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		
Name of Active Ingredient: Risankizumab		

Title of Study:
Risankizumab Versus Placebo in a Randomized, Double Blind, Parallel Group Trial in Moderate to Severe Plaque Psoriasis to Assess Safety and Efficacy After 16 Weeks of Treatment in the Russian Federation (IMMpress)

Coordinating Investigator:
[redacted]

Study Sites:
6 sites in the Russian Federation

Publications: None.

Studied Period (Years): First Subject First Visit: 19 July 2018 Last Subject Last Visit: 19 December 2019	**Phase of Development:** 3

Objective:
The main objective of this study is to assess the safety and efficacy of risankizumab compared to placebo in subjects with moderate to severe chronic plaque psoriasis in the Russian Federation.

Methodology:

This is a Phase 3, multicenter, randomized, double-blind, parallel-design study to compare risankizumab with placebo. Eligible subjects were randomized to receive either risankizumab or placebo in a 4:1 ratio, administered by site staff at the Baseline and Week 4 visits.

Upon completion of the Double-Blind Period (Period A), subjects continued into the Open-Label Period (Period B) and received open-label risankizumab at the Week 16, Week 28, and Week 40 Visits and to be followed through at least Week 52, with a follow-up phone call at Week 60. Subjects who prematurely discontinue study drug completed an Early Termination (ET) Visit as soon as possible and continued to be followed for all regularly scheduled visits. Subjects who prematurely discontinued study participation (withdraw consent) had an ET Visit and, if the subject was willing, a follow-up phone call ≥ 140 days to ≤ 147 days after the last dose of study drug.

Number of Subjects (Planned and Analyzed): The study was designed to randomize approximately 50 subjects (40 subjects in the risankizumab arm and 10 subjects in the placebo arm). A total of 50 eligible subjects were randomly assigned 150 mg risankizumab subcutaneous (SC) injection (41 subjects) or placebo (9 subjects).

Diagnosis and Main Criteria for Inclusion:

Adult male or female subjects were enrolled based on the following primary eligibility criteria:

- Subject had a diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the Baseline Visit, with the following specific criteria at the Screening and Baseline (Randomization) Visits:
  - ≥ 10% body surface area (BSA) involvement
  - Psoriasis Area and Severity Index (PASI) score ≥ 10
  - Static Physician's Global Assessment (sPGA) score ≥ 3
- Subject was a candidate for systemic therapy or phototherapy for psoriasis treatment as assessed by the investigator
- Subjects were permitted to be systemic-therapy-naïve, disease-modifying anti-rheumatic drugs (DMARD)-inadequate-responders, and/or biologics-inadequate responders with the caveat that prior therapy with an anti-interleukin (IL)-17 or anti-IL-12/23p40 or anti-IL-23p19 inhibitor was prohibited
- Concurrent therapy with a biologic and/or other systemic therapy was also prohibited for the duration of this study

The study protocol allowed for subjects who did not initially meet all eligibility criteria for the study to repeat the Screening Visit one time following re-consent.

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

Study Drug	Dosage Form	Formulation	Manufacturer	Bulk Lot
Risankizumab (ABBV-066)	Solution for injection in pre-filled syringe (PFS)	75 mg/0.83 mL (90 mg/mL)	Boehringer-Ingelheim Pharma GmbH & Co. KG	703744 802782

Duration of Treatment: The study duration was up to 64 weeks for each subject, including a Screening Period of approximately 30 days, a 16-week Double-Blind period followed by a 36-week Open-Label Period and an 8-week Follow-Up Period. The Follow-Up Period consisted of a telephone follow-up call at least 20 weeks [≥ 140 days to ≤ 147 days] after the last dose of open-label risankizumab.

Reference Therapy, Mode of Administration and Lot Number:

Study Drug	Dosage Form	Formulation	Manufacturer	Bulk Lot
Placebo for Risankizumab (ABBV-066)	Solution for injection in PFS	N/A	Boehringer-Ingelheim Pharma GmbH & Co. KG	B161003514

Criteria for Evaluation

Efficacy:

The primary endpoint was the proportion of subjects achieving a PASI 90 response (≥ 90% reduction from baseline PASI score) at Week 16.

The secondary endpoints were:

- Proportion of subjects achieving sPGA score of clear or almost clear (0 or 1) at Week 16
- Proportion of subjects achieving ≥ 75% reduction from baseline PASI score (PASI 75) at Week 16
- Proportion of subjects achieving 100% reduction from baseline PASI score (PASI 100) at Week 16
- Proportion of subjects achieving Dermatology Life Quality Index (DLQI) score of 0 or 1 at Week 16.

The following additional endpoints were analyzed for all visits in which the assessments were performed (other than those already included as primary or secondary endpoints):

- Proportion of subjects achieving sPGA score of clear (0) or almost clear (0 or 1)
- Proportion of subjects achieving ≥ 75%/90%/100% reduction from baseline in PASI score
- Change and percent change from baseline in PASI
- Proportion of subjects achieving DLQI score of 0 or 1
- Change from baseline in DLQI.

Pharmacokinetics:

Blood was collected for evaluation of serum risankizumab pharmacokinetic (PK) concentrations, antidrug antibodies (ADA), and neutralizing antibodies (NAb) at Week 16 and Week 52.

Safety:

Safety evaluations included collection of adverse events, clinical laboratory tests, and physical examination findings including vital signs and 12-lead electrocardiograms (ECGs).

Statistical Methods

Efficacy:

Efficacy analyses were based on the intent-to-treat (ITT) principle, comprising all subjects who were randomized. Treatment effect was evaluated based on a two-sided significance level of 0.05. Missing data were handled using non-responder imputation (NRI; primary approach) and last observation carried forward (LOCF; secondary approach) in categorical endpoints. Additional sensitivity analyses for the primary endpoint were performed using multiple imputation to handle missing data, as well as performed on a Per-protocol (PP) Population, defined as all subjects from the ITT Population who met pre-determined criteria as specified in the Statistical Analysis Plan.

Pharmacokinetics:

Serum risankizumab concentrations, ADA, and NAb were determined and summarized at each sampling time point using descriptive statistics. Antidrug antibody titers were tabulated for each subject at the respective study visits. The number and percentage of subjects with ADA and NAb was calculated.

Statistical Methods (Continued)

Safety:

Safety analyses included reporting of adverse events (AEs), laboratory values, physical examination (including vital signs and 12-lead ECGs). Safety summaries were provided using the Safety Population, which consisted of all subjects in the ITT Population of the Double-Blind Period (Period A) who received at least 1 dose of study drug; all subjects in the ITT Population of the Open-Label Period (Period B) who were randomized to risankizumab and continued to Period B (risankizumab/risankizumab [RZB/RZB]); all subjects randomized to placebo who continued to Period B (placebo [PBO]/RZB); and the All Risankizumab Treated Subjects Population, which was defined as all subjects who received at least one dose of risankizumab in the study.

Treatment-emergent adverse events (TEAEs) for Period A were defined as events with an onset date on or after the first dose of study drug in Period A and prior to the first dose of Period B or up to 140 days after the last dose of study drug if the subject discontinued prematurely from Period A. For Period B, TEAEs are defined as any event with an onset after the first dose of study drug in Period B and no more than 140 days after the last dose of study drug in the study.

Summary/Conclusions

Efficacy Results:

The primary endpoint at Week 16 was achieved in this Phase 3 study in subjects with moderate to severe plaque psoriasis.

In this study, eligible subjects were to be randomly assigned in a 4:1 ratio to receive 150 mg risankizumab SC or placebo administered by site staff at the Baseline and Week 4 visits. Efficacy was evaluated for all subjects through Week 16, the Double-Blind Period (Period A). The primary endpoint for Week 16 was the proportion of subjects achieving a PASI 90 response (≥ 90% reduction from Baseline PASI score) at Week 16, and the primary endpoint was achieved in this study. Risankizumab effect on the primary endpoint was supported by sensitivity analyses using the LOCF method and among the PP Population. Treatment effects in all pre-specified subgroups favored risankizumab.

Statistically significant differences were observed between the risankizumab and placebo groups for the secondary endpoints of proportion of subjects achieving sPGA score of clear or almost clear (0 or 1) at Week 16, proportion of subjects achieving PASI 75 at Week 16, and proportion of subjects achieving DLQI score of 0 or 1 at Week 16, all using the NRI method. Additionally, the proportion of subjects achieving PASI 100 at Week 16 was numerically higher in the risankizumab group than in the placebo group (46.3% versus 11.1%, $P = 0.051$). Results for the secondary endpoints were supported by sensitivity analyses using the LOCF method.

Beyond Week 16 and through Week 52 (Period B) of the study, the proportion of subjects achieving PASI 90; PASI 75; PASI 100; sPGA score of clear or almost clear; DLQI score of 0; and DLQI score of 0 or 1 increased or was maintained after Week 16 using NRI. These results were supported by sensitivity analyses using the LOCF method.

Summary/Conclusions (Continued)

Pharmacokinetic Results:

Following administration of risankizumab 150 mg SC doses, exposures to risankizumab were demonstrated at both Week 16 and Week 52. Risankizumab serum trough concentrations at Week 52 were similar in subjects treated with risankizumab throughout and in those who switched from placebo to risankizumab. Approximately 15% (7/48) of the evaluable subjects who received at least 1 dose of risankizumab developed treatment-emergent ADA, with 1 of these subjects testing positive for NAb. Development of ADA appeared to be associated with lower risankizumab serum exposures compared to those in ADA-negative subjects.

Safety Results:

There were no deaths or discontinuations of study drug due to AE in the study. Adverse event profiles were generally similar between treatment groups, and the rates of SAEs, severe AEs, and AEs of safety interest were generally low in all groups, with no meaningful differences between risankizumab and placebo in Period A. Rates were similar with continued risankizumab treatment through the end of study.

Through Week 52 (Period B), and considering all subjects exposed to risankizumab (ALL_RZB), 20 (40.0%) subjects experienced any AEs and 2 (4.0%) subjects reported SAEs. There was no increase in the rates of overall AEs (event/100 patient-year [PY]) observed in the RZB/RZB treatment group compared with the rates observed through Week 16 with continued risankizumab treatment, and there was no notable difference in the subjects who switched from placebo to risankizumab versus those who continued on risankizumab through Week 52.

Overall, the highest incidence of AEs in subjects who received risankizumab through Week 52 was in the system organ class of infections and infestations, mostly driven by upper respiratory infections of nasopharyngitis and respiratory tract infection.

Overall, few AEs of safety interest were reported through Week 52; no subjects experienced serious hypersensitivity reactions, malignancies, or CV events adjudicated as major adverse cardiac events. Two subjects overall experienced hepatic events; 1 of these subjects also experienced concurrent potentially clinically significant abnormal liver function test laboratory values. Notably, there were no potential Hy's law cases in this study.

There were no notable changes in vital sign parameters in the study.

Conclusions:

The superior benefits of risankizumab compared with placebo were demonstrated by the primary, secondary, and other endpoints in subjects with moderate to severe chronic plaque psoriasis. Though safety conclusions are limited by the sample size of 50, risankizumab was shown to be well-tolerated with a similar safety profile to that observed with placebo in this study. 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 chronic plaque psoriasis.