Amsterdam, 11 December 2025
EMADOC-1700519818-2408036
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Entyvio

International non-proprietary name: Vedolizumab

Procedure no.: EMA/PAM/0000291233

Note

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

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Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	22 September 2025	22 September 2025
☐	CHMP comments	6 October 2025	n/a
☐	Updated CHMP Rapporteur AR	9 October 2025	n/a
☐	CHMP outcome - RSI	16 October 2025	16 October 2025
☐	Submission of MAH responses	11 November 2025	11 November 2025
☐	Re-start of procedure	12 November 2025	12 November 2025
☐	CHMP Rapporteur AR	26 November 2025	26 November 2025
☐	CHMP comments	01 December 2025	n/a
☐	Updated CHMP Rapporteur AR	04 December 2025	n/a
☒	CHMP outcome	11 December 2025	n/a

Table of contents

1. Introduction

On 1 August 2025, the MAH submitted a completed study for Entyvio including also pediatric patients, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This was a special drug use-results surveillance study of Entyvio for IV infusion 300 mg in ulcerative colitis (UC) that was conducted as a post approval commitment following approval in Japan for use in adult population to evaluate the long-term safety and effectiveness of vedolizumab IV in UC participants in the routine clinical practice setting. The study could include participants under 18 years of age (It is noted that participants under approximately 15 years of age are considered paediatric according to Japan's labelling guidance).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study Vedolizumab-5033 is not part of a PIP.

Paediatric data with vedolizumab is being generated in a dedicated paediatric program in line with an agreed PIP and the Entyvio Product Information will be updated as appropriate when such data become available. The PIP is in place for vedolizumab in ulcerative colitis (UC) and Crohn's disease (CD) (EMEA-000645-PIP01-09). A waiver is granted for the paediatric population from birth to <2 years of age and the PIP applies to the paediatric population subsets including children aged 2 to <18 years.

No changes to the currently approved Entyvio Product Information are proposed by MAH and no variation is planned as a result of this study. A line listing of the concerned study is annexed.

2.2. Clinical aspects

2.2.1. Introduction

The MAH submitted the final report for the study *Entyvio for Intravenous Infusion 300 mg Special Drug Use-Results Surveillance Study "Ulcerative Colitis",* a post approval observational prospective cohort study in Japan (following approval in adult population) in participants with moderate or severe active UC.

2.2.2. Clinical study

Entyvio for Intravenous Infusion 300 mg Special Drug Use-Results Surveillance Study "Ulcerative Colitis" (Vedolizumab -5033)

Description

Vedolizumab-5033 is a special drug use-results surveillance study of Entyvio for IV infusion 300 mg in UC that was conducted as a post approval commitment following approval in Japan for use in adult population to evaluate the long-term safety and effectiveness of vedolizumab IV **in UC participants in the routine clinical practice setting**. This study **could include participants under 18 years of age**.

Methods

The "central registration system" using the web-based electronic data Capture (EDC) system was used. The investigator or a person appointed by the investigator entered participant registration information into the EDC system and the investigator electronically signed it within 14 days after the start of the treatment with Entyvio. Data on stool frequency and bleeding as part of QoL and Mayo scores were collected via the participant diary (Medidata s electronic patient-reported outcome [ePRO]) in principle.

Study participants

The target population included participants with moderately to severely active UC and who have had an inadequate response to conventional therapy. The study had no age restrictions as per the protocol. Participants for whom Entyvio was contraindicated were excluded.

Treatments

The usual adult dose in Japan is 300 mg of vedolizumab per administration via intravenous infusion. After the initial dose, vedolizumab was administered at Week 2 and Week 6 and then every 8 weeks thereafter until Week 54.

Objective(s)

To examine and evaluate the safety and effectiveness of Entyvio in UC participants for long-term and actual use during the routine clinical setting in Japan.

Outcomes/endpoints

The study collected effectiveness and safety information including complete Mayo Score, Short Inflammatory Bowel Disease Questionnaire (SIBDQ), AEs, concomitant medications, surgical procedures, and laboratory parameters.

Effectiveness analyses were conducted stratified by anti-TNFα use. The effectiveness was analyzed based on response and treatment persistence, complete Mayo score, partial Mayo score, SIBDQ score, and SIBDQ subscores.

Sample size

The planned sample size was 1000 participants with ≥300 participants anti-TNFα antibody exposed and ≥300 participants anti-TNFα antibody naïve.

Randomisation and blinding (masking)

Statistical Methods

The end of induction period analyses included the participants who received 3 doses of vedolizumab (Week 0, Week 2, and Week 6) or who discontinued treatment before 4th dose. For participants who received the 4th dose (Week 14), data collected immediately before the 4th dose administration was used. For participants who did not receive the 4th dose, the data closest to Day 99, which was 8 weeks after the Week 6 dose (=14 x 7+1), was used, with the window +28 days after Week 14 (Day 126).

For Week 52 (maintenance period, the analysis set was limited to participants who received the 4th dose (those who transitioned to the maintenance phase). Participants who discontinued before the 4th dose were included in the end of induction period analysis (after the 3rd dose analyses), while those who discontinued after the 4th dose were included in the Week 52 analysis. Therefore, data at the time of discontinuation was counted either for end of induction period analyses or the Week 52 analyses.

Results

Participant flow and recruitment

The study period was from February 2019 to October 2024 and participant enrolment was from February 2019 to June 2023.

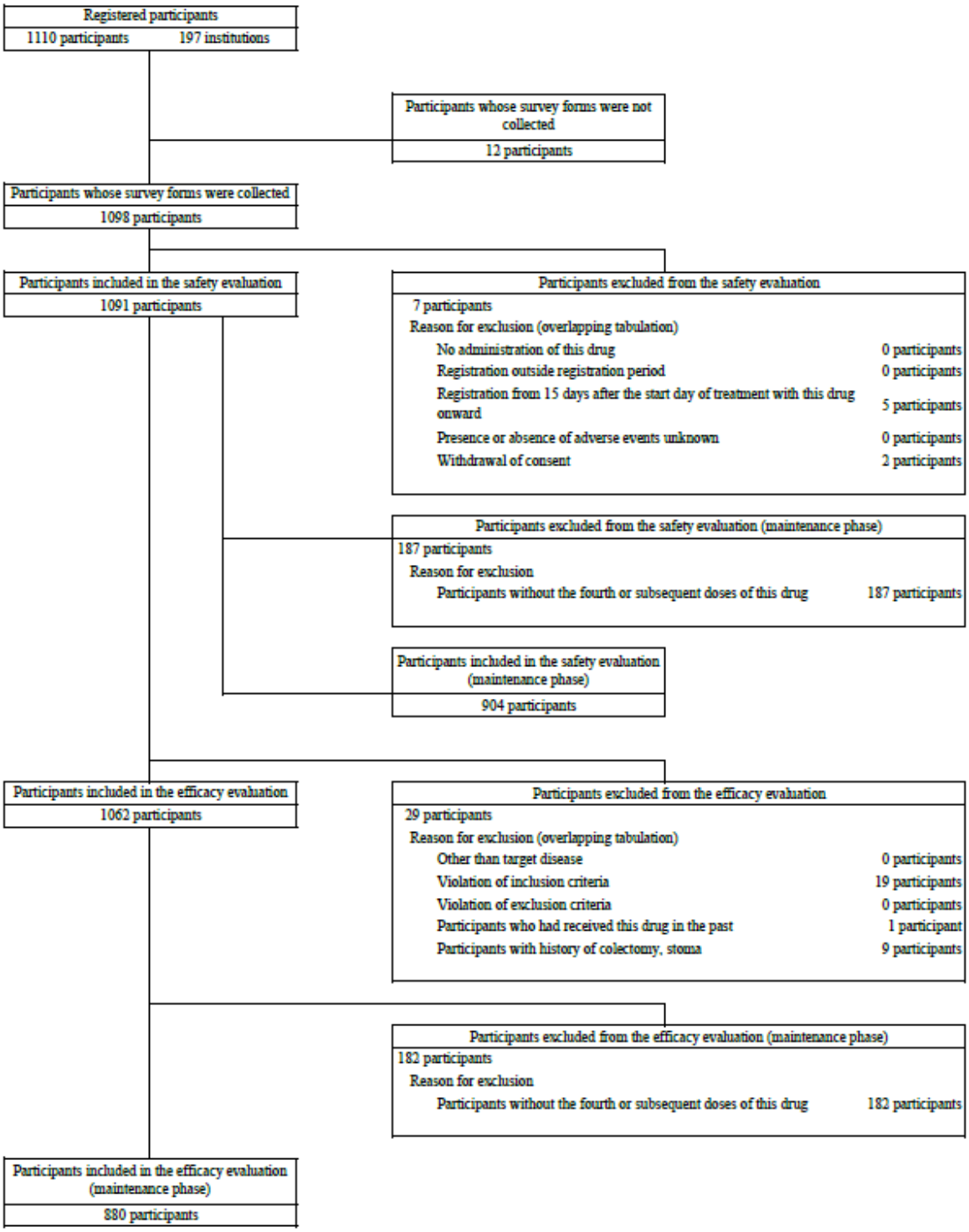

Figure 2.1 Disposition of participants

Among 1110 registered participants, case report forms were collected from 1098 and 1091 were included in the **SAF** (safety analysis set). Overall, 904 participants were included in **SAF-M** (safety maintenance phase set) and 187 participants were excluded as they did not receive the 4th or subsequent doses.

Of the 1091 participants in the SAF, 1062 were included in the efficacy analysis, excluding 19 participants for violation of inclusion criteria, 9 participants with history of colectomy or stoma, and 1 participant who had received vedolizumab in the past. Overall, 880 participants were included in the effectiveness evaluation (maintenance phase) and 182 participants were excluded as they did not receive the 4th or subsequent doses.

A total of 1090 participants received 1st dose of 300 mg vedolizumab and 1 participant received 1st dose of 150 mg vedolizumab. The second dose of 300 mg vedolizumab was received by 1068 participants. The third dose of 300 mg vedolizumab was received by 1010 participants and 75 mg vedolizumab by 1 participant. A total of 904 participants received a **4th** dose of 300 mg vedolizumab, 820 participants received a **5th** dose of 300 mg vedolizumab, 766 participants received a **6th** dose of 300 mg vedolizumab, 734 participants received a **7th** dose of 300 mg vedolizumab, 697 participants received a **8th** dose of 300 mg vedolizumab, and 665 participants received a **9th** dose of 300 mg vedolizumab.

Baseline data

Table 3.1 Participant background

Participants included in the safety evaluation, participants included in the safety evaluation (maintenance phase)

Item		Participants included in the safety evaluation		Participants included in the safety evaluation (maintenance phase)	
		Number of participants (%)		Number of participants (%)	
		1091		904	
Sex	Male	621	(56.9)	514	(56.9)
	Female	470	(43.1)	390	(43.1)
Age (years)	Number of participants	1091		904	
	Mean	44.3		43.8	
	Standard deviation	17.45		17.37	
	Minimum	12		12	
	First quartile	30.0		29.0	
	Median	44.0		43.0	
	Third quartile	56.0		56.0	
	Maximum	94		90	
	Min<= - <35	367	(33.6)	316	(35.0)
	35<= - <=Max	724	(66.4)	588	(65.0)
	Unknown	0	(0.0)	0	(0.0)
	Min<= - <18	34	(3.1)	31	(3.4)
	18<= - <65	892	(81.8)	741	(82.0)
	65<= - <=Max	165	(15.1)	132	(14.6)
	Unknown	0	(0.0)	0	(0.0)
	Min<= - <15	7	(0.6)	7	(0.8)
	15<= - <65	919	(84.2)	765	(84.6)
	65<= - <=Max	165	(15.1)	132	(14.6)
	Unknown	0	(0.0)	0	(0.0)
Disease duration (years)	Number of participants	1025		858	
	Mean	9.3		9.6	
	Standard deviation	8.50		8.51	
	Minimum	1		1	
	First quartile	3.0		3.0	
	Median	6.0		7.0	
	Third quartile	13.0		13.0	
	Maximum	55		55	
	Min<= - <1	0	(0.0)	0	(0.0)
	1<= - <5	390	(35.7)	310	(34.3)
	5<= - <10	263	(24.1)	222	(24.6)
	10<= - <=Max	372	(34.1)	326	(36.1)
Presence or absence of medical history	No	771	(70.7)	644	(71.2)
	Yes	308	(28.2)	253	(28.0)
	Unknown	12	(1.1)	7	(0.8)
Presence or absence of complications	No	709	(65.0)	589	(65.2)
	Yes	382	(35.0)	315	(34.8)
Severity of UC	Moderate	1052	(96.4)	876	(96.9)
	Severe	39	(3.6)	28	(3.1)
Range of UC lesions	Pancolitis	781	(71.6)	644	(71.2)
	Left-sided colitis	267	(24.5)	223	(24.7)
	Proctitis	36	(3.3)	32	(3.5)
	Right-sided or segmental colitis	7	(0.6)	5	(0.6)
Familial history	No	911	(83.5)	762	(84.3)
	Yes	52	(4.8)	45	(5.0)
	Unknown	128	(11.7)	97	(10.7)
Relationship in familial history (overlapping tabulation)	Parent	21	(40.4)	20	(44.4)
	Child	8	(15.4)	7	(15.6)
	Grandparent	1	(1.9)	1	(2.2)
	Sibling	24	(46.2)	19	(42.2)
	Grandchild	0	(0.0)	0	(0.0)
History of tuberculosis infection	No	1037	(95.1)	864	(95.6)
	Yes	9	(0.8)	8	(0.9)
	Unknown	45	(4.1)	32	(3.5)

Participants included in the safety evaluation, participants included in the safety evaluation (maintenance phase)

Item			Participants included in the safety evaluation		Participants included in the safety evaluation (maintenance phase)	
			Number of participants (%)		Number of participants (%)	
			1091		904	
Steroid resistance	No		854	(78.3)	715	(79.1)
	Yes		174	(15.9)	137	(15.2)
	Unknown		63	(5.8)	52	(5.8)
Steroid dependence	No		417	(38.2)	354	(39.2)
	Yes		612	(56.1)	499	(55.2)
	Unknown		62	(5.7)	51	(5.6)
Steroid intolerance	No		994	(91.1)	824	(91.2)
	Yes		32	(2.9)	27	(3.0)
	Unknown		65	(6.0)	53	(5.9)
History of previous therapies for UC other than this drug within 3 months before the start of treatment with this drug (excluding anti-TNFα antibody drugs)	No		33	(3.0)	25	(2.8)
	Yes		1058	(97.0)	879	(97.2)
	Unknown		0	(0.0)	0	(0.0)
History of treatment with anti-TNFα antibody	No		750	(68.7)	627	(69.4)
	Yes		341	(31.3)	277	(30.6)
Details of history of treatment with anti-TNFα antibody (overlapping tabulation)	History of treatment with adalimumab	No	202	(59.2)	164	(59.2)
		Yes	139	(40.8)	113	(40.8)
	History of treatment with infliximab	No	123	(36.1)	97	(35.0)
		Yes	218	(63.9)	180	(65.0)
	History of treatment with golimumab	No	225	(66.0)	179	(64.6)
		Yes	116	(34.0)	98	(35.4)
Breakdown of history of treatment with adalimumab Note: Only when "Yes" for history of treatment with adalimumab	Primary failure		45	(32.4)	36	(31.9)
	Secondary failure		66	(47.5)	57	(50.4)
	Intolerance		19	(13.7)	13	(11.5)
	Discontinuation due to efficacy/remission		6	(4.3)	4	(3.5)
	Other		3	(2.2)	3	(2.7)
Breakdown of history of treatment with infliximab Note: Only when "Yes" for history of treatment with infliximab	Primary failure		71	(32.6)	56	(31.1)
	Secondary failure		83	(38.1)	73	(40.6)
	Intolerance		42	(19.3)	34	(18.9)
	Discontinuation due to efficacy/remission		12	(5.5)	10	(5.6)
	Other		9	(4.1)	7	(3.9)
Breakdown of history of treatment with golimumab Note: Only when "Yes" for history of treatment with golimumab	Primary failure		46	(39.7)	40	(40.8)
	Secondary failure		59	(50.9)	52	(53.1)
	Intolerance		6	(5.2)	3	(3.1)
	Discontinuation due to efficacy/remission		3	(2.6)	3	(3.1)
	Other		2	(1.7)	0	(0.0)

Of the 1091 participants included in the **SAF**, 56.9% were male and 43.1% were female. The proportion of participants aged <18 years was 3.1% (34 participants). This analysis set had 341 anti-TNFα exposed and 750 anti-TNFα naïve participants.

Of the 904 participants included in the **SAF-M**, 56.9% (514 participants) were male and 43.1% (390 participants) were female. The participants aged <18 years were 31. This analysis set had 277 anti-TNFα exposed and 627 anti-TNFα naïve participants.

The mean (SD) age of participants was 44.3 (17.45) years. The proportion of participants aged <15 years was 0.6%, aged <18 years was 3.1%, aged ≤35 years was 33.6%, aged ≥35 years was 66.4%, aged ≥18 to <65 years was 81.8%, and aged ≥65 years was 15.1%. A total of **34 participants (3.1%)** enrolled in the study were **aged 12 to <18 years** at enrolment (of which 7 were aged 12 to <15 years, that is locally considered paediatric participants).

The mean (SD) duration of disease was 9.3 (8.50) years. The duration was ≥1 to <5 years in 35.7%, ≥5 to <10 years in 24.1%, and ≥10 years in 34.1% participants. In the safety population 28.2% participants had a medical history and 35.0% of participants had complications.

UC was moderate in 96.4% participants and severe in 3.6% participants, and the range of UC lesions corresponded to pancolitis in 71.6% participants, left-sided colitis in 24.5% participants.

Steroid resistance was present in 15.9% participants, steroid dependence was present in 56.1% participants, and steroid intolerance was present in 2.9% participants. A history of anti-TNFα antibody treatment was present in 31.3% participants.

Common previous diseases were asthma in 1.5% participants and herpes zoster in 1.1% participants.

Common complications were hypertension in 6.9% participants, osteoporosis in 4.3% participants, gastroesophageal reflux disease in 4.5% participants, and iron deficiency anemia in 4.4% participants.

Number analysed

Overall, 904 participants were included in SAF-M (maintenance phase set) and 880 participants were included in the effectiveness evaluation (maintenance phase). A total of 615 anti-TNFα antibody naïve participants (83.4%) and 265 anti-TNFα antibody exposed participants (81.5%) entered the maintenance phase.

Efficacy results (effectiveness evaluation)

The Applicant clarified that the therapeutic response was assessed by the investigator per their clinical judgement either after the third dose or at the time of treatment discontinuation according to the Japanese package insert for vedolizumab IV 300mg (where "response" was defined as meeting both "Decrease in the complete Mayo score of at least 3 points and at least 30% from baseline", and "Decrease in the rectal bleeding subscore of at least 1 point from baseline, or a rectal bleeding subscore of 1 or less").

Table 6.1 Presence or absence of therapeutic response, continuation of treatment

Participants included in the efficacy evaluation

Item		Overall	
		Number of participants (%)	
		1062	
Presence or absence of therapeutic response after the third dose or at treatment discontinuation	No	158	(14.9)
	Yes	904	(85.1)
	Missing	0	(0.0)
Continuation of treatment (fourth dose)	No	182	(17.1)
	Yes	880	(82.9)

A therapeutic response at the end of induction period was achieved in 85.1% (904 participants).

A therapeutic response at the end of induction period was achieved in 85.2% (628 participants) of anti-TNFα antibody naïve and 84.9% (276 participants) of anti-TNFα antibody exposed participants.

At the start of the treatment there were 285 patients with **complete Mayo score** ≥6 and the endoscopic subscore was ≥ 2. At the end of the induction period, the complete Mayo score **remission** rate was 28.1% (9 participants), and the complete Mayo score **improvement** rate was 40.6% (13 participants) in the effectiveness population:

Table 6.2.1.1 Time course of complete Mayo score

Participants included in the efficacy evaluation

Complete Mayo score at the start of treatment with this drug was ≥ 6 and the endoscopic subscore was ≥ 2.

Item/evaluation time point		Measured value								Change[#1]							
		Number of participants	Mean	Standard deviation	Minimum	First quartile	Median	Third quartile	Maximum	Number of participants	Mean	Standard deviation	Minimum	First quartile	Median	Third quartile	Maximum
Complete Mayo score	At the start of treatment with this drug	285	7.9	1.29	6	7.0	8.0	9.0	12								
	After 3 doses of this drug or at treatment discontinuation	32	5.7	3.50	0	2.0	6.0	9.0	11	32	-2.1	3.67	-8	-5.0	-1.0	1.0	5

#1 Change = measured value at each evaluation time point after the start of treatment with this drug - measured value at the start of treatment with this drug

Item/evaluation time point		Total	Assessment result			
			Remission/response		Non-remission/ non-response	
			Number of participants (%)			
Complete Mayo score remission (handling of missing data (1)[#2])	After 3 doses of this drug or at treatment discontinuation	32	9	(28.1)	23	(71.9)
Complete Mayo score remission (handling of missing data (2)[#3])	After 3 doses of this drug or at treatment discontinuation	32	9	(28.1)	23	(71.9)
Complete Mayo score remission (handling of missing data (3)[#4])	After 3 doses of this drug or at treatment discontinuation	285	9	(3.2)	276	(96.8)
Complete Mayo score response (handling of missing data (1)[#2])	After 3 doses of this drug or at treatment discontinuation	32	13	(40.6)	19	(59.4)
Complete Mayo score response (handling of missing data (2)[#3])	After 3 doses of this drug or at treatment discontinuation	32	13	(40.6)	19	(59.4)
Complete Mayo score response (handling of missing data (3)[#4])	After 3 doses of this drug or at treatment discontinuation	285	13	(4.6)	272	(95.4)

#2 Handling of missing data (1): If only the endoscopic subscore is missing and the partial Mayo score is not missing, the assessment of remission/response is handled as missing and the participant is excluded from the analysis.
For participants whose endoscopic subscore is not missing and who received at least the fourth or subsequent dose of this drug, the assessment of remission/response is handled as missing and the participants are excluded from the analysis.
For participants whose endoscopic subscore is not missing and who did not receive the fourth or subsequent dose of this drug, the assessment of remission/response is handled as non-remission/non-response.

#3 Handling of missing data (2): If only the endoscopic subscore is missing and the partial Mayo score is not missing, the assessment of remission/response is handled as missing and the participant is excluded from the analysis.
If the endoscopic subscore is not missing, the assessment of remission/response is handled as non-remission/non-response.

#4 Handling of missing data (3): The assessment of remission/response is handled as non-remission/non-response.

At the end of the induction period, the partial Mayo score remission rate overall was 57.8% (539 participants), and the partial Mayo score improvement rate was 61.8% (576 participants) in the effectiveness population.

Participants with **partial Mayo score** of ≥5 at baseline, had the partial Mayo score **remission** rate as 53.9% (341 participants), and the partial Mayo score **improvement** rate as 69.0% (437 participants) at the end of the induction period.

Table 6.2.1.2 Time course of partial Mayo score

Participants included in the efficacy evaluation
Partial Mayo score at the start of treatment with this drug was ≥ 5.

Item/evaluation time point		Measured value								Change[#1]							
		Number of participants	Mean	Standard deviation	Minimum	First quartile	Median	Third quartile	Maximum	Number of participants	Mean	Standard deviation	Minimum	First quartile	Median	Third quartile	Maximum
Partial Mayo score	At the start of treatment with this drug	633	6.0	0.91	5	5.0	6.0	7.0	9								
	After 3 doses of this drug or at treatment discontinuation	590	2.6	2.34	0	1.0	2.0	4.0	9	590	-3.4	2.42	-9	-5.0	-4.0	-1.0	3

#1 Change = measured value at each evaluation time point after the start of treatment with this drug - measured value at the start of treatment with this drug

Item/evaluation time point		Total	Assessment result			
			Remission/response		Non-remission/ non-response	
			Number of participants (%)			
Partial Mayo score remission (handling of missing data (1)[#2])	After 3 doses of this drug or at treatment discontinuation	602	341	(56.6)	261	(43.4)
Partial Mayo score remission (handling of missing data (2)[#3])	After 3 doses of this drug or at treatment discontinuation	633	341	(53.9)	292	(46.1)
Partial Mayo score response (handling of missing data (1)[#2])	After 3 doses of this drug or at treatment discontinuation	602	437	(72.6)	165	(27.4)
Partial Mayo score response (handling of missing data (2)[#3])	After 3 doses of this drug or at treatment discontinuation	633	437	(69.0)	196	(31.0)

#2 Handling of missing data (1): For participants who received at least the fourth or subsequent dose of this drug, the assessment of remission/response is handled as missing and the participants are excluded from the analysis. For participants who did not receive the fourth or subsequent dose of this drug, the assessment of remission/response is handled as non-remission/non-response.
#3 Handling of missing data (2): The assessment of remission/response is handled as non-remission/non-response.

At the end of the induction period, in participants with partial Mayo score of ≥5 at baseline, 59.6% (249 participants) of anti-TNFα antibody naïve and 50.0% (92 participants) of anti-TNFα antibody exposed participants achieved remission, while 73.2% (306 participants) of anti-TNFα antibody naïve and 71.2% (131 participants) of anti-TNFα antibody exposed participants achieved a response:

Table 6.4.1.1.3.1| Partial Mayo score by participant background and treatment detail factor (history of treatment with anti-TNFα antibody: Part 1)
(after 3 doses of this drug or at treatment discontinuation: Partial Mayo score at the start of treatment with this drug was ≥ 5.)

Participants included in the efficacy evaluation — Partial Mayo score at the start of treatment with this drug was ≥ 5.

			Partial Mayo score remission (handling of missing data (1)[#1])								Partial Mayo score response (handling of missing data (1)[#1])							
			History of treatment with anti-TNFα antibody: No				History of treatment with anti-TNFα antibody: Yes				History of treatment with anti-TNFα antibody: No				History of treatment with anti-TNFα antibody: Yes			
			Remission		Non-remission		Remission		Non-remission		Response		Non-response		Response		Non-response	
Total			249	(59.6)	169	(40.4)	92	(50.0)	92	(50.0)	306	(73.2)	112	(26.8)	131	(71.2)	53	(28.8)
History of previous therapy for UC other than this drug within 3 months before the start of treatment with this drug (excluding anti-TNFα antibody drugs)	No		6	(85.7)	1	(14.3)	4	(66.7)	2	(33.3)	7	(100.0)	0	(0.0)	5	(83.3)	1	(16.7)
	Yes		243	(59.1)	168	(40.9)	88	(49.4)	90	(50.6)	299	(72.7)	112	(27.3)	126	(70.8)	52	(29.2)
	Unknown		0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-
History of treatment with anti-TNFα antibody	No		249	(59.6)	169	(40.4)					306	(73.2)	112	(26.8)				
	Yes						92	(50.0)	92	(50.0)					131	(71.2)	53	(28.8)
Details of history of treatment with anti-TNFα antibody (overlapping tabulation)	History of treatment with adalimumab	No	0	-	0	-	55	(52.4)	50	(47.6)	0	-	0	-	73	(69.5)	32	(30.5)
		Yes	0	-	0	-	37	(46.8)	42	(53.2)	0	-	0	-	58	(73.4)	21	(26.6)
	History of treatment with infliximab	No	0	-	0	-	35	(51.5)	33	(48.5)	0	-	0	-	52	(76.5)	16	(23.5)
		Yes	0	-	0	-	57	(49.1)	59	(50.9)	0	-	0	-	79	(68.1)	37	(31.9)
	History of treatment with golimumab	No	0	-	0	-	56	(45.5)	67	(54.5)	0	-	0	-	82	(66.7)	41	(33.3)
		Yes	0	-	0	-	36	(59.0)	25	(41.0)	0	-	0	-	49	(80.3)	12	(19.7)
Breakdown of history of treatment with adalimumab Note: Only when "Yes" for history of treatment with adalimumab	Primary failure		0	-	0	-	7	(25.0)	21	(75.0)	0	-	0	-	18	(64.3)	10	(35.7)
	Secondary failure		0	-	0	-	23	(59.0)	16	(41.0)	0	-	0	-	32	(82.1)	7	(17.9)
	Intolerance		0	-	0	-	6	(66.7)	3	(33.3)	0	-	0	-	7	(77.8)	2	(22.2)
	Discontinuation due to efficacy/remission		0	-	0	-	0	(0.0)	2	(100.0)	0	-	0	-	0	(0.0)	2	(100.0)
	Other		0	-	0	-	1	(100.0)	0	(0.0)	0	-	0	-	1	(100.0)	0	(0.0)
Breakdown of history of treatment with infliximab Note: Only when "Yes" for history of treatment with infliximab	Primary failure		0	-	0	-	9	(23.7)	29	(76.3)	0	-	0	-	18	(47.4)	20	(52.6)
	Secondary failure		0	-	0	-	29	(61.7)	18	(38.3)	0	-	0	-	39	(83.0)	8	(17.0)
	Intolerance		0	-	0	-	11	(55.0)	9	(45.0)	0	-	0	-	14	(70.0)	6	(30.0)
	Discontinuation due to efficacy/remission		0	-	0	-	3	(60.0)	2	(40.0)	0	-	0	-	3	(60.0)	2	(40.0)
	Other		0	-	0	-	5	(83.3)	1	(16.7)	0	-	0	-	5	(83.3)	1	(16.7)
Breakdown of history of treatment with golimumab Note: Only when "Yes" for history of treatment with golimumab	Primary failure		0	-	0	-	16	(64.0)	9	(36.0)	0	-	0	-	19	(76.0)	6	(24.0)
	Secondary failure		0	-	0	-	18	(56.3)	14	(43.8)	0	-	0	-	27	(84.4)	5	(15.6)
	Intolerance		0	-	0	-	1	(50.0)	1	(50.0)	0	-	0	-	1	(50.0)	1	(50.0)
	Discontinuation due to efficacy/remission		0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-
	Other		0	-	0	-	1	(50.0)	1	(50.0)	0	-	0	-	2	(100.0)	0	(0.0)

#1 Handling of missing data (1): For participants who received at least the fourth or subsequent dose of this drug, the assessment of remission/response is handled as missing and the participants are excluded from the analysis. For participants who did not receive the fourth or subsequent dose of this drug, the assessment of remission/response is handled as non-remission/non-response.

At the end of induction period, in the effectiveness population the mean (SD) change from baseline in the **SIBDQ** (Short Inflammatory Bowel Disease Questionnaire) score (median score at baseline = 45) was 9.3 (12.86), in the systemic symptom subscore (median score at baseline = 4.5) was 0.60 (1.372), in the social functioning subscore (median score at baseline = 5) was 1.17 (1.731), in the abdominal symptom subscore (median score at baseline = 4.3) was 1.04 (1.452), and in the emotional subscore (median score at baseline = 4.3) was 0.89 (1.404).

Paediatric Participants

Subgroup effectiveness analyses by anti-TNFα exposure are presented below for the 34 paediatric participants (aged <18 years).

Among anti-TNFα antibody naïve paediatric participants (N=25), 92.0% (23 participants), had a therapeutic response at the end of induction period and 92.0% (23 participants) entered the maintenance phase. Of the participants with partial Mayo score of ≥5 at baseline (n=15), 60.0% (9 participants) achieved remission and 73.3% (11 participants) achieved an improvement.

Among anti-TNFα antibody exposed paediatric participants (N=9), 77.8% (7 participants) had a therapeutic response at the end of induction period and 88.9% (8 participants) entered the maintenance phase. Of the participants with partial Mayo score of ≥5 at baseline (N=4), 75.0% (3 participants) achieved remission and 75.0% (3 participants) achieved an improvement.

Table 6.4.1.1.3.1 Partial Mayo score by participant background and treatment detail factor (history of treatment with anti-TNFα antibody: Part 1)
(after 3 doses of this drug or at treatment discontinuation: Partial Mayo score at the start of treatment with this drug was ≥ 5.)

Participants included in the efficacy evaluation — Partial Mayo score at the start of treatment with this drug was ≥ 5.

		Partial Mayo score remission (handling of missing data (1)[#1])								Partial Mayo score response (handling of missing data (1)[#1])							
		History of treatment with anti-TNFα antibody: No				History of treatment with anti-TNFα antibody: Yes				History of treatment with anti-TNFα antibody: No				History of treatment with anti-TNFα antibody: Yes			
		Remission		Non-remission		Remission		Non-remission		Response		Non-response		Response		Non-response	
Total		249	(59.6)	169	(40.4)	92	(50.0)	92	(50.0)	306	(73.2)	112	(26.8)	131	(71.2)	53	(28.8)
Sex	Male	132	(56.2)	103	(43.8)	52	(50.0)	52	(50.0)	166	(70.6)	69	(29.4)	70	(67.3)	34	(32.7)
	Female	117	(63.9)	66	(36.1)	40	(50.0)	40	(50.0)	140	(76.5)	43	(23.5)	61	(76.3)	19	(23.8)
Age (years)	Min<= - <35	81	(60.9)	52	(39.1)	37	(49.3)	38	(50.7)	102	(76.7)	31	(23.3)	55	(73.3)	20	(26.7)
	35<= - <=Max	168	(58.9)	117	(41.1)	55	(50.5)	54	(49.5)	204	(71.6)	81	(28.4)	76	(69.7)	33	(30.3)
	Unknown	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-
	Min<= - <18	9	(60.0)	6	(40.0)	3	(75.0)	1	(25.0)	11	(73.3)	4	(26.7)	3	(75.0)	1	(25.0)
	18<= - <65	202	(59.8)	136	(40.2)	76	(48.1)	82	(51.9)	247	(73.1)	91	(26.9)	111	(70.3)	47	(29.7)
	65<= - <=Max	38	(58.5)	27	(41.5)	13	(59.1)	9	(40.9)	48	(73.8)	17	(26.2)	17	(77.3)	5	(22.7)
	Unknown	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-
	Min<= - <15	2	(100.0)	0	(0.0)	2	(100.0)	0	(0.0)	2	(100.0)	0	(0.0)	2	(100.0)	0	(0.0)
	15<= - <65	209	(59.5)	142	(40.5)	77	(48.1)	83	(51.9)	256	(72.9)	95	(27.1)	112	(70.0)	48	(30.0)
	65<= - <=Max	38	(58.5)	27	(41.5)	13	(59.1)	9	(40.9)	48	(73.8)	17	(26.2)	17	(77.3)	5	(22.7)
	Unknown	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-

Upon request the Applicant presented data from the maintenance phase:

Table 2.a Complete Mayo Score at the End of Week 54 (Analysis of Participants Included in the Effectiveness Evaluation [Maintenance Phase])

Participants included in the efficacy evaluation (maintenance phase)																	
Complete Mayo score at the start of treatment with this drug was ≥6 and the endoscopic subscore was ≥2.																	
Item/evaluation time point		**Measured value**								**Change[#1]**							
		N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max	N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
Complete Mayo score	At the start of treatment with this drug	236	7.9	1.31	6	7.0	8.0	9.0	12								
	At the end of Week 54	42	4.6	3.76	0	1.0	4.0	8.0	12	42	-3.3	4.10	-12	-7.0	-4.0	0	6

[#1] Change = measured value at each evaluation time point after the start of treatment with this drug - measured value at the start of treatment with this drug.

Item/evaluation time point		**Total**	**Assessment result**	
			Remission/response	**Non-remission/non-response**
			Number of participants (%)	
Complete Mayo score remission (handling of missing data (2)[#2])	At the end of Week 54	42	17 (40.5)	25 (59.5)
Complete Mayo score remission (handling of missing data (3)[#3])	At the end of Week 54	236	17 (7.2)	219 (92.8)
Complete Mayo score response (handling of missing data (2)[#2])	At the end of Week 54	42	22 (52.4)	20 (47.6)
Complete Mayo score response (handling of missing data (3)[#3])	At the end of Week 54	236	22 (9.3)	214 (90.7)

[#2] Handling of missing data (2): If only the endoscopic subscore is missing and the partial Mayo score is not missing, the assessment of remission/response is handled as missing and the participant is excluded from the analysis. Otherwise, the assessment of remission/response is handled as non-remission/non-response.

[#3] Handling of missing data (3): The assessment of remission/response is handled as non-remission/non-response.

The remission is defined as a complete Mayo score of 2 or less and all individual Mayo subscores are 1 or less.

The response is defined as a reduction in complete Mayo score of 3 or more points and 30% or more from Baseline with an accompanying decrease in rectal bleeding subscore of 1 or more point or absolute rectal bleeding subscore of 1 or less.

Source: Vedolizumab-5033 CSR Table 6.2.2.1.

Table 2.b Partial Mayo Score at the End of Week 54 (Analysis of Participants Included in the Effectiveness Evaluation [Maintenance Phase])

Participants included in the efficacy evaluation (maintenance phase)																	
Partial Mayo score at the start of treatment with this drug was ≥5.																	
Item/evaluation time point		**Measured value**								**Change[#1]**							
		N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max	N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
Partial Mayo score	At the start of treatment with this drug	518	6.0	0.91	5	5.0	6.0	7.0	9								
	At the end of Week 54	360	2.3	2.51	0	0	1.0	5.0	9	360	-3.7	2.68	-9	-6.0	-5.0	-1.0	4

[#1] Change = measured value at each evaluation time point after the start of treatment with this drug - measured value at the start of treatment with this drug.

Item/evaluation time point		**Total**	**Assessment result**	
			Remission/response	**Non-remission/non-response**
			Number of participants (%)	
Partial Mayo score remission (handling of missing data (2)[#2])	At the end of Week 54	518	223 (43.1)	295 (56.9)
Partial Mayo score response (handling of missing data (2)[#2])	At the end of Week 54	518	267 (51.5)	251 (48.5)

[#2] Handling of missing data (2): The assessment of remission/response is handled as non-remission/non-response.

The remission is defined as a partial Mayo score of 2 or less and all individual partial Mayo subscores are 1 or less.

The response is defined as a reduction in partial Mayo score of 2 or more points and 25% or more from Baseline with an accompanying decrease in rectal bleeding subscore of 1 or more point or absolute rectal bleeding subscore of 1 or less.

Source: Vedolizumab-5033 CSR Table 6.2.2.2.

Changes in SIBDQ were evaluated for subjects in the effectiveness population, who had not undergone colectomy or stoma formation during the observation period and who had SIBDQ data available at the relevant time points (N=654 at baseline; N=440 at Week 54). By end of Week 54, the SIBDQ score and all its subscores had increased compared to baseline: the mean (SD) change from baseline in the SIBDQ score (44.70 [12.45] at baseline) was 11.50 (14.16); in the systemic symptom subscore (4.64 [1.32] at baseline) the change was 0.82 (1.51); in the social functioning subscore (4.60 [1.73] at baseline) it was 1.47 (1.81); in the abdominal symptom subscore (4.42 [1.36] at baseline) it was 1.25 (1.62); and in the emotional subscore (4.33 [1.37] at baseline) it was 1.05 (1.55).

SIBDQ results for the <u>adolescent subgroup:</u>

At the end of induction period (effectiveness population; median score at baseline =4.5), the mean (SD) change from baseline in the SIBDQ score (42.70 [13.21] at baseline) was 7.30 (12.34); in the systemic symptom subscore (4.43 [1.57] at baseline), it was 0.45 (1.63); in the social functioning

subscore (4.48 [1.70] at baseline), it was 0.81 (1.53); in the abdominal symptom subscore (4.20 [1.43] at baseline), it was 0.80 (1.25); and in the emotional subscore (4.09 [1.34] at baseline), it was 0.80 (1.12) (Table 3.a).

At the end of Week 54 (maintenance phase), the mean (SD) change from baseline in the SIBDQ score (44.70 at baseline) was 4.40 (18.50); in the systemic symptom subscore (4.71 [1.47] at baseline), it was -0.04 (1.94); in the social functioning subscore (4.68 [1.74] at baseline), it was 0.54 (2.09); in the abdominal symptom subscore (4.36 [1.36] at baseline), it was 0.33 (1.79); and in the emotional subscore (4.29 [1.33] at baseline), it was 0.80 (2.0) (Table 3.b).

Safety results

Among the 1091 participants included in the SAF, 208 (19.07%) reported at least 1 AE.

Table 5.4.1.1 Status of occurrence of adverse events by seriousness, time of onset, outcome, and their causal relationship with this drug

Participants included in the safety evaluation

	Total	Outcome						Causal relationship with this drug	
		Resolved	Resolving	Not resolved	Resolved with sequelae	Death (due to this event)	Unknown	Related	Not related
(1) Number of participants included in the safety evaluation	1091	1091						1091	
(2) Number of participants who experienced adverse events	208	120	86	21	2	5	5	60	158
(3) Number of adverse events experienced	313	172	104	24	2	6	5	92	221
(4) Incidence of adverse events ((2)/(1) × 100)	19.07%	11.00%	7.88%	1.92%	0.18%	0.46%	0.46%	5.50%	14.48%

Most AEs were reported in gastrointestinal disorders (5.68% participants), and infections and infestations (4.40% participants) SOC. The most frequently reported AEs were UC (3.39%, 37 participants), nasopharyngitis (1.37%, 15 participants), and infusion related reaction (1.37%, 15 participants).

A total of 82 participants (7.52%) reported at least 1 SAE and UC was the most frequently reported SAE among 37 participants (3.39%).

A total of 60 participants (5.50%) reported at least 1 related AE. The most frequently reported related AE was infusion related reaction (1.37%, 15 participants). The most frequently reported related SAE was UC (0.27%, 3 participants).

Most related **SAEs** were reported in gastrointestinal disorders (0.37% participants), respiratory, thoracic and mediastinal disorders (0.18% participants) and infections and infestations (0.18% participants) SOC. Among infections SAEs there were 1 case of liver abscess and 1 case of herpes zoster oticus. Among respiratory SAEs there were 1 case of eosinophilic pneumonia and 1 case of organizing pneumonia. Among gastrointestinal SAEs there was 1 case of pancreatitis. There was also 1 case of colon cancer and 1 serious infusion related reaction (anaphylaxis).

Related **AEs leading to study drug discontinuation** were reported among 2.38% (26 participants) in the SAF, and the most frequently reported related AEs leading to study drug discontinuation were infusion related reaction (0.64%, 7 participants), arthralgia (0.27%, 3 participants), and malaise in (0.27%, 3 participants):

Table 5.5.1 Occurrence of adverse drug reactions/infections for which taking this drug was discontinued

Participants included in the safety evaluation		
(1) Number of participants included in the safety evaluation	1091	
(2) Number of participants with adverse drug reactions for which action taken for this drug was discontinuation	26	
(3) Number of adverse drug reactions for which taking this drug was discontinued	34	
(4) Incidence of adverse drug reactions for which taking this drug was discontinued ((2)/(1) × 100)	2.38%	
Type of adverse drug reactions for which taking this drug was discontinued	Number of participants with adverse drug reactions for which taking this drug was discontinued by type (incidence)	
Infections and infestations	1	(0.09%)
Liver abscess	1	(0.09%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.09%)
Colon cancer	1	(0.09%)
Blood and lymphatic system disorders	1	(0.09%)
Eosinophilia	1	(0.09%)
Nervous system disorders	2	(0.18%)
Dizziness	1	(0.09%)
Headache	1	(0.09%)
Eye disorders	1	(0.09%)
Vision blurred	1	(0.09%)
Respiratory, thoracic and mediastinal disorders	1	(0.09%)
Eosinophilic pneumonia	1	(0.09%)
Gastrointestinal disorders	5	(0.46%)
Colitis ulcerative	2	(0.18%)
Nausea	2	(0.18%)
Pancreatitis	1	(0.09%)
Skin and subcutaneous tissue disorders	3	(0.27%)
Pruritus	1	(0.09%)
Rash	2	(0.18%)
Musculoskeletal and connective tissue disorders	6	(0.55%)
Arthralgia	3	(0.27%)
Arthritis	1	(0.09%)
Back pain	1	(0.09%)
Pain in extremity	1	(0.09%)
Polyarthritis	1	(0.09%)
General disorders and administration site conditions	4	(0.37%)
Gait disturbance	1	(0.09%)
Malaise	3	(0.27%)
Oedema peripheral	1	(0.09%)
Injury, poisoning and procedural complications	7	(0.64%)
Infusion related reaction	7	(0.64%)

A total of 5 deaths and 9 pregnancy cases were reported during the study period.

Six events in 5 participants resulted in "**death** (due to the event)" which included colon cancer, metastases to bone, metastases to lung, cerebral infarction, myocardial infarction, and paroxysmal nocturnal haemoglobinuria.

As for the outcome of **pregnancy** cases, there were 5 cases with no abnormal findings in newborns, 2 cases with delivery reported (details unknown), 1 case with unknown outcome, and 1 case with intrauterine fetal death (32 weeks of gestation) (a diagnosis of umbilical cord hypertorsion was reported by pathological autopsy).

Adverse events corresponding to infusion reactions including hypersensitivity reactions and infection (other than progressive multifocal leukoencephalopathy) among safety specifications in the risk management plan was evaluated. There were no participants with progressive multifocal leukoencephalopathy, and serious events of malignancy occurred in 0.82% (9 participants), among them one case of colon cancer.

Paediatric Participants

A total of 34 participants enrolled in the study were aged 12 to <18 years at enrolment (of which 7 were aged 12 to <15 years, that is locally considered paediatric participants).

Table 5.6.1.1 Occurrence of adverse drug reactions/infections by participant background and treatment detail factor

Participants included in the safety evaluation

Item		Number of participants	Number of participants with adverse drug reactions (%)	
Sex	Male	621	33	(5.31)
	Female	470	27	(5.74)
Age (years)	Min<= - <35	367	16	(4.36)
	35<= - <=Max	724	44	(6.08)
	Unknown	0	0	-
	Min<= - <18	34	0	(0.00)
	18<= - <65	892	50	(5.61)
	65<= - <=Max	165	10	(6.06)
	Unknown	0	0	-
	Min<= - <15	7	0	(0.00)
	15<= - <65	919	50	(5.44)
	65<= - <=Max	165	10	(6.06)
	Unknown	0	0	-

Analysis of related AEs were conducted by age groups (<18 years of age, ≥18 and <65 years and ≥65 years of age).

In the SAF (1091 participants), **the incidence of related AEs was 0% (0/34) in participants aged <18 years**, 5.61% (50/892 participants) in participants aged ≥18 and <65 years, and 6.06% (10/165 participants) in participants aged ≥65 years.

Although the number of participants aged <18 years was relatively small, there were no safety concerns that required special attention in children or adolescents aged <18 years.

2.2.3. Discussion on clinical aspects

The Vedolizumab-5033 study is a post-approval commitment study conducted in Japan to evaluate the long-term safety and effectiveness of Entyvio (vedolizumab) in patients with ulcerative colitis (UC) (following approval in adult population). The study aimed to assess **the drug's performance in a real-world clinical setting**, using a non-randomized, non-blinded design.

The study had no age restrictions and participants under 18 years were allowed.

In Japan Entyvio is authorized for ulcerative colitis and seems to have same indication and posology as in EU. While Entyvio is currently authorized only in adults, it is noted that participants under approximately 15 years of age are considered paediatric according to Japan's labelling guidance, as reported by the MAH.

The target population was patients with moderately to severely active UC who had an inadequate response to conventional therapy.

The treatment regimen consisted of 300 mg of vedolizumab administered via intravenous infusion at weeks 0, 2, and 6, and then every 8 weeks until week 54.

The primary objective was to examine the safety and effectiveness of Entyvio in UC patients in a real-world clinical setting. The study collected data on effectiveness and safety, including complete Mayo Score, SIBDQ, adverse events, concomitant medications, surgical procedures, and laboratory parameters. Effectiveness analyses were conducted stratified by anti-TNFα use.

The study used a planned sample size of 1000 participants, with at least 300 participants exposed to anti-TNFα antibodies and 300 participants naive to anti-TNFα antibodies. The induction analysis sets included participants who received at least 3 doses of vedolizumab and those who discontinued treatment before the 4th dose. For Week 52, the analysis set was limited to participants who received the 4th dose (those who transitioned to the maintenance phase).

The study was conducted from February 2019 to October 2024. A total of 1110 participants were registered, and 1091 were included in the safety analysis (of which 904 participants were included in safety maintenance phase set). The participant demographics showed that 56.9% of participants were male. The age range of the participants largely varied (12-94 years), with 3.1% being under 18 years old, and 0.6% being under 15 years old. The mean age was 44.3 years. **34 participants** were enrolled who were aged **12 to <18 years at enrolment** (of which 7 were aged 12 to <15 years, that is locally considered paediatric participants).

In terms of disease characteristics, the mean duration of disease was 9.3 years. The majority of participants, 96.4%, had moderate UC, while only 3.6% had severe UC. The extent of disease also varied, with 71.6% of participants having pancolitis, and 24.5% having left-sided colitis. Additionally, 15.9% of participants had steroid resistance, 56.1% had steroid dependence, and 2.9% had steroid intolerance.

Effectiveness results: the treatment regimen consisted of vedolizumab administered via intravenous infusion, with 1090 participants receiving the first dose of 300 mg (341 anti-TNFα exposed and 750 anti-TNFα naïve participants), and 904 participants receiving the fourth dose.

The therapeutic response at the end of induction period was achieved in 85.1% (904 participants). Furthermore, the therapeutic response at the end of the induction period was achieved in 85.2% of anti-TNFα antibody-naive participants and 84.9% of anti-TNFα antibody-exposed participants.

At the start of the treatment there were 285 patients with **complete Mayo score** ≥6 and the endoscopic subscore was ≥ 2, from which only 32 had complete Mayo score available after 3 doses of this drug or at treatment discontinuation.

At the end of the induction period, the complete Mayo score remission rate was 28.1% (9 participants), and the complete Mayo score improvement rate was 40.6% (13 participants) in the effectiveness population. Considering that only a limited number of participants was with complete Mayo score at baseline, and in particular at follow up, the effectiveness results have limited interpretability.

The **partial Mayo score** remission rate was 57.8% (539 participants), and the partial Mayo score improvement rate was 61.8% (576 participants) at the end of the induction period. Participants with partial Mayo score of ≥5 at baseline, had the partial Mayo score remission rate as 53.9% (341 participants), and the partial Mayo score improvement rate as 69.0% (437 participants) at the end of the induction period. The percent of patients with partial Mayo score remission and improvement was similar between anti-TNF alfa naïve and anti-TNF alfa exposed patients.

Furthermore, the mean change from baseline in the **SIBDQ** score was 9.3 (SD 12.86). This score measures health related QoL and includes four domains (bowel symptoms, systemic symptoms, emotional and social function, total range 10-70) and usually the improvement of at least 10 points is considered clinically meaningful.

The Applicant stated that vedolizumab effect generally persisted at the end of induction period through Week 54 after the start of treatment. The interpretation of the efficacy data is limited, particularly due to missing information during the long-term follow-up period. However, although with substantial limitations, the effectiveness outcomes observed during the maintenance phase were generally clinically meaningful and seem consistent with results from previous clinical trials of vedolizumab in adults.

The study also included a subgroup analysis of **paediatric** participants, which consisted of 34 participants under 18 years old.

Among the anti-TNFα antibody-naive paediatric participants (n=25), 92.0% (23 subjects) had a therapeutic response at the end of the induction period, and 92.0% entered the maintenance phase. Of the participants with partial Mayo score of ≥5 at baseline (n=15), 60.0% (9 participants) achieved remission and 73.3% (11 participants) achieved an improvement.

Similarly, among the anti-TNFα antibody-exposed paediatric participants (n=9), 77.8% (7 subjects) had a therapeutic response at the end of the induction period, and 88.9% entered the maintenance

phase. Of the participants with partial Mayo score of ≥5 at baseline (N=4), 75.0% (3 participants) achieved remission and 75.0% (3 participants) achieved an improvement.

The results for SIBDQ in pediatric patients were provided and discussed upon request. While the improvements in the scores for paediatric participants were smaller compared to the overall study population, the number of adolescent subjects is very limited and due to the nature of the study no conclusion can be made.

Taking into account the limitations of the observational study, the effectiveness results observed in the pediatric population (consisting only of adolescent patients) are considered supportive and seem to be in line with adult patients with UC in Japan included in this study.

The **safety** analysis of the study included 1091 participants, and 208 (19.07%) of them reported at least one adverse event. The most common AEs were reported in the gastrointestinal disorders and infections and infestations categories, with the most frequently reported AEs being ulcerative colitis, nasopharyngitis, and infusion-related reaction. A total of 82 participants (7.52%) reported at least one serious adverse event (SAE), with UC being the most frequently reported SAE.

The analysis showed that 60 participants (5.50%) reported at least one related AE. The most frequently reported related AE was infusion-related reaction, and the most frequently reported related SAE was UC. The majority of related SAEs were reported in the gastrointestinal disorders, respiratory, thoracic and mediastinal disorders, and infections and infestations categories. There were reports (single cases) of serious infections, including liver abscess and herpes zoster oticus, as well as respiratory SAEs, such as eosinophilic pneumonia and organizing pneumonia. Among gastrointestinal SAEs there was 1 case of pancreatitis. There was also 1 case of colon cancer and 1 serious infusion related reaction (anaphylaxis).

The infections (including herpes zoster infections) are well-known adverse reactions of vedolizumab.

Among respiratory SAEs there was 1 case of eosinophilic pneumonia. Of note, a case of late onset vedolizumab-induced eosinophilic pneumonia in a patient with ulcerative colitis was published (Eur J Gastroenterol Hepatol. 2023 Apr 1;35(4):513-514). Upon request the Applicant further discussed the case observed in the present study. A definitive causal association cannot be established due to confounding by concomitant mesalazine. As eosinophilic pneumonia is a specific type of interstitial lung disease and since "Interstitial Lung Disease", as a broader medical term, is already included in section 4.8 of the current SmPC, no amendments of the section 4.8 are proposed.

Although pancreatitis can occur in UC patients, there is also a case in the literature regarding vedolizumab-associated pancreatitis in paediatric ulcerative colitis ((J Crohns Colitis. 2018 Mar 28;12(4):507-508.) This was further discussed upon request. The safety concern of pancreatitis was also recently examined by PRAC procedure. Based on the available clinical study and cumulative post-marketing data review, the current literature and what is known about the mechanism of action of vedolizumab, and subsequent signal detection activities, the Applicant has concluded that the evidence available at this time is insufficient to support a causal relationship between vedolizumab and developing or recurrent pancreatitis.

A total of 26 participants (2.38%) reported drug related AEs that led to study drug discontinuation, with the most frequently reported related AEs being infusion-related reaction, arthralgia, and malaise. There were also five deaths not related to the drug and nine pregnancy cases reported during the study period. There were no cases of progressive multifocal leukoencephalopathy. However, there were nine cases of malignancy, including colon cancer.

Overall, results from the clinical program to date, as reported in the SmPC, do not suggest an increased risk for malignancy with vedolizumab treatment; however, the number of malignancies was small and long-term exposure was limited. Moreover, UC is a known risk factor for colorectal cancer. As the case of the colon cancer in this study was further discussed upon request. The Applicant concludes that the short duration of vedolizumab exposure, the underlying chronic inflammatory condition, and the confounding history of infliximab use support the conclusion that vedolizumab is unlikely to be causally implicated in the development of colon cancer in this patient.

In terms of safety in **pediatric** participants, the study included 34 participants aged 12 to <18 years at enrollment, and the analysis of related AEs by age group found that there were **no drug related**

AEs reported in participants aged <18 years. Although the number of pediatric participants was relatively small, the safety profile in this age group did not raise any concerns that required special attention.

The safety results of the study suggest that the study drug is generally well-tolerated, especially in the pediatric population, although there are some risks that need to be carefully monitored.

Overall, the results of this observational study in UC subjects conducted in Japan, including a limited number of adolescents, confirmed effectiveness and safety profile of vedolizumab, also in pediatric subgroup.

3. Rapporteur's conclusion and recommendation

Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The prespecified definition of "therapeutic response" used for the evaluation of the effectiveness in the Vedolizumab-5033 study should be provided.
2. The MAH is requested to provide summary tables for main endpoints and discuss the effectiveness results for the maintenance phase of the study.
3. The results for SIBDQ in adolescents should be provided and discussed.
4. The possible causal relationship of vedolizumab with eosinophilic pneumonia and pancreatitis should be discussed and the inclusion of these ADR in the section 4.8 of the SmPC should be considered.
5. As the case of the colon cancer in this study was included among adverse drug reactions, the potential relationship with study drug and the consequent inclusion of this ADR in the section 4.8 of the SmPC should be discussed.

The timetable is a 30 day response timetable without clock stop.

4. MAH responses to Request for supplementary information

1. Vedolizumab-5033 study is a non-interventional PMS study conducted to collect information on the use of vedolizumab IV treatment for UC in routine clinical practice in Japan. Therefore, there is no prespecified definition of "therapeutic response" in this study. The therapeutic response was assessed by the investigator per their clinical judgement either after the third dose or at the time of treatment discontinuation according to the section of "Precautions Concerning Dosage and Administration" in the Japanese package insert for vedolizumab IV 300mg.

   For reference, it is noted that in the section "Clinical Studies for Efficacy and Safety" of the Japanese package insert for vedolizumab IV 300mg, the results from the Japanese local phase 3 study (CCT-101) for UC are reported using a definition of "response". In that study, "response" was defined as meeting both of the following criteria: "Decrease in the complete Mayo score of at least 3 points and at least 30% from baseline", and "Decrease in the rectal bleeding subscore of at least 1 point from baseline, or a rectal bleeding subscore of 1 or less".

Assessor's comment

The Applicant clarified that, due to the non-interventional nature of the study, there was no prespecified definition of "therapeutic response". The therapeutic response was assessed by the investigator per their clinical judgement either after the third dose or at the time of treatment discontinuation according to the Japanese package insert for vedolizumab IV 300mg (where "response" was defined as meeting both "Decrease in the complete Mayo score of at least 3 points and at least 30% from baseline", and "Decrease in the rectal bleeding subscore of at least 1 point from baseline, or a rectal bleeding subscore of 1 or less").

Issue solved.

2. Generally, the main objective of PMS studies in Japan is to collect safety data in routine clinical practice. Accordingly, the primary objective of Study Vedolizuman-5033 was to collect safety data on the use of vedolizumab IV treatment for UC in clinical practice in Japan with limited efficacy related data captured. Therefore, interpretation of the efficacy data is limited, particularly due to missing information during the long-term follow-up period.

Table 2.a, Table 2.b, and Table 2.c summarize effectiveness results for the maintenance phase, using the complete Mayo score, partial Mayo score, and SIBDQ score, respectively. Overall, the effectiveness outcomes observed during the maintenance phase were generally clinically meaningful and consistent with results from previous clinical trials of vedolizumab in adults.

The effectiveness population in the maintenance phase consisted of 880 patients. This effectiveness population in maintenance was defined as patients who met all study inclusion criteria, entered the maintenance phase by receiving at least 4 doses of vedolizumab IV (i.e., completed induction and began maintenance therapy), and did not have major protocol violations, prior colectomy or stoma, or prior vedolizumab treatment. In this population, 276 patients had a complete Mayo score collected at baseline. Among them, 236 patients had a complete Mayo score of ≥6 and an endoscopic subscore of ≥2 at baseline. Forty-two patients had a complete Mayo score collected at the end of Week 54. At the end of Week 54, the complete Mayo score remission rate was 40.5% (17/42), and the complete Mayo score improvement rate was 52.4% (22/42) (Table 2.a).

A total of 765 patients had a partial Mayo score collected at baseline. Among them, 518 patients had a partial Mayo score of ≥5 at baseline. At the end of Week 54, among the effectiveness population in the maintenance phase with partial Mayo score of ≥5 at baseline, the partial Mayo score remission rate was 43.1% (223/518), and the partial Mayo score response rate was 51.5% (267/518) (Table 2.b).

Changes in SIBDQ were evaluated for subjects in the effectiveness population, who had not undergone colectomy or stoma formation during the observation period and who had SIBDQ data available at the relevant time points (N=654 at baseline; N=440 at Week 54). By end of Week 54, the SIBDQ score and all its subscores had increased compared to baseline: the mean (SD) change from baseline in the SIBDQ score (44.70 [12.45] at baseline) was 11.50 (14.16); in the systemic symptom subscore (4.64 [1.32] at baseline) the change was 0.82 (1.51); in the social functioning subscore (4.60 [1.73] at baseline) it was 1.47 (1.81); in the abdominal symptom subscore (4.42 [1.36] at baseline) it was 1.25 (1.62); and in the emotional subscore (4.33 [1.37] at baseline) it was 1.05 (1.55) (Table 2.c)

Assessor's comment

The Applicant argues that primary objective of Study Vedolizuman-5033 was to collect safety data on the use of vedolizumab IV treatment for UC in clinical practice in Japan with limited efficacy related

data captured. Therefore, interpretation of the efficacy data is limited, particularly due to missing information during the long-term follow-up period.

The Applicant provided tables which summarize effectiveness results for the maintenance phase, using the complete Mayo score, partial Mayo score, and SIBDQ score, respectively.

At the end of Week 54, the complete Mayo score remission rate was 40.5% (17/42), and the complete Mayo score improvement rate was 52.4% (22/42) among patients for which complete Mayo score was available also at the end of week 54.

At the end of Week 54, among the effectiveness population in the maintenance phase with partial Mayo score of ≥5 at baseline, the partial Mayo score remission rate was 43.1% (223/518), and the partial Mayo score response rate was 51.5% (267/518).

Regarding the QoL Survey, by end of Week 54, the mean (SD) change from baseline in the SIBDQ score (44.70 [12.45] at baseline) was 11.50 (14.16). Also, all its subscores (systemic symptom, social functioning, abdominal symptom and emotional subscore) had increased compared to baseline.

It is agreed that, although with abovementioned limitations, the effectiveness outcomes observed during the maintenance phase were generally clinically meaningful and consistent with results from previous clinical trials of vedolizumab in adults.

Issue solved.

3. Subgroup analyses of the SIBDQ score in paediatric participants (aged <18 years) are summarized in Table 3.a and Table 3.b. Scores were generally improved both at the end of the induction period and at Week 54 compared to baseline, although there are limitations to the interpretation due to the small number of paediatric participants. While the improvements in the scores for paediatric participants were smaller compared to the overall study population, the difference was not considered clinically meaningful. As a note, no statistical testing was performed in this study.

   At the end of induction period (effectiveness population; median score at baseline =4.5), the mean (SD) change from baseline in the SIBDQ score (42.70 [13.21] at baseline) was 7.30 (12.34); in the systemic symptom subscore (4.43 [1.57] at baseline), it was 0.45 (1.63); in the social functioning subscore (4.48 [1.70] at baseline), it was 0.81 (1.53); in the abdominal symptom subscore (4.20 [1.43] at baseline), it was 0.80 (1.25); and in the emotional subscore (4.09 [1.34] at baseline), it was 0.80 (1.12) (Table 3.a).

   At the end of Week 54 (maintenance phase), the mean (SD) change from baseline in the SIBDQ score (44.70 at baseline) was 4.40 (18.50); in the systemic symptom subscore (4.71 [1.47] at baseline), it was -0.04 (1.94); in the social functioning subscore (4.68 [1.74] at baseline), it was 0.54 (2.09); in the abdominal symptom subscore (4.36 [1.36] at baseline), it was 0.33 (1.79); and in the emotional subscore (4.29 [1.33] at baseline), it was 0.80 (2.0) (Table 3.b).

Assessor's comment

The Applicant provided the results of SIBDQ for the adolescent subgroup, as a change from baseline to the end of induction and maintenance phase. While the improvements in the scores for paediatric participants were smaller compared to the overall study population, the number of adolescent subjects is very limited and due to the nature of the study no conclusion can be made.

Issue solved.

4. Eosinophilic pneumonia

   The eosinophilic pneumonia case referenced in the CSR concerns a female aged with a history of ulcerative colitis (diagnosed in 2015) and a prior history of breast cancer. Concomitant medications included mesalazine, azathioprine, and tamoxifen. On 2020, one day after starting vedolizumab, the patient developed a severe cough. On 2020, a chest X-ray was negative for pneumonia, and the WBC count was 8,800/mm3 (eosinophils 300/mm3); CRP was 5.47 mg/L. She was treated with moxifloxacin 400 mg for one week. On 2020, the patient received the

second dose of vedolizumab. The WBC count was 8,000/mm³ (eosinophil count 1,170/mm³), and the CRP was 0.48 mg/L. On 2020, CT imaging confirmed eosinophilic pneumonia (WBC 6,900/mm³; eosinophils 1,020/mm³), leading to initiation of prednisolone therapy, which was subsequently tapered over several months.

On 2020, a chest X-ray showed improvement, with normalization of WBC (4,200/mm³) and eosinophil count (60/mm³). Eosinophilic pneumonia was considered resolved. The patient was later switched to ustekinumab on an unknown date due to eosinophilic pneumonia experienced while on vedolizumab.

Company Causality Assessment: The temporal association between vedolizumab initiation and event onset suggests a possible relationship; however, a definitive causal association cannot be established due to confounding by concomitant mesalazine, which is recognized as causally associated with eosinophilic pneumonia and is listed as an adverse drug reaction in EU SmPC. Additionally, there is limited information regarding underlying conditions and prior therapies.

Eosinophilic pneumonia is a specific type of interstitial lung disease characterized by an accumulation of eosinophils, a type of white blood cell, in the lungs. Since "Interstitial Lung Disease", as a broader medical term, is already included in section 4.8 of the current SmPC, we consider that the current SmPC is sufficient.

Pancreatitis

The pancreatitis case referenced in the CSR involves a female aged who received vedolizumab (Entyvio) 300 mg IV for UC, diagnosed in 2018. Her medical history included herpes zoster, endometriosis, and cytapheresis. Current medical conditions were gastroesophageal reflux disease, osteoporosis, zinc deficiency, and steroid dependence. Concomitant medications included mesalazine, esomeprazole, prednisolone, sulfamethoxazole/trimethoprim, Bio-three, and ustekinumab.

On 2021, one month after starting vedolizumab, the patient reported epigastric pain and started on acetaminophen 500 mg. The following day, an ultrasound revealed a pancreatic cyst, and her lipase was 992 U/L. As a 5-ASA preparation was suspected as a possible cause, Lialda (mesalazine tablets) was switched to Pentasa (mesalazine granules).

On 2021, the patient presented with back pain in addition to epigastric pain. Laboratory results showed amylase 632 U/L, lipase 2,186 U/L, and urinary amylase 3,280 U/L. Vedolizumab was suspected as being the cause and thus discontinued. Pentasa was switched back to Lialda, which was followed by worsening UC symptoms requiring an increased prednisolone dose and the introduction of ustekinumab therapy. The patient did not take Lialda from 2021, although it had been prescribed.

By 2021, the epigastric and back pain had improved, along with slight improvement in UC symptoms. On 2021, amylase was between 270 and <280 U/L; Lialda was resumed the next day, though back pain persisted. On 2021, amylase was 224 U/L and lipase 762 U/L. On 2021, back pain worsened and Lialda was discontinued due to a possible late-onset 5-ASA intolerance. The discontinuation of Lialda led to normalization of the amylase (115 U/L), and a subsequent ultrasound confirmed pancreatitis. By 2021, epigastric pain had improved, pancreatitis was resolved, and the study observation period was concluded.

The MAH assessed the event of pancreatitis as unlikely related to vedolizumab. The event was confounded by the use of mesalazine, as normalization of pancreatic enzymes and improvement of symptoms following mesalazine withdrawal suggests a stronger association with 5-ASA therapy. Mesalazine is known to be causally associated with pancreatitis which is listed as an ADR in the EU SmPCs.

Takeda's evaluation of the literature case cited in the assessment report was previously submitted to EMA in January 2023 as part of an earlier review on pancreatitis (Data Lock Point: 15 September 2022) in response to a PRAC request for a comprehensive analysis of all known cases of pancreatitis associated with vedolizumab treatment during Procedure Number EMEA/H/C/002782/II/0073, eCTD sequence 0165. Additionally, a cumulative review of pancreatitis cases was submitted to PRAC (Data Lock Point: 19 May 2022) in the most recently

submitted PBRER (covering 20 May 2021 to 19 May 2024; eCTD sequence 0189) evaluated with Procedure Number PSUSA/00010186/202405 that completed in March 2025. Neither of these reviews found evidence of a causal relationship between vedolizumab treatment and pancreatitis.

Patients with IBD have an increased incidence of pancreatitis compared with the general population and have a myriad of conditions that result in direct pancreatic damage. Cholelithiasis, primary sclerosing cholangitis, and ERCP are some of the conditions that predispose patients with IBD to developing pancreatitis (Roberts et al. 2017; Weiss et al. 2019). In addition, concurrent medical conditions and concomitant medications may also contribute to the risk of developing pancreatitis, independent of IBD activity. A recent systematic literature review was conducted using four major databases, which identified eight eligible observational studies for analysis (Tel et al. 2020). This study found that the pooled odds for AP in IBD are 3 times higher (OR, 3.11) than in the non-IBD population, the odds are higher in CD than in UC. Also, the study found that the pooled annual incidence of AP in IBD was 210/100,000 person-years (95% CI, 84–392/100,000 person-years).

Patients with IBDs are at an increased risk of pancreatitis; however, the role of IBD therapy in the development of pancreatitis is currently unclear. Distinguishing IBD from pancreatitis in patients is often difficult owing to similarities in the clinical symptoms presented; for example, abdominal pain and diarrhea are typically experienced by both patient populations. The publication by Joe F. Wernicke et al. (Wernicke et al. 2023) reported that an integrated summary of safety data from six clinical trials evaluating vedolizumab in patients with IBD showed that only 0.7% of patients (n = 12/1723) taking vedolizumab developed acute or chronic pancreatitis; however, no association between taking vedolizumab and onset of pancreatitis was confirmed. Sara Massironi et al. (Massironi et al. 2022) reported that nine studies were identified on biological agents. This study mentioned that drug-induced AP is an extremely rare adverse effect of biological agents with only a few cases reported for infliximab and vedolizumab.

Based on the available clinical study and cumulative post-marketing data review, the current literature and what is known about the mechanism of action of vedolizumab, and subsequent signal detection activities, Takeda has concluded that the evidence available at this time is insufficient to support a causal relationship between vedolizumab and developing or recurrent pancreatitis. In conclusion, the addition of pancreatitis to the ADR in section 4.8 of the SmPC is not warranted. Takeda will continue to monitor the event of pancreatitis in patients exposed to vedolizumab treatment by routine pharmacovigilance activities.

Assessor's comment

The Applicant provided the narratives (both adult patients) and discussion regarding the possible causal relationship of vedolizumab with eosinophilic pneumonia and pancreatitis, as requested.
As regards a case of eosinophilic pneumonia, the temporal association between vedolizumab initiation and event onset suggests a possible relationship; however, a definitive causal association cannot be established due to confounding by concomitant mesalazine, which is recognized as causally associated with eosinophilic pneumonia and is listed as an adverse drug reaction in EU SmPC. The Applicant argues that, as eosinophilic pneumonia is a specific type of interstitial lung disease and since "Interstitial Lung Disease", as a broader medical term, is already included in section 4.8 of the current SmPC, no amendments of the section 4.8 are proposed. This is agreed.
Regarding the case of pancreatitis, the MAH assessed it as unlikely related to vedolizumab. The event was confounded by the use of mesalazine, as normalization of pancreatic enzymes and improvement of symptoms following mesalazine withdrawal suggests a stronger association with 5-ASA therapy. Mesalazine is known to be causally associated with pancreatitis which is listed as an ADR in the EU SmPCs.
The Applicant reported that the evaluation of the literature case cited in the assessment report was previously submitted to EMA in January 2023 as part of an earlier review on pancreatitis (Data Lock Point: 15 September 2022) in response to a PRAC request for a comprehensive

analysis of all known cases of pancreatitis associated with vedolizumab treatment during Procedure Number EMEA/H/C/002782/II/0073. Additionally, a cumulative review of pancreatitis cases was submitted to PRAC (Data Lock Point: 19 May 2022) in the most recently submitted PBRER (covering 20 May 2021 to 19 May 2024) evaluated with Procedure Number PSUSA/00010186/202405 that completed in March 2025. Neither of these reviews found evidence of a causal relationship between vedolizumab treatment and pancreatitis. This is acknowledged.
Patients with IBD have an increased incidence of pancreatitis compared with the general population and have a myriad of conditions that result in direct pancreatic damage. Cholelithiasis, primary sclerosing cholangitis, and ERCP are some of the conditions that predispose patients with IBD to developing pancreatitis (Roberts et al. 2017; Weiss et al. 2019). In addition, concurrent medical conditions and concomitant medications may also contribute. A recent systematic literature review found that the pooled odds for AP in IBD are 3 times higher (OR, 3.11) than in the non-IBD population, the odds are higher in CD than in UC.
Based on the available clinical study and cumulative post-marketing data review, the current literature and what is known about the mechanism of action of vedolizumab, and subsequent signal detection activities, the Applicant has concluded that the evidence available at this time is insufficient to support a causal relationship between vedolizumab and developing or recurrent pancreatitis.
In conclusion, the addition of pancreatitis to the ADR in section 4.8 of the SmPC is not warranted and it will continue to be monitored by routine pharmacovigilance activities.
Issue not further pursued.

5. Clarification of ADR Designation:

The "Adverse Drug Reaction (ADR)" designation throughout the CSR refers to adverse events reported by the investigator as related to study drug; this does not imply a confirmed causal relationship as per ICH E2A/E2D definitions. Takeda conducts an independent assessment in accordance with regulatory standards, which requires a "reasonable possibility" of a causal relationship for SmPC inclusion.

Case Assessment and Epidemiological Context:
This colon cancer case, described in the clinical study report, involves a male aged with UC who received vedolizumab 300 mg IV for the treatment of pancolitis, diagnosed in 2020. The case was reported by the treating physician as part of a specified drug-use survey.

The patient's current medical conditions included Hepatitis B virus infection. At the time of colon cancer discovery, the patient had been diagnosed with UC for 33 months. His medical history included meningitis due to Listeria, iron deficiency anemia, epilepsy, cerebral infarction, deep vein thrombosis, depression, neurogenic bladder, and steroid resistance. Prior medication history included infliximab and concomitant medications included mesalazine and tenofovir alafenamide.

Vedolizumab therapy was initiated in 2022, with subsequent doses administered through 2023. The seventh and final dose was given in 2023.

In 2023, approximately 10 months after starting vedolizumab, a follow-up colonoscopy revealed a suspected ascending colon cancer, which was subsequently confirmed.

In 2023, the patient underwent laparoscopic right hemicolectomy, total colectomy, and ileostomy. Colon cancer was resolved following surgery.

The treating physicians assessed the event of ascending colon cancer as related, noting that a causal relationship with vedolizumab could not be ruled out. However, Takeda assessed the event as unlikely to be related to vedolizumab. This assessment is supported by multiple studies demonstrating that vedolizumab is not associated with an increased risk of malignancy, including colorectal cancer, in patients with IBD. Long-term safety data and comparative analyses with other biologics have consistently shown no elevated cancer risk attributable to vedolizumab (Feagan et al. 2013; Sands et al. 2019; Singh et al. 2022).

Importantly, the development of colorectal cancer in UC patients is primarily driven by chronic inflammation. In this case, the patient had pancolitis for nearly three years prior to cancer detection, suggesting that the malignancy may have been developing independently of vedolizumab exposure. Furthermore, the case is confounded by prior use of infliximab, which carries a boxed warning for malignancies and has been associated with increased cancer risk in some studies (Eaden et al. 2001; Eaden and Mayberry 2002; Remicade (infliximab) 2025).

Taken together, the short duration of vedolizumab exposure, the underlying chronic inflammatory condition, and the confounding history of infliximab use support the conclusion that vedolizumab is unlikely to be causally implicated in the development of colon cancer in this patient.

Based on all available data, there is not sufficient evidence supporting the inclusion of colon cancer in section 4.8 of the SmPC as an ADR.

Assessor's comment

The Applicant provided narrative and discussion regarding the case of colon cancer in an adult patient.

Initially, the Applicant clarified that the "Adverse Drug Reaction (ADR)" designation throughout the CSR refers to adverse events reported by the investigator as related to study drug; this does not imply a confirmed causal relationship as per ICH E2A/E2D definitions. The Applicant conducts an independent assessment, which requires a "reasonable possibility" of a causal relationship for SmPC inclusion.

The Applicant concludes that the short duration of vedolizumab exposure, the underlying chronic inflammatory condition, and the confounding history of infliximab use support the conclusion that vedolizumab is unlikely to be causally implicated in the development of colon cancer in this patient.

Based on all available data, there is not sufficient evidence supporting the inclusion of colon cancer in section 4.8 of the SmPC as an ADR.

Issue solved.

5. CHMP overall conclusion and recommendation

In summary, taking into account the limitations of the observational study, the effectiveness results observed in the pediatric subpopulation (consisting only of adolescent patients) are considered supportive and seem to be in line with the results in adult patients with UC in Japan included in this study. With regards to safety, the adverse events are in line with those reflected in section 4.8 of the EU SmPC. Some additional information regarding eosinophilic pneumonia, pancreatitis, and colon cancer (one adult case each) reported as SAE was requested, and the applicant has provided narratives and discussion. It is agreed with the applicant that these events are currently considered to be unrelated to vedolizumab or already included as a broader term in section 4.8 of the SmPC. No new safety concerns are evoked.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Entyvio Active substance: vedolizumab

Study title	Study number	Date of completion	Date of submission of final study report
Entyvio for Intravenous Infusion 300 mg Special Drug Use-Results Surveillance Study "Ulcerative Colitis"	Vedolizumab 5033	Study period February 2019 to 31 October 2024 Date of study completion (date of completion of the final analysis): 12 February 2025	01 Aug 2025