (4.1)                            | 56 (4.0)                     |
| Headache                                | 6 (2.0)                       | 8 (3.3)                           | 20 (6.6)                         | 1 (2.4)                    | 44 (3.4)                      | 47 (3.5)                            | 48 (3.5)                     |
| Arthralgia                              | 10 (3.3)                      | 3 (1.3)                           | 9 (3.0)                          | 2 (4.9)                    | 32 (2.5)                      | 33 (2.4)                            | 35 (2.5)                     |
| Fatigue                                 | 3 (1.0)                       | 5 (2.1)                           | 7 (2.3)                          | 0                          | 29 (2.2)                      | 29 (2.2)                            | 29 (2.1)                     |
| Back pain                               | 1 (0.3)                       | 3 (1.3)                           | 6 (2.0)                          | 1 (2.4)                    | 21 (1.6)                      | 22 (1.6)                            | 23 (1.7)                     |
| Pruritus                                | 4 (1.3)                       | 4 (1.7)                           | 10 (3.3)                         | 1 (2.4)                    | 19 (1.5)                      | 21 (1.6)                            | 22 (1.6)                     |
| Diarrhoea                               | 5 (1.7)                       | 7 (2.9)                           | 6 (2.0)                          | 0                          | 17 (1.3)                      | 18 (1.3)                            | 18 (1.3)                     |
| Cough                                   | 0                             | 1 (0.4)                           | 2 (0.7)                          | 1 (2.4)                    | 16 (1.2)                      | 17 (1.3)                            | 18 (1.3)                     |
| Hypertension                            | 6 (2.0)                       | 3 (1.3)                           | 8 (2.6)                          | 0                          | 15 (1.1)                      | 15 (1.1)                            | 15 (1.1)                     |
| Urinary tract infection                 | 2 (0.7)                       | 6 (2.5)                           | 3 (1.0)                          | 0                          | 14 (1.1)                      | 15 (1.1)                            | 15 (1.1)                     |
| Nausea                                  | 1 (0.3)                       | 3 (1.3)                           | 3 (1.0)                          | 1 (2.4)                    | 14 (1.1)                      | 14 (1.0)                            | 15 (1.1)                     |
| Oropharyngeal pain                      | 0                             | 3 (1.3)                           | 3 (1.0)                          | 2 (4.9)                    | 12 (0.9)                      | 12 (0.9)                            | 14 (1.0)                     |
| Gastroenteritis                         | 3 (1.0)                       | 2 (0.8)                           | 1 (0.3)                          | 2 (4.9)                    | 12 (0.9)                      | 12 (0.9)                            | 14 (1.0)                     |

Source: Applicant's CSR Table 10

After 52 weeks of risankizumab exposure, 419 (70.1%) subjects experienced 1409 adverse events (228.0 E/100 PY), which was comparable with the active control. The most frequently reported AEs (≥ 5% of subjects) reported with risankizumab treatment were viral upper respiratory tract infection, upper respiratory tract infection, and arthralgia. With longer duration of treatment frequently reported AEs include additional infections. The most frequent AEs reported in ≥ 2% of risankizumab subjects is shown in Table 26.

**Table 26: Most Frequent Adverse Events Reported in ≥ 2% of Risankizumab Subjects, by Frequency of PT in 52 Weeks**

| System Organ Class<br>Preferred Term    | Ustekinumab<br>(N = 199)<br>n (%) | Risankizumab 150 mg<br>(N = 598)<br>n (%) |
|-----------------------------------------|-----------------------------------|-------------------------------------------|
| Any adverse event                       | 157 (78.9)                        | 419 (70.1)                                |
| Viral upper respiratory tract infection | 42 (21.1)                         | 90 (15.1)                                 |
| Upper respiratory tract infection       | 26 (13.1)                         | 70 (11.7)                                 |
| Arthralgia                              | 8 (4.0)                           | 30 (5.0)                                  |
| Headache                                | 13 (6.5)                          | 27 (4.5)                                  |
| Hypertension                            | 8 (4.0)                           | 21 (3.5)                                  |
| Fatigue                                 | 4 (2.0)                           | 20 (3.3)                                  |
| Gastroenteritis                         | 6 (3.0)                           | 19 (3.2)                                  |
| Diarrhoea                               | 10 (5.0)                          | 18 (3.0)                                  |
| Back pain                               | 8 (4.0)                           | 15 (2.5)                                  |
| Influenza                               | 5 (2.5)                           | 14 (2.3)                                  |
| Sinusitis                               | 3 (1.5)                           | 14 (2.3)                                  |
| Folliculitis                            | 6 (3.0)                           | 12 (2.0)                                  |

Source: Applicant CSR Table 11

Over the entire psoriasis program, 1480 (66.2%) subjects experienced 5143 adverse events (236.0 E/100 PY). The exposure-adjusted rates appear to slightly increase over time compared to the 52 week timepoint. The type of common AE (by preferred term) and the percentage of subjects experiencing a given AE were comparable to the 52 week timepoint.

### Laboratory Findings

Evaluation of mean changes over time and individual subject changes in hematology and clinical chemistry values, as well as potentially clinically significant abnormalities in hematology and clinical chemistry, did not identify any significant safety concerns with risankizumab treatment. No special laboratory monitoring is required for safety monitoring with risankizumab therapy.

### Vital Signs

There were no clinically meaningful changes in vital sign parameters (blood pressure, respiratory rate, pulse rate, or temperature in the primary safety pool. Additionally, there were no clinically meaningful changes in vital signs reported in the safety update reporting period.

### Electrocardiograms (ECGs)

ECG changes (such as absolute and interval changes in QTc) were not meaningfully different across treatment groups. Evaluation of mean changes over time and individual subject changes in ECG data did not reveal any significant safety issue.

## QT

The ICH E14 guideline regarding the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs does not specifically address QT assessments for biologic agents. Large proteins and monoclonal antibodies have a low likelihood of direct ion channel interactions. The Agency finds the applicant's request to waive thorough QT (TQT) acceptable based on large size of monoclonal antibody risankizumab. Although a thorough QT study was not performed for risankizumab, ECG monitoring was conducted in the Phase 3 trials. In the Primary Safety Pool, ECG changes (such as absolute and interval changes in QTc) were not meaningfully different across treatment groups.

## Immunogenicity

Because therapeutic proteins have the potential to elicit an immune response, immunogenicity was assessed. Refer to Section 6.2.4.1 for immunogenicity findings. Overall, there was little clinically meaningful impact due to immunogenicity.

Among 1288 evaluable subjects in the Phase 3 studies, approximately 19% of subjects treated with risankizumab developed ADA by Week 16. Of the subjects who developed ADA, approximately 42% (8% of all subjects) had neutralizing antibodies (NAb). The ADA and NAb incidences were 24% and 57% (14% of all subjects), respectively, among 1079 evaluable subjects by Week 52. The findings of ADA impact on bioavailability, efficacy and safety are as follows:

- Antibodies to risankizumab did not appear to affect risankizumab concentrations when ADA titer values were <128. The mean risankizumab concentrations in subjects who had ADA titer values  $\geq 128$  were approximately 30% lower compared with the concentrations in ADA negative subjects.
- The development of ADA with antibody titer values  $\geq 128$  was associated with reduced efficacy.
- Subjects who developed antibodies to risankizumab were more likely to experience injection-site reactions compared to subjects who were ADA negative.

### 7.3.5. Analysis of Submission-Specific Safety Issues

Some categories of AEs were considered to be areas of safety interest due to their higher prevalence in the moderate to severe psoriasis population, concerns with injected immunoglobulin products, or concerns with the immunomodulatory effect of the drug.

The AEs in areas of safety interest, which are discussed in detail include:

- infections (including serious infections, tuberculosis (TB), opportunistic infections, fungal infections, and herpes zoster)

- malignancies (including all possible malignancies, malignant tumors, nonmelanoma skin cancer [NMSC], and malignant tumors excluding NMSC)
- cardiovascular (CV) events (including major adverse cardiovascular events (MACE), extended MACE, and other CV events)
- hypersensitivity and anaphylactic reactions
- injection-site reactions
- neuropsychiatric events [including depression and suicidal ideation and behavior (SIB)]
- hepatic events

### **Infections**

Infections (including serious infections, TB, opportunistic infections, fungal infections, and herpes zoster) are considered to be an area of safety interest for risankizumab. The applicant used a query with a more comprehensive list of PTs from both the infections and infestations SOC and the investigations SOC for the evaluation of opportunistic infections. The analysis appears acceptable and the applicant's data is summarized in this section.

In the first 16 weeks of treatment, more subjects (22.1%) in the risankizumab 150 mg group reported infection AEs (90.8 E/100 PY) compared to 14.7% of subjects in the placebo group (56.5 E/100 PY). Infection rates appear to be comparable to the infection rates seen in the active control groups. The most common infection AEs in the risankizumab 150 mg group ( $\geq 1\%$  of subjects) were viral upper respiratory tract infection, upper respiratory tract infection, urinary tract infection, and sinusitis.

Over the entire psoriasis program, 40.8% of subjects in the All Risankizumab group reported infection AEs (75.5 E/100 PY). The majority of infections (97.8%) were nonserious.

### **Serious**

In the first 16 weeks of treatment, 5 (0.4%) subjects in the risankizumab 150 mg group experienced a total of 7 serious infections (1.7 E/100 PY) compared to 1 (0.3%) of the subjects in the placebo group (1.1 E/100 PY). The risankizumab associated serious infections included cellulitis (2 subjects), herpes zoster, osteomyelitis, sepsis, perirectal abscess and diverticulitis. Cellulitis progressed to sepsis in one subject and to osteomyelitis in another subject. Both subjects had a history of cellulitis and the latter also had a history of osteomyelitis and pre-existing foot ulceration. No risankizumab-treated subjects discontinued study drug due to serious infections.

After 52 weeks of exposure, 8 (1.3%) subjects in the risankizumab group experienced a total of 11 serious infections (1.8 E/100 PY), which was comparable to the active control group. This includes the 7 serious infections listed above plus an additional case of pneumonia, an additional case of sepsis, pyelonephritis, and gastroenteritis.

Over the entire psoriasis program, 39 serious infections were reported in 30 (1.3%) subjects treated with risankizumab (1.7 E/100 PY). Serious infections reported in  $\geq 3$  subjects included sepsis (7), cellulitis (5), and pneumonia (4); the rest of the serious infections were reported in 2 or fewer subjects. Two subjects discontinued due to serious infections (1 due to sepsis and pneumonia and 1 due to pneumonia).

#### Opportunistic and Infections of Interest

In the pivotal Phase 3 studies, subjects with active tuberculosis (TB), HIV or viral hepatitis were excluded; subjects with latent TB were required to start treatment prophylaxis prior to starting on risankizumab. There were no AEs of active or latent TB reported in any treatment arm in the first 16 weeks of treatment. One subject in the risankizumab 150 mg group reported a herpes zoster, which was an SAE, but did not result in discontinuation of treatment. Twenty (1.5%) subjects in the risankizumab 150 mg group experienced fungal infections (5.2 E/100 PY) compared to 1 (0.3%) of the subjects in the placebo group (1.1 E/100PY). Fungal infection rates in the risankizumab group appear to fall within the rates seen in the active control groups. Fungal infections in the risankizumab group were primarily of a type of tinea infection. Mucocutaneous candida reported in the risankizumab group included 1 case each of balanitis and skin candidiasis. There was 1 case of fungal laryngitis. None of the fungal infections were serious or led to discontinuation of study drug.

After 52 weeks of exposure, there were no AEs of active TB reported in any treatment arm. There was 1 case each of latent TB and mycobacterium tuberculosis complex test positive reported in the risankizumab group. There were no new cases of herpes zoster; 1 additional case of mucocutaneous candidiasis (oral candidiasis) was reported. Twenty-four (4.0%) subjects in the risankizumab group experienced a total of 26 fungal infections (4.2 E/100 PY) which was higher than the active comparator in which 2 (1.0%) subjects (1.0 E/ 100 PY) reported fungal infections.

Over the entire psoriasis program, the rates of opportunistic infections among risankizumab-treated subjects with psoriasis were low (0.3 E/100 PY). None of the opportunistic infections were serious or led to discontinuation of study drug. Opportunistic infections include CMV reactivation and esophageal candidiasis (1 subject each) and oral candidiasis (4 subjects).

Herpes zoster was reported in 7 subjects. Two events were considered serious, but do not appear to be multidermatomal from the information provided. Neither subject discontinued study drug due to herpes zoster. Latent TB was reported in 7 subjects and 2 subjects reported a positive test for Mycobacterium tuberculosis complex. A total of 64 (2.9%) subjects (3.4 E/100 PY) treated with risankizumab reported fungal infections.

The additional information provided in the safety update showed that the rate and pattern of overall infections, serious infections and opportunistic and fungal infections remained generally unchanged. There continued to be no cases of active TB.

The following language is recommended to be included in product labeling:

In the first 16 weeks, infections occurred in 22.1% of the TRADENAME group (90.8 events per 100 subject-years) compared to 14.7% of the placebo group (56.5 events per 100 subject-years. Five (0.4%) subjects in the risankizumab 150 mg group experienced a total of 7 serious infections (1.7 E/100 PY) compared to 1 (0.3%) of the subjects in the placebo group (1.1 E/100 PY).

### **Malignancies**

The Phase 2 and Phase 3 trials excluded subjects with 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 uterine cervix.

Due to immunosuppressive properties, the risk of malignancy associated with risankizumab use is a potential concern. Data was evaluated at 16 weeks, 52 weeks and with all data to date including some subjects (85) with up to 3 years of exposure. The review identified some cases which were not included in the applicant's summary or tables. In the narrative summaries, the subject number for these cases are marked with an asterisk (\*).

In the first 16 weeks of the Phase 2 and Phase 3 psoriasis studies (primary safety pool), 3 (0.2%) risankizumab subjects reported non-NMSC malignant tumor AEs (invasive lobular breast carcinoma, malignant melanoma in situ, and esophageal carcinoma. An additional three subjects reported NMSC (2 with squamous cell carcinoma of skin and 1 with basal cell carcinoma). In the placebo group, there were no non-NMSC malignancies, 1 subject reported squamous cell carcinoma of skin. For the active comparators, no malignant tumors were reported for ustekinumab and 1 (0.3%) malignancy (gallbladder cancer) was reported for adalimumab.

After 52 weeks of exposure (ustekinumab-controlled analysis set), additional malignancies were reported in 3 subjects in the risankizumab group. All were NMSCs (2 basal cell carcinoma and 1 squamous cell carcinoma of the skin). The event rate for non-NMSC malignancies was 0.5 E/100 PY. In the active comparator group, there was 1 (0.5%) reported malignancy for prostate cancer.

The All Risankizumab – Psoriasis Analysis Set includes subjects that received a dose of risankizumab who are followed through to the end of exposure (including ongoing LTE studies). In this analysis set, there were 30 reports of malignant tumors, 19 of which were NMSC. A summary of malignancy AEs is shown in Table 27. Of the 11 non-NMSC malignancies, the most frequent non-NMSC malignant tumors were breast cancer in 4 subjects (events of breast cancer, invasive ductal breast carcinoma, and invasive lobular breast carcinoma) and malignant melanoma in situ and prostate cancer that occurred in 2 subjects each. These cases along with additional cases submitted in the safety update are summarized below.

**Table 27: Malignant Tumor and Nonmelanoma Skin Cancer AEs (All Risankizumab – Psoriasis Analysis Set)**

| Category<br>Preferred Term             | Risankizumab 150 mg<br>(N = 1590)<br>(PY = 1681.5) |                 |                     | All Risankizumab<br>(N = 2234)<br>(PY = 2179.0) |                 |                     |
|----------------------------------------|----------------------------------------------------|-----------------|---------------------|-------------------------------------------------|-----------------|---------------------|
|                                        | n (%)                                              | E (E/100 PY)    | [95% CI]            | n (%)                                           | E (E/100 PY)    | [95% CI]            |
| <b>Malignant tumors</b>                | <b>21 (1.3)</b>                                    | <b>25 (1.5)</b> | <b>[0.96, 2.19]</b> | <b>23 (1.0)</b>                                 | <b>29 (1.3)</b> | <b>[0.89, 1.91]</b> |
| Basal cell carcinoma                   | 8 (0.5)                                            | 9 (0.5)         |                     | 10 (0.4)                                        | 13 (0.6)        |                     |
| Bowen's disease                        | 1 (<0.1)                                           | 1 (<0.1)        |                     | 1 (<0.1)                                        | 1 (<0.1)        |                     |
| Breast cancer                          | 1 (<0.1)                                           | 1 (<0.1)        |                     | 1 (<0.1)                                        | 1 (<0.1)        |                     |
| Hepatic cancer metastatic              | 1 (<0.1)                                           | 1 (<0.1)        |                     | 1 (<0.1)                                        | 1 (<0.1)        |                     |
| Intestinal adenocarcinoma              | 1 (<0.1)                                           | 1 (<0.1)        |                     | 1 (<0.1)                                        | 1 (<0.1)        |                     |
| Invasive ductal breast carcinoma       | 1 (<0.1)                                           | 1 (<0.1)        |                     | 1 (<0.1)                                        | 1 (<0.1)        |                     |
| Invasive lobular breast carcinoma      | 1 (<0.1)                                           | 1 (<0.1)        |                     | 1 (<0.1)                                        | 1 (<0.1)        |                     |
| Malignant melanoma in situ             | 2 (0.1)                                            | 2 (0.1)         |                     | 2 (<0.1)                                        | 2 (<0.1)        |                     |
| Oesophageal carcinoma                  | 1 (<0.1)                                           | 1 (<0.1)        |                     | 1 (<0.1)                                        | 1 (<0.1)        |                     |
| Prostate cancer                        | 2 (0.1)                                            | 2 (0.1)         |                     | 2 (<0.1)                                        | 2 (<0.1)        |                     |
| Squamous cell carcinoma of skin        | 4 (0.3)                                            | 5 (0.3)         |                     | 4 (0.2)                                         | 5 (0.2)         |                     |
| <b>NMSC</b>                            | <b>12 (0.8)</b>                                    | <b>15 (0.9)</b> | <b>[0.50, 1.47]</b> | <b>14 (0.6)</b>                                 | <b>19 (0.9)</b> | <b>[0.52, 1.36]</b> |
| Basal cell carcinoma                   | 8 (0.5)                                            | 9 (0.5)         |                     | 10 (0.4)                                        | 13 (0.6)        |                     |
| Bowen's disease                        | 1 (<0.1)                                           | 1 (<0.1)        |                     | 1 (<0.1)                                        | 1 (<0.1)        |                     |
| Squamous cell carcinoma of skin        | 4 (0.3)                                            | 5 (0.3)         |                     | 4 (0.2)                                         | 5 (0.2)         |                     |
| <b>Malignant tumors excluding NMSC</b> | <b>9 (0.6)</b>                                     | <b>10 (0.6)</b> | <b>[0.29, 1.09]</b> | <b>9 (0.4)</b>                                  | <b>10 (0.5)</b> | <b>[0.22, 0.84]</b> |
| Breast cancer                          | 1 (<0.1)                                           | 1 (<0.1)        |                     | 1 (<0.1)                                        | 1 (<0.1)        |                     |
| Hepatic cancer metastatic              | 1 (<0.1)                                           | 1 (<0.1)        |                     | 1 (<0.1)                                        | 1 (<0.1)        |                     |
| Intestinal adenocarcinoma              | 1 (<0.1)                                           | 1 (<0.1)        |                     | 1 (<0.1)                                        | 1 (<0.1)        |                     |
| Invasive ductal breast carcinoma       | 1 (<0.1)                                           | 1 (<0.1)        |                     | 1 (<0.1)                                        | 1 (<0.1)        |                     |
| Invasive lobular breast carcinoma      | 1 (<0.1)                                           | 1 (<0.1)        |                     | 1 (<0.1)                                        | 1 (<0.1)        |                     |
| Malignant melanoma in situ             | 2 (0.1)                                            | 2 (0.1)         |                     | 2 (<0.1)                                        | 2 (<0.1)        |                     |
| Oesophageal carcinoma                  | 1 (<0.1)                                           | 1 (<0.1)        |                     | 1 (<0.1)                                        | 1 (<0.1)        |                     |
| Prostate cancer                        | 2 (0.1)                                            | 2 (0.1)         |                     | 2 (<0.1)                                        | 2 (<0.1)        |                     |

AE = adverse event; CI = confidence interval; E = events; NMSC = nonmelanoma skin cancer; PY = patient years

Source: Applicant SCS Table 28. Note: the reviewer identified an additional report of breast cancer (subject (b) (6) \*). All cases of breast cancer are summarized below.

In the safety update (N=2471; PY=3404.7), 10 new malignant tumors (excluding NMSC) were reported and include anal cancer, bladder cancer, recurrent breast cancer, breast cancer (subject (b) (6) \*), metastases to lymph nodes (breast cancer), gastric cancer, metastatic squamous cell carcinoma of the neck (subject (b) (6) \*), plasma cell myeloma, prostate cancer (subject (b) (6) \*) and rectal cancer. For the development program a total of 21 malignancies (excluding NMSC) were reported, 0.62 E/100 PY. Table 28 summarizes the malignancies.

**Table 28: Malignant Tumor and Nonmelanoma Skin Cancer AEs in Safety Update Report (SUR)**

| Category<br>Preferred Term           | CSS<br>(N = 2234)<br>(PY = 2179.0) |              |              | Safety Update<br>(N = 2471)<br>(PY = 3404.7) |              |              |
|--------------------------------------|------------------------------------|--------------|--------------|----------------------------------------------|--------------|--------------|
|                                      | n (%)                              | E (E/100 PY) | [95% CI]     | n (%)                                        | E (E/100 PY) | [95% CI]     |
| Malignant tumors                     | 23 (1.0)                           | 29 (1.3)     | [0.89, 1.91] | 35 (1.4)                                     | 46 (1.4)     | [0.99, 1.80] |
| NMSC                                 | 14 (0.6)                           | 19 (0.9)     | [0.52, 1.36] | 18 (0.7)                                     | 26 (0.8)     | [0.50, 1.12] |
| Basal cell carcinoma                 | 10 (0.4)                           | 13 (0.6)     |              | 12 (0.5)                                     | 15 (0.4)     |              |
| Bowen's disease                      | 1 (<0.1)                           | 1 (<0.1)     |              | 2 (<0.1)                                     | 2 (<0.1)     |              |
| Metastatic squamous cell carcinoma   | 0                                  | 0            |              | 1 (<0.1)                                     | 1 (<0.1)     |              |
| Squamous cell carcinoma of skin      | 4 (0.2)                            | 5 (0.2)      |              | 6 (0.2)                                      | 7 (0.2)      |              |
| Squamous cell carcinoma of the vulva | 0                                  | 0            |              | 1 (<0.1)                                     | 1 (<0.1)     |              |
| Malignant tumors excluding NMSC      | 9 (0.4)                            | 10 (0.5)     | [0.22, 0.84] | 18 (0.7)                                     | 20 (0.6)     | [0.36, 0.91] |
| Anal cancer                          | 0                                  | 0            |              | 1 (<0.1)                                     | 1 (<0.1)     |              |
| Bladder cancer                       | 0                                  | 0            |              | 1 (<0.1)                                     | 1 (<0.1)     |              |
| Breast cancer                        | 1 (<0.1)                           | 1 (<0.1)     |              | 3 (0.1)                                      | 3 (<0.1)     |              |
| Breast cancer recurrent              | 0                                  | 0            |              | 1 (<0.1)                                     | 1 (<0.1)     |              |
| Gastric cancer                       | 0                                  | 0            |              | 1 (<0.1)                                     | 1 (<0.1)     |              |
| Hepatic cancer metastatic            | 1 (<0.1)                           | 1 (<0.1)     |              | 1 (<0.1)                                     | 1 (<0.1)     |              |
| Intestinal adenocarcinoma            | 1 (<0.1)                           | 1 (<0.1)     |              | 1 (<0.1)                                     | 1 (<0.1)     |              |
| Invasive ductal breast carcinoma     | 1 (<0.1)                           | 1 (<0.1)     |              | 1 (<0.1)                                     | 1 (<0.1)     |              |
| Invasive lobular breast carcinoma    | 1 (<0.1)                           | 1 (<0.1)     |              | 1 (<0.1)                                     | 1 (<0.1)     |              |
| Malignant melanoma in situ           | 2 (<0.1)                           | 2 (<0.1)     |              | 2 (<0.1)                                     | 2 (<0.1)     |              |
| Metastases to lymph nodes            | 0                                  | 0            |              | 1 (<0.1)                                     | 1 (<0.1)     |              |
| Oesophageal carcinoma                | 1 (<0.1)                           | 1 (<0.1)     |              | 1 (<0.1)                                     | 1 (<0.1)     |              |
| Plasma cell myeloma                  | 0                                  | 0            |              | 1 (<0.1)                                     | 1 (<0.1)     |              |
| Prostate cancer                      | 2 (<0.1)                           | 2 (<0.1)     |              | 3 (0.1)                                      | 3 (<0.1)     |              |
| Rectal cancer                        | 0                                  | 0            |              | 1 (<0.1)                                     | 1 (<0.1)     |              |

AE = Adverse event; CI = Confidence interval; CSS = Clinical Summary of Safety; E = Events; NMSC = Non-melanoma skin cancer; PY = Patient-year

Source: Applicant SUR Table 12. Note: the reviewer identified that metastatic squamous cell carcinoma is misclassified in this table. The subject experienced head and neck cancer and not a skin cancer. The rates described below properly classify this case.

Narratives for the non-NMSC malignancies which occurred in more than one subject are as follows:

- Breast cancer (7)
  - Subject (b) (6) a 61-year-old, white, overweight female with a family history of breast cancer who on Day 237 (Post-Treatment Day 40), experienced an event of breast cancer stage I.
  - Subject (b) (6) a 52-year-old, white, obese, diabetic female who on Day 287 (Post-Treatment Day 3), experienced an event of an abnormal mammogram that was later diagnosed invasive ductal breast carcinoma.
  - Subject (b) (6) a 72-year-old, white, female who on Day 63 experienced an event of invasive lobular breast carcinoma, grade III.

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- Subject (b) (6) a 56-year-old, white, female who on Day 385 experienced axillary adenopathy. Post-operative diagnosis showed invasive ductal carcinoma with nodal metastases, staged as pT1a pN3a M0.
- Subject (b) (6) a 48-year-old, white, obese, female who on Day 265 experienced breast cancer. Subject was originally randomized to placebo and reassigned to risankizumab on Day 109.
- Subject (b) (6) a 72-year-old, obese, black, female who on Day 280 experienced recurrent breast cancer (invasive ductal carcinoma). Last dose of risankizumab was administered on Day 344.
- Subject (b) (6) a 61-year-old, white, female who on Day 550 (Post-treatment Day 101) experienced an event of moderately differentiated invasive mammary carcinoma.
- Prostate cancer (3)
  - Subject (b) (6) a 65-year-old, obese, white male, who on Day 324 (Post-Treatment Day 44) experienced an event of prostate cancer.
  - Subject (b) (6) a 64-year-old, overweight, white male, who on Day 301 (treated to risankizumab until Day 112 then converted to placebo on Day 197 Post-Treatment Day 44) experienced an event of prostate cancer (Gleason score 4 plus 3 out of 10, and 7 out of 12 cores positive).
  - Subject (b) (6) a 79-year-old, obese, diabetic, white male, who on Day 639 (Post-Treatment Day 24) experienced an event of prostate cancer.
- Melanoma (2)
  - Subject (b) (6) a 43-year-old, white, obese, male smoker who on Day 102 had an excision of a lesion which was diagnosed as a malignant melanoma in situ.
  - Subject (b) (6) a 62-year-old, overweight, white male who on Day 397 (Post-Treatment Day 11) had an excision of a lesion which was diagnosed as a malignant melanoma in situ, grade 2.

2 additional malignancies were identified which occurred after the applicant's cut-off determination of treatment-related events (105 days after last dose of risankizumab).

These cases are as follows:

- Subject (b) (6) a 67-year-old, white male was diagnosed with follicular B-cell lymphoma on Day 620. The subject received risankizumab for 115 days in study followed by placebo from Day 199-535.
- Subject (b) (6) a 58-year-old, white female was diagnosed with mycosis fungoides Day 337 (Post-Treatment Day 143).

The most common types of malignancy(excluding NMSC) seen in the drug development program are consistent with the most common cancers seen in the United States.

Breast cancer is the most common cancer in the US followed by lung cancer and prostate cancer and the incidence of melanoma of the skin has been rising.

For the overall development program, malignancy rate with risankizumab treatment was 1.4 E/100 PY. The malignancy rate excluding NMSC was 0.62 E/100 PY.

The event rate for risankizumab is increased, but not substantially, as compared to other sources of malignancy data in psoriasis patients. The rates of malignant tumors (excluding NMSC) reported in the ustekinumab, ixekizumab, secukinumab, and guselkumab clinical development programs ranged from 0.31 – 0.49 E/100 PY. The rate of first malignancy among patients who did not have a history of malignancy (excluding NMSC) reported for biologics in the Psoriasis Longitudinal Assessment and Registry<sup>14</sup> (total PYs, 46,041) was 0.55 per 100 PYs (95% CI, 0.48-0.62).

Although the event rate for malignancy is slightly higher than comparable data in psoriasis patients, there was only one death from malignancy in the risankizumab development program. At this juncture a causal link between the product and malignancy is not evident. Additional long-term data is needed.

Skin cancer is the most common class of human malignancies and the elevated risk of skin cancers in chronically immunosuppressed individuals is well-established from studies in organ transplant patients. The ratio of SCC:BCC is 0.2:1.0 in nontransplant patients. After transplant, the ratio changes. The incidence of SCC increases greatly, but BCC increases only slightly, resulting in a ratio of SCC:BCC of 1.8:1.0<sup>15</sup>.

Of the 25 NMSC malignancies reported in subjects on risankizumab, the most common were basal cell carcinoma (15 events) and Bowen's disease/ squamous cell combined included 10 events (ratio of 1:1.5). While the ratio is narrower than that seen in nontransplant patients, it does not invert due to an increase of SCC, suggesting less of an immunosuppressive affect than seen in transplant patients.

There is a concern that this new biologic product may increase the risk of malignancies due to its immunosuppressive effect. The limited duration of observation during the drug development program does not allow detection of rare events with a long latency periods such as malignancy. Therefore, postmarketing data are needed to evaluate the long-term risk of malignancy in patients with psoriasis receiving risankizumab. A PMR is recommended for an observational study to collect additional data on long-term safety and evaluate the occurrence of long-latency safety outcomes, including malignancy that cannot be adequately assessed in the clinical trial program.

### **Cardiovascular (CV) events**

<sup>14</sup> Fiorentino et al. Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry J Am Acad Dermatol Nov 2017: 845-854.

<sup>15</sup> Penn I. Skin disorders in organ transplant recipients: external anogenital lesions. Arch Dermatol 1997;133:221–223.

Based on epidemiologic associations between psoriasis and Cardiovascular (CV) events, and the potential association between anti-cytokine therapies used in the treatment of moderate to severe psoriasis and CV events, the applicant conducted additional analyses on adjudicated major adverse cardiovascular events (MACE), extended MACE, and other CV events. MACE was defined as the composite of CV death, nonfatal myocardial infarction, and nonfatal stroke. Extended MACE was defined as the composite of MACE plus hospitalization for unstable angina and coronary revascularization procedures. Other CV events were defined as thrombotic events, cardiac arrhythmia, and congestive heart failure.

Baseline cardiovascular risk factors and baseline history of cardiovascular disease were evenly distributed among the risankizumab arms and control arms (ustekinumab, adalimumab, and placebo) of the studies comprising the primary safety pool.

The review team has noted that in the 52-week Ustekinumab-controlled safety analysis set, there is an imbalance of cardiac Serious Adverse Events (SAEs). Eight (1.3%) subjects in the risankizumab group had SAEs in the cardiac disorder SOC compared to 1 (0.5%) subject in the ustekinumab group. The imbalance seems to be primarily due to increased events reported as preferred terms “congestive heart failure” and “cardiac arrhythmia”.

Fred Senatore, MD, PhD, FDA Division of Cardiovascular and Renal Products, reviewed the CV adverse event data from the clinical development program.

Cardiovascular events in the primary safety pool dataset are shown in Table 29. The numbers of events were low and comparable across all arms: placebo (1.7%), ustekinumab (1.7%), adalimumab (1.3%), risankizumab 90 mg (2.4%), risankizumab 150 mg (0.7%), and risankizumab 150-180 mg (0.7%). The estimated annualized rates of CV events were: placebo (5%), ustekinumab (5%), adalimumab (4%), risankizumab 90 mg (7%), risankizumab 150 mg (2%), and risankizumab 150-180 mg (2%).

**Table 29: Cardiovascular adverse events from Primary Safety Pool**

| Risk                               | Placebo         | UST             | ADB             | Risankizumab    |                 |                 |
|------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                    |                 |                 |                 | 90 mg           | 150 mg          | 150-180 mg      |
| <b>N</b>                           | 300             | 239             | 304             | 41              | 1306            | 1348            |
| <b>CV events n (%)</b>             | <b>5 (1.7%)</b> | <b>4 (1.7%)</b> | <b>4 (1.3%)</b> | <b>1 (2.4%)</b> | <b>9 (0.7%)</b> | <b>9 (0.7%)</b> |
| <b>Acute Myocardial Infarction</b> | 0               | 0               | 0               | 0               | 1 (<0.1%)       | 1 (<0.1%)       |
| <b>Angina Pectoris</b>             | 0               | 1 (0.4%)        | 0               | 0               | 0               | 0               |
| <b>Aortic Valve Disease</b>        | 1 (0.3%)        | 0               | 0               | 0               | 1 (<0.1%)       | 1 (<0.1%)       |

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|                                   |          |          |          |          |           |           |
|-----------------------------------|----------|----------|----------|----------|-----------|-----------|
| <b>Atrial Fibrillation</b>        | 1 (0.3)  | 0        | 1 (0.3%) | 0        | 1 (<0.1%) | 1 (<0.1%) |
| <b>1<sup>st</sup> AV Block</b>    | 1 (0.3%) | 0        | 0        | 0        | 1 (<0.1%) | 1 (<0.1%) |
| <b>Bradycardia</b>                | 0        | 0        | 1 (0.3%) | 0        | 0         | 0         |
| <b>CHF</b>                        | 0        | 0        | 1 (0.3%) | 0        | 1 (<0.1%) | 1 (<0.1%) |
| <b>Cardiomegaly</b>               | 0        | 0        | 0        | 0        | 1 (<0.1%) | 1 (<0.1%) |
| <b>CAD</b>                        | 0        | 1 (0.4%) | 0        | 0        | 1 (<0.1%) | 1 (<0.1%) |
| <b>IVCD</b>                       | 0        | 0        | 0        | 0        | 1 (<0.1%) | 1 (<0.1%) |
| <b>Hypertensive Heart Disease</b> | 0        | 1 (0.4%) | 0        | 0        | 0         | 0         |
| <b>Palpitations</b>               | 2 (0.7%) | 0        | 0        | 1 (2.4%) | 2 (0.2%)  | 2 (0.1%)  |
| <b>Sinus Tachycardia</b>          | 0        | 1 (0.4%) | 0        | 0        | 1 (<0.1%) | 1 (<0.1%) |
| <b>VPCs</b>                       | 0        | 0        | 1 (0.3%) | 0        | 0         | 0         |

CHF= Congestive Heart Failure; CAD= Coronary Artery Disease; IVCD= Intraventricular Conduction Defect; VPC= Ventricular Premature Contraction. Source: ISS Table 2.2\_1.3

In all the subjects exposed to risankizumab regardless of dose or timing (N=2234), 60 subjects experienced one or more cardiovascular events (2.7% -reference: ISS Table 2.2\_4.3). The most frequent events were 1st degree atrio-ventricular block (n=9), palpitations (n=8), “coronary artery disease” (n=8), tachycardia (n=6), atrial fibrillation (n=6), myocardial infarction (n=3), congestive heart failure (n=3), coronary artery occlusion (n=2), myocardial ischemia (n=2) intraventricular conduction defect (n=2), diastolic dysfunction (n=2), mitral valve incompetence (n=2), atrial flutter (n=2), tricuspid insufficiency (n=2), and a variety of single (n=1) events (e.g., sinus bradycardia, sinus tachycardia, Prinzmetal angina, ventricular extrasystoles, ventricular hypokinesia, ventricular tachycardia, aortic valve disease, mitral valve disease).

A pooling of ustekinumab-controlled trials (study 1311.3 and 1311.28) compared MACE, extended-MACE, and other CV events in the risankizumab 150 mg arms (N=598) to that in the ustekinumab arms (N= 199) (see Table 30). There were no reported events in the ustekinumab arms. The events in the risankizumab 150 mg arms (efficacious dose) were low: MACE (0.3%), extended MACE (0.7%) and “other events” that included cardiac arrhythmia (0.7%) and CHF (0.7%).

**Table 30: Adjudicated CV Endpoints in Ustekinumab controlled Phase 3 Studies**

| Study 1311.3; 1311.28 | UST        | RST 150 mg | 95% CI |
|-----------------------|------------|------------|--------|
| <b>N</b>              | <b>199</b> | <b>598</b> |        |

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|                                 |   |          |            |
|---------------------------------|---|----------|------------|
| <b>MACE n (%)</b>               | 0 | 2 (0.3%) | -0.13—0.80 |
| <b>-CV Death</b>                | 0 | 1 (0.2%) |            |
| <b>-Nonfatal MI</b>             | 0 | 1 (0.2%) |            |
| <b>Extended MACE n (%)</b>      | 0 | 4 (0.7%) | 0.02—1.33  |
| <b>-CV Death</b>                | 0 | 1 (0.2%) |            |
| <b>-Nonfatal MI</b>             | 0 | 1 (0.2%) |            |
| <b>-Hospitalization for UAP</b> | 0 | 2 (0.3%) |            |
| <b>Other CV Events n (%)</b>    | 0 | 7 (1.2%) | 0.57—2.40  |
| <b>-Cardiac Arrhythmia</b>      | 0 | 4 (0.7%) |            |
| <b>-CHF</b>                     | 0 | 4 (0.7%) |            |

UAP= unstable angina pectoris. Source: ISS Table 2.2\_3.14.1

In the “other CV events” category of the ustekinumab-controlled trials, there appeared to be an imbalance (i.e. 4 events of arrhythmia and 4 events of CHF in the risankizumab arms vs 0 events in the ustekinumab arms) that occurred in 7 patients.

The results of a search of the case report forms detailing the adjudicated heart failure and arrhythmia events leading to the apparent imbalance between ustekinumab and risankizumab are shown in Table 31. In the 4 cases of CHF, the verbatim reports were CHF, left cardiac decompensation (each required hospitalization), mitral valve incompetence and acute kidney failure superimposed on chronic kidney disease (each of these 2 required an urgent visit). There were 5 cases of supraventricular arrhythmia (SVA) none of which had ischemia. One of the cases was deemed a pre-existing condition and was not counted likely for that reason. Of the 4 remaining SVA events that were counted, the verbatim reports were atrial flutter with 4:1 AVB, “tachycardia”, atrial fibrillation, and AV nodal reentrant tachycardia. All were described as new onset. Subject (b) (6) had coronary bypass grafting reported as an adverse event one month earlier that may have been a confounder in the SVA event. The other cases of SVA did not have reported cardiac histories suggestive of an arrhythmic risk. In the absence of imbalances in the larger sample size of the primary pooled safety population, this low-incidence observation was likely due to chance.

**Table 31: Patient Data on Arrhythmia and Heart Failure Events from UST-controlled trials**

| Trial Number | Site # | Subject # | Verbatim                  | Adjudication Committee |
|--------------|--------|-----------|---------------------------|------------------------|
| 1311.28      |        | (b) (6)   | Acute superimposed on CKD | HF-urgent visit        |

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|         |         |                             |                                              |
|---------|---------|-----------------------------|----------------------------------------------|
| 1311.28 | (b) (6) | Aflutter 4:1 AVB            | SVA with no ischemia                         |
| 1311.28 |         | Symptomatic AF              | SVA with no ischemia ( <i>pre-existing</i> ) |
| 1311.28 |         | Congestive HF               | HF requiring hospitalization                 |
| 1311.28 |         | Tachycardia                 | SVA with no ischemia                         |
| 1311.3  |         | AF                          | SVA with no ischemia                         |
| 1311.3  |         | AVNRT                       | SVA with no ischemia                         |
| 1311.3  |         | Left Cardiac Decompensation | HF requiring hospitalization                 |
| 1311.3  |         | MV Incompetence             | HF-urgent visit                              |

CKD= Chronic Kidney Disease; HF= Heart Failure; SVA= Supraventricular Arrhythmia; AF= Atrial Fibrillation; AVNRT= AV Nodal Re-Entrant Tachycardia; MV= Mitral Valve. **Source: CRF Event Adjudication**

A literature search produced no evidence of a relationship between interleukin 12/23 agents and arrhythmic potential<sup>16</sup>. In general, the association between MACE and the use of interleukin 12/23 agents is unclear

### **Anaphylaxis and hypersensitivity**

As an immunoglobulin protein, subcutaneous administration of risankizumab may be associated with immunogenicity and/or hypersensitivity reactions. To identify subjects who experienced serious hypersensitivity reactions, the applicant conducted a search using the hypersensitivity (narrow) SMQ and the anaphylactic reaction (narrow) SMQ.

In the first 16 weeks of treatment a slightly greater percent of subjects (2.9%) in the risankizumab treatment group compared to placebo (2.3%) reported hypersensitivity AEs. The percent of reactions seen with risankizumab was within the range of the active controls. The majority of reported hypersensitivity AE associated with risankizumab treatment were skin reactions (dermatitis, contact dermatitis, rash, eczema, and skin reaction). The most frequently reported hypersensitivity AE was eczema, which was reported in 11 (0.8%) of the risankizumab-treated subjects and 1 (0.3%) placebo-treated subjects. Urticaria was reported associated with risankizumab treatment in 6 subjects (0.5%) compared to 1 subject (0.3%) in the placebo group. Urticaria reactions seen in the risankizumab group was within the range of those seen in the active control groups. None of the hypersensitivity reactions were serious or led to study drug discontinuation. There were no reported cases of anaphylaxis identified reaction in any of the treatment groups.

<sup>16</sup> Lebwohl, M, 2012, Interleukin 12/23 agents and major adverse cardiac events, Archives of Dermatology, 148 (11): 1329, <https://jamanetwork.com/journals/jamadermatology/fullarticle/1392590>

After 52 weeks of exposure, 37 subjects (6.2%) in the risankizumab group experienced a hypersensitivity reaction AE (7.9 E/100 PY). There was no change in the general profile of reported PTs and the majority describe dermatitis. None of the hypersensitivity reactions were serious or led to study drug discontinuation. There were no reported cases of anaphylaxis identified reaction in any of the treatment groups.

Over the entire psoriasis program, 137 (6.1%) subjects reported 176 hypersensitivity reaction AEs (8.1 E/100 PY). There was 1 case of erythema multiforme that was considered an SAE and was confounded by concomitant antibiotic therapy. One subject discontinued study drug due to an AE of dermatitis. There was no report of anaphylactic reaction.

The additional information provided in the safety update showed that the rate and pattern of overall hypersensitivity reactions remained generally unchanged. There was no report of anaphylactic reaction.

The applicant conducted a comprehensive review of serious hypersensitivity events regardless of dose or indication. Two cases of anaphylactic reaction have been identified in subjects treated with risankizumab in the other indication studies. These 2 cases are described below:

In the open label Crohn's disease study, [M15-989 (1311.20)], **Subject** <sup>(b) (6)</sup> a 43-year-old white female had an anaphylactic reaction on Day 175 and was hospitalized. The applicant provides the following: "Within minutes of the injection, given on the same day, she became clammy and tachycardic. The subject did not lose consciousness but had chest tightness. Her heart rate was 130 bpm and systolic blood pressure was 140 mmHg." It appears the reaction is temporally related to intravenous ferinject. The relationship of the reaction to the study drug is not clear based on the information provided. Treatment medications included adrenaline, hydrocortisone, and chlopheniramine. Within 2 hours of onset, the subject recovered. Study drug was not interrupted due to this event. The subject had been exposed to previous iron injections without any known reactions. On Day 575 the subject had a ferinject infusion without incident. Both ferinject and a risankizumab injection were given on the day of the reaction. There appears to be a negative rechallenge with both ferinject and risankizumab. There have been reports of reactions associated with iron infusion. However, the contribution of study drug cannot be determined.

In the psoriatic arthritis study, [M16-002 (1311.5)], **Subject** <sup>(b) (6)</sup> a 50-year-old white female reported an anaphylactic reaction. The subject was biologic naïve and 1 hour after the first dose of 150 mg of risankizumab, the subject experienced symptoms of increasing dizziness, weakness, nausea, a macular rash on the thorax (décolleté) and neck, and dyspnea. The subject's blood pressure decreased from a pre-dose measurement of 160/90 to a nadir of 90/60,

70 minutes post dose. The blood pressure increased to 140/90, recorded as supine, 140 minutes post dose. Tachycardia was not recorded.

The subject reported experiencing anxiety prior to the injection. There was no history of facial swelling, mucosal involvement, pruritus, or urticaria. The subject was transported to the hospital. Treatment medications included intravenous electrolytes, ionosteril, fenistil, ranitidine and prednisolone. The subject's condition improved, and she was discharged from the hospital the following day. The drug was permanently discontinued. The event was considered by the investigator, but not the sponsor to have a reasonable possibility of relationship to study drug. While the temporal relationship tends to favor a possible anaphylaxis event, other provided details seem to be more consistent with a possible vasovagal episode. There is insufficient information to attribute this event to an IgE-mediated anaphylactic reaction.

There does not appear to sufficient information to include anaphylactic reactions to section 4 product labeling. Cases of urticaria and edema were reported, but none of the reactions were serious or led to discontinuation. The applicant did not propose hypersensitivity language in section 5 of product labeling. The team discussed including a class warning for hypersensitivity, but opted to not include at this juncture due to the lack of serious cases seen in the clinical trials. It is recommended that the applicant receives a PMR for post-marketing observational study which includes an assessment for hypersensitivity reactions.

#### **Injection-site reaction (ISR)**

In the Phase 3 clinical studies, the applicant used a Local Tolerability Case Report Form, which characterized the subject-reported injection site reactions from the previous dose administration. This form was used to summarize injection-site reactions in the Placebo-Controlled and Ustekinumab-Controlled Analysis Sets. The form assessed swelling, induration, heat, redness, pain and "other." Redness was more frequently reported as occurring in the risankizumab group as compared to placebo. Overall, reports of injection site reaction symptoms were generally low.

Because the Local Tolerability case report form (CRF) was not employed across all studies in the psoriasis program, a search for AEs using the Injection Site Reaction CMQ was performed by the applicant for the Primary Safety Pool and the and the All Risankizumab – Psoriasis Analysis Set. In both analysis sets, none of the injection site reactions were considered severe or led to study discontinuation.

In the Primary Safety Pool, the proportion of subjects in the risankizumab 150 mg group who had injection site reaction AEs was higher than placebo (1.5% vs 1.0%, respectively), but lower than with ustekinumab (3.8%) or adalimumab (5.6%). The most frequently reported injection site-related AEs associated with risankizumab were injection site erythema in 10 (0.7%) subjects and injection site hemorrhage, injection site pain, and injection site pruritus in 3 (0.2%) subjects each.

In the All Risankizumab Psoriasis Analysis Set, injection site reactions were reported for 69 subjects (3.1%), with the most frequently reported injection site related AEs (> 2 subjects) being injection-site erythema in 33 (1.5%) subjects; injection site pain, injection site pruritus, and injection site reaction in 8 (0.4%) subjects each; injection site haematoma and injection site swelling in 7 (0.3%) subjects each; injection site haemorrhage in 6 (0.3%) subjects; and injection site bruising in 3 (0.1%) subjects.

Reported preferred terms that describe injection site reactions (injection site bruising, erythema, extravasation, hematoma, hemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth) were pooled for labeling.

### **Neuropsychiatric events**

Multiple studies have indicated that patients with psoriasis have a greater risk of the development of depression and suicide ideation than the general population. To address the concern that anticytokine therapies may potentiate this risk, depression and suicidal ideation and behavior (SIB) AEs were identified through searches of the MedDRA depression (excluding suicide and self-injury) SMQ and the suicide/self-injury (narrow) SMQ.

The entry criteria for the risankizumab clinical studies did not exclude subjects with a history of SIB. In the first 16 weeks of the Phase 2 and Phase 3 psoriasis studies (primary safety pool), 4 (0.3%) subjects in the risankizumab group had a depression-related event and 2 subjects (0.2%) reported SIB (suicide ideation and suicide attempt). One subject who had a SAE of depression also had an SAE of SIB. None of the depression events led to discontinuation of study drug.

One event of suicide attempt was reported in the adalimumab group. There was 1 subject each, reporting suicidal ideation (SI) in the placebo group and the ustekinumab group. This ustekinumab-treated SI event led to discontinuation of study drug. There were no other discontinuations due to SIB AEs.

In the overall development program (All Risankizumab – Psoriasis Analysis Set), 22 (1.0%) subjects had a depression event. For 2 subjects these events were an SAE. None of the depression events led to discontinuation of study drug. There were no completed suicides in the risankizumab psoriasis clinical studies. There were no additional SIB events with prolonged exposure.

Both risankizumab-treated subject with SIB events had past medical histories of psychiatric illness:

- Subject (b) (6) (Study M16-010), a 55-year-old male with a prior history of bipolar disorder, depression, schizophrenia, and suicidal ideation, experienced an event of suicide attempt and worsening depression on Day 3. Study drug was not discontinued and both events were considered resolved on Day 11.
- Subject (b) (6) (Study M15-992 [1311.4]), a 33-year-old female with a history of bipolar disorder and depression who experienced a nonserious event of

bipolar-self harm thoughts (coded to self-injurious ideation) on Day 54. Study drug was not discontinued.

With the safety update, 6 new subjects experienced a depression event [28 subjects in all (1.1%; 0.9 E/100 PY)]. None of the depression events led to discontinuation of study drug. There were no new cases of suicidal ideation and behavior (SIB) in the safety update.

Based on the clinical trial data available, there is insufficient evidence of increased risk of SIB or other psychiatric issues thus far with risankizumab, in terms of direct drug-related effect. Suicide and self-harm risks are complex behaviors which are influenced by many social, psychological and environmental factors. To better understand the impact, if any, treatment with risankizumab may have, postmarketing data are needed to evaluate the long-term risk in patients with psoriasis receiving risankizumab. A PMR is recommended for an observational study to collect additional data.

### **Hepatic events**

The event rates of hepatic AEs observed at Week 16 (primary safety pool) occurred in 20 (1.5%) subjects in the risankizumab group who experienced a total of 24 hepatic AEs (6.0 E/100 PY) compared to 6 (2.0%) in the placebo group (7.6 E/100 PY), 5 (2.1%) subjects in the ustekinumab group (9.2 E/100 PY), and 3 (1.0%) subjects in the adalimumab group (5.3 E/100 PY). The majority of the hepatic AEs were related to liver enzyme abnormalities. Other events reported that were not related to liver injury/increased transaminase(s) were abnormal ultrasound of the liver (1 event) and hepatic steatosis (4 events).

Two subjects treated with risankizumab and concomitant isoniazid had AEs that were considered serious and subjects discontinued treatment. Two subjects in ustekinumab treatment group and 1 subject in the placebo group also reported drug-induced liver injury/liver injury SAEs for event rates of (1.1 E/100 PY) and (2.6 E/100 PY), respectively compared to the risankizumab group (0.5E/100 PY).

Other notable hepatic AEs included: LFT abnormal (Grade 4) and LFT increased (Grade 3). These events were not SAEs and did not lead to discontinuation of study drug. The cases are described below:

**Subject** (b) (6) in Study M16-008 [1311.3] is a 62-year-old Asian male with a history of alcohol use (2 drinks per week), latent TB, 21-day treatment with isoniazid (INH) prior to study who was treated with risankizumab for chronic plaque psoriasis. Baseline lab values showed a slightly elevated total bilirubin (TbI) and gamma glutamyl transpeptidase (GGT). The subject received 1 dose of risankizumab and discontinued from the study. The reason for which is not clear in the applicant's provided narrative. On Day 20 (Post-Treatment Day 19) the subject experienced drug-induced hepatitis requiring hospitalization. Alanine amino transferase (ALT), aspartate amino transferase (AST) and GGT values

were all > 20 × upper limit of normal (ULN); alkaline phosphatase (ALP) was 2X ULN and TBI was within normal limits (WNL).

INH was discontinued. On Day 92 (Post-Treatment Day 91) laboratory values (AST, ALT, ALP) were within normal laboratory reference range. Laboratory values are shown in Table 32.

**Table 32: Relevant Hepatic Laboratory Values for Subject (b) (6)**

| Treatment Day     | Total Bilirubin (Reference Range: 3 – 21 UMOL/L) | Alkaline Phosphatase (Reference Range: 35 – 125) U/L | Alanine Amino Transferase (Reference Range: 6 – 43) U/L | Aspartate Amino Transferase (Reference Range: 11 – 36) U/L | Gamma Glutamyl Transpeptidase (Reference Range: ) | Lactate dehydrogenase (Reference Range: 53 – 234) U/L |
|-------------------|--------------------------------------------------|------------------------------------------------------|---------------------------------------------------------|------------------------------------------------------------|---------------------------------------------------|-------------------------------------------------------|
| Screening Day –41 | 29                                               | 103                                                  | 32                                                      | 27                                                         | 72                                                | 179                                                   |
| Day 1             | 11                                               | 103                                                  | 40                                                      | 28                                                         | 127                                               | 182                                                   |
| Day 20            | Not Reported                                     | Not Reported                                         | 932                                                     | 893                                                        | 924                                               | Not Reported                                          |
| Day 21            | 1.5                                              | 366                                                  | 885                                                     | 770                                                        | 1012                                              | Not Reported                                          |
| Day 22 Local Lab  | 0.7                                              | Not Reported                                         | 323                                                     | 61                                                         | 606                                               | 425                                                   |
| Day 22            | 23                                               | 307                                                  | 970                                                     | 658                                                        | Not Reported                                      | 425                                                   |
| Unknown Day       | Not Reported                                     | 128                                                  | 35                                                      | 21                                                         | 279                                               | Not Reported                                          |
| Day 92            | 0.9                                              | 92                                                   | 17                                                      | 16                                                         | Not Reported                                      | Not Reported                                          |

Source: Applicant's CSR Narratives

Both the investigator and the sponsor considered the event of drug-induced liver injury as having a reasonable possibility of being related to study drug. The case is confounded by treatment with INH for latent TB. INH is associated with both mild hepatotoxicity and hepatitis, sometimes advancing to fulminant liver failure. The duration of INH treatment prior to onset of liver toxicity has been reported to be between 1-25 weeks duration, with an average duration of 12 weeks. It cannot be determined the degree, if any risankizumab contributed to the reported AE of drug-induced hepatitis.

**Subject** (b) (6) in Study M16-010 [1311.30] is a 59-year-old, white male with a history of obesity, latent TB, 68-day treatment with isoniazid (INH) prior to study, possible daily use of acetaminophen who was treated with risankisumab for chronic plaque psoriasis. Baseline lab values showed a slightly GGT and elevated AST (5X ULN). On Day 30 (Post-Treatment Day 1) the subject experienced hepatic injury. ALT and AST increased to about 12X ULN; ALP and TBI remained WNL.

Risankisumab and INH were discontinued. On Day 138 (Post-Treatment Day 109) laboratory values (AST, ALT) were within normal laboratory reference range. Laboratory values are shown in Table 33.

**Table 33: Relevant Hepatic Laboratory Values for Subject (b) (6)**

| Treatment Day                    | Alanine Aminotransferase Reference Range 6 – 43 | Alkaline Phosphatase Reference Range 35 – 131 | Aspartate Aminotransferase Reference Range 11 – 36 | Gamma Glutamyl Transferase Reference |
|----------------------------------|-------------------------------------------------|-----------------------------------------------|----------------------------------------------------|--------------------------------------|
| Day 1                            | 44                                              | 43                                            | 229                                                | 62 (High)                            |
| Day 31 (Post-Treatment Day 2)    | 550                                             | 64                                            | 424                                                | Not Provided                         |
| Day 48 (Post-Treatment Day 20)   | 94                                              | 53                                            | 51                                                 | Not Provided                         |
| Day 138 (Post-Treatment Day 109) | 17                                              | 48                                            | 19                                                 |                                      |

| Treatment Day                    | Bilirubin UMOL/L Reference Range Not |
|----------------------------------|--------------------------------------|
| Screening                        | 10                                   |
| Day 1                            | 13                                   |
| Day 29                           | 13                                   |
| 32 (Post-Treatment Day 3)        | 16                                   |
| Day 47 (Post-Treatment Day 19)   | 10                                   |
| Day 138 (Post-Treatment Day 109) | 9                                    |

Source: Applicant's CSR Narratives

The investigator, but not the sponsor considered the event of drug-induced liver injury as having a reasonable possibility of being related to study drug. The case is confounded by treatment with INH for latent TB as in the case above. The subject received 14 weeks of INH treatment and approximately 4 weeks of treatment with risankizumab. It cannot be determined the degree, if any risankizumab contributed to the reported AE of drug-induced hepatitis.

**Subject (b) (6)** in Study 1311.2 is a 31-year-old female with a history of hepatic steatosis who was treated with risankisumab (90 mg in the phase 2 study) for chronic plaque psoriasis. On Day 43 the subject experienced Grade 4 elevation of AST, ALT and GGT. The elevation in liver transaminases was > 20 × upper limit of normal (ULN) without concomitant elevation of bilirubin. The subject continued the trial as planned and recovered by Day 92.

After 52 weeks of exposure, the hepatic event rate in the risankizumab group was 6.5 E/100 PY. Twenty-eight (4.7%) subjects in the risankizumab group experienced 40 hepatic events compared with 10 (5.0%) subjects having 13 events in the ustekinumab group (6.4 E/100 PY). Compared to the 16-week analysis, the 52-week event rate for risankizumab increased slightly, but the event rate for ustekinumab decreased to a rate comparable to risankizumab.

In the All Risankizumab – Psoriasis Analysis Set, hepatic AEs were reported in 77 (3.4%) subjects treated with risankizumab (121 events, 5.6 E/100 PY). Of these 2234 subjects, there were 12 cases reporting abnormal transaminases (AST increased, ALT increased, LFT increased, GGT increased, LFT abnormal) that were RCTC Grade  $\geq 3$  ( $> 3 \times$  ULN). Of these, 3 cases were  $\geq 20 \times$  ULN elevation (these include the cases described above). None of the subjects with severe hepatic AEs had bilirubin of Grade 2 or above in severity. One subject (b) (6) with an AE of congestive heart failure had transaminases ( $> 3 \times$  ULN) and elevated TBI ( $> 2 \times$  ULN), however ALP was elevated, and the elevations were likely due to cholestasis. One subject with ALT increased and 1 subject with ALT/AST increased discontinued study drug due to their AEs

In the Phase 2 psoriatic arthritis study, Study M16-002, 1 subject (b) (6) a 57-year-old white male with a history of alcohol use, fatty liver, hypertriglyceridemia, hypercholesterolemia (on atorvastatin), pancreatitis, and cardiomyopathy met laboratory criteria for Hy's with Grade 3 increases in ALT, AST and bilirubin 56 days after the last dose of study drug (Day 170). Steatohepatitis was confirmed by biopsy. The subject was not receiving concomitant methotrexate. Multiple confounders included alcohol abuse (about 1 – 2 bottles of wine per day for past month), baseline increased transaminases (GGT, AST, ALT), and history of fatty liver.

In the All Risankizumab – Psoriasis Analysis Set, shifts in baseline chemistry values of grade 0 to 2 at Baseline to grade 3 to 4 at any time during the study occurred in 16 subjects for ALT, 14 subjects for AST, 27 subjects for GGT.

In the safety update, 112 (4.5%) subjects (183 events, 5.4 E/100 PY) reported hepatic AEs. The updated included one case of autoimmune hepatitis (subject (b) (6) in study M15-997). The subject is a 54-year old white female with a history of dyslipidemia, hypothyroidism and coronary heart disease, and elevated ALT at baseline (ALT 43; ULN 34 U/L). After treatment with risankizumab for approximately 1 year the subject experienced elevated for AST, ALT (both  $> 20 \times$  ULN), total bilirubin ( $> 3 \times$  ULN), ALP ( $> 2 \times$  ULN), lactate dehydrogenase, and GGT and was diagnosed with autoimmune hepatitis based on positive autoimmune serologies and biopsy of the liver. The subject was started on a prednisone with improvement in symptoms and subsequent normalization of her liver tests. Study drug was discontinued.

Overall, 6 subjects (0.2%) discontinued treatment due to hepatic events. Some serious hepatic events occurred. There were no cases of fulminant hepatic failure. Most of the events were confounded with concomitant medication or comorbid conditions. It is possible that risankizumab may exacerbate preexisting conditions, but this has not been

seen with other biologic therapies in the treatment of psoriasis. To better understand the impact, if any, treatment with risankizumab may have, postmarketing data are needed to evaluate the long-term risk in patients with psoriasis receiving risankizumab. A PMR is recommended for an observational study to collect additional data.

### **7.3.6. Safety Analyses by Demographic Subgroups**

Five subgroup categories for intrinsic factors were analyzed to assess if there was any impact of these factors on the overall safety profile of risankizumab. Subgroups included race (White, Black or African American, Other), gender (male, female), age (< 65 years, ≥ 65 years), Baseline static Physician's Global Assessment (sPGA; 3, 4), and body weight (≤ 100 kg, ≥ 100 kg).

There are differences in enrollment based on demographics. The risankizumab psoriasis clinical study population was predominantly white (78%) and male (70%). Overall, baseline sPGA score was moderate (3) in approximately 80% of subjects. Approximately 90% of subjects were between under the age of 65.

All 5 deaths in subjects treated with risankizumab occurred in male subjects, which made up the majority of trial subjects by gender. Differences were noted in the rates of SAEs (11% vs. 5.6%), AEs leading to discontinuation (2.1% vs. 1.5%), severe AEs (8.2% vs. 5.4%) and deaths(0.4% vs. 0.2%), which were higher in the subjects ≥65 as compared to <65 years.

Generally, there are no substantial differences in the risk of adverse reactions in demographic subgroups to warrant restricted use. However, because the trials were not powered for these analyses, the data must be interpreted with caution.

### **7.3.7. Specific Safety Studies/Clinical Trials**

At the time of submission, 2 open-label long-term studies [M15-997 and M16-009 (1311.13)] and 1 random withdrawal study [M15-992 (1311.4)] were ongoing. Safety analysis sets included interim data. These studies are described in section 7.1 of this review.

With the August 16, 2018 submission of the 120 day safety update report, the applicant provided additional exposure data from subjects who initiated risankizumab since the initial submission, as well as continued follow-up data from Studies M15-992 (1311.4), M15-997, and M16-009 (1311.13). The applicant also provided new data from Studies M16-178 and M16-004 (1311.38).

**Table 34: Additional Clinical Trials in Psoriasis Subjects Included in the Safety Update Report**

| Study ID/<br>No. of<br>Centers/<br>Locations/<br>Duration                                                                                        | Design<br>Control<br>Type<br>Primary<br>Endpoints                                                                                                                                                                                                                                                                                               | Study &<br>Control<br>Drugs<br>Dose, Route<br>& Regimen                                                                                                                                                                                    | Study Objective                                                                                                                                                                                                                                                                               | No. of Subjects by<br>Arm Entered/<br>Completed                                                                | Diagnosis Inclusion<br>Criteria                                                                                                                                                                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><a href="#">M16-004</a><br/>(1311.38)/<br/>38/<br/>Japan/<br/>52 weeks<br/>(56 weeks for<br/>subjects not<br/>enrolling in<br/>OLE)</p>       | <p>PASI 90 at<br/>Wk 16<br/>blind, double-<br/>dummy, placebo<br/>controlled, parallel</p>                                                                                                                                                                                                                                                      | <p><u>RZB:</u><br/>Group 1:<br/>75 mg SC at<br/>Wks 0, 4, and q12w<br/><br/>Group 2:<br/>150 mg SC at<br/>Wks 0, 4, and q12w<br/><br/><u>PBO:</u> SC<br/>Wk 0, 4, then<br/>switch to<br/>RZB 75 mg<br/>or 150 mg at<br/>Wk 16 and q12w</p> | <p>Assess the<br/>efficacy and<br/>safety of<br/>2 different<br/>dose regimens<br/>of RZB<br/>compared with<br/>PBO in<br/>subjects with<br/>moderate to<br/>severe chronic<br/>PsO. In a<br/>subset of<br/>subjects with<br/>PsA, evaluate<br/>improvement<br/>in signs and<br/>symptoms</p> | <p>RZB: 113/0<br/>(110 ongoing as of<br/>data cutoff)<br/>PBO: 58/0<br/>(54 ongoing as of<br/>data cutoff)</p> | <p>Adults ≥ 20 years of<br/>age with stable moderate to<br/>severe chronic plaque PsO<br/>≥ 6 months duration;<br/>With or without PsA;<br/>BSA involvement ≥ 10%;<br/>PASI ≥ 12; sPGA ≥ 3;<br/>Candidates for systemic or<br/>phototherapy.</p> |
| <p><a href="#">M16-178</a>/<br/>Approximately<br/>25 sites/Europe/<br/>24 weeks<br/>(31 weeks for<br/>subjects not<br/>enrolling in<br/>OLE)</p> | <p>Randomized,<br/>Controlled,<br/>Multicenter, Open<br/>Label Study with<br/>Blinded Assessment<br/>of the Efficacy of the<br/>Humanized<br/>Anti-IL-23p19<br/>Risankizumab<br/>Compared to<br/>FUMADERM® in<br/>Subjects with<br/>Moderate to Severe<br/>Plaque Psoriasis Who<br/>are Naïve to<br/>and Candidates for<br/>PASI 90 at Wk24</p> | <p><u>RZB:</u> 150 mg<br/>SC at Wk 0,<br/>4, 16<br/>Fumaderm<br/><u>Initial:</u> QD to<br/>TID, Wk 0 to<br/>2<br/><br/>Fumaderm: QD<br/>to TID<br/>Max 6 daily doses<br/>to achieve PASI 90,<br/>Wk 3 to<br/>24</p>                        | <p>Compare the<br/>efficacy and<br/>safety of RZB<br/>and Fumaderm<br/>in subjects<br/>with moderate<br/>to severe PsO</p>                                                                                                                                                                    | <p>Ongoing/data are<br/>included in ISS<br/>tables but are not<br/>summarized for<br/>individual study</p>     | <p>Adults with moderate to<br/>severe PsO ≥ 6 months;<br/>PASI &gt; 10,<br/>BSA Involvement &gt; 10%;<br/>DLQI &gt; 10;<br/>Naïve to and candidates for<br/>systemic therapy</p>                                                                 |

This SUR provides approximately 7 months of additional safety data from the data cutoff for the initial submission (01 September 2017) and includes all data up to 29 March 2018 (SUR data cutoff). The SUR includes data from 2,471 adult subjects (an additional 237 subjects since the initial submission) with moderate to severe plaque psoriasis who received at least 1 dose of risankizumab in Phase 2 and 3 clinical studies representing an additional 1185.0 PY of exposure for a total of 3351.6 PY of exposure.

With additional safety data as of this SUR data cutoff, no new safety signals have been identified compared with the initial submission. Relevant data and/or cases from the SUR are discussed within the review section that pertains to the safety issue. The additional data provided in the SUR supports the conclusions from the integrated safety analyses.

## **Additional Safety Explorations**

### **Human Reproduction and Pregnancy**

In cynomolgus monkeys, a dose-dependent increase in fetal/infant loss was noted in the risankizumab-treated groups compared to the vehicle control group. The percent fetal/infant loss was 19%, 32%, and 43% in the vehicle control, 5 mg/kg, and 50 mg/kg groups, respectively.

In the risankizumab psoriasis clinical development program, male subjects and their female partners were not required as per the protocols to use contraception. It is not expected that large molecule proteins would interact directly with DNA or other chromosomal material and the amount of risankizumab exposure to female partners transferred via seminal fluid is likely to be negligible.

Nine paternal exposure pregnancies were reported in the partner of a male study subject in the risankizumab clinical development program, no congenital anomalies were reported as outcome.

Female subjects of childbearing potential were required to use a highly effective method of birth control (that result in a low failure rate of less than 1% per year). Negative pregnancy tests were required at screening/baseline and urine pregnancy testing was performed at appropriate intervals. Subjects who became pregnant were to withdraw from treatment and were followed until delivery and outcome was reported. Pregnancy in a study subject was not considered an AE.

Seventeen maternal exposure pregnancies occurred in the risankizumab clinical development program, of which 14 occurred in studies for the indication of psoriasis and 3 occurred in studies for other indications. Pregnancy outcome by treatment arm are shown in Table 35.

**Table 35: Summary of Pregnancy Outcomes in Risankizumab Clinical Program**

| Maternal Exposure Outcomes (N = 17)                | Risankizumab | Comparator | Placebo  | Total     |
|----------------------------------------------------|--------------|------------|----------|-----------|
| Live birth without congenital anomaly              | 3            | 0          | 0        | 3         |
| Spontaneous Abortion                               | 2            | 2          | 0        | 4         |
| Elective termination (no fetal defects or unknown) | 5            | 1          | 0        | 6         |
| Ongoing pregnancy                                  | 4            | 0          | 0        | 4         |
| <b>Total</b>                                       | <b>14</b>    | <b>3</b>   | <b>0</b> | <b>17</b> |

Source: Applicant's SCS Table 41

Two pregnancies in which the mother was taking risankizumab occurred since the initial submission. Both cases occurred in subjects with Crohn's disease (CD); 1 pregnancy is ongoing and 1 was an elective termination due to fetal defects cystic hygroma and fetal hydrops. The case is as follows:

A 24-year-old white female with CD who was exposed to risankizumab for approximately 18 months including prior to conception and during the first trimester elected for termination of the pregnancy at 12 weeks due to a fetus with cystic hygroma and fetal hydrops. Concomitant medications included nortriptyline, paracetamol, and desogestrel. Chromosomal analysis from chorionic villus sampling was normal and human parvovirus testing was not suggestive of an acute infection. The Investigator considered the cystic hygroma and fetal hydrops to have a reasonable possibility of being related to study drug; however, AbbVie considered the causality to be not related due to the following:

Transfer of immunoglobulins across the placental syncytiotrophoblast requires the neonatal Fc receptor, which is barely detectable before gestational Week 14. Therefore, immunoglobulin G (IgG) placental transfer is minimal in the first trimester, hence limiting large molecule drug transfer to the fetus during the period of organogenesis (between gestational Weeks 3 and 8).

The Fc neonatal receptor (FcRn) has been demonstrated to play a critical role in mediating IgG transplacental transfer, but recent studies demonstrating distinct transfer efficiencies of different epitope specific-IgG suggest that other mechanisms could also contribute to the regulation of IgG transfer.<sup>17</sup> IgG can be detected in cord blood as early as 8–10 weeks of gestation.<sup>18</sup> IgG1 is the most efficiently transported subclass and

<sup>17</sup> Fouda G. et al. The Impact of IgG transplacental transfer on early life immunity. *Immunohorizons*. 2018 Jan 1; 2(1): 14–25.

<sup>18</sup> Simister NE. Placental transport of immunoglobulin G. *Vaccine*. 2003;21:3365–3369.

efficiency of IgG transfer can vary from one antigen-specificity to another. Most of the information on maternal-fetal transfer comes from measurements of the concentrations of endogenous antibodies. It is unknown how efficiently risankizumab, an exogenous IgG1 antibody would transfer to the fetal circulation at therapeutic concentrations.

Cystic hygromas can occur as an isolated finding or in association with other birth defect as part of a syndrome. They result from environmental factors, genetic factors, or unknown factors. Chromosome abnormality does not appear to be a factor in this case. It is not stated whether viral studies other than parvovirus were done. While there are a number of possible factors (other viral infections, chemical exposures) that could be causal but are difficult to attribute, exposure to risankizumab cannot be ruled out.

One single case in the clinical development is not sufficient to assess a causal relationship between risankizumab and cystic hygromas with fetal hydrops. Because the available data are insufficient to inform risankizumab-associated risk in pregnant women, we will require that the applicant conduct: 1) a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to risankizumab during pregnancy to an unexposed control population, and 2) a retrospective cohort study using claims or electronic medical record data or a case control study to assess adverse pregnancy, neonatal and infant outcomes of women exposed to risankizumab during pregnancy compared to an unexposed control population. Refer to Section 12 Postmarketing Requirements and Commitments for further details.

### **Human Carcinogenicity or Tumor Development**

There is a theoretical risk of increased malignancy for any product that produces immunosuppression and which is indicated for chronic administration. In patients with psoriasis, this risk may be potentiated by prior exposure to other immunosuppressive agents or other therapies that may enhance tumor development such as phototherapy.

No genetic toxicology or carcinogenicity animal studies were conducted with risankizumab. The applicant provided a carcinogenic risk assessment, mainly using information from published literature. Refer to Section 5.1 for Pharmacology /Toxicology.

The limited duration of observation during the drug development program is unlikely to allow detection of rare events with a long latency periods such as malignancy. Therefore, postmarketing data are needed to evaluate the long-term risk of malignancy in patients with psoriasis receiving risankizumab.

### **Pediatrics and Assessment of Effects on Growth**

The applicant has not conducted an evaluation of the safety and efficacy of risankizumab in the pediatric population. Because the proposed product is a new active

ingredient, approval of risankizumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy triggers the Pediatric Research Equity Act (PREA)(21 U.S.C. 355c). Per the Food and Drug Administration Safety and Innovation Act (FDASIA), the applicant submitted an initial Pediatric Study Plan (iPSP) on 8/19/2015. The Agency agreed with the iPSP (Agreement Letter dated 3/9/2016).

In this submission, the applicant requested a partial waiver for studies in the pediatric population from birth to less than 6 years of age as “Necessary studies are impossible or highly impracticable due to the extremely low prevalence of moderate to severe psoriasis in this population.” (Section 505B (a)(4)(B)(i) of the Act). Although the epidemiologic data are limited regarding the pediatric population with moderate to severe plaque psoriasis, in general the prevalence of plaque psoriasis increases with age. In addition, the sponsor requested a deferral of studies in the pediatric population from age 6 years to <18 years “until safety and efficacy in the adult indication has been demonstrated in Phase 3 studies” (Section 505B (a)(3)(A)(ii) of the Act).

In the discussion with PeRC (3/20/2019) regarding the evaluation of risankizumab in the pediatric population, the Division conveyed their agreement with the proposed pediatric development program in the Agreed iPSP and the proposed timeline. PeRC concurred with the Division and recommended requesting earlier submission dates as per the iPSP . Refer to Section 12 for the pediatric study requirement for risankizumab under PREA.

### **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

No cases of risankizumab overdose has been reported. In the Crohn's disease Study M15-993 (1311.6), multiple doses of up to risankizumab 600 mg IV were administered and in the PK Study M16-513 (1311.16), doses of up to risankizumab 1200 mg IV were administered.

There is no data to support an association of monoclonal antibodies including risankizumab with the potential for drug abuse. Therefore, the applicant did not evaluate abuse potential.

The safety of risankizumab in subjects who had treatment withdrawn and restarted was assessed in the Phase 3 Study M15-992 and Phase 3 OLE Study M15-997. From the available data in these studies, no clinically meaningful changes in AEs were observed with subsequent retreatment. There were also no cases of rebound (defined as  $\geq 25\%$  increase in PASI relative to baseline within 60 days after re-randomization) in subjects who had risankizumab treatment withdrawn.

### **7.3.8. Safety in the Postmarket Setting**

#### **Safety Concerns Identified Through Postmarket Experience**

Risankizumab has not been approved for marketing in any country.

### **Expectations on Safety in the Postmarket Setting**

There are no safety concerns that are expected to change the favorable risk/benefit assessment or lead to increased risk with administration of risankizumab in the postmarket setting. However, additional data are needed to characterize the safety profile of the proposed product in special populations (pregnant and lactating females and the pediatric population age  $\geq 6$  years) and assess the risk of adverse events associated with long latency periods (malignancy) assess the risk of adverse events associated with long latency periods (malignancy). Refer to Section 12 of this review for the postmarketing requirements and commitments.

#### **7.3.9. Integrated Assessment of Safety**

The safety profile for risankizumab was adequately characterized during the drug development program. The primary review of safety of risankizumab for the treatment of moderate to severe plaque psoriasis focused on the evaluation of pooled data from Phase 2 Trial 1311.2 and Phase 3 Trials M15-995 (1311.28), M16-008 (1311.3), M16-010 (1311.30) and M15-992 (1311.4). Trials include 1,590 subjects treated with risankizumab at the proposed dose of 150 mg SC. Of these, 1,091 subjects were exposed for at least 12 months, 96 subjects for 24 months, and 30 subjects for 36 months.

Treatment with risankizumab did not appear to increase the risk of mortality. There were 5 deaths among subjects who received 150 mg risankizumab in the first 52 weeks of controlled trials and additional 5 deaths reported as occurring during the ongoing OLE trials (up through the safety update). None of the deaths can be assessed as causally related to the study product.

During the Placebo-controlled period of the pooled trials, SAEs occurred in 2.4% of subjects treated with risankizumab compared to 4% of subjects treated with placebo. SAEs in the risankizumab group leading to discontinuation of study drug were cardiac failure congestive, drug-induced liver injury, liver injury, invasive lobular breast carcinoma, and esophageal carcinoma. The SAEs assessed by the investigators as possibly related to study drug were drug-induced liver injury, liver injury, cellulitis, herpes zoster, osteomyelitis, and asthma.

Because of the mechanism of action of risankizumab, malignancy is a potential risk. After 52 weeks of treatment 3 subjects (0.5 E/100 PY) reported non-NMSC malignancies. For the overall development program, a total of 21 malignancies (excluding NMSC) were reported, 0.62 E/100 PY. The most frequent non-NMSC malignant tumors were breast cancer in 7 subjects, prostate cancer in 3 subjects and malignant melanoma in 2 subjects. For NMSC malignancies the ratio of SCC to BCC was approximately 1:1.5 for the 25 NMSC malignancies reported. Although the event rate for malignancy is slightly higher than other sources of data in psoriasis patients, there was only one death from malignancy in the risankizumab development program. At this juncture a causal link between the product and malignancy is not evident. Additional long-term data is needed to characterize the risk of malignancy.

Infections (including serious infections, TB, opportunistic infections, fungal infections, and herpes zoster) are a safety concern because of the mechanism of action of risankizumab. Compared to placebo, subjects treated with risankizumab experienced more infections, including a higher rate of fungal infections (mostly tinea). Infections and infestations is the SOC with the highest number of subjects with SAE in the safety set for all risankizumab treated subjects. Two subjects discontinued due to serious infections (1 due to sepsis and pneumonia and 1 due to pneumonia). Over the entire psoriasis program, the rates of opportunistic infections among risankizumab-treated subjects with psoriasis were low (0.3 E/100 PY). None of the opportunistic infections were serious or led to discontinuation of study drug. Latent TB was reported in 7 subjects and 2 subjects reported a positive test for Mycobacterium tuberculosis complex. There were no reports of active TB. Subjects with active TB were excluded and those with latent TB were required to start treatment prophylaxis prior to starting on risankizumab. Language pertaining to infections and pre-treatment for tuberculosis is recommended to be included in Section 5.3 (Warnings and Precautions) of risankizumab labeling.

Treatment with risankizumab was not associated with an increased incidence of treatment-related adverse reactions in the categories of suicidal ideation and behavior (SIB) and major adverse cardiovascular events (MACE). In the “other CV events” category of the ustekinumab-controlled trials, there appeared to be an imbalance (i.e. 4 events of arrhythmia and 4 events of CHF in the risankizumab arms vs 0 events in the ustekinumab arms) that occurred in 7 patients. In the absence of imbalances in the larger sample size of the primary pooled safety population, this low-incidence observation may have been due to chance. Because there is a lack of serious hypersensitivity cases and the cases anaphylaxis are confounded, hypersensitivity reactions will not be added to sections 4 and 5 of product labeling. Overall, 6 subjects (0.2%) discontinued treatment due to hepatic events. Some serious hepatic events occurred. There were no cases of fulminant hepatic failure. Most of the events were confounded with concomitant medication or comorbid conditions. It is recommended that the applicant conduct a long-term observational post-marketing study that assesses outcomes that include, but are not limited to, serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events.

During the placebo-controlled period, the most common adverse reactions (AR) in subjects treated with risankizumab were upper respiratory infections (10.1%), fatigue (2.2%), pruritis (1.5%), cough (1.2%), urinary tract infection (1.2%), and nausea (1.1%). The frequency of AR was comparable across all age and demographic groups. These AR are recommended to be included in Section 6 (Adverse Reactions) of risankizumab labeling.

Among subjects receiving risankizumab in the entire development program there were 19 maternal exposure pregnancies. Pregnancy outcomes included a single case of a

fetus with cystic hygroma and fetal hydrops and are described in section 7.3.8 of this review. Because the available data are insufficient to inform risankizumab-associated risk in pregnant women, we will require post-approval prospective and retrospective studies assessing maternal, fetal and neonatal outcomes of women exposed to risankizumab during pregnancy compared to an unexposed control population. Refer to Section 12 Postmarketing Requirements and Commitments for further details.

The safety data currently available demonstrate that risankizumab is safe for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Postmarketing risk management will include professional labeling, prescription status and routine pharmacovigilance. The long-term risk of malignancy will be assessed by a long-term observational study. The maternal, fetal, and infant outcomes of women exposed to risankizumab during pregnancy will be evaluated by a registry based observational exposure cohort study.

## **7.4. Summary and Conclusions**

### **7.4.1. Statistical Issues**

There were no major statistical issues affecting overall conclusions. The treatment effects were large and consistent across trials and endpoints. The amount of missing data was relatively small (<5%) at the primary timepoint, Week 16. Given the relatively large treatment effect along with the relatively small amount of missing data, the impact of the choice of an imputation method was minimal. The results for each of co-primary efficacy endpoint for each of the pivotal trials was statistically significant (p-values < 0.001).

There were no substantial differences in the treatment effect among subgroups. For the pivotal Phase 3 trials, approximately 70% of the subjects were male, 78% of the subjects were White, 88% of subjects were 18-64 years of age, 72% of the subjects were ≤100 kg, 78% of the subjects had no history of prior TNF use, and 82% of the subjects had sPGA score of moderate (3) at baseline. Given the relatively small number of subjects in the complement of the respective subgroups listed above, estimation of treatment effects in these subgroups may not be reliable.

### **7.4.2. Conclusions and Recommendations**

To establish the effectiveness of risankizumab, the applicant submitted results from two randomized, multicenter, placebo- and ustekinumab-controlled, parallel-group, Phase 3 trials (Trials 1311.28 and 1311.3). The trials enrolled subjects at least 18 years of age with moderate to severe psoriasis (i.e., sPGA score of at least 3 (moderate), PASI  $\geq$ 12, and BSA  $\geq$ 10%) at baseline. The co-primary efficacy endpoints were the proportion of subjects achieving a sPGA score of 0 or 1, with at least 2-grade improvement from baseline, at Week 16, and the proportion of subjects achieving PASI 90 at Week 16.

In both trials, risankizumab was statistically superior to placebo (p-values  $<$ 0.001) for both co-primary efficacy endpoints at Week 16. Although the applicant also showed that risankizumab was statistically superior to ustekinumab at Week 16 (p-values  $<$ 0.001), the applicant did not provide an adequate scientific bridge between the US-licensed and the EU-approved ustekinumab. Thus, the EU-approved ustekinumab may be considered distinct from the US-licensed ustekinumab.

The applicant provided adequate safety exposures to conclude a risk/benefit analysis is sufficient for approval of the application. The summary of the safety information includes:

- Treatment with risankizumab did not appear to increase the risk of mortality as compared to placebo through 16 weeks of randomized, blinded treatment.
- A limited number of serious adverse events (SAEs) in the risankizumab group led to discontinuation of study drug.
- An association between the product and malignancy was not observed, given the limited clinical experience to date.
- Treatment with risankizumab does not appear to be associated with an increased incidence of treatment-related adverse suicidal ideation and behavior (SIB)
- Treatment with risankizumab does not appear to be associated with an increased incidence of treatment-related major adverse cardiovascular events (MACE).
- Serious cases of hypersensitivity and injection site reactions did not occur.
- Some serious non-MACE cardiovascular and hepatic events occurred. Most of the events were confounded with concomitant medication or comorbid conditions.
- Compared to placebo, subjects treated with risankizumab experienced more infections, more serious infections and a higher rate of fungal infections. There were no reports of active TB.
- The available data are insufficient to inform risankizumab-associated risk in pregnant women and children.
- There is limited safety data beyond one year for the use of risankizumab 150 mg subcutaneous injection.

Based on the available information, the safety profile appears to be similar to the premarket safety database for guselkumab and tildrakizumab, which are approved

human monoclonal IgG1 antibodies that target the p19 subunit of IL-23.

## **8 Advisory Committee Meeting and Other External Consultations**

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The Agency held no Advisory Committee Meeting regarding this application because the safety profile was expected to be comparable to that of other biologic products approved for this indication. There were no novel or complex regulatory issues that required public discussion at an AC meeting.

## 9 Pediatrics

Pediatric labeling will be informed by studies conducted under PREA post marketing requirement.

Refer to the following sections of this review for the proposed development program for risankizumab in the pediatric population:

- Section 7 *Pediatrics and Assessment of Effects on Growth* for a discussion regarding the Pediatric Study Plan
- Section 12 *Postmarketing Requirements and Commitments* for the deferred pediatric studies, which are required under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)).

## 10 Labeling Recommendations

### 10.1. Prescribing Information

**Table 36: High level Summary of Significant Labeling Changes**

| Summary of Significant High Level Labeling Changes |                                                    |                                                                                                                                                                                                                                |
|----------------------------------------------------|----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Section                                            | Location of Reviewer Comments on Proposed Labeling | Additional Comments                                                                                                                                                                                                            |
| 1 INDICATIONS AND USAGE                            | Section 1.1                                        | Proposed: "the treatment of moderate to severe plaque psoriasis in adults."<br>Recommended: "adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy".                         |
| 2 DOSAGE AND ADMINISTRATION                        |                                                    | Subjects with active TB were excluded and those with latent TB were required to start treatment prophylaxis prior to starting on risankizumab. Tuberculosis assessment prior to initiation is recommended.                     |
| 4 CONTRAINDICATIONS                                | Section 7.3.5                                      | There does not appear to be sufficient information to include anaphylactic reactions to section 4 product labeling.                                                                                                            |
| 5 WARNINGS AND PRECAUTIONS                         | Section 7.3.5                                      | <ul style="list-style-type: none"> <li>• Recommend adding additional language to clarify patient population regarding infection status/history.</li> <li>• Results from a small number of subjects from the IMMANCE</li> </ul> |

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|                               |                     |                                                                                                                                                                                                                                                                   |
|-------------------------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                               |                     | <p>trial who did not received TB prophylaxis is not sufficient for labeling.</p> <ul style="list-style-type: none"> <li>Hypersensitivity language will not be added at this time due to lack of serious reactions.</li> </ul>                                     |
| 6 ADVERSE REACTIONS           | Section 7.3.4       | <p>(b) (4)</p>                                                                                                                                                                                                                                                    |
| 7 DRUG INTERACTIONS           | Section 6.3.2.4     |                                                                                                                                                                                                                                                                   |
| 8 USE IN SPECIFIC POPULATIONS | Section 7.3.6, 13.3 |                                                                                                                                                                                                                                                                   |
| 12 CLINICAL PHARMACOLOGY      | Section 6.1         |                                                                                                                                                                                                                                                                   |
| 14 CLINICAL STUDIES           | Section 7.1         | <ul style="list-style-type: none"> <li>(b) (4)</li> <li>Evidence submitted by the applicant sufficiently demonstrates that the Psoriasis Symptom Scale (PSS) fit-for-purpose for labeling. It is recommended that the PSS is included in labeling. The</li> </ul> |

|                                   |                                                                              |                                                                                                                                                                         |
|-----------------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                   |                                                                              | Dermatology Life Quality Index (DLQI) does not appear to be fit-for-purpose for labeling in the context of this drug development program due to lack of item relevancy. |
| 17 PATIENT COUNSELING INFORMATION | Reflects the data in other sections of labeling, Sections 4, 5, 6, 7 and 14. |                                                                                                                                                                         |

## 10.2. Patient Labeling

The applicant submitted a Medication Guide (MG) and Instructions for Use (IFU) for risankizumab. The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments on the submitted patient labeling. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Morgan Walker, PharmD, MBA, CPH Laurie Buonaccorsi, PharmD (dated 2/6/2019).

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## **11 Risk Evaluation and Mitigation Strategies (REMS)**

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Based on the risk-benefit profile of this product, risk mitigation measures beyond professional labeling and a Medication Guide are not required at this time. Under 21CFR208.1, the Medication Guide is required to help prevent serious adverse effects. See Section 10.1 Labeling Recommendations. As no additional risk management strategies are required, the subsequent subsections are not applicable for this review and are omitted.

## 12 Postmarketing Requirements and Commitments

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Clinical postmarketing requirements are intended to characterize the risks of risankizumab use in special populations (pregnancy) and address the long-term safety of this novel biologic product in the target population. Development of final pharmacovigilance plans is ongoing.

The available safety data regarding risankizumab use during pregnancy are limited. The study population as defined by the entry criteria excluded pregnant and breastfeeding females, and females planning to become pregnant or breastfeed during the trials. Because exposures to risankizumab during pregnancy are likely to occur and the available data are insufficient to characterize the associated risk in pregnant women, the Agency will require the applicant to conduct the post-marketing assessments to characterize the drug associated risk.

Analysis of expected adverse reactions based on biologic plausibility and potential class effects did not identify a definitive safety signal. However, based on the mechanism of action, the Agency will require post-marketing safety studies to assess the risk of malignancy and other serious adverse events which may not be identified during clinical trials due to a long latency period or low incidence rate.

**Based on review of the data in this submission, the following postmarketing requirements (PMRs) were conveyed to the applicant:**

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

#### **PMR 1:**

1. A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to risankizumab during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including neonatal deaths, infections in the first 6 months of life, and effects on postnatal growth and development, will be assessed through at least the first year of life.

Draft Protocol Submission:

Final Protocol Submission:

Trial Completion:

Final Report Submission:

Rationale: Moderate to severe psoriasis occurs in women of child bearing age. Therefore, we expect there will be some exposure of pregnant women to risankizumab. Data on use of risankizumab in pregnant women are needed.

#### **PMR 2:**

1. Conduct a retrospective cohort study using claims or electronic medical record data or a case control study to assess adverse pregnancy outcomes such as major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal

deaths, and infant infections in women exposed to risankizumab during pregnancy compared to an unexposed control population.

Draft Protocol Submission:

Final Protocol Submission:

Trial Completion:

Final Report Submission:

Rationale: Trials in adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy are completed and the product is ready for approval. Pregnant women were excluded from the development program and data are needed in this population.

**PMR 3:**

1. Conduct an observational study to assess the long-term safety of risankizumab compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care. The study's primary outcome is long-term malignancy. Secondary outcomes include, but are not limited to, serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events.

Describe and justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to risankizumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a prespecified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the risankizumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial 4 year period and follow for a minimum of 8 years from the time of enrollment.

Draft Protocol Submission:

Initial Protocol Submission:

Final Protocol Submission:

Study Completion:

Final Report Submission:

Rationale: There is a concern that this new biologic product may increase the risk of malignancies and serious infections due to its immunosuppressive effect. This is an observational study to collect additional data on long-term safety.

**PREA Requirements**

Risankizumab triggers the Pediatric Research Equity Act (PREA) as a new active ingredient.

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In accordance with 21 CFR 314.55(c)(3)(ii), the applicant, AbbVie, requests a partial waiver of pediatric studies with risankizumab for plaque psoriasis patients younger than 6 years of age. We are waiving the pediatric study requirement for ages 0 to less than 6 years because necessary studies are impossible or highly impracticable. This is because:

- The prevalence of psoriasis in the 0 to less than 6 years age group is low (with the highest prevalence published of 0.3%) and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.

In accordance with 21 CFR 314.55(b), the applicant, AbbVie, requests deferral of pediatric studies with risankizumab for the proposed plaque psoriasis indication in 6 to < 18-year-old patients. We are deferring submission of pediatric studies for ages 6 years to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

A planned study in the pediatric population age 6 years to less than 18 years of age was included in the Agreed iPSP and will be deferred. The applicant is proposing to conduct a single clinical trial (1311.PD ) for the pediatric investigation plan to investigate the PK, safety and efficacy of risankizumab in pediatric subjects 6 to < 18 years of age with moderate to severe disease (b) (4)

[Redacted]

[Redacted] (b) (4)

The required study is listed below.

Conduct a Pharmacokinetics (PK), Safety and Efficacy Study in pediatric subjects 6 to <18 years of age with moderate to severe plaque psoriasis (with a duration of exposure to risankizumab of at least one year).

Initial Protocol Submission: 12/2019

Final Protocol Submission: 06/2020

Trial Completion: 09/2025

Final Report Submission: 03/2026

Rationale: Under Section 2 of the Pediatric Research Equity Act (PREA) the applicant is required to submit adequate safety and efficacy data for pediatric subjects. There is no clinical pharmacology and safety data for subjects with plaque psoriasis age 6 to < 18 years to support labeling.

The CMC review recommends one post marketing requirement:

1. To perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS), and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

The timeline for this requirement remains under discussion as of the date of this review.

## 13 Appendices

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### 13.1. References

The references are included in footnotes.

### 13.2. Financial Disclosure

In compliance with 21 CFR Part 54, the applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were Trials 1311.28, 1311.3, 1311.4, and 1311.30. Refer to Section 7.1.1 for a description of clinical trial design.

Additionally, AbbVie evaluated the studies that are included in the BLA as support for safety to determine if any single investigator made a significant contribution to the demonstration of safety. Studies M15-995, M16-008, M15-992, and M16-010. Also, for the studies included in this BLA as support for safety, no single investigator/site made a significant contribution to the demonstration of safety.

This reviewer reviewed the financial interest information submitted by the applicant. Dr. Tying's site was recommended for inspection. See section 4.1 regarding inspection outcome.

**Table 37: Covered Clinical Studies for Financial Disclosure**

|                                                                                                                                                                                                   |                                         |                                                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                    | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from applicant) |
| Total number of investigators identified; some of the investigators participated in multiple studies and therefore may be counted multiple times within the totals listed in the following table: |                                         |                                                           |

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| Study No.         | Total Number of Investigators | Number of Principal Investigators | Number of Sub-investigators |
|-------------------|-------------------------------|-----------------------------------|-----------------------------|
| M15-995 (1311.28) | 273                           | 77                                | 196                         |
| M16-008 (1311.3)  | 392                           | 95                                | 297                         |
| M15-992 (1311.4)  | 292                           | 69                                | 223                         |
| M16-010 (1311.30) | 265                           | 70                                | 195                         |
| <b>TOTAL</b>      | <b>1222</b>                   | <b>311</b>                        | <b>911</b>                  |

Number of investigators who are sponsor employees (including both full-time and part-time employees): 0

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 34

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0

Significant payments of other sorts: 34

Proprietary interest in the product tested held by investigator: 0

Significant equity interest held by investigator in sponsor of covered study: 0

|                                                                                             |                                         |                                                                  |
|---------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request details from applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                    | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request information from applicant) |

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0

|                                            |                                         |                                                                  |
|--------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| Is an attachment provided with the reason: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request explanation from applicant) |
|--------------------------------------------|-----------------------------------------|------------------------------------------------------------------|

A list of Investigators/Sub-investigators [marked with an asterisk (\*)] by study site who have financial interests or arrangements with AbbVie or their development partner, Boehringer Ingelheim are shown in the Table 38. Each investigator indicated that they received payments that total value in excess of \$25,000 from the sponsor or development partner, other than payments for conducting these clinical studies.

**Table 38: Investigators/Sub-investigators [marked with an asterisk (\*)] by Study Site with Reported Financial Interests**

| Investigator Name | Site Name / Post Office | Sub-investigators | Enrolled Subjects |
|-------------------|-------------------------|-------------------|-------------------|
|-------------------|-------------------------|-------------------|-------------------|

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| (Investigator Number) | Address |  |                                                                                                       |
|-----------------------|---------|--|-------------------------------------------------------------------------------------------------------|
| M15-995 (1311.28)     |         |  | (b) (6) This site enrolled 9 subjects in Study M15-995 (1311.28).                                     |
|                       |         |  | This site enrolled 6 subjects in Study M15-995 (1311.28).                                             |
|                       |         |  | This site enrolled 8 subjects in M15-995 (1311.28) and 5 subjects in Study M16-010 (1311.30).         |
|                       |         |  | This site enrolled 8 subjects in Study M15-995 (1311.28).                                             |
|                       |         |  | This site enrolled (b) (6) subjects in Study M15-995 (1311.28).                                       |
|                       |         |  | This site enrolled 10 subjects in Study M15-995 (1311.28) and 14 subjects in Study M16-010 (1311.30). |
|                       |         |  | This site enrolled (b) (6) subjects in Study M15-995 (1311.28).                                       |
|                       |         |  | This site enrolled 29 subjects in Study M15-995 (1311.28) and 17 subjects in Study M15-992 (1311.4).  |
|                       |         |  | This site enrolled 9 subjects in Study M15-995 (1311.28).                                             |

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|                         |  |                                                                                                         |
|-------------------------|--|---------------------------------------------------------------------------------------------------------|
| (b) (6)                 |  | Site was closed due to noncompliance and is not included in the overall site count for this study.      |
| <b>M16-008 (1311.3)</b> |  |                                                                                                         |
| (b) (6)                 |  | This site enrolled 5 subjects in Study M16-008 (1311.3).                                                |
| (b) (6)                 |  | This site enrolled (b) (6) subjects in Study M16-008 (1311.3).                                          |
| (b) (6)                 |  | This site enrolled 6 subjects in Study M16-008 (1311.3).                                                |
| (b) (6)                 |  | This site enrolled 7 subjects in Study M16-008 (1311.3).                                                |
| (b) (6)                 |  | This site enrolled (b) (6) subjects in Study M16-008 (1311.3) and 9 subjects in Study M15-992 (1311.4). |
| (b) (6)                 |  | This site enrolled 9 subjects in Study M16-008 (1311.3).                                                |
| (b) (6)                 |  | This site enrolled 8 subjects in Study M16-008 (1311.3).                                                |
| (b) (6)                 |  | This site enrolled 21 subjects in Study M16-008 (1311.3), 24 subjects in Study M16-010 (1311.30)        |

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|         |  |                                                                                                                                                                                   |
|---------|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (b) (6) |  | and 20 subjects in Study M15-992 (1311.4). Investigator inspected for cause.                                                                                                      |
|         |  | This site enrolled 19 subjects in Study M16-008 (1311.3).                                                                                                                         |
|         |  | This site enrolled 19 subjects in Study M16-008 (1311.3).                                                                                                                         |
| (b) (6) |  | Site did not enroll.                                                                                                                                                              |
|         |  | This site enrolled 18 subjects in Study M15-992 (1311.4).                                                                                                                         |
|         |  | This site enrolled 8 subjects in Study M15-992 (1311.4).                                                                                                                          |
|         |  | This site enrolled 20 subjects in Study M16-010 (1311.30) and 12 subjects in Study M15-992 (1311.4).                                                                              |
|         |  | This site enrolled 10 subjects in Study M15-992 (1311.4).                                                                                                                         |
|         |  | This site enrolled 21 subjects in Study M16-008 (1311.3), 24 subjects in Study M16-010 (1311.30) and 20 subjects in Study M15-992 (1311.4). Sub-investigator inspected for cause. |
|         |  | This site enrolled (b) (6) subjects in Study M16-008 (1311.3) and 9 subjects in Study M15-992 (1311.4).                                                                           |
|         |  | This site enrolled 29 subjects in Study M15-995                                                                                                                                   |

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|                          |  |                                                                                                                                                                               |
|--------------------------|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (b) (6)                  |  | (1311.28) and 17 subjects in Study M15-992 (1311.4).                                                                                                                          |
|                          |  | This site enrolled 21 subjects in Study M16-008 (1311.3), 24 subjects in Study M16-010 (1311.30) and 20 subjects in Study M15-992 (1311.4). Investigator inspected for cause. |
|                          |  | This site enrolled 9 subjects in Study M15-992 (1311.4).                                                                                                                      |
| <b>M16-010 (1311.30)</b> |  |                                                                                                                                                                               |
| (b) (6)                  |  | This site enrolled 8 subjects in M15-995 (1311.28) and 5 subjects in Study M16-010 (1311.30).                                                                                 |
|                          |  | This site enrolled 20 subjects in Study M16-010 (1311.30) and 12 subjects in Study M15-992 (1311.4).                                                                          |
|                          |  | This site enrolled 5 subjects in Study M16-010 (1311.30).                                                                                                                     |
|                          |  | This site enrolled 10 subjects in Study M15-995 (1311.28) and 14 subjects in Study M16-010 (1311.30).                                                                         |
|                          |  | This site enrolled 13 subjects in Study M16-010 (1311.30).                                                                                                                    |
|                          |  | This site enrolled 15 subjects in Study M16-010 (1311.30).                                                                                                                    |
|                          |  | This site enrolled 7 subjects in Study M16-010 (1311.30).                                                                                                                     |
|                          |  | This site enrolled (b) (6)                                                                                                                                                    |

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|                                                                                   |         |                                                                                                                                                                               |
|-----------------------------------------------------------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | (b) (6) | subjects in Study M16-010 (1311.30).                                                                                                                                          |
|                                                                                   |         | This site enrolled 21 subjects in Study M16-008 (1311.3), 24 subjects in Study M16-010 (1311.30) and 20 subjects in Study M15-992 (1311.4). Investigator inspected for cause. |

### 13.3. Nonclinical Pharmacology/Toxicology

#### Recommended revisions to the nonclinical portions of labelling

Revisions to the applicant's proposed wording for the nonclinical and related sections of the labeling are provided below. It is recommended that the underlined wording be inserted into and the ~~strike through~~ wording be deleted from the SKYRIZI label proposed by the applicant. The subheadings in Section 8.1 should be in underlined format which has been proposed by the applicant. Refer to the clinical review for recommended revisions to the clinical portions of labeling in Section 8.

#### HIGHLIGHTS

##### INDICATIONS AND USAGE

TRADENAME SKYRIZI is an interleukin-23 <sup>(b) (4)</sup> antagonist indicated for the treatment of moderate to severe plaque psoriasis in adults.

#### 8.1 Pregnancy

##### Risk Summary

The limited data available with SKYRIZI use in pregnant women are insufficient to evaluate <sup>(b) (4)</sup> drug-associated risk <sup>(b) (4)</sup> of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG is known to cross the placental barrier; therefore, SKYRIZI may be transmitted from the mother to the developing fetus.

In a <sup>(b) (4)</sup> enhanced pre- and post-natal developmental toxicity study, <sup>(b) (4)</sup> <sup>(b) (4)</sup> pregnant cynomolgus monkeys were administered subcutaneous doses of 5 and 50 mg/kg risankizumab <sup>(b) (4)</sup> once weekly during the period of organogenesis up to parturition. Increased fetal/infant loss was noted in pregnant monkeys treated with 50 mg/kg (see Data), which is 20 times (based on mg/kg comparison) the maximum recommended human dose (MRHD; 2.5 mg/kg based on administration of a 150 mg dose to a 60 kg individual). <sup>(b) (4)</sup>

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated 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 at of 5 and/or 50 mg/kg from gestation day 20 to parturition and the cynomolgus monkeys (mothers and infants) were (b) (4) monitored for 6 months (b) (4) after delivery. (b) (4)

(b) (4)

-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-treated groups (32% and 43% in the 5 mg/kg and 50 mg/kg groups, respectively) compared to the vehicle control group (19%). The increased fetal/infant loss in the 50 mg/kg group was considered to be related to risankizumab 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 (b) (4) 17-86% of the respective maternal concentrations. Following delivery, most adult female cynomolgus monkeys and all infants from the risankizumab-treated groups had measurable serum concentrations of risankizumab up to 91 days postpartum. Serum concentrations were below detectable levels at 180 days postpartum.

### 12.1 Mechanism of Action

Risankizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds (b) (4) to the p19 subunit of human interleukin 23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor (b) (4). IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. (b) (4)

(b) (4)

(b) (4) isankizumab inhibits (b) (4) the release of proinflammatory cytokines and chemokines.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Carcinogenicity and mutagenicity studies have not been conducted with SKYRIZI. (b) (4)

(b) (4)

(b) (4)

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

(b) (4)

#### **13.4. Clinical/ Biostatistics**

##### **Static Physician Global Assessment (sPGA) scale**

| Score | Short description | Detailed description                                                                                                                                    |
|-------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0     | clear             | No signs of psoriasis. Post-inflammatory hyperpigmentation may be present                                                                               |
| 1     | almost clear      | Normal to pink coloration<br>Just detectable (possible slight elevation above normal skin)<br>No to minimal focal scaling                               |
| 2     | mild              | Pink to light red coloration<br>Mild thickening (slight but definite elevation, typically edges are indistinct or sloped)<br>Predominantly fine scaling |
| 3     | moderate          | Dull to bright red coloration<br>Clearly distinguishable to moderate thickening<br>Moderate scaling                                                     |
| 4     | severe            | Bright to deep dark red coloration;<br>Severe thickening with hard edges<br>Severe coarse scaling covering almost all or all lesions                    |

Source: Applicant's protocol

### Psoriasis Area Severity Index (PASI)

The protocol specified that in order to calculate the PASI score, the four main body areas were assessed: head (h), trunk (t), upper extremities (u) and lower extremities (l). These corresponded to 10, 30, 20, and 40% of the total body area, respectively. The signs of severity, erythema (E), infiltration (I), and desquamation (D) of lesions were assessed using a 5-point numeric scale (0-4) where 0 is a complete lack of cutaneous involvement and 4 is the severest possible involvement; scores were made independent of each of the areas, h, t, u, and l and represented a composite score for each area. The PASI score was calculated according to the following formula:

$$\text{PASI} = 0.1(\text{Eh} + \text{Ih} + \text{Dh})\text{Ah} + 0.3(\text{Et} + \text{It} + \text{Dt})\text{At} + 0.2(\text{Eu} + \text{Iu} + \text{Du})\text{Au} + 0.4(\text{El} + \text{Il} + \text{Dl})\text{Al}$$

## 13.5. Clinical pharmacology Appendices

The risankizumab psoriasis clinical development program included eight clinical trials in support of the proposed indication:

- Three Phase 1 trials in healthy subjects and subjects with psoriasis
  - Study 1311.1: a single IV and SC dose PK trial in subjects with psoriasis
  - Study M16-513 (1311.16): a single IV and SC dose PK trial to evaluate intrinsic factors in healthy Caucasian, Japanese, and Chinese subjects

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- Study M16-007 (1311.36): a drug interaction trial to assess the effect of risankizumab on the PK of CYP probe substrates in subjects with psoriasis
- One Phase 2 dose-ranging trial in subjects with psoriasis
  - Study 1311.2
- Four Phase 3 pivotal trials in subjects with psoriasis
  - Study M16-008 (1311.3)
  - Study M15-995 (1311.28)
  - Study M16-010 (1311.30)
  - Study M15-992 (1311.4)

The Applicant also conducted population PK analysis to support the characterization of risankizumab PK. The population PK analysis included covariate analyses to evaluate the effect of intrinsic and extrinsic factors. In addition to the results from the Phase 2 dose ranging trial, the applicant conducted integrated E-R (population PK/PD) analyses for efficacy and safety using pooled data from the Phase 2 and Phase 3 trials to justify the proposed dosing regimen.

The biopharmaceutics program is summarized below.

Drug substance

Risankizumab drug substance (DS) is expressed in (b) (4) cell line.



Drug products

Two drug products have been used across the clinical trials: 10 mg/mL solution supplied in vial for IV administration and 90 mg/mL solution supplied in PFS for SC administration (Table 39). The four Phase 3 trials used the 1-mL PFS presentation with a dispensed volume of 0.83 mL of 90 mg/mL solution, delivering a 75 mg dose of

risankizumab. The drug product used in the psoriasis Phase 3 trials is also the to-be-marketed product proposed for registration in the BLA.

Because the to-be-marketed formulation/presentation was used in the Phase 3 trials, there is no need to bridge the to-be-marketed drug product to the clinical trial drug product.

**Table 39 Risankizumab Drug Substance, Formulation and Presentation Used in Clinical Trials**

|         | Clinical Study    | Drug Substance | Formulation          | Presentation |
|---------|-------------------|----------------|----------------------|--------------|
| Phase 1 | 1311.1            | (b) (4)        | 10 mg/mL<br>90 mg/mL | Vial<br>PFS  |
|         | M16-513 (1311.16) | (b) (4)        | 10 mg/mL<br>90 mg/mL | Vial<br>PFS  |
|         | M16-007 (1311.36) | (b) (4)        | 90 mg/mL             | PFS          |
| Phase 2 | 1311.2            | (b) (4)        | 90 mg/mL             | PFS          |
| Phase 3 | M16-008 (1311.3)  | (b) (4)        | 90 mg/mL             | PFS          |
|         | M15-992 (1311.4)  | (b) (4)        | 90 mg/mL             | PFS          |
|         | M15-995 (1311.28) | (b) (4)        | 90 mg/mL             | PFS          |
|         | M16-010 (1311.30) | (b) (4)        | 90 mg/mL             | PFS          |

*(Source of data: Reviewer's summary based on Biopharmaceutics and Analytical Methods, Table 2)*

### 13.5.1 Summary of Bioanalytical Method Validation and Performance

#### 13.5.1.1 PK assays: bioanalytical methods for determination of risankizumab concentrations in human plasma

The Applicant developed and validated an ELISA for measurement of risankizumab concentrations in human plasma samples from all clinical trials. The method is 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 assay, ELISA plates are coated with a polyclonal anti-risankizumab antibody and nonspecific binding is prevented by the addition of blocking buffer. Captured risankizumab is bound by a biotinylated anti-idiotypic risankizumab antibody. The amount of bound biotinylated antibody is quantified with horse-radish peroxidase conjugated to streptavidin. By addition of the peroxidase substrate 3,3',5,5'-tetramethylbenzidine, an enzymatic reaction is initiated and the absorbance is measured at 450 nm using a SpectraMax Plate Reader after termination of the reaction. The validation parameters and performance of the ELISA are summarized in Table 40.

**Table 40 Summary of Validation Parameters of the ELISA for Measurement of Risankizumab Concentrations in Human Plasma**

| Validation parameters/Item                       | Assay performance                                                                                                                                                                                                                                                            |
|--------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Material for calibration curve                   | BI655066<br>Source: Boehringer Ingelheim (BI)<br>Lot E1731F06 (10.2 mg/mL)<br>Lot DS03 (10.0 mg/mL)<br>Lot DS04 (9.9 mg/mL)                                                                                                                                                  |
| LLOQ and validated assay range                   | LLOQ: 5.00 ng/mL<br>Validated assay range: 5.00 to 100 ng/mL                                                                                                                                                                                                                 |
| Source and lot of reagents                       | BI655066 capture antibody<br>Lot 1104056. API (VIY2) Source: BI<br>Biotinylated anti-idiotypic BI655066 antibody<br>Lot 110720IRB 1B1 (VIY2) Source: BI<br>Lot V160810VF-01 (VIY13) Source: (b) (4)<br>Lot V170413VF-01 (VIY16) Source: (b) (4)                              |
| Regression model and weighting                   | Four-parameter logistic; 1/response <sup>2</sup>                                                                                                                                                                                                                             |
| Standard curve performance                       | Range: 5.00 to 100 ng/mL                                                                                                                                                                                                                                                     |
| Number of standard calibrators from LLOQ to ULOQ | 8 standards: 5.00, 10.0, 20.0, 30.0, 40.0, 60.0, 80.0, 100 ng/mL                                                                                                                                                                                                             |
| Cumulative Accuracy (%bias) LLOQ to ULOQ         | -0.568 to 1.43                                                                                                                                                                                                                                                               |
| Cumulative precision (%CV) from LLOQ to ULOQ     | 0.884 to 2.87                                                                                                                                                                                                                                                                |
| QCs performance                                  | LLOQ: 5.00 ng/mL, Backup LLOQ: 10.0 ng/mL, low: 15.0 ng/mL, middle: 50 ng/mL, high: 75.0 ng/mL, Backup ULOQ: 90.0 ng/mL, ULOQ: 100 ng/mL                                                                                                                                     |
| QC accuracy (% bias)                             | -20.2 (LLOQ) to -2.3                                                                                                                                                                                                                                                         |
| QC precision (% CV)                              | Intra-assay: 1.3 to 3.4<br>Inter-assay: 1.9 to 4.3                                                                                                                                                                                                                           |
| Total error of QC's (%)                          | 6.55 to 23.5 (LLOQ)                                                                                                                                                                                                                                                          |
| Selectivity and matrix effect                    | 10 out of 10 unfortified selectivity samples met the acceptance criteria for normal and psoriatic human plasma.<br>10 out of 10 normal human plasma samples and 9 out of 10 psoriatic human plasma samples fortified with BI655066 at 15.0 ng/mL met the acceptance criteria |
| Interference and specificity                     | IL23 blocked detection of BI655066 in a concentration-dependent manner, consistent with the detection of free BI655066.<br>Level of inhibition caused by IL23 at equimolar concentrations was not significantly altered by dilution of the                                   |

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|                                              |                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                              | sample into the range of quantitation. Specificity was tested for Humira <sup>®</sup> and Stelara <sup>®</sup> . Blank matrix, LLOQ and ULOQ QCs were unfortified and fortified with Humira <sup>®</sup> and Stelara <sup>®</sup> . No effect on the quantitation of BI655066 in KEDTA human plasma |
| Hemolysis effect                             | Four out of five selectivity sample lots met the acceptance criteria for hemolytic and lipemic human plasma (unfortified and fortified with 15.0 ng/mL BI655066).                                                                                                                                   |
| Dilution linearity and high dose hook effect | Dilution linearity demonstrate for a sample containing 500,000 ng/mL BI655066 diluted 6250-, 12500-, and 50000-fold<br>No apparent high dose hook effect observed at concentrations up to 500,000 ng/mL                                                                                             |
| Bench-top process stability                  | 24 hours at room temperature validated                                                                                                                                                                                                                                                              |
| Freeze-thaw stability                        | 5 cycles thawed at room temperature validated                                                                                                                                                                                                                                                       |
| Long-term storage stability                  | All samples were analyzed within the 1610 days demonstrated long-term storage stability in human plasma containing K3EDTA at -80°C ± 10°C                                                                                                                                                           |
| Parallelism                                  | Parallelism has been demonstrated within Study M16-533*                                                                                                                                                                                                                                             |
| Carry over                                   | Not applicable for ligand binding assays                                                                                                                                                                                                                                                            |
| ISR results and associated clinical studies  | Study 1311.1(KKY): 97.3%;<br>Study 1311.1 (RBXF): 100%;<br>Study 1311.2: 86.3%;<br>Study M16-008(1311.3): 93.4%,<br>Study M15-992(1311.4): 98.9%;<br>Study M16-513(1311.16):93.4%,<br>Study M15-995(1311.28): 95.2%;<br>Study M16-010(1311.30): 95.4%,<br>Study M16-007(1311.36): 95.5%             |

\*M16-533 is ongoing, final report pending

API=active pharmaceutical ingredient, BI= Boehringer Ingelheim, BI655066=riskankizumab, IL23=interleukin 23, ISR=incurred sample reanalysis, LLOQ=lower limit of quantitation, QC=quality control sample, ULOQ=upper limit of quantification

(*Source of data: Reviewer's summary based on Riskankizumab BLA761105 Agency Response June 20, 2018, Tables 1-5*)

### 13.5.1.2 Immunogenicity assays: bioanalytical methods for testing anti-drug antibodies and neutralizing anti-drug antibodies

The Applicant developed an ECL immunoassay for assessment of ADA in riskankizumab clinical trials. In brief, human plasma samples are diluted 1:2 and treated with acetic acid, then neutralized with buffer containing biotinylated and Sulfo-Tag<sup>™</sup> labeled assay reagents. Biotinylated-riskankizumab and Sulfo-Tag<sup>™</sup> labeled riskankizumab are incubated to form an antibody complex bridge. After incubation, the samples are then pipetted onto a blocked MSD-Streptavidin plate, allowing unbound material to be washed away.

Only the samples that contain antibody bound to both the labeled assay reagents generate an ECL signal.

A cell-based NAb assay was developed and validated for measures NAb in human plasma through assessment of STAT3 phosphorylation. Plasma samples are incubated with a fixed concentration of IL-23. The human large B cell lymphoma cell line used in the assay displays increased phosphorylated STAT3 in the presence of IL-23. Antibodies that bind to and neutralize risankizumab increase IL-23-mediated IL-23R activation and consequent STAT3 phosphorylation. Phosphorylated-STAT3 is measured using the PathScan® Phospho-Stat3 (Tyr705) Sandwich ELISA.

*Sensitivity and drug tolerance of the immunogenicity assays used in the Phase 3 trials*

The ECL bridging assay had drug tolerance level of 5 mcg/mL of risankizumab in plasma for detection of 0.70 ng/mL ADA (Table 41). The mean steady-state  $C_{trough}$  across all phase 3 studies at Weeks 16, 28, 40, and 52 after administration were 1.84 mcg/mL, 1.60 mcg/mL, 1.57 mcg/mL, and 1.52 mcg/mL, respectively, which were lower than the drug tolerance level of the assay (5 mcg/mL). These findings suggest that the ADA levels could be detected as low as 0.7 ng/mL at the proposed clinical dosing regimen.

The NAb assay had drug tolerance levels of 70 ng/mL or 875 ng/mL of risankizumab in plasma for detection of 250 ng/mL or 2 mcg/mL NAb, respectively (Table 41). The detection of NAb could be interfered with the presence of risankizumab in plasma because the  $C_{trough}$  of risankizumab was above the drug tolerance levels of the NAb assay.

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

**Table 41 Summary of Sensitivity and Drug Tolerance of Immunogenicity Assays**

|                             | ADA                                                                                              | NAb                                                                                                                                                     |                                                                                                                                                                 |
|-----------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Method Matrix               | ECL plasma                                                                                       | Cell-based plasma                                                                                                                                       | Cell-based plasma with sample pre-treatment                                                                                                                     |
| Sensitivity                 | 0.14 ng/mL                                                                                       | 125 ng/mL                                                                                                                                               | 2.0-5.0 mcg/mL                                                                                                                                                  |
| Drug tolerance              | <ul style="list-style-type: none"> <li>0.70 ng/mL PC detected in presence of 5 mcg/mL</li> </ul> | <ul style="list-style-type: none"> <li>250 ng/mL PC detected in presence of 70 ng/mL,</li> <li>2 mcg/mL PC detected in presence of 875 ng/mL</li> </ul> | <ul style="list-style-type: none"> <li>2.5 mcg/mL PC detected in presence of 20 mcg/mL;</li> <li>5 mcg/mL detected in presence of at least 50 mcg/mL</li> </ul> |
| $C_{trough\ ss}$ in Phase 3 | 1.5 to 1.8 mcg/mL                                                                                |                                                                                                                                                         |                                                                                                                                                                 |

C<sub>trough</sub>=trough concentration; PC=positive control

(*Source of data*: Reviewer’s summary based on Biopharmaceutic Studies and Analytical Methods, Table 5)

## 13.5.2 Clinical Pharmacology Studies

### 13.5.2.1 Study 1311.1: Single Ascending Dose Study in Subjects with Moderate to Severe Plaque Psoriasis

Study 1311.1 was a randomized, double-blind, single-ascending dose PK study of risankizumab in male and female subjects with psoriasis (n=39) that consisted of two stages:

- In stage 1, six single IV infusion groups at risankizumab doses of 0.01, 0.05, 0.25, 1, 3, and 5 mg/kg, with active : placebo randomization of 3:1 in each dose group.
- In stage 2, two SC dose groups at risankizumab doses of 0.25 and 1 mg/kg with active : placebo randomization of 7:1 and 6:1, respectively.

The results of risankizumab PK parameters are summarized in Table 42. The observed absolute SC bioavailability of risankizumab for the Phase 1 DS supply was 73%.

**Table 42 Pharmacokinetics of Risankizumab in Subjects with Psoriasis Study 1311.1**

|                                     | Geometric Mean (%CV) |            |            |             |           |            |             |            |
|-------------------------------------|----------------------|------------|------------|-------------|-----------|------------|-------------|------------|
|                                     | IV Dose              |            |            |             |           |            | SC Dose     |            |
| Dose (mg/kg)                        | 0.01 (n=3)           | 0.05 (n=3) | 0.25 (n=3) | 1 (n=3)     | 3 (n=3)   | 5 (n=3)    | 0.25 (n=6)  | 1 (n=7)    |
| C <sub>max</sub> (mcg/mL)           | 0.311 (9)            | 1.36 (28)  | 5.95 (11)  | 12.3 (163)  | 66.2 (9)  | 110 (10)   | 0.96 (51)   | 5.73 (19)  |
| T <sub>max</sub> <sup>*</sup> (day) | 0.083                | 0.043      | 0.094      | 0.042       | 0.083     | 0.083      | 13.0 (2-14) | 5.0 (2-10) |
| AUC <sub>∞</sub> (mcg*day/mL)       | 2.93 (25)            | 15.7 (56)  | 85.1 (14)  | 167 (150)   | 952 (9)   | 1650 (24)  | 41.6 (52)   | 219 (29)   |
| t <sub>1/2</sub> (day)              | 19.4 (18)            | 22.5 (21)  | 22.0 (34)  | 27.7 (12)   | 17.9 (47) | 22.8 (36)  | 22.2 (38)   | 27.7 (14)  |
| CL or CL/F (L/day)                  | 0.323 (48)           | 0.323 (47) | 0.276 (14) | 0.549 (142) | 0.281 (8) | 0.226 (29) | 0.496 (61)  | 0.375 (45) |

\*Median and range (minimum to maximum, for SC only)

AUC<sub>∞</sub>=area under the plasma concentration-time curve over the time interval from 0 to infinity, CL=clearance for IV, CL/F=apparent clearance for SC, C<sub>max</sub>=maximal plasma concentration, n=subjects, T<sub>max</sub>=time to achieve maximum plasma concentration; t<sub>1/2</sub>=terminal elimination half-life

(Source of data: Study 1311.1 Clinical Study Report, Tables 11.2.2.1:1 and Table 11.2.2.2:1)

### 13.5.2.2 Study M16-513 (1311.16): Single Dose PK Study in Caucasian, Japanese and Chinese Healthy Subjects

Study M16-513 (1311.16) was a randomized, single-dose PK study of risankizumab (n=89) that consisted of two stages. Eight male subjects (6:2 active : placebo randomization), ages of 21 to 45 years, were enrolled in each dose group for each ethnicity.

In Stage 1: single rising risankizumab doses were administered via SC rout in three sequential groups (18, 90, and 300 mg) in Chinese and Japanese subjects and two sequential groups (18 and 300 mg) in Caucasian subjects.

In Stage 2: single rising risankizumab doses were administered via IV infusion in the three sequential groups (200, 600, and 1200 mg) in Japanese subjects.

The PK results (Table 43) indicated that risankizumab exposures expressed as  $C_{max}$  and AUC were 22% to 31% higher in Chinese and Japanese subjects compared to healthy Caucasians. After accounting for body weight, risankizumab exposure were comparable across ethnic groups.

**Table 43 Pharmacokinetics of Risankizumab in Healthy Subjects Study M16-513 (1311.16)**

| Dose (mg) | Race            | Geometric Mean (%CV) |                   |                               |                      |                    |
|-----------|-----------------|----------------------|-------------------|-------------------------------|----------------------|--------------------|
|           |                 | $C_{max}$ (mcg/mL)   | $T_{max}^*$ (day) | AUC <sub>∞</sub> (mcg*day/mL) | $t_{1/2}^{**}$ (day) | CL or CL/F (L/day) |
| 18 (SC)   | Japanese (n=6)  | 1.64 (30)            | 7.0 (7-14)        | 83.6 (17)                     | 32.5 (28-41)         | 0.215 (20)         |
|           | Chinese (n=6)   | 1.83 (29)            | 7.0 (3-7)         | 75.7 (22)                     | 28.5 (24-34)         | 0.238 (21)         |
|           | Caucasian (n=6) | 1.02 (21)            | 7.0 (3-28)        | 58.5 (18)                     | 30.5 (23-47)         | 0.308 (18)         |
| 90 (SC)   | Japanese (n=6)  | 9.06 (7)             | 7.0 (7-7)         | 377 (6%)                      | 26.9 (25-29)         | 0.239 (6)          |
|           | Chinese (n=6)   | 6.62 (27)            | 5.0 (3-7)         | 330 (22)                      | 26.7 (23-33)         | 0.273 (17)         |
| 300 (SC)  | Japanese (n=6)  | 20.3 (41)            | 7.0 (7-14)        | 1050 (37%)                    | 29.7 (25-36)         | 0.287 (35)         |
|           | Chinese (n=6)   | 18.9 (26)            | 7.0 (3-14)        | 1000 (28%)                    | 33.8 (27-44)         | 0.300 (28)         |

|              |                    |              |                  |              |                 |               |
|--------------|--------------------|--------------|------------------|--------------|-----------------|---------------|
|              | Caucasian<br>(n=6) | 18.8<br>(39) | 7.0<br>(3-7)     | 871<br>(33%) | 28.7<br>(25-37) | 0.344<br>(35) |
| 200<br>(IV)  | Japanese<br>(n=6)  | 59.6<br>(14) | 0.1<br>(0.1-0.2) | 991<br>(12%) | 31.2<br>(24-46) | 0.202<br>(12) |
| 600<br>(IV)  | Japanese<br>(n=6)  | 225<br>(8)   | 0.1<br>(0.1-0.2) | 3610<br>(9%) | 30.7<br>(28-35) | 0.166<br>(8)  |
| 1200<br>(IV) | Japanese<br>(n=6)  | 360<br>(15)  | 0.1<br>(0.1-0.3) | 6760<br>(28) | 32.7<br>(19-46) | 0.178<br>(35) |

\*Median and range (minimum to maximum), \*\*Geometric mean and range (minimum to maximum)  
AUC<sub>∞</sub>=area under the plasma concentration-time curve over the time interval from 0 to infinity,  
CL=clearance (IV), CL/F=apparent clearance for SC, C<sub>max</sub>=maximal plasma concentration, n=subjects,  
T<sub>max</sub>=time to achieve maximum plasma concentration; t<sub>1/2</sub>=terminal elimination half-life  
(Source of data: Study M16-513(1311.16) Clinical Study Report, Tables 14.2\_3.1.1 through 14.2\_3.1.6)

### 13.5.2.3 Study M16-007 (1311.36): A Clinical Drug Interaction Study in Subjects with Psoriasis

Study M16-007 (1311.36) was a Phase 1, open-label, one-sequence, drug interaction study in subjects with psoriasis (n=21) to evaluate potential effect of risankizumab on the CYP enzyme activities.

#### Study design

**Day 1:** Subjects received a single oral dose of a cocktail containing CYP probe substrates: CYP1A2 (caffeine 100 mg), CYP2C9 (warfarin 10 mg), CYP2C19 (omeprazole 20 mg), CYP2D6 (metoprolol 50 mg), and CYP3A (midazolam 2 mg).

**Days 8 to 92:** Subjects received a total of 4 doses of risankizumab 150 mg SC Q4W on Days 8, 36, 64, and 92.

**Day 98:** Subject received the second single dose of the CYP probe substrates cocktail.

Blood sample were collected during the study to evaluate the PK of CYP probe substrates and risankizumab.

#### Study population

The demographic data based on the 21 subjects are summarized below:

- Sex: 19 males (90%) and 2 females (10%)
- Age (median): 47 years (range: 31-66 years)
- Race: 20 White (95%) and 1 Asian (5%)
- Body weight (mean±SD): 88±19 kg

#### Pharmacokinetics of risankizumab

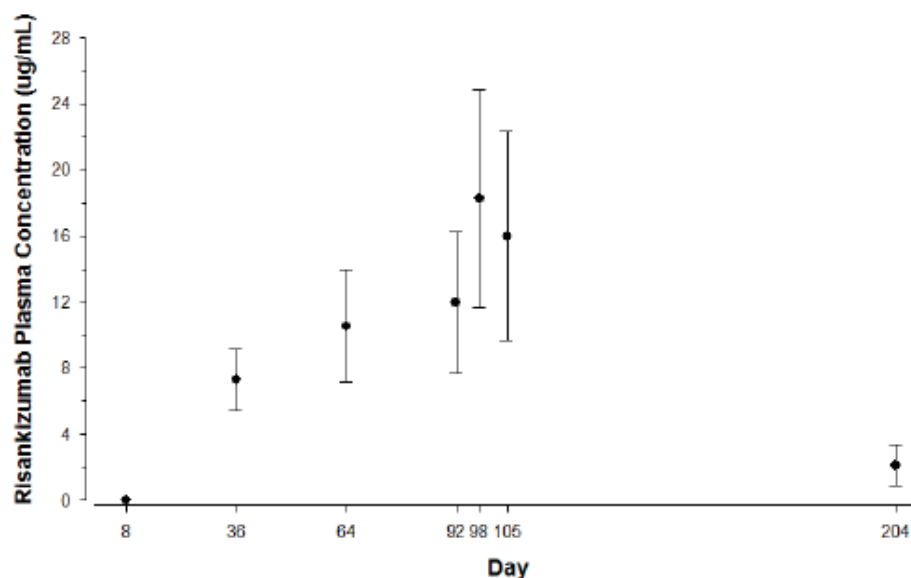
Risankizumab C<sub>trough</sub> values (mean±SD) are presented in Figure 15. Mean C<sub>trough</sub> prior to administration of the 2<sup>nd</sup> (Day 36), 3<sup>rd</sup> (Day 64), and 4<sup>th</sup> (Day 92) dose were 7.3, 10.6, and 12.0 mcg/mL, respectively. The C<sub>trough</sub> at Day 92 was approximately 6-fold higher

than the mean steady-state  $C_{trough}$  of risankizumab at the dosing regimen in the Phase 3 studies.

Effect of risankizumab on Pharmacokinetics of CYP probe substrates

The effect of risankizumab on the PK of caffeine (metabolized by CYP1A2 to form paraxanthine), s-warfarin (metabolized by CYP2C9), omeprazole (metabolized by CYP2C19 to form 5-hydroxy-omeprazole), metoprolol (metabolized by CYP2D6 to form  $\alpha$ -hydroxymetoprolol), and midazolam (metabolized by CYP3A to form 1-hydroxymidazolam) and their corresponding metabolites are summarized in Table 44 to Table 48. Overall, the PK results showed that risankizumab had no clinically meaningful effect on the activities of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A (Table 34).

**Figure 15 Risankizumab Plasma Concentrations Following Administration of 150 mg SC Q4W Regimen (Study M16-007[1311.36])**



(Source of data: Study M16-007(1311.36) Clinical Study Report, Figure 12)

**Table 44 Geometric Mean (%CV) PK of Caffeine and Paraxanthine Following Administration of CYP Cocktail Alone and After Multiple Doses of Risankizumab 150 mg SC Q4W (Study M16-007[1311.36])**

| CYP1A2            | Day1<br>Caffeine 100 mg<br>(n=21) | Day 98<br>Caffeine 100 mg + Risankizumab<br>(n=21) |
|-------------------|-----------------------------------|----------------------------------------------------|
|                   | <u>Caffeine</u>                   |                                                    |
| $C_{max}$ (ng/mL) | 2700 (40)                         | 2950 (77)                                          |

|                                               |                    |                    |
|-----------------------------------------------|--------------------|--------------------|
| AUC <sub>t</sub> (ng*h/mL)                    | 20900 (86)         | 21500 (185)        |
| AUC <sub>∞</sub> (ng*h/mL)                    | 21700 (85)         | 22400 (187)        |
| <b><u>Paraxanthine</u></b>                    |                    |                    |
| C <sub>max</sub> (ng/mL)                      | 850 (48)           | 877 (55)           |
| AUC <sub>t</sub> (ng*h/mL)                    | 15700 (64)         | 15600 (102)        |
| AUC <sub>∞</sub> (ng*h/mL)                    | 17400 (63)         | 15800 (38)         |
| <b><u>Ratio* of Paraxanthine/Caffeine</u></b> |                    |                    |
| AUC <sub>t</sub>                              | 0.74 (0.45 - 1.16) | 0.75 (0.34 – 1.13) |
| AUC <sub>∞</sub>                              | 0.82 (0.50 – 1.17) | 0.83 (0.56 – 1.20) |

\*Median (minimum through maximum)

AUC<sub>t</sub>=area under the plasma concentration-time curve of the analyte from time 0 to the time of the last quantifiable concentration, AUC<sub>∞</sub>=area under the plasma concentration-time curve of the analyte from time 0 extrapolated to infinity, C<sub>max</sub>=maximum observed plasma concentration, n=number of subjects  
(*Source of data: Reviewer's summary based on Study M16-007(1311.36) Clinical Study Report, Table 4*)

**Table 45 Geometric Mean (%CV) PK of S-Warfarin Following Administration of CYP Cocktail Alone and After Multiple Doses of Risankizumab 150 mg SC Q4W (Study M16-007[1311.36])**

|                            | <b><u>Day1</u></b><br>Warfarin 10 mg<br>(n=21) | <b><u>Day 98</u></b><br>Warfarin 10 mg + Risankizumab<br>(n=21) |
|----------------------------|------------------------------------------------|-----------------------------------------------------------------|
| <b><u>S-Warfarin</u></b>   |                                                |                                                                 |
| C <sub>max</sub> (ng/mL)   | 534 (24)                                       | 490 (29)                                                        |
| AUC <sub>t</sub> (ng*h/mL) | 15800 (39)                                     | 14600 (35)                                                      |
| AUC <sub>∞</sub> (ng*h/mL) | 16900 (41)                                     | 15700 (35)                                                      |

AUC<sub>t</sub>=area under the plasma concentration-time curve of the analyte from time 0 to the time of the last quantifiable concentration, AUC<sub>∞</sub>=area under the plasma concentration-time curve of the analyte from time 0 extrapolated to infinity, C<sub>max</sub>=maximum observed plasma concentration, n=number of subjects  
(*Source of data: Reviewer's summary based on Study M16-007(1311.36) Clinical Study Report, Table 5*)

**Table 46 Geometric Mean (CV%) PK of Omeprazole and 5-Hydroxy-Omeprazole Following Administration of CYP Cocktail Alone and After Multiple Doses of Risankizumab 150 mg SC Q4W (Study M16-007[1311.36])**

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|                            | <b>Day1</b><br>Omeprazole 20 mg<br>(n=21)               | <b>Day 98</b><br>Omeprazole 20mg + Risankizumab<br>(n=21) |
|----------------------------|---------------------------------------------------------|-----------------------------------------------------------|
|                            | <b><u>Omeprazole</u></b>                                |                                                           |
| C <sub>max</sub> (ng/mL)   | 226 (48)                                                | 192 (62)                                                  |
| AUC <sub>t</sub> (ng*h/mL) | 464 (78)                                                | 431 (76)                                                  |
| AUC <sub>∞</sub> (ng*h/mL) | 594 (67)                                                | 472 (75)                                                  |
|                            | <b><u>5-Hydroxy-Omeprazole</u></b>                      |                                                           |
| C <sub>max</sub> (ng/mL)   | 182 (33)                                                | 163 (41)                                                  |
| AUC <sub>t</sub> (ng*h/mL) | 493 (27)                                                | 449 (32)                                                  |
| AUC <sub>∞</sub> (ng*h/mL) | 505 (27)                                                | 493 (27)                                                  |
|                            | <b><u>Ratio* of 5-Hydroxy-Omeprazole/Omeprazole</u></b> |                                                           |
| AUC <sub>t</sub>           | 1.13 (0.15 - 4.98)                                      | 1.08 (0.16 – 4.11)                                        |
| AUC <sub>∞</sub>           | 1.13 (0.17 – 1.87)                                      | 1.05 (0.18 – 4.09)                                        |

\*Median (minimum through maximum)

AUC<sub>t</sub>=area under the plasma concentration-time curve of the analyte from time 0 to the time of the last quantifiable concentration, AUC<sub>∞</sub>=area under the plasma concentration-time curve of the analyte from time 0 extrapolated to infinity, C<sub>max</sub>=maximum observed plasma concentration, n=number of subjects  
(*Source of data: Reviewer's summary based on Study M16-007(1311.36) Clinical Study Report, Table 6*)

**Table 47 Geometric Mean (CV%) PK of Metoprolol and α-Hydroxymetoprolol Following Administration of CYP Cocktail Alone and After Multiple Doses of Risankizumab 150 mg SC Q4W (Study M16-007[1311.36])**

|                            | <b>Day1</b><br>Metoprolol 50 mg<br>(n=21) | <b>Day 98</b><br>Metoprolol 50 mg + Risankizumab<br>(n=21) |
|----------------------------|-------------------------------------------|------------------------------------------------------------|
|                            | <b><u>Metoprolol</u></b>                  |                                                            |
| C <sub>max</sub> (ng/mL)   | 32.0 (71)                                 | 31.0 (68)                                                  |
| AUC <sub>t</sub> (ng*h/mL) | 177 (96)                                  | 179 (87)                                                   |
| AUC <sub>∞</sub> (ng*h/mL) | 183 (95)                                  | 184 (86)                                                   |
|                            | <b><u>α-Hydroxymetoprolol</u></b>         |                                                            |
| C <sub>max</sub> (ng/mL)   | 25.3 (38)                                 | 24.4 (38)                                                  |
| AUC <sub>t</sub> (ng*h/mL) | 282 (32)                                  | 281 (35)                                                   |

|                                                        |                     |                     |
|--------------------------------------------------------|---------------------|---------------------|
| AUC <sub>∞</sub> (ng*h/mL)                             | 373 (21)            | 317 (34)            |
| <b><u>Ratio* of α-Hydroxymetoprolol/Metoprolol</u></b> |                     |                     |
| AUC <sub>t</sub>                                       | 1.76 (0.00 – 11.55) | 1.82 (0.00 – 11.79) |
| AUC <sub>∞</sub>                                       | 1.94 (0.37 – 10.89) | 1.81 (0.02 – 11.14) |

\*Median (minimum through maximum)

AUC<sub>t</sub>=area under the plasma concentration-time curve of the analyte from time 0 to the time of the last quantifiable concentration, AUC<sub>∞</sub>=area under the plasma concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity, C<sub>max</sub>=maximum observed plasma concentration, n=number of subjects

(Source of data: Reviewer's summary based on Study M16-007(1311.36) Clinical Study Report, Table 7)

**Table 48 Geometric Mean (CV%) PK of Midazolam and 1-Hydroxymidazolam Following Administration of CYP Cocktail Alone and After Multiple Doses of Risankizumab 150 mg SC Q4W (Study M16-007[1311.36])**

|                                                      | <b><u>Day1</u></b><br>Midazolam 2 mg<br>(n=21) | <b><u>Day 98</u></b><br>Midazolam 2 mg + Risankizumab<br>(n=21) |
|------------------------------------------------------|------------------------------------------------|-----------------------------------------------------------------|
| <b><u>Midazolam</u></b>                              |                                                |                                                                 |
| C <sub>max</sub> (ng/mL)                             | 8.70 (34)                                      | 8.91 (33)                                                       |
| AUC <sub>t</sub> (ng*h/mL)                           | 26.7 (40)                                      | 27.0 (43)                                                       |
| AUC <sub>∞</sub> (ng*h/mL)                           | 27.9 (41)                                      | 28.2 (45)                                                       |
| <b><u>1-Hydroxymidazolam</u></b>                     |                                                |                                                                 |
| C <sub>max</sub> (ng/mL)                             | 2.46 (45)                                      | 2.38 (48)                                                       |
| AUC <sub>t</sub> (ng*h/mL)                           | 6.68 (38)                                      | 6.28 (39)                                                       |
| AUC <sub>∞</sub> (ng*h/mL)                           | 7.09 (37)                                      | 6.69 (38)                                                       |
| <b><u>Ratio* of 1-Hydroxymidazolam/Midazolam</u></b> |                                                |                                                                 |
| AUC <sub>t</sub>                                     | 0.26 (0.14 – 0.19)                             | 0.24 (0.16 – 0.48)                                              |
| AUC <sub>∞</sub>                                     | 0.27 (0.14 – 0.48)                             | 0.25 (0.16 – 0.44)                                              |

\*Median (minimum through maximum)

AUC<sub>t</sub>=area under the plasma concentration-time curve of the analyte from time 0 to the time of the last quantifiable concentration, AUC<sub>∞</sub>=area under the plasma concentration-time curve of the analyte from time 0 extrapolated to infinity, C<sub>max</sub>=maximum observed plasma concentration, n=number of subjects

(Source of data: Reviewer's summary based on Study M16-007(1311.36) Clinical Study Report, Table 8)

**Table 34 Summary of Geometric Mean Ratios and 90% Confidence Intervals for the Effect of Risankizumab on PK of CYP Probe Substrates**

| CYP  | Substrate  | C <sub>max</sub> ratio<br>(Day 98/Day 1) |           | AUC <sub>inf</sub> ratio<br>(Day 98/Day 1) |           |
|------|------------|------------------------------------------|-----------|--------------------------------------------|-----------|
|      |            | GMR                                      | 90%CI     | GMR                                        | 90%CI     |
| 1A2  | Caffeine   | 1.09                                     | 0.96-1.23 | 1.03                                       | 0.90-1.19 |
| 2C9  | S-Warfarin | 0.92                                     | 0.86-0.98 | 0.93                                       | 0.90-0.97 |
| 2C19 | Omeprazole | 0.85                                     | 0.73-0.99 | 0.94                                       | 0.82-1.07 |
| 2D6  | Metoprolol | 0.97                                     | 0.88-1.07 | 1.01                                       | 0.92-1.10 |
| 3A   | Midazolam  | 1.03                                     | 0.96-1.09 | 1.01                                       | 0.94-1.09 |

The potential effect of risankizumab (150 mg SC Q4W x 4) on the activities of CYP1A2 (caffeine), CYP2C9 (warfarin), CYP2C19 (omeprazole), CYP2D6 (metoprolol) and CYP3A (midazolam) was evaluated in subjects with moderate to severe psoriasis using a cocktail approach (Study M16-007[1311.36]). The PK of CYP probe substrates were assessed before (Day 1) and after risankizumab treatments (Day 98). AUC<sub>inf</sub>=AUC from time 0 to infinity, CI=confidence interval, GMR=geometric mean ratio. (*Source of data: Reviewer's summary based on Clinical Study Report M16-007[1311.36], Table 9*)

#### 13.5.2.4 Study 1311.2: A Phase 2 Dose-Ranging Trial in Subjects with Psoriasis

Study 1311.2 was a randomized, parallel-arm, dose-ranging, multiple-dose, active comparator-controlled study in subjects with moderate to severe chronic plaque psoriasis.

##### Study design

- Risankizumab 18 mg SC, single dose at Week 0, n=43
- Risankizumab 90 mg SC, at Weeks 0, 4, and 16, n=41
- Risankizumab 180 mg SC, at Weeks 0, 4, and 16, n=42
- Ustekinumab 45 or 90 mg SC (based on body weight) at Weeks 0, 4, and 16, n=40

Risankizumab in general showed dose-proportional increase in exposure across 90 mg and 180 mg SC doses. Risankizumab median T<sub>max</sub> was 7 days across all SC doses and geometric mean terminal phase t<sub>1/2</sub> was estimated to be 28 days following a single dose of 18 mg.

### 13.5.2.5 Study M16-008 (1311.3), Study M15-992 (1311.4), Study M15-995 (1311.28), Study M16-010 (1311.30): Risankizumab PK in Phase 3 Trials in Subjects with Psoriasis

Observed risankizumab trough plasma concentrations in Phase 3 trials are summarized in Table 49.

**Table 49 Risankizumab Trough Plasma Concentrations in Phase 3 Trials**

| Study                                                | Geometric Mean (mcg/mL) (%CV) |                        |                        |                       |                       |
|------------------------------------------------------|-------------------------------|------------------------|------------------------|-----------------------|-----------------------|
|                                                      | Week 4                        | Week 16                | Week 28                | Week 40               | Week 52               |
| <b>M16-008<br/>(1311.3)</b>                          | 5.54<br>(40)<br>n=297         | 1.85<br>(55)<br>n=297  | 1.68<br>(57)<br>n=293  | 1.73<br>(77)<br>n=297 | 1.58<br>(62)<br>n=289 |
| <b>M15-995<br/>(1311.28)</b>                         | 5.57<br>(39)<br>n=293         | 1.72<br>(62)<br>n=293  | 1.48<br>(60)<br>n=288  | 1.48<br>(60)<br>n=287 | 1.54<br>(66)<br>n=276 |
| <b>M16-010<br/>(1311.30)</b>                         | 5.44<br>(37)<br>n=298         | 2.06<br>(57)<br>n=292  | 1.82<br>(60)<br>n=284  | NA                    | NA                    |
| <b>M15-992<br/>(1311.4)</b>                          | 5.23<br>(38)<br>n=177         | 1.70<br>(71)<br>n=175  | 1.39<br>(65)<br>n=173  | 1.46<br>(89)<br>n=166 | 1.42<br>(66)<br>n=156 |
| <b>Pooled data<br/>across all<br/>Phase 3 trials</b> | 5.47<br>(38)<br>n=1065        | 1.84<br>(60)<br>n=1057 | 1.60<br>(60)<br>n=1038 | 1.57<br>(75)<br>n=750 | 1.52<br>(65)<br>n=721 |

CSR=Clinical Study Report, n=subjects, NA=not available

(Source of data: M16-008 (1311.3) CSR Table 16, M15-995 (1311.28) CSR Table 16; M16-010 (1311.30), CSR, Table 21, M15-992(1311.4), CSR, Table 19, R&D/17/1378 Table 11.1\_1)

## 13.5.3 Immunogenicity

### 13.5.3.1 Immunogenicity incidences

The treatment-emergent anti-drug antibody (TE-ADA) and treatment-emergent neutralizing antibody (TE-NAb) incidences in three Phase 3 trials are summarized in Table 50. The median time to appearance of ADA was 16 weeks across studies. The incidences for NAb among TE-ADA+ subjects were 42% (103/243) and 57% (150/263) over the durations of 16 weeks and 52 weeks, respectively. A total of 16 of 1079 ADA evaluable subjects (1.5%), representing 6% of TE-ADA+ subjects (16 of 263), had ADA titer values of  $\geq 128$  over the duration of 52 weeks.

**Table 50 Summary of Immunogenicity Incidences in Phase 3 Trials**

|                        | Risankizumab Phase 3 Study |          |          |           | Total     |
|------------------------|----------------------------|----------|----------|-----------|-----------|
|                        | M16-008                    | M15-995  | M16-010  | M15-992   |           |
| <b>Week 0-16</b>       |                            |          |          |           |           |
| Subjects (n)           | 297                        | 296      | 295      | 400       | 1288      |
| TE-ADA incidence n (%) | 50 (20%)                   | 46 (16%) | 62 (21%) | 77 (19%)  | 243 (19%) |
| TE-NAb incidence n (%) | 23 (8%)                    | 15 (5%)  | 27 (9%)  | 38 (9.5%) | 103 (8%)  |
| <b>Week 0-52</b>       |                            |          |          |           |           |
| Subjects (N)           | 301                        | 298      | 299      | 181       | 1079      |
| TE-ADA incidence n (%) | 78 (26%)                   | 64 (22%) | 74 (25%) | 47 (26%)  | 263 (24%) |
| TE-NAb incidence n (%) | 44 (15%)                   | 34 (11%) | 43 (14%) | 29 (16%)  | 150 (14%) |

Definitions of subjects ADA status are summarized below

- ADA evaluable subjects: Subjects had at least 1 reportable immunogenicity assessment during the study post baseline.
- Treatment-emergent anti-drug antibody (TE-ADA) or ADA positive: Subjects had (1) ADA negative or missing assessment at baseline (prior to 1<sup>st</sup> risankizumab dose) and became ADA positive at one or more time points post baseline, or (2) ADA positive at baseline and showed a 4-fold (based on 2 dilution steps at the titer determination stage) or greater increase in titer values relative to baseline or a titer value of 2 or greater in at least one post-dose samples if the baseline titer value was less than 1 (in this case 4-fold increment over midpoint of 0.5 was used).
- ADA Negative: All pre- and post-treatment samples were negative for the ADA assay
- Treatment-emergent neutralizing antibody (TE-NAb): The confirmed ADA positive samples were also evaluated in the neutralizing antibody (NAb) assay to test for the presence of NAb.
  - TE-NAb indicated TE-ADA positive and positive for NAb.
  - NAb Negative included 1) ADA negative and 2) TE-ADA positive and negative for NAb

(Source of data: Reviewer's summary based on Immunogenicity Report R&D/17/1378, Table 2 and Table 3)

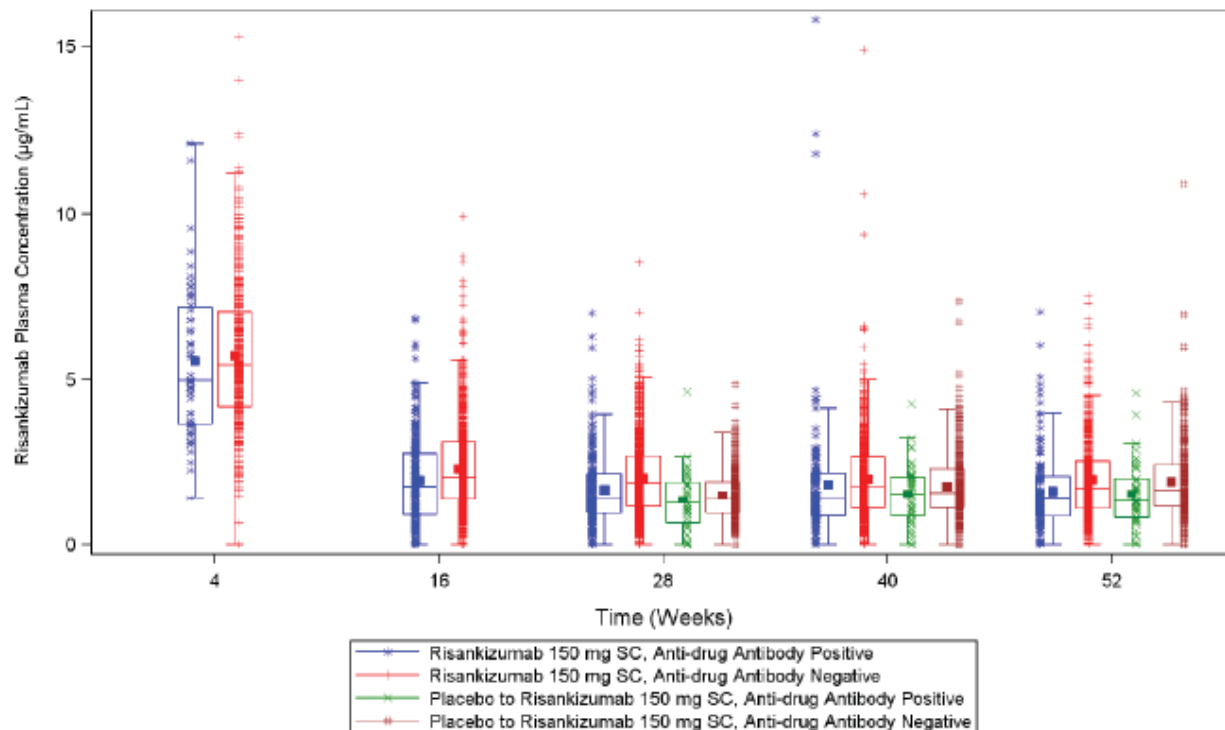
### 13.5.2.2 Immunogenicity impact on pharmacokinetics

As shown in Figure 16, risankizumab trough plasma concentration central tendency and distribution by visit and ADA status using pooled data across all four Phase 3 trials were comparable between subjects who were ADA positive and those who were ADA

negative over time, indicating that ADA to risankizumab did not have a clinically relevant impact on PK of risankizumab in majority of ADA positive subjects.

In a small subset of subjects who developed ADA titer of  $\geq 128$  (6% of ADA positive subjects), risankizumab clearance was estimated to be increase by 43%, resulting in 30% to 40% decrease risankizumab AUC, on average, compared to ADA negative subjects.

**Figure 16 Comparison of Risankizumab Plasma Concentrations by ADA Status**



(Source of data: Immunogenicity Report R&D/17/1378, Figure 1)

### 13.5.2.3 Immunogenicity impact on efficacy

The comparison of PASI90 and sPGA0/1 responses at Week 16 and Week 52 by ADA or NAb status (positive or negative) using pooled data across Phase 3 studies are summarized in Table 51. The results indicate that ADA has no clinically relevant impact on efficacy.

A small subset of subjects (n=16) who had ADA titer of  $\geq 128$  (1.5% of evaluated subjects) was associated with reduced drug concentrations (30%) and reduced efficacy (~50%) compared to ADA negative subjects.

**Table 51 PASI90 and sPGA0/1 Responses by ADA or NAb Status**

| ADA or NAb status    | Proportion of Responders (response rate [%])* |                 |                 |                 |
|----------------------|-----------------------------------------------|-----------------|-----------------|-----------------|
|                      | PASI90                                        |                 | sPGA0/1         |                 |
|                      | Week 16                                       | Week 52         | Week 16         | Week 52         |
| TE-ADA Positive      | 133/181 (73.5%)                               | 109/142 (76.8%) | 154/181 (85.1%) | 122/142 (85.9%) |
| ADA Negative         | 610/819 (74.5%)                               | 377/456 (82.7%) | 695/819 (84.9%) | 385/456 (84.4%) |
| ADA titer $\geq$ 128 | NE                                            | 6/16 (38%)      | NE              | 8/16(50%)       |
| TE-NAb Positive      | 56/76 (73.7%)                                 | 59/78 (75.6%)   | 64/76 (84.2%)   | 67/78 (85.9%)   |
| NAb Negative         | 686/923 (74.3%)                               | 427/520 (82.1%) | 784/923 (84.9%) | 440/520 (84.6%) |

\*Week 16: placebo controlled population; Week 52: Ustekinumab controlled population, NE=not evaluated

(Source of data: Reviewer's summary based on Immunogenicity Report R&D/17/1378, Table 9 and Table 10)

#### 13.5.2.4 Impact of immunogenicity on safety

The incidence of injection site reactions, but not the incidence of hypersensitivity reactions, was numerically higher among ADA positive subjects than the ADA negative subjects in the primary safety pool analysis set (Week 0-16) and the all risankizumab psoriasis analysis set (Week 0-52) of Phase 3 safety results (Table 52).

**Table 52 Incidences of Hypersensitivity and Injection-Site Reaction in Phase 3 Trials**

|                           |        | Incidences (n, %)                              |                                                  |
|---------------------------|--------|------------------------------------------------|--------------------------------------------------|
|                           |        | Primary Safety Pool<br>(Week 0-16)<br>(n=1384) | All Risankizumab Dose<br>(Week 0-52)<br>(n=1807) |
| Hypersensitivity reaction | ADA-   | 34/1128 (3.0%)                                 | 97/1387 (7.0%)                                   |
|                           | TE-ADA | 6/256 (2.3%)                                   | 32/420 (7.6%)                                    |
| Injection-site reaction   | ADA-   | 15/1128 (1.3%)                                 | 46/1387 (3.3%)                                   |
|                           | TE-ADA | 7/256 (2.7%)                                   | 21/420 (5.0%)                                    |

(Source of data: Reviewer's summary based on Immunogenicity Report R&D/17/1378, Table 7 and Table 8)

### 13.5.4 Population PK Analysis Results

A two-compartment pharmacokinetic model with first-order absorption adequately describes the pharmacokinetics of risankizumab. The parameter estimates for the final population PK model are presented in Table 53. Risankizumab clearance was estimated at 0.25 L/day. Risankizumab absolute bioavailability for the to-be-marketed drug product was estimated at 89%.

Between-subject variability (CV%) for clearance, central and peripheral volumes of distribution, and absorption rate were 39%, 69%, 39% and 47%, respectively. Current model residual variability was estimated at 26%, assuming a log normal distribution of this parameter.

The population PK analysis confirmed body weight is an important determinant of risankizumab clearance. The impact of age, sex or smoking status on PK was not deemed clinically meaningful (Table 53). The population PK analysis employed the full covariate model approach where all covariates of interest were evaluated as part of a single analysis run (full model). Figure 17 illustrates the covariate effects on risankizumab clearance in the final population PK model. The effect of body weight on CL was estimated as approximately linear with the power coefficient estimated at 1. Central and peripheral volumes were also found to increase with increasing body weight. The power coefficients for the effect of body weight were 1.25 and 0.52 for the central and peripheral volume of distribution, respectively.

The clearance for a 50 kg subject is predicted to be 67% of the clearance for a 75 kg subject used as a reference individual/population (0.25 L/day). For a 90 or 120 kg subject, the clearance is predicted to be 120% or 160% of the reference population value. A steeper effect of body weight is predicted on the central volume of distribution. Central volume of distribution is predicted to vary from 60% of its reference population value for a 50 kg individual up to 180% for an individual weighting 120 kg. Peripheral volume is predicted to increase less steeply; from 81% to 128% over the same range of body weight.

The population PK analysis results showed that the clearance in subjects who developed ADA titer  $\geq 128$  was 43% higher than in subjects who did not develop ADA.

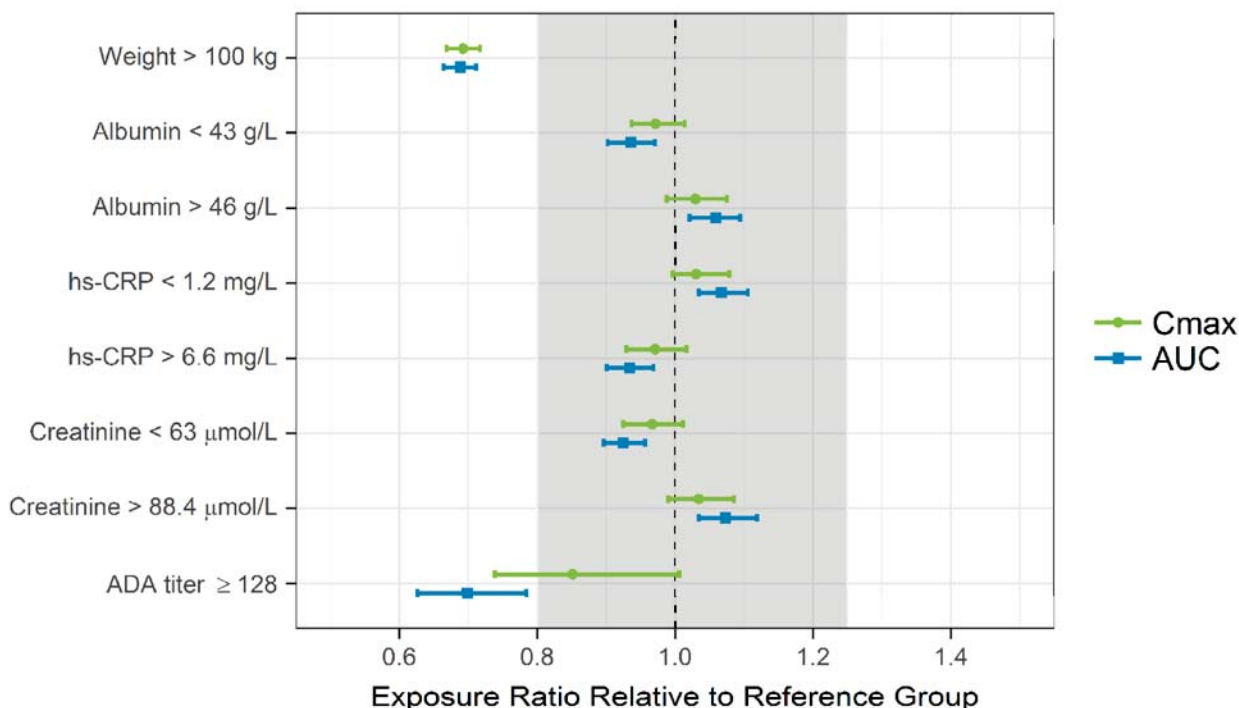
**Table 53: Structural (fixed effects) and variance (random effects) parameters of population PK model**

| $\theta/\omega^2$ | Parameter          | Units   | EST  | SE    | RSE (%) | CV IIV (%) | Description                                 |
|-------------------|--------------------|---------|------|-------|---------|------------|---------------------------------------------|
| 1                 | CL                 | [L/day] | 0.25 | 0.020 | 6.7     | -          | Clearance                                   |
| 2                 | V2 [central]       | [L]     | 5.06 | 0.587 | 12.3    | -          | central volume of distribution              |
| 3                 | V3 [periph]        | [L]     | 3.16 | 0.450 | 11.3    | -          | peripheral volume distribution              |
| 4                 | Q                  | [L/day] | 0.48 | 0.092 | 19.6    | -          | inter-compartmental clearance               |
| 5                 | resid. err         | [-]     | 0.26 | 0.025 | 9.5     | -          | additive error for log transformed data     |
| 6                 | F1                 | [-]     | 0.62 | 0.045 | 7.5     | -          | amt of drug transferred into compartment 1  |
| 7                 | ka (k12)           | [1/day] | 0.18 | 0.014 | 10.2    | -          | absorption rate constant from compartment 1 |
| 8                 | BWT: CL            | [-]     | 1.00 | 0.18  | 17.5    | -          | covariate bwt on CL                         |
| 9                 | BWT:V2             | [-]     | 1.25 | 0.33  | 26.4    | -          | covariate bwt on V2                         |
| 10                | BWT: V3            | [-]     | 0.52 | 0.37  | 70.8    | -          | covariate bwt on V3                         |
| 11                | AGE: CL            | [-]     | 0.11 | 0.09  | 86.1    | -          | covariate age on CL                         |
| 12                | SEX :CL            | [-]     | 1.06 | 0.06  | 5.9     | -          | covariate sex on CL                         |
| 13                | SMKR:CL            | [-]     | 1.04 | 0.06  | 5.6     | -          | covariate smoker on CL                      |
| 1                 | $\omega^2_{(1,1)}$ | [-]     | 0.14 | 0.02  | 12.5    | 38.5       | between subject variance CL                 |
| 2                 | $\omega^2_{(2,1)}$ | [-]     | 0.16 | 0.03  | 17.9    | -          | covariance CL:V2                            |
| 3                 | $\omega^2_{(2,2)}$ | [-]     | 0.33 | 0.07  | 19.9    | 63.0       | between subject variance V2                 |
| 4                 | $\omega^2_{(3,3)}$ | [-]     | 0.14 | 0.06  | 42.1    | 39.0       | between subject variance V3                 |
| 5                 | $\omega^2_{(4,4)}$ | [-]     | 0.20 | 0.04  | 18.6    | 46.8       | between subject variance ka                 |

EST= estimate; RSE= relative standard error; SE= standard error,  $\theta$  fixed effects parameters,  $\omega^2$  random effects parameters, Continuous covariates ( AGE, BWT) of pharmacokinetic parameters were modeled using:  $P_{TV} = \theta_x \left( \frac{R_1}{R_{ref}} \right)^{\theta_y}$ . Categorical covariate relationship was given by  $P_{TV} = \theta_x \cdot \theta_y^{R_1}$ .  $P_{TV}$  is a typical PK parameter,  $\theta_x$ ,  $\theta_y$ ,  $\theta_x$  are its fixed effect parameters,  $R_1$  the continuous or  $R_2$  the categorical covariate (0-1), and  $R_{ref}$  the reference value of a continuous covariate.

Source of data: Table 2 of population PK report

**Figure 17: Forest Plot to Demonstrate the Impact of Statistically Significant Covariates on Risankizumab Steady-State Exposure ( $C_{max}$  and  $AUC_{TAU}$ )**



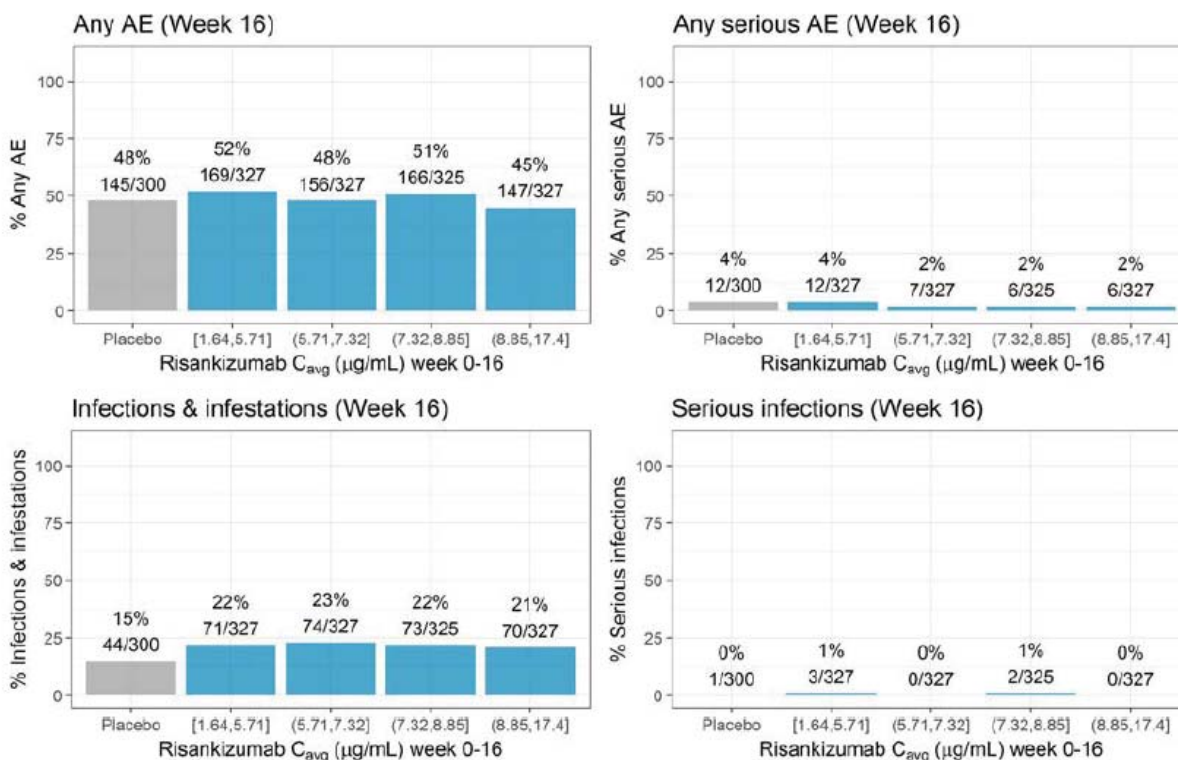
Source of data: Figure 3, Summary of Clinical Pharmacology Studies

### 13.5.5 Exposure-Response for Efficacy and Safety

#### Exposure-Response for Safety:

The relationships between model-predicted risankizumab plasma  $C_{avg}$  from Week 0 to 16 and up to 52 weeks (Week 0 to 52 from Studies M16-008, M15-995 and M15-992 and Week 0 – 44 from Study M16-010) and percentage of subjects who experienced any AE, SAE, infection and infestation, or serious infection, respectively, are presented in Figure 18 and Figure 19. Subjects were binned according to their individual plasma exposures into quartiles and the percent of subjects with the safety events noted above for each quartile were plotted.

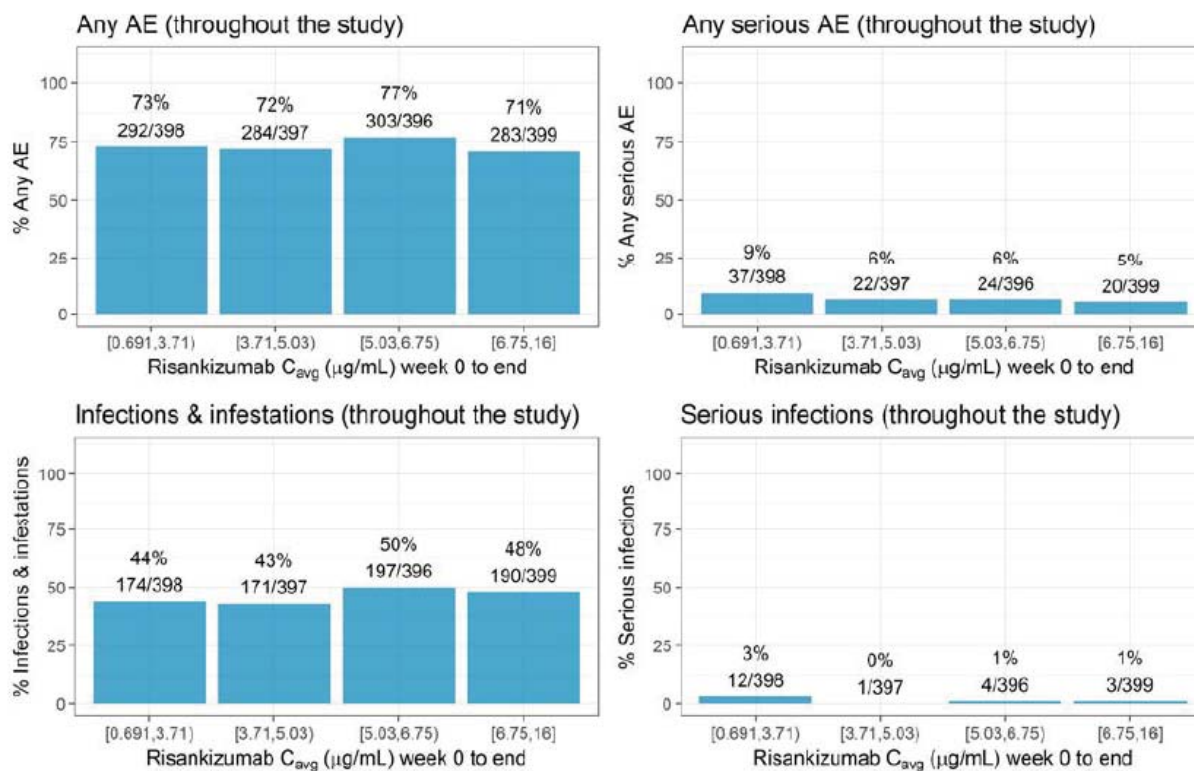
**Figure 18: Exposure-Response Relationships Between Risankizumab Plasma C<sub>avg</sub> and Safety Events of Interest Over the First 16 Weeks (0-16 Weeks)**



Median of average concentrations (Week 0 to 16) (µg/mL): Quartile 1 = 4.76 µg/mL, Quartile 2 = 6.57 µg/mL, Quartile 3 = 8.02 µg/mL, Quartile 4 = 10.13 µg/mL.

Source of data: Figure 11 of exposure response report

**Figure 19: Exposure-Response Relationships Between Risankizumab Plasma C<sub>avg</sub> and Safety Events of Interest Over the First 52 Weeks (Week 0-52)**



Median of average concentrations (Week 0 to 52) (μg/mL): Quartile 1 = 2.98 μg/mL, Quartile 2 = 4.25 μg/mL, Quartile 3 = 5.87 μg/mL, Quartile 4 = 7.93 μg/mL.

Source of data: Figure 12 of exposure response report.

As shown in Figure 18 and Figure 19, there was no apparent relationship between risankizumab exposure and any AE, SAE, infection and infestation or serious infection over the first 16 weeks and up to 52 weeks treatment duration using pooled data from all four Phase 3 studies of risankizumab in subjects with moderate to severe plaque psoriasis.

In the placebo-controlled period (Week 0-16), the incidences of any AE, any SAE and any serious infection were comparable between placebo-treated and risankizumab-treated subjects. The incidence of any infection and infestation appeared to be slightly higher following risankizumab treatment compared to placebo treatment; however, no trend in exposure-response was observed among risankizumab treated subjects.

#### Exposure-Response for Efficacy:

We have conducted exposure-response (E-R) analysis for efficacy using dataset “pasidata.xpt”. There were a total of 1389 patients included in the E-R analysis (Table

54), in which 41 patients received 90mg dosing regimen, 42 patients received 180mg dosing regimen, and 1306 patients received 150mg dosing regimen.

**Table 54: List of Studies, Doses and Patients Included in Exposure-Response for Efficacy Analysis**

| Treatment Arm | Study   | Dose                                                                                      | N    |
|---------------|---------|-------------------------------------------------------------------------------------------|------|
| Trt: 10       | 1311.2  | 90mg RISANKIZUMAB                                                                         | 41   |
| Trt: 11       | 1311.2  | 180mg RISANKIZUMAB                                                                        | 42   |
| TRT: 22       | 1311.30 | 150mg RISANKIZUMAB                                                                        | 301  |
| TRT: 27       | 1311.28 | 150mg RISANKIZUMAB                                                                        | 294  |
| TRT: 30       | 1311.3  | 150mg RISANKIZUMAB                                                                        | 304  |
| TRT: 33       | 1311.4  | 150mg RISANKIZUMAB                                                                        | 182  |
| TRT: 35       | 1311.4  | 150mg RISANKIZUMAB /PLACEBO starting at week 28                                           | 111  |
| TRT: 36       | 1311.4  | 150mg RISANKIZUMAB /PLACEBO starting at week 28/150 mg RISANKIZUMAB at week 44 if sPGA>=3 | 114  |
| total         |         |                                                                                           | 1389 |

Source of data: Reviewer's independent analysis.

The PK metrics for exposure in E-R analysis was the average risankizumab plasma concentration at Week 16. The efficacy was measured as PASI75, PASI90 and PASI100 response rates. E-R for efficacy was conducted by logistic regression and the result is shown in Table 55.

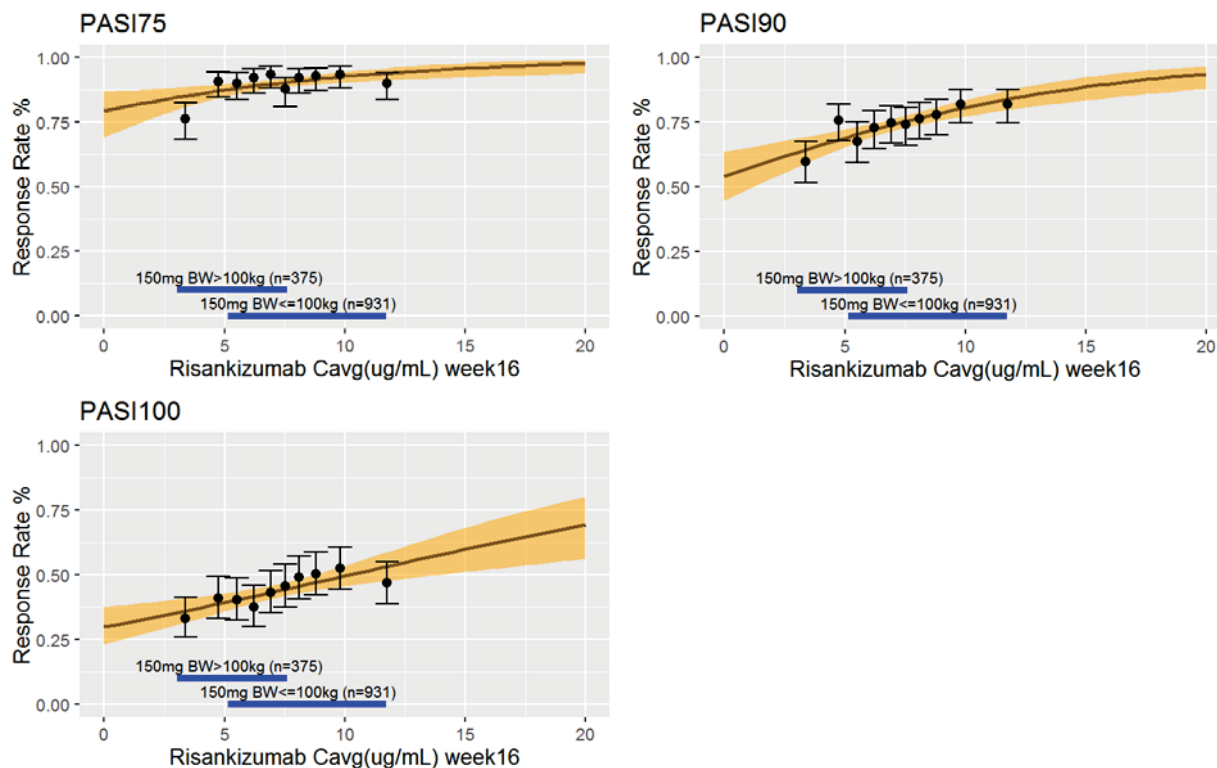
**Table 55: Estimated Parameters in logistic regression for ER relationship for efficacy**

|                                 |                | Estimate | Std. Error | P value |
|---------------------------------|----------------|----------|------------|---------|
| PASI75 ~ C <sub>avg 16-wk</sub> | Intercept      | 1.34     | 0.28       | <0.0001 |
|                                 | Exposure Slope | 0.12     | 0.039      | 0.002   |
| PASI90~ C <sub>avg 16-wk</sub>  | Intercept      | 0.16     | 0.20       | 0.403   |
|                                 | Exposure Slope | 0.13     | 0.027      | <0.0001 |
| PASI100~ C <sub>avg 16-wk</sub> | Intercept      | -0.86    | 0.17       | <0.0001 |
|                                 | Exposure Slope | 0.084    | 0.023      | 0.0002  |

Source of data: Reviewer's independent analysis

The body weight effect is predicted based on logistic regression in Table 55 and the result is shown in Figure 20. The E-R analysis results indicate that the response rates for PASI75 are similar in low body weight subgroup compared with high body weight subgroup. PASI90 and PASI100 response rates are approximately 6-7% higher in patients with BW≤100 kg than in those with BW>100 kg at the proposed dosing regimen (Figure 20 and Table 55**Error! Reference source not found.**).

**Figure 20: Observed versus Predicted Exposure-Response Relationship for Efficacy**



Source of data: FDA reviewer's analysis. Solid line is the logistic regression of the predicted response. The yellow area is the 95% CI. For each exposure decile, the observed response rate and its 95% CI is plotted as circle and error bar vs the mean concentration. The blue bar is 5% to 95% quantile of exposure of risankizumab at the proposed dosing regimen of 150mg.

## **14 Office Director (or designated signatory authority)**

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CRISTINA Petruccelli Attinello  
04/23/2019 09:37:15 AM

KENDALL A MARCUS  
04/23/2019 10:07:58 AM

## CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

Full Review Template version: August 21, 2018

|                                                   |                                                                                                                                                 |
|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>COA ID</b>                                     | C2018213                                                                                                                                        |
| <b>BLA #</b>                                      | 761105                                                                                                                                          |
| <b>Referenced IND for NDA/BLA</b>                 | 113306                                                                                                                                          |
| <b>Established Name/Trade Name</b>                | Risankizumab                                                                                                                                    |
| <b>Sponsor/Applicant</b>                          | AbbVie                                                                                                                                          |
| <b>Indication</b>                                 | Treatment of moderate to severe plaque psoriasis.                                                                                               |
| <b>Meeting Type/Deliverable</b>                   | Advice Letter/Advice to Division                                                                                                                |
| <b>Sponsor Letter Date/SDN #</b>                  | 4/23/2018                                                                                                                                       |
| <b>Date of Consult Request</b>                    | 7/16/2018                                                                                                                                       |
| <b>Review Completion Date</b>                     | 1/23/2019                                                                                                                                       |
| <b>Review Division</b>                            | DDDP                                                                                                                                            |
| <b>Clinical Reviewer/Clinical Team Leader(TL)</b> | Amy Voitach,                                                                                                                                    |
| <b>Review Division PM</b>                         | Cristina Attinello,                                                                                                                             |
| <b>COA Reviewer</b>                               | Julia Ju, PharmD., PhD                                                                                                                          |
| <b>COA TL/Secondary Reviewer</b>                  | Selena Daniels, PharmD., MS                                                                                                                     |
| <b>COA Associate Director</b>                     | Elektra Papadopoulos, MD., MPH                                                                                                                  |
| <b>Instrument 1</b>                               | PSS: Psoriasis Symptom Scale                                                                                                                    |
| <b>COA Type 1 and Endpoint Concepts</b>           | Patient-reported outcome (PRO); psoriasis symptom severity                                                                                      |
| <b>Intended Population</b>                        | Adults with stable moderate to severe chronic plaque psoriasis of $\geq 6$ months duration and candidates for systemic therapy or phototherapy. |
| <b>Internal Meeting</b>                           | Not applicable                                                                                                                                  |
| <b>Sponsor Meeting/WRO</b>                        | Not applicable                                                                                                                                  |

*Please check all that apply:*

- Rare Disease/Orphan Designation  
 Pediatric

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Risankizumab

PSS, severity of psoriasis symptoms

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### A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Dermatology and Dental Products (DDDP) regarding BLA 761105 for risankizumab. The proposed indication is for the treatment of moderate to severe plaque psoriasis in adults.

The Applicant used the following patient-reported outcome (PRO) assessments in their pivotal trials (Studies UltIMMa-1 (M16-008), UltIMMa-2 (M15-995), IMMvent, and IMMhance) in adult patients ( $\geq 18$  years) with moderate to severe plaque psoriasis:

**Table 1.** COAs used in pivotal trials

| <b>Instrument name<br/>(COA Type)</b>                      | <b>Concept(s)</b>                 | <b>Endpoint<sup>1</sup></b> | <b>Copy of Instrument/<br/>Scoring Algorithm</b> |
|------------------------------------------------------------|-----------------------------------|-----------------------------|--------------------------------------------------|
| <i>Psoriasis Area and Severity Index (PASI)(ClinRO)</i>    | <i>Psoriasis severity</i>         | <i>Primary</i>              | <i>Not Applicable</i>                            |
| <i>Static Physician's Global Assessment (sPGA)(ClinRO)</i> | <i>Psoriasis severity</i>         | <i>Co-Primary</i>           | <i>Not Applicable</i>                            |
| <i>Psoriasis Symptom Scale (PSS) (PRO)</i>                 | <i>Psoriasis symptom severity</i> | <i>Key secondary</i>        | <i>Appendix A</i>                                |

The Applicant proposes PRO-related labeling claims for Studies UltIMMa-1 and UltIMMa-2. The PRO efficacy assessment used in these studies as a key secondary endpoint was the PSS. Therefore, the review focused on the adequacy of the PSS to support the Applicant's targeted labeling claims (listed in Section C.1.4 of this review). Further this review will focus only on Studies UltIMMa-1 and UltIMMa-2 since the Applicant's targeted PRO-related labeling claims are related to these two studies.

This submission included an evidence dossier describing the development of the PSS. This review concludes that the evidence submitted by the applicant sufficiently demonstrates that PSS is fit-for-purpose for the context of this drug development program to assess the signs and symptoms of psoriasis. Furthermore, PSS is adequate to support a labeling claim related to improvement in psoriasis signs and symptoms (i.e., pain, itching, redness, and burning). The COA Staff defers to Clinical and Biostatistics whether the data in the label reflects the actual endpoints specified in the statistical analysis plan.

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<sup>1</sup> Please see Section D 1.3 for a complete endpoint hierarchy.

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## B. BACKGROUND

### Materials Reviewed

- Current submission including PRO evidence dossier and draft product label

### Disease background

Psoriasis is a chronic debilitating immunologic disease characterized by marked inflammation and thickening of the epidermis that result in thick, scaly plaques involving the skin.

While the majority of psoriasis patients are managed initially with topical therapies, those with severe and/or refractory disease may require phototherapy and/or systemic therapy. Oral systemic agents provide modest efficacy, but increasingly patients are treated with biological agents, such as TNF-alpha inhibitors (etanercept, adalimumab) and the p40 IL-12/23 inhibitor (ustekinumab).

### Investigational product

Risankizumab is produced in a mammalian cell line using recombinant DNA technology. Risankizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of human interleukin 23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor complex. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. IL-23 supports the development, maintenance and activation of Th17 cells, which produces IL-17A, IL-17F, and IL-22, as well as other proinflammatory cytokines, and plays a key role in driving inflammatory autoimmune diseases, such as psoriasis. IL-23 is up-regulated in lesional skin in comparison to non-lesional skin of patients with plaque psoriasis. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23 dependent cell signaling and release of proinflammatory cytokines. Risankizumab is administered as subcutaneous injection.

## C. CLINICAL OUTCOME ASSESSMENT REVIEW

### 1 CONTEXT OF USE

#### 1. Clinical Trial Population

The target population for Studies UltIMMA-1 and -2 were adults  $\geq 18$  years of age with stable moderate to severe chronic plaque psoriasis of  $\geq 6$  months duration; with or without PsA; body surface area (BSA) involvement  $\geq 10\%$ ; Psoriasis Area and Severity Index (PASI)  $\geq 12$ ; Static Physician Global Assessment (sPGA)  $\geq 3$ ; and candidates for systemic therapy or phototherapy.

For a complete list of inclusion and exclusion criteria, refer to the clinical study protocol.

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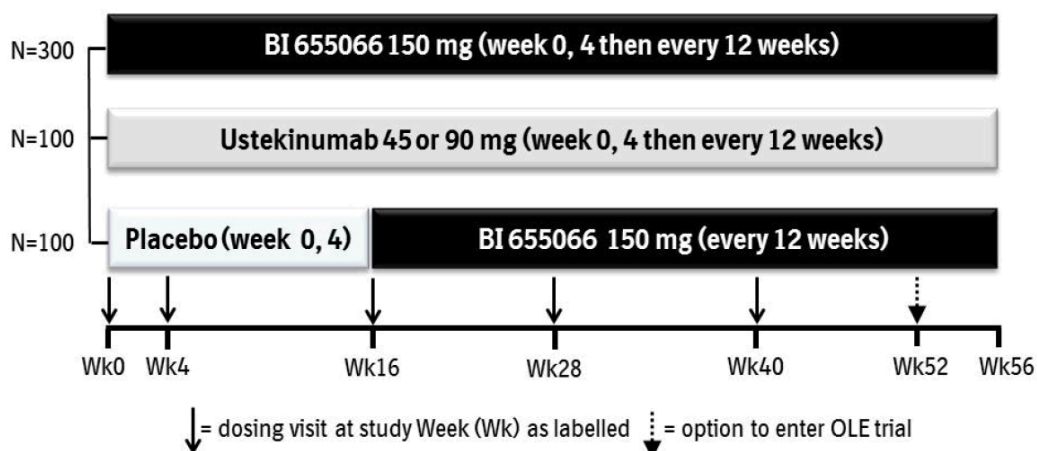
### **Reviewer's comment(s):**

Overall, subjects had a median baseline PASI score of 17.8 and a median BSA of 20.0%. Baseline sPGA score was severe in 19.3% of subjects. A total of 9.8% of study subjects had a history of diagnosed psoriatic arthritis.

## 2. Clinical Trial Design

Studies UltIMMa-1 and UltIMMa-2 were replicate 52-week multi-national, randomized, double-blind, double-dummy, placebo and active comparator controlled, parallel design pivotal studies. The objective of both these studies were to assess the efficacy and safety of risankizumab compared to ustekinumab and placebo in patients with moderate to severe chronic plaque psoriasis. The study schema for Studies UltIMMa-1 and UltIMMa-2 is shown in Figure 1.

**Figure 1.** Study schema for Studies UltIMMa-1 and UltIMMa-2



Refer to the Clinical review for more details on the study design of Studies UltIMMa-1 and UltIMMa-2.

**Reviewer's comment(s):** The COA data was collected electronically via the use of electronic tablets (b) (4). Based on a recent site inspection, it has been identified that there are some data integrity issues regarding the use of the electronic tablets. Those issues include the following:

- The use of proxies for data entry without verification by a GRAPPA-certified assessor;
- The electronic devices recorded the incorrect date and time when the batteries for the (b) (4) were critically low;
- Loss of data due to synchronization errors caused by installation of software updates.

These data integrity issues may affect interpretation of COA data. The COA Staff defers to Clinical and Biostatistics whether the affected data should be excluded from all analyses.

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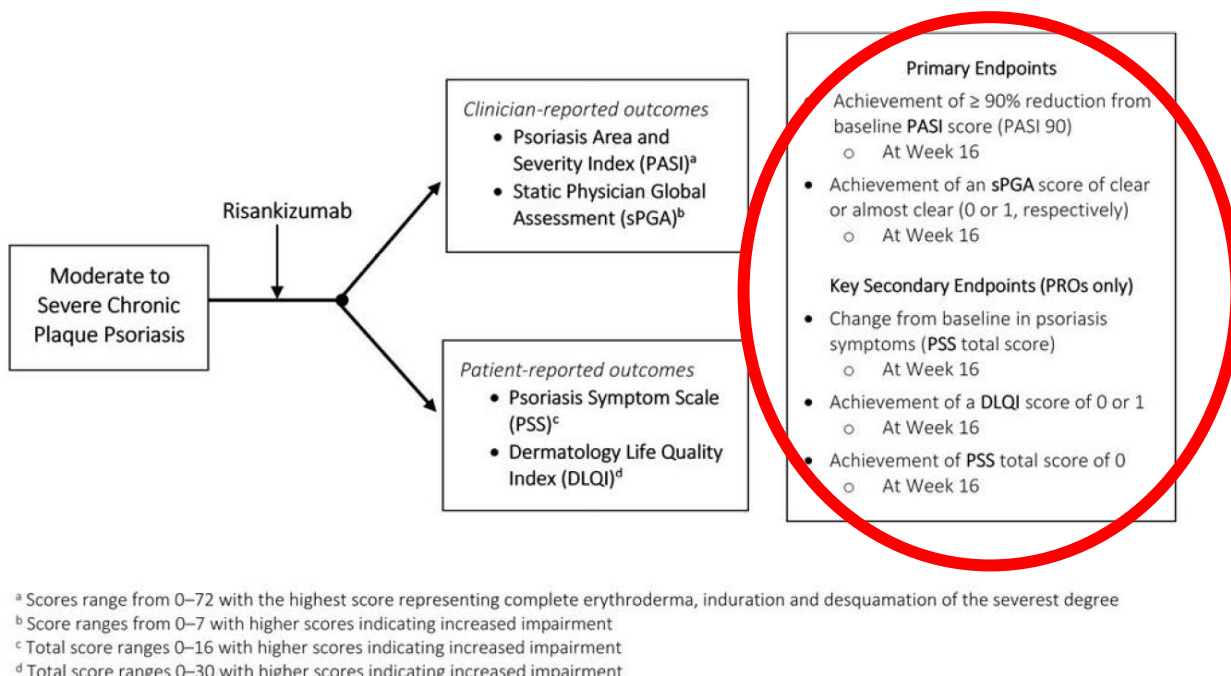
PSS, severity of psoriasis symptoms

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### 3. Endpoint Hierarchy and Definition

The primary and key secondary PRO endpoints are summarized in Figure 2.

**Figure 2.** Endpoint Model for Studies UltIMMa-1 and UltIMMa-2



**Reviewer’s comment(s):** The PSS was utilized as a key secondary endpoint for risankizumab across Studies UltIMMa-1 and UltIMMa-2. The key evaluation of patient symptoms was performed at Week 16, where the risankizumab and placebo arms were compared by change in PSS total score as well as the proportion of subjects achieving a PSS total score of 0 (no itch, pain, burning, or redness).

Other PRO assessments were used in these trials (e.g., Dermatology Life Quality Index, EuroQoL Five-Dimension questionnaire, and Hospital Anxiety and Depression scale), but was not specified in the statistical hierarchy as a key secondary endpoint and is not further discussed in this review.

### 4. Labeling or promotional claim(s) based on the COA

The Applicant proposes the following targeted PRO-related labeling claims<sup>2</sup>:

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<sup>2</sup> Exact wording of labeling claims is not final and still in discussion.

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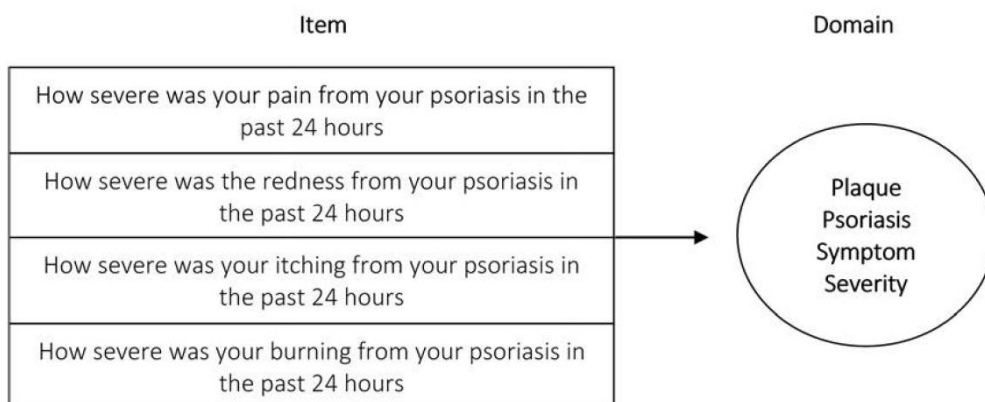
(b) (4)

**Reviewer's Comment(s):** Based on the submitted data from the Applicant, the PSS includes clinically relevant concepts from the patient's perspective (see Section C.2 of this review). Further, the psychometric data supports that this instrument is well-defined and reliable. As such, the PSS appears to be adequate to support the proposed labeling claims. The COA Staff defers to Clinical and Biostatistics whether the data in the label reflects the actual endpoints specified in the statistical analysis plan. The COA Staff also defers to Clinical and Biostatistics whether the quality of the COA data is up to par to support the proposed labeling claims.

## 2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The conceptual framework for the PSS is shown in Figure 3.

**Figure 3.** Conceptual framework for the PSS.



**Reviewer's comment(s):** The concepts included in the PSS appear to be clinically relevant and consistent with the Patient-Focused Drug Development Psoriasis Voice of the Patient report (dated November 2016), literature, and other previously accepted psoriasis-specific instruments. See Section C.4 of this review for more details on the qualitative research.

## 3 CLINICAL OUTCOME ASSESSMENT

### Psoriasis Symptom Scale (PSS)

The PSS is a 4-item PRO instrument designed to assess severity of four psoriasis signs and symptoms (pain, itching, redness, and burning). The PSS is a self-administered questionnaire in an electronic diary (e-Diary) format. Patients rate the severity of their symptoms 'over the past 24 hours' on a 5-point verbal rating scale ("0 = none" to "4 = very severe").

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**Reviewer's comment(s):** *Patients in Studies ULTIMMA-1 and ULTIMMA-2 were asked to complete the PSS on an eDiary once per day in the evening within a specified time window from screening until the Week 16 visit. From Week 22 (visit 7) through Week 40 (EOT) patients completed the PSS during their clinic visit. The recall period was the same, last 24 hours.*

## 4 SCORING ALGORITHM

The PSS scores range from 0 (none) to 4 (very severe) with a total score ranging from 0 to 16. Higher scores indicate increased impairment (i.e., worse signs/symptoms).

## 5 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

- Literature review and/or publications
- Documentation of expert input
- Qualitative study protocols and interview guides for focus group or patient interviews
- Chronology of events for item generation, modification, and finalization (item tracking matrix)
- Qualitative study summary with evidence to support item relevance, item stems and response options, and recall period
- Qualitative support for meaningful change
- Quantitative study summary with evidence to support item retention and scoring
- Transcripts (if available)

The PSS was adapted from the literature and previously published psoriasis symptoms scales such as the Psoriasis Symptom Index (PSI) and the Psoriasis Symptom Diary (PSD), which were developed with extensive patient input. This adapted version was then evaluated for content validity in a qualitative study in moderate to severe plaque psoriasis patients.

Twenty (N=20) patients being treated for moderate to severe plaque psoriasis were interviewed to assess the content validity of the PSS via: 1) concept elicitation of psoriasis-related symptoms during which participants talk about their psoriasis symptom experience; and 2) cognitive debriefing of the PSS during which participants' comprehension and interpretation of the items, recall period and response options is assessed.

The 20 study participants had a mean age of  $50.2 \pm 12.0$  years (range: 25.0–73.0), and 55% were female. While all participants met the inclusion criteria of clinician-diagnosed moderate to severe plaque psoriasis, only 35% of the sample self-reported their psoriasis severity as moderate or severe. The Applicant noted that this discrepancy may be attributed to patients being well-controlled on their psoriasis treatment.

The average time since diagnosis of plaque psoriasis was almost 18 years, ranging from less than one to over 38 years. The most frequently reported symptoms and signs during the concept elicitation portion of the interviews included redness (n= 20, 100%), itching (n = 20, 100%), pain

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(n = 15, 75%), burning (n = 13, 65%), and flaking (n = 11, 55%). Other psoriasis signs, symptoms or impacts described by participants included social impacts (n = 2, 10%), a feeling of inflammation or sunburn (n = 1, 5%), white spots (n = 1, 5%), and swollenness (n = 1, 5%). Most of these problems were mentioned in conjunction with other signs and symptoms.

Participants provided positive feedback on the PSS and felt it was comprehensive and relevant to their experience with psoriasis. Most participants understood the intended timeframe (n=17, 85%), meaning and response options (n=20,100%). No further changes were recommended to the PSS.

For more details on the qualitative research, refer to the PRO evidence dossier.

***Reviewer's comment(s):** The content validity of the PSS appears to be sufficiently established. Generally it is recommended to cautiously use "severe" and "very severe" response options as patients may not be able to distinguish between these response options. In the qualitative interviews, patients did not endorse the "very severe" response option. However, because the key secondary endpoint is proportion of patients achieving a score of 0 (resolution of psoriasis signs/symptoms), the concern for these response options are mitigated.*

## 6 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The measurement properties of the PSI were evaluated in the following two phase 3 studies: UltIMMa-1 (M16-008) and UltIMMa-2 (M15-995).

These two phase 3 trials are multicenter, randomized, double-blind, placebo and ustekinumab-controlled evaluations of the proposed dose and dosing regimen (risankizumab 150 mg SC at Weeks 0, 4, and q12w thereafter) in adults with stable moderate to severe chronic plaque psoriasis  $\geq$  6 months.

Approximately 1000 patients with moderate to severe psoriasis enrolled in the two phase 3 clinical trials. Patients, stratified by weight and prior TNFi-exposure, were randomized 3:1:1 to receive 150 mg risankizumab, 45/90 mg ustekinumab, or placebo (dosing at Weeks 0, 4, 16, 28, and 40; at Week 16, patients initially randomized to placebo began to receive risankizumab). The studies included multiple assessments of efficacy (PASI, sPGA) and PROs (PSS, DLQI, EQ-5D-5L, and HADs). The current analyses utilized data from Visit 2 (baseline) through Visit 6 (Week 16). For study entry, patients had to have moderate to severe chronic plaque psoriasis, defined as  $\geq$ 10% Body Surface Area (BSA) involvement, PASI score  $\geq$ 12 and sPGA score  $\geq$ 3.

Eight hundred and twenty-two (N=822) participants were enrolled and completed Day 1 assessments. Subsequent measurements included Week 4, Week 8, Week 12 and Week 16 assessments. The average age was 47.3 years (SD=13.8 years) with majority of men in the sample (69.9%, n=574). Most of the sample was non-Hispanic or Latino (89.2%, n=732) with a

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majority of white race (77.0%, n=632). About a fifth of the sample (n=183, 22.3%) had previous experience with non-TNF biologics. The mean duration of psoriasis diagnosis was 17.9 years (SD=12.4 years) and 84.4% of the sample (n=693) did not have psoriatic arthritis, as confirmed via CASPAR. The average weight of the participants was 90.1 Kgs (SD= 21.8).

This section provides a synopsis of the psychometric results from Studies M16-0008 and M15-995. The full psychometric findings are in the evidence dossier (Assessment of Other Measurement Properties section of the Evidence Dossier).

### Results

- **Item-level analyses**

- Floor effects (>25% of respondents endorsing the lowest possible score) were observed in all visits except Day 1 for the single day scores and average weekly scores. The maximum floor effect was seen in Item 4, at Week 16 with 68.2% (n=496) endorsing the lowest possible score in the PSS.
- Ceiling effects (>25% of respondents endorsing the highest possible score) were not observed over the 16-week evaluation period for single day scores and average weekly scores.
- Item-item correlations and item-to-total correlations ranged from 0.48-0.93.

*Reviewer's comment(s): The floor effects seen in other visits is not a concern as this is more likely due to patients being on active treatment. There were no floor effects observed on Day 1.*

- **Reliability**

- Test-retest reliability:
  - Test-retest reliability in stable patients ranged from 0.92 (Weeks 8–12) to 0.94 (Weeks 12–16) for the PSS total scores. For the PSS individual item scores, ICCs ranged from 0.85 to 0.93.

*Reviewer's comment(s): The sPGA was used to identify stable patients. Patients who have the same sPGA score at the test-retest assessment time points (Weeks 8 and 12, and Weeks 12 and 16) were defined as stable. The test-retest reliability estimates fall within the acceptable range.*

- Internal consistency reliability: Evidence that items comprising an instrument measure the same general concept.
  - Cronbach's alpha ranged from 0.85-0.92 (Day 1 ( $\alpha=0.85$ ), Week 8 ( $\alpha=0.91$ ) and Week 16 ( $\alpha=0.92$ )).

*Reviewer's comment(s): The internal consistency reliability estimates fall within the acceptable range.*

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- **Construct validity**

- Convergent and discriminant validity

- Moderate to weak associations were observed between PSS total scores and EQ-5D-5L at Day 1, Week 12 and Week 16. The PSS total score was negatively correlated with the index score ( $r=-0.44$ ,  $p<0.0001$ ) and with the EQ-5D VAS ( $r=-0.36$ ,  $p<0.0001$ ) at Day 1 and similar results were found at Week 12 and Week 16.
- Moderate to strong associations were observed between PSS total scores and DLQI at Day 1, Week 12 and Week 16, except for Work and School dimension at Week 12, which was correlated at  $r=0.27$  ( $p<0.0001$ ). individual PSS items were strongly correlated with Item 1 on DLQI and the DLQI total scores at all time points whereas, the individual items demonstrated a weak to moderate association with other individual dimensions of the DLQI.
- PSS total score was moderately associated with HADS total score at all time points ( $r=0.33$ ,  $0.38$  and  $0.40$ ,  $p<0.0001$ ). Individual items demonstrated weak to moderate correlations for all time points.

*Reviewer's comment(s): The association between PSS total scores and EQ-5D-5L, DLQI, and HADS were expected to be moderate to weak except the item 1 in DLQI as the concepts measured in EQ-5D-5L, DLQI (except item 1), and HADS are remotely related to the concept measured by PSS.*

- Known groups validity

- Based on sPGA four group total scores at Week 12 and Week 16, the PSS demonstrated significant differentiation among severity levels of pain, redness, itching and burning (all values at  $p<0.0001$ ;  $F=265.6$ ,  $p<0.0001$  at Week 12 and  $F=170.3$ ,  $p<0.0001$  at Week 16). Similar results were found when the three group total scores of sPGA were evaluated. PSS demonstrated significant differences in severity levels of sPGA scores (all values at  $p<0.0001$ ;  $F=204.1$ ,  $p<0.0001$  at Week 12 and  $F=244.0$ ,  $p<0.0001$  at Week 16)
- Based on DLQI total scores at Week 12, the PSS demonstrated significant differentiation among severity levels of pain, redness, itching and burning (all values at  $p<0.0001$ ;  $F=265.6$ ,  $p<0.0001$  for the overall model). Similarly, at Week 16, the PSS was able to significantly differentiate amongst the total DLQI scores of 0-1 and  $\geq 2$  (overall  $F=384.5$ ,  $p<0.0001$ ).
- The PSS also demonstrated significant differentiation among severity levels for the PASI at Week 12 and Week 16 ( $F=206.3$  for Week 12 and  $F=173.0$  for Week 16,  $p<0.0001$  for overall model)

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**Reviewer's comment(s):** *The results from the known groups analyses appears to demonstrate that the PSS can distinguish among different disease severities. Note that sPGA and PASI may be more relevant outcomes to classify psoriasis disease severity versus DLQI. Also, it is unclear whether the cut-offs chosen or the sPGA scores appropriately classify the psoriasis disease severity; however, the scores for the PSS show a monotonic increase for each category suggesting that the PSS can distinguish between different psoriasis severity levels.*

- **Ability to detect change**

- Mean change from baseline to Week 12 on PSS total score was -5.9 (0.1) for responders and -0.3 (0.2) for non-responders on the PASI  $\geq 50\%$  ( $F=651.7$ ;  $p<0.0001$ ). Significant differences in PSS change scores among PASI  $\geq 75\%$ , PASI  $\geq 90\%$  and PASI 100% responder and non-responder groups were also noted (all  $p<0.0001$ ). Similar pattern of results was found for mean change from baseline to Week 16 on the PSS total scores (all  $p<0.0001$ ) for responders and non-responder groups on PASI  $\geq 50\%$ , PASI  $\geq 75\%$ , PASI  $\geq 90\%$  and PASI 100%.
- Mean change from baseline to Week 12 on PSS total score was -6.2 (0.1) for responders and -2.3 (0.2) for non-responders based on the sPGA ( $F=488.4$ ;  $p<0.0001$ ). Similar pattern of results was found for mean change from baseline to Week 16 on the PSS total scores (all  $p<0.0001$ ) for responder and non-responder groups on sPGA ( $F=542.2$  ( $p<0.0001$ )).

**Reviewer's comment(s):** *The PSS appears to be able to detect change in those who respond to treatment effect.*

## 7 INTERPRETATION OF SCORES

The Applicant used anchor-based methods to help interpret the score changes in the PSS. The PASI and sPGA were used as anchors.

**Reviewer's comment(s):** *The general recommendation is to use multiple anchor scales to provide an accumulation of evidence to help interpret a clinically meaningful within-patient score change in the PSS from the patient perspective. While the Applicant used the PASI and sPGA as anchors, these are clinician-reported anchors. Note that patient-reported anchors are more suitable to assess within-patient meaningful change in a PRO instrument.*

*Using the PASI improvement status at Week 16 to derive the threshold for within-patient meaningful change in the PSS total score, a meaningful score change on PSS ranges from ~5.1 ~6.7 points anchored to PASI 50-75% and PASI  $\geq 90\%$ , respectively. PASI 50-75% reflects that 50-75% of the disease is resolved. PASI  $\geq 90\%$  reflects that  $\geq 90\%$  of the disease is resolved. Clinical tends to focus on PASI90 and PASI 100 when evaluating disease improvement.*

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*Using the sPGA improvement status as an anchor at Week 16, a meaningful score change on the PSS ranges from ~3.7 -6.3 anchored to a 1-point and 2-point improvement on the sPGA, respectively.*

*The Applicant provided an empirical cumulative distribution function (eCDF) curve; however, it was not an anchor-based eCDF curve and doesn't provide any meaningful information.*

*Anchor-based eCDF curves were not requested from the Applicant since the key secondary endpoint was based on the proportion of patients achieving a score of 0 (resolution of psoriasis signs/symptoms) which is indicative of clinical benefit.*

## **8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION**

The PSS was fully linguistically translated and validated based on the FACIT methodology (two forward translations, one reconciled version of the two forward translations, one back-translation into English, independent review, harmonization across languages) to 15 other languages besides English. FACIT trans conducted cognitive interviews to assess the clarity, interpretation, and appropriateness of the questionnaire content. Qualitative analyses of patients' comments confirmed the linguistic equivalence of each translated version.

*Reviewer's comment(s): The method used for language translation and cultural adaptation appears to be appropriate and consistent with ISPOR best practices.*

## **9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION**

Not applicable.

## **10 REVIEW USER MANUAL**

A complete user manual does not exist for the PSS.

## **11 KEY REFERENCES FOR COA**

Not applicable.

## **D. APPENDICES**

Appendix A: Psoriasis symptom scale (PSS)

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SELENA R DANIELS  
01/23/2019 02:55:30 PM

ELEKTRA J PAPADOPOULOS  
01/25/2019 05:02:44 PM