Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

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For more information you can find scientific results at these websites:

www.clinicaltrialsregister.com search for the **EudraCT Number**: 2013-002902-29

www.clinicaltrials.gov search for the **NCT Number**: NCT02031276

Important: The synopsis is provided by Boehringer Ingelheim in cooperation with AbbVie Inc.

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 Phase 2, Multicenter, Randomized, Double-Blind, Multiple Dose, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Pharmacokinetics, and Safety of BI 655066 (Risankizumab), an IL-23 p19 Antagonist Monoclonal Antibody, in Patients With Moderately to Severely Active Crohn's Disease Who Are Naïve to or Were Previously Treated With Anti-TNF Therapy

Investigator:

[redacted], MD
[redacted]

Study Sites:

36 sites across 9 countries (Belgium, Canada, Germany, Republic of Korea, Netherlands, Poland, Spain, United Kingdom, and US)

Publications:

A total of 6 journal manuscripts have been published based on the data in this report.

Studied Period (Years):	**Phase of Development:** 2
First Subject First Visit: 25 February 2014 Last Subject Last Visit: 18 November 2016	

Objectives:

The primary objective was to evaluate the efficacy of risankizumab in inducing clinical remission, after 12 weeks of treatment. The secondary objectives were to evaluate the efficacy of risankizumab in inducing endoscopic response, clinical response, mucosal healing, and deep remission, to evaluate the safety of risankizumab, and to explore the pharmacokinetics (PK) and pharmacodynamics of risankizumab in Crohn's Disease (CD).

Methodology:

Study M15-993 was a proof-of-concept, multi-center, randomized, double-blind (DB), placebo-controlled, parallel-group, Phase 2, dose-ranging study of risankizumab in subjects with moderately to severely active CD. The study consisted of a screening period of up to a maximum of 4 weeks, a 12-week DB intravenous (IV) Period 1, a 14-week open label (OL) IV/wash-out period (Period 2), a 26-week subcutaneous (SC) therapy period (Period 3), and a 15-week follow-up period.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 120 subjects were to be randomized in a ratio of 1:1:1 to 1 of the 3 treatment groups.

Analyzed: A total of 121 subjects were randomized and treated and included in the intent-to-treatment (ITT) data set.

Diagnosis and Main Criteria for Inclusion:

Subjects were men or women 18 to 75 years of age (inclusive) with a diagnosis of CD for at least 3 months prior to Visit 1 confirmed by endoscopic or imaging examination. Subjects were to have moderate to severe CD at Visit 1.1, defined as Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450, and mucosal ulcers in at least 1 segment of the ileum or colon along with a Crohn's Disease Endoscopic Index of Severity (CDEIS) ≥ 7 (for subjects with isolated ileitis ≥ 4), as assessed by ileocolonoscopy and confirmed by central independent reviewer(s) before randomization. Subjects who were naïve or experienced to 1 or more tumor necrosis factor (TNF) antagonists (infliximab, adalimumab, or certolizumab pegol) at a dose approved for CD were eligible.

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

Study Drug Unit Strength	Dosage Form; Dose	Bulk Lot Number
Risankizumab 100 mg risankizumab in a vial with 10 mL solution (concentration 10 mg/mL)	IV infusion (3 infusions separated by 4 weeks); 200 mg or 600 mg	B131002790/E3731F01 B151000581/E4731F02 B141001166/E4731F01
Risankizumab 90 mg risankizumab in a pre-filled syringe with 1 mL solution (concentration 90 mg/mL)	SC (4 injections separated by 8 weeks); 180 mg	B141001267/E3744S03 B141003022/E4744S01 B151000582/E4744S02

Duration of Treatment:

Approximately 67 weeks for all 3 study periods and 15-week follow-up period.

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

Study Drug Unit Strength	Dosage Form; Dose	Bulk Lot Number
Placebo (matching) 0 mg/mL	IV infusion (3 infusions separated by 4 weeks); NA	B131002794/E3732F01 B141001742/E4732F02

Criteria for Evaluation

Efficacy:

The primary endpoint was clinical remission, defined as a CDAI < 150, at Week 12. Secondary endpoints included clinical response at Week 12 (defined by either a CDAI < 150 or a CDAI reduction from baseline of at least 100 points), CDEIS remission (defined as a CDEIS of 4 or less at Week 12; for subjects with initial isolated ileitis a CDEIS of 2 or less), CDEIS response at Week 12 (defined as ≥ 50% reduction from baseline), mucosal healing (defined as the absence of mucosal ulceration at Week 12, and deep remission (defined as clinical remission and CDEIS remission at Week 12). Multiple exploratory endpoints were also assessed.

Pharmacokinetics:

Plasma trough concentration values of risankizumab and relative titers of anti-drug antibody (ADA) for immunogenicity assessment were determined at the planned visits using validated methods of analysis.

Safety:

Safety analyses focused on adverse events (AEs) related to early discontinuation, immune suppression and injection site effects. Analysis of laboratory measures focused on haemotologic measures of immune suppression.

Statistical Methods

Efficacy:

The proportions of subjects in clinical remission at Week 12 were estimated and tested between placebo and the combination of risankizumab 200 mg IV and 600 mg IV with the use of the Cochran-Mantel-Haenszel (CMH) risk difference estimate test, stratified by the randomization factors of naïve or experienced to anti-TNF therapy with weights proposed by Greenland & Robins. Pairwise comparisons of the three treatment arms were conducted using the same methods as the primary analysis. No adjustments were made for multiplicity and nominal P values were provided. All the binary secondary endpoints at Week 12 were estimated and tested between Placebo and the combination of 200 mg IV and 600 mg IV with the use of the CMH test, stratified by the randomization factors in the same manner of the primary endpoint. Pairwise comparisons were conducted in the same manner as for the primary endpoint.

Pharmacokinetics and Immunogenicity:

Plasma trough concentrations were summarized using descriptive statistical methods. In addition, the proportion of subjects with positive or negative results for ADA and neutralizing antibodies (NAb) incidence were summarized using descriptive statistical methods.

Safety:

Summary statistics were presented for subjects who had both baseline and post-baseline values for laboratory parameters and vital signs: the mean value at Baseline and at each respective protocol specified visit, and the mean, standard deviation and median for changes from Baseline. Categorical data were summarized using frequencies and percentages.

Summary/Conclusions

Efficacy Results:

The results at Week 12 demonstrated that selective blockade of IL-23p19 with risankizumab was superior to placebo in achieving clinical (remission and response per CDAI), endoscopic (remission, response, and mucosal healing per CDEIS), deep remission, biomarker (c-reactive protein and fecal calprotectin), and quality of life endpoints (IBDQ). Additionally, dose-dependent improvements were observed, with a greater proportion of subjects in the risankizumab 600 mg IV group achieving both clinical and endoscopic endpoints versus subjects in the risankizumab 200 mg IV group and placebo. These results indicate that treatment with risankizumab 600 mg IV for induction therapy is superior to lower doses. Treatment with higher doses of risankizumab IV during induction warrants further evaluation.

Upon entry to Period 2, all subjects who were not in deep remission received 3 doses of IV risankizumab 600 mg every 4 weeks. Re-induction of 600 mg risankizumab during Period 2 for those subjects who did not achieve deep remission in Period 1 was effective in achieving greater clinical remission rates at Week 26 than those observed at Week 12. Switching from placebo to 600 mg risankizumab led to a clinical remission rate of 54.5%, confirming the efficacy of risankizumab 600 mg IV observed with blinded treatment during Period 1. Extended treatment with 600 mg risankizumab in subjects who received 200 mg or 600 mg during Period 1 led to a clinical remission rate of 52.9%, indicating some subjects may benefit from extended high-dose induction treatment. All 6 subjects who entered the washout arm in Period 2 remained in clinical remission at Week 26, suggesting a durable pharmacodynamic profile of risankizumab.

Treatment during Period 3 with risankizumab SC was effective as therapy for maintaining clinical remission. The greatest rates of achievement of endoscopic endpoints at Week 52 (CDEIS remission, CDEIS response, and mucosal healing) were observed in the subjects who received risankizumab 600 mg IV during Period 1, suggesting that a higher drug exposure during induction is necessary to achieve endoscopic resolution of disease activity.

Pharmacokinetic and Immunogenicity Results:

Approximate dose-proportional increases in risankizumab plasma trough concentrations were observed in subjects with CD who received risankizumab induction treatment of 200 mg IV and 600 mg IV at Weeks 0, 4 and 8 during Period 1. Comparable risankizumab trough concentrations relative to Period 1 were observed during Period 2 in subjects who received 600 mg IV dose. Following the regimen of 180 mg SC dose every 8 weeks starting at Week 26, near steady state levels were achieved by Week 42.

Treatment-emergent ADA-positive responses were observed in 8% of the subjects who received at least 1 dose of risankizumab (9 out of 108 subjects). The time to appearance of the first ADA-positive sample for the risankizumab-treated subjects ranged from 12 to 18 weeks following start of treatment. The majority of the ADA-positive responses were transient. None of the ADA-positive subjects were found to have positive NAb assessment during the study. Although the number of ADA-positive subjects was limited, there does not appear to be any impact of ADA on risankizumab plasma concentrations.

Summary/Conclusions (Continued)

Safety Results:

In this study, risankizumab was generally safe and well-tolerated as evidenced by the results of assessment of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs of special interest as well as laboratory, physical examinations, and vital signs assessments. The most frequently reported AEs were infections, nasopharyngitis in particular. The occurrences of opportunistic infections, tuberculosis, and fungal infections were few during the study. No significant, unexpected safety issues were observed.

Conclusions:

Overall, the findings in this proof-of-concept Phase 2 study demonstrated that selective blockade of IL-23p19 with risankizumab was superior to placebo in achieving improvements in clinical, endoscopic, biomarker and quality of life endpoints for subjects with moderately to severely active CD. Furthermore, study results demonstrated risankizumab SC was effective as a maintenance therapy. Approximate dose-proportional increases in risankizumab plasma trough concentrations were observed and there did not appear to be any impact of ADA on risankizumab plasma concentrations. Risankizumab was generally safe and well-tolerated, and no new safety signals were identified.