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: A Randomized, Controlled, Multicenter, Open Label Study with Blinded Assessment of the Efficacy of the Humanized Anti-IL-23p19 Risankizumab Compared to FUMADERM® in Subjects with Moderate to Severe Plaque Psoriasis Who are Naïve to and Candidates for Systemic Therapy		
Coordinating Investigator: Diamant Thaci, MD		
Study Sites: 21 sites in Germany		
Publications: None.		
Studied Period (Years): First Subject First Visit: 22 Aug 2017 Last Subject Last Visit: 06 July 2018	**Phase of Development:** 3	
Objective: The objective of this study is to compare the efficacy and safety of subcutaneous (SC) risankizumab and oral FUMADERM® provided as study medication in subjects with moderate to severe plaque psoriasis (Ps) who are naïve to and candidates for systemic therapy.		
Methodology: This was a randomized, controlled, multicenter, open-label study with blinded assessment of efficacy to demonstrate the efficacy and safety of SC risankizumab in adult subjects with moderate to severe plaque Ps who are naïve to and candidates for systemic therapy as compared with oral FUMADERM® provided as study medication. The study was to include a 30-day screening period and a 24-week active-controlled treatment period followed by a follow-up phone call at Week 31 for subjects who did not elect to enroll into the extension study. The maximum study duration was to be approximately 35 weeks for subjects who did not elect to enroll into the extension study and approximately 28 weeks for subjects who did participate in the extension study. This study was designed to enroll 110 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.		
Number of Subjects (Planned and Analyzed): Approximately 110 subjects planned; 120 analyzed		

Diagnosis and Main Criteria for Inclusion:

Subjects enrolled in this study were to be adults ≥ 18 and < 80 years of age with moderate to severe plaque psoriasis (Psoriasis Area Severity Index [PASI] score of > 10, affected body surface area [BSA] > 10% and Dermatology Life Quality Index [DLQI] > 10) who were naïve to and candidates for systemic therapy.

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

Study Drug	Dosage Form	Formulation	Manufacturer	Bulk Lot
Risankizumab 75 mg risankizumab in pre-filled syringe (PFS), concentration 90 mg/mL	Solution for injection in pre-filled syringe	75 mg/0.83 mL	Boehringer Ingelheim Pharma GmbH & Co. KG	16-005252

Duration of Treatment:

Up to 16 weeks for risankizumab and 24 weeks for FUMADERM®

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

Study Drug	Dosage Form	Formulation	Manufacturer	Bulk Lot
FUMADERM® INITIAL and FUMADERM® gastro-resistant tablets	Tablets	FUMADERM® INITIAL - 30 mg tablets FUMADERM® - 120 mg tablets	Biogen	17-003494 18-001866 17-007088 17-003495

Criteria for Evaluation

Efficacy:

The primary efficacy endpoint is the proportion of subjects with a ≥ 90% improvement in Psoriasis Area and Severity Index (PASI 90) at Week 24.

Secondary endpoints include:

1. Proportion of subjects with a PASI 50/75/90/100 response at Weeks 4, 8, 12, 16, 20 and 24.
2. Change from baseline in PASI at Weeks 4, 8, 12, 16, 20 and 24.
3. Change from baseline in BSA affected by psoriasis at Weeks 4, 8, 12, 16, 20 and 24.
4. Proportion of subjects with a Static Physician Global Assessment (sPGA) of 0 or 1 at Weeks 4, 8, 12, 16, 20 and 24.
5. Proportion of subjects with sPGA of 0 at Weeks 4, 8, 12, 16, 20 and 24.
6. Change from Baseline in Palmoplantar Psoriasis Area Severity Index (PPASI) Total Score at Weeks 16 and 24.
7. Change from Baseline in Psoriatic Scalp Severity Index (PSSI) Total Score at Weeks 16 and 24.

Criteria for Evaluation (Continued)

8. Change from Baseline on the Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA-CLIN) Total Score at Weeks 16 and 24.
9. Change from Baseline in Psoriasis Symptom Scale (PSS) total score at Weeks 16 and 24.
10. Proportion of subjects achieving PSS (0) at Weeks 16 and 24.
11. Change from Baseline in Dermatology Life Quality Index (DLQI) total score at Weeks 16 and 24.
12. Proportion of subject achieving DLQI (0, 1) at Weeks 16 and 24.
13. Change from Baseline in Short Form - 36 (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores at Weeks 16 and 24.
14. Change from Baseline in Patient Benefit Index (PBI) at Weeks 16 and 24.
15. Change from Baseline on Hospital Anxiety and Depression Scale (HADS) at Weeks 16 and 24.
16. Change from Baseline on Patient Global Assessment (PtGA) at Weeks 16 and 24.
17. Change from Baseline in EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L) Index, EQ-5D Utility Index and VAS at Weeks 16 and 24.

Pharmacokinetic:

Risankizumab serum concentrations were determined. Descriptive statistics were calculated for each sampling time (study visit). The number and percentage of subjects with anti-drug antibody (ADA) and neutralizing antibody (NAb) were calculated.

Safety:

Safety evaluations included adverse event (AE) monitoring, physical examinations, vital sign measurements, 12-lead electrocardiogram, and clinical laboratory testing (hematology, chemistry, and urinalysis).

Statistical Methods

Efficacy:

All efficacy analyses will be performed in the intent-to-treat population consisting of all subjects who were randomized. The primary endpoint will be analyzed using a Cochran-Mantel-Haenszel test stratified by prior phototherapy at level of significance 5%, using non-responder imputation as primary method of imputation for missing values.

Pharmacokinetic:

Individual risankizumab serum concentrations were tabulated and summarized by visits with descriptive statistics. In addition, ADA 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 evaluations included AE monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (hematology, chemistry, and urinalysis). The safety population consists of all subjects who were randomized and received at least one dose of study drug. Treatment-emergent adverse events are defined as events with an onset date on or after the first dose of study drug until 15 weeks (105 days) following the last dose of risankizumab or 1 week (7 days) after the last dose of FUMADERM® provided as study medication or until rollover into the extension study. In a sensitivity analysis, adverse events with an onset date until 7 weeks (49 days) after the last dose of FUMADERM® provided as study medication or until rollover into the extension study will be included. Serious adverse events (SAEs) and protocol-related non-serious AEs with onset after informed consent but before the first study drug administration will be considered as pretreatment events and reported separately. Other safety variables like laboratory data and vital signs will also be described by descriptive statistics for each treatment group.

Summary/Conclusions

Efficacy Results:

The primary endpoint of proportion of subjects who achieved PASI 90 was met, with statistically significant differences in favor of risankizumab compared to the FUMADERM® group observed for the endpoint. Analyses of secondary and other endpoints (including PSS, DLQI, SF-36, PBI, HADS, PtGA, and EQ-5D-5L) supported the findings that risankizumab was superior to FUMADERM® in producing clinically meaningful improvement in the extent and severity of subjects' Ps, as supported by statistically significant proportions of subjects who achieved PASI 50/75/100 and sPGA results of clear and of clear or almost clear across time points compared with FUMADERM®.

Pharmacokinetic Results:

Following administration of risankizumab 150 mg SC doses, risankizumab serum trough concentrations observed in this study were consistent with the Phase 3 studies in subjects with moderate to severe plaque psoriasis. The incidence of ADAs to risankizumab (treatment-emergent) was 17% (10/60), with the majority of these subjects testing positive for neutralizing antibodies. Development of ADAs did not have a consistent apparent impact on risankizumab serum exposures.

Summary/Conclusions (Continued)

Safety Results:

In this study of adult subjects with moderate to severe plaque Ps, no safety issues were identified. The proportions of subjects with SAEs and AEs were low overall and similar across the risankizumab and FUMADERM® treatment groups. There were more AEs leading to discontinuation in the FUMADERM® treatment group than in the risankizumab treatment group where no AEs led to discontinuation. The most frequently reported AEs in the risankizumab treatment group were nasopharyngitis, influenza, headache, oropharyngeal pain, diarrhea, and hypertension. In the FUMADERM® treatment group a higher rate of AEs in the specific system organ class (SOCs) (e.g., gastrointestinal disorders and blood and lymphatic system disorders) was observed. There were no deaths during the study. Fewer subjects in the risankizumab treatment group had an event of hypersensitivity than the subjects in the FUMADERM® treatment group. There was a single case of serious infection (influenza) in the risankizumab treatment group and no cases of major adverse cardiac event (MACE), extended MACE, other cardiovascular events, tuberculosis, opportunistic infections, or herpes zoster-related events in any treatment arm. 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 over FUMADERM®.

Conclusions:

The superior benefits of risankizumab compared with FUMADERM® were consistently demonstrated by the primary endpoints and supported by the secondary endpoints in this Phase 3 study in adult subjects with moderate to severe plaque Ps. Risankizumab was shown to be well-tolerated with meaningful differences from FUMADERM®. There were more AEs leading to discontinuation in the FUMADERM® treatment group than in the risankizumab treatment group where no AEs led to discontinuation. Rates of severe AEs and AEs of safety interest reported in the risankizumab group were low and were lower than rates in the FUMADERM® treatment group. There was a single case of serious infection (influenza) in the risankizumab treatment group and no cases of MACE, extended MACE, other CV events, TB, opportunistic infections or herpes zoster-related events in any treatment arm. Overall, the benefit-risk profile for risankizumab was favorable. Therefore, this study supports risankizumab as an effective and well-tolerated treatment option for adult subjects with moderate to severe plaque Ps.