2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Risankizumab (BI 655066, ABBV-066)		
Name of Active Ingredient: Risankizumab		

Title of Study:
BI 655066/ABBV-066 (Risankizumab) Versus Ustekinumab and Placebo Comparators in a Randomized Double Blind Trial for Maintenance Use in Moderate to Severe Plaque Type Psoriasis

Coordinating Investigator:
Kenneth Gordon, MD

Study Sites:
79 sites across 8 countries: Australia, Canada, Czech Republic, France, Germany, Japan, Republic of Korea, and US

Publications: None.

Studied Period (Years): First Subject First Visit: 24 February 2016 Last Subject Last Visit: 18 September 2017	**Phase of Development:** 3

Objectives:
The main objectives of this study were to assess the efficacy and safety of risankizumab, compared to ustekinumab and placebo, in subjects with moderate to severe chronic plaque psoriasis. In addition, this study was to assess pharmacokinetics (PK) and the emergence of anti-drug antibodies and their effect on efficacy and safety.

Methodology:
This Phase 3, multi-center, multi-national, randomized, double-blind, double dummy, placebo- and active–comparator-controlled, parallel design study compared risankizumab to ustekinumab and placebo in subjects with moderate to severe chronic plaque psoriasis. In Part A, the co-primary efficacy endpoints were evaluated at Week 16. In addition, at Week 16, all subjects initially randomized to placebo began receiving 150 mg risankizumab. Subjects were to continue to receive treatment through Week 40 and were to be followed through at least Week 52 when additional endpoints were evaluated. Safety was evaluated throughout the study period. Subjects who completed the study could enter the open-label extension study (Study M15-997) provided they met eligibility criteria and desired to continue treatment. Subjects who entered the open-label extension did not have a follow-up visit for this study. Subjects who discontinued prematurely or did not continue in the open-label study were to have a final visit after their last dose of study drug.

Number of Subjects (Planned and Analyzed):

500 subjects planned; 506 analyzed

Diagnosis and Main Criteria for Inclusion:

Subjects enrolled in this study were to be adults ≥ 18 years of age with stable moderate to severe chronic plaque psoriasis of ≥ 6 months duration; with or without psoriatic arthritis (PsA); body surface area (BSA) involvement ≥ 10%; psoriasis activity and severity index (PASI) ≥ 12; Static Physician Global Assessment (sPGA) ≥ 3; and candidates for systemic therapy or phototherapy. Subjects who had non-plaque forms of psoriasis, current drug-induced psoriasis, active ongoing inflammatory diseases other than psoriasis, were taking restricted medications, had chronic or relevant acute infections, such as human immunodeficiency virus, viral hepatitis, or active tuberculosis, who had previously received risankizumab, or were pregnant, nursing, or planned to become pregnant were to be excluded.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Study Drug	Dosage Form	Formulation	Manufacturer	Bulk Lot Number
Risankizumab	Injection solution for subcutaneous (SC) use	Injection solution of risankizumab in 4.4 mM succinate buffer, pH 6.2, 225 mM sorbitol, and 0.02% polysorbate 20, presented in a 1 mL pre-filled syringe (PFS) with 0.87 mL. Dispensed volume was 0.83 mL.	Boehringer Ingelheim Pharma GmbH & Co. KG	B151002457/505410 B151002455/505411
Risankizumab placebo	Injection solution for SC use	0.9% sodium chloride solution presented in a 1 mL PFS with 0.87 mL. Dispensed volume was 0.83 mL.	Boehringer Ingelheim Pharma GmbH & Co. KG	B151001739 B151002749

Duration of Treatment:

Up to 40 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Study Drug	Dosage Form	Formulation	Manufacturer	Bulk Lot Number
Ustekinumab	Injection solution for SC use	Water for injection, sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, presented in a 0.5-mL or 1-mL PFS. Dispensed volume was 0.5 mL or 1 mL.	Janssen-Cilag	B151002715/FDS0VME B151002717/FCS4SMG B161001665/FHS3YMF B161001666/FKS06NB B161003339/GCS2YMW
Ustekinumab placebo	Injection solution for SC use	0.9% sodium chloride solution presented in a 0.5-mL or 1-mL PFS. Dispensed volume was 0.5 mL or 1 mL.	Boehringer Ingelheim Pharma GmbH & Co. KG	B151001616 B151002085 B161000967 B161001068

Criteria for Evaluation

Efficacy:

The co-primary endpoints in Part A were the proportion of subjects achieving ≥ 90% reduction from baseline PASI score (PASI 90) and an sPGA score of clear or almost clear at Week 16 between risankizumab and placebo.

Ranked secondary endpoints included the following:

1. Risankizumab is not different from placebo with respect to achieving sPGA of clear at Week 16
2. Risankizumab is not different from placebo with respect to PASI 100 response at Week 16
3. Risankizumab is not different from placebo with respect to achieving a Dermatology Life Quality Index (DLQI) score of 0 or 1 at Week 16
4. Risankizumab is not different from placebo with respect to achieving a Psoriasis Symptoms Scale (PSS) score of 0 at Week 16
5. Risankizumab is not different from ustekinumab with respect to PASI 90 response at Week 16
6. Risankizumab is not different from ustekinumab with respect to achieving an sPGA of clear or almost clear at Week 16
7. Risankizumab is not different from ustekinumab with respect to PASI 100 response at Week 16
8. Risankizumab is not different from ustekinumab with respect to achieving an sPGA of clear at Week 16
9. Risankizumab is not different from ustekinumab with respect to PASI 90 response at Week 52
10. Risankizumab is not different from ustekinumab with respect to PASI 100 response at Week 52
11. Risankizumab is not different from ustekinumab with respect to achieving an sPGA of clear at Week 52
12. Risankizumab is not different from ustekinumab with respect to PASI 75 response at Week 12
13. Risankizumab is not different from ustekinumab with respect to achieving an sPGA of clear or almost clear at Week 12
14. Risankizumab is not different from ustekinumab with respect to achieving a DLQI score of 0 or 1 at Week 16
15. Risankizumab is not different from placebo with respect to mean change from baseline in PSS total score at Week 16

Other secondary endpoints included the following:

- Achievement of PASI 75 at Week 16
- Achievement of an sPGA score of clear or almost clear at Week 52
- Achievement of PASI 75 at Week 52

Pharmacokinetic:

Risankizumab plasma concentrations were determined. For immunogenicity assessment, antidrug-antibodies and neutralizing antibodies against risankizumab were determined.

Safety:

Safety evaluations included collection of adverse events (AEs), clinical laboratory values, physical examinations, and local tolerability.

Statistical Methods

Efficacy:

Efficacy analyses were based on the intent-to-treat principle, comprising all subjects who were randomized. Treatment effect was evaluated based on a two-sided significance level of 0.05.

Pharmacokinetic:

Descriptive statistics for risankizumab plasma concentrations for each sampling time (study visit) were calculated. Immunogenicity (anti-drug antibody [ADA] and neutralizing antibody [NAb]) data were summarized across specific time periods (Weeks 0 to 16 and Weeks 0 to 52) as well as by visit. Risankizumab plasma concentrations were compared by ADA and NAb status (positive or negative) by visit.

Safety:

Safety analyses included reporting of AEs, laboratory, physical examination (including vital signs and 12-lead electrocardiogram), and local tolerability. Safety summaries are provided using the Safety Analysis Set, which consists of all subjects who received at least 1 dose of study medication. For safety parameters, the treatment that was actually used by the subject was applied in the analysis (an as-treated analysis). All AEs described in this report were considered treatment-emergent, defined as any event with an onset after the first dose of study drug and with an onset date within 105 days after the last dose of study drug in the analysis period, or prior to the first dose in the subsequent period for subjects who entered into the subsequent period.

Summary/Conclusions

Efficacy Results:

The co-primary endpoints were proportions of subjects who achieved PASI 90 and who achieved sPGA clear or almost clear at Week 16, and both endpoints were achieved with statistically significant differences in favor of risankizumab. In addition, statistically significant differences were observed in all ranked secondary endpoints in Part A. These findings were supported by results at other response levels that were not specified as ranked endpoints (e.g., PASI 75 at Week 16), where risankizumab was also superior to placebo and ustekinumab.

In Part B, subjects originally randomized to risankizumab or ustekinumab continued to receive their assigned study drug every 12 weeks. Those originally randomized to placebo began receiving risankizumab at Week 16 and continued to do so every 12 weeks. All ranked secondary endpoints in Part B were met as well, with risankizumab consistently demonstrating superiority to ustekinumab at all PASI and sPGA response levels.

Overall, risankizumab was superior to ustekinumab in producing clear or almost clear skin, as demonstrated by statistically significant differences between risankizumab and ustekinumab groups in proportions of subjects who achieved PASI 90, PASI 100, and sPGA clear or almost clear at Weeks 12, 16, and 52. Subjects who received continuous risankizumab generally saw persistent levels of PASI 90 and sPGA clear or almost clear responses that were achieved at Week 16, while PASI 100 and sPGA of clear responses continued to improve after Week 16, with approximately 60% achieving complete clearance at Week 52. Those subjects who initially received placebo and switched to risankizumab also experienced substantial improvements in disease.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

In addition, statistically significant differences in favor of risankizumab treatment were observed between the risankizumab and placebo groups on measures of improvement of nail psoriasis, palmoplantar psoriasis, and scalp psoriasis at Week 16. These improvements generally persisted with continued risankizumab treatment.

Pharmacokinetic Results:

Following administration of risankizumab 150 mg SC dose at Weeks 0, 4 and then E12W in subjects with moderate to severe plaque psoriasis, geometric mean trough plasma concentrations at Weeks 4 and 16 were 5.54 µg/mL and 1.85 µg/mL, respectively, and between Weeks 28 through 52, the geometric mean trough plasma concentrations ranged from 1.58 µg/mL to 1.73 µg/mL.

In subjects who received at least 1 dose of risankizumab, pre-existing ADAs were detected in 4% (17/401) of subjects, and the incidence of ADAs to risankizumab (treatment emergent) was 22% (90/402), with approximately half of these subjects positive for neutralizing ADAs. For the ustekinumab arm (subjects who did not receive risankizumab in the study), the incidence of ADAs and NAbs against risankizumab was 9% and 6%, respectively, suggesting a high background incidence for the assays. Majority of subjects who were ADA positive had relatively low titers, with only 2 subjects having titers over 100. Development of ADAs did not have a clear impact on risankizumab plasma exposures. Further assessment of the potential impact of ADAs on risankizumab plasma exposures will be conducted as part of the population PK analyses using pooled data from all Phase 3 trials.

Safety Results:

Adverse event profiles were generally comparable across the risankizumab, placebo, and ustekinumab treatment groups through Week 16 of the study, with similar rates of AEs, SAEs, severe AEs, study-drug related AEs, AEs leading to discontinuation, and AEs of safety interest. Similarly, through Week 52, the rates of AEs, severe AEs, SAEs, AEs leading to discontinuation, and study drug-related AEs were generally low and similar in the continuous risankizumab and ustekinumab groups. There were no deaths in the study. The event/100 PY rate in the all risankizumab-treated group across the entire study was comparable to the rates observed through Week 16. There were no notable changes in laboratory values, vital signs, or electrocardiogram findings in the study.

Conclusions:

The superior benefits of risankizumab compared with placebo and ustekinumab were consistently demonstrated by the primary and secondary endpoints in this Phase 3 study in subjects with moderate to severe plaque psoriasis. This treatment was shown to be well-tolerated with no meaningful differences from placebo and a comparable safety profile to that of ustekinumab. Overall, the benefit-risk profile for risankizumab was favorable. Therefore, this study supports risankizumab as an effective and well-tolerated treatment option for patients with moderate to severe plaque psoriasis.