

## 2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
<b>Name of Study Drug:</b> Risankizumab (BI 655066, ABBV-066)	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> Risankizumab	<b>Page:</b>	
<b>Title of Study:</b> A Phase II/III, Randomised, Double-Blind Study to Evaluate Efficacy and Safety of Two Different Dose Regimens of BI 655066 (Risankizumab) and Placebo and Maintenance of Response of BI 655066 (Risankizumab) Administered Subcutaneously in Japanese Patients with Moderate to Severe Chronic Plaque Type Psoriasis		
<b>Coordinating Investigator:</b> Mamitaro Ohtsuki, MD, PhD		
<b>Study Sites:</b> 39 sites in Japan		
<b>Publications:</b> None.		
<b>Studied Period (Years):</b> First Subject First Visit: 02 December 2016 Last Subject Last Visit: 20 June 2018	<b>Phase of Development:</b> 2/3	
<b>Objectives:</b> The objectives of this study were to assess the efficacy and safety of 2 different dose regimens of risankizumab compared to placebo in patients with moderate to severe chronic plaque psoriasis. In the subset of enrolled patients with concomitant psoriatic arthritis, the signs and symptoms of psoriatic arthritis were also evaluated. In addition, this study assessed the pharmacokinetics (PK) of risankizumab in Japanese patients and the emergence of anti-drug antibodies (ADA) and their effect on efficacy and safety.		
<b>Methodology:</b> This Phase 2/3, randomized, double-blind, double-dummy, placebo controlled, parallel design study compared 2 different dose regimens of risankizumab with placebo. The primary efficacy endpoint was evaluated at Week 16 (Part A). Additional endpoints were to be evaluated at Week 52. At Week 16, all subjects initially randomized to placebo began receiving either 75 or 150 mg risankizumab. Subjects were to continue to receive treatment through Week 40 and were to be followed through at least 52 weeks (Part B). Subjects could then either end their study participation or enter the open-label extension study (Study M15-997) provided they met eligibility criteria and desired to continue treatment. Subjects not wishing to continue in the open-label study were to have a final visit at 56 weeks.		
<b>Number of Subjects (Planned and Analyzed):</b> Approximately 168 patients planned; 171 analyzed.		

**Diagnosis and Main Criteria for Inclusion:**

Subjects enrolled in this study were to be adults  $\geq 20$  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. 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 (HIV), viral hepatitis, or active tuberculosis (TB); or who had previously received risankizumab 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 prefilled syringe (PFS) with 0.87 mL (total dispensed volume was 0.83 mL).	Boehringer Ingelheim Pharma GmbH & Co. KG	B151002457/505410 B151002941/505413
Risankizumab placebo	Injection solution for SC use	0.9% sodium chloride solution presented in a 1-mL PFS with 0.87 mL (total dispensed volume was 0.83 mL).	Boehringer Ingelheim Pharma GmbH & Co. KG	B151001739 B161001995

**Duration of Treatment:**

Up to 52 weeks

### **Criteria for Evaluation**

#### **Efficacy:**

The primary endpoint in Part A was the proportion of subjects achieving  $\geq 90\%$  reduction from baseline PASI score (PASI 90) at Week 16 between risankizumab 75 mg and 150 mg and placebo.

Secondary endpoints were the following:

- Achievement of PASI 90 at Week 52
- Achievement of an sPGA score of clear or almost clear at Week 16
- Achievement of an sPGA score of clear or almost clear at Week 52
- Achievement of  $\geq 75\%$  reduction from baseline PASI score (PASI 75) at Week 16
- Achievement of PASI 75 at Week 52
- Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 16
- Achievement of PASI 100 at Week 52
- Achievement of an American College of Rheumatology (ACR) 20 response at Week 16, among subjects with confirmed diagnosis of PsA using CASPAR criteria and with baseline total TJC and SJC counts  $\geq 3$  at selected study sites
- Achievement of an ACR 20 at Week 52, among subjects with confirmed diagnosis of PsA using CASPAR criteria and with baseline total TJC and SJC counts  $\geq 3$  at selected study sites

Other efficacy endpoints included:

- Achievement of PASI 50/75/90/100
- Achievement of sPGA of clear and sPGA of clear or almost clear
- Time until the first achievement of PASI 50, PASI 75, PASI 90, PASI 100, sPGA of clear and sPGA of clear or almost clear
- Time until loss of PASI 75, PASI 90, PASI 100, sPGA of clear and sPGA of clear or almost clear response
- Change from baseline in PASI score
- Percent change from baseline in PASI
- Achievement of absolute PASI of  $< 3$
- Change from baseline in psoriasis symptoms evaluated using the total score on the Psoriasis Symptoms Scale (PSS)
- Achievement of a Dermatology Life Quality Index (DLQI) score of 0 or 1
- Achievement of total score on the PSS of 0
- Change from baseline in DLQI

**Criteria for Evaluation (Continued)**

**Efficacy (Continued):**

- Among subjects with confirmed diagnosis of PsA using CASPAR criteria and with baseline total TJC and SJC counts  $\geq 3$  at selected study sites:
  - Change from baseline in TJC/SJC
  - Change from baseline in HAQ-DI
  - Change from baseline in Pain VAS
  - Change from baseline in Patient's Global Assessment VAS
  - Change from baseline in Investigator's Global Assessment VAS
  - Achievement of an ACR 20
  - Investigator's global assessment
  - Change from baseline in CRP

**Pharmacokinetic:**

Risankizumab plasma concentrations were determined. For immunogenicity assessment, anti-drug-antibodies (ADAs) and neutralizing antibodies (NAb) 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 (ADA and 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 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 primary endpoint was met in this study. Approximately 76% of subjects who received risankizumab 75 mg and 75% of subjects who received risankizumab 150 mg achieved PASI 90 at Week 16 compared with 2% in the placebo group.

Subjects who received risankizumab 150 mg reached statistically significant differences compared with placebo somewhat earlier for PASI 90 and PASI 100 than subjects who received risankizumab 75 mg, and rates of complete skin clearance (i.e., PASI 100, sPGA 0) were higher at Week 16 for subjects treated with risankizumab 150 mg versus risankizumab 75 mg.

Risankizumab at either dosage was superior to placebo in producing clear skin, as demonstrated by statistically significant differences between risankizumab and placebo groups in the proportions of subjects who achieved PASI 100 and sPGA of 0 at Week 16.

A majority of subjects who then switched to risankizumab 150 mg or 75 mg after Week 16 achieved PASI 50 and PASI 75 starting at Week 22 and maintained achievement through Week 52.

The proportion of subjects who achieved psoriasis-related secondary endpoints increased after Week 16 and achievement was maintained at Week 52 and among subjects who continued with risankizumab treatment in Part B, nearly all subjects who had achieved PASI 90 and PASI 100 maintained achievement at Week 52.

Both dosage regimens of risankizumab were superior to placebo in improving psoriasis symptoms and QoL, as demonstrated by statistically significant differences between risankizumab and placebo groups in proportions of subjects who had DLQI 0 or 1 at Week 16 and PSS of 0 at Week 16, as well as statistically significant differences in mean changes in PSS from Baseline at Week 16. Subjects in both dose groups either maintained Week 16 response rates or achieved higher response rates during Part B.

### **Pharmacokinetic Immunogenicity Results:**

Following administration of risankizumab 75 mg or 150 mg SC at Weeks 0, 4 and q12w thereafter in subjects with moderate to severe plaque psoriasis with or without psoriatic arthritis, a majority of subjects achieved steady-state starting at Week 16. Risankizumab trough plasma concentrations were approximately dose proportional across the 75 mg and 150 mg SC doses and comparable between subjects with and without concomitant PsA. With the 150 mg SC dose regimen, risankizumab plasma concentrations were comparable to those previously observed in the global Phase 3 trials of risankizumab in subjects with plaque psoriasis.

In subjects who received at least 1 dose of risankizumab during the 52 weeks of the study, the incidence of ADAs to risankizumab (treatment emergent) was 23% (39/171), with approximately half of these subjects testing positive for neutralizing ADAs. Development of ADAs did not have a clear or consistent impact on risankizumab plasma exposures.

### **Safety Results:**

In this study of Japanese subjects with psoriasis, no Japanese specific-safety issues were identified. The rates of serious adverse events (SAEs), AEs leading to discontinuation of study drug, severe AEs, and AEs of safety interest were generally low. There were no deaths in this study and only 1 case of major adverse cardiovascular events (MACE) reported (preferred term [PT] of myocardial infarction) by a subject in the risankizumab 150 mg group which was confounded by multiple risk factors. There were no notable changes in laboratory values in the study, and no indications of liver injury. Overall, risankizumab was well tolerated and offered a favorable benefit-risk profile.

**Summary/Conclusions (Continued)**

**Conclusions:**

The superior benefits of risankizumab compared with placebo were consistently demonstrated by the primary and secondary endpoints in this Phase 2/3 study in subjects with moderate to severe plaque psoriasis. Both risankizumab dosage regimens were effective and showed durability of response as subjects in both dose groups either maintained Week 16 response rates or achieved higher response rates during Part B. The 150 mg dose of risankizumab appeared to yield somewhat faster efficacy and slightly greater rates of skin clearance at Week 16 compared with the 75 mg dose.

Risankizumab was shown to be well tolerated with no meaningful differences from placebo and no apparent dose response in the safety profile. No Japanese-specific safety issues were identified.

Overall, the benefit-risk profile for risankizumab was favorable. Therefore, this study supports risankizumab as an effective and well-tolerated treatment option for Japanese patients with moderate to severe plaque psoriasis.