21 May 2026
EMADOC-1700519818-3226014
Human Medicines Division

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

Entyvio

Vedolizumab

Procedure no: EMA/PAM/0000323359

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	2 March 2026	2 March 2026
☐	CHMP comments	16 March 2026	16 March 2026
☐	Updated CHMP Rapporteur AR	19 March 2026	19 March 2026
☐	CHMP outcome - RSI	26 March 2026	26 March 2026
☐	Submission	21 April 2026	21 April 2026
☐	CHMP Rapporteur AR	06 May 2026	06 May 2026
☐	CHMP comments	11 May 2026	n/a
☐	Updated CHMP Rapporteur AR	13 May 2026	n/a
☒	CHMP outcome	21 May 2026	21 May 2026

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1. Introduction

On 12 January 2026, the MAH submitted a completed paediatric study for Entyvio, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study 2005 is part of a clinical development program. (PIP, EMEA-000645-PIP01-09-M09)

LINE LISTING OF ALL THE STUDIES INCLUDED IN THE DEVELOPMENT PROGRAM:

Study title	Study number	Date of completion	Date of submission of final study report
NA: Study deleted during procedure EMEA-000645-PIP01-09-M08	PIP Study 4	NA	NA
Randomised, double-blind, dose-ranging clinical pharmacology study to determine the pharmacokinetics, safety and tolerability of vedolizumab in paediatric subjects from 2 years to less than 18 years of age with ulcerative colitis (UC) or Crohn's disease (CD).	PIP Study 1: MLN0002-2003	26 May 2020 (Deferred: August 2020)	16 November 2020 (Procedure EMEA/H/C/002782/P46/006)
Modelling and simulation study to evaluate use of vedolizumab via the subcutaneous (SC) route in children and adolescents from 2 years to less than 18 years with UC or CD.	PIP Study 6	2 June 2021 (Deferred: August 2021)	Included in PIP M08; Submission to eCTD will occur with procedure to update product information based on results from PIP Study 5.
Randomised, double-blind, multicentre study comparing two doses to evaluate the efficacy, safety and pharmacokinetics of vedolizumab intravenous (IV) as maintenance therapy in paediatric subjects from 2 years to less than 18 years of age with moderately to severely active UC who achieved clinical response following open-label vedolizumab IV therapy.	PIP Study 3: MLN0002-3024	Last Patient Last Visit: 1 July 2025 (Deferred: November 2025)	By end December 2025
A Phase 2b, Extension Study to Determine the Long-term Safety of Vedolizumab IV in Pediatric Subjects With Ulcerative Colitis or Crohn's Disease	KBE (specific follow-up) of PIP Study 1: Vedolizumab-2005	Last Patient Last Visit: 17 July 2025	Planned January 2026
Open-label study to determine the pharmacokinetics, safety and immunogenicity of vedolizumab SC use in paediatric subjects	PIP Study 5: vedolizumab-3003	Ongoing (Deferred: June 2028)	

2.2. Information on the pharmaceutical formulation used in the study

Vedolizumab was approved in May 2014 in the European Union under the invented name Entyvio (EMEA/H/C/002782) for the treatment of adult patients with moderately to severely active UC or CD who have had an inadequate response, lost response, or were intolerant to conventional therapies. Entyvio

is available as a powder concentration for solution for infusion in vials containing 300 mg of vedolizumab (induction and maintenance treatment), and as solution for injection in prefilled syringes and prefilled pens containing 108 mg of vedolizumab for subcutaneous administration (maintenance treatment). The solution for infusion was used in this trial.

The formulation used in the study was 300 mg/vial in 20 mL vial for IV infusion.

Study Drug, Dose and Mode of Administration, and Lot Number

Study Drug	Dose Strength and Final Form	Study Dosage	Route of Administration	Drug Product Lot Number
Vedolizumab	300 mg/ 20 mL vial	100 mg, 150 mg, 200 mg, 300 mg	IV	

Vedolizumab IV infusion was administered over approximately 30 minutes for all subjects weighing ≥20 kg (longer infusion times up to 60 minutes may have been used). For subjects weighing <20 kg, the infusion was administered over approximately 2 hours.

Dosing regimens in this study were the same as those in the parent Study 2003. Vedolizumab IV doses of 300 or 150 mg Q8W for subjects ≥30 kg body weight and 200 or 100 mg Q8W for subjects <30 kg body weight were continued in Study 2005 after Week 22 visit in Study 2003 (or up to 1 week after) for subjects who consented to participate in this study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final report for:

Vedolizumab-2005: a phase 2b extension study designed to determine the long-term safety of vedolizumab IV in pediatric subjects with UC or CD who had initiated vedolizumab treatment at 2 to 17 years of age, inclusive, in Study 2003 (a phase 2, dose-ranging study). Pediatric subjects who had completed Study 2003, and at Week 22, had achieved clinical response were enrolled in the study.

2.3.2. Clinical study

Vedolizumab-2005 Study: A Phase 2b, Extension Study to Determine the Long-term Safety of Vedolizumab IV in Pediatric Subjects With Ulcerative Colitis or Crohn's Disease

Description

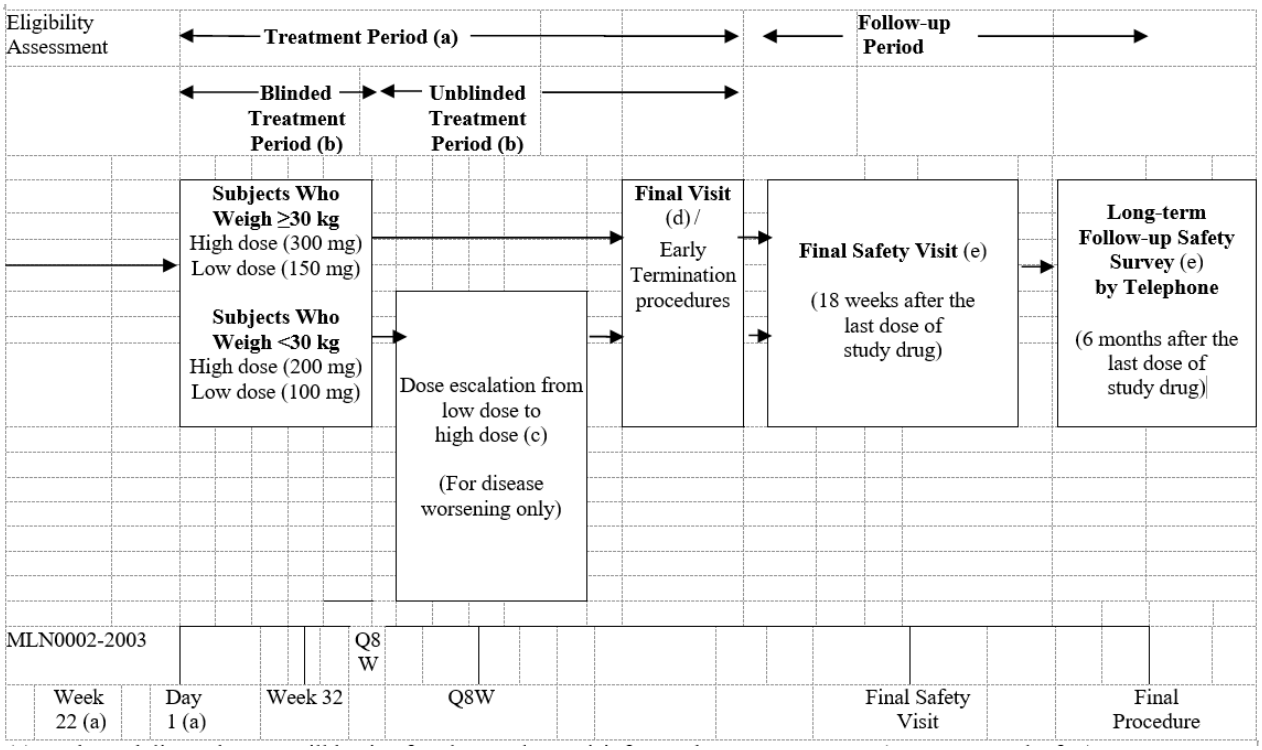
Study 2005 was a phase 2b extension study designed to determine the long-term safety of vedolizumab IV in pediatric subjects with Ulcerative Colitis (UC) or Crohn Disease (CD) who had initiated vedolizumab treatment at 2 to 17 years of age, inclusive, in Study 2003 (a phase 2, dose-ranging study). Pediatric subjects who had completed Study 2003 and, at Week 22, had achieved clinical response were enrolled in the study. Clinical response was defined for patients with UC by a reduction of partial Mayo score of ≥2 points and ≥25% from baseline, or a reduction of the Pediatric Ulcerative Colitis Activity Index (PUCAI) of ≥20 points from baseline; for patients with CD, by a reduction of the CDAI as defined by a ≥70-point decrease from baseline or a decrease of Pediatric Crohn's Disease Activity Index (PCDAI) of ≥15 points.

Eligible subjects received their first dose within 1 week of completing the Week 22 assessments of the preceding study. Dosing regimens in this study were the same as those in the parent Study 2003. Vedolizumab IV doses of 300 or 150 mg once every 8 weeks (Q8W) for subjects ≥30 kg body weight

and 200 or 100 mg Q8W for subjects <30 kg body weight were continued in Study 2005 after Week 22 visit in Study 2003 (or up to 1 week after) for subjects who consented to participate in the study.

The study included Data Safety Monitoring Board (DSMB) to review the safety, pharmacokinetics (PK), and other relevant data. The DSMB was in place until April 2021 and was decommissioned after the study drug dosing was unblinded and following the completion of Week 40 visit by the last subject. The sponsor's Risk Assessment and Minimization Program for progressive multifocal leukoencephalopathy (PML) included a program-level PML Independent Adjudication Committee (IAC), which was in scope for this study to review and adjudicate potential PML events. Although the Risk Assessment and Minimization Program for PML was discontinued in 2019, the PML IAC was in effect till the end of the study.

Figure 1. Study design schematic



Methods

Study participants

This study enrolled pediatric subjects aged 2 to 17 years with UC or CD who completed Study 2003 and demonstrated clinical response at Week 22 of that study. Eligibility criteria required:

• For UC:

– Reduction in the partial Mayo score by ≥2 points and ≥25% from baseline, or

– Reduction in the PUCAI by ≥20 points from baseline.

• For CD:

– Reduction in the CDAI by ≥70 points from baseline, or

– Reduction in the PCDAI by ≥15 points from baseline.

Treatments

Subjects received the initial dose of vedolizumab IV on Day 1 (up to 1 week after the Study 2003 Week 22 visit) and the administered dose was same as that of the Week 14 dose in Study 2003. Subsequent doses were administered Q8W.
Treatment duration depended on the subject's continued benefit, age and withdrawal, availability of other drug access programs (whichever came first), availability of vedolizumab IV for pediatric indications, or sponsor's decision.
Subjects with disease worsening based on PUCAI or PCDAI scores at 2 consecutive visits (scheduled or unscheduled) were eligible for vedolizumab IV dose escalation (150 mg to 300 mg or 100 mg to 200 mg). Dosing was based on the subject's weight at the time of nonresponse in Study 2005. Subjects already receiving the higher dose for their weight group were not eligible for escalation and were discontinued from treatment. Persistent disease worsening despite dose escalation required discontinuation.
Vedolizumab IV infusion was administered over approximately 30 minutes for all subjects weighing ≥20 kg (longer infusion times up to 60 minutes may have been used). For subjects weighing <20 kg, the infusion was administered over approximately 2 hours.

Table 1 Dose and Regimen

Weight Category [a] Vedolizumab Dose at Week 14 in Study 2003	**Extension Study (Day 1)**	**Disease Worsening [b][c]**
≥30 kg		
300 mg (high dose)	300 mg Q8W	Discontinue from study
150 mg (low dose)	150 mg Q8W	Escalate to 300 mg Q8W Discontinue from study for continued disease worsening
<30 kg		
200 mg (high dose)	200 mg Q8W	See footnote (d)
100 mg (low dose)	100 mg Q8W	See footnote (e) Discontinue from study for continued disease worsening

[a] After completion of Study 2003, subjects who had their dose increased based on nonresponse were dosed based on weight at the time of nonresponse.
[b] For UC, disease worsening was defined as an increase in the PUCAI of >20 points at 2 consecutive visits at least 7 days apart, or the PUCAI was >35 points at any scheduled or unscheduled visit. For CD, it was defined as an increase in the PCDAI of >15 points at 2 consecutive visits at least 7 days apart, or the PCDAI was >30 points at any scheduled or unscheduled visit.
[c] Continued disease worsening after a dose escalation was defined as no reduction in the elevated PCDAI or PUCAI scores when next assessed after the increased dose had been administered.
[d] If subjects' weight remained <30 kg at the time of nonresponse, treatment was discontinued. If subjects' weight increased to ≥30 kg at the time of nonresponse, the dose was increased to 300 mg Q8W.
[e] If subjects' weight remained <30 kg at the time of nonresponse, the dose was increased to 200 mg Q8W. If subjects' weight increased to ≥30 kg at the time of nonresponse, the dose was increased to 300 mg Q8W.

Objectives and Outcome/Endpoints

Herein a list of the study objectives and associated endpoint is reported:

Table 1 Primary Objective and Associated Endpoint

Primary Objective	Primary Endpoint
To determine the safety profile of long-term vedolizumab IV treatment in pediatric subjects with UC or CD.	Percentage of subjects with TEAEs.

Table 2 Secondary Objectives and Associated Endpoints

Secondary Objectives	Secondary Endpoints [a]
To evaluate the efficacy of long-term vedolizumab IV in pediatric subjects with UC or CD.	Maintenance of clinical response at Week 32, based on complete Mayo score (defined as a continued reduction in complete Mayo score of ≥3 points and >30% from the baseline [at initiation of Study 2003] and continued decrease in rectal bleeding subscore of ≥1 point from baseline of Study 2003, or absolute rectal bleeding subscore of ≤1 point at Week 32). Maintenance of clinical response at Week 32, based on SES-CD and CDAI (defined as a 50% reduction in SES-CD score on endoscopy compared to the baseline endoscopy [at initiation of Study 2003]; and continued reduction in CDAI that is a ≥70 point decrease from the baseline CDAI score at the initiation of Study 2003).
To determine the effect of long-term vedolizumab IV treatment on time to major IBD-related events (hospitalizations, surgeries, and procedures) in pediatric subjects with UC or CD.	Time to major IBD-related events (defined as time from study treatment start to first major IBD-related hospitalization, surgery, or procedure)
To examine the effect of long-term vedolizumab IV treatment on health-related QOL measurements in pediatric subjects with UC or CD.	Changes from Baseline in IMPACT-III (where translations are available) total and subscale scores at Week 24 and every 24 weeks, thereafter.
To determine the effect of long-term vedolizumab IV treatment on patterns of growth and development in pediatric subjects with UC or CD.	Height velocity at Week 48 and every 48 weeks, thereafter. Change from Baseline in height, weight, and BMI at Week 24 and every 24 weeks, thereafter. Percentage of subjects achieving Tanner stage V at or before age 16 (in females) or age 17 (in males).

[a] Endpoint updated in accordance with SAP Version 4.0. Endpoint definitions in SAP Version 4.0 (Appendix 16.1.9.4) differ slightly from those in the Protocol Amendment 8 (Appendix 16.1.1). For the UC endpoint on maintenance of clinical response at Week 32 based on complete Mayo score, >30% from baseline was added in SAP to align with clinical response definition in Section 3.5 of the Protocol Amendment 8. Please see

Table 3 Additional Objectives and Associated Endpoints

Additional Objectives	Additional Endpoints [a]
To evaluate the development of AVA in pediatric subjects with UC or CD.	Presence of positive AVA and neutralizing AVA.
To characterize vedolizumab PK at steady state in pediatric subjects with UC or CD.	Observed vedolizumab serum concentration at the end of a dosing interval (C_{trough}) at Week 48.
To evaluate the effect of vedolizumab treatment on fistula closure in pediatric subjects with CD.	Fistula remission (defined as the closure of all fistulas that were draining at baseline for at least 2 consecutive visits) and time to fistula remission.

[a] Endpoint updated in accordance with SAP Version 4.0. Minor differences exist between endpoint definitions in the SAP Version 4.0 (Appendix 16.1.9.4) and Protocol Amendment 8 (Appendix 16.1.1). These adjustments were made to improve clarity.

Table 4 Additional Endpoints

Indication	Endpoint	Definition [a]
UC	Maintenance of response based on PUCAI at Weeks 32, 80, 128, 176 and 224	No worsening of disease, with worsening defined as elevation of PUCAI of >20 points above the baseline at the time of entry into Study 2005 or a total PUCAI score of >35 points at Weeks 32, 80, 128, 176 and 224.
	Maintenance of remission based on PUCAI or complete Mayo score [b] at Weeks 32, 80, 128, 176, and 224	Maintenance of remission is defined as a PUCAI score of <10 or a complete Mayo score of ≤2 points with no individual subscore >1 at Week 32, and the subsequent q48-week visits (Weeks 80, 128, 176, and 224) at the time of optional endoscopy.
	Change in partial Mayo score	Change from Study 2003 baseline in partial Mayo score at each visit.
	Change in PUCAI	Change from Study 2003 baseline in PUCAI score at each visit.
CD	Maintenance of response based on PCDAI at Weeks 32, 80, 128, 176, and 224	No worsening of disease, with worsening defined as elevation of PCDAI of >15 points or a total PCDAI of >30 points at Weeks 32, 80, 128, 176, and 224.
	Maintenance of remission based on PCDAI or CDAI [b] at Weeks 32, 80, 128, 176, and 224	Maintenance of remission is defined as a PCDAI score of ≤10 or a CDAI score of ≤150 (assessed at Weeks 32, 80, 128, 176, and 224).
	Change in PCDAI	Change from Study 2003 baseline in PCDAI score at each visit.

Table 4 Additional Endpoints

Indication	Endpoint	Definition [a]
UC and CD	Clinical safety assessments	Clinical safety assessments including AEs, SAEs, vital signs, and results of standard laboratory tests (hematology and clinical chemistry).
	AESIs	AESIs: serious infections including opportunistic infections such as PML, malignancies, liver injury and infusion-related reactions.
	Height z-score	Change from Study 2003 baseline in height z-score.
	Steroid dose increase or decrease from baseline (at entry to Study 2003) at Week 48	Increase of steroid dose from baseline at Week 48. Decrease of steroid dose from baseline at Week 48.
	Change from baseline in CRP	Change from Study 2003 baseline in CRP.
	Exacerbations	Number of exacerbations with reappearance of blood in the stool.

The supplemental endpoints reported in the table below were not defined as study endpoints in the Protocol Amendment 8, but were added in SAP Version 4.0 to support summarizing study data, in line with additional study definitions defined in the Protocol Amendment 8 or as introduced as additional exploratory endpoints in SAP Version 1.0.

Table 5 Supplemental Endpoints

Indication	Endpoint	Definition
UC	Complete Mayo score at Week 32 [a]	Complete Mayo score at each visit
	Modified Mayo score at Week 32 [a]	Modified Mayo score at each visit
	Clinical response based on complete Mayo score or partial Mayo score at Week 32	A reduction in complete Mayo score of ≥3 points and ≥30% from Study 2003 baseline (or a partial Mayo score of ≥2 points and ≥25% from Study 2003 baseline, if the complete Mayo score was not performed at the visit) with an accompanying decrease in rectal bleeding subscore of ≥1 point (from Study 2003 baseline) or absolute rectal bleeding subscore of ≤1 point at Week 32.
	Clinical remission based on complete Mayo score at Week 32	A complete Mayo score of ≤2 points with no individual subscore >1 at Week 32.
	Clinical response based on modified Mayo score at Week 32	A reduction in total score of ≥2 points and ≥25% from Study 2003 baseline with an accompanying

Table 5 Supplemental Endpoints

Indication	Endpoint	Definition
		decrease in rectal bleeding subscore of ≥1 point from Study 2003 baseline or absolute rectal bleeding subscore of ≤1 point at Week 32.
	Clinical response based on PUCAI	A ≥20-point decrease from Study 2003 baseline in PUCAI score. (up to Week 224)
	Clinical remission based on PUCAI	A PUCAI score <10. (up to Week 224)
	Disease worsening based on PUCAI	An increase in the PUCAI of >20 points at 2 consecutive visits at least 7 days apart, or the PUCAI was >35 points at any scheduled or unscheduled visit.
CD	CDAI score at Week 32 [a]	CDAI score at each visit
	SES-CD score at Week 32 [a]	SES-CD at each visit
	Clinical response based on CDAI at Week 32	A ≥70-point decrease from Study 2003 baseline in CDAI score at Week 32.
	Clinical remission based on CDAI at Week 32	CDAI score ≤150 at Week 32.
	Endoscopic response based on SES-CD at Week 32 (referred to as clinical response based on SES-CD at Week 32 in SAP Version 4.0) [a]	A ≥50% reduction in SES-CD score from Study 2003 baseline endoscopy (or meets criteria for clinical remission based on SES-CD score 0 to 2) at Week 32.
	Endoscopic remission based on SES-CD at Week 32 (referred to as clinical remission based on SES-CD at Week 32 in SAP Version 4.0)	SES-CD score 0 to 2 at Week 32.
	Enhanced clinical response based on CDAI at Week 32	A ≥100-point decrease from Study 2003 baseline in CDAI score at Week 32.
	Clinical response based on PCDAI	A ≥15-point decrease from Study 2003 baseline in PCDAI score with total PCDAI ≤30. (up to Week 224)
	Clinical remission based on PCDAI	PCDAI score ≤10. (up to Week 224)
	Disease worsening based on PCDAI	An increase in the PCDAI of >15 points at 2 consecutive visits at least 7 days apart, or the PCDAI was >30 points at any scheduled or unscheduled visit.

Sample size

It was estimated that up to 80 subjects (40 subjects with UC and 40 subjects with CD) who had completed Study 2003 were to enter this study. No formal sample size calculations were performed for this study.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

Efficacy analyses were performed using the FAS and were exploratory; no formal statistical comparisons were made. For response-type binary efficacy endpoints based on Mayo, CDAI, PUCAI, or PCDAI scores, subject having missing data for determination of binary endpoint (that is, missing data for the component of the respective scale) at any time point were handled as described below.

• In general, missing data for response-type endpoints up to and including Week 32 were handled using the non-responder imputation method, that is, any subject with missing information for determination of endpoint status up to Week 32 was considered as a nonresponder in the analysis.

• For Week 32 endpoints based on Mayo or CDAI scores, handling of missing data using nonresponder imputation method was planned with the following exception: missing diary data of subjects who were not dispensed a subject diary (at Week 32) per the protocol version they were enrolled under, were not imputed but instead were removed from the analysis of these endpoints.

For subjects with UC, 2 approaches for the assessment of efficacy by the Mayo scores were used:

• GEMINI Approach: For comparing the efficacy results with GEMINI studies, the complete Mayo score, partial, and modified Mayo score for each subject were calculated using the conventions of calculating Mayo score in GEMINI studies. The GEMINI approach served as the primary method to calculate Mayo score and derive all Mayo score-based efficacy endpoints.

• Draft US FDA UC 2016 Guidance Approach: The complete, partial, and modified Mayo scores were also calculated per draft US FDA UC Guidance (August 2016). The efficacy endpoints based on complete, partial, or modified Mayo scores at Week 32 were derived using this approach as sensitivity analysis.

Pharmacokinetics:

No formal PK analysis was performed. Serum vedolizumab concentrations were descriptively summarized using the PK analysis set. Missing PK data were not imputed.

Immunogenicity:

Immunogenicity of vedolizumab was summarized using the SAF including all evaluable samples collected from baseline/pre-dose to the last subject's last assessment (including the safety follow-up). The subject's anti-vedolizumab antibody (AVA) assessment at Week 22 of Study 2003 was considered as baseline/pre-dose AVA assessment for Study 2005. AVA and neutralizing AVA status were evaluated during the study. In addition, the potential impact of AVA status on vedolizumab PK and safety was explored.

Protocol changes

- **Protocol amendments**

The protocol was amended globally 7 times and locally 1 time for United Kingdom; the first subject was enrolled on 30 July 2018 under Protocol Amendment 4.

Noteworthy changes introduced by global amendments in the conduct of the study were as follows:

• In **Amendment 1 (07 April 2017)** updates were made to allow enrollment of pediatric subjects aged 2 to 17 years, who weighed <30 kg, and vedolizumab IV dose and dosing regimen for these subjects were added.
• **In Amendment 3 (13 October 2017)** updates were made to clarify inclusion criterion 4 and definition of disease worsening.
• In **Amendment 4 (13 February 2018)** initial blinding of dose was incorporated, an addition endoscopy requirement was added, and inclusion and exclusion criteria, definition of disease worsening and concomitant medication usage were clarified.
• In **Amendment 5 (24 August 2018)** subject diaries for symptom assessment was added and information related to endoscopy evaluation tools was clarified.
• In **Amendment 7 (08 March 2023)** the following changes were made:
  - Described the management of study procedures to maintain subject safety, confidentiality, and study integrity in the context of health care delivery challenges due to a pandemic (for example, COVID-19).
  - Removed the data and safety monitoring board.
  - Removed the Risk Assessment and Minimization Program for PML.
  - Described poststudy access to vedolizumab

• In **Amendment 8 (27 September 2024)** updates were made to
  - comply with EU CTR protocol requirements
  - TEAEs definition
  - Harmonize serious infections AESI definition across the vedolizumab program.

- **Changes in the planned analysis**

The Statistical Analysis Plan (SAP) was changed with the introduction of the amendment 8; the table below sums up the main changes.

Table 9 Changes to the Planned Analysis

Protocol Version 8.0	Changes in SAP Version 4.0	Rationale
Sections 5.5.2	For the UC secondary endpoint definition on "maintenance of clinical response at Week 32, based on complete Mayo score", SAP specifies ">30% change from baseline", whereas Section 5.5.2 of the protocol does not include this criterion. Final statistical analyses were done using the SAP definition.	This update was made in SAP to align with the clinical response definition in Section 3.5 of the protocol.
SAP Version 4.0	**Changes in Final Statistical Analyses/Outputs**	**Rationale**
Section 5.2	Endpoint of change from baseline for height specifies every 24 weeks but summary was done using every 48 weeks.	Height, height Z-score and height velocity summarized every 48 weeks to simplify reporting as annual measurements are clinically sufficient in a pediatric population.
Section 7.3	A post hoc reassessment of significant protocol deviations was done, and results are summarized for enrolled set.	A post hoc reassessment of significant protocol deviations was done to understand and identify deviations that had a critical impact on safety, data integrity, or the overall interpretability of the study results.
Section 7.1.4	Endoscopy was mandatory only at Week 32. After that time point, the procedure was optional and was therefore not performed regularly. Therefore, the main assessment for response and remission was focused on Week 32. Response and remission results at other weeks for these tests are not summarized.	Because endoscopy was optional after Week 32, it was not performed regularly. This affected any endpoint and result after Week 32 that used endoscopy results (including the complete Mayo, SES-CD, and CDAI tests) and the associated response and remission assessments.
Section 7.1.4	Results for clinical response and remission based on Mayo and CDAI scores endpoints at Week 32 were derived from observed cases instead of applying non-responder imputation for missing data for subjects required to complete a diary at Week 32.	Date of reconsent under Protocol Amendment 5 was not captured in the study database for all subjects (only the original date of consent was captured). As a result, information needed to determine requirement for diary completion was not available for all subjects. Therefore, this analysis was not conducted, and instead the results were shown based on observed cases.
Section 7.1.4	Results for clinical response and remission based on SES-CD at Week 32 were derived from observed cases instead of applying non-responder imputation.	Rule for non-responder imputation was applied incorrectly.
Section 7.9.1	For PK, the approach of treating values above the ULOQ as missing was removed and the ULOQ values were included in the associated outputs.	Concentration values above the ULOQ were included to ensure the data more accurately reflects the observed concentration ranges, reduces bias introduced by missing data and improves the robustness and interpretability of PK data.
Section 7.10.1	IMPACT-III scoring was done such that if 1 question was missing then the affected subscore and total score were left missing.	Same analysis as in parent study 2003 was followed.

Results

Participant flow and recruitment

As reported in the sample size section, up to 80 subjects (40 with UC and 40 with CD) were planned to complete Study 2003; 67 responder subjects (30 <30 kg; 37 ≥30 kg) completed the parent study.
Of these 67 subjects, 59 (28 <30 kg and 31 ≥30 kg) were enrolled in study 2005: 31 were UC patients (14 <30 kg and 17 ≥30 kg), while 28 presented a diagnosis of CD: 28 subjects (14 subjects <30 kg; 14 subjects ≥30 kg).
Overall, 38.7% of subjects ≥ 30 kg completed study; the main reason for discontinuation were AEs (42%), withdrawal of subjects and other reason in the 26.3% each; in subjects < 30 kg, 42.9% of subjects completed the study. Also in this group, main reasons for study discontinuation were AEs 53.3%, withdrawal of subjects 20% and other reason 13.3%. To note, withdrawal from study was allowed for causes independent from safety and efficacy issues, like in case of achievement of 18 years of age, even in remission status.

Baseline data

Table : Demographic and baseline characteristics

Table 15.1.2
Summary of Eligibility of Subject

Eligible Subjects	59
Total Screen Failures	0
Age (years) [a]	
n	59
Mean (SD)	10.8 (4.08)
Median	11.0
Q1, Q3	8.0, 14.0
Min, Max	2, 17
Age Category [n (%)]	
Children [2-11 years]	33 (55.9)
Adolescents [12-17 years]	26 (44.1)
Sex [n (%)]	
Male	34 (57.6)
Female	25 (42.4)
Missing	0
Ethnicity [n (%)] [b]	
Hispanic or Latino	6 (10.2)
Not Hispanic or Latino	51 (86.4)
Not Reported	1 (1.7)
Unknown	1 (1.7)
Race [n (%)]	
American Indian or Alaska Native	0

[a] Age is calculated as the difference between date of birth and date of informed consent.
[b] Ethnicity is not collected at some study sites in Europe and are counted as "Not Reported".
Note: Screen failures include only those subjects who signed informed consent and were not enrolled in the study.

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Table 15.1.2
Summary of Eligibility of Subject

Asian	2 (3.4)
Asian Indian	0
Chinese	0
Japanese	1 (1.7)
Korean	0
Not Reported	0
Missing	1 (1.7)
Black or African American	4 (6.8)
Native Hawaiian or Other Pacific Islander	0
White	48 (81.4)
Multiple	2 (3.4)
Not Reported	3 (5.1)
Primary Reason Subject Failed Screening [n (%)]	
Adverse Event	0
Protocol Deviation	0
Lost to Follow-up	0
Withdrawal by Subject	0
Did Not Meet Entrance Criteria	0
Other	0

[a] Age is calculated as the difference between date of birth and date of informed consent.
[b] Ethnicity is not collected at some study sites in Europe and are counted as "Not Reported".
Note: Screen failures include only those subjects who signed informed consent and were not enrolled in the study.

Table : Baseline disease characteristics in subjects with UC < 30 kg and ≥ 30 kg

Table 19 Baseline Disease Characteristics in Subjects <30 kg and ≥30 kg With UC (Enrolled Set)

	Subjects <30 kg			Subjects ≥30 kg		
Characteristic	100 mg (N=5)	200 mg (N=9)	Total (N=14)	150 mg (N=10)	300 mg (N=7)	Total (N=17)
Disease duration (years) [a]						
n	5	9	14	10	7	17
Mean (SD)	3.16 (3.657)	3.37 (2.839)	3.29 (3.014)	2.58 (2.151)	3.39 (2.535)	2.91 (2.276)
Median	1.70	1.70	1.70	1.75	2.50	2.10
Min, Max	0.8, 9.5	0.8, 7.7	0.8, 9.5	0.7, 7.9	0.9, 8.6	0.7, 8.6
Disease duration, n (%) [a]						
<1 year	2 (40.0)	3 (33.3)	5 (35.7)	1 (10.0)	1 (14.3)	2 (11.8)
≥1 to <3 years	1 (20.0)	2 (22.2)	3 (21.4)	6 (60.0)	3 (42.9)	9 (52.9)
≥3 to <7 years	1 (20.0)	3 (33.3)	4 (28.6)	2 (20.0)	2 (28.6)	4 (23.5)
≥7 years	1 (20.0)	1 (11.1)	2 (14.3)	1 (10.0)	1 (14.3)	2 (11.8)
Fecal calprotectin (µg/g)						
n	5	8	13	10	7	17
Mean (SD)	709.8 (573.64)	575.9 (849.87)	627.4 (731.86)	454.0 (749.49)	553.7 (747.64)	495.1 (726.73)
Median	831.0	194.0	266.0	79.0	107.0	107.0
Min, Max	100, 1510	41, 2417	41, 2417	10, 2299	10, 1645	10, 2299
Fecal calprotectin, n (%)						
≤250 µg/g	2 (40.0)	4 (44.4)	6 (42.9)	7 (70.0)	4 (57.1)	11 (64.7)
>250 µg/g and ≤500 µg/g	0	2 (22.2)	2 (14.3)	0	1 (14.3)	1 (5.9)
>500 µg/g	3 (60.0)	2 (22.2)	5 (35.7)	3 (30.0)	2 (28.6)	5 (29.4)
CRP (mg/L)						
n	5	8	13	10	7	17
Mean (SD)	5.90 (6.080)	4.26 (8.832)	4.89 (7.649)	0.82 (1.378)	0.69 (0.430)	0.76 (1.069)
Median	3.70	0.70	1.00	0.20	0.80	0.30
Min, Max	0.2, 12.5	0.2, 25.9	0.2, 25.9	0.2, 4.6	0.2, 1.3	0.2, 4.6
CRP [n (%)]						
≤1 mg/L	2 (40.0)	5 (55.6)	7 (50.0)	8 (80.0)	5 (71.4)	13 (76.5)
>1 mg/L and ≤3 mg/L	0	1 (11.1)	1 (7.1)	1 (10.0)	2 (28.6)	3 (17.6)
>3 mg/L and ≤10 mg/L	1 (20.0)	1 (11.1)	2 (14.3)	1 (10.0)	0	1 (5.9)
>10 mg/L	2 (40.0)	1 (11.1)	3 (21.4)	0	0	0
Anti-TNF antagonist history,						

Table 19 Baseline Disease Characteristics in Subjects <30 kg and ≥30 kg With UC (Enrolled Set)

Characteristic	Subjects <30 kg			Subjects ≥30 kg		
	100 mg (N=5)	200 mg (N=9)	Total (N=14)	150 mg (N=10)	300 mg (N=7)	Total (N=17)
n (%)						
Naive	5 (100)	6 (66.7)	11 (78.6)	6 (60.0)	4 (57.1)	10 (58.8)
Exposed/failed	0	3 (33.3)	3 (21.4)	4 (40.0)	3 (42.9)	7 (41.2)
Baseline PUCAI total score						
n	5	8	13	10	7	17
Mean (SD)	9.0 (6.52)	10.0 (11.65)	9.6 (9.67)	3.5 (6.69)	7.9 (11.50)	5.3 (8.92)
Median	10.0	7.5	10.0	0.0	0.0	0.0
Min, Max	0, 15	0, 30	0, 30	0, 20	0, 30	0, 30
Baseline disease activity based on PUCAI, n (%)						
Remission (0 to 9)	2 (40.0)	4 (44.4)	6 (42.9)	8 (80.0)	4 (57.1)	12 (70.6)
Mild (10 to 34)	3 (60.0)	4 (44.4)	7 (50.0)	2 (20.0)	3 (42.9)	5 (29.4)
Moderate (35 to 64)	0	0	0	0	0	0
Severe (65 to 85)	0	0	0	0	0	0
Baseline complete Mayo score						
n	5	8	13	10	7	17
Mean (SD)	2.4 (2.51)	3.0 (2.14)	2.8 (2.20)	2.1 (1.66)	2.6 (2.94)	2.3 (2.20)
Median	1.0	3.0	3.0	2.0	2.0	2.0
Min, Max	0, 6	0, 7	0, 7	0, 4	0, 7	0, 7
Baseline disease activity based on complete Mayo score [n (%)]						
Mild (<6)	4 (80.0)	7 (77.8)	11 (78.6)	10 (100)	5 (71.4)	15 (88.2)
Moderate (6 to 8)	1 (20.0)	1 (11.1)	2 (14.3)	0	2 (28.6)	2 (11.8)
Severe (9 to 12)	0	0	0	0	0	0

Source: Table 15.1.8.2.

Mayo scores and subscores for this table were calculated using the GEMINI approach.

Disease duration and Anti-TNF agonist history were based on the data collected at the entry of Study 2003. Baseline for all variables including partial Mayo score (excluding complete Mayo score) were based on the data collected on Day 1 visit for Study 2005. Baseline for complete Mayo score were based on the data collected on the latest visit on or after Week 14 from the Study 2003. Subscores were presented even if another subscore was missing. Subscores could be part of a complete Mayo score or a partial Mayo score.

One <30 kg subject allocated to the 200 mg arm was enrolled to Study 2005 but not treated.

[a] Disease duration was defined as the date from first diagnosis to date of informed consent.

Table : Baseline disease characteristics in subjects with CD < 30 kg and ≥ 30 kg

Table 20 Baseline Disease Characteristics in Subjects <30 kg and ≥30 kg With CD (Enrolled Set)

Characteristic	Subjects <30 kg			Subjects ≥30 kg		
	100 mg (N=7)	200 mg (N=7)	Total (N=14)	150 mg (N=4)	300 mg (N=10)	Total (N=14)
Disease duration (years) [a]						
n	7	7	14	4	10	14
Mean (SD)	2.39 (0.955)	1.96 (0.529)	2.17 (0.774)	3.40 (1.158)	5.42 (2.672)	4.84 (2.480)
Median	2.80	1.70	1.90	3.80	5.25	4.40
Min, Max	0.8, 3.5	1.5, 2.9	0.8, 3.5	1.7, 4.3	1.3, 8.8	1.3, 8.8
Disease duration, n (%) [a]						
<1 year	1 (14.3)	0	1 (7.1)	0	0	0
≥1 to <3 years	4 (57.1)	7 (100)	11 (78.6)	1 (25.0)	3 (30.0)	4 (28.6)
≥3 to <7 years	2 (28.6)	0	2 (14.3)	3 (75.0)	4 (40.0)	7 (50.0)
≥7 years	0	0	0	0	3 (30.0)	3 (21.4)
Fecal calprotectin (µg/g)						
n	7	7	14	4	10	14
Mean (SD)	704.0 (1509.69)	4041.1 (4789.61)	2372.6 (3825.98)	721.8 (880.59)	1312.8 (1176.51)	1143.9 (1101.82)
Median	146.0	620.0	293.5	418.5	1074.5	633.5
Min, Max	16, 4116	108, 11035	16, 11035	37, 2013	13, 3508	13, 3508
Fecal calprotectin, n (%)						
≤250 µg/g	5 (71.4)	2 (28.6)	7 (50.0)	1 (25.0)	3 (30.0)	4 (28.6)
>250 µg/g and ≤500 µg/g	1 (14.3)	1 (14.3)	2 (14.3)	2 (50.0)	0	2 (14.3)
>500 µg/g	1 (14.3)	4 (57.1)	5 (35.7)	1 (25.0)	7 (70.0)	8 (57.1)
CRP (mg/L)						
n	7	6	13	4	10	14
Mean (SD)	0.44 (0.331)	4.62 (6.342)	2.37 (4.637)	5.20 (5.822)	13.03 (14.003)	10.79 (12.532)
Median	0.20	2.20	0.20	4.25	10.20	7.90
Min, Max	0.2, 0.9	0.2, 16.4	0.2, 16.4	0.3, 12.0	0.2, 49.2	0.2, 49.2
CRP [n (%)]						

Table 20 Baseline Disease Characteristics in Subjects <30 kg and ≥30 kg With CD (Enrolled Set)

Characteristic	Subjects <30 kg			Subjects ≥30 kg		
	100 mg (N=7)	200 mg (N=7)	Total (N=14)	150 mg (N=4)	300 mg (N=10)	Total (N=14)
≤1 mg/L	7 (100)	3 (42.9)	10 (71.4)	2 (50.0)	1 (10.0)	3 (21.4)
>1 mg/L and ≤3 mg/L	0	0	0	0	0	0
>3 mg/L and ≤10 mg/L	0	2 (28.6)	2 (14.3)	1 (25.0)	4 (40.0)	5 (35.7)
>10 mg/L	0	1 (14.3)	1 (7.1)	1 (25.0)	5 (50.0)	6 (42.9)
Anti-TNF antagonist history, n (%)						
Naive	4 (57.1)	3 (42.9)	7 (50.0)	2 (50.0)	2 (20.0)	4 (28.6)
Exposed/failed	3 (42.9)	4 (57.1)	7 (50.0)	2 (50.0)	8 (80.0)	10 (71.4)
Baseline SES-CD score						
n	6	6	12	4	10	14
Mean (SD)	6.7 (8.91)	11.7 (6.56)	9.2 (7.91)	6.8 (5.74)	8.5 (5.87)	8.0 (5.67)
Median	3.0	13.5	10.5	7.5	8.5	8.5
Min, Max	0, 22	0, 19	0, 22	0, 12	2, 22	0, 22
Baseline disease activity based on SES-CD, n (%)						
Inactive (0 to 2)	3 (42.9)	1 (14.3)	4 (28.6)	1 (25.0)	2 (20.0)	3 (21.4)
Mild (3 to 6)	1 (14.3)	0	1 (7.1)	1 (25.0)	2 (20.0)	3 (21.4)
Moderate (7 to 15)	1 (14.3)	4 (57.1)	5 (35.7)	2 (50.0)	5 (50.0)	7 (50.0)
Severe (>15)	1 (14.3)	1 (14.3)	2 (14.3)	0	1 (10.0)	1 (7.1)
Baseline PCDAI score						
n	7	7	14	4	10	14
Mean (SD)	2.50 (2.887)	9.29 (9.096)	5.89 (7.378)	0.63 (1.250)	11.25 (8.995)	8.21 (9.010)
Median	2.50	7.50	3.75	0.00	10.0	5.00
Min, Max	0.0, 7.5	0.0, 27.5	0.0, 27.5	0.0, 2.5	0.0, 27.5	0.0, 27.5
Baseline disease activity based on PCDAI, n (%)						
Inactive (0 to 10)	7 (100)	5 (71.4)	12 (85.7)	4 (100)	5 (50.0)	9 (64.3)
Mild (11 to 30)	0	2 (28.6)	2 (14.3)	0	5 (50.0)	5 (35.7)
Moderate to Severe (>30)	0	0	0	0	0	0
Baseline CDAI total score						
n	7	7	14	4	10	14
Mean (SD)	80.69 (36.476)	129.54 (99.749)	105.11 (76.479)	19.20 (17.706)	109.36 (59.009)	83.60 (65.342)
Median	88.40	118.80	95.90	21.10	109.20	74.60
Min, Max	37.2, 121.8	40.4, 328.4	37.2, 328.4	-2.2, 36.8	11.0, 200.6	-2.2, 200.6

Table 20 Baseline Disease Characteristics in Subjects <30 kg and ≥30 kg With CD (Enrolled Set)

Characteristic	Subjects <30 kg			Subjects ≥30 kg		
	100 mg (N=7)	200 mg (N=7)	Total (N=14)	150 mg (N=4)	300 mg (N=10)	Total (N=14)
Baseline disease activity based on CDAI, n (%)						
Inactive (0 to 330)	0	0	0	0	0	0
Moderate (≤330)	7 (100)	7 (100)	14 (100)	4 (100)	10 (100)	14 (100)
Severe (>330)	0	0	0	0	0	0

Source: Table 15.1.8.3.

Disease duration and anti-TNF agonist history were based on the data collected at the entry of Study 2003. Baseline for all variables except SES-CD and CDAI were based on data collected on the Day 1 visit for Study 2005. Baseline for SES-CD and CDAI was based on the data collected on the latest visit on or after Week 14 from the Study 2003.

* Disease duration was defined as the date from first diagnosis to date of informed consent.

To note, CDAI score is not validated for use in children; its use in some early paediatric studies was applied for descriptive purposes. In adult vedolizumab studies in CD subjects, a CDAI cutoff of 330 was chosen to distinguish moderate from severe disease (with moderate disease defined as CDAI ≤330 and severe disease as CDAI >330): a more detailed classification of disease severity (not used in this assessment) contemplates the use of different thresholds for the definition of "inactive, in remission" (CDAI <150), "mild" (CDAI of 150 to <220), and "moderate" (CDAI of 220 to 330).

Prior and concomitant medications

In subjects with UC, medication history was reported in 26 of 30 subjects (86.7%) with the most frequently (≥20% subjects) reported medications being mesalazine (56.7% subjects), AZA (23.3% subjects), and ferrous sulfate (20.0%); corticosteroids were used in 2 subjects.

In subjects with CD, medication history was reported in 25 of 28 subjects (89.3%), with the most frequently (≥20% subjects) reported medications being AZA (42.9% subjects), cholecalciferol (39.3% subjects), and mesalazine (32.1% subjects); corticosteroids were used by 4 subjects.

Regarding prior history of exposure to biologic treatments, 36.7% subjects with UC had previously experienced biologic treatment, with most subjects receiving infliximab (33,3%) and adalimumab (15,7%), while 60.7% subjects with CD had previously experienced biologic treatment; also in this group, most subjects received infliximab (46.4%) and adalimumab (35.7%).

Overall, concomitant medications were received by 28 of 30 subjects (93.3%) with UC. The most frequently (>25% subjects) reported concomitant medications included mesalazine (63.3% subjects), paracetamol (53.3% subjects), propofol (36.7% subjects), and AZA, citric acid/magnesium oxide/sodium picosulfate, macrogol 3350, and Vitamin D not otherwise specified (26.7% subjects each). All subjects (100%) with CD received concomitant medications. The most frequently (>25% subjects) reported concomitant medications included cholecalciferol, paracetamol, and propofol (46.4% subjects each), AZA (42.9% subjects), mesalazine (32.1% subjects), and omeprazole (28.6% subjects).

Number analysed

Analyses were conducted on the following analysis sets:

- Full analysis set (FAS): 58 subjects (UC: 30, CD: 28)
- Safety analysis set (SAF): 58 subjects (UC: 30, CD: 28)
- PK analysis set: 58 subjects (UC: 30, CD: 28)

Efficacy results

Subjects with UC

Maintenance of Clinical Response

Maintenance of clinical response based on complete Mayo score and clinical response based on complete or partial Mayo score, modified Mayo score, and PUCAI at Week 32 in Study 2005, relative to baseline at the initiation of Study 2003, is presented in the table below.

Table 23 Summary of Clinical Response at Week 32 in Subjects With UC (FAS)

	Subjects <30 kg		Subjects ≥30 kg		
	100 mg Only (N=5)	200 mg Only (N=8)	150 mg Only (N=10)	300 mg Only (N=7)	Total (N=30)
Response based on complete Mayo score [a, b]					
No. of subjects with data, n	3	6	2	2	13
Responder, n (%)	2 (66.7)	6 (100)	2 (100)	1 (50.0)	11 (84.6)
Non-responder, n (%)	1 (33.3)	0	0	1 (50.0)	2 (15.4)
95% Jeffrey interval	(17.7, 96.1)	(67.0, 100)	(33.3, 100)	(6.1, 93.9)	(59.1, 96.7)
95% CI	(9.4, 99.2)	(54.1, 100)	(15.8, 100)	(1.3, 98.7)	(54.6, 98.1)

Table 23 Summary of Clinical Response at Week 32 in Subjects With UC (FAS)

	Subjects <30 kg		Subjects ≥30 kg		
	100 mg Only (N=5)	200 mg Only (N=8)	150 mg Only (N=10)	300 mg Only (N=7)	Total (N=30)
Response based on complete Mayo or partial Mayo Score [b, c]					
No. of subjects with data, n	3	7	2	2	14
Responder, n (%)	3 (100)	7 (100)	2 (100)	2 (100)	14 (100)
Non-responder, n (%)	0	0	0	0	0
95% Jeffrey interval	(46.4, 100)	(70.8, 100)	(33.3, 100)	(33.3, 100)	(83.8, 100)
95% CI	(29.2, 100)	(59.0, 100)	(15.8, 100)	(15.8, 100)	(76.8, 100)
Response based on Modified Mayo Score [b, d]					
No. of subjects with data, n	3	6	2	2	13
Responder, n (%)	3 (100)	6 (100)	2 (100)	2 (100)	13 (100)
Non-responder, n (%)	0	0	0	0	0
95% Jeffrey interval	(46.4, 100)	(67.0, 100)	(33.3, 100)	(33.3, 100)	(82.7, 100)
95% CI	(29.2, 100)	(54.1, 100)	(15.8, 100)	(15.8, 100)	(75.3, 100)
Response based on PUCAI [b, e]					
No. of subjects with data, n	5	8	10	7	30
Responder, n (%)	5 (100)	7 (87.5)	8 (80.0)	7 (100)	27 (90.0)
Non-responder, n (%)	0	1 (12.5)	2 (20.0)	0	3 (10.0)
95% Jeffrey interval	(62.1, 100.0)	(54.6, 98.6)	(49.7, 95.6)	(70.8, 100)	(75.7, 97.1)
95% CI	(47.8, 100.0)	(47.3, 99.7)	(44.4, 97.5)	(59.0, 100)	(73.5, 97.9)

Complete Mayo Score was calculated per GEMINI Approach.

Clinical data based on complete, partial, and modified Mayo scores were presented only for subjects who were dispensed a subject diary to capture daily symptoms, starting with Protocol Amendment 5 (see Table 8). Clinical data based on PUCAI were available for all subjects.

[a] Clinical response was achieved when a reduction in complete Mayo score of ≥3 points and >30% from Study 2003 baseline, with an accompanying decrease in rectal bleeding subscore of ≥1 point from Study 2003 baseline or absolute rectal bleeding subscore of ≤1 point at Week 32. Results are based on observed cases (see Section 9.8.2.1).

[b] Denominator based on total number of subjects with responder/non-responder status.

[c] Clinical response was achieved when a reduction in complete Mayo score of ≥3 points and ≥30% from Study 2003 Baseline (or a partial Mayo score of ≥2 points and ≥25% from Study 2003 Baseline, if the complete Mayo score was not performed at the visit) with an accompanying decrease in rectal bleeding subscore of ≥1 point (from Study 2003 baseline) or absolute rectal bleeding subscore of ≤1 point at Week 32. Results are based on observed cases (see Section 9.8.2.1).

[d] Clinical response was achieved when a reduction in total score of ≥2 points and ≥25% from Study 2003 Baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point from Study 2003 baseline or absolute rectal bleeding subscore of ≤1 point at Week 32. Results are based on observed cases (see Section 9.8.2.1).

[e] Clinical response was achieved when a ≥20-point decrease from Study 2003 Baseline in PUCAI score.

Sensitivity analyses for clinical response

Sensitivity analysis for maintenance of Clinical Response based on complete Mayo score

- **US FDA UC 2016 Guidance:** Responders 84.6%, 95% CI: 54.6-98.1
- **Alternative missing data imputation:** Responders 84.6%, 95% CI: 54.6-98.1
- **Classification of subjects requiring dose escalation as non-responders:** Responders 46.2%, 95% CI: 19.2-74.9

Clinical Remission

Table 24 Summary of Clinical Remission Based on Complete Mayo Score and PUCAI at Week 32 in Subjects With UC (FAS)

	Subjects <30 kg		Subjects ≥30 kg		
	100 mg Only (N=5)	200 mg Only (N=8)	150 mg Only (N=10)	300 mg Only (N=7)	Total (N=30)
Remission based on complete Mayo score [a,b]					
No. of subjects with data, n	3	6	2	2	13
Remitter [n (%)]	2 (66.7)	3 (50.0)	1 (50.0)	0	6 (46.2)
Non-remitter [n (%)]	1 (33.3)	3 (50.0)	1 (50.0)	2 (100)	7 (53.8)
95% Jeffrey interval	(17.7, 96.1)	(16.7, 83.3)	(6.1, 93.9)	(0.0, 66.7)	(22.1, 71.7)
95% CI	(9.4, 99.2)	(11.8, 88.2)	(1.3, 98.7)	(0.0, 84.2)	(19.2, 74.9)
Remission based on PUCAI [b,c]					
No. of subjects with data, n	5	8	10	7	30
Remitter [n (%)]	3 (60.0)	5 (62.5)	9 (90.0)	6 (85.7)	23 (76.7)
Non-remitter [n (%)]	2 (40.0)	3 (37.5)	1 (10.0)	1 (14.3)	7 (23.3)
95% Jeffrey interval	(20.9, 90.6)	(29.5, 88.1)	(61.9, 98.9)	(49.9, 98.4)	(59.6, 88.9)
95% CI	(14.7, 94.7)	(24.5, 91.5)	(55.5, 99.7)	(42.1, 99.6)	(57.7, 90.1)

Source: Table 15.2.7.3.2, Table 15.2.7.4.2.

Complete Mayo Score was calculated per GEMINI Approach.

Clinical data based on complete Mayo score were presented only for subjects who were dispensed a subject diary to capture daily symptoms, starting with Protocol Amendment 5 (see Table 8). Clinical data based on PUCAI was available for all subjects.

[a] Clinical remission was achieved when a complete Mayo score of ≤2 points with no individual subscore >1 at Week 32. Results are based on observed cases (see Section 9.8.2.1).

[b] Denominator based on total number of subjects with remitter/non-remitter status.

[c] Clinical remission was achieved when PUCAI score <10.

Other efficacy results

Clinical Response and Remission after Week 32 in Subjects With UC

Based on PUCAI, both clinical response and remission rates through Week 248 in Study 2005 (more than 5 years) were, at the individual subject final visit, 17 of 30 subjects (56.7%; 95% CI: 37.4, 74.5) for clinical response and 13 of 30 subjects (43.3%; 95% CI: 25.5, 62.6) for clinical remission.

Change from Baseline in PUCAI in Subjects With UC

Table 25 **Change in PUCAI Total Score from Baseline in Study 2005 to Week 32 in Study 2005 - Subjects With UC (FAS)**

	100 mg Only		200 mg Only		150 mg Only		300 mg Only		Escalated to 300 mg		Total	
	N=3	Change from baseline (N=3)	N=6	Change from baseline (N=6)	N=2	Change from baseline (N=2)	N=7	Change from baseline (N=7)	N=12	Change from baseline (N=12)	N=30	Change from baseline (N=30)
Baseline												
n	3		6		2		7		12		30	
Mean (SD)	10.0 (5.00)		11.7 (12.91)		5.0 (7.07)		7.9 (11.50)		4.2 (7.02)		7.2 (9.35)	
Median	10.0		7.5		5.0		0.0		0.0		2.5	
Min, Max	5, 15		0, 30		0, 10		0, 30		0, 20		0, 30	
Week 32												
n	3	3	6	6	2	2	7	7	12	12	30	30
Mean (SD)	3.3 (5.77)	-6.7 (2.89)	18.3 (29.10)	6.7 (19.15)	0.0 (0.00)	-5.0 (7.07)	5.7 (13.05)	-2.1 (6.36)	7.1 (16.71)	2.9 (10.76)	8.2 (17.88)	1.0 (11.70)
Median	0.0	-5.0	7.5	0.0	0.0	-5.0	0.0	0.0	0.0	0.0	0.0	0.0
Min, Max	0, 10	-10, -5	0, 75	-5, 45	0, 0	-10, 0	0, 35	-15, 5	0, 55	-5, 35	0, 75	-15, 45

Source: Table 15.2.6.4.1.

The PUCAI score ranges from 0 to 85; a score of <10 denotes remission, 10 to 34 mild disease, 35 to 64 moderate disease, and 65 to 85 severe disease. Clinical response based on the PUCAI score was defined as a ≥20 point decrease from Baseline in PUCAI score.

Baseline for PUCAI was based on the data collected on Day 1 visit for Study 2005.

Table 26 **Change in PUCAI Total Score from Baseline in Study 2003 to Week 32 in Study 2005 – Subjects With UC (FAS)**

	100 mg Only		200 mg Only		150 mg Only		300 mg Only		Escalated to 300 mg		Total	
	N=3	Change from baseline (N=3)	N=6	Change from baseline (N=6)	N=2	Change from baseline (N=2)	N=7	Change from baseline (N=7)	N=12	Change from baseline (N=12)	N=30	Change from baseline (N=30)
Baseline												
n	3		6		2		7		12		30	
Mean (SD)	55.0 (10.00)		50.8 (11.14)		55.0 (21.21)		45.0 (18.03)		45.8 (17.94)		48.2 (15.73)	
Median	55.0		50.0		55.0		40.0		50.0		50.0	
Min, Max	45, 65		40, 70		40, 70		25, 80		5, 80		5, 80	
Week 32												
n	3	3	6	6	2	2	7	7	12	12	30	30
Mean (SD)	3.3 (5.77)	-51.7 (5.77)	18.3 (29.10)	-32.5 (31.10)	0.0 (0.00)	-55.0 (21.21)	5.7 (13.05)	-39.3 (10.97)	7.1 (16.71)	-38.8 (22.17)	8.2 (17.88)	-40.0 (20.93)
Median	0.0	-55.0	7.5	-45.0	0.0	-55.0	0.0	-40.0	0.0	-37.5	0.0	-42.5
Min, Max	0, 10	-55, -45	0, 75	-55, 25	0, 0	-70, -40	0, 35	-55, -20	0, 55	-80, 0	0, 75	-80, 25

Source: Table 15.2.6.4.2.

The PUCAI score ranges from 0 to 85; a score of <10 denotes remission, 10 to 34 mild disease, 35 to 64 moderate disease, and 65 to 85 severe disease. Clinical response based on the PUCAI score was defined as a ≥20 point decrease from Baseline in PUCAI score.

Baseline for PUCAI was based on the last nonmissing value before the first dose of study drug in Study 2003.

Disease worsening in subjects with UC

Disease worsening based on PUCAI was observed in 2 of 30 (6.7%; 95% CI: 0.8, 22.1) subjects with UC at Week 32 and in 5 of 30 subjects (16.7%; 95% CI: 5.6, 34.7) at the individual subject final visit.

Biomarkers of intestinal inflammation

- **CRP:** The mean (SD) change in CRP level (nmol/L) from baseline at individual subject final visit was -35.87 (67.462) in 3 of 5 subjects in the 100 mg dose group and -15.07 (107.416) in 6 of 8 subjects in the 200 mg dose group. In subjects ≥30 kg with UC, the mean (SD) change in CRP level (nmol/L) from baseline at individual subject final visit was 13.82 (39.534) in 6 of 10 subjects in the 150 mg dose and 59.33 (37.446) in 6 of 7 subjects in the 300 mg dose group.
- **Faecal Calprotectin:** In subjects <30 kg with UC, the mean (SD) change in faecal calprotectin level (µg/g) from baseline at individual subject final visit was 919.7 (2382.59) in 3 of 5 subjects in the 100 mg dose group and -669.0 (849.94) in 2 of 8 subjects in the 200 mg dose group. In subjects ≥30 kg with UC the mean (SD) change in faecal calprotectin level (µg/g) from baseline

at individual subject final visit was 250.0 (-) in 1 of 10 subjects in the 150 mg dose group and 5174.7 (4496.57) in 3 of 7 subjects in the 300 mg dose group.

- **Albumin:** In subjects <30 kg with UC, the mean (SD) change in albumin level (g/L) from baseline at individual subject final visit was 0.0 (2.00) in 3 of 5 subjects in the 100 mg dose group and 0.7 (3.20) in 6 of 8 subjects in the 200 mg dose group. In subjects ≥30 kg with UC, the mean (SD) change in albumin level (g/L) from baseline at individual subject final visit was 1.5 (2.35) in 6 of 10 subjects in the 150 mg dose group and -4.2 (4.75) in 6 of 7 subjects in the 300 mg dose group.

Growth and Development in Subjects With UC

- **Height**

In subjects <30 kg, the mean (SD) change in height (cm) from baseline was 23.69 (16.032) at individual subject final visit and 28.05 (16.440) at safety follow-up visit.
In subjects ≥30 kg, the mean (SD) change in height (cm) from baseline was 10.33 (13.882) at individual subject final visit and 12.73 (12.867) at safety follow-up visit.

- **Height Z-score**

In subjects <30 kg, the mean (SD) height Z-score was negative at baseline (–0.75 [0.766]) and remain negative at individual final visit (-0.62 [1.282]) and safety follow-up visit (-0.61 [1.293]).
In subjects ≥30 kg, the mean (SD) height Z-score was positive at baseline (0.64 [0.705]), at individual subject final visit (0.52 [0.553]) and safety follow-up visit (0.50 [0.601]).

- **Height Velocity**

In subjects <30 kg, the mean (SD) height velocity (cm/weeks between measurements) remained relatively stable over the course of the study, with a value of 0.02 (0.006) at both Week 48 and individual subject final visit and 0.02 (0.005) at safety follow-up visit.
In subjects ≥30 kg, the mean (SD) height velocity (cm/weeks between measurements) remained relatively stable over the course of the study with a value of 0.01 (0.009) at Week 48, 0.01 (0.008) at individual subject final visit, and 0.01 (0.006) at safety follow-up visit.

- **Change in Weight in Subjects With UC**

In subjects <30 kg, the mean (SD) change in weight (kg) from baseline was 17.49 (12.174) at individual subject final visit and 20.64 (12.635) at safety follow-up visit.
In subjects ≥30 kg, the mean (SD) change in weight (kg) from baseline was 12.38 (23.524) at individual subject final visit and 19.69 (23.221) at safety follow-up visit.

- **Change in BMI in Subjects With UC**

In subjects <30 kg, the mean (SD) change in BMI (kg/m2) from baseline was 2.69 (2.200) at individual subject final visit and 3.18 (1.967) at safety follow-up visit.
In subjects ≥30 kg, the mean (SD) change in BMI (kg/m2) from baseline was 2.58 (7.479) at individual subject final visit and 4.49 (7.279) at safety follow-up visit.

- **Tanner Stage in Subjects With UC**

A total of 5 male subjects ≥30 kg reached 17 years of age while on study. All subjects achieved Tanner Stage 5, with development of external genitalia, pubic hair, and growth milestone.

A total of 2 female subjects <30 kg and 3 female subjects ≥30 kg reached 16 years of age while on study. 1 female subject <30 kg and all female subjects ≥30 kg achieved Tanner Stage 5, with breast development, pubic hair, and growth milestone.

Time to Major IBD-Related Events in Subjects With UC

Table 28 Time to Major IBD-Related Events (Hospitalizations, Surgeries, and Procedures) in Subjects With UC (FAS)

	100 mg Only (N=3)	200 mg Only (N=6)	150 mg Only (N=2)	300 mg Only (N=7)	Escalated to 300 mg (N=12)	Total (N=30)
Number of subjects with at least one, n (%)						
Hospitalizations	1 (33.3)	0	0	3 (42.9)	3 (25.0)	7 (23.3)
Surgery	0	0	0	0	2 (16.7)	2 (6.7)
Procedures	0	0	0	0	0	0
Number of subjects with at least one event, n (%)	1 (33.3)	0	0	3 (42.9)	3 (25.0)	7 (23.3)
Number of subjects censored, n (%)	2 (66.7)	6 (100)	2 (100)	4 (57.1)	9 (75.0)	23 (76.7)
No events occurred	0	3 (50.0)	2 (100)	2 (28.6)	5 (41.7)	12 (40.0)
Early termination or lost to follow-up	2 (66.7)	3 (50.0)	0	2 (28.6)	4 (33.3)	11 (36.7)
Percentiles [days] (95% CI)						
25th	482.00 (482.00, NE)	NE	NE	1620.00 (32.00, NE)	825.00 (511.00, NE)	2058.00 (482.00, NE)
50th (Median)	NE (482.00, NE)	NE	NE	2058.00 (32.00, NE)	NE (794.00, NE)	NE (2058.00, NE)
75th	NE (482.00, NE)	NE	NE	NE (1620.00, NE)	NE	NE
Min, Max	334 [a], 785 [a]	281 [a], 2359 [a]	1973 [a], 2417 [a]	32, 2428 [a]	464 [a], 2466 [a]	32, 2466 [a]

Source: Table 15.2.7.2.

Time to major IBD-related event was calculated as the time from Study 2005 entry until major IBD-related event (hospitalizations, surgeries, and procedures). Subjects without documented IBD-related events before reaching the end of study were censored at the date of last assessment/visit/contact, whichever occurred last. Estimates were calculated utilizing the Kaplan-Meier method.

[a] censored observation.

IMPACT III Results in Subjects With UC

At baseline of Study 2005, the mean health-related QOL measured with IMPACT-III scores was 143 (SD 22.85). The registered mean changes during the different time points were:

- 48 weeks time point: mean change from baseline -2 (SD 9.59)
- 96 weeks time point: mean change from baseline 1.7 (SD 11.68)
- 144 weeks time point: mean change from baseline -0.4 (SD 11.75)
- 192 weeks time point: mean change from baseline 0.5 (SD 15.63)
- 240 weeks time point: mean change from baseline -0.2 (SD 16.86)

Subjects with CD

Maintenance of clinical Response

Maintenance of clinical response based on SES-CD and CDAI, clinical response and enhanced clinical response based on CDAI, endoscopic response based on SES-CD, and clinical response based on PCDAI at Week 32 in Study 2005 relative to baseline at the initiation of Study 2003 is presented in the table below.

Table 30 Summary of Response at Week 32 in Subjects With CD (FAS)

	Subjects <30 kg		Subjects ≥30 kg		
	100 mg Only (N=7)	200 mg Only (N=7)	150 mg Only (N=4)	300 mg Only (N=10)	Total (N=28)
Response based on SES-CD and CDAI [a,b]					
No. of subjects with data, n	6	2	1	4	13
Responder [n (%)]	5 (83.3)	2 (100)	0	3 (75.0)	10 (76.9)
Non-responder [n (%)]	1 (16.7)	0	1 (100)	1 (25.0)	3 (23.1)
95% Jeffrey interval	(44.2, 98.1)	(33.3, 100)	(0.0, 85.3)	(28.4, 97.2)	(50.3, 93.0)
95% CI	(35.9, 99.6)	(15.8, 100)	(0.0, 97.5)	(19.4, 99.4)	(46.2, 95.0)
Response based on CDAI [b,c]					
No. of subjects with data, n	5	3	1	4	13
Responder [n (%)]	5 (100)	3 (100)	1 (100)	4 (100)	13 (100)
Non-responder [n (%)]	0	0	0	0	0
95% Jeffrey interval	(62.1, 100)	(46.4, 100)	(14.7, 100)	(55.5, 100)	(82.7, 100)
95% CI	(47.8, 100)	(29.2, 100)	(2.5, 100)	(39.8, 100)	(75.3, 100)
Enhanced response based on CDAI [b,d]					
No. of subjects with data, n	5	3	1	4	13
Responder [n (%)]	5 (100)	3 (100)	1 (100)	3 (75.0)	12 (92.3)
Non-responder [n (%)]	0	0	0	1 (25.0)	1 (7.7)
95% Jeffrey interval	(62.1, 100)	(46.4, 100)	(14.7, 100)	(28.4, 97.2)	(69.3, 99.2)
95% CI	(47.8, 100)	(29.2, 100)	(2.5, 100)	(19.4, 99.4)	(64.0, 99.8)
Response based on SES-CD [b,e]					
No. of subjects with data, n	7	3	4	8	22
Responder [n (%)]	6 (85.7)	3 (100)	2 (50.0)	5 (62.5)	16 (72.7)
Non-responder [n (%)]	1 (14.3)	0	2 (50.0)	3 (37.5)	6 (27.3)
95% Jeffrey interval	(49.9, 98.4)	(46.4, 100)	(12.3, 87.7)	(29.5, 88.1)	(52.2, 87.7)

	Subjects <30 kg		Subjects ≥30 kg		
	100 mg Only (N=7)	200 mg Only (N=7)	150 mg Only (N=4)	300 mg Only (N=10)	Total (N=28)
95% CI	(42.1, 99.6)	(29.2, 100)	(6.8, 93.2)	(24.5, 91.5)	(49.8, 89.3)
Response based on PCDAI [b,f]					
No. of subjects with data, n	7	7	4	10	28
Responder [n (%)]	6 (85.7)	4 (57.1)	4 (100)	7 (70.0)	21 (75.0)
Non-responder [n (%)]	1 (14.3)	3 (42.9)	0	3 (30.0)	7 (25.0)
95% Jeffrey interval	(49.9, 98.4)	(23.5, 86.1)	(55.5, 100)	(39.4, 90.7)	(57.1, 88.1)
95% CI	(42.1, 99.6)	(18.4, 90.1)	(39.8, 100)	(34.8, 93.3)	(55.1, 89.3)

Source: Table 15.2.7.1, Table 15.2.7.3.1, and Table 15.2.7.4.1.

Clinical data for CDAI based endpoints were presented only for subjects who were dispensed a subject diary to capture daily symptoms, starting with Protocol Amendment 5 (Table 8). Clinical data based on PCDAI was available for all subjects.

[a] Clinical response was achieved when at Week 32 50% reduction in SES-CD score on endoscopy compared to the baseline endoscopy (at initiation of Study 2003); and reduction in CDAI that was a ≥70 point decrease from the baseline CDAI at the initiation of Study 2003. Results are based on observed cases (see Section 9.8.2.1).

[b] Denominator based on total number of subjects with responder/non-responder status.

[c] Clinical response was achieved when a ≥70-point decrease from Study 2003 Baseline in CDAI score at Week 32. Results are based on observed cases (see Section 9.8.2.1).

[d] Enhanced clinical response was achieved when a ≥100-point decrease from Study 2003 Baseline in CDAI score at Week 32. Results are based on observed cases (see Section 9.8.2.1).

[e] Endoscopic response was achieved when a ≥50% reduction in SES-CD score from Study 2003 Baseline endoscopy (or met criteria for clinical remission based on SES-CD score 0 to 2) at Week 32. Results are based on observed cases (see Section 9.8.2.1).

[f] Clinical response was achieved when a ≥15-point decrease from Study 2003 Baseline with total PCDAI ≤30.

Sensitivity analyses for clinical response

Sensitivity analysis for maintenance of Clinical Response based on SES-CD and CDAI

- **Aternative missing data imputation:** Responders 76.9%, 95% CI: 46.2-95
- **Classification of subjects requiring dose escalation as non-responders:** Responders 61.5%, 95% CI: 31.6-86.1

Clinical Remission

Table 31 Summary of Remission Based on CDAI, SES-CD, and PCDAI at Week 32 in Subjects With CD (FAS)

	Subjects <30 kg		Subjects ≥30 kg		
	100 mg Only (N=7)	200 mg Only (N=7)	150 mg Only (N=4)	300 mg Only (N=10)	Total (N=28)
Remission based on CDAI [a,b]					
No. of subjects with data, n	5	3	1	4	13
Remitter [n (%)]	5 (100)	3 (100)	1 (100)	4 (100)	13 (100)
Non-remitter [n (%)]	0	0	0	0	0
95% Jeffrey interval	(62.1, 100)	(46.4, 100)	(14.7, 100)	(55.5, 100)	(82.7, 100)
95% CI	(47.8, 100)	(29.2, 100)	(2.5, 100)	(39.8, 100)	(75.3, 100)
Remission based on SES-CD [b,c]					
No. of subjects with data, n	7	3	4	8	22
Remitter [n (%)]	6 (85.7)	2 (66.7)	2 (50.0)	3 (37.5)	13 (59.1)
Non-remitter [n (%)]	1 (14.3)	1 (33.3)	2 (50.0)	5 (62.5)	9 (40.9)
95% Jeffrey interval	(49.9, 98.4)	(17.7, 96.1)	(12.3, 87.7)	(11.9, 70.5)	(38.5, 77.5)
95% CI	(42.1, 99.6)	(9.4, 99.2)	(6.8, 93.2)	(8.5, 75.5)	(36.4, 79.3)
Remission based on PCDAI [b,d]					
No. of subjects with data, n	7	7	4	10	28
Remitter [n (%)]	7 (100)	4 (57.1)	3 (75.0)	5 (50.0)	19 (67.9)
Non-remitter [n (%)]	0	3 (42.9)	1 (25.0)	5 (50.0)	9 (32.1)
95% Jeffrey interval	(70.8, 100)	(23.5, 86.1)	(28.4, 97.2)	(22.4, 77.6)	(49.5, 82.8)
95% CI	(59.0, 100)	(18.4, 90.1)	(19.4, 99.4)	(18.7, 81.3)	(47.6, 84.1)

Source: Table 15.2.7.3.2, Table 15.2.7.4.2.

Clinical data for CDAI based endpoints were presented only for subjects who were dispensed a subject diary to capture daily symptoms, starting with Protocol Amendment 5 (Table 8). Clinical data based on PCDAI was available for all subjects.

[a] Clinical remission was achieved when a CDAI score ≤150 at Week 32. Results are based on observed cases (see Section 9.8.2.1).

[b] Denominator based on total number of subjects with remitter/non-remitter status.

[c] Endoscopic remission was achieved when a SES-CD score 0 to 2 at Week 32. Results are based on observed cases (see Section 9.8.2.1).

[d] Clinical remission was achieved when PCDAI score ≤10.

Other efficacy results

Clinical Response and Remission After Week 32 in Subjects With CD

Based on PCDAI, both clinical response and remission rates through Week 248 in Study 2005 (more than 5 years) were, at the individual subject final visit, 17 of 30 subjects (56.7%; 95% CI: 37.4, 74.5) for clinical response and 13 of 30 subjects (43.3%; 95% CI: 25.5, 62.6) for clinical remission.

Clinical response and remission rates based on PCDAI remained higher than 30% and 35%, respectively, through Week 240 in Study 2005, which corresponds to more than 5 years following enrolment in the parent Study 2003; at the individual subject final visit, 13 of 28 subjects (46.4%; 95% CI: 27.5, 66.1) had achieved clinical response, and 12 of 28 subjects (42.9%; 95% CI: 24.5, 62.8) had achieved clinical remission.

Change from Baseline in PCDAI in Subjects With CD

Table 32 Change in PCDAI Total Score from Baseline in Study 2005 to Week 32 in Study 2005 - Subjects With CD (FAS)

	100 mg Only		200 mg Only		150 mg Only		300 mg Only		Escalated to 300 mg		Total	
	N=5	Change from baseline (N=5)	N=5	Change from baseline (N=5)	N=2	Change from baseline (N=2)	N=10	Change from baseline (N=10)	N=6	Change from baseline (N=6)	N=28	Change from baseline (N=28)
Baseline												
n	5		5		2		10		6		28	
Mean (SD)	3.0 (3.26)		11.5 (10.09)		0.0 (0.00)		11.3 (8.99)		2.1 (1.88)		7.1 (8.17)	
Median	2.5		10.0		0.0		10.0		2.5		5.0	
Min, Max	0, 8		0, 28		0, 0		0, 28		0, 5		0, 28	
Week 32												
n	5	5	2	2	2	2	8	8	6	6	23	23
Mean (SD)	0.5 (1.12)	-2.5 (2.50)	2.5 (3.54)	-2.5 (3.54)	0.0 (0.00)	0.0 (0.00)	11.9 (12.30)	1.6 (15.00)	4.6 (4.31)	2.5 (5.48)	5.7 (8.80)	0.4 (9.19)
Median	0.0	-2.5	2.5	-2.5	0.0	0.0	7.5	-3.8	3.8	0.0	2.5	0.0
Min, Max	0, 3	-5, 0	0, 5	-5, 0	0, 0	0, 0	0, 38	-10, 35	0, 13	-3, 13	0, 38	-10, 35

Source: Table 15.2.6.6.1.

The PCDAI scores are sums of the 11 subscores, ranging from 0-100, with higher scores signifying more active disease. A score of <10 is consistent with inactive disease, 11 to 30 indicates mild disease, and >30 is moderate-to-severe disease.

Baseline for PCDAI was based on the data collected on Day 1 visit for Study 2005.

Table 33 Change in PCDAI Total Score from Baseline in Study 2003 to Week 32 in Study 2005- Subjects With CD (FAS)

	100 mg Only		200 mg Only		150 mg Only		300 mg Only		Escalated to 300 mg		Total	
	N=5	Change from baseline (N=5)	N=5	Change from baseline (N=5)	N=2	Change from baseline (N=2)	N=10	Change from baseline (N=10)	N=6	Change from baseline (N=6)	N=28	Change from baseline (N=28)
Baseline												
n	5		5		2		10		6		28	
Mean (SD)	28.5 (13.30)		32.5 (8.66)		30.0 (21.21)		31.3 (8.60)		30.0 (7.42)		30.6 (9.52)	
Median	32.5		27.5		30.0		32.5		31.3		32.5	
Min, Max	5, 38		28, 48		15, 45		18, 45		20, 38		5, 48	
Week 32												
n	5	5	2	2	2	2	8	8	6	6	23	23
Mean (SD)	0.5 (1.12)	-28.0 (12.92)	2.5 (3.54)	-27.5 (7.07)	0.0 (0.00)	-30.0 (21.21)	11.9 (12.30)	-20.3 (13.72)	4.6 (4.31)	-25.4 (9.14)	5.7 (8.80)	-24.8 (12.03)
Median	0.0	-32.5	2.5	-27.5	0.0	-30.0	7.5	-25.0	3.8	-25.0	2.5	-25.0
Min, Max	0, 3	-35, -5	0, 5	-33, -23	0, 0	-45, -15	0, 38	-33, 13	0, 13	-38, -15	0, 38	-45, 13

Source: Table 15.2.6.6.2.

The PCDAI scores are sums of the 11 subscores, ranging from 0-100, with higher scores signifying more active disease. A score of <10 is consistent with inactive disease, 11 to 30 indicates mild disease, and >30 is moderate-to-severe disease.

Baseline for PCDAI was based on the last nonmissing value before the first dose of study drug in Study 2003.

Disease worsening in subjects with CD

Disease worsening based on PCDAI was defined as an increase in PCDAI of >15 points at 2 consecutive visits at least 7 days apart, or the PUCAI was >30 points at any scheduled or unscheduled visit.

At Week 32, disease worsening based on PCDAI was observed in 1 of 28 (3.6%; 95% CI: 0.1, 18.3) subjects with CD. At the individual subject final visit, 3 of 28 subjects (10.7%; 95% CI: 2.3, 28.2) had experienced disease worsening.

Biomarkers of intestinal inflammation

- **CRP:** The mean (SD) change in CRP level (nmol/L) from baseline at individual subject final visit was 3.50 (6.582) in 6 of 7 subjects in the 100 mg dose group and 51.42 (87.005) in 5 of 7 subjects in the 200 mg dose group. In subjects ≥30 kg, the mean (SD) change in CRP level (nmol/L) from baseline at individual subject final visit was -98.10 (-) in 1 of 4 subjects in the 150 mg dose group and 3.80 (209.114) in 7 of 10 subjects in the 300 mg dose group.

- **Fecal Calprotectin:** In subjects <30 kg, the mean (SD) change in fecal calprotectin level (µg/g) from baseline at individual subject final visit was -8.8 (101.00) in 4 of 7 subjects in the 100 mg dose group and 2626.2 (5994.07) in 5 of 7 subjects in the 200 mg dose group. In subjects ≥30 kg, the mean (SD) change in fecal calprotectin level (µg/g) from baseline at individual subject final visit was -1490.0 (-) in 1 of 4 subjects in the 150 mg dose group and 2438.8 (3384.15) 4 of 10 subjects in the 300 mg dose group
- **Albumin:** In subjects <30 kg, the mean (SD) change in albumin level (g/L) from baseline at individual subject final visit was 1.7 (2.58) in 6 of 7 subjects in the 100 mg dose group and -1.5 (5.32) in 6 of 7 subjects in the 200 mg dose group. In subjects ≥30 kg, the mean (SD) change in albumin level (g/L) from baseline at individual subject final visit was 4.0 (-) in 1 of 4 subjects in the 150 mg dose group and 0.6 (3.55) in 7 of 10 subjects in the 300 mg dose group.

Growth and Development in Subjects With CD

- Height

In subjects <30 kg, the mean (SD) change in height (cm) from baseline was 23.68 (11.846) at individual subject final visit, and 26.95 (10.813) at safety follow-up visit.
In subjects ≥30 kg, the mean (SD) change in height (cm) from baseline was 6.81 (8.274) at individual subject final visit, and 5.18 (8.663) at safety follow-up visit.

- **Height Z-score**

In subjects <30 kg, a mean (SD) height Z-score was negative at baseline (–0.77 [0.819]) but remained generally stable and slightly improved numerically with a value of -0.39 (0.918) at individual subject final visit and -0.42 (0.990) at safety follow-up visit.
In subjects ≥30 kg, the mean (SD) height Z-score was positive at baseline (0.68 [0.569]) and remained positive over time with a slight numerical decline at the individual subject final visit (0.42 [0.771]) and safety follow-up visit (0.25 [0.827]).

- **Height Velocity**

In subjects <30 kg, the mean (SD) height velocity (cm/weeks between measurements) remained relatively stable over the course of the study, with a value of 0.02 (0.007) at Week 48, 0.02 (0.004) at individual subject final visit, and 0.02 (0.003) at safety follow-up visit. In subjects ≥30 kg, the mean (SD) height velocity (cm/weeks between measurements) remained relatively stable over the course of the study, with a value of 0.01 (0.008) at Week 48, 0.01 (0.007) at individual subject final visit, and 0.00 (0.005) at safety follow-up visit.

- **Change in Weight in Subjects With CD**

In subjects <30 kg, the mean (SD) change in weight (kg) from baseline was 13.01 (8.660) at individual subject final visit and 16.86 (8.369) at safety follow-up visit.
In subjects ≥30 kg, the mean (SD) change in weight (kg) from baseline was 11.89 (21.645) at individual subject final visit and 10.44 (23.365) at safety follow-up visit.

- **Change in BMI in Subjects With CD**

In subjects <30 kg, the mean (SD) change in BMI (kg/m2) from baseline was 1.62 (1.735) at individual subject final visit and 2.20 (2.033) at safety follow-up visit.
In subjects ≥30 kg, the mean (SD) change in BMI (kg/m2) from baseline was 2.85 (6.317) at individual subject final visit and 2.51 (6.375) at safety follow-up visit.

- **Tanner Stage in Subjects With CD**

One male subject <30 kg and 3 male subjects ≥30 kg reached 17 years of age while on study. All these subjects achieved Tanner Stage 5, with development of external genitalia, pubic hair, and growth milestone.

One female subject ≥30 kg reached 16 years of age while on study and achieved Tanner Stage 5, with breast development, pubic hair, and growth milestone.

Time to Major IBD-Related Events in Subjects With CD

Table 35 Time to Major IBD-Related Events (Hospitalizations, Surgeries, and Procedures) in Subjects With CD (FAS)

	100 mg Only (N=5)	200 mg Only (N=5)	150 mg Only (N=2)	300 mg Only (N=10)	Escalated to 300 mg (N=6)	Total (N=28)
Number of subjects with at least one, n (%)						
Hospitalizations	0	1 (20.0)	0	3 (30.0)	0	4 (14.3)
Surgery	0	0	0	1 (10.0)	0	1 (3.6)
Procedures	0	0	0	0	0	0
Number of subjects with at least one event, n (%)	0	1 (20.0)	0	3 (30.0)	0	4 (14.3)
Number of subjects censored, n (%)	5 (100)	4 (80.0)	2 (100)	7 (70.0)	6 (100)	24 (85.7)
No events occurred	3 (60.0)	2 (40.0)	0	2 (20.0)	3 (50.0)	10 (35.7)
Early termination or lost to follow-up	2 (40.0)	2 (40.0)	2 (100)	5 (50.0)	3 (50.0)	14 (50.0)
Percentiles [days] (95% CI)						
25th	NE	NE (78.00, NE)	NE	1426.00 (49.00, NE)	NE	NE (78.00, NE)
50th (Median)	NE	NE (78.00, NE)	NE	NE (49.00, NE)	NE	NE
75th	NE	NE (78.00, NE)	NE	NE (1426.00, NE)	NE	NE
Min, Max	284 [a], 1963 [a]	78, 1965 [a]	732 [a], 1845 [a]	49, 2393 [a]	561 [a], 2314 [a]	49, 2393 [a]

Source: Table 15.2.7.2.

Time to major IBD-related event was calculated as the time from Study 2005 Entry until major IBD-related event (hospitalizations, surgeries, and procedures). Subjects without documented IBD-related events before reaching the end of study were censored at the date of last assessment/visit/contact, whichever occurred last. Estimates were calculated utilizing the Kaplan-Meier method.

[a] censored observation.

- **IMPACT III Results in Subjects With CD**

At baseline of Study 2005, the mean health-related QOL measured with IMPACT-III scores was 143 (SD 22.85). The registered mean changes during the different time points were:

- 48 weeks time point: mean change from baseline 8.5 (SD 14.53)
- 96 weeks time point: mean change from baseline 12.1 (SD 22.62)
- 144 weeks time point: mean change from baseline 1.9 (SD 13.48)
- 192 weeks time point: mean change from baseline 5.1 (SD 16.78)
- 240 weeks time point: mean change from baseline 1.2 (SD 10.09)
- 312 weeks time point: mean change from baseline 6.5 (SD 7.78)

Pharmacokinetics results

A **PK blood sample** was collected on Day 1 (postdose). PK blood samples were also collected at Week 8 (predose and postdose) and Q8W thereafter (predose) for all subjects. Predose PK samples were to be obtained within 30 minutes before dosing. Postdose samples were to be collected within 60 minutes from the end of infusion.

AVA samples were to be collected within 30 minutes prior to dosing, where possible.

Table 37 Summary of Serum Concentrations (µg/mL) at Selected Visits in Subjects With UC (PK Analysis Set)

Visit	Subjects <30 kg		Subjects ≥30 kg		
Statistic	100 mg (N=5)	200 mg (N=8)	150 mg (N=10)	300 mg (N=7)	Total (N=30)
Baseline					
n	5	8	10	7	30
Mean (SD)	7.8 (8.78)	12.0 (11.03)	8.3 (6.45)	21.0 (15.99)	12.2 (11.54)
Median	6.8	9.9	5.8	22.2	8.1
Min, Max	0, 21.7	1.42, 37.2	0, 19.6	0.857, 40.1	0, 40.1
Day 1 postdose					
n	5	8	9	6	28
Mean (SD)	91.2 (29.55)	172.4 (30.57)	91.9 (27.88)	204.7 (76.84)	138.9 (64.39)
Median	96.8	172.0	102.0	200.0	123.5
Min, Max	51.9, 127	118, 211	54.5, 133	118, 311	51.9, 311
Week 16 predose					
n	5	8	10	6	29
Mean (SD)	7.3 (8.98)	11.8 (7.74)	8.0 (5.84)	20.9 (17.60)	11.6 (10.92)
Median	4.0	9.3	6.5	21.4	7.9
Min, Max	0, 21.5	5.39, 29.4	0, 20.7	1.37, 39.9	0, 39.9
Week 32 predose					
n	5	7	9	7	28
Mean (SD)	7.5 (9.30)	11.7 (8.48)	7.6 (5.74)	18.4 (14.86)	11.3 (10.40)
Median	3.6	11.8	5.6	22.9	8.9
Min, Max	0, 21.4	2.2, 27.2	0, 17.7	0.991, 33	0, 33
Week 48 predose					
n	4	7	10	6	27
Mean (SD)	8.4 (7.59)	11.4 (10.48)	8.9 (5.57)	19.6 (13.50)	11.8 (9.84)
Median	7.4	8.8	8.1	24.8	8.8
Min, Max	0.245, 18.4	0, 32.7	0.7, 18.6	0.614, 33.1	0, 33.1

*Serum Concentrations of Vedolizumab in **Subjects With UC***

The summary statistics of vedolizumab concentrations at selected time points in subjects with UC is presented in Table 37.

Table 37 Summary of Serum Concentrations (µg/mL) at Selected Visits in Subjects With UC (PK Analysis Set)

Visit / Statistic	Subjects <30 kg		Subjects ≥30 kg		
	100 mg (N=5)	200 mg (N=8)	150 mg (N=10)	300 mg (N=7)	Total (N=30)
Week 96 predose					
n	3	7	9	5	24
Mean (SD)	7.6 (3.55)	10.7 (11.68)	12.6 (7.74)	19.9 (11.07)	13.0 (9.74)
Median	8.3	5.8	10.5	21.6	10.1
Min, Max	3.71, 10.7	2.5, 36.2	3.08, 26.3	2.5, 30.3	2.5, 36.2
Week 144 predose					
n	2	6	8	4	20
Mean (SD)	7.1 (0.38)	12.5 (5.93)	12.2 (9.16)	16.3 (9.98)	12.6 (7.88)
Median	7.1	13.3	9.9	20.4	13.2
Min, Max	6.79, 7.33	6.11, 22.1	2.38, 26.9	1.61, 23	1.61, 26.9
Week 192 predose					
n	2	4	7	3	16
Mean (SD)	3.0 (2.14)	13.8 (5.39)	10.1 (6.56)	19.1 (15.78)	11.8 (8.94)
Median	3.0	12.9	8.3	24.2	8.7
Min, Max	1.45, 4.48	8.56, 20.7	2.59, 22.7	1.4, 31.7	1.4, 31.7
Week 240 predose					
n	2	4	7	3	16
Mean (SD)	17.5 (16.58)	11.3 (5.89)	9.9 (8.17)	17.2 (6.84)	12.6 (8.34)
Median	17.5	11.9	8.0	15.6	10.9
Min, Max	5.75, 29.2	4.68, 16.7	2.32, 26.2	11.3, 24.7	2.32, 29.2
Individual subject final visit					
n	4	6	6	6	22
Mean (SD)	6.8 (7.35)	10.7 (8.19)	32.2 (28.83)	26.9 (34.70)	20.2 (24.94)
Median	5.0	7.5	20.7	17.9	13.1
Min, Max	0, 17.1	3.58, 21.4	0.287, 73.3	0, 94.5	0, 94.5

Source: Table 15.2.8.3.

Baseline PK results were from Study 2003 at Week 22.

*Serum Concentrations of Vedolizumab in **Subjects With CD***

The summary statistics of vedolizumab concentrations at selected time points in subjects with CD is presented in Table 38.

Table 38 Summary of Serum Concentrations (µg/mL) at Selected Visits in Subjects With CD (PK Analysis Set)

Visit / Statistic	Subjects <30 kg		Subjects ≥30 kg		
	100 mg (N=7)	200 mg (N=7)	150 mg (N=4)	300 mg (N=10)	Total (N=28)
Baseline					
n	5	6	4	10	25
Mean (SD)	6.4 (1.40)	14.5 (10.04)	3.7 (2.93)	7.6 (7.37)	8.4 (7.53)
Median	6.4	17.7	3.4	6.7	6.4
Min, Max	4.43, 8.15	1.15, 24.5	0.757, 7.37	0, 24.2	0, 24.5
Day 1 postdose					
n	6	7	3	10	26
Mean (SD)	90.6 (24.13)	214.4 (78.63)	91.8 (25.40)	164.0 (45.74)	152.3 (69.94)
Median	89.3	191.0	87.7	153.5	136.0
Min, Max	64.3, 133	144, 371	68.7, 119	98.5, 246	64.3, 371
Week 16 predose					
n	6	6	4	9	25
Mean (SD)	10.7 (6.95)	15.3 (13.86)	3.8 (3.06)	5.9 (5.60)	9.0 (8.97)
Median	8.4	15.9	3.5	6.1	6.1
Min, Max	4.73, 22.8	0, 32.3	0.409, 7.72	0, 17	0, 32.3
Week 32 predose					
n	7	4	4	8	23
Mean (SD)	9.0 (6.09)	68.2 (80.84)	3.7 (2.61)	9.8 (10.55)	18.6 (38.51)
Median	5.7	31.8	3.7	4.7	6.4
Min, Max	2.47, 19.3	20.2, 189	0.467, 6.75	0.638, 28.7	0.467, 189
Week 48 predose					
n	6	4	4	6	20
Mean (SD)	9.2 (6.92)	20.3 (15.20)	5.7 (1.30)	10.5 (8.81)	11.1 (9.74)
Median	8.1	18.8	5.7	6.5	6.8

Table 38 Summary of Serum Concentrations (µg/mL) at Selected Visits in Subjects With CD (PK Analysis Set)

Visit	Subjects <30 kg		Subjects ≥30 kg		
Statistic	100 mg (N=7)	200 mg (N=7)	150 mg (N=4)	300 mg (N=10)	Total (N=28)
Min, Max	2.32, 21	5.7, 37.9	4.3, 7.21	3.01, 24.4	2.32, 37.9
Week 96 predose					
n	6	4	3	4	17
Mean (SD)	8.4 (5.68)	24.1 (4.82)	5.1 (3.60)	17.8 (7.25)	13.8 (9.02)
Median	6.2	25.7	5.9	17.5	12.2
Min, Max	3.52, 18	17.2, 27.9	1.22, 8.3	11, 25.3	1.22, 27.9
Week 144 predose					
n	6	3	2	4	15
Mean (SD)	6.0 (4.57)	17.2 (5.31)	5.4 (6.56)	16.7 (11.23)	11.0 (8.61)
Median	4.1	18.1	5.4	16.9	7.4
Min, Max	2.25, 14.7	11.5, 22	0.726, 10	6.49, 26.5	0.726, 26.5
Week 192 predose					
n	5	3	2	4	14
Mean (SD)	34.0 (55.07)	16.4 (4.75)	5.1 (5.82)	17.3 (16.17)	21.3 (33.35)
Median	13.2	15.3	5.1	11.7	12.8
Min, Max	2.06, 132	12.3, 21.6	0.94, 9.17	5.71, 40.3	0.94, 132
Week 240 predose					
n	4	1	2	3	10
Mean (SD)	11.1 (7.33)	13.2 (-)	4.4 (5.20)	14.6 (6.69)	11.0 (6.74)
Median	10.2	13.2	4.4	14.7	10.5
Min, Max	3.56, 20.4	13.2, 13.2	0.676, 8.03	7.82, 21.2	0.676, 21.2
Individual subject final visit					
n	6	6	1	7	20
Mean (SD)	14.9 (10.32)	15.6 (18.45)	20.5 (-)	14.2 (22.17)	15.1 (16.58)
Median	13.5	10.1	20.5	2.5	10.1
Min, Max	2.97, 33	0, 52	20.5, 20.5	0, 55.2	0, 55.2

Source: Table 15.2.8.3.

Baseline PK results were from Study 2003 at Week 22.

AVA Results

The overall positive AVA rate was 13.3% (4 of 30 subjects) for **subjects with UC**. Among the 4 subjects with positive AVA, 1 subject was transiently positive and 3 subjects were persistently positive; 3 subjects (10.0%) developed neutralizing antibodies.

Table 57 Overall AVA Status in Subjects With UC (SAF)

Variable, n (%)	Number of Subjects (%)					
	100 mg Only (N=3)	200 mg Only (N=6)	150 mg Only (N=2)	300 mg Only (N=7)	Escalated to 300 mg (N=12)	Total (N=30)
Subjects with at least 1 evaluable AVA sample	3	6	2	7	12	30
Overall AVA/nAVA status						
n	3	6	2	7	12	30
AVA Negative [a], n (%)	2 (66.7)	6 (100)	2 (100)	7 (100)	9 (75.0)	26 (86.7)
AVA Positive [b], n (%)	1 (33.3)	0	0	0	3 (25.0)	4 (13.3)
Transiently positive [c], n (%)	0	0	0	0	1 (8.3)	1 (3.3)
Baseline positive only [d], n (%)	0	0	0	0	1 (8.3)	1 (3.3)
Persistently positive [e], n (%)	1 (33.3)	0	0	0	2 (16.7)	3 (10.0)
Negative nAVA, n (%)	0	0	0	0	0	0
Positive nAVA [f], n (%)	1 (33.3)	0	0	0	2 (16.7)	3 (10.0)

Source: Table 15.2.9.2.

Percentages were based on the number of subjects with at least 1 evaluable AVA sample.

Overall AVA/nAVA status was derived from baseline (inclusive) through safety follow-up. Baseline AVA results were from Study 2003 at Week 22.

[a] AVA negative was defined as a negative (not confirmed positive) AVA result at all visits.

[b] AVA positive was defined as a confirmed AVA positive result at 1 or more visits.

[c] Transiently positive was defined as at least 1 confirmed positive AVA sample and no consecutive positive AVA samples.

[d] Baseline positive only was defined as confirmed positive AVA sample at baseline and no positive sample post-baseline.

[e] Persistently positive was defined as confirmed positive AVA sample at 2 or more consecutive visits.

[f] Positive nAVA was defined as a positive result in the neutralizing AVA assay at any visit.

The overall positive AVA rate was 10.7% (3 of 28 subjects) for **subjects with CD**. Among the 3 subjects with positive AVA, 2 subjects were transiently positive and 1 subject was persistently positive; 0 subjects developed neutralizing antibodies

Table 60 Overall AVA Status in Subjects With CD (SAF)

Variable, n (%)	Number of Subjects (%)					
	100 mg Only (N=5)	200 mg Only (N=5)	150 mg Only (N=2)	300 mg Only (N=10)	Escalated to 300 mg (N=6)	Total (N=28)
Subjects with at least 1 evaluable AVA sample	5	5	2	10	6	28
Overall AVA/nAVA status						
n	5	5	2	10	6	28
AVA Negative [a], n (%)	5 (100)	5 (100)	2 (100)	9 (90.0)	4 (66.7)	25 (89.3)
AVA Positive [b], n (%)	0	0	0	1 (10.0)	2 (33.3)	3 (10.7)
Transiently positive [c], n (%)	0	0	0	1 (10.0)	1 (16.7)	2 (7.1)
Baseline positive only [d], n (%)	0	0	0	0	0	0
Persistently positive [e], n (%)	0	0	0	0	1 (16.7)	1 (3.6)
Negative nAVA, n (%)	0	0	0	1 (10.0)	2 (33.3)	3 (10.7)
Positive nAVA [f], n (%)	0	0	0	0	0	0

Source: Table 15.2.9.2.

Percentages were based on the number of subjects with at least 1 evaluable AVA sample.

Overall AVA/nAVA status was derived from baseline (inclusive) through safety follow-up. Baseline AVA results were from Study 2003 at Week 22.

[a] AVA negative was defined as a negative (not confirmed positive) AVA result at all visits.

[b] AVA positive was defined as a confirmed AVA positive result at 1 or more visits.

[c] Transiently positive was defined as at 1 one confirmed positive AVA sample and no consecutive positive AVA samples.

[d] Baseline positive only was defined as confirmed positive AVA sample at baseline and no positive sample post-baseline.

[e] Persistently positive was defined as confirmed positive AVA samples at 2 or more consecutive visits.

[f] Positive nAVA was defined as a positive result in the neutralizing AVA assay at any visit.

Safety results

- **Ulcerative Colitis**

Drug exposure

Table 41 Study Drug Exposure in Subjects With UC (FAS)

	100 mg Only (N=3)	200 mg Only (N=6)	150 mg Only (N=2)	300 mg Only (N=7)	Escalated to 300 mg (N=12)	Total (N=30)
Mean (SD)	1022.0 (754.63)	1648.8 (875.27)	2200.5 (316.08)	1468.3 (818.94)	1542.3 (663.24)	1534.4 (730.41)
Median	799.0	2087.0	2200.5	1696.0	1833.0	1862.0
Min, Max	404, 1863	295, 2364	1977, 2424	351, 2423	464, 2487	295, 2487

Source: Table 15.1.14.

[a] Completed infusions were defined as infusions where the total amount of study drug was infused.

[b] The extent of exposure was calculated by the duration between the first and last dose of study drug plus 18 weeks to account for the known duration of detectable vedolizumab serum concentration after the last dose; that is, date of last dose of vedolizumab – date of first dose of vedolizumab (in Study 2005) + 1 + 126 days.

Adverse Events (AE)

Table 43 Overview of TEAEs in Subjects With UC (SAF)

	Number of Subjects (%)											
	100 mg Only (N=3)		200 mg Only (N=6)		150 mg Only (N=2)		300 mg Only (N=7)		Escalated to 300 mg (N=12)		Total (N=30)	
	Events	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)
TEAEs	35	3 (100)	81	5 (83.3)	29	2 (100)	77	7 (100)	138	12 (100)	360	29 (96.7)
Related	1	1 (33.3)	1	1 (16.7)	1	1 (50.0)	1	1 (14.3)	11	3 (25.0)	15	7 (23.3)
Not related	34	3 (100)	80	5 (83.3)	28	2 (100)	76	7 (100)	127	12 (100)	345	29 (96.7)
Mild	22	3 (100)	59	5 (83.3)	20	2 (100)	53	6 (85.7)	90	12 (100)	244	28 (93.3)
Moderate	12	3 (100)	22	5 (83.3)	9	2 (100)	19	6 (85.7)	35	7 (58.3)	97	23 (76.7)
Severe	1	1 (33.3)	0	0	0	0	5	3 (42.9)	13	4 (33.3)	19	8 (26.7)
Leading to study drug discontinuation	2	2 (66.7)	1	1 (16.7)	0	0	1	1 (14.3)	3	3 (25.0)	7	7 (23.3)
Serious TEAEs	2	1 (33.3)	1	1 (16.7)	1	1 (50.0)	7	3 (42.9)	9	4 (33.3)	20	10 (33.3)
Related	0	0	0	0	0	0	0	0	0	0	0	0
Not related	2	1 (33.3)	1	1 (16.7)	1	1 (50.0)	7	3 (42.9)	9	4 (33.3)	20	10 (33.3)
Leading to study drug discontinuation	0	0	0	0	0	0	1	1 (14.3)	1	1 (8.3)	2	2 (6.7)
Deaths	0	0	0	0	0	0	0	0	0	0	0	0

Source: Table 15.3.1.

MedDRA Dictionary (Version 28.0) was used for coding AEs.

A TEAE was either an AE whose date of onset occurred on or after the first dose of study drug, or an already-present AE that worsened in intensity or frequency following the treatment start, occurring from the first dose of study drug to the day of last dose of study drug + 18 weeks.

Relatedness and severity within the TEAEs and the SAEs were not mutually exclusive, and subjects could be counted in multiple categories.

A subject with more than 1 AE was counted once per category in the subjects column and was counted as many times as he/she had events satisfying the category in the events column.

TEAEs by SOC and PT

Table 45 TEAEs by SOC and PT (Occurring in >1 Subject in Total) in Subjects With UC (SAF)

SOC PT	Number of Subjects (%)					
	100 mg Only (N=3)	200 mg Only (N=6)	150 mg Only (N=2)	300 mg Only (N=7)	Escalated to 300 mg (N=12)	Total (N=30)
Subjects with any TEAEs [n (%) EAIR]	3 (100) 268.6	5 (83.3) 100.6	2 (100) 260.9	7 (100) 594.6	12 (100) 114.6	29 (96.7) 156.7
Gastrointestinal disorders	3 (100)	4 (66.7)	2 (100)	6 (85.7)	10 (83.3)	25 (83.3)
Colitis ulcerative	1 (33.3)	3 (50.0)	0	3 (42.9)	6 (50.0)	13 (43.3)
Colitis	1 (33.3)	1 (16.7)	0	1 (14.3)	0	3 (10.0)
Vomiting	1 (33.3)	3 (50.0)	1 (50.0)	0	4 (33.3)	9 (30.0)
Nausea	0	0	1 (50.0)	0	4 (33.3)	5 (16.7)
Abdominal pain	0	1 (16.7)	1 (50.0)	1 (14.3)	4 (33.3)	7 (23.3)
Abdominal pain upper	1 (33.3)	0	0	1 (14.3)	0	2 (6.7)
Diarrhoea	1 (33.3)	1 (16.7)	1 (50.0)	0	4 (33.3)	7 (23.3)
Constipation	1 (33.3)	1 (16.7)	0	1 (14.3)	0	3 (10.0)
Gastrooesophageal reflux disease	0	2 (33.3)	0	0	0	2 (6.7)
Haematochezia	0	0	1 (50.0)	0	2 (16.7)	3 (10.0)
Dyspepsia	0	0	0	1 (14.3)	1 (8.3)	2 (6.7)
Infections and infestations	2 (66.7)	5 (83.3)	2 (100)	5 (71.4)	9 (75.0)	23 (76.7)
Upper respiratory tract infection	1 (33.3)	2 (33.3)	0	1 (14.3)	4 (33.3)	8 (26.7)
Pharyngitis	1 (33.3)	2 (33.3)	0	0	2 (16.7)	5 (16.7)
Nasopharyngitis	1 (33.3)	0	1 (50.0)	1 (14.3)	1 (8.3)	4 (13.3)
Tonsillitis	0	1 (16.7)	0	1 (14.3)	1 (8.3)	3 (10.0)
Rhinitis	0	0	1 (50.0)	1 (14.3)	0	2 (6.7)
COVID-19	0	3 (50.0)	0	1 (14.3)	2 (16.7)	6 (20.0)

Table 45 TEAEs by SOC and PT (Occurring in >1 Subject in Total) in Subjects With UC (SAF)

SOC PT	Number of Subjects (%) 100 mg Only (N=3)	200 mg Only (N=6)	150 mg Only (N=2)	300 mg Only (N=7)	Escalated to 300 mg (N=12)	Total (N=30)
Respiratory tract infection	1 (33.3)	1 (16.7)	0	0	1 (8.3)	3 (10.0)
Viral infection	1 (33.3)	1 (16.7)	0	1 (14.3)	1 (8.3)	4 (13.3)
Influenza	0	2 (33.3)	1 (50.0)	0	0	3 (10.0)
Pharyngitis streptococcal	0	2 (33.3)	0	1 (14.3)	0	3 (10.0)
Clostridium difficile infection	1 (33.3)	1 (16.7)	0	0	0	2 (6.7)
Oral herpes	0	0	1 (50.0)	1 (14.3)	0	2 (6.7)
Bronchitis	0	0	0	0	2 (16.7)	2 (6.7)
General disorders and administration site conditions	1 (33.3)	4 (66.7)	1 (50.0)	3 (42.9)	6 (50.0)	15 (50.0)
Pyrexia	1 (33.3)	4 (66.7)	1 (50.0)	2 (28.6)	4 (33.3)	12 (40.0)
Fatigue	0	1 (16.7)	0	1 (14.3)	0	2 (6.7)
Investigations	1 (33.3)	1 (16.7)	2 (100)	3 (42.9)	6 (50.0)	13 (43.3)
Faecal calprotectin increased	1 (33.3)	0	0	1 (14.3)	4 (33.3)	6 (20.0)
Weight decreased	0	0	0	0	3 (25.0)	3 (10.0)
Gastrointestinal examination abnormal	0	0	0	1 (14.3)	1 (8.3)	2 (6.7)
Haemoglobin decreased	0	1 (16.7)	1 (50.0)	0	1 (8.3)	3 (10.0)
Injury, poisoning and procedural complications	0	2 (33.3)	0	5 (71.4)	4 (33.3)	11 (36.7)
Ligament sprain	0	0	0	1 (14.3)	1 (8.3)	2 (6.7)
Musculoskeletal and connective tissue disorders	0	4 (66.7)	1 (50.0)	3 (42.9)	2 (16.7)	10 (33.3)
Arthralgia	0	3 (50.0)	1 (50.0)	2 (28.6)	0	6 (20.0)
Pain in extremity	0	1 (16.7)	0	1 (14.3)	0	2 (6.7)
Muscle spasms	0	1 (16.7)	0	0	1 (8.3)	2 (6.7)
Nervous system disorders	1 (33.3)	1 (16.7)	1 (50.0)	3 (42.9)	4 (33.3)	10 (33.3)
Headache	1 (33.3)	1 (16.7)	1 (50.0)	2 (28.6)	2 (16.7)	7 (23.3)
Migraine	0	0	0	1 (14.3)	1 (8.3)	2 (6.7)
Respiratory, thoracic and mediastinal disorders	0	2 (33.3)	1 (50.0)	1 (14.3)	5 (41.7)	9 (30.0)
Cough	0	2 (33.3)	0	1 (14.3)	1 (8.3)	4 (13.3)
Oropharyngeal pain	0	0	0	1 (14.3)	1 (8.3)	2 (6.7)
Epistaxis	0	0	0	0	2 (16.7)	2 (6.7)
Blood and lymphatic system disorders	2 (66.7)	0	1 (50.0)	3 (42.9)	1 (8.3)	7 (23.3)

Table 45 TEAEs by SOC and PT (Occurring in >1 Subject in Total) in Subjects With UC (SAF)

SOC PT	Number of Subjects (%)					
	100 mg Only (N=3)	200 mg Only (N=6)	150 mg Only (N=2)	300 mg Only (N=7)	Escalated to 300 mg (N=12)	Total (N=30)
Iron deficiency anaemia	0	0	1 (50.0)	2 (28.6)	0	3 (10.0)
Anaemia of chronic disease	1 (33.3)	0	0	1 (14.3)	0	2 (6.7)
Eosinophilia	1 (33.3)	0	0	0	1 (8.3)	2 (6.7)
Skin and subcutaneous tissue disorders	0	2 (33.3)	1 (50.0)	1 (14.3)	2 (16.7)	6 (20.0)
Dry skin	0	0	0	1 (14.3)	1 (8.3)	2 (6.7)
Psychiatric disorders	0	0	0	1 (14.3)	1 (8.3)	2 (6.7)
Depression	0	0	0	1 (14.3)	1 (8.3)	2 (6.7)

Source: Table 15.3.1.1.

MedDRA Dictionary (Version 28.0) was used for coding AEs.

A TEAE was either an AE whose date of onset occurred on or after the first dose of study drug, or an already-present AE that worsened in intensity or frequency following the treatment start, occurring from the first dose of study drug to the day of last dose of study drug + 18 weeks.

Subjects with 1 or more AEs within a level of MedDRA term were counted only once in that level.

EAIR was defined as the number of subjects with any TEAEs / Sum of ([date of first TEAE or date of last dose or end of study + 126 days] - date of first dose) +1 per 100 person years.

Drug-Related TEAEs by SOC and PT in Subjects With UC (SAF)

Table 47 Drug-Related TEAEs by SOC and PT in Subjects With UC (SAF)

SOC PT	Number of Subjects (%)					
	100 mg Only (N=3)	200 mg Only (N=6)	150 mg Only (N=2)	300 mg Only (N=7)	Escalated to 300 mg (N=12)	Total (N=30)
Subjects with any drug-related TEAEs	1 (33.3)	1 (16.7)	1 (50.0)	1 (14.3)	3 (25.0)	7 (23.3)
Gastrointestinal disorders	1 (33.3)	1 (16.7)	0	0	2 (16.7)	4 (13.3)
Colitis	1 (33.3)	0	0	0	0	1 (3.3)
Colitis ulcerative	0	1 (16.7)	0	0	0	1 (3.3)
Nausea	0	0	0	0	2 (16.7)	2 (6.7)
Vomiting	0	0	0	0	1 (8.3)	1 (3.3)
Investigations	0	0	1 (50.0)	0	1 (8.3)	2 (6.7)
Faecal calprotectin increased	0	0	0	0	1 (8.3)	1 (3.3)
White blood cell count decreased	0	0	1 (50.0)	0	0	1 (3.3)
Blood and lymphatic system disorders	0	0	0	0	1 (8.3)	1 (3.3)
Eosinophilia	0	0	0	0	1 (8.3)	1 (3.3)
Hepatobiliary disorders	0	0	0	1 (14.3)	0	1 (3.3)
Hepatic cytolysis	0	0	0	1 (14.3)	0	1 (3.3)
Nervous system disorders	0	0	0	0	1 (8.3)	1 (3.3)
Central nervous system lesion	0	0	0	0	1 (8.3)	1 (3.3)

Source: Table 15.3.1.2.

MedDRA Dictionary (Version 28.0) was used for coding AEs.

A TEAE was either an AE whose date of onset occurred on or after the first dose of study drug, or an already-present AE that worsened in intensity or frequency following the treatment start, occurring from the first dose of study drug to the day of last dose of study drug + 18 weeks.

SAEs by SOC and PT in Subjects With UC (SAF)

Table 49 SAEs by SOC and PT in Subjects With UC (SAF)

SOC PT	Number of Subjects (%)					
	100 mg Only (N=3)	200 mg Only (N=6)	150 mg Only (N=2)	300 mg Only (N=7)	Escalated to 300 mg (N=12)	Total (N=30)
Subjects with any SAEs	1 (33.3)	1 (16.7)	1 (50.0)	3 (42.9)	4 (33.3)	10 (33.3)
Gastrointestinal disorders	1 (33.3)	0	0	2 (28.6)	4 (33.3)	7 (23.3)
Colitis ulcerative	1 (33.3)	0	0	2 (28.6)	1 (8.3)	4 (13.3)
Abdominal pain	0	0	0	0	1 (8.3)	1 (3.3)
Intestinal obstruction	0	0	0	0	1 (8.3)	1 (3.3)
Large intestine perforation	0	0	0	0	1 (8.3)	1 (3.3)
Large intestinal stenosis	0	0	0	0	1 (8.3)	1 (3.3)
Vomiting	0	0	0	0	1 (8.3)	1 (3.3)
Infections and infestations	1 (33.3)	0	1 (50.0)	1 (14.3)	2 (16.7)	5 (16.7)
Campylobacter infection	0	0	0	1 (14.3)	0	1 (3.3)
Clostridium difficile colitis	1 (33.3)	0	0	0	0	1 (3.3)
Infectious mononucleosis	0	0	1 (50.0)	0	0	1 (3.3)
Pelvic abscess	0	0	0	0	1 (8.3)	1 (3.3)
Bronchitis	0	0	0	0	1 (8.3)	1 (3.3)
Blood and lymphatic system disorders	0	0	0	1 (14.3)	0	1 (3.3)
Anaemia of chronic disease	0	0	0	1 (14.3)	0	1 (3.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1 (14.3)	0	1 (3.3)
Papillary thyroid cancer	0	0	0	1 (14.3)	0	1 (3.3)
Nervous system disorders	0	0	0	0	1 (8.3)	1 (3.3)
Headache	0	0	0	0	1 (8.3)	1 (3.3)
Renal and urinary disorders	0	0	0	1 (14.3)	0	1 (3.3)
Haematuria	0	0	0	1 (14.3)	0	1 (3.3)
Skin and subcutaneous tissue disorders	0	1 (16.7)	0	0	0	1 (3.3)
Cutaneous vasculitis	0	1 (16.7)	0	0	0	1 (3.3)

Source: Table 15.3.1.5.

All SAEs were assessed as not related to the study drug by the investigator.

Deaths

No deaths were reported during the study.

Study Discontinuations due to TEAEs by Subjects With UC

Table 51 TEAEs Leading to Study Drug Discontinuation in Subjects With UC (SAF)

SOC PT	Number of Subjects (%)					
	100 mg Only (N=3)	200 mg Only (N=6)	150 mg Only (N=2)	300 mg Only (N=7)	Escalated to 300 mg (N=12)	Total (N=30)
Subjects with any TEAEs leading to study drug discontinuation	2 (66.7)	1 (16.7)	0	1 (14.3)	3 (25.0)	7 (23.3)
Gastrointestinal disorders	1 (33.3)	1 (16.7)	0	1 (14.3)	3 (25.0)	6 (20.0)
Colitis ulcerative	0	1 (16.7)	0	1 (14.3)	3 (25.0)	5 (16.7)
Colitis	1 (33.3)	0	0	0	0	1 (3.3)
Investigations	1 (33.3)	0	0	0	0	1 (3.3)
Faecal calprotectin increased	1 (33.3)	0	0	0	0	1 (3.3)

AESI

- **Infections**

Table 53 AESIs of Serious Infections in Subjects With UC (SAF)

SOC PT	Number of Subjects (%)					
	100 mg Only (N=3)	200 mg Only (N=6)	150 mg Only (N=2)	300 mg Only (N=7)	Escalated to 300 mg (N=12)	Total (N=30)
Subjects with any TEAE of Serious Infections	1 (33.3)	0	1 (50.0)	1 (14.3)	2 (16.7)	5 (16.7)
Infections and infestations	1 (33.3)	0	1 (50.0)	1 (14.3)	2 (16.7)	5 (16.7)
Campylobacter infection	0	0	0	1 (14.3)	0	1 (3.3)
Clostridium difficile colitis	1 (33.3)	0	0	0	0	1 (3.3)
Infectious mononucleosis	0	0	1 (50.0)	0	0	1 (3.3)
Pelvic abscess	0	0	0	0	1 (8.3)	1 (3.3)
Bronchitis	0	0	0	0	1 (8.3)	1 (3.3)

Source: Table 15.3.1.6.

MedDRA Dictionary (Version 28.0) was used for coding AEs.

AESI includes malignancies, infusion reactions, any serious TEAEs within the SOC of hypersensitivity reactions, "infections, and infestations", liver injury, and PML.

Subjects with 1 or more AEs within a level of MedDRA term were counted only once in that level.

- **Hypersensitivity**

Table 54 AESIs of Hypersensitivity Reactions in Subjects With UC (SAF)

SOC PT	Number of Subjects (%)					
	100 mg Only (N=3)	200 mg Only (N=6)	150 mg Only (N=2)	300 mg Only (N=7)	Escalated to 300 mg (N=12)	Total (N=30)
Subjects with any TEAE of Hypersensitivity Reactions	1 (33.3)	4 (66.7)	1 (50.0)	1 (14.3)	3 (25.0)	10 (33.3)
Skin and subcutaneous tissue disorders	0	2 (33.3)	0	0	1 (8.3)	3 (10.0)
Erythema nodosum	0	1 (16.7)	0	0	0	1 (3.3)
Rash	0	0	0	0	1 (8.3)	1 (3.3)
Cutaneous vasculitis	0	1 (16.7)	0	0	0	1 (3.3)
Blood and lymphatic system disorders	1 (33.3)	0	0	0	1 (8.3)	2 (6.7)
Eosinophilia	1 (33.3)	0	0	0	1 (8.3)	2 (6.7)
General disorders and administration site conditions	0	1 (16.7)	0	1 (14.3)	0	2 (6.7)
Peripheral swelling	0	0	0	1 (14.3)	0	1 (3.3)
Injection site rash	0	1 (16.7)	0	0	0	1 (3.3)
Immune system disorders	0	0	0	1 (14.3)	1 (8.3)	2 (6.7)
Hypersensitivity	0	0	0	1 (14.3)	0	1 (3.3)
Multiple allergies	0	0	0	0	1 (8.3)	1 (3.3)
Eye disorders	0	1 (16.7)	0	0	0	1 (3.3)
Conjunctivitis allergic	0	1 (16.7)	0	0	0	1 (3.3)
Infections and infestations	0	0	0	0	1 (8.3)	1 (3.3)
Conjunctivitis	0	0	0	0	1 (8.3)	1 (3.3)
Respiratory, thoracic and mediastinal disorders	0	0	1 (50.0)	0	0	1 (3.3)
Asthma	0	0	1 (50.0)	0	0	1 (3.3)

Source: Table 15.3.1.6.

MedDRA Dictionary (Version 28.0) was used for coding AEs.

AESI includes malignancies, infusion reactions, any serious TEAEs within the SOC of hypersensitivity reactions,

- **Infusion-Related Reactions**

There were no reports of the AESI of infusion-related reactions in subjects with UC during the study.

- **Malignancy**

The AESI of papillary thyroid cancer was reported in 1 subject (3.3%) with UC. The AESI of papillary thyroid cancer was serious, severe in severity, and assessed as not related to the study drug. The dose was not changed and the outcome was reported as recovered/resolved.

- **Liver Injury**

The AESI of liver injury was reported in 2 subjects (6.7%) with UC. The AESI of hepatic cytolysis was reported in 1 subject and the AESI of gamma-glutamyl transferase increased was reported in 1 subject. Both AESIs were not serious and were mild in severity. Hepatic cytolysis was assessed as related to the study drug while gamma-glutamyltransferase increased was assessed as not related to the study drug. For hepatic cytolysis, the outcome was reported as recovered/resolved, while the outcome for gamma-glutamyltransferase increased was reported as not recovered/not resolved.

- **PML**

No events related to PML were reported in subjects with UC during the study. One nonserious mild TEAE of central nervous system lesion considered related by the investigator was evaluated with all performed PML checklists being negative. Two neurologists suspected the brain changes were due to perinatal hypoxia from congenial heart disease. No action was taken by the investigator and the subject continued with the study.

Crohn's Disease

Drug exposure

Table 42 Study Drug Exposure in Subjects With CD (FAS)

	100 mg Only (N=5)	200 mg Only (N=5)	150 mg Only (N=2)	300 mg Only (N=10)	Escalated to 300 mg (N=6)	Total (N=28)
Completed infusion [a]						
n	5	5	2	10	6	28
Mean (SD)	24.8 (11.21)	14.4 (16.13)	23.5 (14.85)	16.5 (14.93)	27.3 (11.64)	20.4 (13.86)
Median	30.0	3.0	23.5	10.0	29.5	24.0
Min, Max	6, 33	2, 34	13, 34	1, 41	11, 40	1, 41
Extent of Exposure (Days) [b]						
n	5	5	2	10	6	28
Mean (SD)	1484.0 (645.72)	877.0 (901.94)	1391.5 (819.54)	996.6 (838.44)	1602.2 (652.41)	1220.3 (779.83)
Median	1751.0	248.0	1391.5	630.0	1721.5	1418.5
Min, Max	410, 1972	183, 1971	812, 1971	127, 2386	687, 2317	127, 2386

Source: Table 15.1.14.

[a] Completed infusions were defined as infusions where the total amount of study drug was infused.

Adverse Events

Table 44 Overview of TEAEs in Subjects With CD (SAF)

	Number of Subjects (%)											
	100 mg Only (N=5)		200 mg Only (N=5)		150 mg Only (N=2)		300 mg Only (N=10)		Escalated to 300 mg (N=6)		Total (N=28)	
	Events	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)
TEAEs	28	5 (100)	47	5 (100)	9	2 (100)	88	10 (100)	66	6 (100)	238	28 (100)
Related	1	1 (20.0)	1	1 (20.0)	0	0	5	2 (20.0)	0	0	7	4 (14.3)
Not related	27	5 (100)	46	5 (100)	9	2 (100)	83	10 (100)	66	6 (100)	231	28 (100)
Mild	26	5 (100)	31	4 (80.0)	4	2 (100)	49	9 (90.0)	47	6 (100)	157	26 (92.9)
Moderate	2	1 (20.0)	10	4 (80.0)	4	1 (50.0)	38	7 (70.0)	19	5 (83.3)	73	18 (64.3)
Severe	0	0	6	3 (60.0)	1	1 (50.0)	1	1 (10.0)	0	0	8	5 (17.9)
Leading to study drug discontinuation	0	0	1	1 (20.0)	0	0	3	2 (20.0)	2	2 (33.3)	6	5 (17.9)
Serious TEAEs	0	0	8	4 (80.0)	1	1 (50.0)	6	4 (40.0)	1	1 (16.7)	16	10 (35.7)
Related	0	0	1	1 (20.0)	0	0	0	0	0	0	1	1 (3.6)
Not related	0	0	7	4 (80.0)	1	1 (50.0)	6	4 (40.0)	1	1 (16.7)	15	10 (35.7)
Leading to study drug discontinuation	0	0	0	0	0	0	1	1 (10.0)	0	0	1	1 (3.6)
Deaths	0	0	0	0	0	0	0	0	0	0	0	0

Source: Table 15.3.1.

MedDRA Dictionary (Version 28.0) was used for coding AEs.

A TEAE was either an AE whose date of onset occurred on or after the first dose of study drug, or an already-present AE that worsened in intensity or frequency following the treatment start, occurring from the first dose of study drug to the day of last dose of study drug + 18 weeks.

Relatedness and severity within the TEAEs and the SAEs were not mutually exclusive, and subjects could be counted in multiple categories.

A subject with more than 1 AE was counted once per category in the subjects column and was counted as many times as he/she had events satisfying the category in the events column.

TEAEs by SOC and PT

Table 46 TEAEs by SOC and PT (Occurring in >1 Subject in Total) in Subjects With CD (SAF)

	Number of Subjects (%)					
SOC PT	100 mg Only (N=5)	200 mg Only (N=5)	150 mg Only (N=2)	300 mg Only (N=10)	Escalated to 300 mg (N=6)	Total (N=28)
Subjects with any TEAEs [n (%) EAIR]	5 (100) 115.4	5 (100) 673.9	2 (100) 59.7	10 (100) 217.3	6 (100) 440.1	28 (100) 194.6

Table 46 TEAEs by SOC and PT (Occurring in >1 Subject in Total) in Subjects With CD (SAF)

SOC PT	Number of Subjects (%)					
	100 mg Only (N=5)	200 mg Only (N=5)	150 mg Only (N=2)	300 mg Only (N=10)	Escalated to 300 mg (N=6)	Total (N=28)
Gastrointestinal disorders	1 (20.0)	5 (100)	0	8 (80.0)	6 (100)	20 (71.4)
Crohn's disease	0	3 (60.0)	0	6 (60.0)	4 (66.7)	13 (46.4)
Abdominal pain	0	2 (40.0)	0	3 (30.0)	1 (16.7)	6 (21.4)
Vomiting	0	2 (40.0)	0	1 (10.0)	1 (16.7)	4 (14.3)
Nausea	0	0	0	1 (10.0)	1 (16.7)	2 (7.1)
Toothache	1 (20.0)	0	0	2 (20.0)	0	3 (10.7)
Diarrhoea	0	0	0	1 (10.0)	2 (33.3)	3 (10.7)
Faeces soft	0	1 (20.0)	0	1 (10.0)	0	2 (7.1)
Gastritis	0	0	0	1 (10.0)	1 (16.7)	2 (7.1)
Constipation	0	0	0	2 (20.0)	0	2 (7.1)
Infections and infestations	2 (40.0)	3 (60.0)	2 (100)	6 (60.0)	6 (100)	19 (67.9)
Upper respiratory tract infection	1 (20.0)	2 (40.0)	0	2 (20.0)	1 (16.7)	6 (21.4)
Pharyngitis	1 (20.0)	1 (20.0)	0	2 (20.0)	1 (16.7)	5 (17.9)
Nasopharyngitis	0	1 (20.0)	0	2 (20.0)	1 (16.7)	4 (14.3)
Rhinitis	0	1 (20.0)	0	0	1 (16.7)	2 (7.1)
COVID-19	1 (20.0)	1 (20.0)	0	0	1 (16.7)	3 (10.7)
Ear infection	0	1 (20.0)	1 (50.0)	0	1 (16.7)	3 (10.7)
Otitis externa	0	0	1 (50.0)	0	1 (16.7)	2 (7.1)
Viral infection	0	0	1 (50.0)	1 (10.0)	1 (16.7)	3 (10.7)
Respiratory tract infection	0	1 (20.0)	0	0	1 (16.7)	2 (7.1)
Influenza	0	1 (20.0)	0	0	1 (16.7)	2 (7.1)
Bronchitis	1 (20.0)	0	0	1 (10.0)	0	2 (7.1)
Pharyngitis streptococcal	0	1 (20.0)	0	1 (10.0)	0	2 (7.1)
Respiratory, thoracic and mediastinal disorders	2 (40.0)	2 (40.0)	0	4 (40.0)	2 (33.3)	10 (35.7)
Oropharyngeal pain	0	0	0	1 (10.0)	2 (33.3)	3 (10.7)
Catarrh	0	0	0	1 (10.0)	1 (16.7)	2 (7.1)
Cough	0	0	0	1 (10.0)	1 (16.7)	2 (7.1)
Tonsillar hypertrophy	0	1 (20.0)	0	0	1 (16.7)	2 (7.1)
Skin and subcutaneous tissue disorders	2 (40.0)	2 (40.0)	0	2 (20.0)	1 (16.7)	7 (25.0)
Rash	1 (20.0)	0	0	1 (10.0)	0	2 (7.1)
Blood and lymphatic system disorders	1 (20.0)	1 (20.0)	0	3 (30.0)	1 (16.7)	6 (21.4)
Anaemia	1 (20.0)	1 (20.0)	0	2 (20.0)	1 (16.7)	5 (17.9)
Investigations	0	0	1 (50.0)	3 (30.0)	2 (33.3)	6 (21.4)

Table 46 TEAEs by SOC and PT (Occurring in >1 Subject in Total) in Subjects With CD (SAF)

SOC PT	Number of Subjects (%)					
	100 mg Only (N=5)	200 mg Only (N=5)	150 mg Only (N=2)	300 mg Only (N=10)	Escalated to 300 mg (N=6)	Total (N=28)
Weight decreased	0	0	0	2 (20.0)	0	2 (7.1)
General disorders and administration site conditions	1 (20.0)	0	1 (50.0)	2 (20.0)	1 (16.7)	5 (17.9)
Fatigue	1 (20.0)	0	0	1 (10.0)	0	2 (7.1)
Metabolism and nutrition disorders	0	2 (40.0)	1 (50.0)	1 (10.0)	0	4 (14.3)
Decreased appetite	0	1 (20.0)	0	1 (10.0)	0	2 (7.1)
Musculoskeletal and connective tissue disorders	0	2 (40.0)	0	1 (10.0)	1 (16.7)	4 (14.3)
Pain in extremity	0	1 (20.0)	0	1 (10.0)	1 (16.7)	3 (10.7)
Arthralgia	0	1 (20.0)	0	1 (10.0)	0	2 (7.1)
Nervous system disorders	0	0	0	3 (30.0)	0	3 (10.7)
Hypoaesthesia	0	0	0	2 (20.0)	0	2 (7.1)

Source: Table 15.3.1.1.

MedDRA Dictionary (Version 28.0) was used for coding AEs.

A TEAE was either an AE whose date of onset occurred on or after the first dose of study drug, or an already-present AE that worsened in intensity or frequency following the treatment start, occurring from the first dose of study drug to the day of last dose of study drug + 18 weeks.

Subjects with 1 or more AEs within a level of MedDRA term were counted only once in that level.

EAIR was defined as the number of subjects with any TEAEs / Sum of ([date of first TEAE or date of last dose or end of study + 126 days] - date of first dose) +1 per 100 person years.

Drug-Related TEAEs by SOC and PT in Subjects With CD (SAF)

Table 48 Drug-Related TEAEs by SOC and PT in Subjects With CD (SAF)

SOC PT	Number of Subjects (%)					
	100 mg Only (N=5)	200 mg Only (N=5)	150 mg Only (N=2)	300 mg Only (N=10)	Escalated to 300 mg (N=6)	Total (N=28)
Subjects with any drug-related TEAEs	1 (20.0)	1 (20.0)	0	2 (20.0)	0	4 (14.3)
Gastrointestinal disorders	0	1 (20.0)	0	1 (10.0)	0	2 (7.1)
Crohn's disease	0	1 (20.0)	0	1 (10.0)	0	2 (7.1)
Respiratory, thoracic and mediastinal disorders	1 (20.0)	0	0	1 (10.0)	0	2 (7.1)
Asthma	1 (20.0)	0	0	0	0	1 (3.6)
Cough	0	0	0	1 (10.0)	0	1 (3.6)
Infections and infestations	0	0	0	1 (10.0)	0	1 (3.6)
Nasopharyngitis	0	0	0	1 (10.0)	0	1 (3.6)

Source: Table 15.3.1.2.

MedDRA Dictionary (Version 28.0) was used for coding AEs.

A TEAE was either an AE whose date of onset occurred on or after the first dose of study drug, or an already-present AE that worsened in intensity or frequency following the treatment start, occurring from the first dose of study drug to the day of last dose of study drug + 18 weeks.

Overall, the maximum severity of the TEAEs in the majority of subjects (14 [50.0%]) with CD were moderate intensity. TEAEs with a maximum severity of mild intensity were reported in 9 subjects (32.1%). TEAEs with a maximum severity of severe intensity were reported in 5 subjects (17.9%).

Drug-related TEAEs with a maximum severity of mild intensity were reported in 2 subjects (7.1%). Drug-related TEAEs with a maximum severity of moderate and severe intensity were reported in 1 subject (3.6%) each.

SAEs by SOC and PT in Subjects With CD (SAF)

Table 50 SAEs by SOC and PT in Subjects With CD (SAF)

SOC PT	Number of Subjects (%)					
	100 mg Only (N=5)	200 mg Only (N=5)	150 mg Only (N=2)	300 mg Only (N=10)	Escalated to 300 mg (N=6)	Total (N=28)
Subjects with any SAEs	0	4 (80.0)	1 (50.0)	4 (40.0)	1 (16.7)	10 (35.7)
Gastrointestinal disorders	0	2 (40.0)	0	4 (40.0)	1 (16.7)	7 (25.0)
Crohn's disease	0	1 (20.0)	0	4 (40.0)	0	5 (17.9)
Colitis	0	1 (20.0)	0	0	0	1 (3.6)
Colitis ulcerative	0	1 (20.0)	0	0	0	1 (3.6)
Gastritis	0	0	0	0	1 (16.7)	1 (3.6)
Abdominal pain	0	1 (20.0)	0	0	0	1 (3.6)
Rectal haemorrhage	0	1 (20.0)	0	0	0	1 (3.6)
Vomiting	0	1 (20.0)	0	0	0	1 (3.6)
Infections and infestations	0	0	0	1 (10.0)	0	1 (3.6)
Viral infection	0	0	0	1 (10.0)	0	1 (3.6)
Injury, poisoning and procedural complications	0	0	1 (50.0)	0	0	1 (3.6)
Post procedural haemorrhage	0	0	1 (50.0)	0	0	1 (3.6)
Musculoskeletal and connective tissue disorders	0	1 (20.0)	0	0	0	1 (3.6)
Exostosis	0	1 (20.0)	0	0	0	1 (3.6)
Skin and subcutaneous tissue disorders	0	1 (20.0)	0	0	0	1 (3.6)
Urticaria	0	1 (20.0)	0	0	0	1 (3.6)

Source: Table 15.3.1.5

The SAE of Crohn's disease (disease worsening) was assessed as related to the study drug and was reported in 1 subject (3.6%) with CD. This event was severe in intensity and the outcome was reported as resolved/recovered. Action taken with study drug due to the event was reported as "not applicable".

Deaths

No deaths were reported during the study.

Study Discontinuations due to TEAEs by Subjects With CD

Table 52 TEAEs Leading to Study Drug Discontinuation in Subjects With CD (SAF)

SOC PT	Number of Subjects (%)					
	100 mg Only (N=5)	200 mg Only (N=5)	150 mg Only (N=2)	300 mg Only (N=10)	Escalated to 300 mg (N=6)	Total (N=28)
Subjects with any TEAEs leading to study drug discontinuation	0	1 (20.0)	0	2 (20.0)	2 (33.3)	5 (17.9)
Gastrointestinal disorders	0	1 (20.0)	0	2 (20.0)	1 (16.7)	4 (14.3)
Crohn's disease	0	1 (20.0)	0	1 (10.0)	1 (16.7)	3 (10.7)
Anal stenosis	0	0	0	1 (10.0)	0	1 (3.6)
Injury, poisoning and procedural complications	0	0	0	1 (10.0)	0	1 (3.6)
Intestinal anastomosis complication	0	0	0	1 (10.0)	0	1 (3.6)
Investigations	0	0	0	0	1 (16.7)	1 (3.6)
Faecal calprotectin increased	0	0	0	0	1 (16.7)	1 (3.6)

AESI

-Infections

Table 55 AESIs (Infections and Infestations) in Subjects With CD (SAF)

SOC PT	Number of Subjects (%)					
	100 mg Only (N=5)	200 mg Only (N=5)	150 mg Only (N=2)	300 mg Only (N=10)	Escalated to 300 mg (N=6)	Total (N=28)
Subjects with any TEAE of Serious Infections	0	0	0	1 (10.0)	0	1 (3.6)
Infections and infestations	0	0	0	1 (10.0)	0	1 (3.6)
Viral infection	0	0	0	1 (10.0)	0	1 (3.6)

Source: Table 15.3.1.6.

MedDRA Dictionary (Version 28.0) was used for coding AEs.

AESI includes malignancies, infusion reactions, any serious TEAEs within the SOC of hypersensitivity reactions, "infections, and infestations", liver injury, and PML.

Subjects with 1 or more AEs within a level of MedDRA term were counted only once in that level.

- **Hypersensitivity**

Table 56 AESIs (Hypersensitivity) in Subjects With CD (SAF)

SOC PT	Number of Subjects (%)					
	100 mg Only (N=5)	200 mg Only (N=5)	150 mg Only (N=2)	300 mg Only (N=10)	Escalated to 300 mg (N=6)	Total (N=28)
Subjects with any TEAE of Hypersensitivity Reactions	2 (40.0)	2 (40.0)	0	2 (20.0)	1 (16.7)	7 (25.0)
Skin and subcutaneous tissue disorders	2 (40.0)	2 (40.0)	0	1 (10.0)	1 (16.7)	6 (21.4)
Dermatitis	0	0	0	0	1 (16.7)	1 (3.6)
Dermatitis atopic	1 (20.0)	0	0	0	0	1 (3.6)
Eczema	0	1 (20.0)	0	0	0	1 (3.6)
Rash	1 (20.0)	0	0	1 (10.0)	0	2 (7.1)
Pruritus	0	1 (20.0)	0	0	0	1 (3.6)
Dermatitis psoriasiform	0	0	0	1 (10.0)	0	1 (3.6)
Urticaria	0	1 (20.0)	0	0	0	1 (3.6)
Gastrointestinal disorders	0	0	0	1 (10.0)	0	1 (3.6)
Mouth ulceration	0	0	0	1 (10.0)	0	1 (3.6)
Immune system disorders	1 (20.0)	0	0	0	0	1 (3.6)
Hypersensitivity	1 (20.0)	0	0	0	0	1 (3.6)
Respiratory, thoracic and mediastinal disorders	1 (20.0)	0	0	0	0	1 (3.6)
Asthma	1 (20.0)	0	0	0	0	1 (3.6)
Rhinitis allergic	1 (20.0)	0	0	0	0	1 (3.6)

Source: Table 15.3.1.6.

MedDRA Dictionary (Version 28.0) was used for coding AEs.

AESI includes malignancies, infusion reactions, any serious TEAEs within the SOC of hypersensitivity reactions, "infections, and infestations", liver injury, and PML.

Subjects with 1 or more AEs within a level of MedDRA term were counted only once in that level.

- **Infusion-Related Reactions**

There were no reports of the AESI of infusion-related reactions in subjects with CD during the study.

- **Malignancy**

The AESI of haemangioma was reported in 1 subject (3.6%) with CD. The haemangioma was not serious, mild in severity, assessed as not related to the study drug.

- **Liver Injury**

The AESIs of alanine aminotransferase increased and gamma-glutamyltransferase increased were reported in 1 subject (3.6%) with CD. Both AESIs were not serious, mild in severity, assessed as not related to the study drug, and the dose was not changed. For alanine aminotransferase increased, the outcome was reported as not recovered/not resolved, while the outcome for gamma-glutamyltransferase increased was reported as recovered/resolved.

- **PML**

No events related to PML were reported in subjects with CD during the study.

2.3.3. Discussion on clinical aspects

Study 2005 is a completed phase 2b, open-label, long-term extension study enrolling male and female paediatric subjects with UC or CD who had initiated vedolizumab IV treatment at age 2 to 17 years, inclusive, in Study 2003 (a phase 2, dose-ranging study). Pediatric subjects who completed Study 2003 and achieved clinical response at Week 22 were enrolled in the study. The clinical response was defined, for patients with UC, by a reduction of partial Mayo score of ≥2 points and ≥25% from baseline, or a reduction of the Pediatric Ulcerative Colitis Activity Index (PUCAI) of ≥20 points from baseline; for patients with CD, by a reduction of the CDAI as defined by a ≥70-point decrease from baseline or a decrease of Pediatric Crohn's Disease Activity Index (PCDAI) of ≥15 points**.**
The definition of response in study 2003 is considered in line with the current approach for treatment of the Inflammatory Bowel Diseases (IBDs). In general, the approach used in GEMINI studies (long term safety studies in adults with UC and CD treated with vedolizumab IV) served as the primary method to calculate Mayo score and derive all Mayo score-based efficacy endpoints. Moreover, the complete, partial, and modified Mayo scores were also calculated per draft US FDA UC Guidance (August 2016). The efficacy endpoints based on complete, partial, or modified Mayo scores at Week 32 were derived using this approach as sensitivity analysis.

Eligible subjects received their first dose within 1 week of completing the Week 22 assessments of the preceding study: dosing regimens were the same as those in the parent Study 2003. Vedolizumab IV doses of 300 or 150 mg once every 8 weeks (Q8W) for subjects ≥30 kg body weight and 200 or 100 mg Q8W for subjects <30 kg body weight were continued in Study 2005 after Week 22 visit in Study 2003 (or up to 1 week after) for subjects who consented to participate in the study. In subjects with disease worsening based on PUCAI or PCDAI scores at 2 consecutive visits (scheduled or unscheduled) were eligible for vedolizumab IV dose escalation (150 mg to 300 mg or 100 mg to 200 mg). Dosing was based on the subject's weight at the time of nonresponse in Study 2005; subjects already receiving the higher dose for their weight group were not eligible for escalation and were discontinued from treatment. Persistent disease worsening despite dose escalation required discontinuation. In general, a weight-based approach for pediatric subjects is endorsed; the possibility of dose escalation is contemplated in vedolizumab SmPC for adult patients, while no specific information is reported for pediatric ones. In absence of specific contraindications for posology increasing in this setting, the proposed approach seems acceptable.

As reported before, efficacy analyses were defined as exploratory; therefore, it is acceptable that formal statistical comparisons were not contemplated. Consequently, no formal sample size calculations were performed; it was estimated that up to 80 subjects (40 subjects with UC and 40 subjects with CD) who had completed Study 2003 as responders were to enter this study. Given the long-term nature of this study, the risk of missing data during the follow up was recognized and the MAH included strategies for handling this risk; in general, in presence of missing data, the non-responder imputation method was used. This strategy is accepted.

This protocol was amended 8 times (7 globally and locally 1 time for United Kingdom); as reported in amendments history, substantial changes (possibility of enrolment of pediatric subjects aged 2 to 17 years, subjects who weighed <30 kg, and relative vedolizumab IV dosing regimen in amendment 1 and definition of disease worsening in amendment 3) were all included before the first subject was enrolled on 30 July 2018, under Protocol Amendment 4. Therefore, no relevant impact on study integrity can be expected by protocol amendments. Similarly, the change of the Statistical Analysis Plan (SAP) related to the introduction of the amendment 8 is not considered to have a substantial impact, considering the observational nature of study 2005.

Study enrolment resulted to be slightly below the predicted number of 80 subjects (40 subjects with UC and 40 subjects with CD); this reduction is mainly due to a reduced number of patients that actually completed the parent study (67 subjects:30 subjects <30 kg, 37 subjects ≥30 kg), associated with physiologically further reduction expected at study 2005 start. On the whole, 58 (28 <30 kg and 31 ≥30 kg) were enrolled in study 2005: 30 were UC patients (13 <30 kg and 17 ≥30 kg), while 28 presented

a diagnosis of CD: 28 subjects (14 subjects <30 kg; 14 subjects ≥30 kg). In both groups (< 30 kg and ≥ 30 kg) less than half of patients completed the study: 42.9% in the first one and 38.7% in the other. Main reason for study discontinuation were AEs 53.3%, withdrawal of subjects 20% and other reason 13.3%.
Withdrawal from study was allowed for subjects who achieved 18 years of age, even in remission status. In general, for the 17 subjects for whom the attainment of the age of majority was confirmed during the course of the protocol, information about the completion of the study was available for 8 subjects (5 with UC and 3 with CD). In the UC setting, 3/5 were considered "responders" and 2 "remitters"; 1 subject completed the study, 3 discontinued to AE and 1 moved to the commercial drug. In the CD all the 3 subjects were considered responders and 2 of them achieved also a clinical remission; 2 of them completed the study, while the remaining 1 discontinued for AE. In general, the limitations in identifying subjects who withdrew study for age are understood; the small number of subjects for whom this information is available does not permit definitive conclusions to be drawn. Overall, the risk of protocol driven discontinuations in a clinical remission or in absence of safety issues due to this point is considered negligible.

Although a less than expected enrolment in this study is considered a suboptimal condition, it should be highlighted that, in absence of a pre-specified sample size, the actual impact of a reduced number of patients can be considered limited if subjects included in the study are representative of the target population. In respect to that, it should be reported that demographic and baseline characteristics (except age, height, weight, and BMI) were collected at entry to Study 2003 (before the first dose of study drug), while for age, height, weight, and BMI a new baseline collection was done on the data collected on Day 1 in Study 2005. Overall, no specific issues were noted about the representativeness of the enrolled population.

Demographic and disease characteristics

The enrolled population is in line with the disease characteristic of pediatric long-term responders to vedolizumab.
In the whole population, the median age of the subjects was 11 (8-14) years; the study included 34 (57.6%) male and 25 (42.4%) female subjects. The majority of subjects were not of Hispanic or Latino ethnicity (51 [86.4%] subjects) and reported their race as White (48 [81.4%] subjects).
For the definition of disease specific characteristics, patients were divided basing on their body weight (< or ≥ 30 kg): this decision is accepted, considering that the threshold of 30 kg is clinically important for the definition of the dosing regimen. Overall, although this subdivision is considered informative in a clinical point of view, the small number of patients enrolled does not allow to draw definitive conclusions about the two different weight groups.

- **Subjects with UC**

The FAS for UC included 30 subjects (13 subjects < 30 kg, 17 ≥ 30 kg). In general, patients with body weight < 30 kg presented a lower median duration of disease in respect to subjects with ≥ 30 kg (1.7 years [0.8-9.5] vs 2.1 [0.7-8.6]); as expected, the most frequently reported disease duration in the first group was ≥ 3-<7 years (28.6%), while in patients ≥ 30 kg was ≥ 1 < 3 years (52.9%). The difference in disease duration may have been influenced by the median age of the subjects enrolled, which resulted, as expected, lower in patients < 30 kg (median age: 8.5 years [4-13]) than in patients weighted ≥ 30 kg (14 years [8-17]).
In both groups, the majority of patients were naïve to anti-TNF antagonist therapy (78.8% and 52.9%, respectively). Most of patients were enrolled with a controlled disease according to both PUCAI and Mayo score: remission of disease was registered according PUCAI score in the 42.9% of patients weighted < 30 kg (median value: 10 [0-30]) and in the 70.6% of subjects ≥ 30 kg (median value: 0 [0-30]). Similar results were obtained with the disease activity index evaluated with the Mayo score: a mild score was registered in the 78.6% of subjects < 30 kg (median value 3 [0-7]) and in the 88.2% of patients ≥ 30

kg (median value 2[0-7]). Markers of disease (faecal calprotectin and CRP) were in line with the disease activity evaluation measured with both PUCAI and Mayo score.

- **Subjects with CD**

The FAS for CD included 28 subjects (14 < 30 kg, 14 ≥ 30 kg). Similarly to what reported for patients with UC, patients with body weight < 30 kg presented a lower median duration of disease in respect to subjects with ≥ 30 kg (1.9 years [0.8-3.5] and 4.4 [1.3-8.8], respectively); the most frequently reported disease duration in the first group was ≥ 1-< 3 years (78.6%), while in patients ≥ 30 kg was ≥ 3 < 7 Kg (50%). Also in this setting, the different median age reported in the two groups (8 years [2-13] in patients < 30 kg and 14 [10-17] in patients ≥ 30 kg) may explain the difference reported in terms of disease duration.

Most of subjects with CD were exposed to a previous anti-TNF antagonist therapy (50% and 71.4%, respectively); the most common disease activity recorded with SES-CD score and CDAI was "moderate" (SES-CD: < 30 kg= 35.7% ≥ 30 kg= 50%; CDAI: < 30 kg= 100% ≥ 30 kg: 100%), while when the disease was assessed with PCDAI, CD was reported as "Inactive" in the 85.7% of subjects weighted < 30 kg and 64.3% of patients ≥ 30 kg.

Biologic markers of disease (faecal calprotectin and CRP) presented a different behaviour across the two groups: high level of faecal calprotectin and CRP were reported in patients ≥ 30 kg (fecal calprotectin > 500 µg/g: 57%, CRP > 10 mg/L: 42.9 %), while in patients < 30 kg were lower (fecal calprotectin > 500 µg/g: 35.7%, CRP > 10 mg/L: 7.1 %) and were in line with results obtained with the different disease scores. Notably, CDAI score is not validated for use in children; its use in some early paediatric studies was applied for descriptive purposes. In adult vedolizumab studies in CD subjects, a CDAI cutoff of 330 was chosen to distinguish moderate from severe disease (with moderate disease defined as CDAI ≤330 and severe disease as CDAI >330). When using a more detailed classification of disease severity based on CDAI with the classes "inactive, in remission" (CDAI <150), "mild" (CDAI of 150 to <220), and "moderate" (CDAI of 220 to 330), the distribution of the baseline disease severity is more consistent with the classification based on the PCDAI, with rated of inactive disease of 78.5% (22/28), Mild of 17.8% (5/28) and Moderate of 3.5% (1/28) which resulted substantially alligned to what reported with the PCDAI score.

Results

- **Subjects with UC**

Long term of vedolizumab in pediatric patients is associated with high rated of maintenance of the clinical response; results at week 32 show similar rates of results when Complete Mayo score (84.6%, 95% CI: 54.6-98.1), Partial Mayo score (100%, 95% CI: 76.8-100), Modified Mayo score (100%, 95% CI: 75.3-100), and PUCAI (90%, 95% CI: 75.7-97.1). When sensitivity analyses were applied to the complete Mayo score, they confirmed similar rates of responses when the "US FDA UC 2016 Guidance" (84.6%, 95% CI: 54.6-98.1) and the "alternative missing data imputation" (84.6%, 95% CI: 54.6-98.1). An inferior rate of response is recorded when subjects requiring dose escalation were classified as non-responders (46.2%, 95% CI: 19.2-74.9), but this result is expected, considering that this sensitivity analysis isolates only patients who initially were considered responders, without any need of dose increase. The rate of clinical remission sec. complete Mayo score is comparable to the sensitivity analysis and this is expected, considering the way in which the sensitivity analysis was defined, and resulted higher when the PUCAI score is used (76.7%; 95% CI: 57.7, 90.1); overall, more than 50% of treated patients achieved a remission.

Steroid use was assessed through the predefined endpoint evaluating percentage of subjects requiring steroid dose increase or decrease from baseline at Week 48. Neither of the 2 subjects with UC who were receiving corticosteroids at baseline required steroid therapy.

When response rates were evaluated in a post hoc analysis in respect to the initial population enrolled in study 2003, the rates of clinical response and remission remain acceptable, 61.4% (range 45.5-75.6)

for UC and 52.3% (range 36.7-67.5) for CD, respectively; clinical remission were 52.3% (range 36.7-67.5) and 43.2% (range 28.3- 59.0)

Overall, no substantial changes were reported in the PUCAI total score from baseline of study 2005 to week 32 of the same study (mean change: 1, SD 11.7); when the analysis is performed from study 2003 start, a substantial reduction of disease activity (mean change: -40, SD 20.93), confirming the long term efficacy in disease control of vedolizumab.
Disease worsening based on PUCAI was observed in 2 of 30 (6.7%; 95% CI: 0.8, 22.1) subjects with UC at Week 32 and in 5 of 30 subjects (16.7%; 95% CI: 5.6, 34.7) at the individual subject final visit.

The impact of vedolizumab on physical development was evaluated on height, weight and BMI progress. In respect to the height improvement, an absolute increase was noted in patients weighted < 30 kg, but the comparison in respect to Z score showed a stable negative trend in respect to the healthy population. A substantial improvement was recorded also for the other items used for growth evaluation. In absence of a control arm, it is difficult to isolate the contribution of vedolizumab on physical development; nevertheless, considering the disease control obtained with vedolizumab treatment, a positive effect of the overall improvement in nutritional status can be postulated.

Health related QOL measured with IMPACT-III showed a stabilization of the measures across all the evaluated timepoints, with slight positive and negative oscillations during the follow up until the last time point at 240 weeks.

Finally, the effect of the long-term therapy on the time to major IBD-related events (hospitalization, surgeries and procedures) showed an overall incidence of events of 23.3% (7/30) of patients; in two cases, hospitalization was due to surgery, while no procedures were registered.

- **Subjects with CD**

Similarly to what noted for UC subjects, long term of vedolizumab in pediatric patients is associated with high rated of maintenance of the clinical response; results at maintenance of response rate at week 32 were similar, with percentage of response sec. SES-CD and CDAI of 76.9% (95% CI: 46.2-95), CDAI score of 100% (95% CI: 75.3-100), enhanced CDAI score of 92.3% (95% CI: 64-99.8), SES-CD of 72.7% (95% CI: 52.2-87.7) and PCDAI of 75% (95% CI 55.1-89.3).

The application of sensitivity analyses to the results obtained with SES-CD and CDAI confirmed similar results with an "alternative missing data imputation" (76.9%, 95% CI: 46.2-95); a lower rate of response is recorded when subjects requiring dose escalation were classified as non-responders (61.5%, 95% CI: 31.6-86.1), but this last result is expected. The same considerations applied to the sensitivity analysis in UC patients are valid also for the CD group. Clinical remission rates varied from 100% (95% CI: 75.3-100) with CDAI to 67.9% (95% CI: 47.6, 84.1) based on PCDAI; the endoscopic remission based on SES-CD was observed in 13 of 22 subjects (59.1%; 95% CI: 36.4, 79.3). In general, more than half of patients treated with vedolizumab reached a clinical remission during the long term treatment. Three of 4 subjects with baseline steroid use were able to discontinue steroids, and the remaining 1 subject required a dose reduction at Week 48. No subjects with CD experienced fistula during the study.

Overall, no substantial changes were reported in the PCDAI total score from baseline of study 2005 to week 32 of the same study (mean change: 0.4, SD 9.19); when the analysis is performed from study 2003 start, a substantial reduction of disease activity (mean change: -24.8, SD 12.03) can be noted, confirming the long term efficacy of vedolizumab also in this group. Overall, the rate of disease worsening based on PCDAI was observed in 1 of 28 (3.6%; 95% CI: 0.1, 18.3) subjects with CD; at the individual subject final visit, 3 of 28 subjects (10.7%; 95% CI: 2.3, 28.2) had experienced disease worsening.

The post hoc analysis of the long-term response in respect to the initial population included at study 2003 start, showed an acceptable rates of disease control in terms of clinical response (47.7%, range 32.5-63.3) and clinical remission (43.2%, range 28.3-59).

The analysis of the effects of vedolizumab treatments on items of physical development, showed a trend in height increase, which resulted more pronounced in subjects < 30 kg. The analysis of the Z score showed little oscillations in respect to the standard, with slightly negative values for patients < 30 kg and positive for subjects ≥ 30 kg. Effects on body weight showed a positive trend in weight increase, as well as for BMI. Data on Tanner stage were too limited for drawing definitive conclusions. Taken together, it could be assumed that vedolizumab treatment may have contributed to disease control and to an overall improvement in nutritional status.

The analysis of the Health related QOL measured with IMPACT-III showed a positive trend in the improvement of the results across all the evaluated timepoints until the last one, at 312 weeks.

Major IBD-related events were reported for 14.3% (4/28) of patients; in one case, hospitalization was due to surgery, while no procedures were registered.

A post hoc comparison in terms of major IBD related events between study 2003 and 2005 showed a similar percentage of events for both UC (2003: 20.5%; 2005: 23.3%) and CD (2003: 22.7%; 2005: 17.9%); hospitalization remains the main cause of major IBD related events in both disease groups. Overall, the small number of events reported in both studies does not allow drawing definitive conclusions about the trend of occurrence of those event during the long term exposure to vedoluzimab; in general, the pattern and nature of IBD-related events (hospitalisations, surgeries, and procedures) observed in Study 2005 seems consistent with those identified in Study 2003 for both UC and CD.

Overall, the long-term treatment with vedolizumab seems able to maintain a sufficient control of disease in the paediatric population, but the small number of subjects enrolled in the long-term phase does not allow to draw definitive conclusions about the maintenance of clinical benefit with long term treatment in IBDs.

Pharmacokinetics

The primary objective of study 2005 was to assess the safety of long-term treatment with vedolizumab IV, while the evaluation of efficacy and PK was included as secondary and exploratory objectives, respectively.

Serum vedolizumab concentrations increased in an overall dose-proportional manner, from 100 mg to 200 mg in subjects <30 kg and from 150 mg to 300 mg in subjects ≥30 kg, showing a trend of trough concentrations higher in subjects with UC compared to those with CD but only in the ≥30 kg group.

Antibodies to vedolizumab seem to be developed at a low rate. Due to the low number of patients and then the low amount of data collected, no relevant information related to PK and immunogenicity status can be obtained from this study.

Safety

The primary objective of this study was to evaluate the long-term safety of pediatric exposure to vedolizumab. The MAH confirms that the upcoming paediatric indication variation includes comprehensive analysis of safety, in which data from this database will be included and based on which conclusions can be reached about the safety in short- and long- term. Therefore, the MAH proposes to report those results in the following submission in a more comprehensive way. The MAH's proposal may be acceptable, provided that the safety analysis clearly shows a comparison between the short- and long-term safety profile, in order to understand whether there is an increase in adverse events over time.

In subjects with OC, a mean (SD) of 25.7 (12.76) infusions were completed by 30 subjects with UC and the mean (SD) extent of exposure was 1534.4 (730.41) days (approximately 4.2 [2.0] years). A total of 12 subjects with UC receiving 100, 150, or 200 mg were escalated to 300 mg dose during the study. No subjects were escalated to the 200 mg dose.

Overall, slight lower mean (SD) infusions (20.4 [SD 13.86]) were recorded in the 28 subjects with CD; as a consequence, the mean (SD) extent of exposure was consequently lower, with values of 1220.3 (779.83) days (approximately 3.3 [2.1] years). A total of 6 subjects with CD receiving 100, 150, or 200 mg were escalated to 300 mg dose during the study. No subjects were escalated to the 200 mg dose.

-Safety Profile in subjects with UC

A general analysis of the safety profile in the UC population showed that 29/30 subjects (96.7%) experienced at least one TEAEs. Most of them were mild (93.3%) to moderate (76.7%) in severity and considered unrelated to the study drug (76.7%). TEAEs with a maximum severity of severe intensity were reported in 8 subjects (26.7%).

The most frequently reported TEAEs by SOC were gastrointestinal disorders (83.3%), infections and infestations (76.7%), and general disorders and administration site conditions (50%). In the gastrointestinal disorder SOC, most of the more frequently reported TEAE can be ascribed to UC, as confirmed also by the analysis of the most frequently reported TEAEs by PT, which showed, as the most frequently reported TEAE, disease worsening of UC (43.3%), pyrexia (40%), and vomiting (30%). The overall rate of exacerbation of UC was reported by 13.3% of subjects. In respect to the infectious complications, the most frequently TEAE by PT were upper respiratory tract infections (26.7%), COVID-19 infection (20%), while gastrointestinal infections sustained by *Clostridium difficile* were recorded in the 6.7% of patients.

When TEAEs were analyzed in relation to vedolizumab exposure, the overall incidence of drug-related TEAEs was 23.3%; "gastrointestinal disorders" remains the most commonly recorted PT (13.3%) and nausea was the most frequently described drug-related TEAE (6.7%). No vedolizumab-related infections were reported in the UC group.

SAEs were reported in a total of 10 subjects (33.3%); the most frequently reported SAEs by SOC were gastrointestinal disorders (23.3%) and infections and infestations (16.7%), with the most commonly reported SAE by PT was colitis ulcerative (disease worsening) in the 13.3% of patients. The rest of the SAEs were reported in 1 subject each. All SAEs were not considered drug related by the Investigators.

Study drug discontinuations due to TEAEs were reported in a total of 7 subjects (23.3%) with UC. The most common TEAE by SOC leading to study drug discontinuations was gastrointestinal disorders. The most frequent TEAE by PT leading to study drug discontinuation was colitis ulcerative (disease worsening). The rest of the events were reported in 1 subject each.

In this study serious infections, hypersensitivity, infusion-related reactions, malignancy, liver injuries and PML were considered as Adverse Event of Special Interest. The most frequently reported class of AESI was Hypersensitivity (33.3%), followed by serious infections (16.7%). Serious complications reported in these groups were considered as not related to vedolizumab. One case of papillary thyroid cancer was reported and also in this case it was not considered as drug-related. One case of liver injury (hepatic cytolysis) was considered vedolizumab related; this risk is acknowledged and reported in product SmPC as a common Adverse Drug Reaction (ADR).

- **Safety profile in subjects with CD**

All pediatric subjects with CD (100%) experienced at least one TEAE during the study; A majority of subjects experienced TEAEs that were mild (92.9%) to moderate (64.3%) in severity. Most TEAEs were considered unrelated to the study drug (85.7%).

As reported also for patients with UC, the most frequently reported TEAEs by SOC were gastrointestinal disorders (71.4%), infections and infestations (67.9%) and respiratory, thoracic and mediastinal disorders (35.7%). Also in this group, the most frequently TEAE by PT in the Gastrointestinal disorders PT can be ascribed to the underlying disease, like worsening of Chron's disease (46.4%), abdominal pain (21.4%), and vomiting (14.3%). The overall rate of exacerbation of CD was reported by 7.1% of subjects.

In respect to the infectious complications, the most frequently TEAE by PT were upper respiratory tract infections (21.4%), pharyngitis (17.9%) and COVID-19 infection (10.7%); the analysis of the TEAEs recorded in the "Respiratory, thoracic and mediastinal disorders" were mostly represented by oropharyngeal pain (10.7%), which can be considered related to upper respiratory infections. Overall, the maximum severity of the TEAEs in the majority of subjects (14 [50.0%]) with CD was moderate. TEAEs with a maximum severity of mild intensity were reported in 9 subjects (32.1%), while those with maximum severity of severe intensity were reported in 5 subjects (17.9%).

The overall incidence of drug-related TEAEs was low (14.3%), if compared to the overall incidence of TEAEs. Gastrointestinal disorders remains the most commonly recorded PT (2 cases: 7.1%), with Crohn's disease as the unique reported TEAE by PT registered; respiratory, thoracic and mediastinal disorders accounted for 7.1% of drug-related TEAEs (2 cases: 1 of asthma and 1 of cough), followed by infections and infestations (3.6%, 1 case of nasopharyngitis).

SAEs were reported in a total of 10 subjects (35.7%); the most frequently reported SAEs by SOC were gastrointestinal disorders (25%) and infections and infestations (3.6%), with the most frequently reported SAE by PT was Crohn's disease in the 17.9% of patients (one of which was considered as drug-related); 1 case of serious viral infection was recorded too.

Study drug discontinuations due to TEAEs were reported in a total of 5 subjects (17.9%) with CD; also in this case, the most common TEAE leading to study drug discontinuations by SOC were gastrointestinal disorders (14.3%).

Regarding the AESIs, the most frequently reported class was Hypersensitivity (25%), followed by serious infections (3.6%). The most common hypersensitivity AESI reported was cutaneous rash (7.1%), while the serious infection reported is due to the viral infection already mentioned in the SAE section. One case of haemangioma was reported (not drug related). Finally, one case of liver injury (increase in alanine aminotransferase and gamma-glutamyltransferase) was described, but not considered vedolizumab related.

3. Rapporteur's CHMP overall conclusion and recommendation

Results of the long-term extension study in pediatric patients, responders to vedolizumab, seem to confirm the long-term safety and clinical benefit of vedolizumab IV as maintenance treatment in IBDs subjects, although the small number of enrolled patients does not allow to draw firm conclusions. Specifically, the long-term treatment is associated with a satisfactory percentage of long-term responder patients, most of which achieved also a clinical remission. A clinical benefit was also observed in terms of physical development. Although that less than half of subjects discontinued study, it should be noted that many discontinuations were protocol-driven for causes different from disease worsening, while the occurrence of AEs remains the main cause for discontinuation. In terms of safety, the administration with exposure up to 2487 days (6.8 years) in UC and up to 2386 days (6.5 years) in CD populations was generally safe and well tolerated, although further data are requested in order to establish a possible reduction of adverse event occurrence with long term exposure. These results will be provided in a subsequent submission in a more comprehensive way. No new safety signals were identified across weight or dose groups, and the overall profile remained consistent with established prior adult experiences. In conclusion, despite the small number of enrolled subjects, the results of this study support a long-term favorable benefit-risk profile for vedolizumab IV as maintenance therapy for pediatric patients with UC or CD. No changes in SmPC are needed. The overall benefit risk evaluation is deemed positive in presence of satisfactory responses to the RFI.

☐ **Fulfilled:**

☒ Not fulfilled:

Based on the data submitted, the MAH should provide satisfactory responses to the Request for supplementary information list reported in the following paragraph (see section "Request for supplementary information")

4. Request for supplementary information

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

1) In respect to the efficacy results reported in this long term study, the MAH is invited to report the rates of Clinical response and remission at week 32, divided for disease, evaluated in respect to the whole pediatric population initially enrolled at the baseline of study 2003, and not only to the population of responders who started long term study 2005.

2) The MAH is requested to report the overall number of patients ≥ 30 kg and < 30 kg who withdrew the study for achieving 18 year of age while in clinical remission.

3) Regarding to the description of the disease characteristics of CD patients, the MAH is requested to discuss the difference in terms of disease activity registered at the baseline obtained with the different disease scores, with a particular attention to the high rates of "inactive disease" reported with the PCDAI scores, in respect to the higher frequencies of "moderate disease" obtained with CDAI and SES-CD.

4) The MAH is requested to report the global incidence of IBD-related events registered in study 2003 and compare it with what reported in 2005 for both CD and UC populations.

The timetable is a 30 day response timetable with clock stop.

30-day responses to RSI assessment timetable

Submission of responses after clockstop

	Deadline for Submission (*)	Start date	CHMP Rapporteur AR	Comments from CHMP (~)	Updated CHMP Rapporteur AR (#)	CHMP conclusion
B17	21/04/2026	22/04/2026	06/05/2026	11/05/2026	13/05/2026	21/05/2026

MAH responses to Request for supplementary information

Question 1

In respect to the efficacy results reported in this long term study, the MAH is invited to report the rates of Clinical response and remission at week 32, divided for disease, evaluated in respect to the whole pediatric population initially enrolled at the baseline of study 2003, and not only to the population of responders who started long term study 2005.

MAH Response 1

A post hoc analysis of integrated 1-year efficacy including all subjects who enrolled and received at least 1 dose of study drug in Study 2003 (Study 2003 FAS; 44 subjects with UC and 44 subjects with CD) was conducted, combining data from Study 2003 and its extension Study 2005.

This post hoc analysis provides an overview of the treatment course of subjects who initiated treatment with vedolizumab IV in Study 2003 and continued treatment to Week 32 in Study 2005. Week 32 in Study 2005 corresponds to approximately 1 year (Week 54) of treatment across both studies and mirrors the treatment duration of the pivotal phase 3 studies (Study 3024 and Study 3025). In this analysis, disease activity is monitored based on the PUCAI (in UC) and PCDAI (in CD). Response and remission endpoints based on PUCAI and PCDAI were used since these scales are targeted to the paediatric population and were assessed frequently in Study 2005 (PUCAI every 8 weeks, PCDAI every 16 weeks) as they do not require an endoscopic assessment (as needed for the Mayo score and SES-CD [Study 2005 CSR Table 8]). Furthermore, as explained in the Study 2005 CSR, the Mayo and CDAI scores at Week 32 were not available for all subjects who reached Week 32 because the completion of subject diary for collection corresponding patient-reported outcomes was not mandatory for all subjects per the protocol version they were enroled under (Study 2005 CSR Section 9.7.1 and Section 9.8.2.1 for details). Subjects who did not enrol into Study 2005 or discontinued Study 2005 prior to Week 32 are considered as non-responder/non-remitter for time points after their discontinuation.

The proportions of subjects who achieved clinical remission or clinical response at Week 54 (Study 2005 Week 32) by indication across all weight cohorts are provided in Table 1.a.

After 1 year of treatment initiation in Study 2003, at Week 32 of Study 2005, clinical remission was achieved by 23 of 44 subjects with UC (52.3%; 95% CI: 36.7, 67.5) based on PUCAI score and 19 of 44 subjects with CD (43.2% 95% CI: 28.3, 59.0) based on PCDAI score.

At the same timepoint, clinical response relative to Study 2003 baseline was achieved by 27 of 44 subjects with UC (61.4%; 95% CI: 45.5, 75.6) based on PUCAI score and 21 of 44 subjects with CD (47.7%; 95% CI: 32.5, 63.3) based on PCDAI score.

Table 1.a Proportion of Subjects with Clinical Remission or Clinical Response (Relative to 2003 Day 1) at Study 2005 Week 32 for UC and CD Subjects – Full Analysis Set

	Clinical Remission		Clinical Response	
Remission/Response Status	**UC (N=44)**	**CD (N=44)**	**UC (N=44)**	**CD (N=44)**
Yes n (%) (95% CI) [a]	23 (52.3) (36.7, 67.5)	19 (43.2) (28.3, 59.0)	27 (61.4) (45.5, 75.6)	21 (47.7) (32.5, 63.3)
No n (%) (95% CI) [a]	21 (47.7) (32.5, 63.3)	25 (56.8) (41.0, 71.7)	17 (38.6) (24.4, 54.5)	23 (52.3) (36.7, 67.5)

Source: Study 2003/2005 Post hoc analysis Table 1.1, Table 1.2, Table 2.1, Table 2.2.
Week 32 of Study 2005 correlates to Week 54 from treatment initiation in Study 2003 (approximately 1 year of treatment).
For UC subjects, clinical remission based on the PUCAI was defined as PUCAI score <10. Clinical response based on the PUCAI score was defined as a ≥20-point decrease from 2003 baseline in PUCAI score.
For CD subjects, clinical remission based on the PCDAI was defined as a PCDAI score ≤10. Clinical response based on the PCDAI was defined as a ≥15-point decrease from 2003 baseline in PCDAI score with total PCDAI ≤30.
Subjects who have completed or withdrawn from 2003/2005 with missing data for determination of endpoint status are imputed as "No".
[a] The exact 95% CI was based on Clopper-Pearson method.

CHMP Rapporteur evaluation of response

The MAH provided the results of a post-hoc analysis in which results in terms of clinical response and remission showed acceptable rates of long term response (UC: 61.4%, range 45.5-75.6, CD: 47.7%, range 32.5-63.3) and remission (UC:52.3%, range 36.7-67.5, CD: 43.2%, range 28.3-59) in respect to the initial population enrolled in study 2003. Overall, these results are deemed clinically important because provide information about long term efficacy of vedolizumab in this setting.

Issue considered resolved; CHMP AR was updated accordingly.

Question 2

The MAH is requested to report the overall number of patients > 30 kg and < 30 kg who withdrew the study for achieving 18 year of age while in clinical remission.

MAH Response 2

Per Study 2005 Protocol (Amendment 8), treatment duration of vedolizumab varied by subject on the basis of continued benefit, but could continue until vedolizumab IV was commercially available for paediatric indication(s) in the subject's country or until other drug access programs became available (whichever came first), the subject turned 18 years of age and transitioned to commercial drug, the subject withdrew from the study, or the sponsor decided to close the study. Therefore, subjects were allowed to continue in the study after reaching 18 years of age.

Identifying subjects who discontinued the study for achieving 18 years of age has some limitations. Due to privacy reasons in data collection and dependent on local regulations, the exact date of birth of the study subjects is unknown and therefore it cannot be accurately determined when a subject reached 18 years of age. At enrolment of Study 2003, age was collected only in years and months, therefore the calculated age of subjects at the time of Study 2005 completion may slightly differ from the subject's actual age at end of study. The reason for a subject's premature discontinuation at end of study (EOS)/end of study treatment (EOT) was captured in the eCRF using one of 10 pre-defined reasons. The eCRF offers one option as "other" which allows specific information to be added if the reason is not applicable to the pre-defined options. Specifically, the eCRF did not include the pre-defined reason for discontinuation for reaching 18 years of age and therefore discontinuation for this reason could not be consistently reported. Subjects who completed the study at 18 years of age then transitioned to commercially available drug would only be captured in the eCRF as having completed the study.

A post hoc summary table and listing presenting the subjects who discontinued the study at age 18 are provided for this response (Appendix 1 and Appendix 2). The table and listing include all subjects who reached age of 18 years during Study 2005. Age at EOT and EOS in Study 2005 was calculated from the subject's available age data reported at study entry in Study 2003.

Of the 59 subjects enrolled in Study 2005, 17 subjects (10 UC; 7 CD) reached 18 years of age during Study 2005 (2 out of 40 subjects in the <30 kg weight group; 15 out of 49 subjects in the ≥30 kg weight group) (see Appendix 1 and Appendix 2).

Of the 17 subjects, 8 subjects completed EOT or EOS at 18 years of age (Table 2.a): 4 subjects (3 UC; 1 CD) received their last administration of study drug at 17 years of age and 4 subjects (2 UC; 2 CD) at 18 years of age. The remaining 9 subjects continued receiving study drug in the study after reaching 18 years of age (Appendix 1 and Appendix 2).

Only for 1 subject discontinuation of the study due to reaching age of 18 years and transitioning to commercial drug was explicitly reported.

Table 2.a Subjects Who Completed Study 2005 at Age of 18 Years

Subject ID	Weight Cohort	Age at EOT	Age at EOS	Last Response Status	Last Remission Status	Discontinuation or Completed Study [a]
UC						
	<30 kg			Non-responder	Non-remitter	Discontinued (other: subject turned

				18 and moved to commercial drug)
[b]	≥30 kg	Responder	Non-remitter	Discontinued (adverse event)
	≥30 kg	Responder	Remitter	Discontinued (adverse event)
	≥30 kg	Non-responder	Non-remitter	Discontinued (adverse event)
[b]	≥30 kg	Responder	Remitter	Completed
CD				
	<30 kg	Responder	Remitter	Completed
	≥30 kg	Responder	Non-remitter	Discontinued (adverse event)
	≥30 kg	Responder	Remitter	Completed

Source: Study 2005 ST-02367 Listing 1.
UC: Clinical remission was defined as PUCAI <10; clinical response was defined as a ≥20-point decrease from Study MLN0002-2003 baseline.
CD: Clinical remission was defined as PCDAI ≤10; clinical response was defined as a ≥15-point decrease from Study MLN0002-2003 baseline with a total PCDAI ≤30.
[a] EOS status reason was captured in the eCRF and reported per the EDC.
[b] Subjects received vedolizumab as a concomitant medication between EOT and EOS.

CHMP Rapporteur evaluation of response

The limitations in identifying subjects who discontinued the study for achieving 18 years are acknowledged. Therefore, these results suffered from some limits that impaired the robustness of the analysis.

In general, for the 17 subjects for whom the attainment of the age of majority was confirmed during the course of the protocol, information about the completion of the study was available for 8 subjects (5 with UC and 3 with CD). In the UC setting, 3/5 were considered "responders" and 2 "remitters"; 1 subject completed the study, 3 discontinued to AE and 1 moved to the commercial drug. In the CD all the 3 subjects were considered responders and 2 of them achieved also a clinical remission; 2 of them completed the study, while the remaining 1 discontinued for AE.

Issue not further pursued; CHMP AR was updated accordingly

Question 3

Regarding to the description of the disease characteristics of CD patients, the MAH is requested to discuss the difference in terms of disease activity registered at the baseline obtained with the different disease scores, with a particular attention to the high rates of "inactive disease" reported with the PCDAI scores, in respect to the higher frequencies of "moderate disease" obtained with CDAI and SES-CD.

MAH Response 3

For enrolment into Study 2005, paediatric subjects with CD had to have completed Study 2003 and had to achieve clinical response at Week 22, defined as a reduction of the CDAI by at ≥70-point from baseline or a decrease of PCDAI of ≥15 points. No eligibility criterion was applied with respect to absolute disease activity level or severity category (for example, inactive, mild, or moderate disease) at entry into Study 2005.

Disease activity (or severity) at entry to Study 2005 was summarised in the CSR using different scales: CDAI, PCDAI, and SES-CD. Minor inconsistencies in the disease severity classifications are expected when using different scales and as described in detail below. Overall, there is no true discordance in baseline disease activity across different severity assessments.

PCDAI is specifically designed to assess disease severity in children. The PCDAI score can range from 0 to 100, with higher scores signifying more active disease (<10: inactive disease, 11 to 30: mild disease, and >30: moderate-to-severe disease).

While CDAI is not validated for use in children, it has been included in some early paediatric studies for descriptive purposes, mainly to allow comparison with adult CD cohorts and adult clinical trial data.

In adult vedolizumab studies in CD subjects, a CDAI cutoff of 330 was applied to distinguish moderate from severe disease (with moderate disease defined as CDAI ≤330 and severe disease as CDAI >330).

In Study 2005, disease activity based on CDAI was summarised using the same 330-point cutoff; however, this approach intentionally grouped subjects with inactive disease, remission, mild disease, and moderate disease within the ≤330 category.

When using a more detailed classification of disease severity based on CDAI with the classes "inactive, in remission" (CDAI <150), "mild" (CDAI of 150 to <220), and "moderate" (CDAI of 220 to 330), the distribution of the baseline disease severity is more consistent with the classification based on the PCDAI. Baseline disease severity classifications based on CDAI (with the categories described above) and PCDAI is summarised in Table 3.a.

Table 3.aBaseline CDAI and PCDAI Scores Presented by Category in Study 2005

CDAI Classification	Study 2005 (N=28)	PCDAI Classification	Study 2005 (N=28)
Inactive/remission (<150)	22	Inactive (<10)	21
Mild (150 to <220)	5	Mild (11 to 30)	7
Moderate (220 to 330)	1	Moderate to severe (>30)	0
Severe (>330)	0	-	-

Source: Study 2005 Listing 16.2.6.2, Table 15.1.8.3.
Baseline score for CDAI was based on the data collected on the latest visit on or after Week 14 from Study 2003. Baseline score for PCDAI was based on data collected on Day 1 visit for Study 2005.

CHMP Rapporteur evaluation of response

The MAH provided useful information about the use of the different disease scores used in CD studies; in particular, it was reported that CDAI score is not a validated score in pediatric subjects and its use in some early paediatric studies was implemented for descriptive purposes. In adult vedolizumab studies in CD subjects, a CDAI cutoff of 330 was applied to distinguish moderate from severe disease (with moderate disease defined as CDAI ≤330 and severe disease as CDAI >330). When using a more detailed classification of disease severity based on CDAI with the classes "inactive, in remission" (CDAI <150), "mild" (CDAI of 150 to <220), and "moderate" (CDAI of 220 to 330), the distribution of the baseline disease severity is more consistent with the classification based on the PCDAI, with rated of inactive disease of 78.5% (22/28), Mild of 17.8% (5/28) and Moderate of 3.5% (1/28) which resulted substantially aligned to what reported with the PCDAI score.

Issue considered resolved

CHMP AR was updated accordingly

Question 4

The MAH is requested to report the global incidence of IBD-related events registered in study 2003 and compare it with what reported in 2005 for both CD and UC populations.

MAH Response 4

Overall in Study 2005, 7 of 30 (23.3%) subjects with UC experienced at least 1 major IBD related event. The most frequently reported event was hospitalisation (23.3%).
Among subjects with CD, 5 of 28 subjects (17.9%) experienced at least 1 major IBD-related event, with the most commonly reported of hospitalisation reported in 5 subjects (17.9%); surgery which was reported in 2 subjects (7.1%) and procedures in 1 subject (3.6%) (Study 2005 CSR Addendum).
In Study 2003, IBD-related events were not captured or defined prospectively as done in Study 2005 as time to IBD-related event was not an objective in Study 2003 while it was a secondary objective in Study 2005. Therefore, a post hoc assessment was conducted to identify IBD-related events (that is, hospitalisations, surgeries, and procedures) in Study 2003 from Day 1 to last available assessment in subjects who received at least 1 dose of study drug.
Overall, 9 of 44 subjects with UC (20.5%) and 10 of 44 subjects with CD (22.7%) experienced at least 1 IBD-related event during Study 2003 (Appendix 3). No apparent trend in the incidence of IBD-related events by weight cohort was identified.
Direct comparison of event rates between Study 2003 and Study 2005 should be interpreted with caution, as Study 2003 was of substantially shorter duration (14 weeks) compared with the long-term exposure in Study 2005. Detailed event listings and weight-based summaries are provided in Appendix 2.
Overall, despite differences in study duration, the pattern and nature of IBD-related events (hospitalisations, surgeries, and procedures) observed in Study 2005 were consistent with those identified in Study 2003 for both UC and CD.

CHMP Rapporteur evaluation of response

The MAH provided data about the incidence of major IBD-related events occurred during study 2003 for both UC and CD and provide a comparison with study 2005. Overall, the small number of events reported in both studies does not allow definitive conclusions to be drawn about the trend of occurrence of those event during the long term exposure to vedoluzimab. In general, similar percentage of events can be noted for both UC (2003: 20.5%; 2005: 23.3%) and CD (2003: 22.7%; 2005: 17.9%); hospitalization remains the main cause in both disease groups.

Overall, Rapp agrees that the pattern and nature of IBD-related events (hospitalisations, surgeries, and procedures) observed in Study 2005 seems consistent with those identified in Study 2003 for both UC and CD.

Issue considered resolved; CHMP AR was updated accordingly.