



2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)		
Name of Study Drug: Risankizumab	Volume:			
Name of Active Ingredient: Risankizumab	Page:			
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Dose-Ranging Study of BI 655066/ABBV-066/Risankizumab in Patients with Active Psoriatic Arthritis				
Coordinating Investigator: Philip Mease, MD; Seattle Rheumatology Associates				
Study Sites: 47 sites in Belgium, Canada, Czech Republic, Finland, France, Germany, Japan, Poland, Spain, Taiwan, and United States.				
Publications: 1 abstract				
Studied Period (Years): First Subject First Visit: 05 May 2016 Last Subject Last Visit: 24 August 2017	Phase of Development: 2			
Objectives: The primary objective was to provide proof-of-concept for the efficacy of risankizumab as a treatment for psoriatic arthritis. Secondary objectives were to provide further support of efficacy, establish safety, and provide dose-ranging data of risankizumab in patients with active psoriatic arthritis. In addition, risankizumab pharmacokinetics (PK) exposure was assessed to provide data for subsequent PK-PD modelling. The risankizumab exposure-response profile was characterized through a relatively wide exposure range achieved by risankizumab 150 mg every 4 weeks to risankizumab 75 mg single dosing.				
Methodology: This Phase 2, multi-national, randomized, parallel-design, dose-ranging, multiple-dose, placebo-controlled, double-blind study compared risankizumab with placebo in subjects with active psoriatic arthritis. Subjects with active psoriatic arthritis were to be randomized at a 2:2:2:1:2 ratio, stratified based on prior tumor necrosis factor inhibitor (TNFi) use and concurrent methotrexate (MTX) use into 5 treatment arms as follows: <ul style="list-style-type: none">• Arm 1: risankizumab 150 mg every 4 weeks• Arm 2: risankizumab 150 mg Weeks 0, 4, and 16• Arm 3: risankizumab 150 mg Weeks 0 and 12• Arm 4: risankizumab 75 mg Week 0• Arm 5: placebo Enrollment of subjects with prior TNFi experience was capped at approximately 70%.				



Number of Subjects (Planned and Analyzed): 180 subjects were planned; 185 subjects were randomized and analyzed				
Diagnosis and Main Criteria for Inclusion: Subjects were adults ≥ 18 years of age with psoriatic arthritis symptoms for at least 6 months prior to screening and a diagnosis of psoriatic arthritis on the basis of the Classification Criteria for Psoriatic Arthritis (CASPAR) with peripheral symptoms at the screening visit, as assessed by the investigator. Subjects were to have active psoriatic arthritis, defined as ≥ 5 tender joints and ≥ 5 swollen joints at the screening and randomization visits, as assessed by the investigator. Subjects who had symptoms inadequately controlled by standard doses of nonsteroidal anti-inflammatory drugs (NSAIDs) administered for ≥ 4 weeks, traditional disease-modifying antirheumatic drugs (DMARDs) administered for ≥ 3 months, or TNFi agents or who were intolerant to NSAIDs, DMARDs, or TNFi agents, as assessed by the investigator, were eligible.				
Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:				
Study Drug	Dosage Form	Formulation	Manufacturer	Bulk Lot
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 syringe prefilled with 0.87 mL. Dispensed volume is 0.83 mL.	Boehringer Ingelheim Pharma GmbH & Co. KG	B151002457/505410 B151002941/505413
Duration of Treatment: Overall study treatment duration was 16 weeks with additional 16 weeks of follow-up. Subjects who completed all doses of study drug and the Week 24 visit had the option to enroll into a separate open-label extension (OLE) study. Those subjects rolling over to the OLE study did not complete any remaining follow-up visits in this study and followed the procedures in the OLE study protocol.				
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:				
Study Drug	Dosage Form	Formulation	Manufacturer	Bulk Lot
Placebo	Injection solution for SC use	0.9% sodium chloride solution presented in a 1 mL syringe prefilled with 0.87 mL; dispensed volume is 0.83 mL	Boehringer Ingelheim Pharma GmbH & Co. KG	B151001739 B151002749 B161001995

Criteria for Evaluation

Efficacy: The primary endpoint was American College of Rheumatology (ACR) 20 response at Week 16. Secondary efficacy variables were as follows:

- ACR 50 response at Week 16
- ACR 70 response at Week 16
- Change in Tender Joint Count at Week 16 as compared to Baseline
- Change in Swollen Joint Count at Week 16 as compared to Baseline
- Change in Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 16 as compared to Baseline
- Change in Short Form-36 Health Status Survey (SF-36) at Week 16 as compared to Baseline
- Change in Dactylitis count at Week 16 as compared to Baseline (in subjects with dactylitis at Baseline)
- Change in Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index at Week 16 as compared to Baseline (in subjects with enthesitis at Baseline)
- Change in Modified Nail Psoriasis Severity Index (mNAPSI) at Week 16 as compared to Baseline (in subjects with nail psoriasis)
- Psoriasis Area and Severity Index (PASI) 90 response at Week 16 assessed in patients with a $\geq 3\%$ Baseline psoriasis body surface area (BSA)

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

Safety: Safety will be assessed descriptively based on:

- Adverse events (AEs), including serious adverse events (SAEs)
- Clinical laboratory values (hematology, clinical chemistry, and urinalysis) and immunogenicity
- Physical examination, including vital signs and electrocardiogram
- Local tolerability

Statistical Methods

Efficacy: Efficacy analyses were based on the Full Analysis Set (FAS), which consisted of all randomized subjects who received at least 1 dose of assigned study medication. The subjects were grouped by the treatment group assigned at the time of randomization regardless of the actual treatment they received during the study. The difference in proportion of participants that achieved the primary endpoint of ACR 20 between the combined groups of risankizumab (Arm 1 and Arm 2) and the placebo arm (Arm 5) were estimated and tested using the stratified Cochran-Mantel-Haenszel risk difference estimate, stratified based on prior TNFi use and concurrent MTX use. Pairwise comparisons of the risankizumab dose groups versus the placebo group were conducted using the same stratified Cochran-Mantel-Haenszel methods.

Pharmacokinetic: Descriptive statistics for risankizumab plasma concentrations for each sampling time (study visit) were calculated. Immunogenicity (anti-drug antibody and NAb antibody) data were summarized across specific time periods (Week 0 – 16 and Week 0 – 32) as well as by visit. Risankizumab plasma concentrations were compared by anti-drug antibody status (positive or negative) by visit.

Statistical Methods (Continued)

Safety: The Safety Analysis Set consisted 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). Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 20.0, and analyses focused on treatment-emergent AEs (TEAEs). 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, physical examinations, and other safety-related data were assessed with regard to changes compared to findings before the start of treatment.

Summary/Conclusions

Efficacy Results: The primary endpoint was achieved. Subjects with psoriatic arthritis who received risankizumab experienced improvement in signs and symptoms of psoriatic arthritis, as demonstrated by meeting the primary endpoint of ACR 20 response at Week 16 and multiple secondary endpoints. However, a plateau of dose response was observed across all risankizumab regimens.

Statistically significant differences between the combined Arm 1 + 2 risankizumab group and placebo in ACR 70 response ($P = 0.006$) and PASI 90 response ($P < 0.001$) were observed at Week 16. Subjects who received risankizumab did not show significant improvement in dactylitis or enthesitis compared with subjects who received placebo. The SF-36 mental component summary (MCS) and physical component summary (PCS) and HAQ-DI scores did not show statistical improvement in comparison with placebo at Week 16.

Pharmacokinetic Results: A dose- and dosing-frequency-dependent increase in risankizumab plasma concentrations was observed across the different regimens evaluated in subjects with psoriatic arthritis in the study.

In subjects who received at least 1 dose of risankizumab in the study, no regimen-dependent trend in the incidence of risankizumab anti-drug antibodies was observed. Anti-drug antibody incidence (treatment emergent) to risankizumab over the entire study duration (32 weeks) was approximately 12 % (17/140) in evaluable subjects and none of them were positive for NAb. Development of anti-drug antibodies did not appear to have an impact on risankizumab plasma exposures in this study.

Safety Results: Risankizumab 75 mg or 150 mg was generally safe and well-tolerated in subjects with psoriatic arthritis. There were no discernible differences between treatment groups as assessed by TEAEs, laboratory abnormalities, and vital signs. Most TEAEs were mild to moderate in intensity. There were no deaths and no reported cases of tuberculosis (TB) (either new cases or reactivation) in this study. Few subjects experienced TEAEs in the pre-specified areas of safety interest, including serious infections, major adverse cardiovascular event (MACE), and malignancies.

There were no notable changes in laboratory values in the study.

Conclusions: The benefits of risankizumab compared with placebo were consistently demonstrated by the primary and most secondary endpoints in this Phase 2 proof-of-concept study in subjects with active psoriatic arthritis. A dose- and dosing-frequency-dependent increase in risankizumab plasma concentrations was observed across the different regimens evaluated in the study. Risankizumab treatment was shown to be well-tolerated. Therefore, risankizumab was shown to be an effective and well-tolerated treatment option for patients with active psoriatic arthritis.