EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 March 2020
EMA/154686/2020
Committee for Medicinal Products for Human Use (CHMP)

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

Entyvio

vedolizumab

Procedure no: EMEA/H/C/002782/P46/004.1

Note

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

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1. Introduction

On 04/11/2019 the MAH submitted a completed paediatric study for Entyvio in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study MLN0002/CCT-001 is a phase 3 study of vedolizumab 300 mg (powder for concentrate for solution for infusion) in Crohn's disease (CD) conducted in Japan.

2.2. Information on the pharmaceutical formulation used in the study

300 mg for infusion

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for **Study MLN0002/CCT-001**, a phase 3 study of vedolizumab 300 mg (powder for concentrate for solution for infusion) in CD conducted in Japan. This study **is not** part of the vedolizumab Paediatic Investigational Plan (PIP) in UC and CD, EMEA-000645-PIP01-09.
Study MLN0002/CCT-001 in CD is part of the phase 3 clinical program to support registration in Japan, along with study MLN0002/CCT-101 which is a phase 3 study of vedolizumab 300 mg (powder for concentrate for solution for infusion) in UC.

Clinical study

Study MLN0002/CCT-001

Description

A phase 3, multicenter, randomized, double-blinded, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and pharmacokinetics of intravenous MLN0002 (300 mg) infusion in induction and maintenance therapy in Japanese subjects (from 15 to 80 years) with moderate or severe CD.

Methods

Objectives:

Primary Objective for the Induction Phase: To evaluate efficacy
Secondary Objective for the Induction Phase: To evaluate safety
Primary Objective for the Maintenance Phase: To evaluate efficacy
Secondary Objective for the Maintenance Phase: To evaluate safety

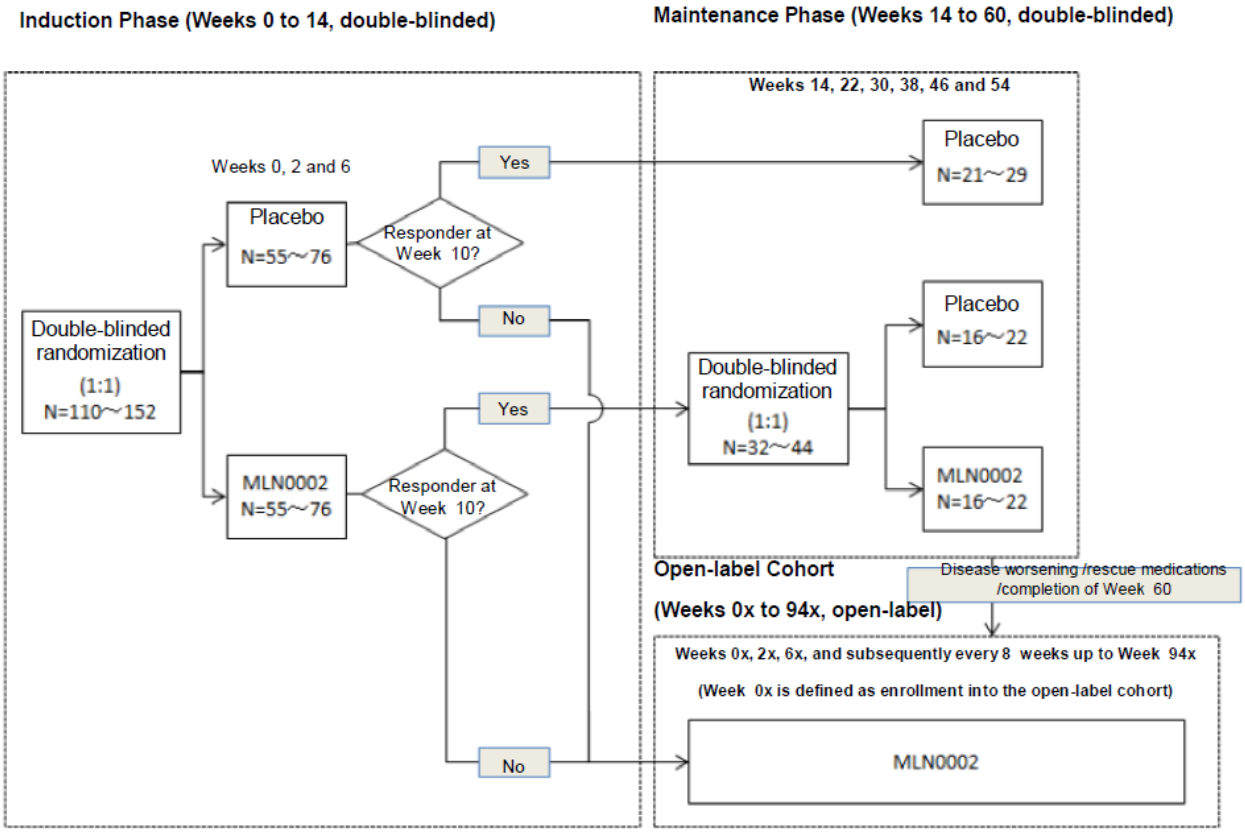
Study design

This study consisted of the screening phase, the induction phase, the maintenance phase, and an open-label phase.

Subjects enrolled into the induction phase were randomized 1:1 to placebo or MLN0002 and received placebo or 300 mg of MLN0002 at Weeks 0, 2, and 6 in a double-blinded manner. Primary efficacy evaluation in the induction phase was performed at Week 10.
Subjects showing Crohn's disease activity index (CDAI) -70 response at Week 10 were enrolled into the maintenance phase at Week 14. Subjects who received the placebo in the induction phase continued to receive the placebo at Weeks 14, 22, 30, 38, 46, and 54 in a double-blinded manner. Subjects who received MLN0002 in the induction phase were randomized 1:1 to the placebo or MLN0002 and received the placebo or 300 mg of MLN0002 at Weeks 14, 22, 30, 38, 46, and 54 in a double-blinded manner. The primary efficacy evaluation in the maintenance phase was performed at Week 60.

Subject not showing CDAI-70 response at Week 10 were allowed to be enrolled into the open-label cohort at Week 10. In addition, subjects who experienced disease worsening or received rescue medications during the maintenance phase, or subjects who completed Week 60 of the maintenance phase were also allowed to be enrolled into the open-label cohort. The day individual subject was enrolled into the open-label cohort was defined as Week 0x, and the subject received 300 mg of MLN0002 at Weeks 0x, 2x, and 6x followed by doses every 8 weeks up to Week 46x (minimum) or Week 94x (maximum) in an un-blinded manner. Administration of MLN0002 was to be terminated in all subjects at Week 46x of the last subject enrolled into the open-label cohort.

The end-of-study examination was performed at 16 weeks after the last dose in all subjects who received the study drug. In addition, the follow-up survey was to be performed every 6 months from the last dose of the study drug, for up to 2 years thereafter or until the marketing approval date of the study drug, whichever comes earlier.



Study population /Sample size

Study MLN0002/CCT-001 enrolled a total of 157 subjects in the induction phase, of these only 6 were aged 15 to 18 years at entry (1 was 15 years old, 2 were 16 years old and 3 were 17 years old): 1 was randomized in vedolizumab and 5 in placebo arm. Subjects enrolled in the maintenance phase were 41 and subjects enrolled in the open-label cohort were 134.

Treatments

Subjects in induction phase were randomized 1:1 in a double-blinded manner to receive placebo or vedolizumab 300 mg at Weeks 0, 2, and 6. Subjects not responder at Week 10 of induction phase, subjects who experienced disease worsening or received rescue medications during the maintenance phase, or subjects who completed Week 60 of the maintenance phase were enrolled in open-label Cohort to receive vedolizumab 300 mg at Weeks 0x to 94x in an unblinded manner.

Outcomes/endpoints

Induction Phase

Primary Endpoint

- CDAI-100 response at Week 10

Secondary Endpoints

- Clinical remission at Week 10
- Change in CRP level over time in the subpopulation of subjects with the baseline CRP level of >0.30 mg/dL

Maintenance Phase

Primary Endpoint

- Clinical remission at Week 60

Secondary Endpoints

- CDAI-100 response at Week 60
- Durable remission in the maintenance phase
- Corticosteroid-free remission at Week 60

Statistical Methods

"Full Analysis Set in induction phase," a primary population for the efficacy analysis in the induction phase, was defined as subjects who were randomized and received at least one dose of the study drug in the induction phase.

The superiority of MLN0002 over the placebo on CDAI-100 response at Week 10 in the primary analysis of the induction phase was demonstrated when a statistically significant difference was observed between the treatment groups.

For the other efficacy analysis (e.g. CDAI-100 response at Week 60, durable response in the maintenance phase and corticosteroid-free remission at Week 60) were summarized in the same manner as the primary analysis in the induction phase.

Significance Level and Confidence Coefficient
• Significance level:
• 10% (two-sided test): only for CDAI-100 response at Week 10 and clinical remission at Week 10 in the induction phase
• 5% (two-sided test): other than those above
• Confidence coefficient (CI): 95% (two-sided estimation)

Results

Recruitment/ Number analysed

A total of 157 subjects entered into the induction phase at 60 sites in Japan; these subjects were randomized to the placebo group (78 subjects) or the MLN0002 group (79 subjects), and received the study drug in a double-blinded manner. A total of 139 subjects (88.5%) completed the planned infusions of the study drug in the induction phase and 18 subjects (11.5%) prematurely discontinued the study drug. The reasons for study drug discontinuation were AE in 14 subjects, lack of efficacy in 2 subjects, and voluntary withdrawal in 2 subjects.

Baseline data

In overall subjects who entered in the induction phase, the proportion of male subjects was 65.6%. The overall mean age was 33.3 years, the majority (61.1%) was less than 35 years, and 2 subjects (1.3%) were ≥65 years of age.
The mean duration of CD was 9.03 years, and the mean CDAI score was 299.5 at Baseline (Week 0).
No marked differences were observed between treatment groups in Baseline CD characteristics.
In the category of "worst prior treatment failures," prior TNF α antagonist failure, prior immunomodulators failure (excluding TNF α antagonist failure), and prior corticosteroids failure only were categorized by 121 subjects (77.1%), 21 subjects (13.4%), and 15 subjects (9.6%), respectively.
The study was projected to have subjects without prior TNF α antagonist use accounting for 25% of the planed sample size. As a result, 21.7% (34/157) of subjects who entered in the induction phase had no prior TNF α antagonist use.

Maintenance phase

Table 11-M.d Baseline Demographics (Subjects Who Entered in Maintenance Phase)

	Randomized Set in Maintenance Phase		Placebo Continuation	Total
	Placebo (N=12)	MLN0002 (N=12)	(N=17)	(N=41)
Age (years) (N [%])				
Min≤-≤34	7 (58.3)	7 (58.3)	13 (76.5)	27 (65.9)
35≤-≤Max	5 (41.7)	5 (41.7)	4 (23.5)	14 (34.1)
Min≤-≤64	12 (100.0)	11 (91.7)	17 (100.0)	40 (97.6)
65≤-≤Max	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.4)
Age (years)				
N	12	12	17	41
Mean	35 .2	36 .7	29 .8	33 .4
SD	12 .97	16 .80	8 .38	12 .72
Minimum	20	19	15	15
Median	32 .5	32 .5	30 .0	31 .0
Maximum	60	79	46	79
Gender (N [%])				
Male	9 (75.0)	6 (50.0)	13 (76.5)	28 (68.3)
Female	3 (25.0)	6 (50.0)	4 (23.5)	13 (31.7)
Weight (kg) at Baseline				
N	12	12	17	41
Mean	62 .53	60 .54	55 .86	59 .18
SD	13 .696	16 .682	9 .309	13 .091
Minimum	48 .9	36 .0	38 .0	36 .0
Median	58 .45	57 .25	57 .50	57 .50
Maximum	94 .0	98 .4	77 .9	98 .4
BMI (kg/m^2) at Baseline				
N	12	12	17	41
Mean	21 .93	22 .12	20 .01	21 .19
SD	3 .665	6 .236	3 .097	4 .385
Minimum	17 .7	16 .9	15 .4	15 .4
Median	21 .65	19 .75	19 .40	19 .60
Maximum	28 .7	36 .6	27 .6	36 .6

Source: Section 15.1 Table 1.2.1.1m.

Table 11-M.e Baseline CD Characteristics (Subjects Who Entered in Maintenance Phase)

	Randomized Set in Maintenance Phase		Placebo Continuation	Total
	Placebo (N=12)	MLN0002 (N=12)	(N=17)	(N=41)
Duration of CD (years) (N [%])				
MIn≤-<1	0 (0.0)	0 (0.0)	1 (5.9)	1 (2.4)
1≤-<3	3 (25.0)	1 (8.3)	4 (23.5)	8 (19.5)
3≤-<7	4 (33.3)	3 (25.0)	3 (17.6)	10 (24.4)
7≤-≤Max	5 (41.7)	8 (66.7)	9 (52.9)	22 (53.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Duration of CD (years)				
N	12	12	17	41
Mean	7 .45	8 .98	7 .26	7 .82
SD	6 .576	4 .918	5 .203	5 .472
Minimum	1 .3	2 .3	0 .3	0 .3
Median	5 .60	9 .25	7 .50	7 .10
Maximum	25 .1	16 .2	19 .7	25 .1
CRP level at Baseline (N [%])				
Min≤-≤0.3	2 (16.7)	2 (16.7)	1 (5.9)	5 (12.2)
0.3<- ≤0.5	2 (16.7)	0 (0.0)	1 (5.9)	3 (7.3)
0.5<-≤1.0	0 (0.0)	3 (25.0)	4 (23.5)	7 (17.1)
1.0<-≤1.6	2 (16.7)	0 (0.0)	5 (29.4)	7 (17.1)
1.6<-≤Max	6 (50.0)	7 (58.3)	6 (35.3)	19 (46.3)
CRP level at Baseline (mg/dL)				
N	12	12	17	41
Mean	2 .414	1 .987	2 .837	2 .464
SD	2 .5325	1 .5629	3 .8264	2 .9018
Minimum	0 .03	0 .12	0 .03	0 .03
Median	1 .810	1 .965	1 .430	1 .540
Maximum	6 .74	4 .41	15 .97	15 .97

Footnotes are on the following page.

Table 11-M.e Baseline CD Characteristics (Subjects Who Entered in Maintenance Phase) (continued)

	Randomized Set in Maintenance Phase		Placebo Continuation	Total
	Placebo (N=12)	MLN0002 (N=12)	(N=17)	(N=41)
CDAI Score at Baseline (N [%])				
Min<-≤220	0 (0.0)	0 (0.0)	1 (5.9)	1 (2.4)
220<-≤330	8 (66.7)	7 (58.3)	13 (76.5)	28 (68.3)
330<-≤450	3 (25.0)	5 (41.7)	2 (11.8)	10 (24.4)
450<-≤Max	1 (8.3)	0 (0.0)	1 (5.9)	2 (4.9)
CDAI Score at Baseline				
N	12	12	17	41
Mean	303 .3	319 .8	283 .1	299 .7
SD	81 .71	79 .32	58 .19	71 .85
Minimum	222	229	219	219
Median	279 .1	280 .1	270 .4	276 .8
Maximum	469	448	451	469
Disease Localization (N [%])				
Small intestinal	2 (16.7)	2 (16.7)	4 (23.5)	8 (19.5)
Large intestinal	1 (8.3)	5 (41.7)	3 (17.6)	9 (22.0)
Small/large intestinal	9 (75.0)	5 (41.7)	10 (58.8)	24 (58.5)
Smoking Classification (N [%])				
Never smoked	5 (41.7)	10 (83.3)	9 (52.9)	24 (58.5)
Current smoker	1 (8.3)	0 (0.0)	1 (5.9)	2 (4.9)
Ex-smoker	6 (50.0)	2 (16.7)	7 (41.2)	15 (36.6)
Extraintestinal Manifestations (Based on CDAI subscore) (N [%])				
No	4 (33.3)	6 (50.0)	6 (35.3)	16 (39.0)
Yes	8 (66.7)	6 (50.0)	11 (64.7)	25 (61.0)
Extraintestinal Manifestations (Based on CRF) (N [%])				
No	4 (33.3)	9 (75.0)	10 (58.8)	23 (56.1)
Yes	8 (66.7)	3 (25.0)	7 (41.2)	18 (43.9)
Surgical history for CD (N [%])				
No	9 (75.0)	9 (75.0)	11 (64.7)	29 (70.7)
Yes	3 (25.0)	3 (25.0)	6 (35.3)	12 (29.3)
Current medical condition related to fistula (N [%])				
No	11 (91.7)	12 (100.0)	15 (88.2)	38 (92.7)
Yes	1 (8.3)	0 (0.0)	2 (11.8)	3 (7.3)
CDAI-70 Response at Week 10 (N [%])	11 (91.7)	12 (100.0)	17 (100.0)	40 (97.6)
CDAI-100 Response at Week 10 (N [%])	10 (83.3)	10 (83.3)	12 (70.6)	32 (78.0)
Clinical Remission at Week 10 (N [%])	6 (50.0)	8 (66.7)	8 (47.1)	22 (53.7)

Source: Section 15.1 Table 1.2.1.1m.

Efficacy results

Primary Efficacy Endpoint, Induction

CDAI-100 Response at Week 10 (Full Analysis Set in Induction Phase)

	Placebo (N=78)	MLN0002 (N=79)
CDAI-100 Response at Week 10 (N [%])	13 (16.7)	21 (26.6)
95% CI (%)	(9.184, 26.813)	(17.268, 37.720)
Difference From Placebo (a) (%)		9.9
95% CI (%)		(-2.863, 22.695)
Adjusted Odds Ratio (b)		1.80
95% CI		(0.816, 3.958)
p-value (c)		0.1448

Source: Section 15.1 Tables 2.1.1.1.1, 2.1.1.1.2, and 2.1.1.3.
Note: Missing data is treated as non-response.
(a) MLN0002 group - placebo group.
(b) MLN0002 group/placebo group. CMH estimates and test with stratification according to prior TNFα antagonist use (yes/no)
(c) Significance level: 10% (two-sided test)

Examination of age Subgroups for CDAI-100 at Week 10 (Full Analysis Set in Induction Phase)

							Difference from placebo(a)		
				Response	95% CI			95% CI	
Item	Category	Treatment	N	(N [%])	Lower	Upper	Estimate	Lower	Upper
Age (years)	Min≤-≤34	MLN0002	46	13 (28.3)	15.987	43.460	4.3	-13.330	21.852
		Placebo	50	12 (24.0)	13.061	38.169			
	35≤-≤Max	MLN0002	33	8 (24.2)	11.092	42.259	20.7	4.514	36.828
		Placebo	28	1 (3.6)	0.090	18.348			
	Min≤-≤64	MLN0002	78	21 (26.9)	17.501	38.164	10.0	-2.879	22.959
		Placebo	77	13 (16.9)	9.307	27.139			
	65≤-≤Max	MLN0002	1	0 (0.0)	NA	NA	0.0	NA	NA
		Placebo	1	0 (0.0)	NA	NA			

Secondary Efficacy Endpoints, Induction

Clinical Remission at Week 10 (Full Analysis Set in Induction Phase)

	Placebo (N=78)	MLN0002 (N=79)
Clinical Remission at Week 10 (N [%])	8 (10.3)	14 (17.7)
95% CI (%)	(4.533, 19.213)	(10.041, 27.942)
Difference From Placebo (a) (%)		7.5
95% CI (%)		(-3.316, 18.246)
Adjusted Odds Ratio (b)		1.83
95% CI		(0.720, 4.673)
p-value (c)		0.1963
Adjusted Risk Difference (d)		6.9
95% CI		(-3.696, 17.573)

Source: Section 15.1 Tables 2.2.1.1, 2.2.1.2, 2.2.3.1, and 2.2.3.2.
Note: Missing data is treated as non-remission.
(a) MLN0002 group - placebo group.
(b) MLN0002 group/placebo group. CMH estimates and test with stratification according to prior TNFα antagonist use (yes/no).
(c) Significance level: 10% (two-sided test).
(d) MLN0002 group - placebo group. CMH estimates and test with stratification according to prior TNFα antagonist use (yes/no).

Results by prior exposure to antiTNF-alpha

Table 11-I.t CDAI-100 Response at Week 6 and Week 10, Clinical Remission at Week 6 and Week 10 in Subjects Without Prior TNFα Antagonist use and in Subjects With Prior TNFα Antagonist Failure (Full Analysis Set in Induction Phase)

	Subjects Without Prior TNFα Antagonist use		Subjects With Prior TNFα Antagonist Failure	
	Placebo (N=16)	MLN0002 (N=18)	Placebo (N=62)	MLN0002 (N=61)
CDAI-100 Response				
Week 6 (N [%])	4 (25.0)	7 (38.9)	6 (9.8)	12 (20.0)
95% CI (%)	(7.266, 52.377)	(17.299, 64.255)	(3.696, 20.190)	(10.784, 32.330)
Difference from placebo (a) (%)		13.9		10.2
95% CI (%)		(-17.052, 44.830)		(-2.417, 22.745)
Week 10 (N [%])	4 (25.0)	9 (50.0)	9 (14.8)	12 (20.0)
95% CI (%)	(7.266, 52.377)	(26.019, 73.981)	(6.975, 26.169)	(10.784, 32.330)
Difference from placebo (a) (%)		25.0		5.2
95% CI (%)		(-6.364, 56.364)		(-8.232, 18.723)
Clinical Remission				
Week 6 (N [%])	3 (18.8)	7 (38.9)	7 (11.5)	4 (6.7)
95% CI (%)	(4.047, 45.646)	(17.299, 64.255)	(4.740, 22.225)	(1.846, 16.199)
Difference from placebo (a) (%)		20.1		-4.8
95% CI (%)		(-9.407, 49.685)		(-14.997, 5.380)
Week 10 (N [%])	2 (12.5)	9 (50.0)	6 (9.8)	5 (8.3)
95% CI (%)	(1.551, 38.348)	(26.019, 73.981)	(3.696, 20.190)	(2.761, 18.386)
Difference from placebo (a) (%)		37.5		-1.5
95% CI (%)		(9.284, 65.716)		(-11.738, 8.732)

Source: Section 15.1 Tables 2.3.1.5.1, 2.3.1.5.2, 2.3.1.2.1, 2.3.1.2.2, 2.3.1.20.1.1, 2.3.1.20.1.2, 2.3.1.20.2.1, and 2.3.1.20.2.2.
Note: Missing data is treated as non-response or non-remission.
(a) MLN0002 group - placebo group.

Summary of change from baseline in CRP level by visit (Full Analysis Set in Induction Phase)

	Placebo (N=78)	MLN0002 (N=79)
Baseline (Week 0)		
N	70	64
Median (Q1, Q3) (mg/dL)	2.040 (0.880, 3.970)	2.225 (1.065, 3.970)
Week 2		
N	70	64
Median (Q1, Q3) (mg/dL)	2.030 (1.010, 4.380)	1.925 (0.785, 3.370)
Change From Baseline		
Median (Q1, Q3) (mg/dL)	0.115 (-0.670, 1.020)	-0.120 (-0.1080, 0.460)
p-value (a)		0.3666
Week 6		
N	65	61
Median (Q1, Q3) (mg/dL)	1.880 (0.930. 4.070)	1.470 (0.640, 3.240)
Change From Baseline		
Median (Q1, Q3) (mg/dL)	0.220 (-0.590, 1.170)	-0.180 (-1.180, 0.460)
p-value (a)		0.1628
Week 10		
N	59	60
Median (Q1, Q3) (mg/dL)	2.160 (1.000, 3.250)	1.440 (0.730, 3.605)
Change From Baseline		
Median (Q1, Q3) (mg/dL)	0.220 (-0.900, 1.390)	-0.295 (-1.600, 0.550)
p-value (a)		0.1375

Source: Section 15.1 Tables 2.2.4.1, 2.2.4.2, and 2.2.6.
(a) van Elteren test stratified by prior TNFα antagonist use (yes/no).

Paediatric subset

6 subjects were aged 15 to 18 years at entry (1 was 15 years old, 2 were 16 years old and 3 were 17 years old): 1 in vedolizumab and 5 in placebo for CD in induction phase. Two subjects in the placebo group had response in the induction phase and thus continued on placebo in the maintenance phase. The other 4 subjects (1 in vedolizumab and 3 in placebo) had no response in the induction phase. All 6 subjects continued into the open-label extension cohort.

The study did not stratify by age and no subgroup analysis was planned or conducted for subjects aged 15 to 18 years.

Induction Phase Immunogenicity Results:

A total of 1 subject (1.6%) in the MLN0002 group was AVA positive at any time points during the induction phase, and the subject was positive for both AVA and neutralizing antibodies at Week 10. No infusion reactions occurred in this subject.

Additionally, another 1 subject (1.6%) was AVA positive at Baseline (Week 0) before administration of the study drug, and no infusion reactions occurred in this subject.

Maintenance Phase Efficacy Results:

A very limited number of patients are included in the maintenance analysis.

Primary Efficacy Endpoint

The primary efficacy endpoint of the maintenance phase was clinical remission at Week 60, 16.7% and 41.7% in the placebo and MLN0002 groups, respectively.

Table 11-M.l Clinical Remission at Week 60 (Full Analysis Set in Maintenance Phase)

	Placebo (N=12)	MLN0002 (N=12)
Clinical Remission at Week 60 (N [%])	2 (16.7)	5 (41.7)
95% CI (%)	(2.086, 48.414)	(15.165, 72.333)
p-value (a)		0.1779
Difference From Placebo (b) (%)		25.0
95% CI (%)		(-9.967, 59.967)
Odds Ratio (c)		3.57
95% CI		(0.532, 23.953)

Source: Section 15.1 Tables 2.1.1.1.1m, 2.1.1.1.2m, 2.1.1.3.1m, and 2.1.1.3.2m
Note: Missing data is treated as non-remission.
(a) Pearson's chi-square test.
(b) MLN0002 group - placebo group.
(c) MLN0002 group/placebo group.

Table 11-M.m Clinical Remission at Week 60 by Prior TNFα Antagonist use (Full Analysis Set in Maintenance Phase)

	Subjects Without Prior TNFα Antagonist use		Subjects With Prior TNFα Antagonist use	
	Placebo (N=5)	MLN0002 (N=4)	Placebo (N=7)	MLN0002 (N=8)
Clinical Remission at Week 60 (N [%])	2 (40.0)	2 (50.0)	0 (0.0)	3 (37.5)
95% CI (%)	(5.274, 85.337)	(6.759, 93.241)	(0.000, 40.962)	(8.523, 75.514)
Difference From Placebo (a) (%)		10.0		37.5
95% CI (%)		(-55.152, 75.152)		(3.953, 71.047)

Source: Section 15.1 Tables 2.1.1.2.1m and 2.1.1.2.2m.
Note: Missing data is treated as non-remission.
(a) MLN0002 group - placebo group.

Secondary endpoints

Table 11-M.n CDAI-100 Response at Week 60 (Full Analysis Set in Maintenance Phase)

	Placebo (N=12)	MLN0002 (N=12)
CDAI-100 Response at Week 60 (N [%])	1 (8.3)	7 (58.3)
95% CI (%)	(0.211, 38.480)	(27.667, 84.835)
p-value (a)		0.0094
Difference From Placebo (b) (%)		50.0
95% CI (%)		(18.022, 81.978)
Odds Ratio (c)		15.40
95% CI		(1.473, 160.972)

Source: Section 15.1 Tables 2.2.1.1.1.1m, 2.2.1.1.1.2m, 2.2.1.1.3.1m, and 2.2.1.1.3.2m.
Note: Missing data is treated as non-response.
(a) Pearson's chi-square test.
(b) MLN0002 group - placebo group.
(c) MLN0002 group/placebo group.

Table 11-M.p Durable Remission (Full Analysis Set in Maintenance Phase)

	Placebo (N=12)	MLN0002 (N=12)
Durable Remission (N [%])	3 (25.0)	4 (33.3)
95% CI (%)	(5.486, 57.186)	(9.925, 65.112)
p-value (a)		0.6534
Difference From Placebo (b) (%)		8.3
95% CI (%)		(-27.883, 44.549)
Odds Ratio (c)		1.50
95% CI		(0.254, 8.844)

Source: Section 15.1 Tables 2.2.1.2.1.1m, 2.2.1.2.1.2m, 2.2.1.2.3.1m, and 2.2.1.2.3.2m.
Note: Missing data is treated as non-remission.
(a) Pearson's chi-square test.
(b) MLN0002 group - placebo group.
(c) MLN0002 group/placebo group.

Table 11-M.r Corticosteroid-free Remission at Week 60 in Subjects With Oral Corticosteroid use at Baseline (Full Analysis Set in Maintenance Phase)

	Placebo (N=3)	MLN0002 (N=5)
Corticosteroid-free Remission at Week 60 (N [%])	0 (0.0)	2 (40.0)
95% CI (%)	(0.000, 70.760)	(5.274, 85.337)
p-value (a)		0.2059
Difference From Placebo (b) (%)		40.0
95% CI (%)		(-2.941, 82.941)
Odds Ratio (c) (%)		NE
95% CI (%)		(NE, NE)

Source: Section 15.1 Tables 2.2.1.3.1.1m, 2.2.1.3.1.2m, 2.2.1.3.3.1m, and 2.2.1.3.3.2m
Note: Missing data is treated as non-remission.
NE: Not Evaluable
(a) Pearson's chi-square test.
(b) MLN0002 group - placebo group.
(c) MLN0002 group/placebo group.

Paediatric subset: Two subjects in the placebo group had response in the induction phase and thus continued on placebo in the maintenance phase.

Open-Label Cohort

Of the 157 subjects who received at least one dose of study drug in the induction phase or the maintenance phase, 134 subjects (85.4%) entered into the open-label cohort, and all of them received MLN0002 in the open-label cohort. Of the 134 subjects, a total of 77 subjects (57.5%) discontinued the study drug in the open-label cohort. The reasons for study drug discontinuation were PTE/AE in 43 subjects, lack of efficacy in 23 subjects, voluntary withdrawal in 7 subjects, lost to follow-up in 1 subject, pregnancy in 1 subject and other in 2 subjects.

All the 134 subjects who entered in the open-label cohort received at least one dose of study drug in the open-label cohort and were included in the "Full Analysis Set in open-label cohort" and "Safety Analysis Set in open-label cohort."

Paediatric subset: all the six subjects aged 15 to 18 years continued into the open-label extension cohort.

At Week 94x (LOCF), mean CDAI score was 230.4 and mean change from Baseline in CDAI score was -63.6 points. The mean CDAI score decreased from Week 0x to Week 46x, and thereafter was generally unchanged.

Overall, the effect of MLN0002 was sustained up to Week 94x.

Of 109 subjects who underwent proper AVA/neutralizing AVA test out of the "Full Analysis Set in open-label cohort," 4 subjects (3.7%) were AVA positive at least 1 time point in the induction phase, the maintenance phase or the open-label cohort. Of these, 3 subjects (2.8%) were persistently positive and 1 subject (0.9%) was transiently positive. Of these 4 AVA positive subjects, 3 subjects were positive for neutralizing antibodies.

Infusion reactions occurred in 1 subject of AVA positive. This subject received MLN0002 in the induction phase and placebo in the maintenance phase, then, experienced throat irritation during the open-label cohort. This event was mild in intensity, non-serious, considered related to the study drug and resolved. This event was not a TEAE leading to study drug discontinuation.

Paediatric subset: no subgroup analysis was planned or conducted for subjects aged 15 to 18 years.

Safety results

Induction phase

The incidence of TEAEs was 53.8% (42/78 subjects) in the placebo group, and 62.0% (49/79 subjects) in the MLN0002 group. The incidence of TEAEs in the MLN0002 group was comparable with that in the placebo group. The incidence of drug-related TEAEs was 14.1% (11/78 subjects) in the placebo group, and 12.7% (10/79 subjects) in the MLN0002 group, and no marked difference was observed between the treatment groups. Most of TEAEs were mild or moderate in intensity. Severe TEAEs were observed in 3 subjects (3.8%) in the placebo group and in 1 subject (1.3%) in the MLN0002 group.

The incidence of TEAEs leading to study drug discontinuation was 15.4% (12/78 subjects) in the placebo group, and 3.8% (3/79 subjects) in the MLN0002 group, and was higher in the placebo group than in the MLN0002 group. The incidence of serious TEAEs was 12.8% (10/78 subjects) in the placebo group, and 10.1% (8/79 subjects) in the MLN0002 group. Drug-related serious TEAEs were observed in 4 subjects (5.1%) in the placebo group, and 1 subject (1.3%) in the MLN0002 group. No deaths occurred.

TEAEs by SOC with an incidence of ≥10% in any treatment groups were, "Infections and infestations" (23.1% in the placebo group and 30.4% in the MLN0002 group, same applies hereafter), "Gastrointestinal disorders" (28.2% and 16.5%), "Skin and subcutaneous tissue disorders" (6.4% and 12.7%), and "General disorders and administration site condition" (3.8% and 10.1%).

Infusion reactions in the induction phase were observed in 1 subject (1.3%) in the placebo group and in 4 subjects (5.1%) in the MLN0002 group. All events occurred in only 1 subject each. These events were mild in intensity, and were resolved during the study period.

TEAEs in the "Infections and infestations" SOC were observed in 18 subjects (23.1%) in the placebo group, 24 subjects (30.4%) in the MLN0002 group. Of these TEAEs, the most frequently reported TEAE by PT was nasopharyngitis, that was reported in 11 subjects (14.1%) in the placebo group, and 11 subjects (13.9%) in the MLN0002 group.

The TEAEs in the "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" SOC were pyogenic granuloma (mild in intensity, nonserious, and related to study drug) in 1 subject in the placebo group and thyroid adenoma (moderate in intensity, serious, and related to study drug) in 1 subject in the MLN0002 group.

Maintenance phase

The incidence of TEAEs was 83.3% (10/12 subjects) in the placebo group, 75.0% (9/12 subjects) in the MLN0002 group, and 70.6% (12/17 subjects) in the placebo continuation group. The incidence of drug-related TEAEs was 8.3% (1/12 subjects) in the placebo group, 16.7% (2/12 subjects) in the MLN0002 group and no subjects in the placebo continuation group, and no marked difference was observed between the treatment groups. All of TEAEs were mild or moderate in intensity, and no severe TEAEs were observed in any treatment groups.

The incidence of TEAEs leading to study drug discontinuation was 33.3% (4/12 subjects) in the placebo group, 16.7% (2/12 subjects) in the MLN0002 group, and 11.8% (2/17 subjects) in the placebo continuation group.

The incidence of serious TEAEs was 33.3% (4/12 subjects) in the placebo group, 16.7% (2/12 subjects) in the MLN0002 group, and 11.8% (2/17 subjects) in the placebo continuation group. Drug-related serious TEAEs were observed in 1 subject in the MLN0002 group. No deaths occurred.

TEAEs by SOC with an incidence of ≥10% in any treatment groups were observed in 1 subject in the "Infections and infestations" (50.0%, 50.0%, and 52.9% in the placebo, MLN0002, and placebo continuation groups, respectively), "Gastrointestinal disorders" (41.7%, 33.3%, and 35.3%, respectively),"Skin and subcutaneous tissue disorders" (16.7%, 25.0%, and 5.9%, respectively),

"General disorders and administration site conditions" (8.3%, 8.3%, and 11.8%, respectively), and "Injury, poisoning and procedural complications" (0%, 16.7%, and 0%, respectively).

TEAEs by PT which occurred in at least 2 subjects in any treatment groups were nasopharyngitis (4, 4, and 4 subjects in the placebo, MLN0002, and placebo continuation groups, respectively), Crohn's disease (2, 1, and 3 subjects, respectively), and conjunctivitis (0, 0, and 2 subjects, respectively). TEAEs by PT which occurred in at least 2 subjects in the MLN0002 group was only nasopharyngitis. No marked difference was observed between the treatment groups in the maintenance phase.

Open-label cohort

Overview of TEAEs, Including Serious TEAEs (Safety Analysis Set in Open-Label Cohort)

	MLN0002 (N=134)	
	Events	Subjects
TEAEs	783	130(97.0)
Causality (a)		
Not Related	731	99(73.9)
Related (b)	52	31(23.1)
Intensity (c)		
Mild	587	41(30.6)
Moderate	169	67(50.0)
Severe	27	22(16.4)
Leading to Study Drug Discontinuation	47	43(32.1)
Serious TEAEs	104	70(52.2)
Causality (a)		
Not Related	84	53(39.6)
Related	20	17(12.7)
Leading to Study Drug Discontinuation	30	29(21.6)
Deaths	0	0(0.0)

Source: Section 15.1 Table 3.1.1o.
Note: Number of subjects (%).
(a) A subject is counted only once within a "related" category, if the subject has both drug-related and drug-unrelated TEAEs reported.
(b) Related: TEAEs of which causal relationship to study drug were "related."
(c) A subject is counted only once within the most severe category, if a subject has multiple TEAEs reported.

TEAEs by SOC with an incidence of ≥10% were "Gastrointestinal disorders" (69.4%),"Infections and infestations" (69.4%), "General disorders and administration site conditions"(23.1%), "Skin and subcutaneous tissue disorders" (20.1%), "Nervous system disorders"(17.2%), "Injury, poisoning and procedural complications" (17.2%), "Respiratory, thoracic and mediastinal disorders" (15.7%), "Investigations" (14.9%), "Blood and lymphatic system disorders"(14.2%), "Metabolism and nutrition disorders" (14.2%), "Hepatobiliary disorders"(12.7%), and "Musculoskeletal and connective tissue disorders" (12.7%).

TEAEs by PT with an incidence of ≥5% were Crohn's disease (42.5%), nasopharyngitis (41.0%), pyrexia (14.2%), influenza (11.9%), dental caries (11.2%), anaemia (9.7%), hepatic function abnormal (8.2%), nausea (8.2%), upper respiratory tract infection (7.5%), abdominal pain upper (6.7%), anal abscess (6.7%), headache (6.7%), insomnia (6.7%), back pain (6.0%), gastroenteritis (6.0%) and pharyngitis (5.2%).

The trend of TEAEs in the ”Safety Analysis Set in open-label cohort” was not markedly different from that in the “Safety Analysis Set in induction phase” or the “Safety Analysis Set in maintenance phase”.

Paediatric subjects

Three pediatric patients (15, 16, and 17 years old), experienced a serious TEAEs, as reported in the “Narratives of other Serious Adverse Events”. However, they were considered not treatment related by the investigator and the Applicant, as follows:

1): Japanese Male 15 years old.

<Aggravation of Crohn's disease>

Investigator’s comment:

The event is considered as symptomatic relapse due to lack of efficacy of the drugs for the primary disease and the study drug. Thus, the event is considered not causally related to the study drug. Since the event interfered with the patient's daily life, its intensity is moderate. Since the patient was hospitalized for bowel rest, close examination, and treatment, the event is reported as a serious adverse event. The event is considered not causally related to study procedures.

Applicant’s comment:

Crohn's disease is characterized by repeated recurrence/relapse and remission, and thus the event is considered part of the natural course of the primary disease.

<Abdominal pain>

Investigator’s comment:

The patient had an acute onset of abdominal pain after a marathon race, and he had similar episodes of exercise-induced abdominal pain in past. Thus, the event is considered not causally related to the study drug. Since the patient's status including hyperpnea interfered with his daily life, the intensity of the event is moderate. Since the patient was hospitalized for bed rest and observation, the event is reported as a serious adverse event. The event is considered not causally related to study procedures.

Applicant’s comment:

Crohn's disease is characterized by repeated recurrence/relapse and remission, and thus the event is considered part of the natural course of the primary disease.

2): Japanese Male 17 years old.

<Crohn's disease>

Investigator’s comment:

The patient experienced aggravation of his primary disease, and the event is considered not related to the study drug or study procedures.

Applicant’s comment:

Crohn’s disease is characterized by repeated recurrence/relapse and remission, and thus the event is considered part of the natural course of the primary disease.

3): Japanese Male 16 years old.

<Aggravation of Crohn's disease>

Investigator’s comment:

Since the patient's Crohn's disease worsened to the level exceeding his usual fluctuations, it was considered as an adverse event. The patient experienced similar episode prior to study participation, and

thus the event is considered not related to the study drug. The event is considered not causally related to study procedures.

Applicant's comment:

Crohn's disease is characterized by repeated recurrence/relapse and remission, and thus the event is considered part of the natural course of the primary disease.

<Aggravation of Crohn's disease>

Investigator's comment:

The event occurred after the dose increase of steroid used as a rescue medication for aggravation of Crohn's disease. The event is considered not related to the study drug.

Applicant's comment:

Crohn's disease is characterized by repeated recurrence/relapse and remission, and thus the event is considered part of the natural course of the primary disease.

No PMLs were observed in the open-label cohort. In the open-label cohort, positive Subjective PML checklist was observed in 4 subjects. Of these subjects, the 2 subjects also having positive Objective PML checklist were evaluated by the Independent Adjudication Committee for PML, but PML was ruled out.
There was no new safety signal reported in this study.

2.3.2. Discussion on clinical aspects

In order to comply with Article 46 of the Paediatric Regulation, the MAH submitted a final report(s) for Study MLN0002/CCT-001, a phase 3 study of vedolizumab 300 mg (powder for concentrate for solution for infusion) in Crohn's disease (CD) conducted in Japan. This study is not part of the vedolizumab Paediatric Investigational Plan (PIP) EMEA-000645-PIP01-09.

In this phase 3 program in Japan the age entry criteria was from 15 to 80 years old subjects.
Six paediatric subjects entered the study for the induction phase (1 randomized in the vedolizumab and 5 in the placebo arm). Two subjects in the placebo group had response in the induction phase and thus continued on placebo in the maintenance phase. The other 4 subjects (1 in vedolizumab and 3 in placebo) had no response in the induction phase. All 6 subjects continued into the open-label extension cohort.

An assessment of efficacy results for the whole study is out of the scope of this AR. Moreover, stratified data on pediatric patients have not been provided not allowing any efficacy evaluation of vedolizumab in this target population, which is the object of this assessment.

However, in the overall population results on both primary and secondary endpoints do not formally support efficacy, as only a limited numerical gain over placebo is seen.
The number of Japanese pediatric patients included in this Study is considered too low to add important efficacy information on the vedolizumab treatment in this patient population. Moreover, the lack of a subgroup analysis does not allow to draw firm conclusion. Therefore, the information provided are considered not informative and, as consequence, an update of the SmPC is at present not required.

Overall, from a **safety** point of view no new signal seems to be occurred in this study. Stratified safety data in the six pediatric patients have not been provided, therefore the vedolizumab safety profile in these very few Japanese pediatric patients remains unknown. Two SAEs were identified in 15-, 16-, and 17-year old patients from the Narratives of other Serious Adverse Events. They were both considered not to be related to study treatment by the investigators (however, lack of efficacy indicates relationship with study drug). Overall, no firm conclusion can be drawn regarding the safety profile in pediatric patients.

3. Rapporteur's overall conclusion and recommendation

In order to comply with Article 46 of the Paediatric Regulation, the MAH submitted a final report for Study MLN0002/CCT-001, a phase 3 study of vedolizumab 300 mg in CD conducted in Japan, not part of the vedolizumab PIP EMEA-000645-PIP01-09.
Overall, the very low number of Japanese pediatric patients included in this Study (1 randomized in the vedolizumab and 5 in the placebo arm) does not add efficacy information on the vedolizumab treatment in pediatric patient population and the lack of a subgroup analysis does not allow to draw firm conclusion. Moreover, stratified safety data in the six pediatric patients have not been provided, therefore the vedolizumab safety profile in these very few Japanese pediatric patients remains unknown. Two SAEs were identified in 15-, 16-, and 17-year old patients, but they were both considered not to be related to study treatment by the investigators (although one was lack of efficacy).
In conclusion, the information provided are considered not informative and, as consequence, an update of the SmPC is at present not required.

☒ Fulfilled:

No regulatory action required.