2.0 Synopsis

<table>
<tr><td>AbbVie Inc.</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
Risankizumab (BI 655066, ABBV-066)</td></tr>
<tr><td>Name of Active Ingredient:
Risankizumab</td></tr>
<tr><td colspan="3">Title of Study:
BI 655066 [risankizumab] Versus Placebo in a Multicenter Randomized Double-Blind Study in Patients with Moderate to Severe Chronic Plaque Psoriasis Evaluating the Efficacy and Safety with Randomized Withdrawal and Re-Treatment</td></tr>
<tr><td colspan="3">Coordinating Investigator:
Andrew Blauvelt, M.D., M.B.A.</td></tr>
<tr><td colspan="3">Study Sites:
60 sites in 9 countries (Australia, Belgium, Canada, Czech Republic, France, Germany, Japan, Korea, United States)</td></tr>
<tr><td colspan="3">Publications: 1 abstract</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 07 March 2016
Last Subject Last Visit: 26 July 2018</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="3">Objectives:
The main objectives of this study were to assess the efficacy and safety of risankizumab compared with placebo in subjects with moderate to severe chronic plaque psoriasis, the maintenance of response following drug withdrawal after Week 28 through Week 104, and the response after re-treatment in subjects who experienced relapse after drug withdrawal and were re-treated with risankizumab.
In addition, this study was designed to assess the pharmacokinetics (PK) of risankizumab, emergence of anti-drug antibodies, and the effect of anti-drug antibodies on efficacy and safety.</td></tr>
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Methodology:

This Phase 3, multinational, multicenter, randomized, double-blind, placebo controlled study compared risankizumab with placebo in the treatment of moderate to severe chronic plaque psoriasis. Eligible subjects were randomized at a ratio of 4:1, stratified by weight and prior exposure to tumor necrosis factor antagonists, to receive risankizumab 150 mg or placebo subcutaneously (SC) on Day 1 of Week 0 (Randomization) and at Week 4. Subjects initially randomized to placebo switched to risankizumab at Week 16 and every 12 weeks thereafter until the last dose at Week 88. Subjects initially randomized to risankizumab received risankizumab at Week 0, 4, and 16. Subjects who did not achieve Static Physician Global Assessment (sPGA) clear or almost clear at Week 28 received open-label risankizumab at Week 28 and every 12 weeks thereafter until Week 88. Subjects who achieved sPGA clear or almost clear at Week 28 were re-randomized to continuous risankizumab treatment or to withdrawal (placebo) in a 1:2 ratio, and received double-blind study drug every 12 weeks thereafter until Week 88. Starting from Week 32, subjects with an sPGA of moderate or worse (≥ 3) received open-label risankizumab as re-treatment. After the end of treatment, patients continued in the 16-week follow-up period.

In this 2-part study, efficacy was first assessed at Week 16 of treatment. The maintenance of response following drug withdrawal after Week 28 through Week 104, as well as the response after re-treatment in subjects who relapsed after drug withdrawal and were re-treated with risankizumab, were also evaluated. Efficacy assessments of skin condition included the Psoriasis Area and Severity Index (PASI) and sPGA; disability and quality of life were also assessed. Safety was evaluated throughout the study period.

Number of Subjects (Planned and Analyzed):

500 subjects planned; 507 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 involvement ≥ 10%; PASI ≥ 12; sPGA ≥ 3; and candidates for systemic or phototherapy. Subjects who had non-plaque forms of psoriasis, current drug-induced psoriasis, or 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; 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 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 syringe pre-filled with 0.87 mL. Dispensed volume is 0.83 mL.	Boehringer Ingelheim Pharma GmbH & Co. KG	B151002457/ 505410 B151002941/ 505413 B151002942/ 505412 B161003345/ 606471
Risankizumab placebo	Injection solution for SC use	0.9% sodium chloride solution presented in a prefilled syringe	Boehringer Ingelheim Pharma GmbH & Co. KG	B151001739 B151002749 B161001995

Duration of Treatment:

Up to 88 weeks.

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

None.

Criteria for Evaluation

Efficacy:

The co-primary endpoints in Part A1 (Baseline to Week 16) were the proportion of subjects who achieved ≥ 90% improvement from baseline in PASI score (PASI 90) at Week 16 and sPGA of clear or almost clear (0 or 1) at Week 16.

The primary endpoint in Part B (after Week 28) was the proportion of subjects re-randomized at Week 28 who achieved sPGA of clear or almost clear at Week 52.

Ranked secondary endpoints in Part A were:

1. Achievement of ≥ 75% reduction from baseline PASI score (PASI 75) at Week 16
2. Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 16
3. Achievement of sPGA of clear (0) at Week 16
4. Achievement of Dermatology Life Quality Index (DLQI) score of 0 or 1 at Week 16

The ranked secondary endpoint in Part B was:

1. Achievement of sPGA of clear or almost clear (0 or 1) at Week 104

Pharmacokinetics:

Risankizumab plasma concentrations were determined. For immunogenicity assessment, anti-drug antibodies, and neutralizing antibodies (NAbs) 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. The co-primary endpoints in Part A1 and ranked secondary endpoints were tested in a hierarchical order using 2-sided tests with a type I error rate of 0.05. The primary and secondary endpoints in Part B among re-randomized subjects were tested in a separate hierarchy using 2-sided tests with a type I error rate of 0.05.

Pharmacokinetics:

Descriptive statistics for risankizumab plasma concentrations for each sampling time (study visit) were calculated. Immunogenicity (anti-drug antibodies and NAbs) data were summarized across specific time periods (Week 0 – 16, Week 0 – 52, and Week 0 – 104) and by visit.

Safety:

All treated subjects were included in the safety analyses. Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 21.0, and analyses focused on treatment-emergent AEs. Frequency, severity, and causal relationship were tabulated by system organ class and preferred term. Laboratory data were analyzed quantitatively and qualitatively through comparison with reference ranges. Vital signs and electrocardiograms were assessed with regard to changes compared to findings before the start of treatment as well as categorized criteria. Local tolerability was analyzed by number of events.

Summary/Conclusions

Efficacy Results:

In the double-blind, placebo-controlled period (Part A1), the co-primary endpoints (the proportions of subjects who achieved PASI 90 and sPGA of clear or almost clear at Week 16) were met. For each endpoint, statistically significant differences in favor of risankizumab were observed. In addition, risankizumab was statistically significantly superior to placebo for all ranked secondary endpoints of the proportions of subjects who achieved PASI 75, PASI 100, sPGA of clear, and DLQI 0/1 at Week 16. The primary endpoint in Part B also was achieved: a statistically significantly larger proportion of subjects re-randomized to continue risankizumab treatment maintained sPGA of clear or almost clear at Week 52 compared with subjects re-randomized to withdraw from risankizumab treatment (placebo). The secondary endpoint in Part B also was achieved: a statistically significantly larger proportion of subjects re-randomized to continue risankizumab treatment maintained sPGA of clear or almost clear at Week 104 compared with subjects re-randomized to withdraw from risankizumab treatment (placebo).

Additional secondary endpoints were achieved: statistically significantly larger proportions of subjects re-randomized to continue risankizumab treatment achieved PASI 75, PASI 90, and PASI 100 at Week 52 compared with subjects re-randomized to withdraw from risankizumab treatment (placebo). Of 153 sPGA responders at Week 28 who were re-randomized to withdraw from risankizumab treatment (placebo) in Part B, relapsed (sPGA $\geq$ 3), and were re-treated for at least 16 weeks, 84% (128/153) regained sPGA of clear or almost clear. Statistically significant differences in favor of risankizumab treatment were also observed between groups on measures of improvement of PsA (changes from Baseline in tender joint count [TJC], swollen joint count [SJC], disease activity score [28 joints] [DAS28], and Disability Index of the Health Assessment Questionnaire [HAQ-DI]), nail psoriasis, palmoplantar psoriasis, and scalp psoriasis at Week 16.

Summary/Conclusions (Continued)

Pharmacokinetic Results:

Following administration of risankizumab 150 mg SC dose at Weeks 0, 4, and every 12 weeks thereafter in subjects with moderate to severe plaque psoriasis, geometric mean trough plasma concentrations at Study Weeks 4 and 16 were approximately 5.3 µg/mL and 1.7 µg/mL, respectively. Risankizumab geometric mean trough plasma concentrations ranged from approximately 1.4 µg/mL to 1.7 µg/mL over Weeks 16 through 88, indicating that risankizumab steady state exposures were approximately achieved by Week 16.

In subjects who received risankizumab treatment throughout the study, pre-existing anti-drug antibodies were detected in 4% (8/182) of subjects, and the incidence of anti-drug antibodies and NAbs to risankizumab (treatment emergent) was approximately 30% (54/181) and approximately 21% (38/181), respectively. The majority of subjects who were anti-drug antibody positive had relatively low titers, with only 2 subjects having titers of 128 or greater. Development of anti-drug antibodies did not have a consistent apparent impact on risankizumab plasma exposures.

Safety Results:

Adverse event profiles were generally similar between risankizumab and placebo groups in Part A1 of the study, as well as between subjects who were re-randomized to continue risankizumab treatment or to withdraw from risankizumab treatment (placebo) in Part B. Risankizumab withdrawal did not result in any cases of "psoriasis rebound." The rates of serious AEs (SAEs), AEs leading to discontinuation of study drug, severe AEs, and AEs of safety interest were generally low.

Overall, the highest incidence of AEs in subjects who received risankizumab (Part A, re-randomized subjects in Part B, and all subjects who received ≥ 1 dose of risankizumab) was in the Infections and infestations system organ class (SOC), mostly driven by upper respiratory infections (nasopharyngitis and upper respiratory tract infection). The rates of major adverse cardiac events (MACE) (0.9 events [E]/100 patient years [PYs]) and malignancies (2.2 E/100 PYs) in all subjects who received ≥ 1 dose of risankizumab were low. Non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma) comprised a significant proportion of malignancies. Incidence and exposure-adjusted rates of serious infections were similar in the 2 groups of re-randomized subjects. A larger proportion of subjects re-randomized to risankizumab had reported fungal infections compared with subjects who had treatment withdrawn (placebo).

There were no notable changes in laboratory values or vital sign parameters.

Conclusions:

The superior benefits of risankizumab compared with placebo were consistently demonstrated by the primary and secondary endpoints in this Phase 3 study in subjects with moderate to severe chronic plaque psoriasis. This treatment was shown to be well-tolerated with a similar safety profile to that observed with placebo at Week 16. Continuous treatment with risankizumab was shown to be a favorable treatment strategy compared with treatment withdrawal after initial response, based on superior efficacy maintenance and generally similar safety profile up to Week 104. 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.