27 January 2022
EMA/95539/2022
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Skyrizi

risankizumab

Procedure no: EMEA/H/C/004759/P46/008

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 8th November 2021, the MAH submitted a completed paediatric study for Adult and Adolescent Subjects with Moderately to Severely active Crohn´s Disease who failed prior biologic therapy, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that A Phase 3, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Study to Evaluate Efficacy and Safety of Risankizumab in Adult and Adolescent Subjects with Moderately to Severely active Crohn´s Disease who Failed Prior Biologic Therapy (Clinical Study Report R&D/20/0587, Risankizumab/ Protocol M15-991) is part of a clinical development program. **The extension application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted by applicant in Q4 2021.**

2.2. Information on the pharmaceutical formulation used in the study

Blinded study drug (risankizumab 1200 mg, risankizumab 600 mg, or placebo) was administered intravenously (IV) during 12-Week Induction Period at Weeks 0, 4, and 8.

Blinded study drug (risankizumab 1200 mg) was administered IV during Induction Period 2 at Weeks 12, 16, and 20. Blinded study drug (360 mg risankizumab, or 180 mg risankizumab) was administered subcutaneously (SC) in Induction Period 2 at Weeks 12 and 20.

Risankizumab was provided as 90 mg/mL solution for infusion in vial (bulk lot numbers: 16-006818, 17-007126, 17-008086, 18-004230, 18-006696, 18-005859, 19-003343) and 90 mg/mL solution for injection in pre-filled syringe (PFS) (bulk lot numbers: 17-002008, 17-004111, 18-004857, 18-007358, 19-001854). Placebo was provided as placebo solution for infusion in vial

2.3. Clinical aspects

2.3.1. Introduction

The purpose of this submission is to comply with Article 46 of Regulation (EC) No 1901/2006, as amended, by submitting data available from patients less than 18 years of age recruited to the following study:

A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study to Assess the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease Who Failed Prior Biologic Treatment.
Clinical Study Report R&D/20/0587, Risankizumab/ Protocol M15-991.

2.3.2. Clinical study

A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study to Assess the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease Who Failed Prior Biologic Treatment.
Clinical Study Report R&D/20/0587, Risankizumab/ Protocol M15-991.

Description

Methods

Study M15-991 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of risankizumab as induction treatment in subjects with moderately to severely active CD, defined as:

1. Average daily stool frequency (SF) $\geq$ 4 and/or average daily abdominal pain score (APS) $\geq$ 2; plus

2. Crohn's disease activity index (CDAI) of 220-450 at baseline; plus

3. An eligible Simple Endoscopic Score for CD (SES-CD) of $\geq$ 6 (or $\geq$ 4 for isolated ileal disease).

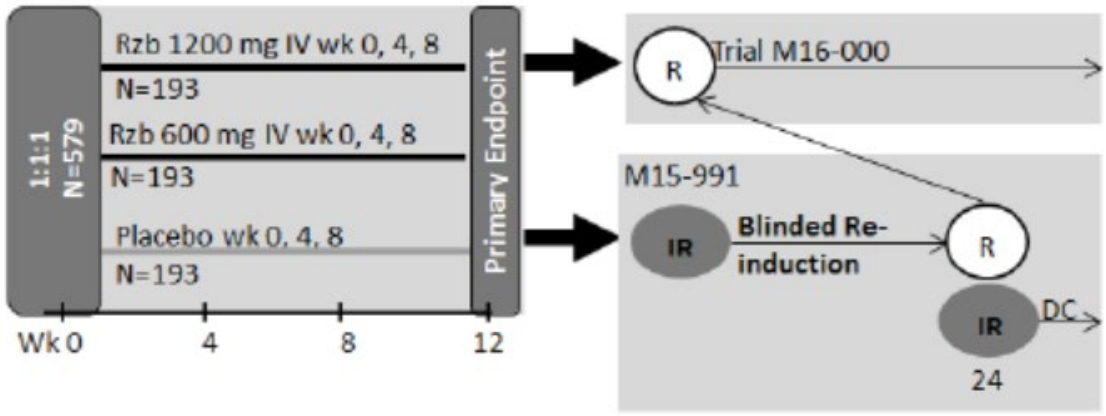
The study enrolled subjects who had an inadequate response (IR) to prior biologic therapy (Bio-IR). The Bio-IR population was defined as subjects with documented intolerance or inadequate response to one or more of the approved biologics for CD.

Subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled into the study and randomized in a 1:1:1 ratio into the pivotal 12-Week Induction Period. Visits for clinical evaluation occurred at Baseline, and Weeks 4, 8, and 12 or premature discontinuation (PD). Subjects in the risankizumab treatment arms who did not achieve SF/APS clinical response at Week 12 were offered to enter into an exploratory Induction Period 2, where subjects were randomized 1:1:1 to blinded reinduction IV or SC maintenance therapy with risankizumab in a double-dummy fashion. Subjects receiving placebo and who did not achieve SF/APS clinical response at Week 12 were assigned to receive risankizumab 1200 mg IV during Induction Period 2. Visits in Induction Period 2 occurred at Weeks 12, 16, 20 and 24.

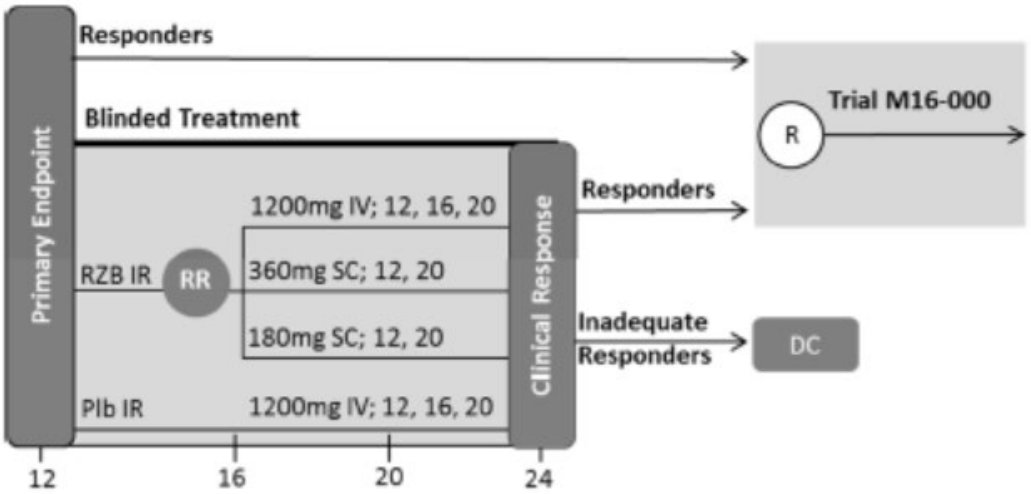
Study duration was up to 49 weeks, including a Screening period of up to 35 days, a 12- week induction period, a 12-week Induction Period 2 for those subjects who did not achieve SF/APS clinical response at Week 12, and a 140-day safety follow up period from the last dose of study drug. The study design schematic is shown in Figure 1.

Figure 1. Study Design Schematic

a. 12-Week Induction Period



b. Induction Period 2



DC = discontinued; IR = subjects with inadequate SF/APS clinical response to induction; IV = intravenous; Plb = placebo; R = subjects with SF/APS clinical response; RR = re-randomize; RZB = risankizumab; SC = subcutaneous; Wk = week

Study participants

Subjects were male or female aged ≥ 18 to ≤ 80 years (and subjects 16 to < 18 years of age who met the definition of Tanner stage 5 for development) with a confirmed diagnosis of CD for at least 3 months prior to Baseline, Crohn's disease activity index (CDAI) score 220 – 450 at Baseline, endoscopic evidence of mucosal inflammation as documented by the SES-CD of ≥ 3 (for no more than 58 subjects) or an SES-CD of ≥ 6 for ileocolonic or colonic disease or SES-CD of ≥ 4 for isolated ileal

disease, with an average daily stool frequency (SF) ≥ 4 and/or average daily abdominal pain score (APS) ≥ 2 at Baseline.

Treatments

Blinded study drug (risankizumab 1200 mg, risankizumab 600 mg, or placebo) was administered intravenously (IV) during 12-Week Induction Period at Weeks 0, 4, and 8.

Blinded study drug (risankizumab 1200 mg) was administered IV during Induction Period 2 at Weeks 12, 16, and 20. Blinded study drug (360 mg risankizumab, or 180 mg risankizumab) was administered subcutaneously (SC) in Induction Period 2 at Weeks 12 and 20.

Objective(s)

The objective of Study M15-991 is to evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in subjects with moderately to severely active Crohn's disease (CD) who have failed a prior biologic.

Outcomes/endpoints

Efficacy:

The co-primary endpoints for the outside the United States (OUS) protocol were:

- Proportion of subjects with SF/APS clinical remission at Week 12
- Proportion of subjects with endoscopic response at Week 12

The co-primary endpoints for the US protocol were:

- Proportion of subjects with CDAI clinical remission at Week 12
- Proportion of subjects with endoscopic response at Week 12

The ranked secondary endpoints for the OUS protocol were:

1. Proportion of subjects with CDAI clinical remission at Week 12

2. Proportion of subjects with CDAI clinical response at Week 4

3. Proportion of subjects with SF/APS clinical remission at Week 4

4. Proportion of subjects with CDAI clinical response at Week 12

5. Mean change from baseline of induction in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT) fatigue at Week 12

6. Mean change from baseline of induction in Inflammatory Bowel Disease Questionnaire (IBDQ) total score at Week 12

7. Proportion of subjects with enhanced SF/APS clinical response and endoscopic response at Week 12

8. Proportion of subjects with endoscopic remission at Week 12

9. Proportion of subjects with enhanced SF/APS clinical response at Week 4

10. Proportion of subjects with ulcer-free endoscopy at Week 12

11. Enhanced SF/APS clinical response at Week 12

12. Proportion of subjects with resolution of extra-intestinal manifestations (EIMs) at Week 12, in subjects with any EIMs at Baseline

13. Proportion of subjects with CD-related hospitalization through Week 12

14. Proportion of subjects without draining fistulas at Week 12 in subjects with draining fistulas at Baseline

The ranked secondary endpoints for the US protocol were:

1. Proportion of subjects with SF/APS clinical remission at Week 12

2. Proportion of subjects with CDAI clinical response at Week 4

3. Proportion of subjects with CDAI clinical response at Week 12

4. Change from baseline of FACIT fatigue at Week 12

5. Proportion of subjects with CDAI clinical remission at Week 4

6. Proportion of subjects with CDAI clinical response and endoscopic response at Week 12

7. Proportion of subjects with SF remission at Week 12

8. Proportion of subjects with AP remission at Week 12

9. Proportion of subjects with endoscopic remission at Week 12

10. Proportion of subjects with enhanced SF/APS clinical response at Week 4

11. Proportion of subjects with ulcer-free endoscopy at Week 12

12. Proportion of subjects with enhanced SF/APS clinical response at Week 12

13. Proportion of subjects with resolution of extra-intestinal manifestations (EIMs) at Week 12, in subjects with any EIMs at Baseline

14. Proportion of subjects with CD-related hospitalization through Week 12

15. Proportion of subjects without draining fistulas at Week 12 in subjects with draining fistulas at Baseline

Pharmacokinetics and Immunogenicity:

Serum risankizumab concentrations, anti-drug antibodies (ADA), and neutralizing antibodies (NAb) were determined.

Safety:

Incidence of adverse events (AEs), changes in vital signs, physical examination results, clinical laboratory data, and product complaints were assessed throughout the study.

Sample size

Sample size calculation was based on the larger sample size needed to detect treatment differences between the risankizumab treatment arms and the placebo arm for each of the co-primary endpoints. Assuming the clinical remission (SF/APS) rate at Week 12 would be 23.5% for one of the risankizumab treatment arms and 10% for the placebo arm, a sample size of 193 subjects for each risankizumab arm and 193 for the placebo arm would have approximately 89% power to detect the treatment difference between risankizumab and placebo using a Fisher's exact test at alpha level of 0.025 (two-

sided). Assuming the CDAI clinical remission rate at Week 12 would be 34% for one of the risankizumab treatment arms and 15% for the placebo arm, this sample size would have 97% power to detect the treatment difference between risankizumab and placebo using a Fisher's exact test at a 0.025 significant level (two-sided). Assuming the endoscopic response rate a Week 12 will be 17% for one of the risankizumab treatment arms and 5% for the placebo arm, this sample size would have 93% power to detect treatment difference between risankizumab and placebo using a Fisher's exact test at a 0.025 significant level (two-sided).

Statistical Methods

Efficacy:

The co-primary endpoints were analyzed between placebo and each of risankizumab 600 mg IV and 1200 mg IV arms using the Cochran-Mantel-Haenszel (CMH) test, stratified by the randomization factors of number of prior biologics failed (≤ 1, > 1) and baseline steroid use (Yes, No) based on intent to-treat (ITT)1A. A CMH based two-sided 95% confidence interval (CI) for the difference between treatment groups was constructed. For the co-primary efficacy endpoints, an additional analysis using the same CMH test was performed using As Observed (AO) data handling without any imputation. The analysis was conducted using the ITT1A population.

In general, continuous secondary efficacy endpoints with repeat measurements were analyzed using a mixed effect model repeat measurement (MMRM) model including factors for treatment group, visit, visit by treatment interaction, stratification variables and the continuous fixed covariates of baseline measurement. The MMRM analysis was considered primary for inferential purposes. Continuous secondary efficacy variables were analyzed using ANCOVA-C approach.

Categorical secondary efficacy variables were analyzed using the CMH test controlling for stratification variables (prior biologics failed [≤ 1, > 1] and baseline steroid use [Yes, No]), except for the endpoints related to draining fistulas and CD-related hospitalization. A CMH based two-sided 95% CI for the difference between each risankizumab treatment group and placebo group was constructed. The endpoints of "The achievement of no draining fistulas at Week 12 in subjects with draining fistulas at baseline" and "Occurrence of CD-related hospitalization through Week 12" were analyzed using Chisquare test (or Fisher's exact test if $\geq$ 20% of the cells have expected cell count < 5).

Pharmacokinetics and Immunogenicity:

Serum risankizumab concentrations were summarized at each time point for each dosing regimen using descriptive statistics. In addition, ADA incidence was summarized by cohorts and study visits. ADA titers were tabulated for each subject at the respective study visits.

Safety:

Incidence of AEs, including those related to study drug, changes in vital signs, physical examination results, and clinical laboratory values were analyzed.

Results

Study M15-991 enrolled 618 patients with 5 paediatric patients. Of the paediatric patients 1 subject each was randomized to risankizumab 1200 IV treatment and 1 subject to 600 mg IV, and 3 subjects to placebo (2 placebo subjects entered Induction Period 2 and received risankizumab 1200 mg IV).

A <18 year old subject was randomised to receive risankizumab 600 mg IV in the 12-Week Induction Period. The subject completed all dosing and was classified as a responder at the end of the 12-Week Induction Period. There were no AEs reported for this subject.

A <18 year old subject was randomised to risankizumab 1200 mg IV in the 12-Week Induction Period. The subject was considered a responder and completed the study. On Day 15, the subject experienced a non-serious, mild AE of arthropathy. No treatments were administered, the event was considered ongoing and intermittent at the end of study conduct, and the event was considered by the investigator to have no reasonable possibility of being related to study drug.

A <18 year old subject was randomised to receive placebo in the 12-Week Induction Period and then risankizumab 1200 mg IV for Induction Period 2. The subject completed all dosing and study conduct.

On Day 1 during the 12-Week Induction Period (placebo treatment), the subject experienced a non-serious, moderate AE of anaemia and on Day 2, experienced a non-serious, mild AE of tinea. Treatment was administered for the anaemia, but not for the tinea. Both events were considered resolved on Day 105 and Day 163, respectively, and both events were considered by the investigator to have no reasonable possibility of being related to study drug.

On Day 5, the subject experienced a non-serious, moderate AE of CD aggravated. Treatment was administered for the event, the event was considered resolved on Day 82, and the investigator considered the event to have no reasonable possibility of being related to study drug.

On Day 27 the subject experienced a non-serious, moderate AE of vomiting. Treatment was administered for the event, the event was considered resolved on Day 139, and the investigator considered the event to have no reasonable possibility of being related to study drug.

On Day 83 the subject experienced a serious AE of severe CD aggravated that required hospitalization. On the same day, the subject experienced a non-serious, moderate AE of hypokalaemia. Treatment was administered for both events. The AE of hypokalaemia was considered resolved on Day 170. The investigator considered the event to have no reasonable possibility of being related to study drug. The event of CD aggravated was considered ongoing at the end of study conduct. Both the investigator and AbbVie considered the event to have no reasonable possibility of being related to study drug and an alternative aetiology of worsening disease was cited.

On Day 91 the subject experienced a non-serious, severe AE of haematemesis. Treatment administered for the event, dose was not changed, the event was considered resolved on Day 92, and the investigator considered the event to have no reasonable possibility of being related to study drug.

On Day 92 the subject experienced a non-serious, mild AE of sinus tachycardia as confirmed by ECG. No treatments were administered and study drug dose was not changed. The event was considered resolved on Day 98 and the investigator considered the event to have no reasonable possibility of being related to study drug.

On Days 101, 106, 126, and 157 of Induction Period 2 (risankizumab 1200 mg IV treatment), the subject experienced non-serious AEs of moderate arthralgia aggravated, severe anaemia aggravated, moderate anaemia, and mild tinea cruris, respectively. Treatments were administered for all events except the tinea cruris. The AEs of arthralgia aggravated, anaemia aggravated, and anaemia were considered resolved on Days 107, 125, and 170, respectively, while the AE of tinea cruris was considered ongoing at the end of study conduct. The AEs of arthralgia aggravated, anaemia aggravated, and anaemia were considered by the investigator to have no reasonable possibility of being related to study drug, while the AE of tinea cruris was considered by the investigator to have a reasonable possibility of being related to study drug.

A <18 year old subject was randomised to placebo in the 12-Week Induction Period and then to risankizumab 1200 mg IV for Induction Period 2. On Day 26 during the 12-Week Induction Period (placebo treatment), the subject experienced a non-serious mild AE of nasopharyngitis. No treatments were administered, the event was considered resolved on Day 29, and the event was considered by

the investigator to have no reasonable possibility of being related to study drug. No AEs were reported during Induction Period 2.

A <18 year old subject was randomised to placebo in the 12-Week Induction Period. The subject reported multiple non-serious mild AEs during the 12-Week Induction Period, none of which were considered by the investigator to have a reasonable possibility of being related to study drug. On Day 58, the subject reported a non-serious mild AE of COVID-19 infection. No treatments were administered at the time and the event was considered ongoing. The subject did not enter Induction Period 2.

2.3.3. Discussion on clinical aspects

The purpose of this submission was to comply with Article 46 of Regulation (EC) No 1901/2006, as amended, by submitting data available from patients less than 18 years of age recruited to Phase 3, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Study to Evaluate Efficacy and Safety of Risankizumab in Adult and Adolescent Subjects with Moderately to Severely active Crohn´s Disease who failed prior biologic therapy.

This study was designed to evaluate the efficacy and safety of risankizumab as induction treatment in subjects with moderately to severely active CD with prior failure to biologic therapy. This study enrolled adult patients ≥ 18 to ≤ 80 years but it also could enrol subjects 16 to < 18 years of age who met the definition of Tanner stage 5 for development.

The objective of Study M15-991 is to evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in subjects with moderately to severely active CD who failed prior biologic therapy.

The co-primary endpoints for the outside the United States protocol were:

- Proportion of subjects with SF/APS clinical remission at Week 12
- Proportion of subjects with endoscopic response at Week 12

The co-primary endpoints for the US protocol were:

- Proportion of subjects with CDAI clinical remission at Week 12
- Proportion of subjects with endoscopic response at Week 12

A total of 618 subjects were randomized in the study including 5 paediatric subjects.

According to the MAH, overall, the study met the co-primary endpoints of clinical remission (as assessed by the CDAI in the US-specific protocol and by SF/APS in the OUS protocol) at Week 12 and endoscopic response at Week 12. Analysis of this data is not the subject of this current procedure and will be assessed during the application to extend the indication for Skyrizi to include the treatment of CD (expected submission Q42021). This assessment focuses only on the paediatric data. This study enrolled 5 paediatric subjects four 17 year olds and one 16 year old.

Treatment for the paediatric group consisted of; 1 subject who was randomised to risankizumab 1200 IV treatment and 1 subject randomised to 600 mg IV, and 3 subjects to placebo (2 placebo subjects entered Induction Period 2 and received risankizumab 1200 mg IV). Two paediatric subjects were randomised to active treatment in the induction phase and both were both classified as responders at 12 weeks.

No conclusions can be made on the efficacy of risankizumab in the paediatric cohort as the number of paediatric patients was too small.

In general, the risankizumab treatment seems to be tolerated in this study by paediatric patients however, once again no firm conclusion could be made on safety aspects as the number of paediatric patients was too small. No changes to the SmPC are proposed at the moment.

3. CHMP’s overall conclusion and recommendation

In the context of this PAM for a completed paediatric study for Skyrizi (risankizumab), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, the MAH has met their obligations.

In relation to paediatric patients, no conclusions on safety and efficacy could be made as the number of paediatric patients was too small.

It should be noted that the variation application to add a new indication for the treatment of Crohn's Disease is planned to be submitted by the applicant shortly.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

N/A

MAH responses to Request for supplementary information

N/A