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SCIENCE MEDICINES HEALTH

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Human Medicines Division

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

Humira

adalimumab

Procedure no: EMEA/H/C/000481/P46/121

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 July 2020, the MAH submitted a completed paediatric study for Humira, 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 submitted a final report for:

- M11-290, A Multicenter, Randomized, Double-Blind Study of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Ulcerative Colitis

The main study results were submitted as a Type II variation to add the paediatric ulcerative colitis indication that is currently under review (EMEA/H/C/000481/II/0198). This submission is the final report for Study M11-290 that contains an exploratory re-run of efficacy analyses and final safety analyses based on subjects enrolled at all study sites, including Japan.

2.2. Information on the pharmaceutical formulation used in the study

Treatment was given with either placebo or Humira (adalimumab) prefilled syringe 40 mg/0.8 mL solution for injection. This formulation is approved for various paediatric indications.

2.3. Clinical aspects

2.3.1. Clinical study

M11-290, A Multicenter, Randomized, Double-Blind Study of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Ulcerative Colitis

Description

Study M11-290 was a Phase 3, randomized, double blind (DB) trial designed to evaluate the efficacy and safety of adalimumab in pediatric subjects with moderate to severe UC who have failed therapy with corticosteroids and/or immunosuppressant (IMM).

Methods

Objective(s)

The objective of the study was to demonstrate the efficacy and safety, and to assess the pharmacokinetics of adalimumab administered subcutaneously in paediatric subjects with moderate-to-severe UC.

Study design

Prior to Amendment 4, enrolled subjects were randomized 3:2 at Baseline to 1 of 2 DB adalimumab induction doses, induction high dose (I-HD) or induction standard dose (I-SD). At Week 8, subjects

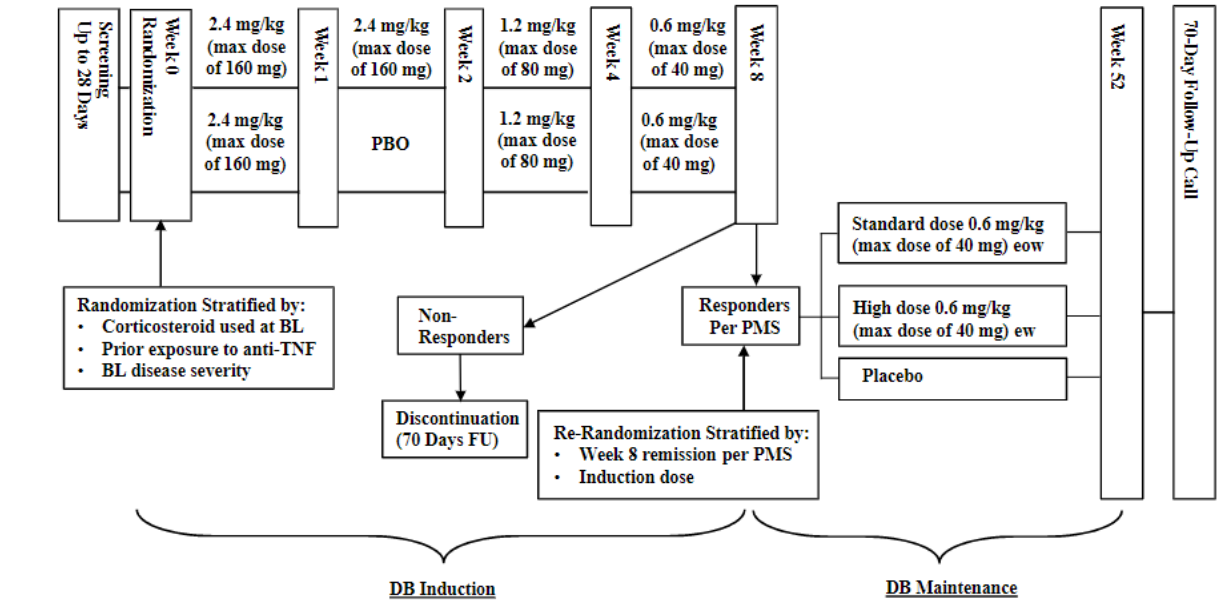
demonstrating a clinical response per Partial Mayo Score (PMS) were randomized to the following groups in a 2:2:1 ratio: adalimumab maintenance standard dose (M-SD), adalimumab maintenance high dose (M-HD), or placebo. Subjects continued their blinded treatment during the maintenance period until Week 52.

After Amendment 4, enrolled subjects receive adalimumab induction high dose open-label (I-HD-OL). At Week 8, subjects demonstrating a clinical response per PMS were randomized and stratified by Week 8 remission status per PMS in a 1:1 ratio to 1 of 2 adalimumab maintenance treatment groups, M-SD or M-HD. Subjects continued their blinded treatment during the maintenance period until Week 52.

Prior to Amendment 4, internal placebo was chosen as the control group during maintenance period. Over the course of study, there were significant recruitment difficulties (the primary reason being objection to the placebo group in the maintenance period) despite efforts to reduce subject burden and study complexity. As a result, after Amendment 4, per agreement with the regulatory agencies, randomization to the internal placebo group was ceased, and external placebo derived from a meta-analysis of placebo-controlled studies in adult subjects with moderate to severe UC who had failed conventional therapy was used as comparator for the confirmatory analysis of co-primary and ranked secondary efficacy endpoints instead.

The duration of the study was up to 66 weeks, which included a screening period of up to 28 days, an 8-week induction period and a 44-week DB maintenance period and a 70-day follow-up phone call. Upon completion of the study, subjects had the option to enroll into an OLE study (Study M10-870 Main) where they continued to receive OL adalimumab.

Study M11-290 Study Design Prior to Amendment 4



Study M11-290 Study Design After Amendment 4

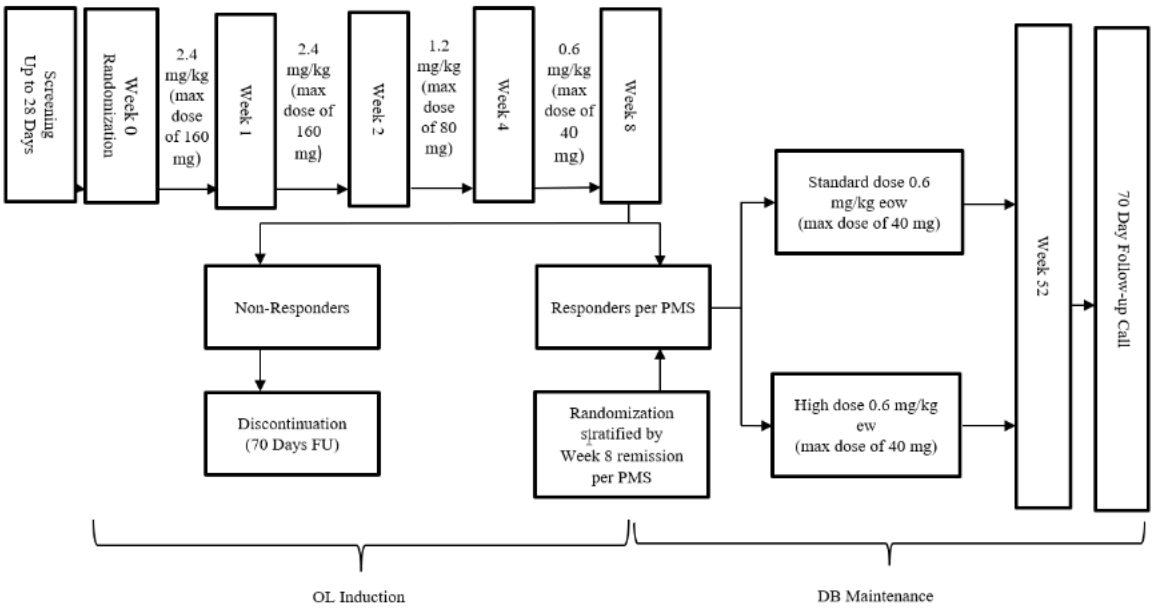


Figure 1. Study M11-290 Study Design

Study population /Sample size

Paediatric subjects with moderate to severe UC (Mayo score of 6 to 12 points and endoscopy sub score of 2 to 3) from 4 to less than 18 years old, who have failed therapy with corticosteroids and/or immunosuppressant (IMM) were eligible for the study.

Sample size was determined as displayed in Table 1. In addition, approximately 20 subjects were planned to be included in the Japan Substudy.

Table 1. **Sample size based on Week 8 and Week 52 co-Primary Endpoints**

Endpoints	External Placebo Upper 95% CI	Assumption for High ADA Group	Power	N in High ADA Group	Randomization Ratio	Total Induction Phase Sample Size
Week 8 PMS Remission Rate	19.25%[a]	30%	85%	135	Induction High:Standard 3:2 = 135:90	225

Endpoints	Internal Placebo	Assumption for High ADA Group	Power	N in High ADA Group	Randomization Ratio	Total Maintenance Phase Sample Size
Week 52 FM Remission Rate	15%	45%	80%	62	Maintenance High:Standard:Placebo 2:2:1 = 62:62:31	155[b]

PMS = partial Mayo score; FM = full Mayo score

a. The upper limit of 95% CI for placebo from adult UC studies. Sample size calculation is based on a one group chi-square test.

b. Sample size calculation is based on a two-sided Fisher's exact test at a 0.05 significance level. 225 subjects at baseline are required assuming 70% response rate at Week 8.

Changes to the sample size calculation:
The sample size was changed in amendment 5 to 93 patients for the main study and up to approximately 9 subjects for the Japan Substudy. The ordering of the secondary endpoints was changed. Here a 48% remission rate per PMS at Week 8 for the combined standard and high adalimumab induction dose groups was assumed. A 52% remission rate per PMS at Week 8 for the high adalimumab induction dose group was assumed.

Treatments

Prior to Amendment 4,

Subjects randomized to I-HD group receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Subjects randomized to I-SD group receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

At Week 8, subjects randomized to M-SD group receive 0.6 mg/kg (maximum dose of 40 mg) every other week (eow), and subjects randomized to M-HD group receive 0.6mg/kg (maximum dose of 40 mg) every week (ew).

After Amendment 4, enrolled subjects (I-HD-OL group) receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week4 and Week 6. At Week 8, subjects received either M-SD or M-HD.

Outcomes/endpoints

Co-primary efficacy endpoints:

1. The proportion of subjects who achieve clinical remission at Week 8 as measured by PMS (defined as a PMS ≤ 2 and no individual subscore > 1)
2. The proportion of subjects who responded at Week 8 per PMS and achieve clinical remission at Week 52 as measured by Mayo score (defined as a Mayo Score ≤ 2 and no individual subscore> 1).

Ranked secondary efficacy endpoints:

1. Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS;
2. Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 responders per PMS
3. Proportion of subjects who achieve Mayo clinical remission at Week 52 in Week 8 remitters per PMS;
4. Proportion of subjects receiving corticosteroid at Baseline who have discontinued corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS.

Statistical Methods

The efficacy analysis was performed in the intent-to-treat (ITT) population for the Week 8 efficacy endpoints and in the modified ITT (mITT) population for the Week 52 efficacy endpoints. The ITT-E population is a subpopulation of the ITT population (includes all subjects who received at least one dose of the study medication during induction period), where subjects who received open-label high induction dose are excluded. The mITT population consists of all Week 8 PMS Responders who were randomized at Week 8 and received at least one dose of the study medication during maintenance period. The non-responder imputation (NRI) was used to impute missing values for binary efficacy endpointsMissing values were only to be imputed for study periods which a subject had actually entered, Subjects who received rescue therapy during the maintenance period were considered as failures from that time point forward. Both last observation carried forward (LOCF) and observed case analyses were performed for continuous efficacy endpoints.

In order to derive robust external placebo assumptions for the co-primary and ranked secondary endpoints, a thorough literature search of placebo-controlled clinical studies in subjects with moderate to severe UC who had failed conventional therapy was performed. Studies M06-826 and M06-827 in adults and Studies GEMINI 1 and OCTAVE Sustain in adults were chosen based on a number of criteria. For all co-primary and ranked secondary endpoints where available, separate estimates for anti-tumor necrosis factor (TNF) naïve placebo patients and anti-TNF experienced placebo patients were derived by endpoint. The estimates for anti-TNF naïve placebo patients and anti-TNF experienced placebo patients were then combined as a weighted mean according to the assumed proportion of anti-TNF naïve and experienced subjects. To be conservative, the upper limit of the 95% confidence interval for the weighted mean was used as the external placebo assumption.

<u>Japan Substudy Only</u>

Efficacy analyses were performed for subjects enrolled at sites outside of Japan (Main Study), for subjects enrolled at sites in Japan (Japan Substudy), and for subjects enrolled at all sites (Integrated population).

Results

Recruitment/ Number analysed

A total of 101 subjects at 24 sites (93 subjects at 19 global sites outside of Japan [Austria, Belgium, Canada, Spain, United Kingdom, Israel, Poland, Slovakia, and the United States]; 8 subjects at 5 sites in Japan) enrolled in Study M11-290. All 101 enrolled subjects were included in the Integrated intent-to-treat (ITT) and Safety Populations. The Integrated ITT-E Population (83 subjects) excluded subjects who received I-HD-OL and was the primary population for the confirmatory Induction period efficacy analyses for the Japan Substudy. The Integrated modified ITT (mITT) Population (80 subjects) included all Week 8 PMS responders who were randomized at Week 8 and received at least 1 dose of the study medication during the Maintenance period. The Integrated modified ITT-E Population (mITT-E; 68 subjects) excluded subjects who received placebo and was the primary population for the confirmatory Maintenance period efficacy analyses for the Japan Substudy. A total of 6 subjects were included in the Japanese ITT-E and mITT populations.

Baseline data

In the Integrated ITT/Safety Population, the mean age was 14.1± 2.90 years at enrollment, ranging from 5 to 17 years. There was 1 more female subject (51, 50.5%) than male subjects. The majority of subjects were White (88, 87.1%), resided in Eastern Europe (72,71.3%), had no prior exposure to anti-TNF (85, 84.2%), and had IMM use (63, 62.4%) at Baseline. About half had no systemic corticosteroid use (52, 51.5%) at Baseline. In the Integrated ITT/Safety Population, the mean duration of UC was 2.4 ± 2.28 years at Baseline, ranging from 0.3 to 11.4 years. At this time, the sites of UC were left sided UC (38, 37.6%) and extensive UC/pancolitis (63, 62.4%), and the mean Mayo Score and mean PMS was 7.8 ± 1.20 and 5.6 ± 1.17, respectively (Table 2).

Table 2. Demographic Characteristics (Integrated ITT/Safety Population)

Variable	I-SD (N = 32) n (%)	I-HD (N = 51) n (%)	I-HD-OL (N = 18) n (%)	Total (N = 101) n (%)
Sex				
Female	15 (46.9)	23 (45.1)	13 (72.2)	51 (50.5)
Male	17 (53.1)	28 (54.9)	5 (27.8)	50 (49.5)
Age (year)				
Mean (SD)	14.7 (2.66)	13.8 (3.06)	13.8 (2.82)	14.1 (2.90)
Median	15.5	15.0	14.0	15.0
Min, Max	6, 17	5, 17	7, 17	5, 17
Age group 1 (year)[a]				
< 13	4 (12.5)	17 (33.3)	5 (27.8)	26 (25.7)
≥ 13	28 (87.5)	34 (66.7)	13 (72.2)	75 (74.3)
Age group 2 (year)				
< 12	3 (9.4)	12 (23.5)	4 (22.2)	19 (18.8)
≥ 12	29 (90.6)	39 (76.5)	14 (77.8)	82 (81.2)
Race				
White	28 (87.5)	45 (88.2)	15 (83.3)	88 (87.1)
Black	1 (3.1)	2 (3.9)	0	3 (3.0)
Asian	3 (9.4)	4 (7.8)	2 (11.1)	9 (8.9)
Multiple	0	0	1 (5.6)	1 (1.0)
Geographic region				
North America	2 (6.3)	8 (15.7)	3 (16.7)	13 (12.9)
Western Europe	3 (9.4)	4 (7.8)	1 (5.6)	8 (7.9)
Eastern Europe	25 (78.1)	35 (68.6)	12 (66.7)	72 (71.3)
Japan	2 (6.3)	4 (7.8)	2 (11.1)	8 (7.9)

The most frequently reported prior UC-related medications were mesalazine (83.2%), azathioprine (AZA; 71.3%), and prednisone (47.5%)/prednisolone (8.9%); all other prior UC-related medications were used by < 20% of subjects (Integrated ITT/Safety population). These medications were also the most frequently reported UC-related medications at Baseline: mesalazine (77.2%), AZA (59.4%), and prednisone (26.7%)/prednisolone (5.9%), respectively, for the Integrated ITT/Safety population. All other baseline UC-related medications were reported by < 9% of subjects for the Integrated ITT/Safety population.

Efficacy results (exploratory re-run of the primary efficacy analysis)

Co-primary endpoint

The first co-primary endpoint, clinical remission per PMS at Week 8, was achieved by 58.8% of subjects randomized to adalimumab I-HD group and 40.6% of subjects randomized to the I-SD group (Integrated ITT-E population) (Table 3).

Table 3. Proportion of Adalimumab-Treated Subjects Who Achieved Clinical Remission Per PMS at Week 8 (Integrated ITT-E and Japan ITT-E Populations, NRI)

Treatment Group	n/N (%)	95% CI[a]	*P* Value[b]
Integrated ITT-E			
I-SD + I-HD	43/83 (51.8)	(40.56, 62.92)	< 0.001[c]
I-HD	30/51 (58.8)	(44.17, 72.42)	< 0.001[c]
I-SD	13/32 (40.6)	(23.70, 59.36)	0.003
Japan ITT-E			
I-SD + I-HD	2/6 (33.3)	(4.33, 77.72)	NS
I-HD	2/4 (50.0)	(6.76, 93.24)	NS
I-SD	0/2	(0.00, 84.19)	NS

CI = confidence interval; I-HD = induction high dose group; I-SD = induction standard dose group; ITT = intent-to-treat; NRI = nonresponder imputation; NS = not statistically significant; PMS = Partial Mayo score

a. Clopper-Pearson confidence interval for proportion in remission.

b. Nominal *P* value from a 1-sample 2-sided chi-square test.

c. Statistically significant per prespecified sequentially rejective multiple test procedure (Figure 1).

Note: External placebo rate for statistical comparison = 19.83% (upper limit of 95% CI from meta-analysis).
No *P* values are shown for the Japan Substudy dose groups due to small numbers of subjects.

Second Co-Primary Endpoint

The second co-primary endpoint, clinical remission per Mayo score at Week 52 in PMS responders at Week 8, was achieved by 42.9% of subjects in the adalimumab M-HD group and 27.3% of subjects in the M-SD group (Integrated mITT-E population).

Table 4. Proportion of Adalimumab-Treated Subjects with Clinical Remission per FMS at Week52 in Week 8 Responders per PMS (Integrated mITT-E and Japan mITT-E Populations, NRI)

Treatment Group	n/N (%)	95% CI[a]	*P* Value[b]
Integrated mITT-E			
M-SD + M-HD	24/68 (35.3)	(24.08, 47.83)	< 0.001[c]
M-HD	15/35 (42.9)	(26.32, 60.65)	< 0.001[c]
M-SD	9/33 (27.3)	(13.30, 45.52)	0.187
Japan mITT-E			
M-SD + M-HD	1/6 (16.7)	(0.42, 64.12)	NS
M-HD	1/4 (25.0)	(0.63, 80.59)	NS
M-SD	0/2	(0.00, 84.19)	NS

CI = confidence interval; FMS = full Mayo score; mITT = modified intent-to-treat; M-HD = maintenance high dose group; M-SD = maintenance standard dose group; NRI = nonresponder imputation; NS = not statistically significant; PMS = Partial Mayo score

a. Clopper-Pearson confidence interval for proportion in remission.

b. Nominal *P* value from a 1-sample 2-sided chi-square test.

c. Statistically significant per prespecified sequentially rejective multiple test procedure (Figure 1).

Note: External placebo rate for statistical comparison = 18.37% (upper limit of 95% CI from meta-analysis).
No *P* values are shown for the Japan Substudy dose groups due to small numbers of subjects.

Cross reference: Table 14.2__1.1.2_A, Table 14.2__1.1.2_J, Figure 14.2__7_A

According to the applicant, efficacy results for the Japan ITT-E and mITT-E populations were consistent with the results for the respective Integrated ITT populations.

Safety results

Overall, 81 of the 101 (80.2%) subjects in the Integrated Safety population experienced at least 1 TEAE with adalimumab exposure, including adalimumab as rescue therapy after a disease flare (Table

5). Exposure-adjusted incidence rates are shown below. No death, malignancy, active tuberculosis (TB), or demyelinating disorder were reported throughout the study. According to the applicant, serious AEs and TEAEs leading to study drug discontinuation were low in frequency and consistent with the underlying disorder.

Table 5. Overview of Any-Adalimumab Treatment-Emergent Adverse Events and All Deaths per 100 Patient-Years (PYS) of overall ADA exposure Throughout the Study (Integrated Safety Population)

	Any ADA				
	I-HD/HD-OL				
	--$ (N=10) (PYS=1.4)	M-PL (N=8) (PYS=3.7)	M-SD (N=25) (PYS=22.6)	M-HD (N=26) (PYS=24.8)	Total (N=101) (PYS=70.9)
	Events (E/100PY)	Events (E/100PY)	Events (E/100PY)	Events (E/100PY)	Events (E/100PY)
Any treatment-emergent					
Adverse event (AE)	16 (1142.9)	30 (810.8)	103 (455.8)	119 (479.8)	359 (506.3)
Serious AE	4 (285.7)	0	9 (39.8)	6 (24.2)	30 (42.3)
Severe AE	1 (71.4)	0	6 (26.5)	2 (8.1)	15 (21.2)
AEs leading to discontinuation of study drug	1 (71.4)	0	2 (8.8)	0	8 (11.3)
AEs rated as possibly related to study drug by the investigator (reasonable possibility)#	3 (214.3)	6 (162.2)	21 (92.9)	25 (100.8)	72 (101.6)
SAEs rated as possibly related to study drug by the investigator (reasonable possibility)#	2 (142.9)	0	0	1 (4.0)	6 (8.5)
AEs leading to Death	0	0	0	0	0
Infections	3 (214.3)	11 (297.3)	25 (110.6)	27 (108.9)	88 (124.1)
Serious infections	0	0	2 (8.8)	3 (12.1)	6 (8.5)

I-SD = induction standard dose group, I-HD = induction high dose group, I-HD-OL = induction high dose open-label group,
M-PL = maintenance placebo group, M-SD = maintenance standard dose group, M-HD = maintenance high dose group.
Note: Treatment-emergent adverse events are defined as events with an onset date on or after the first dose date of adalimumab and up to 70 days after the last dose date of adalimumab and prior to the first dose date in M10-870 if applicable, whichever comes first. For subjects who received placebo during the maintenance period of study M11-290, the TEAE collection period ends 70 days after last induction dose of ADA and re-starts with their next ADA dose, if applicable.
E/100PY = Events per 100 patient-years.
AEs with unknown relationship were counted as 'reasonable possibility of being related'.
AEs with unknown severity were counted as 'severe'.
$ Patients who discontinued as non-responders from the study at week 8.
# As assessed by investigator.

In the Japan Safety population, 8 subjects (100%) experienced at least 1 TEAE (33 E [589.3 E/100 PYs]), Table 6.

Table 6. Overview of Any-Adalimumab Treatment-Emergent Adverse Events and All Deaths per 100 Patient-Years (PYS) of overall ADA exposure Throughout the Study (Japan Safety Population)

	Any ADA				
	I-HD/HD-OL				
	--$ (N=0) (PYS=0.0)	M-PL (N=0) (PYS=0.0)	M-SD (N=2) (PYS=1.7)	M-HD (N=4) (PYS=3.7)	Total (N=8) (PYS=5.6)
	Events (E/100PY)	Events (E/100PY)	Events (E/100PY)	Events (E/100PY)	Events (E/100PY)
Any treatment-emergent					
Adverse event (AE)	0	0	14 (823.5)	16 (432.4)	33 (589.3)
Serious AE	0	0	1 (58.8)	0	1 (17.9)
Severe AE	0	0	0	0	0
AEs leading to discontinuation of study drug	0	0	0	0	1 (17.9)
AEs rated as possibly related to study drug by the investigator (reasonable possibility)#	0	0	5 (294.1)	3 (81.1)	9 (160.7)
SAEs rated as possibly related to study drug by the investigator (reasonable possibility)#	0	0	0	0	0
AEs leading to Death	0	0	0	0	0
Infections	0	0	5 (294.1)	6 (162.2)	11 (196.4)
Serious infections	0	0	1 (58.8)	0	1 (17.9)

I-SD = induction standard dose group, I-HD = induction high dose group, I-HD-OL = induction high dose open-label group,
M-PL = maintenance placebo group, M-SD = maintenance standard dose group, M-HD = maintenance high dose group.
Note: Treatment-emergent adverse events are defined as events with an onset date on or after the first dose date of adalimumab and up to 70 days after the last dose date of adalimumab and prior to the first dose date in M10-870 if applicable, whichever comes first. For subjects who received placebo during the maintenance period of study M11-290, the TEAE collection period ends 70 days after last induction dose of ADA and re-starts with their next ADA dose, if applicable.
E/100PY = Events per 100 patient-years.
AEs with unknown relationship were counted as 'reasonable possibility of being related'.
AEs with unknown severity were counted as 'severe'.
$ Patients who discontinued as non-responders from the study at week 8.
# As assessed by investigator.

For the Japan Safety population, no subject experienced an SAE and 1 subject (I-SD) had a TEAE leading to study drug discontinuation during Induction; 1 subject (M-SD) had an SAE during Maintenance. The proportion of subjects who experienced TEAEs assessed by the investigator as having at least a reasonable possibility of being related to study drug was low and similar between the I-SD and the I-HD groups during Induction and the M-SD and M-HD groups during Maintenance (Integrated Safety population). According to the applicant, most TEAEs were mild to moderate in severity during both Induction and Maintenance (Integrated Safety population).

For the Integrated Safety population, the system organ classes (SOCs) with the most frequently reported TEAEs (≥ 20% of adalimumab-treated subjects) during Induction and Maintenance up to the first disease flare were Infections and Infestations (22.8% and 40.7%, respectively) and Gastrointestinal Disorders (19.8% and 27.2%, respectively). The most frequently reported (≥ 5% of subjects) TEAEs by preferred term (PT) during Induction were headache, anaemia, colitis ulcerative, and nasopharyngitis; the most frequently reported TEAEs by PT during Maintenance up to the first disease flare in subjects who received adalimumab were colitis ulcerative, headache, nasopharyngitis, upper respiratory infection, anaemia, and pharyngitis. Slightly higher incidences of colitis ulcerative, headache, and anaemia were reported in subjects who received the adalimumab standard dose regimens compared with subjects who were treated with the high dose regimens.

Injection site reactions and infections were the only AESIs reported by subjects in Japan (Table 7).

Table 7. Treatment-Emergent AESIs: Subjects Who Received Adalimumab During the Study by Period and Dose Group

	n (%) of Subjects						
	Safety					RR	Safety
	Induction[a]			Maintenance Up to First Disease Flare[b]		After First Disease Flare with Re-Induction[c]	
AESI Category	I-SD	I-HD	I-HD-OL	M-SD	M-HD		Any Adalimumab[d]
Integrated population	N = 32	N = 51	N = 18	N = 33	N =36	N = 8	N = 101
Infection	6 (18.8)	11 (21.6)	6 (33.3)	11 (33.3)	16 (44.4)	4 (50.0)	49 (48.5)
Serious infection	0	0	0	3 (9.1)	3 (8.3)	0	6 (5.9)
Opportunistic infection excluding oral candidiasis and TB	0	0	0	0	0	1 (12.5)[e]	1 (1.0)
Latent TB	0	0	0	0	1 (2.8)	0	1 (1.0)
Allergic reactions including angioedema/ anaphylaxis	0	1 (2.0)	0	1 (3.0)	2 (5.6)	0	4 (4.0)
Pancreatitis	0	1 (2.0)	0	0	0	0	1 (1.0)
Worsening or new onset of psoriasis	0	0	0	0	0	0	0
Hematologic disorders including pancytopenia	3 (9.4)	3 (5.9)	1 (5.6)	3 (9.1)	1 (2.8)	0	12 (11.9)
Injection site reaction	1 (3.1)	3 (5.9)	0	4 (12.1)	2 (5.6)	0	10 (9.9)

	n (%) of Subjects						
	Safety					RR	Safety
	Induction[a]			Maintenance Up to First Disease Flare[b]		After First Disease Flare with Re-Induction[c]	Any Adalimumab[d]
AESI Category	I-SD	I-HD	I-HD-OL	M-SD	M-HD		
Japan population	N = 2	N = 4	N = 2	N = 2	N = 4	–	N = 8
Infection	0	3 (75.0)	0	1 (50.0)	3 (75.0)	–	5 (62.5)
Serious infection	0	0	0	1 (50.0)	0	–	1 (12.5)
Latent TB	0	0	0	0	0	–	0
Allergic reactions including angioedema/ anaphylaxis	0	0	0	0	0	–	0
Pancreatitis	0	0	0	0	0	–	0
Worsening or new onset of psoriasis	0	0	0	0	0	–	0
Hematologic disorders including pancytopenia	0	0	0	0	0	–	0
Injection site reaction	1 (50.0)	1 (25.0)	0	0	0	–	2 (25.0)

AESI = adverse event of special interest; I-HD = induction high dose; I-HD-OL = induction high dose open-label; I-SD = induction standard dose; M-HD = maintenance high dose; M-SD = maintenance standard dose; RR = re-randomized population; TB = tuberculosis

a. Integrated Safety population; TEAEs are defined as events with an onset date on or after the date of the first dose of study drug in the Induction period and prior to the first dose date of study drug in the Maintenance period (if applicable).

According to the applicant, the safety results for the subjects in Japan were consistent with the results for the integrated population, and consistent with the established safety profile of adalimumab and with the underlying colitis disorder.

2.3.2. Discussion on clinical aspects

Study M11-290 was a Phase 3, randomized, double blind (DB) trial designed to evaluate the efficacy and safety of adalimumab in paediatric subjects with moderate to severe UC who have failed therapy with corticosteroids and/or immunosuppressant (IMM). The study consisted of a Main Study (conducted in subjects enrolled outside of Japan,) and a Japan Substudy (conducted in subjects enrolled at sites in Japan only).

The main study results were submitted as a Type II variation to add the paediatric ulcerative colitis indication that is currently under review (EMEA/H/C/000481/II/0198). At time for data cut-off for that submission (March 2020), the Japanese substudy was not yet finalised. This submission pertains to the final report for Study M11-290 that contains an exploratory re-run of efficacy analyses and final safety analyses based on subjects enrolled at all study sites, including Japan.

Details on the study design has been assessed within variation II/198 and the assessment is not repeated here.

Prior to Amendment 4, enrolled subjects were randomized 3:2 at Baseline to 1 of 2 DB adalimumab induction doses, induction high dose (I-HD) or induction standard dose (I-SD). At Week 8, subjects demonstrating a clinical response per Partial Mayo Score (PMS) were randomized to the following groups in a 2:2:1 ratio: adalimumab maintenance standard dose (M-SD), adalimumab maintenance high dose (M-HD), or placebo. Subjects continued their blinded treatment during the maintenance period until Week 52.

After Amendment 4, enrolled subjects receive adalimumab induction high dose open-label (I-HD-OL). At Week 8, subjects demonstrating a clinical response per PMS were randomized and stratified by Week 8 remission status per PMS in a 1:1 ratio to 1 of 2 adalimumab maintenance treatment groups,

M-SD or M-HD. Subjects continued their blinded treatment during the maintenance period until Week 52.

The duration of the study was up to 66 weeks, which included a screening period of up to 28 days, an 8-week induction period and a 44-week DB maintenance period and a 70-day follow-up phone call. Upon completion of the study, subjects had the option to enrol into an OLE study (Study M10-870 Main) where they continued to receive OL adalimumab.

The recommended maintenance dose in the UC population is doubled compared to the standard maintenance dose in the paediatric Crohn's disease population. This is further discussed in variation II/198.

A total of 101 subjects at 24 sites (93 subjects at 19 global sites outside of Japan; 8 subjects at 5 sites in Japan) enrolled in Study M11-290. All 101 enrolled subjects were included in the Integrated intent-to-treat (ITT) and Safety Populations.

The first co-primary endpoint, clinical remission per PMS at Week 8, was achieved by 58.8% of subjects randomized to adalimumab I-HD group and 40.6% of subjects randomized to the I-SD group (Integrated ITT-E population). In the Japanese subpopulation, a total of 2/6 patients (33.3%) achieved clinical remission. Although the response rates (also for secondary endpoints) were numerically lower in the Japanese subpopulation, the comparison is hampered by the limited number of study subjects.

With regards to safety, overall, 81 of the 101 (80.2%) subjects in the Integrated Safety population experienced at least 1 TEAE with adalimumab exposure. In the Japan Safety population, 8 subjects (100%) experienced at least 1 TEAE. For the Japan Safety population, no subject experienced an SAE and 1 subject had a TEAE leading to study drug discontinuation during Induction; 1 subject had an SAE during Maintenance (worsening of ulcerative colitis). No death, malignancy, active tuberculosis (TB), or demyelinating disorder were reported throughout the study. Injection site reactions and infections were the only AESIs reported by subjects in Japan.

According to the applicant, the safety results for the subjects in Japan were consistent with the results for the integrated population, and consistent with the established safety profile of adalimumab and with the underlying colitis disorder. This is agreed by CHMP.

3. CHMP overall conclusion and recommendation

The presented data includes additional data for 8 Japanese children, not included in the interim data from study M11-290 submitted in variation II/198 to support the new indication of paediatric ulcerative colitis. With regard to efficacy, the response rates were numerically lower in the Japanese subpopulation, however the comparison is hampered by the very limited number of study subjects. Regarding safety, it is agreed by CHMP that the safety results for the subjects in Japan were consistent with the results for the integrated population, and consistent with the established safety profile of adalimumab and with the underlying colitis disorder. No new safety signals evoked.

☒ **Fulfilled:**

No regulatory action required.