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Human Medicines Evaluation Division

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

Note

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

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1. Introduction

On 28/01/2019 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.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study MLN0002/CCT-101, a phase 3 study of vedolizumab 300 mg (powder for concentrate for solution for infusion) in ulcerative colitis (UC) conducted in Japan is a stand alone study.

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-101**, a phase 3 study of vedolizumab 300 mg (powder for concentrate for solution for infusion) in ulcerative colitis (UC) conducted in Japan. This study **is not** part of the vedolizumab Paediatric Investigational Plan (PIP) in UC and Crohn disease (CD), EMEA-000645-PIP01-09.
Study MLN0002/CCT-101 in UC is part of the phase 3 clinical program to support registration in Japan (Study MLN0002/CCT-101 in UC and Study MLN0002/CCT-001 in CD) and including subjects from 15 to 80 years old.

2.3.2. Clinical study

Study MLN0002/CCT-101

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 with moderate or severe ulcerative colitis.

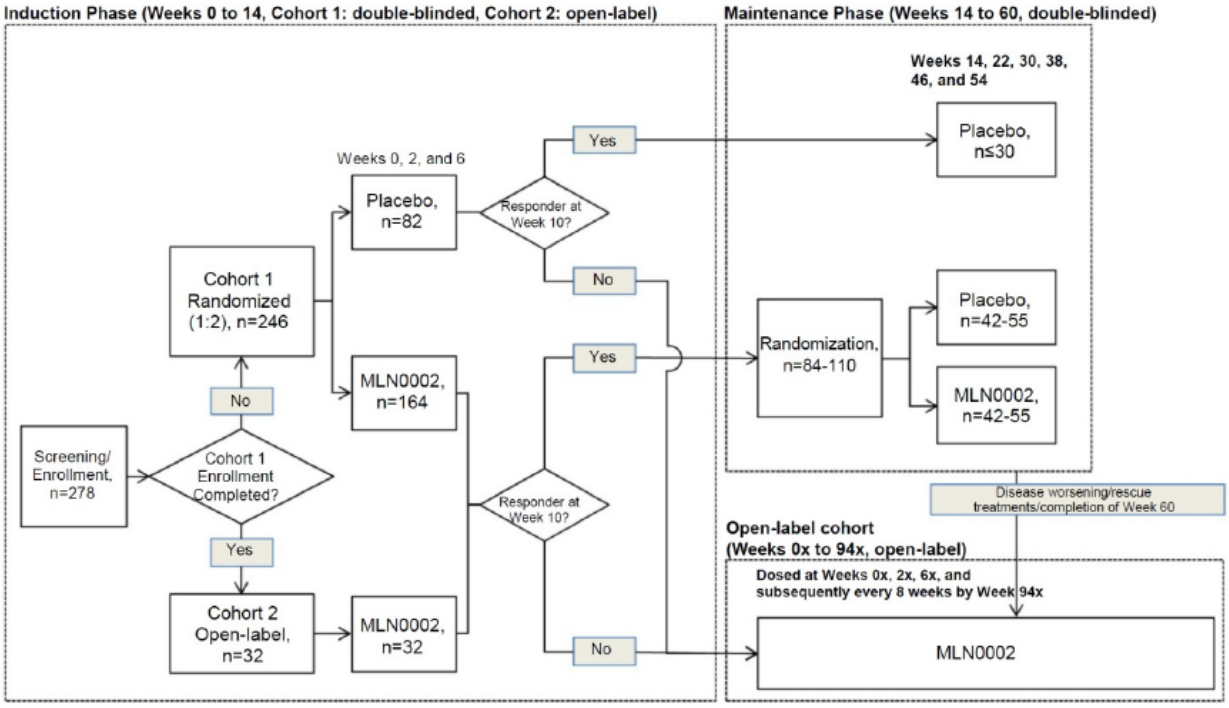
Methods

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 screening, induction, and maintenance phases, and an open-label cohort. Subjects enrolled into the induction phase that consisted of 2 cohorts and enrolment into Cohort 2 started only after completion of enrolment into Cohort 1. Subjects in Cohort 1 were randomized 1:2 in a double-blinded manner to receive placebo or vedolizumab 300 mg at Weeks 0, 2, and 6. Subjects in Cohort 2 received vedolizumab 300 mg at Weeks 0, 2, and 6 in an unblinded manner. Subjects not showing a clinical response to the study drug at Week 10 were allowed to be enrolled into the openlabel cohort. In addition, subjects who experienced disease worsening or received rescue treatments during the maintenance phase, or those who completed Week 60 of the maintenance phase were also allowed to be enrolled into the open-label cohort.



Study population /Sample size

Study MLN0002/CCT-101 enrolled a total of 292 subjects in the induction phase, of these only 4 were aged 15 to 18 years at entry (2 were 16 years old and 2 were 17 years old): 2 were randomized in vedolizumab and 2 in placebo arm. Subjects enrolled in the maintenance phase were 109 and subjects enrolled in the open-label cohort were 259.

Treatments

Subjects in Cohort 1 were randomized 1:2 in a double-blinded manner to receive placebo or vedolizumab 300 mg at Weeks 0, 2, and 6. Subjects in Cohort 2 received vedolizumab 300 mg at Weeks 0, 2, and 6 in an unblinded manner.

Outcomes/endpoints

The primary efficacy evaluation in the **induction phase** (clinical response) was performed at Week 10. The following 2 conditions had to be fulfilled for clinical response: a) decrease of the complete

Mayo score by ≥3 points and by ≥30% from baseline, and b) decrease of the subscore of rectal bleeding by ≥1 point from baseline, or ≥1 in the subscore of rectal bleeding. Subjects showing clinical 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 placebo at Weeks 14, 22, 30, 38, 46, and 54 in a double-blinded manner and subjects who received vedolizumab in the induction phase were randomized 1:1 in a double-blinded manner to receive placebo or vedolizumab 300 mg at Weeks 14, 22, 30, 38, 46, and 54.

The primary efficacy evaluation in the **maintenance phase** (clinical remission, defined as ≤2 in the complete Mayo score and ≤1 in all subscores) was performed at Week 60. Subjects who completed Week 60 of the maintenance phase, subjects not showing a clinical response at Week 10, and subjects who experienced disease worsening or received rescue treatments during the maintenance phase could enroll into the open-label cohort. In the openlabel cohort subjects received vedolizumab 300 mg at Weeks 0x, 2x, 6x, and then every 8 weeks thereafter for 46 weeks (minimum) to 94 weeks (maximum).

Statistical Methods

Induction Phase

Primary Endpoint

–evaluated in the Full Analysis Set."

-superiority of MLN0002 over the placebo on clinical response at Week 10.

-no adjustments for multiplicity were made between the analyses of the two phases setting the significance level at 5% each.

Secondary Endpoints

The superiority of MLN0002 over the placebo on clinical remission at Week 10 in the primary analysis of the induction phase was demonstrated when a statistically significant difference was observed in both the clinical response at Week 10 and clinical remission at Week 10.

For the other efficacy analysis, mucosal healing at Week 10 was summarized in the same manner as those in the primary analysis in the induction phase.

Results

Recruitment / Number analysed

A total of 292 subjects entered into the induction phase at 86 sites in Japan; 246 subjects entered into Cohort 1 and 46 subjects entered into Cohort 2. The 246 subjects who entered into Cohort 1 were randomized to the placebo group (82 subjects) or the MLN0002 group (164 subjects), and all subjects received the placebo or MLN0002 in a double-blinded manner. The 46 subjects who entered into Cohort 2 all received open-label MLN0002. Of the 292 subjects who received study drug in the induction phase, 269 subjects (92.1%) completed the planned infusions in the induction phase and 23 subjects (7.9%) discontinued the study drug. The reasons for study drug discontinuation were PTE/AE in 17 subjects, lack of efficacy in 5 subjects, and major protocol deviation in 1 subject. By treatment group, the proportion of subjects who discontinued the study drug was higher in the Cohort 2 MLN0002 group than in the Cohort 1 placebo and MLN0002 groups

Baseline data

In overall subjects who entered in the induction phase, the proportion of male subjects was 61.6%. The overall mean age was 42.8 years, and 26 subjects (8.9%) were ≥65 years. The mean duration of UC was 7.91 years, and the mean complete Mayo score at Week 0 was 8.3. The study was projected to have subjects without prior TNFα antagonist use accounting for 50% of the planed sample size. As a result, 48.6% (142/292) of subjects who entered in the induction phase had no prior TNFα antagonist use. No clear differences were observed between treatment groups in demographic and other baseline characteristics of subjects who entered in the induction phase.

Efficacy results

Primary Efficacy Endpoint, Induction

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

	Placebo (N=82)	MLN0002 (N=164)
Clinical Response at Week 10 (N [%])	27 (32.9)	65 (39.6)
95% CI	(22.942, 44.186)	(32.093, 47.557)
Difference From Placebo (a)		6.7
95% CI		(-5.922, 19.337)
Adjusted Odds Ratio (b)		1.37
95% CI		(0.779, 2.399)
p-value		0.2722

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).

Examination of Subgroups for Clinical Response at Week 10 (Full Analysis Set in Induction Phase)

( ): Percent

Variable / <Item> / Category			Treatment	Response	Not Response	Total	95% CI Lower	95% CI Upper
Clinical Response at Week 10	<Age (years)>	Min<= - <=34	MLN0002	23 (41.1)	33 (58.9)	56	28.097	55.024
			Placebo	8 (29.6)	19 (70.4)	27	13.753	50.181
		35<= - <=Max	MLN0002	42 (38.9)	66 (61.1)	108	29.656	48.747
			Placebo	19 (34.5)	36 (65.5)	55	22.237	48.581
	<Age (years)>	Min<= - <=64	MLN0002	61 (40.4)	90 (59.6)	151	32.499	48.680
			Placebo	25 (34.7)	47 (65.3)	72	23.881	46.863
		65<= - <=Max	MLN0002	4 (30.8)	9 (69.2)	13	9.092	61.426
			Placebo	2 (20.0)	8 (80.0)	10	2.521	55.610

Secondary Efficacy Endpoints, Induction

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

	Placebo (N=82)	MLN0002 (N=164)
Clinical Remission at Week 10 (N [%])	10 (12.2)	30 (18.3)
95% CI	(6.006, 21.286)	(12.695, 25.072)
Difference From Placebo (a)		6.1
95% CI		(-3.131, 15.326)
Adjusted Odds Ratio (b)		1.66
95% CI		(0.762, 3.596)
p-value		0.1980
Adjusted Risk Difference (c)		6.4
95% CI		(-2.803, 15.507)

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) MLN0002 group - placebo group. CMH estimates and test with stratification according to prior TNFα antagonist use (yes/no).

Mucosal Healing

Mucosal Healing at Week 10 (Full Analysis Set in Induction Phase)

	Placebo (N=82)	MLN0002 (N=164)
Mucosal Healing at Week 10 (N [%])	25 (30.5)	60 (36.6)
95% CI	(20.796, 41.638)	(29.213, 44.452)
Difference From Placebo (a)		6.1
95% CI		(-6.297, 18.492)
Adjusted Odds Ratio (b)		1.33
95% CI		(0.755, 2.356)
p-value		0.3168
Adjusted Risk Difference (c)		6.4
95% CI		(-5.979, 18.745)

Source: Section 15.1 Tables 2.2.7.1, 2.2.7.2, 2.2.9.1 and 2.2.9.2.
Note: Missing data is treated as non-healing.
(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) MLN0002 group - placebo group. CMH estimates and test with stratification according to prior TNFα antagonist use (yes/no).

Paediatric subset

4 subjects were aged 15 to 18 years at entry (2 were 16 years old and 2 were 17 years old): 2 in vedolizumab and 2 in placebo for UC in induction phase. All of these subjects had no response in the induction phase and moved to 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:

The total of 3 subjects (2.0%) in the Cohort 1 MLN0002 group and in the Cohort 2 MLN0002 group were AVA positive at any time point during the induction phase. All subjects were assessed as AVA positive at only 1 time point. One subject was AVA positive at Week 10, and other 2 subjects were AVA positive at the time point 16 weeks after the last administration of MLN0002. All subjects with AVA positive were also positive for neutralizing antibody.

Maintenance Phase Efficacy Results:

Primary Efficacy Endpoint

Clinical remission at Week 60 was 31.0% and 56.1% in the placebo and MLN0002 groups, respectively. The difference (95% two-sided CI) between the MLN0002 and placebo groups in clinical remission at Week 60 was 25.1% (4.500, 45.790) with the adjusted odds ratio of 2.88 (1.168, 7.108). Therefore, the MLN0002 group was superior to the placebo group (p=0.0210). Regardless of prior TNF α antagonist use, the MLN0002 group exceeded the placebo group in clinical remission at Week 60.

Paediatric subset No pediatric patients entered in the maintenance phase.

Open-Label Cohort

Of the 292 subjects who received at least 1 dose of study drug in the induction phase or maintenance phase, 259 subjects (88.7%) entered into the open-label cohort at 84 sites in Japan. All the 259 subjects received MLN0002 in the open-label cohort. A total of 71 subjects (27.4%) discontinued the study drug in the open-label cohort. The reasons for study drug discontinuation were lack of efficacy in

44 subjects, PTE/AE in 19 subjects, voluntary withdrawal in 7 subjects, and major protocol deviation in 1 subject.

All 259 subjects who entered in the open-label cohort received at least one dose of the 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 four subjects aged 15 to 18 years moved to the open-label extension cohort.

In general, efficacy results of MLN0002 in the open-label cohort was favorable when MLN0002 was administered 300 mg IV at Weeks 0x (enrollment day to the open-label cohort), 2x, 6x, and every 8 weeks thereafter to Japanese subjects with moderate or severe UC.

Eleven subjects (11/194 subjects, 5.7%) were AVA positive at any time point in the open-label cohort. Of these, 3 subjects (3/194 subjects, 1.5%) were persistently positive and 8 subjects (8/194 subjects, 4.1%) were transiently positive. Of these 11 AVA positive subjects, 7 subjects were positive for neutralizing antibodies. No infusion reactions (based on the investigator assessment recorded on CRF) occurred in the AVA positive subjects.

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 52.4% (43/82 subjects) in the Cohort 1 placebo group, 50.0% (82/164 subjects) in the Cohort 1 MLN0002 group, and 71.7% (33/46 subjects) in the Cohort 2 MLN0002 group. The incidence of **TEAEs** in the Cohort 1 MLN0002 group was comparable with that in the Cohort 1 placebo group. The incidence of TEAEs in the Cohort 2 MLN0002 group was higher than that in the Cohort 1 placebo and MLN0002 groups. On the other hand, the incidence of **drug-related TEAEs** was 14.6% (12/82 subjects) in the Cohort 1 placebo group, 10.4% (17/164 subjects) in the Cohort 1 MLN0002 group, and 15.2% (7/46 subjects) in the Cohort 2 MLN0002 group, and no clear difference was observed between the treatment groups. Most of TEAEs were mild or moderate in intensity. One severe TEAE was observed in 1 subject in the Cohort 1 placebo group and 7 severe TEAEs were observed in 5 subjects in the combined MLN0002 group. Most of TEAEs were mild or moderate in intensity.

The incidence of **TEAEs leading to study drug discontinuation** was 2.4% (2/82 subjects) in the Cohort 1 placebo group, 4.9% (8/164 subjects) in the Cohort 1 MLN0002 group, and 13.0% (6/46 subjects) in the Cohort 2 MLN0002 group. The incidence of **serious TEAEs** was 4.9% (4/82 subjects) in the Cohort 1 placebo group, 6.1% (10/164 subjects) in the Cohort 1 MLN0002 group, and 13.0% (6/46 subjects) in the Cohort 2 MLN0002 group. Drug-related serious TEAEs were observed in 2 subjects in the Cohort 1 placebo group, 1 subject in the Cohort 1 MLN0002 group, and 1 subject in the Cohort 2 MLN0002 group. No deaths occurred in the induction phase.

TEAEs by SOC with an incidence of ≥10% in any treatment groups were "infections and infestations" (22.0%, 22.0%, and 39.1% in the Cohort 1 placebo, Cohort 1 MLN0002, and Cohort 2 MLN0002 groups, respectively), "gastrointestinal disorders" (13.4%, 13.4%, and 19.6%, respectively), respiratory, thoracic, and mediastinal disorders" (7.3%, 7.3%, and 10.9%, respectively), and "metabolism and nutrition disorders" (3.7%, 1.2%, and 10.9%, respectively).

Infusion reactions in the induction phase were observed in 2 subjects (2.4%) in the Cohort 1 placebo group and in 5 subjects (3.0%) in the Cohort 1 MLN0002 group, and none was observed in the Cohort 2 MLN0002 group. Infections were observed in 18 subjects (22.0%) in the Cohort 1 placebo group, 36 subjects (22.0%) in the Cohort 1 MLN0002 group, and 18 subjects (39.1%) in the Cohort 2 MLN0002 group. The TEAEs in the neoplasms benign, malignant, and unspecified (including cysts and polyps)

SOC were observed in 1 subject each in the Cohort 1 MLN0002 group and in the Cohort 2 MLN0002 group.

One subject in the Cohort 1 MLN0002 group had a positive finding (visual field disorder) on the Subjective PML checklist at Week 6 but she had no positive findings on the Objective PML checklist. There were no other subjects with positive findings on the Subjective PML checklist. No PMLs were observed.

Maintenance phase

No paediatric patients entered in the maintenance phase.

Open-label cohort

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

	MLN0002 (N=259)	
	Events	Subjects
TEAEs	1360	241 (93.1)
Causality (a)		
Not Related	1250	191 (73.7)
Related (b)	110	50 (19.3)
Intensity (c)		
Mild	1189	139 (53.7)
Moderate	157	88 (34.0)
Severe	14	14 (5.4)
Leading to Study Drug Discontinuation	27	23 (8.9)
Serious TEAEs	62	48 (18.5)
Causality (a)		
Not Related	51	38 (14.7)
Related	11	10 (3.9)
Leading to Study Drug Discontinuation	15	14 (5.4)
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 "infections and infestations" (73.7%), "gastrointestinal disorders" (44.8%), "musculoskeletal and connective tissue disorders" (25.9%), "skin and subcutaneous tissue disorders" (23.2%), , "respiratory, thoracic and mediastinal disorders" (18.5%), "nervous system disorders" (17.4%), "general disorders and administration site conditions" (17.0%), and "eye disorders" (12.0%).

TEAEs by PT with an incidence of ≥5% were viral upper respiratory tract infection (50.2%), colitis ulcerative (16.2%), influenza (9.3%), headache (8.9%), back pain (8.5%), upper respiratory tract infection (7.7%), pyrexia (6.6%), pharyngitis (6.2%), gastroenteritis (5.4%), arthralgia (5.4%), upper respiratory tract inflammation (5.4%), stomatitis (5.4%), and eczema (5.0%). The trend of TEAEs in the "Safety Analysis Set in open-label cohort" was not clearly different from that in the "Safety Analysis Set in induction phase" or the "Safety Analysis Set in maintenance phase."

Paediatric subjects

Two pediatric patients (16 and 17 years old) in open-label cohort, 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 follow:

Subject: Japanese Male 16 years old.

Investigator's comment: It is considered that the patient experienced upper respiratory tract infection. Since this event developed after the discontinuation of the study drug, there is no causal relation between the event and the study drug. The severity of the event is mild. Since the patient was ***hospitalized for further examination*** *and treatment, the event is reported as a serious one. The event is assessed as resolved, then the patient was discharged from the hospital with improved general condition. Causal relation to the study procedure: not related*

Subject: Japanese Male 17 years old.

Investigator's comment: The patient was withdrawn from the study on 18 February 2015 because of **lack of efficacy***. Although a workup performed on 19 February 2015 showed no aggravation of the ulcerative colitis which the patient had been suffering from since before the start of the study drug, salvage treatment with total parenteral nutrition (TPN) and ciclosporin was given. However, the patient experienced adverse reactions to ciclosporin, which led to discontinuation. The medical therapy was determined to be ineffective, and surgery was considered as an option. The patient was then transferred to the surgery dept, then the event was determined to be a serious adverse event of "aggravation of ulcerative colitis". It is lack of efficacy of the study drug which was seen in this case, therefore the event is assessed as not causally related to the study drug.*

No PMLs were observed in the open-label cohort. Positive findings on the Subjective PML checklist were observed in 6 subjects in the open-label cohort. Of these subjects, 2 subjects also having positive findings on the 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.

2.3.3. 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-101, a phase 3 study of vedolizumab 300 mg (powder for concentrate for solution for infusion) in ulcerative colitis (UC) conducted in Japan. This study is not part of the vedolizumab Paediatic Investigational Plan (PIP) in UC and Crohns disease (CD), EMEA-000645-PIP01-09.
Study MLN0002/CCT-101 in UC is part of the phase 3 clinical program to support registration in Japan (Study MLN0002/CCT-101 in UC and Study MLN0002/CCT-001 in CD).
In this phase 3 program in Japan the age entry criteria was from 15 to 80 years old subjects.
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.

Four paediatric subjects entered the study (2 randomized in the vedolizumab and 2 in the placebo arm). All of these subjects had no response in the induction phase and moved to the open-label extension cohort. Therefore efficacy is not supported. Only 4 subjects aged 15 to 18 years at entry (2 were 16 years old and 2 were 17 years old) were included in the Study (2 in vedolizumab and 2 in placebo for UC in induction phase). All of these subjects had no response in the induction phase and moved to the open-label extension cohort.

In the overall population at induction phase results coming from both primary and secondary endpoints didn't support efficacy.
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 have occurred in this study. Stratified safety data in the four 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 a 16 years old and a 17 years old (one case of upper respiratory tract infection and one of aggravation of ulcerative colitis, respectively) from the Narratives of other Serious Adverse Events. However, they were both considered not to be related to study treatment by the investigators. Therefore, 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-101, a phase 3 study of vedolizumab 300 mg in ulcerative colitis (UC) conducted in Japan. Overall, the very low number of Japanese pediatric patients included in this Study (2 randomized in the vedolizumab and 2 in the placebo arm) does not add important 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 four 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 a 16- and 17-years old patients (one case of upper respiratory tract infection and one of aggravation of ulcerative colitis, respectively), but they were both considered not to be related to study treatment by the investigators.

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.