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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/P46/006

Note

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

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1. Introduction

On 28 Aug 2021, the MAH submitted a completed paediatric study for risankizumab, 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

Risankizumab is a fully humanized monoclonal antibody of the IgG1 subclass directed towards IL-23 p19 and for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. The MAH also submitted an extension of indication for treatment of active psoriatic arthritis (PsA) in adults (EMEA/H/C/004759/II/0014).

The objective of Study M16-813 was to assess the safety and efficacy of risankizumab versus placebo for the treatment of moderate to severe Atopic dermatitis (AD) in adult and adolescent subjects

2.2. Information on the pharmaceutical formulation used in the study

Treatment was given with either placebo or Risankizumab (ABBV-066) Solution for injection in pre-filled syringe (PFS) 75 mg/0.83 mL (90 mg/mL) solution for injection.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final study report for:

M16-813 A Phase 2, Multicenter, Randomized, Placebo- Controlled, Double-Blind Study to Evaluate Risankizumab in Adult and Adolescent Subjects with Moderate to Severe Atopic Dermatitis.

2.3.2. Clinical study

Study M16-813

Description

Study M16-813 was a Phase 2, randomized, double-blind, placebo-controlled multicentre study to evaluate the safety and efficacy of risankizumab for the treatment of moderate to severe AD in adult and adolescent subjects with onset of symptoms at least 2 years before the Baseline Visit. The duration of the study was up to 65 weeks and included a screening period of up to 35 days, a 16-week double-blind treatment period (Period A), a 36-week double-blind treatment period (Period B), and a safety phone call approximately 20 weeks after the last dose of study drug. The primary analysis was performed when all subjects completed Week 16. Eligible subjects were randomized at Baseline to receive risankizumab 150 mg, risankizumab 300 mg, or matching placebo (2:2:1, respectively) at Week 0 and Week 4 of Period A. In Period B, subjects in the placebo group were re-randomized at Week 16 in a 1:1 ratio to receive either risankizumab 150 mg or 300 mg for the remainder of the study. Subjects originally randomized to risankizumab 150 mg or 300 mg in Period A stayed on their previously assigned treatment through the end of the study.

All subjects received risankizumab at the Week 16, Week 28, and Week 40 visits. The last visit to the study site occurred at Week 52. Subjects had a final follow up call 20 weeks after the last dose administration. During Period B, subjects with less than 50% reduction from Baseline in the Eczema Area and Severity Index (< EASI 50) were allowed to begin approved concomitant rescue treatment. Rescue treatment was limited to up to twice-daily application of topical corticosteroids.

Methods

Objective(s)

The following primary and key secondary objectives were evaluated:

- Primary endpoint: proportion of subjects achieving at least a 75% reduction from Baseline in EASI (EASI 75) at Week 16;
- Key secondary endpoint: proportion of subjects achieving validated Investigator Global Assessment Scale for Atopic Dermatitis of "0" or "1" (on a 5-point scale) with a reduction from Baseline of ≥ 2 points at Week 16;
- Key secondary endpoint: proportion of subjects achieving a reduction of ≥ 4 points in worst pruritus numerical rating scale from Baseline to Week 16.

Study population /Sample size

The intent-to-treat population consisted of 172 subjects who were randomized in Study M16-813. All randomized subjects received at least 1 dose of study drug in Study M16-813. Of all subjects, 55.8% were male, 53.5% were white, and the median age was 42.5 years (14 years min and 83 years max age). The median EASI (overall score) at Baseline was 26.80 (range: 16.0, 72.0), indicative of a population with moderate to severe AD disease activity.

Key inclusion/exclusion criteria

Eligible subjects were adults who were ≥ 18 years old and, where locally permissible and approved, adolescent subjects who were at least 12 years old. Subjects must have had:

- Diagnosis of AD with onset of symptoms at least 2 years prior to Baseline.
- Moderate to severe AD at the Baseline Visit, defined by Eczema Area and Severity Index ≥ 16, body surface area (BSA) ≥ 10%, and validated Investigator Global Assessment Scale for Atopic Dermatitis (vIGA-AD) score of ≥ 3.
- History of inadequate response to previous topical corticosteroid and/or topical calcineurin inhibitor treatments or a medical inability to receive these treatments.

Subjects with prior exposure to any biologic immunomodulatory agent or Janus kinase inhibitor were excluded from the study. Concurrent treatment with systemic therapy that can also be used for the treatment of AD (biologic or non-biologic), as well as use of topical and/or phototherapy treatments, was prohibited throughout the study.

Treatments

Period A (Baseline up to Week 16)

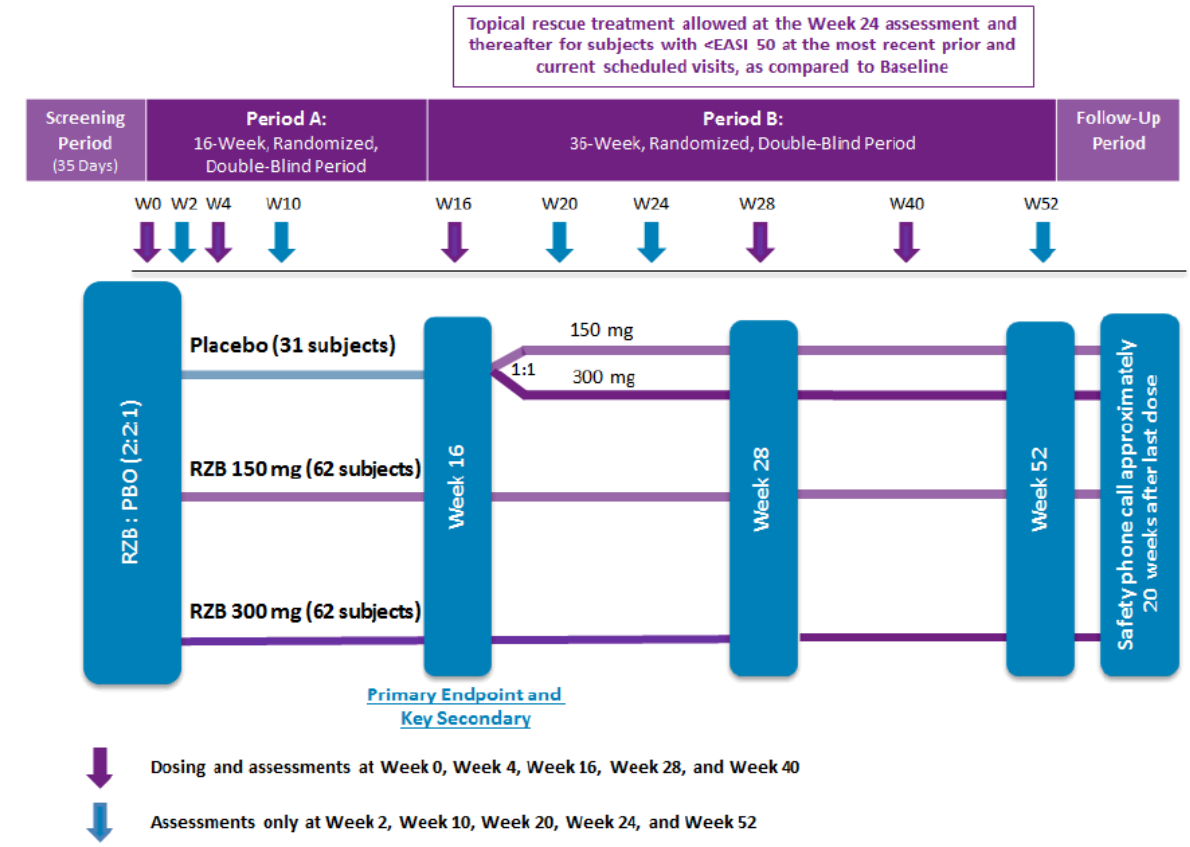
Study site staff administered study drug; risankizumab 75 mg/0.83 mL (90 mg/mL) injected subcutaneously (SC) as risankizumab 150 mg (2 × 75 mg pre-filled syringe (PFS) and 2 × placebo

PFS), risankizumab 300 mg (4 × 75 mg PFS) or matching placebo (4 x placebo PFS) at Week 0 and Week 4.

Period B (Week 16 up through Week 52)

Study site staff administered either a risankizumab 150 mg or risankizumab 300 mg dose subcutaneously at the Week 16, 28, and 40 visits.

Figure 1. Study Schematic



EASI = Eczema Area and Severity Index; PBO = placebo; RZB = risankizumab; W = week

Outcomes/endpoints

Primary Endpoint

The primary endpoint is the proportion of subjects achieving at least a 75% reduction from Baseline in Eczema Area and Severity Index (EASI 75) at Week 16.

Secondary Endpoints

Key Secondary Endpoints

The key secondary endpoints for this study were:

1. The proportion of subjects achieving validated Investigator Global Assessment Scale for Atopic Dermatitis (vIGA-AD) of "0" or "1" (on a 5-point scale) with a reduction from Baseline of ≥ 2 points at Week 16.

2. The proportion of subjects achieving a reduction of ≥ 4 points in worst pruritus numerical rating scale (NRS) from Baseline to Week 16.

Other Secondary Endpoints

Other secondary endpoints for each of the specified time points include:

- Percent change in EASI from Baseline to Week 16, Week 28, and Week 52.
- Proportion of subjects achieving EASI 75 at Week 28 and Week 52.
- Proportion of subjects achieving EASI 50 at Week 16, Week 28, and Week 52.
- Proportion of subjects achieving EASI 90 at Week 16, Week 28, and Week 52.
- Proportion of subjects achieving vIGA-AD of "0" or "1" with a reduction from Baseline of ≥ 2 points to Week 28 and Week 52.
- Change in body surface area (BSA) from Baseline to Week 16, Week 28, and Week 52.
- Proportion of subjects achieving 50% improvement in SCORing Atopic Dermatitis (SCORAD 50) at Week 16, Week 28, and Week 52.
- Proportion of subjects achieving SCORAD 75 at Week 16, Week 28, and Week 52.
- Proportion of subjects achieving SCORAD 90 at Week 16, Week 28, and Week 52.
- Proportion of subjects achieving Dermatology Life Quality index (DLQI) of "0" or "1" at Week 16, Week 28, and Week 52.
- Proportion of subjects achieving Children's Dermatology Life Quality index (CDLQI) of "0" or "1" at Week 16, Week 28, and Week 52.
- Proportion of subjects achieving a DLQI improvement of ≥ 4 points at Week 16, Week 28, and Week 52 among subjects with a DLQI ≥ 4 at Baseline.
- Change in DLQI from Baseline to Week 16, Week 28, and Week 52.
- Change in CDLQI from Baseline to Week 16, Week 28, and Week 52.
- Change in worst pruritus NRS from Baseline to Week 16, Week 28, and Week 52.
- Proportion of subjects achieving a reduction of ≥ 4 points in worst pruritus NRS from Baseline to Week 28 and Week 52.

Additional Endpoints

All variables listed as primary or secondary endpoints will be analyzed at all visits in addition to those listed above. In addition, the following additional endpoints will be evaluated at applicable visits:

- Proportion of subjects achieving EASI 100.
- Proportion of subjects achieving vIGA-AD of "0" with a reduction from Baseline of ≥ 2 points.
- Percent change in SCORAD from Baseline.
- Change from Baseline in Patient Oriented Eczema Measure (POEM).
- Proportion of subjects achieving an improvement (reduction) in POEM of ≥ 4 from Baseline among subjects with a POEM ≥ 4 at Baseline.
- Change from Baseline in Patient Global Impression of Severity (PGIS).

- Proportion of subjects who report symptoms to be "Minimal" or "Absent" for PGIS.
- Proportion of subjects who have "Very much improved" or "Much improved" for Patient Global Impression of Change (PGIC).
- Change from Baseline in Atopic Dermatitis Symptom Scale (ADerm-SS) total score.
- Change from Baseline in ADerm-SS skin pain score.
- Change from Baseline in Atopic Dermatitis Impact Scale (ADerm-IS) total score.
- Change from Baseline in ADerm-IS sleep domain score.
- Proportion of subjects achieving an improvement (reduction) in ADerm-SS total score ≥ minimal clinically important difference (MCID) from Baseline for subjects with ADerm-SS total score ≥ MCID at Baseline.
- Proportion of subjects achieving an improvement (reduction) in ADerm-SS skin pain score ≥ MCID from Baseline for subjects with ADerm-SS skin pain score ≥ MCID at Baseline.
- Proportion of subjects achieving an improvement (reduction) in ADerm-IS total score ≥ MCID from Baseline for subjects with ADerm-IS total score ≥ MCID at Baseline.
- Proportion of subjects achieving an improvement (reduction) in ADerm-IS sleep disturbance score ≥ MCID from Baseline for subjects with ADerm-IS sleep disturbance score ≥ MCID at Baseline.
- Change from Baseline in EuroQoL-5D-5L (EQ-5D-5L).

Safety Endpoints

- Treatment emergent adverse events (TEAEs)
- Serious adverse events (SAEs)
- Areas of safety interest (ASIs)
- Adverse events (AEs) leading to study drug discontinuation
- Vital signs, laboratory tests and electrocardiogram (ECG) parameters.

Pharmacokinetic and Immunogenicity Endpoints

Serum risankizumab concentrations, anti-drug antibodies (ADA), and neutralizing antibodies (nAb) were determined from blood collected by venipuncture at scheduled visits.

Statistical Methods

Efficacy: Pairwise comparison of the primary endpoint and the key secondary endpoints was conducted between each risankizumab group (risankizumab 150 mg and 300 mg, respectively) versus the placebo group using the Cochran-Mantel-Haenszel test, stratified by baseline disease severity (moderate [vIGA-AD 3] versus severe [vIGA-AD 4]). For the analysis of the primary endpoint and key secondary endpoints, non-responder imputation (NRI) with multiple imputation to handle missing data due to COVID-19 (NRI-C) was used as the primary approach. Efficacy data for subjects who switched to rescue medications was imputed from the point of rescue using an NRI approach for the primary endpoint and key secondary endpoints.

Pharmacokinetics and Immunogenicity: Serum risankizumab concentrations were summarized at each sampling time point for each dose group using descriptive statistics. ADA titres were tabulated for

each subject at the respective study visits. The number and percentage of subjects with ADA and NAb were calculated by dose group.

Safety: All safety analyses were performed on the Safety Population for both treatment periods, respectively, as well as the All Risankizumab Treated population, based on the treatment subjects actually received. Safety was assessed by AEs, laboratory tests, vital signs, and ECG variables. Missing safety data was not imputed for safety analysis. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) was defined as an AE with onset or worsening on or after the first dose of study drug and within 140 days (20 weeks) after the last dose of study treatment injection. The number and percentage of subjects experiencing TEAEs was tabulated using MedDRA system organ class (SOC) and preferred term, as well as by severity and by relationship to the study drug as assessed by the investigator. Summaries (i.e., number, percentages, and events per 100 patient-years) of TEAEs, SAEs, deaths, AEs leading to discontinuation, and areas of safety interest were provided. Pre-treatment AEs were summarized separately.

For laboratory test and vital signs variables, mean change from baseline and percentage of subjects with evaluations meeting criteria for pre-defined Potentially Clinically Significant values were summarized.

Results

Recruitment/ Number analysed

A total of 172 subjects were randomized in this study. Twenty-eight subjects (16.3%) discontinued the study in Period A. The most common primary reason for study discontinuation in Period A was withdrawal of consent. Seventy-three subjects (50.7%) discontinued the study in Period B. The most common primary reason for study discontinuation in Period B was "other," including 43 subjects who discontinued the study due to the early termination of the study by the Sponsor. Seventy-one subjects (49.3%) completed the study.

Efficacy results

A summary of the primary and key secondary endpoint results is presented in the table below.

Summary of Primary and Key Secondary Endpoint Results
(ITT Population)

Endpoint [A] Treatment	N	Within Group Point Estimate [95% CI]	------ Between Group Difference (Risankizumab - Placebo) ------ Point Estimate [95% CI]#	Nominal P-Value@	Multiplicity Adjusted Results [B]
Proportion of Subjects Achieving EASI 75 at Week 16					
Placebo	34	11.8 [0.9, 22.6]			
RZB 150 mg	69	24.6 [14.5, 34.8]	13.0 [-1.7, 27.7]	0.084	Not Significant
RZB 300 mg	69	21.7 [12.0, 31.5]	10.0 [-4.6, 24.6]	0.179	Not Significant
Proportion of Subjects Achieving vIGA-AD of 0 or 1 with at Least Two Grades of Reduction at Week 16					
Placebo	34	5.9 [0.0, 13.8]			
RZB 150 mg	69	14.5 [6.2, 22.8]	8.7 [-2.5, 20.0]	0.129	Not Significant
RZB 300 mg	69	5.8 [0.3, 11.3]	-0.0 [-9.4, 9.4]	0.994	Not Significant
Proportion of Subjects Achieving an Improvement (Reduction) in Worst Pruritus Numerical Rating Scale (NRS) >= 4 from Baseline at Week 16 for Subjects with Pruritus NRS >= 4 at Baseline					
Placebo	33	0.0			
RZB 150 mg	66	13.6 [5.4, 21.9]	13.7 [5.4, 22.1]	0.001**	Not Significant
RZB 300 mg	66	15.2 [6.5, 23.8]	15.3 [6.6, 24.0]	<0.001***	Not Significant

Note: Placebo: Subjects randomized at baseline to receive placebo in Period A.
RZB 150 mg: Subjects randomized at baseline to receive Risankizumab 150 mg in Period A.
RZB 300 mg: Subjects randomized at baseline to receive Risankizumab 300 mg in Period A.
EASI = Eczema Area and Severity Index; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis; NRS = Numerical Rating Scale.
[A]: Results for categorical endpoints are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C).
[B]: Multiplicity adjusted results are obtained via the sequential multiple testing procedure controlling the overall type I error rate of all primary and ranked secondary endpoints at the two-sided 0.05 level.
95% CI for adjusted difference was calculated according to the Cochran-Mantel-Haenszel test for the comparison of two treatment groups.
@ P-value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata.
***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively.

Study M16-813 did not meet the primary endpoint, the proportion of subjects achieving at least a 75% reduction from Baseline in EASI (EASI 75) at Week 16 (table above). Neither risankizumab 150 mg nor risankizumab 300 mg showed a statistically significantly greater percentage of subjects achieving an EASI 75 response at Week 16 compared with the placebo group.

CHMP comments

The primary endpoint, the proportion of subjects achieving EASI 75 at Week 16, was not met. Neither risankizumab 150 mg nor risankizumab 300 mg showed a statistically significantly greater percentage of subjects achieving an EASI 75 response at Week 16 compared with the placebo group. Secondary endpoints, (the proportion of subjects achieving IGA-AD of "0" or "1" (on a 5-point scale) with a reduction from Baseline of $\geq$ 2 points at Week 16 and the proportion of subjects achieving a reduction of $\geq$ 4 points in worst pruritus numerical rating scale from Baseline to Week 16) were also not met. The MAH has outlined that the indication of AD will not be further pursued.

Pharmacokinetic Results

A summary of risankizumab serum concentrations during study duration is presented in Table 4.

Table 4. Summary of Risankizumab Serum Concentrations (µg/mL) at Planned Visits

	Geometric Mean (Arithmetic Mean, %CV) [N]			
	Week 4	Week 10	Week 16	Week 52
Risankizumab 150 mg SC	5.78 (6.29, 37) [57]	5.67 (6.58, 44) [52]	1.64 (2.33, 69) [48]	1.66 (2.12, 69) [27]
Risankizumab 300 mg SC	11.7 (12.7, 38) [52]	11.4 (12.6, 43) [54]	3.20 (3.84, 58) [45]	2.82 (3.38, 61) [26]
Placebo to Risankizumab 150 mg SC	NA	NA	NA	0.885 (1.00, 63) [4]
Placebo to Risankizumab 300 mg SC	NA	NA	NA	5.21 (5.26, 18) [3]

CV = coefficient of variation; N = sample size; NA = not applicable; SC = subcutaneous

Immunogenicity of risankizumab was assessed using a 3-tiered approach. In this tiered approach, all ADA samples were first analysed in a screening assay (Tier 1). The samples that were screened positive were confirmed in the confirmatory assay (Tier 2) followed by the titre determination step (Tier 3) in which titres were determined for the confirmed positive samples. The confirmed positive samples were also evaluated in the NAb assay to detect the presence of NAb. Incidence of ADAs (treatment-emergent) to risankizumab was defined when a subject was (1) ADA–negative or missing assessment at Baseline and became ADA-positive at 1 or more time points post Week 0 visit in this study, or (2) ADA-positive at Baseline and showed a 4-fold or greater increase in titer values relative to Baseline.

The summary of treatment-emergent ADAs and NAbs to risankizumab in subjects who received at least 1 dose of risankizumab during the study duration (52 weeks) is presented in Table 5.

Table 5. Incidence of Anti-Drug Antibodies and Neutralizing Antibodies over the Study Duration (52 Weeks)

Description	Risankizumab 150 mg SC	Risankizumab 300 mg SC	Placebo/ Risankizumab 150 mg SC	Placebo/ Risankizumab 300 mg SC	Total
Evaluable subjects; N	65	65	5	3	138
Anti-drug antibody incidence (treatment emergent); N (%)	8 (12.3%)	7 (10.8%)	0 (0%)	0 (0%)	15 (10.9%)
NAb incidence (treatment emergent); N (%)	3 (4.6%)	1 (1.5%)	0 (0%)	0 (0%)	4 (2.9%)

SC = subcutaneous; N = sample size; NAb = neutralizing antibody

Notes: Anti-drug antibody evaluable: subjects with at least 1 reportable assessment at any time in the study postbaseline. Neutralizing antibody incidence was assessed only when the anti-drug antibody assessment was positive.

As shown in Table 6, the geometric mean serum risankizumab concentrations in ADA-positive subjects appeared to be lower than that of ADA-negative subjects. Only 2 subjects developed NAb at Week 16 and Week 52 in the risankizumab 150 mg treatment arm and 1 subject developed NAb at Week 16 in risankizumab 300 mg treatment arm, resulting in risankizumab exposures within the range of NAb-negative subjects in the same treatment arms. Given the limited number of subjects who developed ADA and/or NAb, these data should be interpreted with caution. None of the subjects switching from placebo to risankizumab 150 mg SC or risankizumab 300 mg SC treatment arms at Week 16 developed ADA at Week 52.

Table 6. Summary of Risankizumab Trough Serum Concentrations (µg/mL) by ADA Status over the Study Duration (52 Weeks)

	Geometric Mean (Arithmetic Mean, %CV) [N]					
	ADA Positive			ADA Negative		
	Week 4	Week 16	Week 52	Week 4	Week 16	Week 52
Risankizumab 150 mg SC	4.85 (5.08, 42) [2]	0.979 (1.21, 66) [7]	0.197 (0.197, -) [1]	5.81 (6.33, 37) [55]	1.79 (2.52, 65) [41]	1.80 (2.19, 65) [26]
Risankizumab 300 mg SC	9.75 (10.4, 36) [4]	2.57 (2.99, 66) [4]	1.56 (1.56, -) [1]	11.9 (12.9, 38) [48]	3.27 (3.92, 58) [41]	2.89 (3.45, 60) [25]

ADA = anti-drug antibody; CV = coefficient of variation; N = sample size; SC = subcutaneous

Note: Subjects who had both risankizumab concentration and ADA assessment at each visit are included in this summary.

Similar proportions of ADA-positive and ADA-negative subjects achieved the primary efficacy endpoint in the risankizumab 150 mg treatment arm (28.6% versus 25.9%), but in the risankizumab 300 mg treatment arm, a higher proportion of ADA-positive subjects achieved the primary efficacy endpoint (42.9% vs. 20.7%) (Table 7). However, these data should be interpreted with caution due to the small number of subjects who developed ADA and NAb.

Table 7. Risankizumab EASI 75 Responses by ADA and NAb Status at Week 16

	Proportion of Subjects Achieving EASI 75 at Week 16, n (%)			
	ADA Positive (N = 7)	ADA Negative (N = 58)	NAb Positive (N = 1)	NAb Negative (N = 64)
Risankizumab 150 mg SC	2 (28.6%)	15 (25.9%)	0 (0%)	17 (26.6%)
Risankizumab 300 mg SC	3 (42.9%)	12 (20.7%)	1 (100%)	14 (21.9%)

ADA= antidrug antibody; EASI 75 = achievement of ≥75% reduction from baseline EASI score; N = sample size; NAb = neutralizing antibody; SC = subcutaneous

Note: Subjects who had both risankizumab concentration and ADA assessment at each visit are included in this summary.

CHMP comments

The incidence of the ADA and NAb to risankizumab in M16-813 across the study duration of weeks 0 to 52 (ADAs in 10.9% or 15/138 of evaluable subjects and NAbs in 4 subjects (2.9%) is lower than those observed in phase 3 trials which made up the plaque psoriasis development programme (where the anti-drug antibody and NAb incidence to risankizumab 150mg at Week 0, Week 4, and q12w thereafter) was 19% and 8%, respectively over 16 weeks duration (based on 1288 evaluable subjects) and 24% and 14% respectively over 52 weeks duration).

Whereas the presence of neutralizing antibodies (NAb) to risankizumab was not correlated with risankizumab clearance in the psoriasis programme, the risankizumab concentrations in ADA-positive subjects treated in M16-813 appeared to be lower than that of ADA-negative subjects though similar proportions of ADA-positive and ADA-negative subjects achieved the primary efficacy endpoint in the risankizumab 150 mg treatment arm (28.6% versus 25.9% and in fact in the risankizumab 300 mg treatment arm, a higher proportion of ADA-positive subjects achieved the primary efficacy endpoint (42.9% vs. 20.7%).

It is agreed however that the low numbers of subjects who developed ADA and/or Nab mean that all these findings should be interpreted with caution and the impact of immunogenicity on risankizumab exposure and efficacy cannot be adequately assessed from these data.

Safety results

The safety population in Period A was defined as all subjects who were randomized at baseline and received at least 1 dose of study drug in Treatment Period A. The safety population in Period B was defined as all subjects who received at least 1 dose of study drug in Treatment Period B. Subjects were assigned to a treatment group based on the treatment actually received. The All Risankizumab Treated population consisted of all subjects who received at least 1 dose of risankizumab in the study. This population was used to provide a comprehensive summary of safety. Mean extent of exposure for the All Risankizumab Treated population was 272.4 days (SD, 104.76).

A summary of Adverse Events experienced by patients in period A is presented below in Table 9.

Table 9. Overview of Treatment-emergent Adverse Events and All Deaths in Period A (Safety A Population)

		Active		
	Placebo (N = 34) n (%)	RZB 150 mg (N = 69) n (%)	RZB 300 mg (N = 69) n (%)	Total RZB (N = 138) n (%)
Subjects with any treatment-emergent:				
AE	24 (70.6)	38 (55.1)	39 (56.5)	77 (55.8)
AE with reasonable possibility of being drug related[a]	5 (14.7)	9 (13.0)	11 (15.9)	20 (14.5)
Severe AE	4 (11.8)	7 (10.1)	3 (4.3)	10 (7.2)
Serious AE (SAE)	3 (8.8)	0	0	0
AE leading to discontinuation of study drug	7 (20.6)	4 (5.8)	2 (2.9)	6 (4.3)
MACE	0	0	0	0
Adjudicated anaphylactic reaction	0	0	0	0
Serious infections	1 (2.9)	0	0	0
Tuberculosis	0	0	0	0
Opportunistic infections excluding tuberculosis and herpes zoster	1 (2.9)	1 (1.4)	0	1 (0.7)
Malignant tumours	1 (2.9)	0	0	0
Malignant tumours excluding NMSC	1 (2.9)	0	0	0
Serious hypersensitivity	1 (2.9)	0	0	0
AE results in death	1 (2.9)	0	0	0
Any COVID-19 related TEAE	1 (2.9)	0	0	0
All deaths[b]	1 (2.9)	0	0	0
COVID-19 related deaths	1 (2.9)	0	0	0
Occurring ≤ 140 days after last dose	1 (2.9)	0	0	0
Occurring > 140 days after last dose	0	0	0	0

AE = adverse event; COVID-19 = coronavirus disease – 2019; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; RZB = risankizumab; SAE = serious adverse event; TEAE = treatment-emergent adverse event

a. As assessed by investigator.

b. Includes non-treatment-emergent deaths.

Notes: Placebo: Subjects randomized at Baseline and received placebo in Period A.
RZB 150 mg: Subjects randomized at Baseline and received risankizumab 150 mg in Period A.
RZB 300 mg: Subjects randomized at Baseline and received risankizumab 300 mg in Period A.
Subjects were counted once in each row, regardless of the number of events they may have had.
For subjects who did not enter Period B, TEAEs were defined as any event with an onset or worsening date on or after the first dose of study drug and no more than 140 days after the last dose of study drug.
For subjects who entered Period B, TEAEs were defined as any event with an onset or worsening date on or after the first dose of study drug in Period A and before the first dose of study drug in Period B.

Three subjects (8.8%) in the placebo group experienced SAEs; no SAEs were experienced by subjects in the risankizumab 150 mg or 300 mg treatment groups. Adverse events leading to discontinuation of study drug were reported in 4 subjects (5.8%) in the risankizumab 150 mg treatment group, 2 subjects (2.9%) in the risankizumab 300 mg treatment group, and 7 subjects (20.6%) in the placebo group. There was 1 treatment-emergent death during Period A of a subject in the placebo group.

A summary of Adverse Events experienced by patients in period B is presented below in Table 10.

Table 10. Overview of Treatment-emergent Adverse Events and All Deaths in Period B (Safety B Population)

	Placebo/ RZB 150 mg (N = 13) n (%)	Placebo/ RZB 300 mg (N = 11) n (%)	RZB 150 mg/ RZB 150 mg (N = 61) n (%)	RZB 300 mg/ RZB 300 mg (N = 57) n (%)	Overall (N = 142) n (%)
Subjects with any treatment-emergent:					
AE	6 (46.2)	5 (45.5)	29 (47.5)	29 (50.9)	69 (48.6)
AE with reasonable possibility of being drug related[a]	2 (15.4)	2 (18.2)	10 (16.4)	3 (5.3)	17 (12.0)
Severe AE	0	0	3 (4.9)	2 (3.5)	5 (3.5)
Serious AE (SAE)	0	0	2 (3.3)	3 (5.3)	5 (3.5)
AE leading to discontinuation of study drug	2 (15.4)	0	2 (3.3)	0	4 (2.8)
MACE	0	0	0	0	0
Adjudicated anaphylactic reaction	0	0	0	0	0
Serious infections	0	0	1 (1.6)	1 (1.8)	2 (1.4)
Tuberculosis	0	0	0	0	0
Opportunistic infections excluding tuberculosis and herpes zoster	0	0	1 (1.6)	1 (1.8)	2 (1.4)
Malignant tumours	0	0	1 (1.6)	0	1 (0.7)
Malignant tumours excluding NMSC	0	0	0	0	0
Serious hypersensitivity	0	0	0	0	0
AE results in death	0	0	0	0	0
Any COVID-19 related TEAE	0	0	0	1 (1.8)	1 (0.7)
All deaths[b]	0	0	0	0	0
COVID-19 related deaths	0	0	0	0	0
Occurring ≤ 140 days after last dose	0	0	0	0	0
Occurring > 140 days after last dose	0	0	0	0	0

AE = adverse event; COVID-19 = coronavirus disease – 2019; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; RZB = risankizumab; SAE = serious adverse event; TEAE = treatment-emergent adverse event

a. As assessed by investigator.

b. Includes non-treatment-emergent deaths.

Notes: Subjects were counted once in each row, regardless of the number of events they may have had.
Placebo/RZB 150 mg: Subjects randomized at Baseline and received placebo in Period A, re-randomized at Week 16 and received risankizumab 150 mg in Period B.
Placebo/RZB 300 mg: Subjects randomized at Baseline and received placebo in Period A, re-randomized at Week 16 and received risankizumab 300 mg in Period B.
RZB 150 mg/RZB 150 mg: Subjects randomized at Baseline and received risankizumab 150 mg.
RZB 300 mg/RZB 300 mg: Subjects randomized at Baseline and received risankizumab 300 mg.
TEAEs were defined as any event with an onset or worsening date on or after the first dose of study drug in Period B and no more than 140 days after the last dose of study drug.

In Period B, a total of 142 subjects (13 subjects in the placebo to risankizumab 150 mg treatment group, 11 subjects in the placebo to risankizumab 300 mg treatment group, 61 subjects in the risankizumab 150 mg treatment group, and 57 subjects in the risankizumab 300 mg treatment group) received at least one dose of study drug. Six subjects (46.2%) in the placebo/ risankizumab 150 mg treatment group, 5 subjects (45.5%) in the placebo/ risankizumab 300 mg treatment group, 29 subjects (47.5%) in the risankizumab 150 mg treatment group, and 29 subjects (50.9%) in the risankizumab 300 mg treatment group experienced at least 1 AE. Two subjects (15.4%) in the placebo/ risankizumab 150 mg treatment group, 2 subjects (18.2%) in the placebo/ risankizumab 300 mg treatment group, 10 subjects (16.4%) in the risankizumab 150 mg treatment group, and 3 subjects (5.3%) in the risankizumab 300 mg treatment group experienced treatment-emergent AEs with a reasonable possibility of being drug-related, as assessed by the investigator. No subjects in the placebo/ risankizumab 150 mg treatment group or the placebo/ risankizumab 300 mg treatment groups, 2 subjects (3.3%) in the risankizumab 150 mg treatment group, and 3 subjects (5.3%) in the risankizumab 300 mg treatment group experienced SAEs. Adverse events leading to discontinuation of study drug were reported in 2 subjects (15.4%) in the placebo/ risankizumab 150 mg treatment group, no subjects in the placebo/ risankizumab 300 mg treatment group, 2 subjects (3.3%) in the risankizumab 150 mg treatment group, and no subjects in the risankizumab 300 mg treatment group. There were no treatment-emergent deaths during Period B.

In the All Risankizumab Treated population, 112 subjects (69.1%) experienced at least 1 AE, including 57 subjects (69.5%) treated with risankizumab 150 mg and 55 subjects (68.8%) treated with risankizumab 300 mg (Table 11). Thirty-two subjects (19.8%) experienced AEs with a reasonable possibility of being drug-related as assessed by the investigator, including 17 subjects (20.7%) treated with risankizumab 150 mg and 15 subjects (18.8%) treated with risankizumab 300 mg. Five subjects (3.1%) experienced SAEs, including 2 subjects (2.4%) treated with risankizumab 150 mg and 3 subjects (3.8%) treated with risankizumab 300 mg.

Table 11. Overview of Treatment-emergent Adverse Events and All Deaths (All RZB Population)

	RZB 150 mg (N = 82) n (%)	RZB 300 mg (N = 80) n (%)	Overall (N = 162) n (%)
Subjects with any treatment-emergent:			
AE	57 (69.5)	55 (68.8)	112 (69.1)
AE with reasonable possibility of being drug related[a]	17 (20.7)	15 (18.8)	32 (19.8)
Severe AE	10 (12.2)	5 (6.3)	15 (9.3)
Serious AE (SAE)	2 (2.4)	3 (3.8)	5 (3.1)
AE leading to discontinuation of study drug	8 (9.8)	2 (2.5)	10 (6.2)
MACE	0	0	0
Adjudicated anaphylactic reaction	0	0	0
Serious infections	1 (1.2)	1 (1.3)	2 (1.2)
Tuberculosis	0	0	0
Opportunistic infections excluding tuberculosis and herpes zoster	1 (1.2)	1 (1.3)	2 (1.2)
Malignant tumors	1 (1.2)	0	1 (0.6)
Malignant tumours excluding NMSC	0	0	0
Serious hypersensitivity	0	0	0
AE results in death	0	0	0
Any COVID-19 related TEAE	0	1 (1.3)	1 (0.6)
All deaths[b]	0	0	0
COVID-19 related deaths	0	0	0
Occurring ≤ 140 days after last dose	0	0	0
Occurring > 140 days after last dose	0	0	0

AE = adverse event; COVID-19 = coronavirus disease – 2019; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; RZB = risankizumab; SAE = serious adverse event; TEAE = treatment-emergent adverse event

a. As assessed by investigator.

b. Includes non-treatment-emergent deaths.

Notes: Subjects were counted once in each row, regardless of the number of events they may have had.
RZB 150 mg: Subjects received at least 1 dose of risankizumab 150 mg during the study.
RZB 300 mg: Subjects received at least 1 dose of risankizumab 300 mg during the study.
TEAEs were defined as any event with an onset or worsening date on or after the first dose of risankizumab and no more than 140 days after the last dose of risankizumab in the study.

Common Adverse Events

Overall, in the All Risankizumab Treated population, the most commonly reported (> 2% subjects) treatment-emergent adverse events by preferred terms (PTs) were dermatitis atopic (47 subjects, 29.0%), nasopharyngitis (15 subjects, 9.3%), pruritis (9 subjects, 5.6%), upper respiratory tract infection (6 subjects, 3.7%), hypertension and impetigo (5 subjects, 3.1% each), and blood creatine phosphokinase increased and urticaria (4 subjects, 2.5% each).

Table 17. Subjects with Treatment-emergent Adverse Events by System Organ Class and Preferred Term Reported for > 2 Subjects Overall (All RZB Population)

MedDRA 23.1 System Organ Class Preferred Term	RZB 150 mg (N = 82) n (%)	RZB 300 mg (N = 80) n (%)	Overall (N = 162) n (%)
Any adverse event	57 (69.5)	55 (68.8)	112 (69.1)
Gastrointestinal disorders	3 (3.7)	6 (7.5)	9 (5.6)
Toothache	0	3 (3.8)	3 (1.9)
Infections and infestations	23 (28.0)	28 (35.0)	51 (31.5)
Cellulitis	1 (1.2)	2 (2.5)	3 (1.9)
Ear infection	3 (3.7)	0	3 (1.9)
Impetigo	1 (1.2)	4 (5.0)	5 (3.1)
Nasopharyngitis	8 (9.8)	7 (8.8)	15 (9.3)
Upper respiratory tract infection	2 (2.4)	4 (5.0)	6 (3.7)
Investigations	7 (8.5)	7 (8.8)	14 (8.6)
Alanine aminotransferase increased	1 (1.2)	2 (2.5)	3 (1.9)
Blood creatine phosphokinase increased	1 (1.2)	3 (3.8)	4 (2.5)
C-reactive protein increased	3 (3.7)	0	3 (1.9)
Nervous system disorders	6 (7.3)	3 (3.8)	9 (5.6)
Headache	2 (2.4)	1 (1.3)	3 (1.9)
Skin and subcutaneous tissue disorders	34 (41.5)	28 (35.0)	62 (38.3)
Dermatitis atopic	27 (32.9)	20 (25.0)	47 (29.0)
Pruritus	4 (4.9)	5 (6.3)	9 (5.6)
Urticaria	1 (1.2)	3 (3.8)	4 (2.5)
Vascular disorders	1 (1.2)	5 (6.3)	6 (3.7)
Hypertension	1 (1.2)	4 (5.0)	5 (3.1)

MedDRA = Medical Dictionary for Regulatory Activities; RZB = risankizumab; TEAE = treatment-emergent adverse event

Notes: RZB 150 mg: Subjects received at least 1 dose of risankizumab 150 mg during the study.
RZB 300 mg: Subjects received at least 1 dose of risankizumab 300 mg during the study.
Subjects were counted once in each row, regardless of the number of events they may have had.
TEAEs were defined as any event with an onset or worsening date on or after the first dose of risankizumab and no more than 140 days after the last dose of risankizumab in the study.

Adverse events leading to discontinuation

Adverse events leading to discontinuation of study drug were reported by 10 subjects (6.2%), including 8 subjects (9.8%) treated with risankizumab 150 mg and 2 subjects (2.5%) treated with risankizumab 300 mg. No treatment-emergent deaths occurred in subjects treated with risankizumab during the study.

Adverse Events Related to Areas of Safety Interest

Adjudicated Cardiovascular Events

No subjects experienced treatment-emergent adjudicated cardiovascular (CV) events.

Hypersensitivity

A treatment-emergent hypersensitivity reaction was experienced by 1 subject (2.9%) in the placebo group (dermatitis atopic) and no subjects receiving risankizumab treatment throughout this study.

Infections

In the All Risankizumab Treated population, 2 (1.2%) subjects experienced a treatment-emergent serious infection, with cellulitis being the only reported PT. No events of serious infection led to study drug discontinuation. In the All Risankizumab Treated population, 2 (1.2%) subjects experienced an opportunistic infection excluding TB and herpes zoster, with cellulitis and Kaposi's varicelliform eruption being the only reported PTs. No events in this category led to study drug discontinuation.

Malignancies

In the All Risankizumab Treated population, 2 subjects (2.4%) experienced at least 1 treatment-emergent malignancy, including 1 event of neoplasm and 1 event of Bowen's disease. Neither event was serious. Neither event in this category led to study drug discontinuation.

Hepatic Events

In the All Risankizumab Treated population, 4 subjects (2.5%) experienced at least 1 treatment-emergent hepatic event, with ALT increased being the most commonly reported (> 2 subjects) PT (3 subjects; 1.9%). None of the events were serious. No events in this category led to study drug discontinuation.

Discussion on Paediatric Data

Study M16-813 enrolled 3 paediatric patients. The first paediatric subject was randomized to receive risankizumab 150 mg. The subject completed all dosing up to the Week 28 visit and was discontinued when the study was terminated by the sponsor. There were no AEs reported for this subject.

The second paediatric subject had a history of food allergies (allergic to peanuts since 2015 and allergic to seafood since 2010) was randomized to receive risankizumab 300 mg. The subject completed the first dose of study drug. On Day 12 following initial drug administration, the site reported that the subject experienced one non-serious allergic reaction event of moderate severity with symptoms of eye swelling, lip swelling, and swelling face, went to the emergency room, and received IV fluids, an antihistamine (diphenhydramine), a H2 receptor antagonist (famotidine), and methylprednisolone to manage the symptoms. The subject claimed not to be exposed to either of the known allergens outlined in the medical history. The associated AE was considered by the investigator to have no reasonable possibility of being related to study drug. The subject and parent decided to discontinue the study (i.e., withdrew consent) on Day 31 after 3 failed attempts to collect blood samples and after given the option to continue study participation without receiving study drug.

The third paediatric subject was randomized to receive risankizumab 300 mg. The subject completed all dosing up to the Week 28 visit and withdrew consent to continue study participation on Day 192. The subject specified reason of withdrawn consent was "not satisfied with the skin condition." There were no AEs reported for this subject.

CHMP comments

There were no SAEs experienced by subjects in the risankizumab 150 mg or 300 mg treatment groups during the blinded period, and AEs leading to discontinuation occurred at greater frequency in the placebo group (reported in 4 subjects (5.8%) in the risankizumab 150 mg treatment group, 2 subjects (2.9%) in the risankizumab 300 mg treatment group, and 7 subjects (20.6%) in the placebo group).

The most common AEs in the all risankizumab treated population were in line with the known safety profile/underlying diseased population and included AEs from infections and infestations SOC (28% of

150mg treated patients and 35% of 300mg treated patients), Skin and subcutaneous tissue disorders SOC with 41.5% of 150mg treated patients and 35% of 300mg treated patients – the majority of which were (a worsening of) atopic dermatitis 32.9% nd 25% respectively. There were no events of note for the important potential risks of MACE and Serious hypersensitivity reactions. Serious infections occurred in 2 (1.2%) subjects with cellulitis being the only reported PT. No events of serious infection led to study drug discontinuation. In the All Risankizumab Treated population, 2 (1.2%) subjects experienced an opportunistic infection excluding TB and herpes zoster, with cellulitis and Kaposi's varicelliform eruption being the only reported PTs. No events in this category led to study drug discontinuation. In the All Risankizumab Treated population, 2 subjects (2.4%) experienced at least 1 treatment-emergent malignancy, including 1 event of neoplasm and 1 event of Bowen's Disease. The data relating to paediatric patients does not provide any new safety concerns.

Overall, it is agreed that no new safety signals have been identified.

2.3.3. Discussion clinical aspects.

Study M16-813 was a Phase 2, multicenter, randomized, placebo-controlled, double-blind study to evaluate risankizumab in adult and adolescent subjects with moderate to severe AD. Of the 172 subjects randomized, 71 subjects (49.3%) completed the study.

The primary endpoint, the proportion of subjects achieving EASI 75 at Week 16, was not met. Neither risankizumab 150 mg nor risankizumab 300 mg showed a statistically significantly greater percentage of subjects achieving an EASI 75 response at Week 16 compared with the placebo group. Secondary endpoints, (the proportion of subjects achieving IGA-AD of "0" or "1" (on a 5-point scale) with a reduction from Baseline of $\geq$ 2 points at Week 16 and the proportion of subjects achieving a reduction of $\geq$ 4 points in worst pruritus numerical rating scale from Baseline to Week 16) were also not met. The MAH has outlined that the indication of AD will not be further pursued.

In this study no new safety signals have been identified. The benefit-risk profile of risankizumab remains unchanged, and therefore no update to the Summary of Product Characteristics have been proposed as a result of these data.

3. CHMP overall conclusion and recommendation

Study M16-813 was a Phase 2, global, randomized, double-blind, placebo-controlled multicenter study evaluating the efficacy and safety of Risankizumab 150 mg and 300 mg in adult and adolescent subjects with moderate to severe Atopic Dermatitis (AD). This study failed to meet primary and secondary endpoints and based on the efficacy results, this Phase 2 AD study was discontinued. There were no new safety concerns identified that would impact ongoing trials for other indications.

☒ **Fulfilled:**

No regulatory action required.